EU Risk Management Plan

For

mRESVIA dispersion for injection in pre-filled syringe

Respiratory Syncytial Virus mRNA Vaccine

(single-stranded 5'capped mRNA encoding the RSV-A glycoprotein F stabilised in the prefusion conformation)

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP version number: 5.1

Data lock point for this RMP: 30 May 2025

Date of final sign off: 27 Feb 2026

Rationale for submitting an updated RMP:

To update Module SI of the RMP based on the responses to CHMP/PRAC Request for Supplementary Information (RSI) related to the Type II variation (EMA/VR/0000312911) to extend the indication for the prevention of LRTD caused by RSV in adults 18 years of age and older.

Summary of significant changes in this RMP:

Compared to the previously submitted mRESVIA European Union (EU) RMP version 5.0, this RMP version 5.1 has been updated as summarised in the table below:

RMP Module:	**Significant Changes:**
Part I **Product Overview**	No changes.
Part II **Safety Specification**	
Module SI **Epidemiology of the indication and target population**	Updated the natural history text for adults 18 through 59 years of age.
Module SII **Non-clinical part of the safety specification**	No changes.

RMP Module:	Significant Changes:
Module SIII **Clinical trial exposure**	No changes.
Module SIV **Populations not studied in clinical trials**	No changes.
Module SV **Post-authorisation experience**	No changes.
Module SVI **Additional EU requirements for the safety specification**	No changes.
Module SVII **Identified and potential risks**	No changes.
Module SVIII **Summary of the safety concerns**	No changes.
Part III **Pharmacovigilance Plan**	No changes.
Part IV **Plans for post-authorisation efficacy studies**	No changes.
Part V **Risk minimisation measures**	No changes.
Part VI **Summary of risk management plan**	No changes.
Part VII **Annexes**	Annex 8 – Updated to reflect the changes made to the RMP.

Other RMP versions under evaluation:

RMP version number	Date submitted to EMA	Procedure number
6.0	18 Dec 2025	EMA/VR/0000320244

Details of the currently approved RMP:

Version number: 4.0

Approved with procedure: EMA/VR/0000310233

Date of approval: 26 Nov 2025

EU QPPV name[1]: Marie-Pierre Caby-Tosi, EU QPPV

[1] EU QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the

QPPV oversight declaration: The content of this RMP has been reviewed and approved by Moderna's QPPV. The electronic signature is available on file.

identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Acronym	Definition
ACE2	angiotensin-converting enzyme 2
ADEM	acute disseminated encephalomyelitis
AE	adverse event
AESI	adverse event of special interest
AUC	area under the concentration versus time curve
BMI	body mass index
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CEAC	Cardiac Event Adjudication Committee
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	disease caused by the 2019 coronavirus
CSR	clinical study report
DMG	dimyristoyl glycerol
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
eCRF	electronic case report form
EEA	European Economic Area
EFS	Edmonton Frail Scale
EMA	European Medicines Agency
EOS	end of study
EPAR	European public assessment report
ERD	enhanced respiratory disease
EU	European Union
FDA	Food and Drug Administration
FI-RSV	formalin-inactivated respiratory syncytial virus
GBS	Guillain-Barré syndrome
GLP	Good Laboratory Practice
GMT	geometric mean titre

Acronym	Definition
GVP	Good Pharmacovigilance Practices
HD	high dose
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IM	intramuscular
IP	investigational product
IV	intravenous(ly)
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LRTD	lower respiratory tract disease
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
Max	maximum
MedDRA	medical dictionary for regulatory activities
Min	minimum
mRNA	messenger ribonucleic acid
nAb	neutralising antibody(ies)
NHP	nonhuman primate
NOAEL	no observed adverse effect level
NPA	National Prescription Audit
O/E	observed-to-expected
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PL	package leaflet
PolyA	polyadenylated
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	preferred term
PV	pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	risk management plan
RNA	ribonucleic acid
RSV	respiratory syncytial virus

Acronym	Definition
RSV-NET	Respiratory Syncytial Virus Hospitalization Surveillance Network
RSV-LRTD	respiratory syncytial virus lower respiratory tract disease
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
SM-102	a custom-manufactured ionizable lipid
SOT	solid organ transplant
SSP	Signaling Strategy Plan
Th1	T helper type 1
Th2	T helper type 2
UK	United Kingdom
US	United States
UTR	untranslated region
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization
WOCBP	women of child-bearing potential

Part I: Product Overview

Table 1: Product Overview

Active substance (INN or common name)	Single-stranded 5' capped mRNA encoding the RSV-A glycoprotein F stabilised in the prefusion confirmation
Pharmacotherapeutic group (ATC Code)	Vaccine, other viral vaccines (J07BX05)
Marketing Authorisation Holder	MODERNA BIOTECH SPAIN, S.L. C/ Julián Camarillo nº 31 28037 Madrid Spain
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	mRESVIA dispersion for injection in pre-filled syringe Respiratory Syncytial Virus mRNA Vaccine
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** The messenger RNA (mRNA) drug substance in mRESVIA is chemically similar to naturally-occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N-methyl-pseudouridine, a naturally-occurring pyrimidine base present in mammalian transfer RNAs (Rozenski et al 1999; Karikó et al 2005). This nucleoside is included in mRESVIA drug substance in place of the normal uridine base to minimise the indiscriminate recognition of the mRESVIA mRNA by pathogen-associated molecular pattern receptors (eg, toll-like receptors) (Desmet and Ishii 2012). The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure (Kozak 1991; Fechter and Brownlee 2005). **Structure of mRNA**  Abbreviations: mRNA = messenger RNA; PolyA = polyadenylated; UTR = untranslated region.
	Summary of mode of action: mRESVIA is an mRNA-based vaccine encoding the membrane anchored RSV-A F glycoprotein stabilised in the prefusion conformation through changes to the amino acid sequence. The RSV-A prefusion glycoprotein is antigenically cross-reactive to the RSV-B prefusion glycoprotein. The prefusion F glycoprotein is the target of neutralising antibodies that mediate protection against RSV-associated respiratory tract disease. mRESVIA stimulates production of RSV-A and RSV-B neutralising antibodies and induction of antigen-specific cellular immune responses.
	Important information about its composition: mRESVIA is an mRNA-based vaccine encoding the membrane-anchored RSV-A F glycoprotein stabilised in the prefusion conformation through changes to the amino acid sequence. The RSV-A prefusion glycoprotein is antigenically cross-reactive to the RSV B prefusion glycoprotein. The prefusion F glycoprotein is the target of neutralising antibodies that mediate protection against RSV-associated respiratory tract disease. One dose (0.5 mL) contains 50 micrograms of RSV mRNA vaccine (nucleoside modified) encapsulated in lipid nanoparticles.
Hyperlink to the Product Information	mRESVIA Product Information (Module 1.3.1)

Indication in the EEA	Current: mRESVIA is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in: • adults 60 years of age and older; • adults 18 through 59 years of age who are at increased risk for LRTD caused by RSV. The use of this vaccine should be in accordance with official recommendations.
	Proposed: mRESVIA is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in adults 18 years of age and older. The use of this vaccine should be in accordance with official recommendations.
Dosage in the EEA	Current: The recommended dose of mRESVIA is one single dose of 0.5 mL.
	Proposed: Not applicable
Pharmaceutical forms and strengths	Current: Dispersion for injection White to off-white dispersion (pH: 7.0 – 8.0) One dose (0.5 mL) contains 50 micrograms of RSV mRNA vaccine (nucleoside modified) encapsulated in lipid nanoparticles.
	Proposed: Not applicable
Vaccine Construct and the formulation	One dose (0.5 mL) contains 50 micrograms of RSV mRNA vaccine (nucleoside modified) encapsulated in lipid nanoparticles. The active substance is a single-stranded 5’ capped mRNA encoding the RSV-A glycoprotein F stabilised in the prefusion confirmation. The excipients include 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, and water for injections.
Is the product subject to additional monitoring in the EU?	Yes

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication and Target Populations

Indication: mRESVIA is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in adults 18 years of age and older.

- **Adults 60 years of age and older**

Incidence: RSV is increasingly recognised as an important cause of morbidity and mortality in adults, particularly among older individuals (Casas et al 2025; Urchueguía-Fornes et al 2025; Haeberer et al 2024; Havers et al 2024; Branche et al 2022a). Prospective cohort studies conducted in the US and Europe estimate annual RSV infection rates of 3% to 7% among otherwise healthy older adults (Falsey et al 2005; Korsten et al 2021). Studies in high income countries attribute 2% to 10% of community-acquired pneumonia, 3% to 5% of hospital admissions for acute cardiorespiratory diseases, and approximately 6000 excessive respiratory-related deaths in the US during seasonal peaks in older adults to RSV (Mitratza et al 2024; Haeberer et al 2024; Hansen et al 2022; Katsurada et al 2017; Murata and Falsey 2007). In 2019, RSV was estimated to have caused 5.2 million acute respiratory infections, 466,000 hospitalisations, and 21,000 to 33,000 in-hospital deaths among adults ≥60 years in high income countries (Zhang et al 2025; Savic et al 2023). Within Europe, this corresponds to 3.0 million acute respiratory infections, 145,000 to 274,000 hospitalisations, and 20,000 in-hospital deaths (Osei-Yeboah et al 2023; Savic et al 2023). In the US, RSV causes an estimated 63,000 to 153,000 hospitalisations and 4,170 to 7,690 in-hospital deaths annually in adults >60 years (Havers et al 2024).

In low- or middle-income countries, data on the RSV disease burden in older adults remain limited; however, available data suggest a significant burden. In India, a prospective cohort study reported an RSV-associated lower respiratory tract infection incidence of 6.2 per 1000 person-years in adults ≥60 years, and increasing to 10.1 per 1000 person-years in adults ≥75 years (Kumar et al 2021). Another prospective cohort study conducted in Thailand estimated the RSV-associated acute respiratory infection incidence to be 12.3 per 1000 person-years in adults ≥65 years, increasing to 23.2 per 1000 person-years among older adults with underlying cardiac or pulmonary conditions (Praphasiri et al 2021).

Despite the significant documented global burden of RSV, emerging data suggest that the true burden may be underestimated by up to 6.4-fold in adults (Zhang et al 2025; Li et al 2023; McLaughlin et al 2022). In low- or middle-income countries, limited access to care and restricted care-seeking behaviours have been speculated to further underestimate the burden of RSV disease in older adults (Shi et al 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease: The incidence of RSV infection and its associated severe outcomes, such as hospitalisation, increases with advancing age. A study that extrapolated RSV hospitalisation data from 2006 to 2017 for Denmark, England, Finland, Norway, Netherlands, and Scotland to 28 EU countries found that among adults, the average annual RSV hospitalisation incidence increases from 0.04 to 0.66 to 2.24 to 2.99 per 1,000 adults for those aged 18 to 64, 65 to 74, 75 to 84, and ≥85 years-old, respectively. The authors concluded that the average annual number of RSV hospitalisations in adults (≥18 years-old) was

lower (158,229) but of a similar magnitude to the estimate in young children 0 to 4 year-old (245,244); of note, 92% of adult hospitalisations occurred in those ≥65 years-old (Osei-Yeboah et al 2023). Similar age-related trends in RSV-associated respiratory and cardiovascular hospitalisations have been reported in the US and multiple European countries (Casas et al 2025; Urchueguía-Fornes et al 2025; Haeberer et al 2024; Havers et al 2024; Branche et al 2022a).

Although data on race or ethnicity remain limited, US hospital surveillance data suggest that Black adults aged 60 to 74 years have higher rates of RSV hospitalisations than non-Hispanic White or Asian/Pacific Islanders but lower rates when aged ≥75 years (CDC 2025b). Additionally, risk factors for severe RSV outcomes are more prevalent in non-White adults populations as well as those living in more socially vulnerable areas (Horn et al 2025). Residence in a long-term care facility is another well-recognised risk factor, as congregate settings facilitate RSV transmission among older, medically vulnerable adults (Osei-Yeboah et al 2024; Childs et al 2019). Other risk factors are discussed in the section addressing important comorbidities.

The main existing treatment options: Currently, there are no approved drugs for treatment of RSV in adults (CDC 2025c). Although antiviral treatments can be considered (ECDC 2025). RSV management is primarily supportive. Patients with respiratory compromise/failure may require ventilatory support including oxygen supplementation delivered via high-flow nasal cannula, continuous positive airway pressure, or invasive mechanical ventilation (Jain et al 2023). Hospitalisation is recommended for patients experiencing or at risk of moderate to severe disease, especially those with cardiopulmonary comorbidities, fluid or electrolyte imbalance, or requiring respiratory support.

Table 2 details the three RSV vaccines currently approved in the EU and US to prevent RSV-LRTD in adults aged ≥60 years including mRESVIA, Arexvy and Abrysvo (EMA 2025a; EMA 2025b; EMA 2025c; FDA 2025a; FDA 2025b; FDA 2025c).

Table 2: Summary of RSV Vaccine Approvals and Indications

Vaccine (Manufacturer)	Region	Approved Age Group	Indication(s)	Regulatory References
Arexvy (GSK)	EU & US	Adults ≥60 years	Active immunisation to prevent LRTD caused by RSV	EMA 2025a; FDA 2025a
	EU & US	Adults 50 to 59 years at increased risk for severe RSV		
Abrysvo (Pfizer)	EU	Adults ≥18 years	Active immunisation to prevent LRTD caused by RSV	EMA 2025b
	US	Adults ≥60 years		FDA 2025b
	US	Adults 18 to 59 years at increased risk for severe RSV		FDA 2025b
	EU & US	Pregnant individuals (maternal immunisation)	Protection against LRTD in infants from birth to 6 months	EMA 2025b; FDA 2025b
mRESVIA (Moderna)	EU & US	Adults ≥60 years	Active immunisation to prevent LRTD caused by RSV	EMA 2025c; FDA 2025c
	EU & US	Adults 18 to 59 years at increased risk for severe RSV		

Natural history of the indicated condition in the population, including mortality and morbidity: RSV is primarily transmitted through direct or close contact with virus-containing secretions or contaminated fomites, although aerosol droplet transmission can occur (Walsh and Hall 2015). The incubation period ranges from 2 to 8 days (mean: 4 to 6 days) and varies by age and prior RSV infection status (Jain et al 2023). Shedding may persist for up to four weeks in infants and immunocompromised individuals after symptom resolution (CDC 2025a). Serologic studies demonstrate high RSV antibody levels throughout later childhood and adulthood (Shoji et al 2025; Teodoro et al 2025; Poniedziałek et al 2025), indicating ongoing exposure across the lifespan. While most adults demonstrate immunity to RSV from prior infection, correlates of protection are continuing to be characterised.

In older adults, RSV illness ranges from a mild cold to severe respiratory distress (Falsey and Walsh 2000). Common symptoms include cough, fever, sore throat, sputum production, dyspnoea, myalgia, and wheezing (Falsey and Walsh 2000; Belongia et al 2018; Davis et al 2022). Lower respiratory tract involvement is common, with up to 40% of patients exhibiting rales and wheezing on chest examination (Falsey and Walsh 2000). Shortness of breath is associated with hospital admission, emergency department visit, or pneumonia (Belongia et al 2018; Panozzo et al 2025). Pneumonia can be observed in 30% to 66% of adults hospitalised with RSV, which is among the most common pathogens detected in community-acquired pneumonia (Boattini et al 2021; Jain et al 2015; Tseng et al 2020; Volling et al 2014).

Illness severity does not appear to differ for RSV subgroups (A and B), which co-circulate globally (Belongia et al 2018; Yoon et al 2020; Nuttens et al 2024). Severe outcomes in older adults include cardiopulmonary complications, readmission, functional decline, and death. In a prospective French study of influenza-like illness hospitalisations, 58% of adults with RSV developed cardiopulmonary complications (Loubet et al 2017). In a multi-country study, 26.9% of adults, predominantly aged ≥65 years, hospitalised with RSV were readmitted to the hospital for any cause within 3 months of discharge (Falsey et al 2021). In the US, RSV hospitalisation was associated with significant functional decline among older adults, with 14% of patients requiring a higher level of care at discharge compared to preadmission status (Branche et al 2022b). A meta-analysis of high-income countries reported that many adults experience persistent functional loss, cardiovascular events, and reduced lung function following RSV hospitalisation (Ubamadu et al 2024).

A global meta-analysis found that case fatality ratios for older adults hospitalised with RSV vary and can be substantial, depending on patient characteristics and geography (Nguyen-Van-Tam et al 2022). Published mortality rates among older adults hospitalised with RSV in Europe range from 7.9% to 12.1% (Heppe-Montero et al 2022; Boattini et al 2021; Loubet et al 2017).

Important comorbidities: Among older adults, the risk of RSV hospitalisation is higher among individuals with underlying conditions compared to those without (Polkowska-Kramek et al 2024; Brosh-Nissimov 2024; Prasad et al 2021). This burden is increased further with multi-morbidity (CDC 2025b). Certain chronic medical conditions have been linked to elevated RSV hospitalisation rates in older adults and incorporated into RSV vaccination recommendations (Britton et al 2024). CDC reported that the most common underlying conditions among adults >60 years hospitalised with RSV were cardiovascular disease, diabetes, COPD or chronic bronchitis, chronic kidney disease and neurologic disorders (CDC 2025b). Chronic conditions that have been associated with higher rates of RSV hospitalisation among older adults include

chronic kidney disease, immunocompromising conditions / immunosuppression, diabetes, chronic lung disease, coronary artery disease, and severe obesity (CDC 2025b; Branche et al 2022a; Prasad et al 2021). Among older adults, the presence of one of these comorbidities can increase the risk of RSV-associated hospitalisation by approximately two- to thirteen-fold compared with those without underlying conditions.

- **Adults 18 through 59 years of age**

Incidence: Evidence suggests that the true RSV burden in younger adults is underestimated due to low testing rates, shorter viral shedding duration, and incomplete diagnostic coding (Nguyen-Van-Tam et al 2022; McLaughlin et al 2022; Urchueguía-Fornes et al 2025; Johannesen et al 2025).

RSV respiratory hospitalisation rates in younger adults increase by age with the lowest rates in those aged 18 to 49 years (Casas et al 2025; Haeberer et al 2024; Havers et al 2024; Branche et al 2022a). In a Europe-wide modelling study extrapolating national data to 28 EU countries, this corresponds to roughly 13,000 RSV respiratory hospitalisations annually among adults aged 18 to 64 years (Osei-Yeboah et al 2023). In a prospective US study of adults ≥18 years hospitalised with acute respiratory infection, 31% of the laboratory-confirmed RSV hospitalisations with mechanical ventilation and/or death were among those <60 years old (Surie et al 2024). Despite lower incidence, the clinical severity of RSV hospitalisation in younger adults appears comparable to that of influenza with similar lengths of stay as well as rates of invasive mechanical ventilation, complications, readmission, and mortality (Martinón-Torres et al 2024; Inoue et al 2025).

Although younger adults experience lower rates of RSV hospitalisation, their other related healthcare utilisation remains substantial. In the UK, adults aged 18 to 49 years are estimated to account for a large proportion of RSV-related care and costs including approximately 30% of National Health Service (NHS) 111 calls, 30% of general practitioner consultations, 5% of hospital admissions, 2% of deaths, 13% of direct healthcare costs, and 50% of productivity losses (Herbert et al 2024). Recent European studies using health insurance data show that younger adults contribute to the overall RSV burden through related work loss, healthcare utilisation, and outpatient costs (Huebbe et al 2024; Marijic et al 2025). In Germany, an RSV event cost approximately €5,315-€10,090 per hospitalisation and €59-€80 per outpatient visit among adults aged 18 to 59 years, and in those aged >60 years, costs averaged €4,147-€7,253 for a hospitalisation and €111-€488 for an outpatient visit (Huebbe et al 2024). In Spain, mean hospitalisation costs for adults <60 years were comparable for RSV and influenza (€4,295-€4,315 per episode) (Haeberer et al 2025). Indirect costs linked to absenteeism, reduced productivity, and prescription use further increase the burden for younger adults. In Germany, younger adults aged 18 to 59 years with RSV lost approximately 9.8 days of work for a hospitalisation and 1 to 2 days with an outpatient RSV visit (Huebbe et al 2024, Marijic et al 2025). Moreover, younger adults with emergency department visits for RSV experience higher rates of subsequent hospital admission compared to those with influenza or COVID-19 (Hedberg et al 2024).

A global systematic review reported RSV-associated hospitalization incidence ranging from 0.9 to 4.1 per 100,000 person-years in adults 20 to 49 years in low- and middle-income settings,

underscoring the scarcity of age-specific data outside high-income countries (Tin Tin Htar et al 2020).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease: In both the EU and the US, epidemiologic studies consistently show that adult RSV respiratory hospitalisation rates increase with age (Casas et al 2025; Urchueguía-Fornes et al 2025; Haeberer et al 2024; Havers et al 2024; Branche et al 2022a).

A US review found that racial/ethnic minority groups and socio-economically disadvantaged populations are more likely to have risk factors for, and experience worse outcomes of, RSV infection in adulthood (Horn et al 2025). Similarly, in New Zealand, adults ≥18 years of age of Indigenous Māori or Pacific descent had increased risk of RSV-associated hospitalisation compared to adults of Asian or European/Other descents (Prasad et al 2020).

Workplace exposures, especially healthcare roles, have been identified as sources of RSV risk for younger adults (Foulkes et al 2025; Azziz-Baumgartner et al 2024). Other risk factors are discussed in the section addressing important comorbidities.

The main existing treatment options: The treatment options for adults aged 18 to 59 years are the same as those for older adults. Table 2 includes the current approved RSV vaccines.

Natural history of the indicated condition in the population, including mortality and morbidity: Among adults hospitalised for RSV, younger adults have similar symptom profiles for RSV as older adults (Davis et al 2022) but overall experience substantially lower rates of hospitalisation and in-hospital mortality than adults ≥60 years (Casas et al 2025; Urchueguía-Fornes et al 2025; Haeberer et al 2024; Havers et al 2024; Branche et al 2022a). Severity among younger adults is strongly modified by comorbidity status (CDC 2025b; Branche et al 2022a; Prasad et al 2020). In a US multi-centre analysis of adults hospitalised with RSV, ICU admission rates were similar for those aged 18 to 59, 50 to 64, and 65 to 74 years (20.2% to 21.9%) (Havers et al 2024).

Important comorbidities: Among younger adults, the risk of RSV hospitalisation increases with age and is higher among individuals with underlying conditions compared to those without (Weycker et al 2024; McLaughlin et al 2022; Casas et al 2025; Urchueguía-Fornes et al 2025; Polkowska-Kramek et al 2024). The US CDC reported that the most common underlying conditions among adults aged 50 to 59 years hospitalised with RSV were similar to those for older adults (CDC 2025b). Specific chronic conditions that have been associated with higher rates of RSV hospitalisation among younger adults include diabetes, chronic lung disease, coronary artery disease, and congestive heart failure. The presence of one of these comorbidities can increase the risk of RSV-associated hospitalisation by approximately two- to over thirty-fold in the youngest age group and by roughly three- to over 18-fold for middle aged adults (Branche et al 2022a; Prasad et al 2021).

Part II: Module SII - Non-Clinical Part of the Safety Specification

Table 3 summarises the key nonclinical findings and their relevance to safety in humans. In summary, the nonclinical package, which consisted of both studies performed with mRNA-1345 and with mRNA vaccines formulated in the same SM-102 LNP vaccine matrix to support mRNA-1345 use in human, identified no safety concerns.

Table 3: Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Findings	Relevance to Human Use
Safety pharmacology		
Consistent with the WHO regulatory guidelines on the nonclinical evaluation of vaccines (WHO 2005), no safety pharmacology studies have been performed with mRNA-1345 because primary effects of the vaccines were related to the immune system/inflammatory response. Effects on vital organ function were assessed using clinical observations and/or histopathological evaluations in the GLP and non-GLP repeat-dose toxicity studies conducted with mRNA-1345 or other mRNA vaccines formulated in SM-102-containing LNPs. No findings of concern on vital functions or organs, such as the cardiovascular, respiratory, or central nervous system were observed in any study.		Nonclinical findings do not suggest a specific risk to cardiovascular, respiratory, or central nervous systems.
Pharmacokinetics and drug metabolism		
Single dose IM tissue distribution study	To support characterisation of the distribution of mRNA-1345, a biodistribution study was performed with mRNA-1647, a mRNA-based vaccine against human cytomegalovirus also formulated in SM-102-containing LNPs. As observed with other IM-delivered vaccines, the highest mRNA concentrations were observed at the injection site of the male rat followed by the proximal (popliteal) and distal (axillary) lymph nodes, consistent with distribution via the lymphatic system. These tissues, as well as spleen and eye, had tissue-to-plasma AUC ratios >1.0. Overall, only a relatively small fraction of the mRNAs in mRNA-1647 distributed to distant tissues (ie, lung, liver, heart, kidney, axillary distal lymph nodes [bilateral pooled], proximal popliteal and inguinal lymph nodes [bilateral pooled], spleen, brain, stomach, testes, eye, bone marrow femur [bilateral pooled], jejunum [middle region], and injection site muscle), and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen where it persisted in general 5 days.	The biodistribution of mRNA-based vaccines formulated in LNPs is consistent with administration of IM drug products and distribution via the lymphatics. mRNA does not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen where it persisted in general 5 days.
Metabolite profile and identification of SM-102 in rat plasma, urine, and bile	Metabolism occurred primarily by hydrolysis of the ester groups and subsequent β-oxidation of the resulting aliphatic acidic linkers. In addition to SM-102, low abundances of eight metabolites appeared in plasma from 2 to 6 hours. SM-102 is extensively metabolised through multiple high-capacity systems leading to almost complete clearance of SM-102 within 24 hours. Intact SM-102 was not detected in urine above the LLOQ (0.2 ng/mL) at any time tested (2 to 24 hours post dose). No human specific metabolites were detected.	SM-102 is unlikely to accumulate on repeat IM dosing or be a risk for elimination in patients with hepatic or renal insufficiency.
Identification and profiling of metabolites of SM-102 in rat, monkey, and human	SM-102 and 5 metabolites (M1, M3, M4, M6 and M7) were detected in human and NHP hepatocytes. Metabolites (M1, M4, M6 and M7) were detected in rat hepatocytes. SM-102 metabolites were formed by ester	The similarities in formation of SM-102 metabolites between animals and humans suggest low risk for

Study Type	Important Nonclinical Findings	Relevance to Human Use
hepatocytes	hydrolysis, ester hydrolysis with beta-oxidation chain shortening or N-dealkylation followed by ester hydrolysis.	human-specific metabolites.
Repeat-dose toxicity studies		
Platform GLP toxicity studies evaluating mRNA vaccines formulated in the same SM-102 LNP vaccine matrix as mRNA-1345 in male and female Sprague Dawley rats (administered IM at doses ranging from 9 to 150 µg/dose once every 2 weeks for up to 6 weeks with a 2-week recovery period)	Clinical observations included generally dose-dependent erythema and oedema at the injection site and transient increases in body temperature at 6 hours post-vaccination returning to baseline 24 hours post-vaccination were observed at ≥9 µg/dose. These observations resolved or were considered resolving within 72 hrs. There were clinical chemistry and haematology changes consistent with inflammatory responses (ie, increases in white blood cells, neutrophils, eosinophils, and decreased lymphocytes); minimal coagulation changes consisting of a slightly increased activated partial thromboplastin time and an associated increase in fibrinogen were observed. Clinical chemistry results indicated a decrease in albumin, increase in globulin, and a corresponding decrease in albumin/globulin ratio. Consistent with other indicators of systemic inflammation in response to vaccine administration, transient cytokine increases were observed at ≥9 µg/dose at 6 hours post-vaccination including interferon gamma, monocyte chemoattractant protein-1, and macrophage inflammatory protein 1alpha. Macroscopic and microscopic changes were observed and included skin thickening at the injection site and enlarged lymph nodes. These observations were correlated with microscopic changes that included mixed cell inflammation at the injection site; increased cellularity and mixed cell inflammation in the lymph nodes. Additionally, decreased cellularity in the splenic periarteriolar lymphoid sheath; increased myeloid cellularity in the bone marrow; and hepatocyte vacuolation and Kupffer cell hypertrophy was occasionally observed in the liver. All findings were fully or partially resolved by the end of the 2-week recovery period. The NOAEL was always the highest dose tested (ranging from 89 to 150 µg/dose).	Potential for treatment-related effects at the injection site and systemic inflammatory responses to administration to the LNP and/or induction of an immune response to the expressed antigen(s). Data suggest potential for other clinical findings such as increased body temperature, injection site pain, and other inflammation related findings.
GLP toxicity study of mRNA-1345 in male and female Sprague Dawley rats (administered IM two times at 98 µg/dose once every 3 weeks)	Transient clinical observations including oedema and/or erythema, limited use of hindlimb, skin discolouration or swelling which were attributed to the IM injection. Lower mean body weight gain and food consumption, which resulted in a lower body weight in males only and changes in clinical pathology parameters (such as increased neutrophils, eosinophils, and globulin and decreased albumin and subsequently albumin/globulin ratio, as well as lymphocytes) that were consistent with a local and/or systemic inflammatory/immune system response. mRNA-1345-related target organ effects were indicative of an inflammatory response and were limited to the injection site, iliac, inguinal lymph nodes, popliteal lymph nodes, connective tissue surrounding the sciatic	Same as above.

Study Type	Important Nonclinical Findings	Relevance to Human Use
	nerve, and spleen. NOAEL was identified as 98 µg/dose.	
GLP perinatal/ postnatal developmental and reproductive toxicity with 96 µg/dose mRNA-1345 (administered via IM twice prior to mating and twice during gestation)	No adverse effects on maternal mating and fertility, ovarian/uterine examinations, natural delivery or litter assessments. Further, there were no foetal and/or pup effects on in-life parameters, gross pathology, foetal sex, external or visceral assessments, or skeletal malformations. Transient and slight reductions in mean maternal food consumption were correlated with the reductions in mean body weight gain and were attributed to hindlimb discomfort following the IM injection.	The risk for adverse pregnancy outcomes after exposure is unknown in humans, but nonclinical findings do not suggest a specific risk. Pregnancy was an exclusion criterion in the initial clinical trials but with the indication extended to cover younger adults ≥18 to ≤59 years of age, use in pregnancy is missing information (Module SVII.3.2). Study mRNA-1345-P201 is currently ongoing to evaluate the reactogenicity, safety, and immunogenicity of mRESVIA in pregnant women, and the safety and immunogenicity in infants born to vaccinated mothers (Part III).
Other nonclinical toxicology studies		
Genotoxicity studies with SM-102, the ionizable lipid, and PEG2000-DMG as individual agents (in vitro) or as formulated LNPs containing mRNA (in vivo)	In vitro GLP studies (bacterial reverse mutation [Ames] tests in Salmonella typhimurium and Escherichia coli and in vitro micronucleus tests in human peripheral blood lymphocytes) were negative for both SM-102 and PEG2000-DMG. To support the use of SM-102 lipid and PEG2000-DMG in formulated mRNA-based drug products, 2 in vivo micronucleus studies were completed in rats using an IV route of administration to maximise systemic exposure (1 GLP-compliant and another non-GLP-compliant) using representative mRNA drug products formulated in SM-102 LNPs. Results from 1 of the in vivo SM-102 micronucleus studies were negative, while results from the other in vivo study were weakly positive, albeit with no dose dependency or consistency across sexes. The weakly positive results were at SM-102 doses that were similar to or lower than the doses of SM-102 in the study with negative results. The totality of toxicological and genotoxicity data with mRNA-1345 and other mRNA vaccines in SM-102 LNPs 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.	The genotoxic risk to humans is considered to be low for SM-102-containing mRNA vaccines due to minimal systemic exposure following IM administration, limited duration of exposure, negative in vitro, and equivocal in vivo results, the latter of which are considered the result of the transient hyperthermia produced by the systemic inflammatory response.
Other nonclinical pharmacology studies		
Nonclinical pharmacology studies to assess the ERD risk of mRNA-1345 in female BALB/c mice and female cotton rats	In the mouse study the RSV antibody response induced by mRNA-1345 was largely functional (neutralising). In contrast, the antibody response induced by FI-RSV was primarily nonfunctional (non-neutralising) and directed to the postF conformation. mRNA-1345 induced a Th1 response, as indicated by 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 a IgG1-	The mouse and cotton rat studies assessing the potential ERD risk of mRNA-1345 demonstrated the vaccine inducing an immunologic profile characteristic of protection that was distinct from the disease-enhancing phenotype induced by FI-RSV. No ERD is expected in humans.

Study Type	Important Nonclinical Findings	Relevance to Human Use
	biased antibody response. These data demonstrate that mRNA-1345 induced an immunologic profile characteristic of protection that was distinct from the disease-enhancing phenotype induced by FI-RSV. In the cotton rat study, mRNA-1345 induced a dose-dependent increase in RSV neutralising antibody that correlated with protection from RSV challenge. mRNA-1345 did not induce enhanced lung inflammation or a Th2-biased response after RSV viral challenge, both features historically associated with FI-RSV-associated ERD, even at an mRNA dose level that induced suboptimal immunity and breakthrough virus replication.	

There are no safety concerns for mRNA-1345 based on nonclinical data.

Part II: Module SIII - Clinical Trial Exposure

Two clinical trials supported the initial authorisation for adults ≥60 years of age: a completed Phase 1, randomised, observer-blind, placebo-controlled, dose escalation study (mRNA-1345-P101; US) and an ongoing Phase 2/3, randomised, observer-blind, placebo-controlled case driven pivotal efficacy trial (mRNA-1345-P301; 22 countries globally including sites located in Belgium; Germany; Spain; Poland; Finland and UK).

To support the authorisation for adults ≥18 to ≤59 years of age who are at increased risk for LRTD caused by RSV, Part A of Phase 3 study mRNA-1345-P303 evaluated tolerability, safety and immunogenicity of mRNA-1345 in adults ≥18 to ≤59 years of age with increased risk for RSV-LRTD due to comorbidities in the US, Canada, and the UK. Study mRNA-1345-P303 comprises 2 parts: Part A (in adults at increased risk for LTRD caused by RSV) and Part B (in immunocompromised adult solid organ transplant recipients). Only data from Part A of the study is included in the RMP.

To support extension of the indication to all adults ≥18 years of age, data from Studies mRNA-1345-P101, mRNA-1345-P301, mRNA-1345-P303 Part A, and mRNA-1345-P302 Part A and Part B were used to demonstrate that mRNA-1345 provides a consistent safety profile and an efficacy and immunogenicity profile supportive of protection across the adult age spectrum, supporting use of mRNA-1345 for the prevention of RSV-LRTD in all adults regardless of comorbidity status.

Table 4: Summary of Vaccination Exposure by Dose (µg) in Studies mRNA-1345-P301, mRNA-1345-P101, and mRNA-1345-P303 Part A (Safety Set)

Study	Placebo	mRNA-1345 12.5 µg	mRNA-1345 25 µg	mRNA-1345 30 µg	mRNA-1345 50 µg	mRNA-1345 100 µg	mRNA-1345 200 µg	Total mRNA-1345
mRNA-1345-P301								
Adults ≥60 years, single injection	18184	0	0	0	18245	0	0	18245
mRNA-1345-P101								
Adults 18 to 49 years, single injection	15	0	0	0	19	20	20	59
Adults 18 to 49 years, three injections	5	0	0	0	0	20	0	20
Adults 65 to 79 years, single injection and booster injection [a]	59 (52)	48 (21)	48 (22)	0	47 (18)	48 (18)	48 (20)	239 (99)
Adults of Japanese descent ≥60 years single injection	4	0	0	0	0	21	0	21
WOCBP, single injection	30	50	49	0	49	0	0	148
mRNA-1345-P303 Part A								
Adults ≥18 to ≤59 years, single injection [b]	0	0	0	497	502	0	0	999
Total	18267	48	48	497	18813	109	68	19583

Abbreviations: WOCBP = women of child-bearing potential.
Numbers are participants included in the Safety Set for each study or study part.

[a] 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. Numbers in brackets do not represent additional participants exposed and only participants for whom the booster was the same as the first injection are presented.
[b] Part A of mRNA-1345-P303.
Source: mRNA-1345-P301CSR Table 14.1.2.1 (30 Apr 2023).
mRNA-1345-P101 CSR Table 14.1.2.1 (27 Sep 2021); Table 14.1.2.2.1 (03 Oct 2022); Table 14.1.2.2.2 (03 Oct 2022); Table 14.1.2.5 (06 Feb 2023).
mRNA-1345-P101 CSR Addendum 2 Table 14.1.1.3 (24 Feb 2022).
mRNA-1345-P303 Part A CSR Table 14.1.8.1.1 (18 Sep 2024).

To support co-administration of mRNA-1345 with standard dose influenza vaccine (Afluria Quadrivalent®), high dose influenza vaccine (Fluzone® HD Quadrivalent), and COVID-19 vaccine, 2 Phase 3 studies were conducted with participants who received mRNA-1345 co-administered with seasonal influenza vaccines or an mRNA COVID-19 vaccine; Study mRNA-1345-P302 (Part A and Part B) in participants ≥50 years and Study mRNA-1345-P304 in participants ≥65 years.

Clinical trial exposure data are presented for the studies below.

Study mRNA-1345-P301

Study mRNA-1345-P301 is an ongoing Phase 2/3, randomised, observer-blind, placebo-controlled, case-driven, pivotal efficacy trial to evaluate the safety, tolerability, and efficacy of mRNA-1345 compared with placebo in adults ≥60 years of age. The primary objectives are to evaluate the safety and tolerability of the mRNA-1345 vaccine, and to evaluate the efficacy of a single dose of 50 µg mRNA-1345 in the prevention of a first episode of RSV-LRTD with ≥2 symptoms and ≥3 symptoms as compared with placebo within the period of 14 days post-injection up to 12 months post-injection. Furthermore, the immunogenicity of mRNA-1345 vaccine will be characterised and an investigation for correlates of risk undertaken. Overall, the Phase 2/3 study planned to enrol approximately 37,000 participants to receive a single injection of 50 µg mRNA-1345 or placebo in a 1:1 randomisation ratio with assignment stratified by age (60 to 74 years versus ≥75 years) and risk factors for LRTD (presence or absence of CHF and/or COPD).

A total of 36,557 participants were 1:1 randomly assigned to study treatment and at the time of the data cutoff (30 Apr 2023), a total of 36,429 participants had received 1 dose of either mRNA-1345 (N=18245) or placebo (N=18184) (Table 14.1.2.1).

In the mRNA-1345 group, 17,152 (94.0%) participants had at least 6 months follow-up (Table 5). Older adults were well represented with 38% of participants administered mRNA-1345 over the age of 70 years (Table 6), and there was high racial diversity including 12% of participants of Black or African American descent, 11% of Asian descent, and 14.7% were from other racial groups including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, or Multiple (Table 7; Table 14.1.3.6).

Table 5: Summary of Study Duration in Study mRNA-1345-P301 (Safety Set)

Duration of exposure	Placebo (N=18184)	mRNA-1345 50 µg (N=18245)	Total (N=36429)
Number of participants, n (%)			
≥7 days since injection	18157 (99.9)	18225 (99.9)	36382 (99.9)
≥14 days since injection	18127 (99.7)	18192 (99.7)	36319 (99.7)
≥28 days since injection	18059 (99.3)	18140 (99.4)	36199 (99.4)
≥6 months since injection	17050 (93.8)	17152 (94.0)	34202 (93.9)
≥7 months since injection	14058 (77.3)	14102 (77.3)	28160 (77.3)
≥8 months since injection	10487 (57.7)	10461 (57.3)	20948 (57.5)
≥9 months since injection	7548 (41.5)	7578 (41.5)	15126 (41.5)
≥10 months since injection	5007 (27.5)	5019 (27.5)	10026 (27.5)
≥11 months since injection	3444 (18.9)	3440 (18.9)	6884 (18.9)
≥12 months since injection	2335 (12.8)	2351 (12.9)	4686 (12.9)
≥18 months since injection	0	0	0
≥24 months since injection	0	0	0
Number of participants, n (%)			
<7 days since injection	27 (0.1)	20 (0.1)	47 (0.1)
≥7 days to <14 days since injection	30 (0.2)	33 (0.2)	63 (0.2)
≥14 days to <28 days since injection	68 (0.4)	52 (0.3)	120 (0.3)
≥28 days to <6 months since injection	1009 (5.5)	988 (5.4)	1997 (5.5)
≥6 months to <12 months since injection	14715 (80.9)	14801 (81.1)	29516 (81.0)
≥12 months to <18 months since injection	2335 (12.8)	2351 (12.9)	4686 (12.9)
≥18 months to <24 months since injection	0	0	0
Study duration from injection (days)			
n	18184	18245	36429
Mean (SD)	271.5 (82.84)	271.8 (82.15)	271.6 (82.49)
Median	257.0	257.0	257.0
Min, Max	1, 530	1, 530	1, 530

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set.
1 month=30.4375 days.
If the participant has discontinued from or completed the study, study duration, in days, is derived as: date of study discontinuation/completion — date of investigational product injection +1; otherwise, if the participant is ongoing at the time of the data cutoff, study duration is derived as: Data cutoff date — date of investigational product injection +1.
Source: Study mRNA-1345-P301 Table 14.1.7.1
Data from ongoing trial as of 30 Apr 2023.

Table 6: Participant Age and Sex in Study mRNA-1345-P301 (Safety Set)

Characteristic	Placebo (N=18184)	mRNA-1345 50 µg (N=18245)	Total (N=36429)
Age group 1, n (%) [a]			
60 to 74 years	14879 (81.8)	14943 (81.9)	29822 (81.9)
≥75 years	3305 (18.2)	3302 (18.1)	6607 (18.1)
Age group 2, n (%) [a]			
60 to 69 years	11253 (61.9)	11314 (62.0)	22567 (61.9)
70 to 79 years	5482 (30.1)	5493 (30.1)	10975 (30.1)
≥80 years	1449 (8.0)	1438 (7.9)	2887 (7.9)
Age at enrolment (years)			
n	18184	18245	36429
Mean (SD)	68.5 (6.62)	68.5 (6.60)	68.5 (6.61)
Median	67.0	67.0	67.0
Min, Max	60, 105	60, 108	60, 108
Sex, n (%)			
Male	9241 (50.8)	9352 (51.3)	18593 (51.0)
Female	8943 (49.2)	8893 (48.7)	17836 (49.0)

Abbreviations: eCRF = electronic case report form; max = maximum; min = minimum; SD = standard deviation
Percentages are based on the number of participants in the Safety Set.
[a] Derived from age and risk collected on eCRFs.
Source: Study mRNA-1345-P301 Table 14.1.3.6
Data from ongoing trial as of 30 Apr 2023.

Table 7: Participant Race in Study mRNA-1345-P301 (Safety Set)

Characteristic	Placebo (N=18184)	mRNA-1345 50 µg (N=18245)	Total (N=36429)
Race, n (%)			
White	11252 (61.9)	11273 (61.8)	22525 (61.8)
Black or African American	2160 (11.9)	2203 (12.1)	4363 (12.0)
Asian	1995 (11.0)	2013 (11.0)	4008 (11.0)
American Indian or Alaska Native	893 (4.9)	906 (5.0)	1799 (4.9)
Native Hawaiian or Other Pacific Islander	19 (0.1)	27 (0.1)	46 (0.1)
Other	1009 (5.5)	994 (5.4)	2003 (5.5)
Multiple	751 (4.1)	760 (4.2)	1511 (4.1)
Unknown	20 (0.1)	10 (<0.1)	30 (<0.1)

Characteristic	Placebo (N=18184)	mRNA-1345 50 µg (N=18245)	Total (N=36429)
Not reported	85 (0.5)	59 (0.3)	144 (0.4)

Percentages are based on the number of participants in the Safety Set.
Source: Study mRNA-1345-P301 Table 14.1.3.6
Data from ongoing trial as of 30 Apr 2023.

Table 8: Participant Ethnicity in Study mRNA-1345-P301 (Safety Set)

Characteristic	Placebo (N=18184)	mRNA-1345 50 µg (N=18245)	Total (N=36429)
Ethnicity, n (%)			
Hispanic or Latino	6148 (33.8)	6092 (33.4)	12240 (33.6)
Not Hispanic or Latino	11827 (65.0)	11968 (65.6)	23795 (65.3)
Unknown	22 (0.1)	27 (0.1)	49 (0.1)
Not reported	187 (1.0)	158 (0.9)	345 (0.9)

Percentages are based on the number of participants in the Safety Set.
Source: Study mRNA-1345-P301 Table 14.1.3.6
Data from ongoing trial as of 30 Apr 2023.

Study mRNA-1345-P101

Study mRNA-1345-P101 is a completed Phase 1, randomised, observer-blind, placebo-controlled, dose-escalation study to assess the safety, reactogenicity, and immunogenicity of the mRNA-1345 vaccine. The study comprised 5 parts (randomised participants): healthy young adults (18 to 49 year old, N=100; Cohorts 1 to 4), healthy older adults (65 to 79 year old, N=300; Cohorts 7 to 11), Japanese older adults (≥60 years old, N=25; Cohort 15), WOCBP (18 to 40 year old, N=180; Cohorts 12 to 14) and RSV-seropositive children (12 to 59 months old, N=38-46; Cohorts 5 and 6). The primary objective of the Phase 1 mRNA-1345-P101 study was to evaluate the safety and tolerability of mRNA-1345. The secondary objectives of the study were to evaluate the immune response to each vaccine dose level.

Adults Aged 18 to 49 years (Younger Adult Cohort Safety Set; Cohorts 1 to 4)

A total of 75 participants aged 18 to 49 years were randomised to receive a single injection of 50 µg, 100 µg, or 200 µg mRNA-1345 (20 participants per group) or placebo (15 participants). One participant in the 50 µg mRNA-1345 group withdrew consent and did not receive the injection.

A total of 25 participants aged 18 to 49 years were randomised to receive 3 injections of 100 µg mRNA-1345 (20 participants) or placebo (5 participants). 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. In the placebo group, 2 participants discontinued the study.

Exposure for the Younger Adult Cohort Safety Set is presented in Table 9 to Table 12.

Table 9: Summary of Study Duration in Adults Aged 18 to 49 Years in Study mRNA-1345-P101 (Younger Adult Cohort Safety Set)

Duration of exposure	1-injection					3-injections		Overall (N=99)
	Placebo (N=15)	mRNA-1345				Placebo (N=5)	mRNA-1345 100 µg (N=20)	
		50 µg (N=19)	100 µg (N=20)	200 µg (N=20)	Total (N=59)			
Number of participants, n (%)								
≥7 days since first injection	15 (100.0)	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)	5 (100.0)	20 (100.0)	99 (100.0)
≥14 days since first injection	15 (100.0)	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)	5 (100.0)	20 (100.0)	99 (100.0)
≥28 days since first injection	15 (100.0)	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)	5 (100.0)	20 (100.0)	99 (100.0)
≥6 months since first injection	1 (6.7)	0	0	0	0	3 (60.0)	17 (85.0)	21 (21.2)
≥10 months since first injection	0	0	0	0	0	0	1 (5.0)	1 (1.0)
Number of participants, n (%)								
≥7 days to <14 days since first injection	0	0	0	0	0	0	0	0
≥14 days to <28 days since first injection	0	0	0	0	0	0	0	0
≥28 days to <6 months since first injection	14 (93.3)	19 (100.0)	20 (100.0)	20 (100.0)	59 (100.0)	2 (40.0)	3 (15.0)	78 (78.8)
≥6 months to <10 months since first injection	1 (6.7)	0	0	0	0	3 (60.0)	16 (80.0)	20 (20.2)
≥10 months since first injection	0	0	0	0	0	0	1 (5.0)	1 (1.0)
Study duration from injection (days)								
n	15	19	20	20	59	5	20	99
Mean (SD)	165.8 (22.01)	166.9 (12.96)	163.2 (27.36)	170.0 (13.29)	166.7 (19.06)	191.8 (124.11)	242.4 (83.69)	183.1 (56.57)
Median	169.0	169.0	169.0	171.5	169.0	281.0	281.0	169.0
Min, Max	88, 186	114, 176	47, 172	116, 181	47, 181	48, 285	56, 307	47, 307

Abbreviations: max = maximum; min = minimum; SD = standard deviation
1 month=30.4375 days.
Percentages are based on the number of participants in the Safety Set.
If the participant has discontinued from or completed the study, study duration, in days, is derived as: date of study discontinuation/completion – date of investigational product injection +1.
Source: Study mRNA-1345-P101 Table 14.1.7.1
Data from trial as of 02 Oct 2022.

Table 10: Participant Age and Sex in Adults Aged 18 to 49 Years in Study mRNA-1345-P101 (Younger Adult Cohort Safety Set)

Characteristic	1-injection					3-injections		Overall (N=99)
	Placebo (N=15)	mRNA-1345				Placebo (N=5)	mRNA-1345 100 µg (N=20)	
		50 µg (N=19)	100 µg (N=20)	200 µg (N=20)	Total (N=59)			
Age (years), n (%)								
n	15	19	20	20	59	5	20	99
Mean (SD)	37.5 (6.64)	36.2 (7.70)	33.4 (7.56)	31.8 (4.81)	33.7 (6.93)	24.8 (4.09)	32.0 (9.55)	33.5 (7.74)
Median	40.0	37.0	34.0	30.0	34.0	24.0	30.5	33.0
Min, Max	27, 46	20, 45	20, 46	21, 43	20, 46	20, 29	18, 49	18, 49
Sex, n (%)								
Male	3 (20.0)	9 (47.4)	9 (45.0)	14 (70.0)	32 (54.2)	2 (40.0)	4 (20.0)	41 (41.4)
Female	12 (80.0)	10 (52.6)	11 (55.0)	6 (30.0)	27 (45.8)	3 (60.0)	16 (80.0)	58 (58.6)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.1.2
Data from trial as of 02 Oct 2022.

Table 11: Participant Race in Adults Aged 18 to 49 Years in Study mRNA-1345-P101 (Younger Adult Cohort Safety Set)

Characteristic	1-injection					3-injections		Overall (N=99)
	Placebo (N=15)	mRNA-1345				Placebo (N=5)	mRNA-1345 100 µg (N=20)	
		50 µg (N=19)	100 µg (N=20)	200 µg (N=20)	Total (N=59)			
Race, n (%)								
White	11 (73.3)	14 (73.7)	16 (80.0)	18 (90.0)	48 (81.4)	3 (60.0)	16 (80.0)	78 (78.8)
Black or African American	4 (26.7)	5 (26.3)	4 (20.0)	0	9 (15.3)	2 (40.0)	4 (20.0)	19 (19.2)
Asian	0	0	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0
Multiple	0	0	0	2 (10.0)	2 (3.4)	0	0	2 (2.0)
Other	0	0	0	0	0	0	0	0

N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.1.2
Data from trial as of 02 Oct 2022.

Table 12: Participant Ethnicity in Adults Aged 18 to 49 Years in Study mRNA-1345-P101 (Younger Adult Cohort Safety Set)

Characteristic	1-injection					3-injections		Overall (N=99)
	Placebo (N=15)	mRNA-1345				Placebo (N=5)	mRNA-1345 100 µg (N=20)	
		50 µg (N=19)	100 µg (N=20)	200 µg (N=20)	Total (N=59)			
Ethnicity, n (%)								
Hispanic or Latino	1 (6.7)	0	1 (5.0)	0	1 (1.7)	0	0	2 (2.0)
Not Hispanic or Latino	14 (93.3)	19 (100.0)	19 (95.0)	20 (100.0)	58 (98.3)	5 (100.0)	20 (100.0)	97 (98.0)

N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.1.2
Data from trial as of 02 Oct 2022.

Adults Aged 65 to 79 years (Older Adult Cohort Safety Set; Cohorts 7 to 11)

A total of 300 participants aged 65 to 79 years were randomised to receive a first injection of 12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg mRNA-1345 (47-48 participants per group) or placebo (60 participants). Two participants did not receive the first injection, 1 participant in the 50 µg mRNA-1345 group and 1 participant in the placebo group.

Among the 298 participants 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.

Exposure for the Older Adult Cohort Safety Set is presented in Table 13 to Table 16.

Table 13: Summary of Study Duration in Adults Aged 65 to 79 Years in Study mRNA-1345-P101 (Older Adult Cohort Safety Set)

Duration of exposure	Placebo (N=59)	mRNA-1345						Overall (N=298)
		12.5 µg (N=48)	25 µg (N=48)	50 µg (N=47)	100 µg (N=48)	200 µg (N=48)	Total (N=239)	
Number of participants, n (%)								
≥7 days since injection	59 (100.0)	48 (100.0)	48 (100.0)	47 (100.0)	48 (100.0)	47 (97.9)	238 (99.6)	297 (99.7)
≥14 days since injection	59 (100.0)	48 (100.0)	48 (100.0)	47 (100.0)	48 (100.0)	47 (97.9)	238 (99.6)	297 (99.7)
≥28 days since injection	59 (100.0)	48 (100.0)	48 (100.0)	47 (100.0)	48 (100.0)	47 (97.9)	238 (99.6)	297 (99.7)
≥6 months since injection	55 (93.2)	45 (93.8)	48 (100.0)	47 (100.0)	44 (91.7)	45 (93.8)	229 (95.8)	284 (95.3)
≥12 months since injection	4 (6.8)	4 (8.3)	3 (6.3)	6 (12.8)	10 (20.8)	13 (27.1)	36 (15.1)	40 (13.4)
Number of participants, n (%)								

Duration of exposure	Placebo (N=59)	mRNA-1345						Overall (N=298)
		12.5 µg (N=48)	25 µg (N=48)	50 µg (N=47)	100 µg (N=48)	200 µg (N=48)	Total (N=239)	
≥7 days to <14 days since injection	0	0	0	0	0	0	0	0
≥14 days to <28 days since injection	0	0	0	0	0	0	0	0
≥28 days to <6 months since injection	4 (6.8)	3 (6.3)	0	0	4 (8.3)	2 (4.2)	9 (3.8)	13 (4.4)
≥6 months to <10 months since injection	51 (86.4)	41 (85.4)	45 (93.8)	41 (87.2)	34 (70.8)	32 (66.7)	193 (80.8)	244 (81.9)
≥12 months since injection	4 (6.8)	4 (8.3)	3 (6.3)	6 (12.8)	10 (20.8)	13 (27.1)	36 (15.1)	40 (13.4)
Study duration from injection (days)								
n	59	48	48	47	48	48	239	298
Mean (SD)	280.3 (76.15)	262.0 (83.73)	268.4 (59.05)	307.4 (64.16)	312.4 (95.95)	319.3 (100.79)	293.9 (85.22)	291.2 (83.56)
Median	272.0	250.0	251.0	284.0	279.0	284.0	272.0	272.0
Min, Max	166, 620	36, 607	244, 564	241, 540	139, 636	3, 609	3, 636	3, 636

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
1 month=30.4375 days.
Percentages are based on the number of participants in the Safety Set.
If the participant has discontinued from or completed the study, study duration, in days, is derived as: date of study discontinuation/completion – date of investigational product injection +1.
Source: Study mRNA-1345-P101 Table 14.1.7.2.1
Data from trial as of 02 Oct 2022.

Table 14: Participant Age and Sex in Adults Aged 65 to 79 Years in Study mRNA-1345-P101 (Older Adult Cohort Safety Set)

Characteristic	Placebo (N=59)	mRNA-1345						Overall (N=298)
		12.5 µg (N=48)	25 µg (N=48)	50 µg (N=47)	100 µg (N=48)	200 µg (N=48)	Total (N=239)	
Age (years), n (%)								
n	59	48	48	47	48	48	239	298
Mean (SD)	69.9 (3.75)	69.9 (3.23)	70.7 (3.71)	70.1 (3.85)	70.2 (3.88)	69.9 (3.94)	70.2 (3.71)	70.1 (3.71)
Median	69.0	69.0	71.0	69.0	69.0	69.0	69.0	69.0
Min, Max	65, 78	65, 78	65, 79	65, 78	65, 78	65, 79	65, 79	65, 79
Sex, n (%)								
Male	27 (45.8)	19 (39.6)	22 (45.8)	23 (48.9)	23 (47.9)	20 (41.7)	107 (44.8)	134 (45.0)
Female	32 (54.2)	29 (60.4)	26 (54.2)	24 (51.1)	25 (52.1)	28 (58.3)	132 (55.2)	164 (55.0)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.2.1.2
Data from trial as of 02 Oct 2022.

Table 15: Participant Race in Adults Aged 65 to 79 Years in Study mRNA-1345-P101 (Older Adult Cohort Safety Set)

Characteristic	Placebo (N=59)	mRNA-1345						Overall (N=298)
		12.5 µg (N=48)	25 µg (N=48)	50 µg (N=47)	100 µg (N=48)	200 µg (N=48)	Total (N=239)	
Race, n (%)								
White	49 (83.1)	44 (91.7)	43 (89.6)	44 (93.6)	42 (87.5)	46 (95.8)	219 (91.6)	268 (89.9)
Black or African American	7 (11.9)	4 (8.3)	2 (4.2)	1 (2.1)	6 (12.5)	1 (2.1)	14 (5.9)	21 (7.0)
Asian	1 (1.7)	0	2 (4.2)	1 (2.1)	0	0	3 (1.3)	4 (1.3)
American Indian or Alaska Native	0	0	0	0	0	1 (2.1)	1 (0.4)	1 (0.3)
Native Hawaiian or Other Pacific Islander	1 (1.7)	0	0	0	0	0	0	1 (0.3)
Multiple	0	0	0	1 (2.1)	0	0	1 (0.4)	1 (0.3)
Other	1 (1.7)	0	1 (2.1)	0	0	0	1 (0.4)	2 (0.7)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.2.1.2
Data from trial as of 02 Oct 2022.

Table 16: Participant Ethnicity in Adults Aged 65 to 79 Years in Study mRNA-1345-P101 (Older Adult Cohort Safety Set)

Characteristic	Placebo (N=59)	mRNA-1345						Overall (N=298)
		12.5 µg (N=48)	25 µg (N=48)	50 µg (N=47)	100 µg (N=48)	200 µg (N=48)	Total (N=239)	
Ethnicity, n (%)								
Hispanic or Latino	4 (6.8)	2 (4.2)	2 (4.2)	3 (6.4)	0	4 (8.3)	11 (4.6)	15 (5.0)
Not Hispanic or Latino	55 (93.2)	44 (91.7)	46 (95.8)	44 (93.6)	48 (100.0)	44 (91.7)	226 (94.6)	281 (94.3)
Not reported	0	2 (4.2)	0	0	0	0	2 (0.8)	2 (0.7)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.2.1.2
Data from trial as of 02 Oct 2022.

Adults of Japanese Descent Aged ≥60 Years (Japanese Older Adult Cohort Safety Set; Cohort 15)

A total of 25 adults of Japanese descent aged ≥60 years received 1 injection of 100 µg mRNA-1345 (21 participants) or placebo (4 participants), and all participants completed the study.

Exposure for the Japanese Older Adult Cohort Safety Set is presented in Table 17 to Table 20.

Table 17: Summary of Study Duration in Adults of Japanese Descent Aged ≥60 Years in Study mRNA-1345-P101 (Japanese Older Adult Cohort Safety Set)

Duration of exposure	1-injection		Overall (N=25)
	Placebo (N=4)	mRNA-1345 100 µg (N=21)	
Number of participants, n (%)			
≥7 days since injection	4 (100.0)	21 (100.0)	25 (100.0)
≥14 days since injection	4 (100.0)	21 (100.0)	25 (100.0)
≥28 days since injection	4 (100.0)	21 (100.0)	25 (100.0)
≥6 months since injection	0	0	0
Number of participants, n (%)			
≥7 days to <14 days since injection	0	0	0
≥14 days to <28 days since injection	0	0	0
≥28 days to <6 months since injection	4 (100.0)	21 (100.0)	25 (100.0)
≥6 months since injection	0	0	0
Study duration from injection (days)			
n	4	21	25
Mean (SD)	170.0 (2.00)	169.8 (4.10)	169.8 (3.81)
Median	169.0	169.0	169.0
Min, Max	169, 173	156, 176	156, 176

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
1 month=30.4375 days.
Percentages are based on the number of participants in the Safety Set.
If the participant has discontinued from or completed the study, study duration, in days, is derived as: date of study discontinuation/completion – date of investigational product injection +1.
Source: Study mRNA-1345-P101 Table 14.1.7.5
Data from trial as of 02 Oct 2022.

Table 18: Participant Age and Sex in Adults of Japanese Descent Aged ≥60 Years in Study mRNA-1345-P101 (Japanese Older Adult Cohort Safety Set)

Characteristic	1-injection		Overall (N=25)
	Placebo (N=4)	mRNA-1345 100 µg (N=21)	
Age (years), n (%)			

Characteristic	1-injection		Overall (N=25)
	Placebo (N=4)	mRNA-1345 100 µg (N=21)	
n	4	21	25
Mean (SD)	64.5 (4.36)	68.6 (6.72)	67.9 (6.51)
Median	63.5	67.0	66.0
Min, Max	61, 70	60, 82	60, 82
Sex, n (%)			
Male	2 (50.0)	11 (52.4)	13 (52.0)
Female	2 (50.0)	10 (47.6)	12 (48.0)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
N = Number of participants in the Safety Set. N = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.5.2
Data from trial as of 02 Oct 2022.

Table 19: Participant Race in Adults of Japanese Descent Aged ≥60 Years in Study mRNA-1345-P101 (Japanese Older Adult Cohort Safety Set)

Characteristic	1-injection		Overall (N=25)
	Placebo (N=4)	mRNA-1345 100 µg (N=21)	
Race, n (%)			
White	0	0	0
Black or African American	0	0	0
Asian	4 (100.0)	21 (100.0)	25 (100.0)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Multiple	0	0	0
Other	0	0	0

N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.5.2
Data from trial as of 02 Oct 2022.

Table 20: Participant Ethnicity in Adults of Japanese Descent Aged ≥60 Years in Study mRNA-1345-P101 (Japanese Older Adult Cohort Safety Set)

Characteristic	1-injection		Overall (N=25)
	Placebo (N=4)	mRNA-1345 100 µg (N=21)	
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4 (100.0)	21 (100.0)	25 (100.0)

N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: Study mRNA-1345-P101 Table 14.1.5.1.5.2
Data from trial as of 02 Oct 2022.

WOCBP (WOCBP Cohort Safety Set; Cohorts 12 to 14)

A total of 180 participants aged 18 to 40 years were randomised in the WOCBP part of the study and of these, 178 (98.9%) received study intervention (single injection of mRNA-1345 12.5 µg [N=50], mRNA-1345 25 µg [N=49], mRNA-1345 50 µg [N=49], or placebo [N=30]) and 157 (87.2%) participants completed the study (mRNA-1345-P101 CSR Addendum 2, Section 5.1).

Exposure for the WOCBP Cohort Safety Set is presented in Table 21 to Table 24.

Table 21: Summary of Study Duration in WOCBP in Study mRNA-1345-P101 (WOCBP Cohort Safety Set)

Duration of exposure	1-injection					Overall (N=178)
	Placebo (N=30)	mRNA-1345 12.5 µg (N=51)	mRNA-1345 25 µg (N=49)	mRNA-1345 50 µg (N=48)	mRNA-1345 Total (N=148)	
Number of participants, n (%)						
≥7 days since first injection	30 (100.0)	51 (100.0)	49 (100.0)	48 (100.0)	148 (100.0)	178 (100.0)
≥14 days since first injection	29 (96.7)	51 (100.0)	49 (100.0)	47 (97.9)	147 (99.3)	176 (98.9)
≥28 days since first injection	29 (96.7)	51 (100.0)	47 (95.9)	47 (97.9)	145 (98.0)	174 (97.8)
≥6 months since first injection	3 (10.0)	1 (2.0)	6 (12.2)	4 (8.3)	11 (7.4)	14 (7.9)
Number of participants, n (%)						
≥7 days to <14 days	1 (3.3)	0	0	1 (2.1)	1 (0.7)	2 (1.1)

Duration of exposure	1-injection					Overall (N=178)
	Placebo (N=30)	mRNA-1345 12.5 µg (N=51)	mRNA-1345 25 µg (N=49)	mRNA-1345 50 µg (N=48)	mRNA-1345 Total (N=148)	
since first injection						
≥14 days to <28 days since first injection	0	0	2 (4.1)	0	2 (1.4)	2 (1.1)
≥28 days to <6 months since first injection	26 (86.7)	50 (98.0)	41 (83.7)	43 (89.6)	134 (90.5)	160 (89.9)
≥6 months since first injection	3 (10.0)	1 (2.0)	6 (12.2)	4 (8.3)	11 (7.4)	14 (7.9)
Study duration from injection (days)						
n	30	51	49	48	148	178
Mean (SD)	166.5 (31.41)	165.5 (28.29)	165.2 (31.77)	161.6 (36.01)	164.1 (31.93)	164.5 (31.77)
Median	170.0	172.0	170.0	169.0	170.0	170.0
Min, Max	8, 197	29, 183	16, 194	9, 211	9, 211	8, 211

Abbreviations: max = maximum; min = minimum; SD = standard deviation; WOCBP = women of child-bearing potential.
1 month=30.4375 days.
Percentages are based on the number of participants in the Safety Set.
If the participant has discontinued from or completed the study, study duration, in days, is derived as: date of study discontinuation/completion – date of investigational product injection +1.
Source: mRNA-1345-P101 CSR Addendum 2, Table 14.1.7.3 (24 Feb 2022).

Table 22: Participant Age and Sex in WOCBP in Study mRNA-1345-P101 (WOCBP Cohort Safety Set)

Characteristic	1-injection					Overall (N=178)
	Placebo (N=30)	mRNA-1345 12.5 µg (N=51)	mRNA-1345 25 µg (N=49)	mRNA-1345 50 µg (N=48)	mRNA-1345 Total (N=148)	
Age (years), n (%)						
n	30	51	49	48	148	178
Mean (SD)	29.7 (6.29)	29.7 (6.65)	30.2 (5.74)	31.2 (6.31)	30.4 (6.24)	30.2 (6.23)
Median	30.0	31.0	31.0	33.0	31.0	31.0
Min, Max	19, 40	18, 40	19, 38	19, 40	18, 40	18, 40
Sex, n (%)						
Male	0	0	0	0	0	0

Characteristic	1-injection					Overall (N=178)
	Placebo (N=30)	mRNA-1345 12.5 µg (N=51)	mRNA-1345 25 µg (N=49)	mRNA-1345 50 µg (N=48)	mRNA-1345 Total (N=148)	
Female	30 (100)	51 (100)	49 (100)	48 (100)	148 (100)	178 (100)

Abbreviations: max = maximum; min = minimum; SD = standard deviation; WOCBP = women of child-bearing potential.
N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: mRNA-1345-P101 CSR Addendum 2, Table 14.1.5.1.3.2 (24 Feb 2022).

Table 23: Participant Race in WOCBP in Study mRNA-1345-P101 (WOCBP Cohort Safety Set)

Characteristic	1-injection					Overall (N=178)
	Placebo (N=30)	mRNA-1345 12.5 µg (N=51)	mRNA-1345 25 µg (N=49)	mRNA-1345 50 µg (N=48)	mRNA-1345 Total (N=148)	
Race, n (%)						
White	27 (90.0)	45 (88.2)	36 (73.5)	42 (87.5)	123 (83.1)	150 (84.3)
Black or African American	1 (3.3)	5 (9.8)	8 (16.3)	3 (6.3)	16 (10.8)	17 (9.6)
Asian	0	1 (2.0)	2 (4.1)	3 (6.3)	6 (4.1)	6 (3.4)
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (3.3)	0	0	0	0	1 (0.6)
Multiple	0	0	3 (6.1)	0	3 (2.0)	3 (1.7)
Other	0	0	0	0	0	0
Not reported	1 (3.3)	0	0	0	0	1 (0.6)

Abbreviations: WOCBP = women of child-bearing potential.
N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: mRNA-1345-P101 CSR Addendum 2, Table 14.1.5.1.3.2 (24 Feb 2022).

Table 24: Participant Ethnicity in WOCBP in Study mRNA-1345-P101 (WOCBP Cohort Safety Set)

Characteristic	1-injection					Overall (N=178)
	Placebo (N=30)	mRNA-1345 12.5 µg (N=51)	mRNA-1345 25 µg (N=49)	mRNA-1345 50 µg (N=48)	mRNA-1345 Total (N=148)	
Ethnicity, n (%)						
Hispanic or Latino	4 (13.3)	6 (11.8)	1 (2.0)	4 (8.3)	11 (7.4)	15 (8.4)
Not Hispanic or Latino	26 (86.7)	45 (88.2)	48 (98.0)	44 (91.7)	137 (92.6)	163 (91.6)

Abbreviations: WOCBP = women of child-bearing potential.
N = Number of participants in the Safety Set. n = Number of safety participants in the category with non-missing data
% = n/N * 100
Source: mRNA-1345-P101 CSR Addendum 2, Table 14.1.5.1.3.2 (24 Feb 2022).

Study mRNA-1345-P302

Study mRNA-1345-P302 is a Phase 3, randomised, observer-blind study that compared the co-administration of mRNA-1345 with a standard dose influenza (Part A) or an mRNA COVID-19 (Part B) vaccine versus the respective vaccines alone in medically stable adults ≥50 years. Part A and Part B are completed.

Part A evaluated the safety, tolerability, and immunogenicity of mRNA-1345 when co-administered with Afluria Quadrivalent. Part A was conducted in the US in participants ≥50 years who could have one or more chronic medical diagnoses but were medically stable. A total of 1631 participants were randomised in Part A, of whom 1623 (99.5%) participants received study intervention: 685, 249, and 689 participants in the co-administration (mRNA-1345+Afluria Quadrivalent), mRNA-1345 alone, and Afluria Quadrivalent vaccine alone groups, respectively (mRNA-1345-P302 CSR Table 14.1.1.1.1).

Part B evaluated the safety, tolerability, and immunogenicity of mRNA-1345 when given alone or co-administered with mRNA-1273.214, a SARS-CoV-2 variant containing mRNA vaccine (hereafter referred to as COVID-19 vaccine). Part B was conducted in the US in participants ≥50 years who could have one or more chronic medical diagnoses but were medically stable. A total of 1686 participants were randomised in Part B, of whom 1676 (99.4%) participants received study intervention: 562, 556 and 558 participants in the co-administration (mRNA-1345+COVID-19 vaccine), mRNA-1345 alone, and COVID-19 vaccine alone groups, respectively (mRNA-1345-P302 CSR Table 14.1.1.1.2.1).

Part C is a single arm, open-label study that is evaluating the safety, tolerability, and immunogenicity of revaccination with mRNA-1345 given at 1 year following a primary dose in adults ≥50 years of age. Part C is ongoing.

Table 25: Summary of Study Duration in Part A of Study mRNA-1345-P302 (Safety Set)

Duration of exposure	mRNA-1345 (50 µg) + Placebo (N=249)	mRNA-1345 (50 µg) + Afluria Quadrivalent (60 µg) (N=685)	Afluria Quadrivalent (60 µg) + Placebo (N=689)	Total (N=1623)
Time on Study from Injection (Days)				
n	249	685	689	1623
Mean (SD)	173.9 (26.28)	176.4 (21.39)	174.7 (28.82)	175.3 (25.53)
Median	176.0	180.0	180.0	180.0
Q1, Q3	169.0, 183.0	170.0, 183.0	170.0, 183.0	169.0, 183.0
Min, Max	9, 255	1, 240	1, 261	1, 261

Abbreviations: max = maximum; min = minimum; Q1 = quarter 1; Q3 = quarter 3; SD = standard deviation.
Time on study from randomisation = Date of study discontinuation/completion - date of randomisation + 1.
Time on study from injection = Date of study discontinuation/completion - date of the 1st injection + 1.
Source: mRNA-1345-P302 CSR Part A Final Analysis Table 14.1.8.1.1 (14 Jun 2024)

Table 26: Participant Age and Sex in Part A of Study mRNA-1345-P302 (Safety Set)

Characteristic	mRNA-1345 (50 µg) + Placebo (N=249)	mRNA-1345 (50 µg) + Afluria Quadrivalent (60 µg) (N=685)	Afluria Quadrivalent (60 µg) + Placebo (N=689)	Total (N=1623)
Age group 1, n (%) [a]				
50 to 59 years	110 (44.2)	156 (22.8)	155 (22.5)	421 (25.9)
60 to 74 years	125 (50.2)	466 (68.0)	474 (68.8)	1065 (65.6)
≥75 years	14 (5.6)	63 (9.2)	60 (8.7)	137 (8.4)
Age group 2, n (%) [a]				
50 to 59 years	110 (44.2)	156 (22.8)	155 (22.5)	421 (25.9)
≥60 years	139 (55.8)	529 (77.2)	534 (77.5)	1202 (74.1)
Age (years)				
n	249	685	689	1623
Mean (SD)	61.3 (7.40)	64.5 (7.49)	64.1 (7.10)	63.8 (7.39)
Median	61.0	64.0	64.0	63.0
Min, Max	50, 80	50, 89	50, 86	50, 89
Sex, n (%)				
Male	108 (43.4)	322 (47.0)	316 (45.9)	746 (46.0)

Characteristic	mRNA-1345 (50 µg) + Placebo (N=249)	mRNA-1345 (50 µg) + Afluria Quadrivalent (60 µg) (N=685)	Afluria Quadrivalent (60 µg) + Placebo (N=689)	Total (N=1623)
Female	141 (56.6)	363 (53.0)	373 (54.1)	877 (54.0)

Abbreviations: CRF = case report form; max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set.
[a] Age groups are derived based on the age provided by the investigators on CRF.
Source: mRNA-1345-P302 CSR Part A Final Analysis Table 14.1.3.5.1 (14 Jun 2024)

Table 27: Participant Race in Part A of Study mRNA-1345-P302 (Safety Set)

Characteristic	mRNA-1345 (50 µg) + Placebo (N=249)	mRNA-1345 (50 µg) + Afluria Quadrivalent (60 µg) (N=685)	Afluria Quadrivalent (60 µg) + Placebo (N=689)	Total (N=1623)
Race, n (%)				
White	189 (75.9)	520 (75.9)	511 (74.2)	1220 (75.2)
Black or African American	59 (23.7)	156 (22.8)	166 (24.1)	381 (23.5)
Asian	0	4 (0.6)	3 (0.4)	7 (0.4)
Japanese	0	1 (0.1)	1 (0.1)	2 (0.1)
Chinese	0	2 (0.3)	0	2 (0.1)
Korean	0	0	0	0
Asian (non-Japanese, non-Chinese, or non-Korean)	0	1 (0.1)	2 (0.3)	3 (0.2)
American Indian or Alaska Native	1 (0.4)	1 (0.1)	4 (0.6)	6 (0.4)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	3 (0.4)	4 (0.2)
Other	0	1 (0.1)	1 (0.1)	2 (0.1)
Multiple	0	2 (0.3)	0	2 (0.1)
Not reported	0	0	1 (0.1)	1 (<0.1)
Unknown	0	0	0	0

Percentages are based on the number of participants in the Safety Set.
Source: mRNA-1345-P302 CSR Part A Final Analysis Table 14.1.3.5.1 (14 Jun 2024)

Table 28: Participant Ethnicity in Part A of Study mRNA-1345-P302 (Safety Set)

Characteristic	mRNA-1345 (50 µg) + Placebo (N=249)	mRNA-1345 (50 µg) + Afluria Quadrivalent (60 µg) (N=685)	Afluria Quadrivalent (60 µg) + Placebo (N=689)	Total (N=1623)
Ethnicity, n (%)				
Hispanic or Latino	91 (36.5)	238 (34.7)	247 (35.8)	576 (35.5)
Not Hispanic or Latino	158 (63.5)	442 (64.5)	441 (64.0)	1041 (64.1)
Not reported	0	5 (0.7)	0	5 (0.3)
Unknown	0	0	1 (0.1)	1 (<0.1)

Percentages are based on the number of participants in the Safety Set.
Source: mRNA-1345-P302 CSR Part A Final Analysis Table 14.1.3.5.1 (14 Jun 2024)

Table 29: Summary of Study Duration in Part B of Study mRNA-1345-P302 (Safety Set)

Duration of exposure	D1: mRNA-1345 (50 µg) + Placebo and D29: mRNA-1273.214 (50 µg) (N=554)	D1: mRNA-1345 (50 µg) + mRNA-1273.214 (50 µg) and D29: Placebo (N=562)	D1: mRNA-1273.214 (50 µg) + Placebo and D29: Placebo (N=560)	Total (N=1676)
Time on Study from Day 1 Injection (Days)				
n	554	562	560	1676
Mean (SD)	199.7 (36.11)	200.1 (36.67)	200.2 (34.29)	200.0 (35.68)
Median	208.0	208.0	207.5	208.0
Q1, Q3	200.0, 213.0	199.0, 213.0	199.0, 212.0	199.0, 213.0
Min, Max	8, 250	9, 262	8, 281	8, 281
Time on Study from Day 29 Injection (Days)				
n	550	558	556	1664
Mean (SD)	174.1 (33.46)	174.4 (34.00)	174.9 (31.06)	174.4 (32.85)
Median	182.0	181.0	181.0	181.0
Q1, Q3	175.0, 186.0	175.0, 186.0	175.0, 186.0	175.0, 186.0
Min, Max	1, 223	1, 232	9, 254	1, 254
Time on Study from Day 29 Injection in Participants who Received Day 29 Injection (Days)				
n	528	535	538	1601
Mean (SD)	177.9 (23.26)	179.8 (16.77)	178.1 (22.06)	178.6 (20.88)

Duration of exposure	D1: mRNA-1345 (50 µg) + Placebo and D29: mRNA-1273.214 (50 µg) (N=554)	D1: mRNA-1345 (50 µg) + mRNA-1273.214 (50 µg) and D29: Placebo (N=562)	D1: mRNA-1273.214 (50 µg) + Placebo and D29: Placebo (N=560)	Total (N=1676)
Median	182.0	182.0	181.0	182.0
Q1, Q3	175.0, 186.0	176.0, 186.0	175.0, 186.0	175.0, 186.0
Min, Max	8, 223	13, 232	9, 254	8, 254

Abbreviations: max = maximum; min = minimum; Q1 = quarter 1; Q3 = quarter 3; SD = standard deviation.
Time on study from randomisation = Date of study discontinuation/completion - date of randomisation + 1.
Time on study from Day 1/Day 29 injection = Date of study discontinuation/completion — date of Day 1/Day 29 injection + 1.
For participants who did not receive Day 29 injection and continued after study Day 29, study duration from Day 29 injection = date of study discontinuation/completion — date of study Day 29 + 1.
Source: mRNA-1345-P302 CSR Part B Final Analysis Table 14.1.8.1.2 (04 Sep 2024)

Table 30: Participant Age and Sex in Part B of Study mRNA-1345-P302 (Safety Set)

Characteristic	D1: mRNA-1345 (50 µg) + Placebo and D29: mRNA-1273.214 (50 µg) (N=554)	D1: mRNA-1345 (50 µg) + mRNA-1273.214 (50 µg) and D29: Placebo (N=562)	D1: mRNA-1273.214 (50 µg) + Placebo and D29: Placebo (N=560)	Total (N=1676)
Age group 1, n (%) [a]				
50 to 59 years	206 (37.2)	206 (36.7)	210 (37.5)	622 (37.1)
60 to 74 years	308 (55.6)	315 (56.0)	310 (55.4)	933 (55.7)
≥75 years	40 (7.2)	41 (7.3)	40 (7.1)	121 (7.2)
Age group 2, n (%) [a]				
50 to 59 years	206 (37.2)	206 (36.7)	210 (37.5)	622 (37.1)
≥60 years	348 (62.8)	356 (63.3)	350 (62.5)	1054 (62.9)
Age (years)				
n	554	562	560	1676
Mean (SD)	62.6 (7.68)	62.5 (7.42)	62.6 (7.80)	62.6 (7.63)
Median	62.0	62.0	62.0	62.0
Min, Max	50, 89	50, 91	50, 88	50, 91
Sex, n (%)				
Male	243 (43.9)	245 (43.6)	265 (47.3)	753 (44.9)
Female	311 (56.1)	317 (56.4)	295 (52.7)	923 (55.1)

Abbreviations: CRF = case report form; max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set.
[a] Age groups are derived based on the age provided by the investigators on CRF.
Source: mRNA-1345-P302 CSR Part B Final Analysis Table 14.1.3.5.2 (04 Sep 2024)

Table 31: Participant Race in Part B of Study mRNA-1345-P302 (Safety Set)

Characteristic	D1: mRNA-1345 (50 µg) + Placebo and D29: mRNA-1273.214 (50 µg) (N=554)	D1: mRNA-1345 (50 µg) + mRNA-1273.214 (50 µg) and D29: Placebo (N=562)	D1: mRNA-1273.214 (50 µg) + Placebo and D29: Placebo (N=560)	Total (N=1676)
Race, n (%)				
White	428 (77.3)	427 (76.0)	434 (77.5)	1289 (76.9)
Black or African American	109 (19.7)	113 (20.1)	113 (20.2)	335 (20.0)
Asian	6 (1.1)	7 (1.2)	1 (0.2)	14 (0.8)
Japanese	0	1 (0.2)	0	1 (<0.1)
Chinese	1 (0.2)	0	0	1 (<0.1)
Korean	0	0	0	0
Asian (non-Japanese, non-Chinese, or non-Korean)	5 (0.9)	6 (1.1)	1 (0.2)	12 (0.7)
American Indian or Alaska Native	5 (0.9)	4 (0.7)	2 (0.4)	11 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.2)	3 (0.5)	0	4 (0.2)
Other	1 (0.2)	0	3 (0.5)	4 (0.2)
Multiple	1 (0.2)	0	3 (0.5)	4 (0.2)
Not reported	3 (0.5)	8 (1.4)	4 (0.7)	15 (0.9)
Unknown	0	0	0	0

Percentages are based on the number of participants in the Safety Set.
Source: mRNA-1345-P302 CSR Part B Final Analysis Table 14.1.3.5.2 (04 Sep 2024)

Table 32: Participant Ethnicity in Part B of Study mRNA-1345-P302 (Safety Set)

Characteristic	D1: mRNA-1345 (50 µg) + Placebo and D29: mRNA-1273.214 (50 µg) (N=554)	D1: mRNA-1345 (50 µg) + mRNA-1273.214 (50 µg) and D29: Placebo (N=562)	D1: mRNA-1273.214 (50 µg) + Placebo and D29: Placebo (N=560)	Total (N=1676)
Ethnicity, n (%)				
Hispanic or Latino	210 (37.9)	214 (38.1)	222 (39.6)	646 (38.5)
Not Hispanic or Latino	339 (61.2)	347 (61.7)	333 (59.5)	1019 (60.8)
Not reported	5 (0.9)	1 (0.2)	5 (0.9)	11 (0.7)

Characteristic	D1: mRNA-1345 (50 µg) + Placebo and D29: mRNA-1273.214 (50 µg) (N=554)	D1: mRNA-1345 (50 µg) + mRNA-1273.214 (50 µg) and D29: Placebo (N=562)	D1: mRNA-1273.214 (50 µg) + Placebo and D29: Placebo (N=560)	Total (N=1676)
Unknown	0	0	0	0

Percentages are based on the number of participants in the Safety Set.
Source: mRNA-1345-P302 CSR Part B Final Analysis Table 14.1.3.5.2 (04 Sep 2024)

Study mRNA-1345-P303 (Part A)

Study mRNA-1345-P303 is an ongoing Phase 3, randomised, double-blind study to evaluate the immunogenicity and safety of mRNA-1345 in adults ≥18 to ≤59 years with increased risk for LTRD. The study's primary objectives include the evaluation of safety as well as immunogenicity. Adults who had documented confirmation of at least one of the following conditions were enrolled: CAD and/or CHF, chronic lung disease (including but not limited to COPD or persistent asthma), or Type 1 or Type 2 diabetes mellitus controlled with at least 1 medication. Enrolment was structured to achieve an approximate distribution of 30% of participants with CAD/CHF, 30% with chronic lung diseases, and 40% with diabetes mellitus as the primary risk factor. Participants were randomised into each dose group according to their primary risk factor, ensuring a similar representation of these high-risk conditions across both groups.

Participants were randomised 1:1 to receive a single dose of 30 or 50 µg of mRNA-1345. A total of 1003 participants were randomised, with 502 participants in the 30 µg group and 501 participants in the 50 µg group.

At the time of the data cutoff (18 Sep 2024), a total of 999 participants had received 1 dose of either 30 µg mRNA-1345 (N=497) or 50 µg mRNA-1345 (N=502) (Table 33).

Table 33: Summary of Study Duration in Study mRNA-1345-P303 Part A (Safety Set)

Duration of exposure	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
Number of participants, n (%)			
≥28 days since injection	496 (99.8)	500 (99.6)	996 (99.7)
≥180 days since injection	488 (98.2)	492 (98.0)	980 (98.1)
≥360 days since injection	0	0	0
≥540 days since injection	0	0	0
≥720 days since injection	0	0	0
Number of participants, n (%)			
<28 days since injection	1 (0.2)	2 (0.4)	3 (0.3)
≥28 days to <180 days since injection	8 (1.6)	8 (1.6)	16 (1.6)

Duration of exposure	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
≥180 days to <360 days since injection	488 (98.2)	492 (98.0)	980 (98.1)
≥360 days to <540 days since injection	0	0	0
≥540 days to <720 days since injection	0	0	0
Time on study from injection (days)			
n	497	502	999
Mean (SD)	251.8 (45.47)	251.7 (48.25)	251.8 (46.87)
Median	253.0	253.0	253.0
Q1, Q3	231.0, 282.0	231.0, 283.0	231.0, 282.0
Min, Max	28, 348	8, 349	8, 349

Abbreviations: max = maximum; min = minimum; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set.
Time on study from injection = Date of study discontinuation/completion - Date of injection + 1.
If the study is ongoing, data cutoff date is used instead of date of study discontinuation/completion to calculate time on study.
Source: Study mRNA-1345-P303 Part A Table 14.1.8.1.1 (data cutoff date: 18 Sep 2024)

Table 34: Participant Age and Sex in Study mRNA-1345-P303 Part A (Safety Set)

Characteristic	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
Age group 1, n (%)			
18 to 49 years	196 (39.4)	196 (39.0)	392 (39.2)
50 to 59 years	301 (60.6)	306 (61.0)	607 (60.8)
Age group 2, n (%)			
18 to 29 years	19 (3.8)	26 (5.2)	45 (4.5)
30 to 39 years	62 (12.5)	47 (9.4)	109 (10.9)
40 to 49 years	115 (23.1)	123 (24.5)	238 (23.8)
50 to 59 years	301 (60.6)	306 (61.0)	607 (60.8)
Age (years)			
n	497	502	999
Mean (SD)	49.1 (9.09)	49.6 (9.16)	49.3 (9.12)
Median	52.0	53.0	52.0
Min, Max	19, 59	19, 59	19, 59
Sex, n (%)			
Male	240 (48.3)	233 (46.4)	473 (47.3)
Female	257 (51.7)	269 (53.6)	526 (52.7)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set.
Source: Study mRNA-1345-P303 Part A Table 14.1.3.4.1 (data cutoff date: 18 Sep 2024)

Table 35: Participant Race in Study mRNA-1345-P303 Part A (Safety Set)

Characteristic	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
Race, n (%)			
White	383 (77.1)	401 (79.9)	784 (78.5)
Black or African American	92 (18.5)	85 (16.9)	177 (17.7)
Asian	13 (2.6)	4 (0.8)	17 (1.7)
American Indian or Alaska Native	3 (0.6)	2 (0.4)	5 (0.5)
Native Hawaiian or Other Pacific Islander	1 (0.2)	3 (0.6)	4 (0.4)
Other	1 (0.2)	0	1 (0.1)
Multiple	2 (0.4)	4 (0.8)	6 (0.6)
Not reported	2 (0.4)	3 (0.6)	5 (0.5)
Unknown	0	0	0

Percentages are based on the number of participants in the Safety Set.
Source: Study mRNA-1345-P303 Part A Table 14.1.3.4.1 (data cutoff date: 18 Sep 2024)

Table 36: Participant Ethnicity in Study mRNA-1345-P303 Part A (Safety Set)

Characteristic	mRNA-1345 30 µg (N=497)	mRNA-1345 50 µg (N=502)	Total (N=999)
Ethnicity, n (%)			
Hispanic or Latino	144 (29.0)	140 (27.9)	284 (28.4)
Not Hispanic or Latino	346 (69.6)	360 (71.7)	706 (70.7)
Not reported	5 (1.0)	0	5 (0.5)
Unknown	2 (0.4)	2 (0.4)	4 (0.4)

Percentages are based on the number of participants in the Safety Set.
Source: Study mRNA-1345-P303 Part A Table 14.1.3.4.1 (data cutoff date: 18 Sep 2024)

Study mRNA-1345-P304

Study mRNA-1345-P304 is a completed Phase 3, randomised, observer-blind study that evaluated the safety, tolerability, and immunogenicity of mRNA-1345 when co-administered with or given sequentially 21 days after HD, quadrivalent, seasonal influenza vaccine (Fluzone HD Quadrivalent) in adults ≥65 years. The study was conducted in the US in participants ≥65 years who could have one or more stable, chronic medical diagnoses.

A total of 1900 participants were randomised into the study, with 950 participants randomised to each study arm. In the co-administration arm, 946/950 (99.6%) participants received Fluzone HD Quadrivalent vaccine+mRNA-1345 injections, and 919/950 (96.7%) participants received the subsequent placebo injection at Day 22. In the sequential administration arm, 947/950 (99.7%)

participants received the Fluzone HD Quadrivalent vaccine, and 911/950 (95.9%) participants subsequently received mRNA-1345 at Day 22 (Study mRNA-1345-P304 CSR Table 14.1.1.1).

Table 37: Summary of Study Duration in the Completed Study mRNA-1345-P304 (Safety Set)

Duration of exposure	D1: Fluzone HD + mRNA-1345 (50 µg) and D22: placebo (N=947)	D1: Fluzone HD + placebo and D22: mRNA-1345 (50 µg) (N=946)	Total (N=1893)
Time on Study from Day 1 Injection (Days)			
n	947	946	1893
Mean (SD)	190.9 (27.92)	189.9 (31.28)	190.4 (29.64)
Median	193.0	193.0	193.0
Q1, Q3	190.0, 200.0	190.0, 199.0	190.0, 199.0
Min, Max	8, 236	1, 236	1, 236

Abbreviations: HD = high dose; max = maximum; min = minimum; Q1 = quarter 1; Q3 = quarter 3; SD = standard deviation.
Time on study from Day 1 injection = Date of study discontinuation/completion — date of Day 1 injection + 1.
Source: mRNA-1345-P304 CSR Final Analysis Table 14.1.8.1 (24 Jul 2024)

Table 38: Participant Age and Sex in the Completed Study mRNA-1345-P304 (Safety Set)

Characteristic	D1: Fluzone HD + mRNA-1345 (50 µg) and D22: placebo (N=947)	D1: Fluzone HD + placebo and D22: mRNA-1345 (50 µg) (N=946)	Total (N=1893)
Age group, n (%) [a]			
65 to <75 years	759 (80.1)	759 (80.2)	1518 (80.2)
≥75 years	188 (19.9)	187 (19.8)	375 (19.8)
Age (years)			
n	947	946	1893
Mean (SD)	70.7 (4.80)	70.7 (4.80)	70.7 (4.80)
Median	70.0	70.0	70.0
Min, Max	65, 92	65, 92	65, 92
Sex, n (%)			
Male	401 (42.3)	418 (44.2)	819 (43.3)
Female	546 (57.7)	528 (55.8)	1074 (56.7)

Abbreviations: CRF = case report form; HD = high dose; max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set.
[a] Age group is derived based on the age provided by the investigators on CRF.
Source: mRNA-1345-P304 CSR Final Analysis Table 14.1.3.4 (24 Jul 2024)

Table 39: Participant Race in the Completed Study mRNA-1345-P304 (Safety Set)

Characteristic	D1: Fluzone HD + mRNA-1345 (50 µg) and D22: placebo (N=947)	D1: Fluzone HD + placebo and D22: mRNA-1345 (50 µg) (N=946)	Total (N=1893)
Race, n (%)			
White	732 (77.3)	734 (77.6)	1466 (77.4)
Black or African American	187 (19.7)	191 (20.2)	378 (20.0)
Asian	13 (1.4)	12 (1.3)	25 (1.3)
American Indian or Alaska Native	7 (0.7)	2 (0.2)	9 (0.5)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	1 (<0.1)
Other	0	1 (0.1)	1 (<0.1)
Multiple	7 (0.7)	3 (0.3)	10 (0.5)
Not reported	1 (0.1)	2 (0.2)	3 (0.2)
Unknown	0	0	0

Abbreviations: HD = high dose
Percentages are based on the number of participants in the Safety Set.
Source: mRNA-1345-P304 CSR Final Analysis Table 14.1.3.4 (24 Jul 2024)

Table 40: Participant Ethnicity in the Completed Study mRNA-1345-P304 (Safety Set)

Characteristic	D1: Fluzone HD + mRNA-1345 (50 µg) and D22: placebo (N=947)	D1: Fluzone HD + placebo and D22: mRNA-1345 (50 µg) (N=946)	Total (N=1893)
Ethnicity, n (%)			
Hispanic or Latino	209 (22.1)	221 (23.4)	430 (22.7)
Not Hispanic or Latino	724 (76.5)	720 (76.1)	1444 (76.3)
Not reported	14 (1.5)	5 (0.5)	19 (1.0)
Unknown	0	0	0

Abbreviations: HD = high dose
Percentages are based on the number of participants in the Safety Set.
Source: mRNA-1345-P304 CSR Final Analysis Table 14.1.3.4 (24 Jul 2024)

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

The exclusion criteria from pivotal studies mRNA-1345-P301 and mRNA-1345-P303 Part A that are common to other clinical trials are listed below and not discussed further:

- Participation in another clinical research study where participant has received an investigational product (drug/biologic/device with the exception of investigational RSV products) within 6 months before the planned date of the Day 1 study injection. Current participation in another RSV investigational trial is exclusionary.
- History of a diagnosis or condition that, in the judgment of the investigator, is clinically unstable or may affect participant safety, assessment of safety endpoints, assessment of immune response, or adherence to study procedures. Clinically unstable is defined as a diagnosis or condition requiring significant changes in management or medication within the 2 months prior to Screening and includes ongoing workup of an undiagnosed illness that could lead to a new diagnosis or condition.
- Any medical, psychiatric, or occupational condition, including reported history of drug or alcohol abuse, that, in the opinion of the investigator, might pose additional risk due to participation in the study or could interfere with the interpretation of study results.
- Member of study personnel or is an immediate family member or household member of study personnel.

The important exclusion criteria from pivotal studies mRNA-1345-P301 and mRNA-1345-P303 Part A are presented below in Table 41 and may be grouped together.

Table 41: Important Exclusion Criteria in the Pivotal Study

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mRESVIA vaccine or any components of the mRESVIA vaccine.	Similar to the majority of clinical trials, individuals with a known history of anaphylaxis or severe hypersensitivity to the vaccine or vaccine components were excluded to protect the safety of the study participants.	No	Individuals with a hypersensitivity to the active substance or to any of the excipients are contraindicated from receiving mRESVIA, as stated in the mRESVIA SmPC. Furthermore, the SmPC advises healthcare professionals that appropriate medical treatment and supervision should always be readily available in case of a severe hypersensitivity reaction, including anaphylaxis, following administration of the vaccine.
History of myocarditis, pericarditis, or myopericarditis.	Including this population could have impacted the safety outcome of the study.	No	Myocarditis/ pericarditis is an important potential risk (Module SVII.3.1).

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
Dermatologic conditions that could affect local solicited adverse reaction assessments (eg, tattoos, psoriasis patches affecting skin over the deltoid areas).	Including this population could have impacted the assessment of safety outcomes for the study.	No	Local solicited adverse reactions were expected during the study.
Reported history of bleeding disorder that is considered a contraindication to IM injection or phlebotomy. Known uncontrolled disorder of coagulation.	Study participants have a potential risk of haematoma due to the puncture of the deep tissues. Including this population could have impacted the safety outcome of the study.	No	It is common medical practice not to administer a product by the intramuscular route in individuals with coagulopathy or bleeding disorders, although the use of a needle with proper gauge can decrease the risk. The mRESVIA SmPC warns healthcare professionals that as with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.
History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome.	Including this population could have impacted the safety outcome of the study.	No	New onset of or worsening of neurologic diseases, including GBS, acute disseminated encephalomyelitis, idiopathic peripheral facial nerve palsy (Bell's palsy), seizures including but not limited to febrile seizures and/or generalised seizures/convulsions, were AESI in Study mRNA-1345-P301 as they are recognised to occur with some vaccines. In Study mRNA-1345-P303, new onset or worsening of pre-specified neurologic diseases (Bell's palsy/facial paralysis, GBS, ADEM, and seizures) were included as AESI (Module 2.7.4, Section 1.16). The AESI neurological conditions will be further monitored as Safety Topics of Interest using additional and routine pharmacovigilance activities (Part III).
Received or plans to receive any nonstudy vaccine (including authorised or approved vaccines for the prevention of COVID-19 regardless of type of vaccine) within 28 days before or after the Day 1 study injection.	Including this population could have impacted the efficacy or safety outcome of the study.	No	Co-administration with other vaccines is not considered missing information based on the data from studies mRNA-1345-P302 (Parts A and B) and mRNA-1345-P304. Co-administration of mRNA-1345 with standard dose influenza vaccine, high dose influenza vaccine, and an mRNA COVID-19 vaccine was well tolerated and led

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
Nonstudy vaccination(s) should not be delayed.			to robust humoral immune responses and supports vaccine effectiveness against these respiratory diseases. The mRESVIA SmPC informs healthcare professionals that mRESVIA can be administered concomitantly with seasonal influenza vaccines, either standard dose or high dose unadjuvanted and COVID-19 mRNA vaccine.
Reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease [a] (HIV positive participants with CD4 count ≥350 cells/mm^3 and an undetectable HIV viral load within the past year [low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy] and participants with stable autoimmune diseases that do not require systemic immunosuppressants are permitted.)	It is generally expected that participants with immunocompromised status may not reach the protective antibody level achieved in healthy individuals with vaccines. Including this population could have impacted the efficacy outcome of the study.	Yes. Use in immunocompromised individuals is missing information (Module SVII.3.2).	
Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.	Including this population could have impacted the efficacy outcome of the study.	Yes. Use in immunocompromised individuals is missing information (Module SVII.3.2). Use in individuals with autoimmune or inflammatory disorders is missing information (Module SVII.3.2).	
Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the study injection or during the study.	Including this population could have impacted the efficacy outcome of the study.	Yes. Use in immunocompromised individuals is missing information (Module SVII.3.2).	

Criterion	Reason for Exclusion	Included as Missing Information? (Yes/No)	Rationale (if not included as missing information)
Acute disease at the time of enrolment (defined as the presence of moderate or severe illness with or without fever, or an oral temperature ≥37.8°C (100.0°F) on the planned day of vaccine administration).	Including individuals with moderate or severe illness with or without fever could have impacted the efficacy and safety outcome as these individuals may have underlying RSV infection.	No	It is good practice not to administer a vaccine to an individual who has a fever. To this effect, the mRESVIA SmPC advises healthcare professionals that vaccination should be postponed in individuals suffering from acute infection or febrile illness. The presence of a minor infection, such as a cold, should not delay vaccination.
Known history of poorly controlled hypertension (per determination of the investigator), or systolic blood pressure >160 mmHg at the Screening or baseline (Day 1) visit.[b] Diastolic blood pressure >90 mmHg at the Screening or baseline (Day 1) visit.[b]	Including this population could have impacted the safety outcome of the study.	No	There is no suspected reason to expect the safety or efficacy of mRESVIA in these individuals would be different from the rest of the population receiving mRESVIA.
Known history of hypotension, or systolic blood pressure <85 mmHg at the Screening or baseline (Day 1) visit.[b]	Including this population could have impacted the safety outcome of the study.	No	There is no suspected reason to expect the safety or efficacy of mRESVIA in these individuals would be different from the rest of the population receiving mRESVIA. It is recognised that individuals with hypotension are at increased risk of syncope. The mRESVIA SmPC advises that anxiety-related reactions including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection and that it is important that precautions are in place to avoid injury from fainting.
Donated ≥450 mL of blood products <14 days prior to Screening.	Including this population could have impacted the safety outcome of the study.	No	It is common practice to not allow participants to give blood prior to entering a clinical trial in which phlebotomy is occurring as part of the study procedures to avoid undue risk to the participant. There is no suspected reason to expect the safety or efficacy of mRESVIA in these individuals would be different from the rest of the population receiving mRESVIA.

[a] Not an exclusion criterion for Study mRNA-1345-P303 Part A. Adults who were receiving chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 180 days prior to Day 1 were excluded.

[b] Not an exclusion criterion for Study mRNA-1345-P303 Part A.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The current studies supporting the authorisation of mRESVIA in the clinical development programme are unlikely to detect certain types of adverse reactions such as very rare (<1/10,000) adverse reactions or adverse reactions with a long latency.

The safety profile is based on the ongoing, global, randomised, observer-blind, placebo-controlled Phase 2/3 study mRNA-1345-P301, in which 18,245 adult participants aged ≥60 years received one injection of 50 µg mRESVIA; and 17,152 of these participants had at least 6 months of follow-up after injection at the time of the data cutoff (30 Apr 2023).

This is supported by supplementary safety data from completed observer-blind, placebo-controlled Phase 1 dose-escalation study mRNA-1345-P101 in which 66 participants received 50 µg mRESVIA.

In addition, safety data are available from ongoing Phase 3, randomised, double-blind study mRNA-1345-P303 Part A in which 999 adult participants aged ≥18 to ≤59 years with increased risk for LTRD received 1 dose of either 30 µg mRESVIA (N=497) or 50 µg mRESVIA (N=502); 492/502 (98%) participants in the 50 µg group reached ≥6 months of follow-up after injection at the time of the data cutoff (18 Sep 2024).

Long-term safety is considered missing information although over 17,500 recipients of 50 µg mRESVIA have at least 6 months of safety follow-up (Module SVII.3.2).

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 42: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Paediatric participants	Not included in the clinical development programme to support the indication in adults ≥18 years.
Pregnant women	Not included in the clinical development programme to support the indication in adults ≥18 years. In Study mRNA-1345-P303 Part A, 3 pregnancies were reported, including 1 participant in the mRESVIA 50 µg group (resulting in a healthy male infant delivered via caesarean section at 34 weeks gestation without complications or congenital abnormalities) and 2 participants in the mRESVIA 30 µg group (one resulting in elective termination with no known congenital anomalies; the other ongoing without reported acute illnesses or pregnancy complications as of the data cutoff [18 Sep 2024], with the estimated due date as Feb 2025) (Module 2.7.4, Section 6.4). In Study mRNA-1345-P101 WOCBP, 2 pregnancies were reported, including 1 participant in the mRESVIA 25 µg group (positive pregnancy test on Study Day 49) that resulted in elective termination and 1 participant in the mRESVIA 50 µg group (positive pregnancy test on Study Day 85) that resulted in a live birth and normal vaginal delivery with no problems reported during pregnancy and delivery (mRNA-1345- P101 CSR Addendum 2, Section 7.3.3). Use in pregnancy is missing information (Module SVII.3.2).
Breastfeeding women	Not included in the clinical development programme to support the indication in adults ≥18 years.

Type of Special Population	Exposure
Participants with relevant comorbidities	
Participants with hepatic impairment	Hepatic impairment at baseline was not evaluated in the clinical development programme.
Participants with renal impairment	Renal impairment at baseline was not evaluated in the clinical development programme.
Participants with cardiovascular impairment	Individuals with CHF, including heart failure with preserved ejection fraction, were permitted to participate in Study mRNA-1345-P301 if they were assessed as medically stable. At study entry, 1.5% (277 of 18245) participants in the mRESVIA group and 1.5% (273 of 18184) participants in the placebo group had a targeted medical history grouped term of CHF that included the PT cardiac failure congestive (Table 14.1.4.2). In Study mRNA-1345-P303, 26% (129 of 497) participants in the mRNA-1345 30 µg group had CAD/CHF (19.5% CAD and 10.7% CHF) and 25.7% (129 of 502) participants in the mRNA-1345 50 µg group had CAD/CHF (20.7% CAD and 9.0% CHF) (Table 14.1.3.4.1).
Immunocompromised participants	Not included in the clinical development programme (Module SIV.1). Use in immunocompromised individuals is missing information (Module SVII.3.2).
Participants with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	Participant exposure by race and ethnicity in Study mRNA-1345-P301 are presented in Table 7 and Table 8 (Module SIII), respectively. In this study, the majority of participants in the mRESVIA and placebo groups were White (61.8% and 61.9%), followed by Black or African American (12.1% and 11.9%), Asian (11.0% and 11.0%), other (5.4% and 5.5%), American Indian or Alaska Native (5.0% and 4.9%), multiple (4.2% and 4.1%), Native Hawaiian or Other Pacific Islander (0.1% and 0.1%); in <0.1% and 0.1% of participants the race was unknown and in 0.3% and 0.5% of participants the race was not reported, respectively (Table 14.1.3.6). In terms of ethnicity, the majority of participants in the mRESVIA and placebo groups in mRNA-1345-P301 were Not Hispanic or Latino (65.6% and 65.0%), followed by Hispanic or Latino (33.4% and 33.8%); in 0.1% and 0.1% of participants ethnicity was unknown and in 0.9% and 1.0% of participants ethnicity was not reported, respectively (Table 14.1.3.6). Participant exposure by race and ethnicity in Study mRNA-1345-P303 are presented in Table 35 and Table 36, respectively. The majority of participants in the mRESVIA 30 µg and 50 µg groups were White (77.1% and 79.9%), followed by Black or African American (18.5% and 16.9%), Asian (2.6% and 0.8%), American Indian or Alaska Native (0.6% and 0.4%), Native Hawaiian or Other Pacific Islander (0.2% and 0.6%); multiple (0.4% and 0.8%), other (0.2% and 0); in 0.4% and 0.6% of participants the race was not reported, respectively (Table 14.1.3.4.1). In this study, the majority of participants in the mRESVIA 30 µg and 50 µg groups were Not Hispanic or Latino (69.6% and 71.7%), followed by Hispanic or Latino (29.0% and 27.9%); in 1.0% and 0 of participants ethnicity was not reported and in 0.4% and 0.4% of participants ethnicity was unknown, respectively (Table 14.1.3.4.1).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Others	

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>Participants ≥ 75 years of age</td><td>Participant exposure by age in Study mRNA-1345-P301 is presented in Table 6 (Module SIII). In this study, 18.1% and 18.2% of participants were ≥75 years of age in the mRESVIA and placebo groups; 81.9% and 81.8% of participants were 60 to 74 years, respectively (Table 14.1.3.6).</td></tr>
<tr><td>Frail participants</td><td>In Study mRNA-1345-301, frailty status of participants was assessed at baseline using the EFS as presented in the table below.

Participant Frailty (Safety Set) in the Ongoing Study mRNA-1345-P301
<table>
<tr><th>Characteristic</th><th>Placebo (N=18184)</th><th>mRESVIA 50 µg (N=18245)</th><th>Total (N=36429)</th></tr>
<tr><td colspan="4">Frailty Status, n (%)</td></tr>
<tr><td>0-3: Fit</td><td>13362 (73.5)</td><td>13515 (74.1)</td><td>26877 (73.8)</td></tr>
<tr><td>4-5: Vulnerable</td><td>2907 (16.0)</td><td>2841 (15.6)</td><td>5748 (15.8)</td></tr>
<tr><td>6 or more: Mild frailty</td><td>1027 (5.6)</td><td>1009 (5.5)</td><td>2036 (5.6)</td></tr>
<tr><td>Missing</td><td>888 (4.9)</td><td>880 (4.8)</td><td>1768 (4.9)</td></tr>
</table>
Abbreviations: EFS = Edmonton Frail Scale; IP = investigational product; max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Safety Set.
Baseline value for EFS total score is defined as the most recent non missing measurement (scheduled or unscheduled) collected on or before the date of IP injection.
Source: Study mRNA-1345-P301 Table 14.1.3.6
Data from ongoing trial as of 30 Apr 2023.</td></tr>
<tr><td>Diabetes (Type 1, Type 2)</td><td>In Study mRNA-1345-P301, 17.9% (3262 of 18245) participants in the mRESVIA group and 17.4% (3172 of 18184) participants in the placebo group had a targeted medical history grouped term of diabetes at study entry (Table 14.1.4.2). This included PTs Type 2 diabetes mellitus (17.4% and 17.0%), Type 1 diabetes mellitus (0.4% and 0.4%), diabetes mellitus (<0.1% and <0.1%), diabetic neuropathy (<0.1% and <0.1%), and Type 3 diabetes mellitus (0 and <0.1%) in the mRESVIA and placebo groups, respectively (Table 14.1.4.2).
In Study mRNA-1345-P303, 55.9% (278 of 497) participants in the mRESVIA 30 µg group had Type 1 or Type 2 diabetes mellitus and 59.6% (299 of 502) participants in the mRESVIA 50 µg group had Type 1 or Type 2 diabetes mellitus (Table 14.1.3.4.1).</td></tr>
<tr><td>Chronic lung disease</td><td>Individuals with COPD were permitted to participate in Study mRNA-1345-P301 if they were assessed as medically stable.
In this study, 6.0% (1097 of 18245) participants in the mRESVIA group and 6.1% (1107 of 18184) participants in the placebo group had a targeted medical history grouped term of COPD at study entry (Table 14.1.4.2). This included PTs COPD (5.5% and 5.6%), emphysema (0.4% and 0.4%), bronchitis chronic (0.3% and 0.3%), and asthma-chronic obstructive pulmonary disease overlap syndrome (0 and <0.1%), in the mRESVIA and placebo groups, respectively (Table 14.1.4.2). Furthermore, 0.8% (144 of 18245) participants in the mRESVIA group and 0.8% (152 of 18184) participants in the placebo group had a targeted medical history grouped term of chronic respiratory disease at study entry (Table 14.1.4.2).
In Study mRNA-1345-P303, 47.5% (236 of 497) participants in the mRESVIA 30 µg group had chronic lung disease (10.3% COPD, 38.8% asthma, 3.6% chronic respiratory disease, and 0.2% pulmonary fibrosis) and 44.8% (225 of 502) participants</td></tr>
</table>

Type of Special Population	Exposure
	in the mRESVIA 50 µg group had chronic lung disease (10.4% COPD, 38.8% asthma, 2.4% chronic respiratory disease, and 0.2% pulmonary fibrosis) (Table 14.1.3.4.1).
Severe obesity (BMI ≥40 kg/m^2)	Not included in the clinical development programme. A BMI from ≥18 kg/m^2 to ≤35 kg/m^2 was an inclusion criterion in Study mRNA-1345-P301. In Study mRNA-1345-P303, 17.1% (85 of 497) participants in the mRESVIA 30 µg group and 17.7% (89 of 502) participants in the mRESVIA 50 µg group had a BMI ≥40 kg/m^2 (Table 14.1.3.4.1).
HIV infection	In Study mRNA-1345-P301, 0.7% (136 of 18245) participants in the mRESVIA group and 0.8% (151 of 18184) participants in the placebo group had a targeted medical history of HIV infection (PT) at study entry (Table 14.1.4.2). Other HIV related targeted medical history PTs at study entry included HIV test positive (<0.1% and <0.1%), HIV infection CDC category A (<0.1% and 0), and blood HIV RNA below assay limit (0 and <0.1%), in the mRESVIA and placebo groups, respectively (Table 14.1.4.2). In Study mRNA-1345-P303, 1.6% (8 of 497) participants in the mRESVIA 30 µg group and 1.6% (8 of 502) participants in the mRESVIA 50 µg group had a medical history of HIV infection (Table 14.1.4.1.1).

Part II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Experience

mRESVIA was first approved in the US on 31 May 2024 for active immunisation for the prevention of LRTD caused by RSV in individuals 60 years of age and older. As of 30 May 2025, mRESVIA is currently authorised in 39 countries.

SV.1.1 Method Used to Calculate Exposure

The worldwide administered doses of mRESVIA in the post-market setting were estimated based on the cumulative global distributed doses as of 30 May 2025. This estimate was adjusted by applying the lower and upper ranges of the proportion of commercial doses administered versus doses commercially distributed in the US, using the following two data sources:

- Moderna’s internal supply chain data provides daily tracking of dose distribution by product and receiving country.
- The lower-range cumulative commercial administrations of mRESVIA doses in the US were derived from IQVIA’s NPA data for retail pharmacies across the country, and dose administrations were provisioned and documented in a US integrated delivery healthcare network. IQVIA’s NPA data are refreshed weekly, and the estimated proportions are subject to updates as uptake patterns in the US evolve and NPA data are updated. The upper-range commercial administrations of mRESVIA doses in the US were estimated by accounting for additional doses administered in physicians’ offices, using CDC weekly data on RSV vaccinations administered in retail pharmacies and physicians' offices for adults aged 60 years and older across manufacturers.

The estimated lower- and upper-range proportions (doses administered divided by doses distributed) in the US were then applied to global commercial dose distributions to estimate

lower- and upper-range commercial dose administrations worldwide cumulatively through 30 May 2025.

SV.1.2 Exposure

Based on the assumptions described in Module SV.1.1, it is estimated that approximately 83,386 to 86,638 doses of mRESVIA had been administered worldwide in the post-market setting through 30 May 2025 cumulatively.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

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

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Please refer to the initial RMP (version 0.4, 18 Jun 2024) (EMEA/H/C/6278).

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Please refer to the initial RMP (version 0.4, 18 Jun 2024) (EMEA/H/C/6278).

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 43: Presentation of Important Potential Risks

Important Potential Risk	**Myocarditis/pericarditis**
Potential mechanism	Myocarditis is an inflammatory condition of the myocardium triggered by various factors including infectious agents, toxic substances, drugs or autoimmune disorders rather than a distinct cardiovascular disease. The most common aetiology of myocarditis are viral infections, accounting for 50-70% of all cases (Baral et al 2020). Although rare, RSV has been reported to cause extrapulmonary complications such as arrhythmias and myocarditis (Huang et al 1998; Miura et al 2018; O'Brien et al 2021). Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterised by chest pain, pericardial friction rub, changes in the electrocardiogram and occasionally, a pericardial effusion. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases and other common causes include infection, renal failure, myocardial infarction, post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women and it more commonly affects adults aged 50 years and older than the younger population.

Important Potential Risk	**Myocarditis/pericarditis**
	Myocarditis has previously been reported following vaccines including smallpox vaccine (Halsell et al 2003). The occurrence of myocarditis/pericarditis following COVID-19 mRNA vaccines was very rare (Ling et al 2022), with higher incidence rates in young male and within a short risk window (7 days) after the second dose (Yasuhara et al 2023; Knudsen and Prasad 2022). Mechanistic investigations into COVID-19 infection and mRNA COVID-19 vaccine-associated myocarditis have pointed to antigen-specific biological factors rather than to the mRNA platform itself. Elevated expression of the SARS-CoV-2 spike receptor, ACE2, on cardiomyocytes and pericytes (Pannucci et al 2023), and the detection of circulating spike or cleaved S1 protein fragments in affected individuals (Yonker et al 2023; Borkotoky et al 2023) suggest that spike-mediated interactions with ACE2 and downstream immune activation contribute to this phenomenon. These mechanisms are unique to SARS-CoV-2 spike biology and are not relevant to RSV infection or to the RSV pre-F antigen encoded by mRNA-1345. Consistent with this antigen-specific distinction, no myocarditis or pericarditis events were reported in any of the clinical studies evaluating mRESVIA in participants who received mRNA-1345, including Study mRNA-1345-P301 within 28 days postinjection.
Evidence source and strength of evidence	Myocarditis/pericarditis can be caused by a variety of factors; the most common aetiology is viral infection. In Study mRNA-1345-P301, there were no CEAC adjudicated cases of acute myocarditis up to the data cutoff (30 Apr 2023) and no CEAC adjudicated cases of acute pericarditis up to 42 days after study injection in either the mRESVIA or placebo groups. While two participants in the mRESVIA group had CEAC adjudicated events of acute pericarditis with onset >42 days, they were assessed by the investigator as unrelated to study vaccine as other confounding factors provide an alternative causal association. No cases of acute pericarditis were reported in the placebo group up to data cutoff. In Study mRNA-1345-P303 Part A, no events of myocarditis or pericarditis were reported in participants ≥18 to ≤59 years of age vaccinated with mRNA-1345 30 µg or 50 µg up to the data cutoff (18 Sep 2024) (Study mRNA-1345-P303 CSR Section 7.5.1.2). Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur post-authorisation.
Characterisation of risk	In Study mRNA-1345-P301, no investigator assessed AESIs of myocarditis or pericarditis were reported in either group up to 7 days after injection (Table 14.3.2.8.2.1). In Study mRNA-1345-P301, there were no CEAC adjudicated cases of acute myocarditis up to the data cutoff (30 Apr 2023) and no CEAC adjudicated cases of acute pericarditis up to 42 days after study injection in either the mRESVIA or placebo groups. Up to 28 days after injection, no AESIs of myocarditis or pericarditis were reported after mRESVIA vaccination (N=18245); 1 AESI of pericarditis was reported in a participant in the placebo group (1 of 18184; <0.1%) (Table 14.3.2.2.1.1) with onset on Day 8 that was adjudicated by the CEAC as not a charter-defined event (Study mRNA-1345-P301 CSR Section 7.6.1.2). This was the only event that was reported within 42 days after injection. Up to the data cutoff (30 Apr 2023), pericarditis was reported as an AESI for 2 participants (<0.1%) in the mRESVIA group (one participant had 2 events, on Day 48 and Day 223) and myocarditis was reported as an AESI for one participant (<0.1%) in the mRESVIA group (onset Day 62) (Table 14.3.2.6.1.2; Study

Important Potential Risk	**Myocarditis/pericarditis**
	mRNA-1345-P301 CSR Section 7.6.1.2), in addition to the one AESI of pericarditis reported in the placebo group (onset on Day 8 as described above). All events in the mRESVIA group had onset >42 days after study injection and were considered unrelated to study injection per investigator. The CEAC adjudicated the AESI of myocarditis in the mRESVIA group as not a charter-defined event (Study mRNA-1345-P301 CSR Section 7.6.1.2). While two participants in the mRESVIA group had CEAC adjudicated events of acute pericarditis with onset >42 days, they were assessed by the investigator as unrelated to study vaccine as other confounding factors provide an alternative causal association. Other possible confounding factors included a preceding viral upper respiratory tract infection, administration of a second dose of monkeypox vaccine and a bivalent COVID-19 vaccine 3 days before the recurrent event of pericarditis, and an unlikely temporal association with mRESVIA. One event that was not reported as an AESI also underwent adjudication by the CEAC as it was initially reported with verbatim term “nonsustained cardiac arrhythmia potential myocarditis,” (PT myocarditis) in a participant who received mRESVIA (Study mRNA-1345-P301 CSR Section 7.6.1.2). This was adjudicated by the CEAC as not a charter-defined event and the investigator later updated the event term to palpitations (verbatim: worsening of heart palpitations) as of the data cutoff. All of the myocarditis and pericarditis events described above that were reported by the investigator as AESIs were also identified in the narrow noninfectious myocarditis and pericarditis SMQ (Study mRNA-1345-P301 CSR Section 7.6.2.14). The incidence of event PTs identified by the narrow/broad noninfectious myocarditis and pericarditis SMQ was balanced between the groups up to 28 days after injection (<0.1% in each group; Table 14.3.2.10.4.2) and up to data cutoff (0.6% in each group; Table 14.3.2.10.4.3). In summary, no CEAC-adjudicated cases of myocarditis or pericarditis occurred within 42 days after injection. No CEAC-adjudicated cases of acute myocarditis were reported up to data cutoff (30 Apr 2023) in either group. Two participants in the mRESVIA group had CEAC-adjudicated cases of acute pericarditis that had onset >42 days after study injection and were considered to be unrelated to study injection per investigator. There were no CEAC-adjudicated cases of acute pericarditis in the placebo group up to the data cutoff. In Study mRNA-1345-P101, no unsolicited treatment-emergent AESIs including pericarditis were reported in either of the mRESVIA or placebo groups in any of the cohorts (Table 14.3.2.4.1.1; Table 14.3.2.4.1.2.1; Table 14.3.2.4.1.2.2; Table 14.3.2.4.1.5). In Study mRNA-1345-P303 Part A, no events of myocarditis or pericarditis were reported in participants ≥18 to ≤59 years of age vaccinated with mRESVIA 30 µg or 50 µg up to the data cutoff (18 Sep 2024) (Study mRNA-1345-P303 CSR Section 7.5.1.2).
Risk factors and risk groups	Acute myocarditis is overall more common in men than in women (Kytö et al 2013). The incidence rate occurs with two peaks: the highest in those under one year old with both genders combined (Vasudeva et al 2021) and young males aged 16 to <40 years old (Vasudeva et al 2021; Kytö et al 2013). Similarly, acute pericarditis is overall more common in men than in women. However, the gender difference is reduced with advancing age and became nominal in persons aged >65 years (Kytö et al 2014). In males, the incidence rate of acute pericarditis declines between 16 to 45 years followed by an increase in older individuals aged >50 years (Kytö et al 2014). In females, the incidence rate of acute pericarditis

Important Potential Risk	**Myocarditis/pericarditis**
	gradually increases with age, with a peak in the population aged 65 to 74 years (Kytö et al 2014; Kumar et al 2016).
Preventability	Myocarditis presents with a spectrum of symptoms ranging from mild dyspnoea or chest pain that spontaneously resolves without treatment to cardiogenic shock and sudden death. The major long-term consequence is dilated cardiomyopathy with chronic heart failure. Common viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated (Blauwet and Cooper 2010). Pericarditis may be caused by many disorders (eg, infection, myocardial infarction, trauma, tumours, metabolic disorders) but is often idiopathic. Symptoms include chest pain or tightness, often worsened by deep breathing. Cardiac output may be greatly reduced if cardiac tamponade or constrictive pericarditis develops. Diagnosis is based on symptoms, a friction rub, electrocardiographic changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram (Hoit 2022). Pericarditis may result in one of two serious complications: cardiac tamponade and chronic constrictive pericarditis. Cardiac tamponade is considered a medical emergency and, if left untreated, can quickly become fatal. Myocarditis and pericarditis have yet to be confirmed as causally associated with mRESVIA but can be managed in clinical practice with supportive treatment should they occur.
Impact on the benefit-risk balance of the product	Respiratory syncytial virus is a significant contributor of both upper and lower respiratory tract illness and hospitalisation worldwide. It results in substantial associated morbidity and economic burden across the older adult population and other groups at higher risk for severe disease, including infants, young children, and persons with certain underlying conditions such as chronic heart or lung disease, or immunocompromising conditions. The potential clinical consequences of myocarditis/pericarditis are serious. However, there is insufficient evidence that mRESVIA causes myocarditis or pericarditis. The very rare case of myocarditis/pericarditis that have occurred with the mRNA vaccine Spikevax generally developed within just a few days after vaccination, primarily within 14 days. Individuals tend to recover within a short time following standard treatment and rest. The majority of these cases were reported in young males, and shortly after the second dose of the vaccine. The benefit of mRESVIA as a preventive vaccine for RSV is considered to outweigh the risk of myocarditis/pericarditis, a risk for which a causal association with mRESVIA has not been established.
Public health impact	The potential impact on public health is expected to be low since myocarditis and pericarditis are very rare reactions that have yet to be confirmed as causally associated with mRESVIA. Although the potential clinical consequences of myocarditis and pericarditis are serious, these adverse effects, should they occur, can be managed with supportive treatment.

SVII.3.2 Presentation of the Missing Information

Table 44: Presentation of Missing Information

Missing Information	**Use in immunocompromised individuals**
Evidence source	Individuals with a reported history of congenital or acquired immunodeficiency, immunosuppressive condition, or immune-mediated disease were excluded from participation in Study mRNA-1345-P301 as it is expected that participants with immunocompromised status may not reach the protective antibody level achieved in healthy individuals with vaccines (Module SIV.1). Individuals receiving chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection were excluded from participation in studies mRNA-1345-P301 and mRNA-1345-P303 Part A. HIV positive individuals with CD4 count ≥350 cells/mm^3 and an undetectable HIV viral load within the past year (low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy) and individuals with stable autoimmune diseases that do not require systemic immunosuppressants were permitted in Study mRNA-1345-P301. A total of 136 participants (136 of 18245; 0.7%) in the mRESVIA group and 151 participants (151 of 18184; 0.8%) in the placebo group had a targeted medical history of HIV infection at study entry (Table 42; Module SIV.3). In Study mRNA-1345-P303 Part A, 1.6% (8 of 497) participants in the mRESVIA 30 µg group and 1.6% (8 of 502) participants in the mRESVIA 50 µg group had a medical history of HIV infection (Table 42, Module SIV.3). Overall, use of mRESVIA in immunocompromised individuals is limited. The mRESVIA SmPC advises healthcare professionals that safety and immunogenicity data on mRESVIA are not available for immunocompromised individuals. Individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine.
Population in need of further characterisation	Use in immunocompromised individuals will be further characterised through the ongoing Studies mRNA-1345-P303 Part B, mRNA-1345-P902, and mRNA-1345-P903, in addition to routine pharmacovigilance activities (Part III).
Missing Information	**Use in individuals with autoimmune or inflammatory disorders**
Evidence source	Individuals receiving chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study injection were excluded from participation in studies mRNA-1345-P301 and mRNA-1345-P303 Part A (Module SIV.1). This would have excluded individuals with autoimmune or inflammatory disorders. While individuals with stable autoimmune diseases that do not require systemic immunosuppressants were permitted in Study mRNA-1345-P301, mRESVIA exposure is limited in individuals with autoimmune or inflammatory disorders. In Study mRNA-1345-P301, overall, 1.0% of mRESVIA participants and 1.1% of placebo participants had a targeted medical history within the “immune disease” category, which included events autoimmune conditions such as psoriasis and rheumatoid arthritis (Table 14.1.4.2). There were 16 participants with a targeted medical history of autoimmune thyroiditis at study entry; 8 participants (8 of 18245; <0.1%) in the mRESVIA group and 8 participants (8 of 18184; <0.1%) in the placebo group (Table 14.1.4.2). A total of 18 participants had a targeted medical history of rheumatoid arthritis; 7 participants (7 of 18245; <0.1%) in the mRESVIA group and 11 participants (11 of 18184; <0.1%) in the placebo group (Table 14.1.4.2). A targeted medical history of systemic lupus erythematosus (2 of

	18245; <0.1%) or chronic cutaneous lupus erythematosus (1 of 18245; <0.1%) at study entry was limited in the mRESVIA group; no participants had either condition in the placebo group (Table 14.1.4.2). There were also limited participants with a targeted medical history of Sjögren's syndrome and Basedow's disease in the mRESVIA (4 of 18245 and 3 of 18245; both <0.1%) and placebo (2 of 18184 and 2 of 18184; both <0.1%) groups, respectively (Table 14.1.4.2). There were 5 participants with a medical history of inflammatory bowel disease included in the study; 2 participants (2 of 18245; <0.1%) in the mRESVIA group and 3 participants (3 of 18184; <0.1%) in the placebo group (Table 14.1.4.1). Twelve participants had a medical history of pelvic inflammatory disease; 6 participants (6 of 18245; <0.1%) in the mRESVIA group and 6 participants (6 of 18184; <0.1%) in the placebo group (Table 14.1.4.1).
Population in need of further characterisation	Use in individuals with autoimmune or inflammatory disorders will be further characterised through the ongoing Studies mRNA-1345-P902 and mRNA-1345-P903, in addition to routine pharmacovigilance activities (Part III).
Missing Information	**Long-term safety**
Evidence source	The safety profile of mRESVIA is based on the ongoing, global randomised, observer-blind, placebo-controlled Phase 2/3 clinical study mRNA-1345-P301 in which 18,245 adult participants aged ≥60 years received one injection of 50 µg mRESVIA; and 17,152 of these participants had at least 6 months of follow-up after injection. At the time of the data cutoff of 30 Apr 2023, the median study duration from injection (days) in the mRESVIA group (N=18245) was 257 days (1, 530 days) (Table 5, Module SIII). This is supported by supplementary safety data from completed observer-blind, placebo-controlled Phase 1 dose-escalation study mRNA-1345-P101 in which 66 participants received 50 µg mRESVIA. At the time of the analysis (02 Oct 2022) for mRNA-1345-P101 the following groups were analysed: • Younger adult cohort: Adults aged 18 to 49 years (Cohorts 1 to 4) from Day 1 through EOS (Month 6 for Cohort 1, Cohort 2, and Cohort 4; Month 10 for Cohort 3) (Final analysis). • Older adult cohort: Adults aged 65 to 79 years (Cohorts 7 to Cohort 11) from Day 1 through Month 14, reflecting 12 months of follow-up after the first injection, and 2 months follow-up after booster injection (Interim analysis). • Older adult Japanese cohort: Adults of Japanese descent aged >60 years (Cohort 15) from Day 1 through EOS (Month 6) (Final analysis). • WOCBP cohort: WOCBP aged 18 to 40 years (Cohorts 12 to 14) from Day 1 through EOS (Month 6) (Final analysis). In addition, safety data are available from ongoing Phase 3, randomised, double-blind study mRNA-1345-P303 Part A in which 999 adult participants aged ≥18 to ≤59 years with increased risk for LTRD received 1 dose of either mRESVIA 30 µg (N=497) or mRESVIA 50 µg (N=502); 492/502 (98%) participants in the 50 µg group reached ≥6 months of follow-up after injection at the time of the data cutoff (18 Sep 2024). It is recognised that long-term safety data are limited.
Population in need of further characterisation	Long-term safety will be further characterised through the ongoing Studies mRNA-1345-P301, mRNA-1345-P302, mRNA-1345-P303, mRNA-1345-P902, and mRNA-1345-P903, in addition to routine pharmacovigilance activities (Part III).

Missing Information	Use in pregnancy
Evidence source	Pregnant individuals were not included in the clinical development programme to support the indication in adults ≥18 years. Pregnant individuals were not included in Study mRNA-1345-P303. The inclusion criteria stipulated that female participants of childbearing potential could be enrolled in Study mRNA-1345-P303 if the participant had a negative pregnancy test at the Screening visit and on the day of injection (Day 1), practiced adequate contraception or abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1, and agreed to continue adequate contraception through 90 days following injection. mRESVIA exposure during pregnancy is limited. In Study mRNA-1345-P303 Part A, 3 pregnancies were reported, including 1 participant in the mRESVIA 50 µg group (resulting in a healthy male infant delivered via caesarean section at 34 weeks gestation without complications or congenital abnormalities) and 2 participants in the mRESVIA 30 µg group (one resulting in elective termination with no known congenital anomalies; the other ongoing without reported acute illnesses or pregnancy complications as of the data cutoff [18 Sep 2024], with the estimated due date as Feb 2025) (Module 2.7.4, Section 6.4). In Study mRNA-1345-P101 WOCBP, 2 pregnancies were reported, including 1 participant in the mRESVIA 25 µg group (positive pregnancy test on Study Day 49) that resulted in elective termination and 1 participant in the mRESVIA 50 µg group (positive pregnancy test on Study Day 85) that resulted in a live birth and normal vaginal delivery with no problems reported during pregnancy and delivery (mRNA-1345- P101 CSR Addendum 2, Section 7.3.3). A nonclinical developmental toxicity study found no vaccine-related foetal malformations or variations and no adverse effects on postnatal development (Module SII).
Population in need of further characterisation	Use in pregnancy will be further characterised through the ongoing Study mRNA-1345-P201 and routine pharmacovigilance activities (Part III).

Part II: Module SVIII - Summary of the Safety Concerns

Table 45: Summary of Safety Concerns

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

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Moderna has an established signal management process including signal detection, validation and evaluation of spontaneous reports from all sources, which follows the principle of the Guideline on Good Pharmacovigilance Practices (GVP) Module IX for Signal Management (GVP Module IX – Signal Management (Rev.1)). During signal detection, data sources will be screened for new safety information related to mRESVIA. Following initial review of the available data, a determination will be made on the basis of the nature and the quality of the new information whether further investigation is warranted, at which point those topics referred for further investigation are considered "validated signals". Potential signals may be identified from any data source including, but not limited to, safety data from Moderna-sponsored clinical trials and noninterventional studies, spontaneous AE reports, published literature, regulatory safety surveillance databases (eg, EudraVigilance, VAERS) and communications from external sources, including regulatory agencies, and (if applicable) business partners. As part of Moderna's routine pharmacovigilance activities, Moderna performs periodic signal detection analyses, in line with the product's SSP. These analyses include but not limited to safety concerns, AESIs, and missing information. The following data sources are routinely reviewed: Moderna global PV database (Argus platform) using a defined signal detection methodology (both qualitative and quantitative aggregated analyses), signals of disproportionate reporting from regulatory databases (eg, EudraVigilance, VAERS), published literature that involves targeted keyword searches in widely recognised databases (ie, MEDLINE, EMBASE), health authority websites screening, review of publicly available competitors' labels, as well as social media.

Moderna employs routine pharmacovigilance consistent with that described in the ICH E2F Pharmacovigilance Planning Guideline. Moderna's standard processes and systems for collecting and recording information about all events potentially related to drug/product safety, and for expedited and periodic reporting are in compliance with current local regulations and defined in globally applied Moderna Standard Operating Procedures.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

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.

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional Pharmacovigilance Activities

Table 46: Additional Pharmacovigilance Activities

Study Number ***Country(ies)***	**Study Title** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
mRNA-1345-P301 *Global* *(22 countries)*	A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥60 Years of Age *Ongoing*	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of the mRNA-1345 vaccine. • To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of a BD of mRNA-1345 administered 24 months after the primary dose. • To demonstrate noninferiority of the serum RSV-A nAb response of a BD of mRNA-1345 compared with a primary dose. • To demonstrate noninferiority of the serum RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose.	Phase 2/3, randomised, observer-blind, placebo-controlled study	Adults ≥60 years of age	Study initiation: 17 Nov 2021 Study completion: 28 Jul 2025 Final study report: Jul 2026
mRNA-1345-P302 *US*	A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥50 Years of Age *Ongoing*	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of mRNA-1345 coadministered with a seasonal influenza vaccine (Afluria® Quadrivalent). • To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A. • To evaluate the impact of coadministered RSV vaccine on the immune response to influenza. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345 coadministered with mRNA-1273.214. • To evaluate the effect of coadministered	Phase 3 randomised, observer-blind study	Adults ≥50 years of age	Study initiation: Part A: 01 Apr 2022 Part B: 27 Jul 2022 Part C: 25 Aug 2023 Study completion: 08 Nov 2024 Final study report: Mar 2026

Study Number *Country(ies)*	**Study Title** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		mRNA-1273.214 on the immune response to RSV-A. • To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2. **Primary Objectives (Part C):** • To evaluate the safety and tolerability of a BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate the immune response to RSV-A of a BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 Year following a primary dose.			
mRNA-1345-P303 *US (including Puerto Rico), Canada, UK*	A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults *Ongoing*	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the immune response to RSV-A and RSV-B nAbs after a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to <60 years) compared with a single dose of 50 µg mRNA-1345 injection in the pivotal Phase 2/3 efficacy trial (mRNA-1345-P301). **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the RSV-A and RSV-B nAb GMTs after 2 doses of 50 µg mRNA-1345 injection administered 56 days apart in participants ≥18 years of age who received SOT.	Phase 3 immunogenicity and safety study	Part A: High-risk adults (≥18 to <60 years) Part B: Immunocompromised participants ≥18 years of age	Study initiation: 06 Oct 2023 Study completion: 31 Mar 2026 Final study report: Feb 2027
mRNA-1345-P902 *US*	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in the United States	**Primary Objectives:** 1) Describe the utilization of the mRNA-1345 vaccine and mRNA-1345 vaccine recipients' characteristics, and estimate incidence rates of safety topics of interest among mRNA-1345 vaccine recipients using large-scale	Active surveillance real-world safety study using secondary data	Vaccinated adults, immunocompromised patients, patients with autoimmune or inflammatory disorders	Protocol completion: Aug 2024 Final report: Dec 2027 [a]

Study Number *Country(ies)*	**Study Title** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
	Ongoing	administrative claims data in the US. 2) Assess the risk of safety topics of interest using large-scale administrative claims data in the US, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA-1345 vaccine, using a comparative cohort design. **Secondary Objectives:** 1) Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were co-administered with other non-RSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2) Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion of the Sponsor or request of regulatory agencies.			
mRNA-1345-P903 *Europe*	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe *Ongoing*	**Primary Objectives:** 1) Monitor when and where the mRNA-1345 vaccine is distributed in Europe. 2) Describe utilization of the mRNA-1345 vaccine and vaccine recipients' characteristics, and estimate the incidence rates of safety topics of interest among	Active surveillance real-world safety study using secondary data	Vaccinated adults, immunocompromised patients, patients with autoimmune or inflammatory disorders	Protocol completion: Nov 2024 Final report: Dec 2028 [a]

Study Number *Country(ies)*	**Study Title** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		mRNA-1345 vaccine recipients in Europe. 3) Assess the risk of safety topics of interest in Europe, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA-1345 vaccine, using a comparative cohort design, when thresholds for sample size requirements are met or deemed necessary by the MAH or regulatory agencies. **Secondary Objectives:** 1) Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were co-administered with other non-RSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2) Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion of the MAH or request of regulatory agencies.			
mRNA-1345-P201 Multiple countries	A Phase 2, randomized, observer-blind, placebo-controlled, dose-escalation study to evaluate the reactogenicity, safety, and immunogenicity of mRNA-1345, an mRNA vaccine	**Primary objectives:** Maternal participants: • To evaluate the reactogenicity and safety of mRNA-1345 administered during pregnancy. Infant participants: • To evaluate the safety profile in infants born to women	Phase 2, randomised, observer-blind, placebo-controlled, dose-escalation study	Vaccinated adults ≥18 years to <40 years who become pregnant and infants born to women vaccinated with mRNA-1345 during pregnancy	Study initiation: Nov 2023 End of enrolment: 24 Feb 2025

Study Number *Country(ies)*	Study Title *Study Status*	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
	targeting respiratory syncytial virus, in pregnant women, and safety, and immunogenicity in infants born to vaccinated mothers Ongoing	vaccinated with mRNA-1345 during pregnancy. **Secondary objectives:** Maternal participants: • To evaluate the immunogenicity of a single injection of mRNA-1345 in pregnant women. Infant participants: • To evaluate RSV antibody levels in infants born to women who receive a single mRNA-1345 injection during pregnancy.			Study completion: 31 Dec 2026 Final study report: Jun 2027

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

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 47: Ongoing and Planned Additional Pharmacovigilance Activities

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
mRNA-1345-P301 A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥60 Years of Age Ongoing	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of the mRNA-1345 vaccine. • To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of a BD of mRNA-1345 administered 24 months after the primary dose. • To demonstrate noninferiority of the serum RSV-A nAb response of a BD	• Myocarditis/ pericarditis • Long-term safety	Study initiation: Study completion: Final study report:	17 Nov 2021 28 Jul 2025 Jul 2026

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	of mRNA-1345 compared with a primary dose. • To demonstrate noninferiority of the serum RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose.			
mRNA-1345-P302 A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥50 Years of Age Ongoing	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of mRNA-1345 coadministered with a seasonal influenza vaccine (Afluria® Quadrivalent). • To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A. • To evaluate the impact of coadministered RSV vaccine on the immune response to influenza. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345 coadministered with mRNA-1273.214. • To evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-A. • To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2. **Primary Objectives (Part C):** • To evaluate the safety and tolerability of a BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate the immune response to RSV-A of a BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 Year following a primary dose.	• Myocarditis/ pericarditis • Long term safety	Study initiation: Study completion: Final study report:	Part A: 01 Apr 2022 Part B: 27 Jul 2022 Part C: 25 Aug 2023 08 Nov 2024 Mar 2026
mRNA-1345-P303 A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults Ongoing	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the immune response to RSV-A and RSV-B nAbs after a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to <60 years) compared with a single dose of 50 µg mRNA-1345 injection in the pivotal Phase 2/3 efficacy trial (mRNA-1345-P301). **Primary Objectives (Part B):** • To evaluate the safety and tolerability of mRNA-1345.	• Myocarditis/ pericarditis • Use in immunocompromised individuals • Long term safety	Study initiation: Study completion: Final study report:	06 Oct 2023 31 Mar 2026 Feb 2027

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	• To evaluate the RSV-A and RSV-B nAb GMTs after 2 doses of 50 µg mRNA-1345 injection administered 56 days apart in participants ≥18 years of age who received SOT.			
mRNA-1345-P902 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in the United States Ongoing	**Primary Objectives:** 1) Describe the utilization of the mRNA-1345 vaccine and mRNA-1345 vaccine recipients' characteristics, and estimate incidence rates of safety topics of interest among mRNA-1345 vaccine recipients using large-scale administrative claims data in the US. 2) Assess the risk of safety topics of interest using large-scale administrative claims data in the US, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA-1345 vaccine, using a comparative cohort design. **Secondary Objectives:** 1) Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were co-administered with other non-RSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2) Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion of the Sponsor or request of regulatory agencies.	• Myocarditis/ pericarditis • Use in immunocompromised individuals • Use in individuals with autoimmune or inflammatory disorders • Long-term safety	Protocol completion: Final report:	Aug 2024 Dec 2027 [a]
mRNA-1345-P903 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World	**Primary Objectives:** 1) Monitor when and where the mRNA-1345 vaccine is distributed in Europe. 2) Describe utilization of the mRNA-1345 vaccine and vaccine recipients' characteristics, and estimate the incidence rates of safety topics of	• Myocarditis/ pericarditis • Use in immunocompromised individuals • Use in individuals with autoimmune or	Protocol completion: Final report:	Nov 2024 Dec 2028 [a]

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe Ongoing	interest among mRNA-1345 vaccine recipients in Europe. 3) Assess the risk of safety topics of interest in Europe, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA-1345 vaccine, using a comparative cohort design, when thresholds for sample size requirements are met or deemed necessary by the MAH or regulatory agencies. **Secondary Objectives:** 1) Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were co-administered with other non-RSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2) Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion of the MAH or request of regulatory agencies.	inflammatory disorders • Long-term safety		
mRNA-1345-P201 A Phase 2, randomized, observer-blind, placebo-controlled, dose-escalation study to evaluate the reactogenicity, safety, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in pregnant women, and safety, and immunogenicity in	**Primary objectives:** <u>Maternal participants:</u> • To evaluate the reactogenicity and safety of mRNA-1345 administered during pregnancy. <u>Infant participants:</u> • To evaluate the safety profile in infants born to women vaccinated with mRNA-1345 during pregnancy. **Secondary objectives:** <u>Maternal participants:</u> • To evaluate the immunogenicity of a single injection of mRNA-1345 in pregnant women. <u>Infant participants:</u>	• Use in pregnancy	Study initiation: End of enrolment: Study completion: Final study report:	Nov 2023 24 Feb 2025 31 Dec 2026 Jun 2027

Study Number, Title, and Categories (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
infants born to vaccinated mothers Ongoing	• To evaluate RSV antibody levels in infants born to women who receive a single mRNA-1345 injection during pregnancy.			

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

Part IV: Plans for Post-Authorisation Efficacy Studies

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

V.1. Routine Risk Minimisation Measures

Table 48: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Myocarditis/pericarditis	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None
Use in immunocompromised individuals	Routine risk communication: • Information that safety and immunogenicity data on mRESVIA are not available for immunocompromised individuals. Individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine (SmPC Section 4.4 Special warnings and precautions for use) Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning for the individual to talk to their doctor, pharmacist or nurse before they are given mRESVIA if they have a weakened immune system which may prevent them from getting the full benefit from mRESVIA (PL Section 2 What you need to know before you take mRESVIA) Other routine risk minimisation measures beyond the Product Information: • None
Use in individuals with autoimmune or inflammatory disorders	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None
Long-term safety	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • None
Use in pregnancy	Routine risk communication: • Information that there are no or limited amount of data from the use of mRESVIA in pregnant women and that animal studies do not indicate direct or indirect

Safety Concern	Routine Risk Minimisation Activities
	harmful effects with respect to pregnancy (SmPC Section 4.6 Fertility, pregnancy and lactation) • Information that there were no vaccine-related adverse effects on female fertility, pregnancy, embryo-foetal or offspring development or postnatal development found in a combined developmental and reproductive toxicity study (SmPC Section 5.3 Preclinical safety data) Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that as a precautionary measure, it is preferable to avoid the use of mRESVIA during pregnancy (SmPC Section 4.6 Fertility, pregnancy and lactation) • Guidance for the individual to ask their doctor or pharmacist for advice before they are given this vaccine if they are pregnant, think they may be pregnant or are planning to have a baby (PL Section 2 What you need to know before you take mRESVIA) • Guidance that mRESVIA should not be used in women who are pregnant (PL Section 2 What you need to know before you take mRESVIA) Other routine risk minimisation measures beyond the Product Information: • None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of mRESVIA.

V.3. Summary of Risk Minimisation Measures

Table 49: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis/ pericarditis	Routine risk minimisation measures: • *None* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Targeted follow-up questionnaire for myocarditis/pericarditis* Additional pharmacovigilance activities: • *mRNA-1345-P301* • *mRNA-1345-P302* • *mRNA-1345-P303* • *mRNA-1345-P902* • *mRNA-1345-P903*
Use in immunocompromised	Routine risk minimisation measures: • *Information that safety and immunogenicity data on*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
individuals	*mRESVIA are not available for immunocompromised individuals, and that individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine in SmPC Section 4.4* • *Warning for the individual to talk to their doctor, pharmacist or nurse before they are given mRESVIA if they have a weakened immune system which may prevent them from getting the full benefit from mRESVIA in PL Section 2* Additional risk minimisation measures: • *None*	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-P301* • *mRNA-1345-P302* • *mRNA-1345-P303* • *mRNA-1345-P902* • *mRNA-1345-P903*
Use in pregnancy	Routine risk minimisation measures: • *Information that there are no or limited amount of data in pregnant women and that animal studies do not indicate direct or indirect harmful effects with respect to pregnancy in SmPC Section 4.6 and Section 5.3* • *Guidance that as a precautionary measure, it is preferable to avoid the use of mRESVIA during pregnancy in SmPC Section 4.6* • *Guidance that mRESVIA should not be used in*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *mRNA-1345-P201*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	women who are pregnant in PL Section 2 • *Guidance for the individual to ask their doctor or pharmacist for advice before they are given this vaccine if they are pregnant, think they may be pregnant or are planning to have a baby in PL Section 2* Additional risk minimisation measures: • *None*	

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for mRESVIA (single-stranded 5' capped mRNA encoding the RSV-A glycoprotein F stabilised in the prefusion conformation)

This is a summary of the risk management plan (RMP) for mRESVIA. The RMP details important risks of mRESVIA, how these risks can be minimised, and how more information will be obtained about RESVIA's risks and uncertainties (missing information).

mRESVIA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how mRESVIA should be used.

This summary of the RMP for mRESVIA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of mRESVIA's RMP.

I. The Medicine and What it is Used for

mRESVIA is authorised for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in adults 18 years of age and older (see SmPC for the full indication). The active substance in mRESVIA is a single-stranded 5' capped mRNA encoding the RSV-A glycoprotein F stabilised in the prefusion conformation and it is given by intramuscular route.

Further information about the evaluation of mRESVIA's benefits can be found in mRESVIA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/mresvia.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise These Risks

Important risks of mRESVIA, together with measures to minimise such risks and the proposed studies for learning more about mRESVIA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - so that

immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of mRESVIA is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of mRESVIA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of mRESVIA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 50: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important Identified Risks	None
Important Potential Risks	Myocarditis/pericarditis
Missing Information	Use in immunocompromised individuals Use in individuals with autoimmune or inflammatory disorders Long-term safety Use in pregnancy

II.B Summary of Important Risks

Table 51: Important Potential Risk: Myocarditis/pericarditis

Important Potential Risk: Myocarditis/pericarditis	
Evidence for linking the risk to the medicine	Myocarditis/pericarditis can be caused by a variety of factors; the most common aetiology is viral infection. In Study mRNA-1345-P301, there were no CEAC adjudicated cases of acute myocarditis up to the data cutoff (30 Apr 2023) and no CEAC adjudicated cases of acute pericarditis up to 42 days after study injection in either the mRESVIA or placebo groups. While two participants in the mRESVIA group had CEAC adjudicated events of acute pericarditis with onset >42 days, they were assessed by the investigator as unrelated to study vaccine as other confounding factors provide an alternative causal association. No cases of acute pericarditis were reported in the placebo group up to data cutoff. In Study mRNA-1345-P303 Part A, no events of myocarditis or pericarditis were reported in participants ≥18 to ≤59 years of age vaccinated with mRNA-1345 30 µg or 50 µg up to the data cutoff (18 Sep 2024) (Study mRNA-1345-P303 CSR Section 7.5.1.2). Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur post-authorisation.
Risk factors and risk groups	Acute myocarditis is overall more common in men than in women overall (Kytö et al 2013). The incidence rate occurs with two peaks: the highest in those under one year old with both genders combined (Vasudeva et al 2021) and young males aged 16 to <40 years old (Vasudeva et al 2021; Kytö et al 2013). Similarly, acute pericarditis is more common in men than in women overall. However, the gender difference is reduced with advancing age and became nominal in persons aged >65 years (Kytö et al 2014). In males, the incidence rate of acute pericarditis declines between 16 to 45 years followed by an

Important Potential Risk: Myocarditis/pericarditis	
	increase in older individuals aged >50 years (Kytö et al 2014). In females, the incidence rate of acute pericarditis gradually increases with age, with a peak in the population aged 65 to 74 years (Kytö et al 2014; Kumar et al 2016).
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1345-P301 mRNA-1345-P302 mRNA-1345-P303 mRNA-1345-P902 mRNA-1345-P903 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 52: Missing Information: Use in Immunocompromised Individuals

Missing Information: Use in immunocompromised individuals	
Risk minimisation measures	Routine risk minimisation measures: Information that safety and immunogenicity data on mRESVIA are not available for immunocompromised individuals, and that individuals receiving immunosuppressant therapy or patients with immunodeficiency may have a diminished immune response to this vaccine in SmPC Section 4.4 Warning for the individual to talk to their doctor, pharmacist or nurse before they are given mRESVIA if they have a weakened immune system which may prevent them from getting the full benefit from mRESVIA in PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1345-P303 mRNA-1345-P902 mRNA-1345-P903 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 53: Missing Information: Use in Individuals with Autoimmune or Inflammatory Disorders

Missing Information: Use in individuals with autoimmune or inflammatory disorders	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1345-P902 mRNA-1345-P903 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 54: Missing Information: Long-Term Safety

Missing Information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1345-P301 mRNA-1345-P302 mRNA-1345-P303 mRNA-1345-P902 mRNA-1345-P903 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 55: Missing Information: Use in Pregnancy

Missing Information: Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: Information that there are no or limited amount of data in pregnant women and that animal studies do not indicate direct or indirect harmful effects with respect to pregnancy in SmPC Section 4.6 and Section 5.3 Guidance that as a precautionary measure, it is preferable to avoid the use of mRESVIA during pregnancy in SmPC Section 4.6 Guidance that mRESVIA should not be used in women who are pregnant in PL Section 2 Guidance for the individual to ask their doctor or pharmacist for advice before they are given this vaccine if they are pregnant, think they may be pregnant or are planning to have a baby in PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: mRNA-1345-P201 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tradename.

II.C.2 Other Studies in Post-Authorisation Development Plan

The following studies are considered ongoing and/or planned additional pharmacovigilance activities:

Table 56: Other Studies in the Post-Authorisation Development Plan

Study Title and Number	Purpose of the Study
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 (mRNA-1345-P301)	**Primary Objectives (Part A):** • To evaluate the safety and tolerability of the mRNA-1345 vaccine. • To evaluate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection. **Primary Objectives (Part B):** • To evaluate the safety and tolerability of a BD of mRNA-1345 administered 24 months after the primary dose. • To demonstrate noninferiority of the serum RSV-A nAb response of a BD of mRNA-1345 compared with a primary dose. • To demonstrate noninferiority of the serum RSV-B nAb response of a BD of mRNA-1345 compared with a primary dose.
A Phase 3 Randomized, Observer-Blind, Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥50 Years of Age (mRNA-1345-P302)	**Primary Objectives Part A:** • To evaluate the safety and tolerability of mRNA-1345 coadministered with a seasonal influenza vaccine (Afluria® Quadrivalent). • To evaluate the impact of coadministered influenza vaccine on the immune response to RSV-A. • To evaluate the impact of coadministered RSV vaccine on the immune response to influenza. **Primary Objectives Part B:** • To evaluate the safety and tolerability of mRNA-1345 coadministered with mRNA-1273.214. • To evaluate the effect of coadministered mRNA-1273.214 on the immune response to RSV-A. • To evaluate the effect of coadministered RSV vaccine on the immune response to SARS-CoV-2. **Primary Objectives Part C:** • To evaluate the safety and tolerability of a BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate immune response to RSV-A of a BD of mRNA-1345 administered at 1 Year following a primary dose. • To evaluate the immune response to RSV-B of a BD of mRNA-1345 administered at 1 Year following a primary dose.
A Phase 3 Study to Evaluate the Immunogenicity and Safety of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in High-risk Adults (mRNA-1345-P303)	**Primary Objectives Part A:** • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the immune response to RSV-A and RSV-B nAbs after a single dose of 50 µg mRNA-1345 injection in high-risk adults (≥18 to <60 years) compared with a single dose of 50 µg mRNA-1345 injection in the pivotal Phase 2/3 efficacy trial (mRNA-1345-P301). **Primary Objectives Part B:** • To evaluate the safety and tolerability of mRNA-1345. • To evaluate the RSV-A and RSV B nAb GMTs after 2 doses of 50 µg mRNA-1345 injection administered 56 days apart in participants ≥18 years of age who received SOT.
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial	**Primary Objectives:** 1) Describe the utilization of the mRNA-1345 vaccine and mRNA-1345 vaccine recipients' characteristics, and estimate incidence rates of safety topics of interest among mRNA-1345 vaccine recipients using large-scale administrative claims data in the US.

Study Title and Number	Purpose of the Study
virus (RSV) in the United States (mRNA-1345-P902)	2) Assess the risk of safety topics of interest using large-scale administrative claims data in the US, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA-1345 vaccine, using a comparative cohort design. **Secondary Objectives:** 1) Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were co-administered with other non-RSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2) Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion of the Sponsor or request of regulatory agencies.
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe (mRNA-1345-P903)	**Primary Objectives:** 1) Monitor when and where the mRNA-1345 vaccine is distributed in Europe. 2) Describe utilization of the mRNA-1345 vaccine and vaccine recipients' characteristics, and estimate the incidence rates of safety topics of interest among mRNA-1345 vaccine recipients in Europe. 3) Assess the risk of safety topics of interest in Europe, comparing the risk among mRNA-1345 vaccine recipients with that from persons who have not received the mRNA-1345 vaccine, using a comparative cohort design, when thresholds for sample size requirements are met or deemed necessary by the MAH or regulatory agencies. **Secondary Objectives:** 1) Assess the risk of safety topics of interest among the following subgroups, when deemed feasible based on power and sample size calculation: • Age groups (eg, 60 to 64, 65 to 69, 70 to 74, and ≥75 years, as feasible) • Sex (Male, Female) • Individuals who were coadministered with other non-RSV vaccines, such as influenza, COVID-19, herpes zoster, pneumococcal • Immunocompromised patients • Patients with autoimmune/inflammatory disorders 2) Assess the risk of safety topics of interest using a self-control risk interval design if necessary analytic conditions are met, or at the discretion of the MAH or request of regulatory agencies.
A Phase 2, randomized, observer-blind, placebo-controlled, dose-escalation study to evaluate the reactogenicity, safety, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in pregnant women, and safety, and immunogenicity in infants born to vaccinated mothers (mRNA-1345-P201)	**Primary objectives:** Maternal participants: • To evaluate the reactogenicity and safety of mRNA-1345 administered during pregnancy. Infant participants: • To evaluate the safety profile in infants born to women vaccinated with mRNA-1345 during pregnancy. **Secondary objectives:** Maternal participants: • To evaluate the immunogenicity of a single injection of mRNA-1345 in pregnant women. Infant participants: • To evaluate RSV antibody levels in infants born to women who receive a single mRNA-1345 injection during pregnancy.

Part VII: Annexes

Table of Contents (Annexes)

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms

Follow-Up Forms

Myocarditis/pericarditis follow-up questionnaire

MCN:

Follow-up Questionnaire for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna's Product (mRNA-XXXX)

Privacy notice: ModernaTX (325 Binney Street, Cambridge, MA 02142, USA) and its worldwide affiliates as co-controllers process your personal data for the purposes of monitoring the safety of medicinal products, which includes detecting, assessing and preventing adverse events and reporting to health authorities, and to manage your contact details as the person who reported the adverse health event or as the health professional who may be contacted to obtain, in compliance with applicable laws, details of the reported adverse health event. To know more about our pharmacovigilance processing, please consult our privacy statement https://report.moderna.convergehealthsafety.com/legal-notice. If you would like to receive further information regarding our use of your Personal Data, or if you would like to exercise your rights such as your right to access, correct, or restrict processing of your personal data, please contact the privacy office at privacy@modernatx.com. When processing of personal data occurs because of an adverse event, this processing is based on a legal obligation, and the rights to object, to erase data, or data portability are not available.

Please only provide information that has not been previously reported. When providing date(s), please use the format DD/MMM/YYYY and be as accurate as possible. You may attach additional pages as needed.

INFORMATION ABOUT PERSON COMPLETING THIS FORM	**INFORMATION ABOUT FACILITY WHERE PRODUCT WAS GIVEN**
Form Completed By (Name): _____ **Country**: _____ **Address**: _____ **City**: _____ **State/Province**: ____ **Postal Code**: _____ **Phone**: _____ **Email**: _____ **Relationship to Patient:** ☐ Self ☐ Physician ☐ Nurse ☐ Pharmacist ☐ Other: _____	**Type of Facility:** ☐ Doctor's office or urgent care ☐ Hospital ☐ Public health clinic ☐ Nursing home ☐ Senior living facility ☐ Pharmacy ☐ Workplace clinic ☐ School or student health clinic ☐ Military clinic ☐ Unknown ☐ Other:_____ **Facility/Clinic Name**: _____ **Country**: _____ **Address**: _____ **City**: _____ **State/Province**: _____ **Postal Code**: _____ **Phone**: _____ **Fax**: _____

If you consent to Moderna contacting the patient's doctor/healthcare provider, please provide their contact information:
Name: _____ **Phone:** _____ **Fax:** _____ **Email:** _____

PATIENT INFORMATION

Initials: _____ **Sex at Birth:** ☐ Male ☐ Female **Height:** _____ ☐ in. ☐ cm. **Weight:** _____ ☐ lb. ☐ kg.

If female, pregnant? ☐ Yes (Due Date: ___ /___ /___) ☐ No	*Do not complete if prohibited by local laws (e.g. if you reside in Europe).* **Race** (check all that apply): ☐ White ☐ Black ☐ Aborigine ☐ Asian ☐ Australian ☐ African American ☐ American Indian/Alaska Native ☐ Native Hawaiian/Other Pac Islander ☐ Unknown ☐ Other: _____
Age (in years) at Vaccination or **Date of Birth:** _____ **Age Group at Time of Vaccination (if age/DOB unknown):** ☐ Neonate (birth to 2 months) ☐ Infant (3 months to 2 years) ☐ Child (2 to 11 years) ☐ Adolescent (12 to 17 years) ☐ Adult (18 to 64 years) ☐ Elderly (≥ 65 years)	*Do not complete if prohibited by local laws (e.g. if you reside in Europe).* **Ethnicity:** ☐ Hispanic or Latino ☐ Not Hispanic or Latino

Allergies to medications, food, and other products: ☐ Yes (please describe) ☐ None ☐ Unknown

MODERNA VACCINE / OTHER SUSPECT PRODUCT INFORMATION

Product Name: _____

Date Administered: _____ / _____ / _____ **Lot/Batch #:** _____ **Route/Site of Administration:** _____

Product Name: _____

Date Administered: _____ / _____ / _____ **Lot/Batch #:** _____ **Route/Site of Administration:** _____

MYOCARDITIS / PERICARDITIS ADVERSE EVENT INFORMATION

Adverse Event: _____ **Start Date and Time:** ___ /___ /___ and ___ : ___ am / pm

Did the event cause the patient to seek medical care? ☐ Yes (if yes, please select below) ☐ No ☐ Unknown

☐ Doctor's office / urgent care / emergency department visit ☐ Hospital admission: ____ /____ /____ to ____ /____ /____

Event outcome: ☐ Resolved (Date resolved: ____ /____ /____) ☐ Ongoing/Not resolved ☐ Unknown

☐ Resolved with residual effects (Date resolved: ____ /____ /____ Residual effects: _____)

☐ Death (Date of death: ____ /____ /____ Cause of death: _____ Autopsy done: ☐ Yes ☐ No ☐ Unknown)

Were there any other factors that could have led to the adverse event? ☐ Yes (please describe) ☐ No ☐ Unknown

Has the patient experienced a similar event in the past? ☐ Yes (please describe) ☐ No ☐ Unknown

Has the patient experienced any of the following symptoms associated with the myocarditis / pericarditis event?

☐ New onset chest pain/pressure ☐ Cough ☐ Abnormal tiredness ☐ Abdominal pain ☐ Shortness of breath ☐ Weakness
☐ Swelling in feet/ankles ☐ Dizziness/fainting ☐ Sudden excessive sweating ☐ Nausea ☐ Vomiting ☐ Diarrhea
☐ Shoulder pain ☐ Upper back pain ☐ Palpitations/irregular heartbeats

PATIENT MEDICAL HISTORY

Condition	Start Date	Stop Date
	_____/_____/_____	_____/_____/_____ ☐ Ongoing
	_____/_____/_____	_____/_____/_____ ☐ Ongoing
	_____/_____/_____	_____/_____/_____ ☐ Ongoing
	_____/_____/_____	_____/_____/_____ ☐ Ongoing

Has the patient specifically experienced any of the following conditions in the past 6 months?

☐ Bacterial infection ☐ Viral infection ☐ Fungal infection ☐ Tick-borne disease ☐ Autoimmune disorder ☐ HIV
☐ Use of immunosuppressant medications ☐ Cancer ☐ Radiation ☐ Chemotherapy treatment

Condition	Start Date	Stop Date	Treatment Details (medications, surgeries, other procedures, etc., as applicable)
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	

CARDIOVASCULAR HISTORY

Has the patient experienced any other heart or vascular conditions in the past (e.g., myocarditis, pericarditis, hypertension, thrombosis,

cardiac arrythmia, myocardial infarction, coronary artery disease, etc.)? ☐ Yes (please provide details below) ☐ No ☐ Unknown

Condition	Start Date	Stop Date	Treatment Details (medications, surgeries, other procedures, etc., as applicable)
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	
	_____/_____/_____	_____/_____/_____ ☐ Ongoing	

OTHER VACCINES RECEIVED ON THE SAME DAY AS OR WITHIN ONE MONTH PRIOR TO ANY DOSE OF MODERNA VACCINE

Vaccine Type	Manufacturer	Lot Number	Route	Body Site	Date Received
					_____/_____/_____
					_____/_____/_____
					_____/_____/_____

CONCOMITANT MEDICATIONS

Please list any prescriptions, over-the-counter medications, dietary supplements, or herbal remedies being taken at the time the patient received the Moderna product and/or at the time of the adverse event.

Product Name	Dosage/Frequency	Route	Indication for Use	Start Date	Stop Date
				_____/_____/_____	____/____/____ ☐ Ongoing
				_____/_____/_____	____/____/____ ☐ Ongoing
				_____/_____/_____	____/____/____ ☐ Ongoing
				_____/_____/_____	____/____/____ ☐ Ongoing
				_____/_____/_____	____/____/____ ☐ Ongoing

LABORATORY RESULTS

Please provide the results for the following laboratory tests, if available.

Test	Date	Result (with units)	Normal Range
Troponin T	_____/_____/_____		
Troponin I	_____/_____/_____		
CK-MB	_____/_____/_____		
C-reactive protein (CRP)	_____/_____/_____		
D-dimer	_____/_____/_____		
Erythrocyte sedimentation rate (sed rate, ESR, Westergren sed rate)	_____/_____/_____		

DIAGNOSTIC EXAMINATIONS

Please provide the results of the following diagnostic examinations, if available.

Exam	Date	Interpretation/Results

Physical Exam	_____ /_____ /_____	
Chest x-ray	_____ /_____ /_____	
Electrocardiogram (EKG)	_____ /_____ /_____	
Echocardiogram	_____ /_____ /_____	
Magnetic Resonance Imaging/Cardiac MRI	_____ /_____ /_____	
Computed Tomography/CT scan	_____ /_____ /_____	
Pericardial/ Endomyocardial biopsy	_____ /_____ /_____	

TREATMENT

Please provide details of any treatment for the potential/confirmed myocarditis/pericarditis event.

Treatment	**Dose/Frequency**	**Route**	**Start Date**	**Stop Date**
			_____ /_____ /_____	_____ /_____ /_____ ☐ Ongoing
			_____ /_____ /_____	_____ /_____ /_____ ☐ Ongoing
			_____ /_____ /_____	_____ /_____ /_____ ☐ Ongoing

Describe provide any additional relevant information (use additional pages or attach records, if necessary).

Signature of Person Completing Form: _____ **Date**: _____ /_____ /_____ ☐ Additional pages attached

Annex 6: Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.

Annex 7: Other Supporting Data (Including Referenced Material)

REFERENCES

Azziz-Baumgartner E, Hirsch A, Yoo YM, Peretz A, Greenberg D, Avni YS, et al. Incidence of laboratory-confirmed influenza and RSV and associated presenteeism and absenteeism among healthcare personnel, Israel, influenza seasons 2016 to 2019. Euro Surveill. 2024 Aug;29(31):2300580.

Baral N, Adhikari P, Adhikari G, Karki S. Influenza myocarditis: a literature review. Cureus. 2020 Dec 10;12(12):e12007.

Belongia EA, King JP, Kieke BA, Pluta J, Al-Hilli A, Meece JK, et al. Clinical features, severity, and incidence of RSV illness during 12 consecutive seasons in a community cohort of adults ≥60 years old. Open Forum Infect Dis. 2018;5(12):ofy316.

Blauwet LA, Cooper LT. Myocarditis. Prog Cardiovasc Dis. 2010;52(4):274-288.

Boattini M, Almeida A, Christaki E, Marques TM, Tosatto V, Bianco G, et al. Severity of RSV infection in Southern European elderly patients during two consecutive winter seasons (2017-2018). J Med Virol. 2021;93(8):5152-7.

Borkotoky S, Dey D, Hazarika Z. Interactions of angiotensin-converting enzyme-2 (ACE2) and SARS-CoV-2 spike receptor-binding domain (RBD): a structural perspective. Mol Biol Rep. 2023;50(3):2713-21.

Branche AR, Saiman L, Walsh EE, Falsey AR, Jia H, Barrett A, et al. Change in functional status associated with respiratory syncytial virus infection in hospitalized older adults. Influenza Other Respir Viruses. 2022b;16(6):1151-60.

Branche AR, Saiman L, Walsh EE, Falsey AR, Sieling WD, Greendyke W, et al. Incidence of respiratory syncytial virus infection among hospitalized adults, 2017-2020. Clin Infect Dis. 2022a;74(6):1004-11.

Britton A, Roper LE, Kotton CN, Hutton DW, Fleming-Dutra KE, Godfrey M, et al. Use of respiratory syncytial virus vaccines in adults aged ≥60 years: updated recommendations of the Advisory Committee on Immunization Practices - United States, 2024. MMWR Morb Mortal Wkly Rep. 2024 Aug 15;73(32):696-702.

Brosh-Nissimov T, Ostrovsky D, Cahan A, Maaravi N, Leshin-Carmel D, Burrack N, et al. Adult respiratory syncytial virus infection: Defining incidence, risk factors for hospitalization, and poor outcomes, a regional cohort study, 2016-2022. Pathogens. 2024 Aug 31;13(9):750.

Casas M, Liang C, Molden T, Bruyndonckx R, Esnaola M, Basu S, et al. Estimated incidence of hospitalisations and deaths attributable to respiratory syncytial virus infections in adults in Norway between 2010 and 2019: A time-series modelling study. J Epidemiol Glob Health. 2025 Aug 14;15(1):107.

CDC 2025a. Respiratory syncytial virus infection (RSV). How RSV spreads. Last reviewed: Jul 08, 2025. Available from: https://www.cdc.gov/rsv/causes/index.html Accessed 07 Nov 2025.

CDC 2025b. Evidence to Recommendations Framework (EtR): RSV vaccination in adults aged 50–59 years. Amadea Britton, MD, Co-Lead Adult RSV Vaccine Work Group Michael Melgar, MD, Co-Lead Adult RSV Vaccine Work Group Diya Surie, MD, Co-Lead Adult RSV Vaccine

Work Group Coronavirus and Other Respiratory Viruses Division (CORVD) Advisory Committee on Immunization Practices (ACIP) April 16, 2025. Available from: https://www.cdc.gov/acip/downloads/slides-2025-04-15-16/06-Melgar-Surie-adult-rsv-508.pdf Accessed 21 Oct 2025.

CDC 2025c. Respiratory syncytial virus infection (RSV). Symptoms and care of RSV. Last reviewed: Jul 08, 2025. Available from: https://www.cdc.gov/rsv/symptoms/index.html Accessed 07 Nov 2025.

CDC RSV-NET: Respiratory Syncytial Virus Hospitalization Surveillance Network, Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/rsv/php/surveillance/rsv-net.html Accessed 21 Oct 2025.

Childs A, Zullo AR, Joyce NR, McConeghy KW, van Aalst R, Moyo P, et al. The burden of respiratory infections among older adults in long-term care: a systematic review. BMC Geriatr. 2019 Aug 5;19(1):210.

Davis W, Duque J, Huang QS, Olson N, Grant CC, Newbern EC, et al. Sensitivity and specificity of surveillance case definitions in detection of influenza and respiratory syncytial virus among hospitalized patients, New Zealand, 2012-2016. J Infect. 2022 Feb;84(2):216-226.

Desmet CJ, Ishii KJ. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. Nat Rev Immunol. 2012;12(7):470-91.

ECDC 2025. Respiratory syncytial virus (RSV). Available from: https://www.ecdc.europa.eu/en/respiratory-syncytial-virus-rsv Accessed 07 Nov 2025.

EMA 2025a. Arexvy. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/arexvy Accessed 23 Oct 2025.

EMA 2025b. Abrysvo. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/abrysvo Accessed 23 Oct 2025.

EMA 2025c. mRESVIA. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/mresvia Accessed 23 Oct 2025.

Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005;352(17):1749-59.

Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. Clin Micro Rev. 2000;13:371-84.

Falsey AR, Walsh EE, House S, Vandenijck Y, Ren X, Keim S, et al. Risk factors and medical resource utilization of respiratory syncytial virus, human metapneumovirus, and influenza-related hospitalizations in adults - a global study during the 2017-2019 epidemic seasons (Hospitalized Acute Respiratory Tract Infection [HARTI] Study). Open Forum Infect Dis. 2021 8(11):ofab491.

FDA 2025a. AREXVY. Available from: https://www.fda.gov/vaccines-blood-biologics/arexvy Accessed 23 Oct 2025.

FDA 2025b. ABRYSO. Available from: https://www.fda.gov/vaccines-blood-biologics/abrysvo Accessed 23 Oct 2025.

FDA 2025c. MRESVIA. Available at: https://www.fda.gov/vaccines-blood-biologics/vaccines/mresvia Accessed 23 Oct 2025.

Fechter P, Brownlee GG. Recognition of mRNA cap structures by viral and cellular proteins. J Gen Virol. 2005;86(5):1239-49.

Foulkes S, Munro K, Sparkes D, Khawam J, Russell S, Dunne A, et al; Respiratory Virus and Microbiome Initiative (RVI) team; Bellis K, Huang YL, Forbes M, Frick-Kretschmer A, Knoll M, Harrison EM; SIREN study group; Brown CS, Atti A, Islam J, Hopkins S, Hall V. Prevalence and impact of SARS-CoV-2, influenza, respiratory syncytial virus (RSV) infection and respiratory illness on UK healthcare workers during winter 2023/24 (September 2023 to March 2024): SIREN cohort study. J Infect. 2025 Oct;91(4):106620.

Frivold C, Cox SN, Starita L, Babu TM, Hoffman KL, Carone M, et al. Correlates of risk of respiratory syncytial virus disease: a prospective cohort study. Nat Commun. 2025 Sep 26;16(1):8490.

GVP Module IX - Signal Management (Rev 1) EMA/827661/2011 Rev 1. 9 October 2017. [Internet] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf Accessed 24 Sep 2024.

Haeberer M, Bruyndonckx R, Polkowska-Kramek A, Torres A, Liang C, Nuttens C, et al. Estimated respiratory syncytial virus-related hospitalizations and deaths among children and adults in Spain, 2016-2019. Infect Dis Ther. 2024 Mar;13(3):463-480.

Haeberer M, López-Ibáñez de Aldecoa A, Seabroke S, Ramirez Agudelo JL, Mora L, Sarabia L, et al. Hospitalization cost estimates of respiratory syncytial virus and influenza infections in adults in Spain, 2016-2019. Vaccine. 2025 Feb 6;46:126683.

Hall CB, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis. 1991;163(4):693-8.

Halsell JS, Riddle JR, Atwood JE, Gardner P, Shope R, Poland GA et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. JAMA. 2003;289(24):3283-3289.

Hansen CL, Chaves SS, Demont C, Viboud C. Mortality associated with influenza and respiratory syncytial virus in the US, 1999-2018. JAMA Netw Open. 2022;5(2):e220527.

Havers FP, Pham H, Patel K, Whitaker M, Reingold A, Meek J, et al. Laboratory-confirmed RSV hospitalization rates among adults in the United States, by race and ethnicity across four seasons – RSV-NET, 2018-2019 through 2021-2022. Presented at RSV'VW in Lisbon, Portugal in February 2023. Available at: https://resvinet.org/conferences-rsvvw23/ Abstract #52.

Havers FP, Whitaker M, Melgar M, Pham H, Chai SJ, Austin E, et al. Burden of respiratory syncytial virus-associated hospitalizations in US adults, October 2016 to September 2023. JAMA Netw Open. 2024 Nov 4;7(11):e2444756.

Hedberg P, Karlsson Valik J, Abdel-Halim L, Alfvén T, Nauclér P. Outcomes of SARS-CoV-2 omicron variant infections compared with seasonal influenza and respiratory syncytial virus infections in adults attending the Emergency Department: a multicenter cohort study. Clin Infect Dis. 2024;78(4):900-7.

Heppe-Montero M, Gil-Prieto R, Del Diego Salas J, Hernández-Barrera V, Gil-de-Miguel Á. Impact of respiratory syncytial virus and influenza virus infection in the adult population in Spain between 2012 and 2020. Int J Environ Res Public Health. 2022 Nov 9;19(22):14680.

Herbert K, Cabling M, Morris S, Olumogba F, Stockwell S, Todsen AL, et al. The burden of respiratory syncytial virus in adults in the UK. Santa Monica, CA: RAND Corporation, 2024. Available from: https://www.rand.org/pubs/research_reports/RRA3133-1.html. Accessed 09 Oct 2025.

Hoit BD. The Merck Manual. Professional edition. Case Western Reserve University. Jun 2022.

Horn EK, La EM, Bektas M, Khan S, Gerber SI. Disparities in respiratory syncytial virus risk factors, diagnosis, and outcomes in adults by race, ethnicity, and other social determinants of health in the United States. Expert Rev Pharmacoecon Outcomes Res. 2025 Apr;25(4):459-471.

Huang M, Bigos D, Levine M. Ventricular arrhythmia associated with respiratory syncytial viral infection. Pediatr Cardiol. 1998 Nov-Dec;19(6):498-500.

Huebbe B, Mocek A, Manz KC, Vivirito A, Bayer LJ, Norris R, et al. Economic burden of respiratory syncytial virus in adults in Germany - a health claims analysis between 2015 and 2018. J Med Econ. 2024 Jan-Dec;27(1):1063-1075.

Inoue N, Nagai H, Fushimi K. Severity and outcomes of adult respiratory syncytial virus inpatient compared with influenza: observational study from Japan. Infect Dis (Lond). 2025 Apr;57(4):366-375.

Jain H, Schweitzer JW, Justice NA. Respiratory Syncytial Virus Infection in Children. [Updated 2023 Jun 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459215/ Accessed 07 Nov 2025.

Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373(5):415-27.

Johannesen CK, Gideonse D, Osei-Yeboah R, Lehtonen T, Jollivet O, Cohen RA, et al; PROMISE investigators. Estimation of respiratory syncytial virus-associated hospital admissions in five European countries: a modelling study. Lancet Reg Health Eur. 2025 Feb 5;51:101227.

Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity. 2005;23(2):165-75.

Katsurada N, Suzuki M, Aoshima M, Yaegashi M, Ishifuji T, Asoh N, et al; Adult Pneumonia Study Group-Japan. The impact of virus infections on pneumonia mortality is complex in adults: a prospective multicentre observational study. BMC Infect Dis. 2017;17(1):755.

Knudsen B, Prasad V. COVID-19 vaccine induced myocarditis in young males: a systematic review. Eur J Clin Invest. 2022 Dec 28:e13947.

Korsten K, Adriaenssens N, Coenen S, Butler C, Ravanfar B, Rutter H, et al; RESCEU investigators. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. Eur Respir J. 2021;57(4):2002688.

Kozak M. Structural features in eukaryotic mRNAs that modulate the initiation of translation. J Biol Chem. 1991;266(30):19867-70.

Kumar N, Pandey A, Jain P, Garg N. Acute pericarditis-associated hospitalization in the USA: a nationwide analysis, 2003-2012. Cardiology. 2016;135(1):27-35.

Kumar R, Dar L, Amarchand R, Saha S, Lafond KE, Purakayastha DR, et al. Incidence, risk factors, and viral etiology of community-acquired acute lower respiratory tract infection among older adults in rural north India. J Glob Health 2021;11:04027.

Kytö V, Sipilä J, Rautava P. Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis. Circulation. 2014 Oct 28;130(18):1601-6.

Kytö V, Sipilä J, Rautava P. The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood. Heart. 2013 Nov;99(22):1681-4.

Lambert L, Sagfors AM, Openshaw PJ, Culley FJ. Immunity to RSV in early-life. Front Immunol. 2014 Sep 29;5:466.

Lee N, Lui GCY, Wong KT, Li TCM, Tse ECM, Chan JYC, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis. 2013;57(8):1069-77.

Li Y, Kulkarni D, Begier E, Wahi-Singh P, Wahi-Singh B, Gessner B, et al. Adjusting for case under-ascertainment in estimating RSV hospitalisation burden of older adults in high-income countries: a systematic review and modelling study. Infect Dis Ther. 2023:1-13.

Ling RR, Ramanathan K, Tan FL, Tai BC, Somani J, Fisher D, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med. 2022 Jul;10(7):679-688.

Loubet P, Lenzi N, Valette M, Foulongne V, Krivine A, Houhou N, et al; FLUVAC Study Group. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. Clin Microbiol Infect. 2017;23(4):253-9.

Lui G, Wong CK, Chan M, Chong KC, Wong R, Chu I, et al. Host inflammatory response is the major marker of severe respiratory syncytial virus infection in older adults. J Infect. 2021;83(6):686-92.

Marijic P, Kliemt R, Krammer M, Kolb N, Last T, Ambrosch A, et al. Costs and complications of respiratory syncytial virus and acute respiratory infections in the adult population: analysis of a German claims database. Pharmacoecon Open. 2025 May;9(3):445-459.

Martinón-Torres F, Gutierrez C, Cáceres A, Weber K, Torres A. How does the burden of respiratory syncytial virus compare to influenza in Spanish adults? Influenza Other Respir Viruses. 2024 Jun;18(6):e13341.

McLaughlin JM, Khan F, Begier E, Swerdlow DL, Jodar L, Falsey AR. Rates of medically attended RSV among US adults: a systematic review and meta-analysis. Open Forum Infect Dis. 2022;9(7):ofac300.

Mitratza M, Elsobky M, Liang C, Bruyndonckx R, Polkowska-Kramek A, Ewnetu WB, et al. Estimated incidence of hospitalizations attributable to RSV infection among adults in Ontario, Canada, between 2013 and 2019. Infect Dis Ther. 2024 Sep;13(9):1949-1962.

Miura H, Hattori F, Uchida H, Hata T, Kudo K, Sato M, Yoshikawa T. Case report of severe myocarditis in an immunocompromised child with respiratory syncytial virus infection. BMC Pediatr. 2018 Feb 12;18(1):51.

Murata Y, Falsey AR. Respiratory syncytial virus infection in adults. Antivir Ther. 2007;12(4 Pt B):659-70.

Nguyen-Van-Tam JS, O'Leary M, Martin ET, Heijnen E, Callendret B, Fleischhackl R, et al. Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries. Eur Respir Rev. 2022; 31(166):220105.

Nuttens C, Moyersoen J, Curcio D, Aponte-Torres Z, Baay M, Vroling H, et al. Differences between RSV-A and RSV-B subgroups and implications for pharmaceutical preventative measures. Infect Dis Ther. 2024;13:1725-1742.

O'Brien S, Ajam S, Han A. Myocarditis in the presence of respiratory syncytial virus (RSV) infection: a case study. Proceedings of IMPRS. 2021 Dec 10;4(1).

Osei-Yeboah R, Amankwah S, Begier E, Adedze M, Nyanzu F, Appiah P, et al. Burden of respiratory syncytial virus (RSV) infection among adults in nursing and care homes: a systematic review. Influenza Other Respir Viruses. 2024 Sep;18(9):e70008.

Osei-Yeboah R, Spreeuwenberg P, Del Riccio M, Fischer TK, Cavling A, Boas H, et al; the RESCEU investigators. Estimation of the number of RSV-associated hospitalisations in adults in the European Union. J Infect Dis. 2023 Nov 28;228(11):1539-1548.

Pannucci P, Jefferson SR, Hampshire J, Cooper SL, Hill SJ, Woolard J. COVID-19-induced myocarditis: pathophysiological roles of ACE2 and toll-like receptors. Int J Mol Sci. 2023;24(6):5374.

Panozzo CA, Walsh EE, Yang Z, Wilson E, Goswami J, Stoszek SK, et al. Leveraging real-world evidence to define severe RSV lower respiratory tract disease in adults. Infect Dis Ther. 2025 Jan;14(1):275-281.

Polkowska-Kramek A, Begier E, Bruyndonckx R, Liang C, Beese C, Brestrich G, et al. Estimated incidence of hospitalizations and deaths attributable to respiratory syncytial virus infections among adults in Germany between 2015 and 2019. Infect Dis Ther. 2024 Apr;13(4):845-860.

Poniedziałek B, Majewska W, Kondratiuk K, Masny A, Poznańska A, Szymański K, et al. Seroprevalence of RSV IgG antibodies across age groups in Poland after the COVID-19 pandemic: data from the 2023/2024 epidemic season. Vaccines. 2025;13(7):741.

Praphasiri P, Shrestha M, Patumanond J, Nakphook S, Chawalchitiporn S, Ditsungnoen D, et al. Underlying cardiopulmonary conditions as a risk factor for influenza and respiratory syncytial virus infection among community-dwelling adults aged ≥65 years in Thailand: findings from a two-year prospective cohort study. Influenza Other Respir Viruses. 2021;15(5):634-40.

Prasad N, Newbern EC, Trenholme AA, Thompson MG, McArthur C, Wong CA, et al. The health and economic burden of respiratory syncytial virus associated hospitalizations in adults. PLoS One. 2020 Jun 11;15(6):e0234235.

Prasad N, Walker TA, Waite B, Wood T, Trenholme AA, Baker MG, et al. Respiratory syncytial virus-associated hospitalizations among adults with chronic medical conditions. Clin Infect Dis. 2021 Jul 1;73(1):e158-e163.

Rozenski J, Crain P, McCloskey J. The RNA modification database: 1999 update. Nucleic Acids Res. 1999;27(1):196-7.

Savic M, Penders Y, Shi T, Branche A, Pirçon JY. Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: a systematic literature review and meta-analysis. Influenza Other Respir Viruses. 2023;17(1):e13031.

Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, et al. Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. J Infect Dis. 2020;222(Suppl 7):S577-83.

Shoji K, Yamada M, Hisano M, Okubo Y, Obikane E, Yamaguchi K. Factors associated with respiratory syncytial virus-neutralizing antibody titers in adults. J Infect Chemother. 2025 Oct;31(10):102801.

Surie D, Yuengling KA, DeCuir J, Zhu Y, Lauring AS, Gaglani M, et al. Severity of respiratory syncytial virus vs COVID-19 and influenza among hospitalized US adults. JAMA Netw Open. 2024;7(4):e244954.

Teodoro LI, Ovsyannikova IG, Grill DE, Poland GA, Kennedy RB. Seroprevalence of RSV antibodies in a contemporary (2022-2023) cohort of adults. Int J Infect Dis. 2025;158:107964.

Tin Tin Htar M, Yerramalla MS, Moïsi JC, Swerdlow DL. The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiol Infect. 2020 Feb 13;148:e48.

Tseng HF, Sy LS, Ackerson B, Solano Z, Slezak J, Luo Y, et al. Severe morbidity and short- and mid- to long-term mortality in older adults hospitalized with respiratory syncytial virus infection. J Infect Dis. 2020 Sep 14;222(8):1298-1310.

Ubamadu E, Betancur E, Gessner BD, Menon S, Vroling H, Curcio D, et al. Respiratory syncytial virus sequelae among adults in high-income countries: a systematic literature review and meta-analysis. Infect Dis Ther. 2024 Jul;13(7):1399-1417.

Urchueguía-Fornes A, Osei-Yeboah R, Jollivet O, Johannesen CK, Lehtonen T, van Boven M, et al; PROMISE investigators. Hospitalisation trends of respiratory syncytial virus (RSV) infection in adults, six European countries, before and during COVID-19, 2016 to 2023. Euro Surveill. 2025 Jun;30(25):2400624.

Vasudeva R, Bhatt P, Lilje C, Desai P, Amponsah J, Umscheid J, et al. Trends in acute myocarditis related pediatric hospitalizations in the United States, 2007-2016. Am J Cardiol. 2021 Jun 15;149:95-102.

Volling C, Hassan K, Mazzulli T, Green K, Al-Den A, Hunter P, et al. Respiratory syncytial virus infection-associated hospitalization in adults: a retrospective cohort study. BMC Infect Dis. 2014;14:665.

Walsh EE, Hall CB. Respiratory syncytial virus (RSV). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015:1948–1960.e3. Available from:

https://www.sciencedirect.com/science/chapter/edited-volume/pii/B9781455748013001600 Accessed 05 Nov 2025.

Weycker D, Averin A, Houde L, Ottino K, Shea K, Sato R, et al. Rates of lower respiratory tract illness in US adults by age and comorbidity profile. Infect Dis Ther. 2024 Jan;13(1):207-220.

World Health Organization (WHO). Annex 1 WHO guidelines on non-clinical evaluation of vaccines. WHO Technical Report Series, No. 927 [Internet]. 2005 Jan 01 [cited 2022 Dec 20]. Available from: https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccinesannex-1-trs-no-927.

Yasuhara J, Masuda K, Aikawa T, Shirasu T, Takagi H, Lee S, et al. Myopericarditis after COVID-19 mRNA vaccination among adolescents and young adults: a systematic review and meta-analysis. JAMA Pediatr. 2023 Jan 1;177(1):42-52.

Yonker LM, Swank Z, Bartsch YC, Burns MD, Kane A, Boribong BP, et al. Circulating spike protein detected in post-COVID-19 mRNA vaccine myocarditis. Circulation. 2023;147(11):867-76.

Yoon JG, Noh JY, Choi WS, Park JJ, Suh YB, Song JY, Cheong HJ, Kim WJ. Clinical characteristics and disease burden of respiratory syncytial virus infection among hospitalized adults. Sci Rep. 2020 Jul 21;10(1):12106.

Zhang T, Reeves RM, Ma S, Miao Y, Sun S, Orrico-Sánchez A, et al; Respiratory Virus Global Epidemiology Network. Estimating the respiratory syncytial virus-associated hospitalisation burden in older adults in European countries: a systematic analysis. BMC Med. 2025 Aug 4;23(1):453.

Zylbersztejn A, Pembrey L, Goldstein H, Berbers G, Schepp R, van der Klis F, et al. Respiratory syncytial virus in young children: community cohort study integrating serological surveys, questionnaire and electronic health records, born in Bradford cohort, England, 2008 to 2013. Euro Surveill. 2021;26(6):2000023.