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Summary Basis for Regulatory Action

Date:	May 31, 2024
From:	Santosh Nanda, DVM, PhD Review Committee Chair Division of Review Management and Regulatory Review Office of Vaccines Research and Review
BLA STN:	125796/0
Applicant:	ModernaTX Inc.
Submission Receipt Date:	September 12, 2023
Action Due Date:	May 12, 2024
Proper Name:	Respiratory Syncytial Virus Vaccine
Proprietary Name:	MRESVIA
Indication:	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older.

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR/DVP) • Facilities (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	 Judy Beeler, OVRR/DVP Roberta Lynne Crim, OVRR/DVP Alena Dabrazhynetskaya, OVRR/DVP Erin Hill, OCBQ/DMPQ Erin Hill, OCBQ/DMPQ M. Nahid Parvin, OCBQ/DBSQC Hsiaoling (Charlene) Wang, OCBQ/DBSQC Emnet Yitbarek, OCBQ/DBSQC Hyesuk Kong, OCBQ/DBSQC
Clinical • Clinical (OVRR/DCTR) • Postmarketing Safety, Pharmacovigilance (OBPV/DE) Benefit / Risk Analysis • BIMO	 Robin Wisch, OVRR/DCTR Adachukwu Ezenekwe, OVRR/DCTR Margarita Maria Gomez Lorenzo, OBPV/DE Malcolm Nasirah, OCBQ/DIS/BMB
Statistical (OBPV/DB) • Clinical Data • Nonclinical Data	 Ross Peterson, OBPV/DB Ho-Hsiang Wu, OBPV/DB
Nonclinical/Pharmacology/Toxicology • Toxicology, Developmental Toxicology (OVRR/DCTR) • Nonclinical Data (OVRR/DVP)	 Nabil Al-Humadi, OVRR/DCTR Judy Beeler, OVRR/DVP
Labeling • Promotional (OCBQ/APLB) • PNR (OCBQ/APLB) • Carton and Container	 Oluchi Elekwachi, OCBQ/DCM/APLB Oluchi Elekwachi, OCBQ/DCM/APLB Daphne Stewart, OVRR/DRMRR Ching Yim-Banzuelo, OVRR/DRMRR
Other Reviews: • Regulatory Project Management • Data Integrity • Devices • Human Factors	 Nikunj Sharma, OVRR/DRMRR Moonsuk Choi, OVRR/DRMRR CAPT Edward Wolfgang, OVRR/DRMRR Brenda Baldwin, OVRR/DRMRR Andrea Gray, ORO/DROP/RPB Avani Bhalodia, CDER/DMEPA

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I

1. Introduction

ModernaTX Inc. (Moderna) submitted a Biologics License Application (BLA) (STN BL 125796/0) for licensure of their respiratory syncytial virus (RSV) vaccine. The proper name of the vaccine is Respiratory Syncytial Virus Vaccine and the proprietary name is MRESVIA. MRESVIA is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older.

MRESVIA contains 50 micrograms (mcg) of nucleoside modified mRNA, encoding the RSV F glycoprotein stabilized in the prefusion conformation (preF protein), that is encapsulated in lipid nanoparticles (LNPs) composed of four lipids: SM-102 [heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate), polyethylene glycol 2000 dimyristoyl glycerol (PEG2000-DMG), cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)]. The mode of action is based on delivery of the mRNA-LNPs into host cells to allow expression of the RSV preF protein. The vaccine elicits an immune response to the preF protein antigen, which protects against LRTD caused by RSV.

MRESVIA is a sterile white to off-white injectable suspension for intramuscular use, supplied in a carton of 1 single dose pre-filled plastic syringe or a carton of 10 single dose pre-filled syringes (PFSs), each syringe containing a single (0.5 mL) dose.

The dating period for Respiratory Syncytial Virus Vaccine shall be 18 months from the date of manufacture when stored at -40°C to -15°C, inclusive of up to 1 month storage at 2°C to 8°C. The date of manufacture shall be defined as the date of labeling and packaging of the PFSs. Following final sterile filtration, no reprocessing/reworking is allowed. The dating period for the drug substances shall be (b) (4) when stored at (b) (4). We have approved the stability protocol in the license application for the purpose of extending the expiration dating period of the drug product.

2. Background

Recent epidemiological data reinforced the evidence of the many faces of RSV infection throughout all age groups, with a disproportionately high impact in elderly individuals. RSV infection has a wide range of clinical presentations, from asymptomatic infections to severe lower respiratory tract infections (LTRIs), including exacerbations of underlying chronic conditions. Those who are hospitalized may require oxygen, intubation, and/or mechanical ventilation.

RSV has a seasonal pattern of infectivity, commonly seen in respiratory viruses, including influenza, with annual recurrence. In temperate climate countries, it spreads throughout the winter season, with a peak between December and January, whereas in tropical countries, it circulates in the summer season. Either a single subgroup or both (A and B) circulate during each season, determining reinfection and seasonal outbreaks. Reinfections are common throughout life due to a short-term, or incomplete, immune response.

RSV is a major cause of morbidity and mortality associated with LRTI in older individuals (ages >60 years) worldwide. Individuals (aged ≥ 65 years) with chronic heart or lung disease, or with weakened immune systems are particularly vulnerable for severe illness and mortality. In the United States, RSV is responsible for roughly 60,000-120,000

hospitalizations and 5,000 to 10,000 deaths among individuals aged ≥65 years. In 2015, an estimated 33.1 million cases of patients with acute LRTI associated with RSV occurred worldwide, a million hospitalizations and up to 199,000 deaths. This level of disease is due in part to the lack of long-term immunity after RSV infection. As a typical seasonal virus, RSV usually peaks in winter and declines by early spring in most temperate countries, with a median duration of 10 to 21 weeks. A systematic analysis of the global burden of disease in individuals found that approximately 500,000 and 250,000 annual deaths were caused by influenza and RSV, respectively. Clinical presentation is similar for influenza, RSV, and hMPV infections, including in those at greatest risk for progression to severe disease (older individuals [≥ 65 years], immunocompromised individuals, and those with underlying comorbidities, including asthma, COPD, cardiovascular disease, and diabetes). Immunosenescence is an aggravating risk factor. RSV infection can also trigger the worsening of some medical conditions that are common in individuals, including asthma, congestive heart failure, and chronic obstructive pulmonary disease.

RSV infection is the third most commonly identified viral cause of hospitalization. RSV disease among individuals 65 years of age and older results in an average of 177,000 hospitalizations in the United States (US) each year; during 1999-2018, the highest mortality was seen in this age group with a mortality rate of 14.7 per 100,000. A recent modeling study projected 3.6 to 4.8 million symptomatic RSV acute respiratory infection cases per year among persons aged ≥60 years, with up to 2.0 million symptomatic cases per year potentially prevented with a hypothetical vaccine (assuming 70% vaccine efficacy and 60% vaccine coverage) and 690 000 cases per year prevented in the nonvaccinated population, based on a 50% vaccine effect on infectiousness. Stabilization of the RSV-F glycoprotein in the prefusion (preF) conformation advanced the development of RSV vaccines, given that the preF conformation is the primary target of potent RSV-neutralizing antibodies and is highly conserved across the two RSV subtypes (A and B). Approval of two RSV vaccines [the RSVpreF3 with AS01E adjuvant (AREXVY from GSK) and bivalent RSVpreF (ABRYSVO from Pfizer) indicated for preventing LRTD caused by RSV in older individuals confirmed the success of a RSVpreF protein-based vaccination strategy in reducing the risk of developing RSV associated LRTD in individuals aged 60 years or older. Several mRNA-based RSV vaccines encoding the stabilized RSV prefusion F glycoprotein have recently been investigated.

Table 1. Regulatory History

Regulatory Events / Milestones	**Date**
1. Pre-IND meeting	January 29, 2020
2. IND submission	July 20, 2020
3. Fast Track designation granted (if applicable)	July 30, 2021

Regulatory Events / Milestones	Date
4. Pre-BLA meeting Clinical and Nonclinical CMC	 March 21, 2023 April 6, 2023
5. BLA 125796/0 submission – Rolling Submission Part 1 (CMC and Nonclinical) Part 2 (Clinical)	 June 29, 2023 September 12, 2023
6. BLA filed	November 9, 2023
7. Mid-Cycle communication	Cancelled by Applicant
8. Major Amendment Letter issued	March 7, 2024
9. Reconsideration -Major Amendment letter issued	April 11, 2024
10. Action Due Date	May 12, 2024

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Description of Active Ingredient

MRESVIA is an mRNA-based vaccine that consists of lipid nanoparticles (LNPs) that encapsulate linear mRNA encoding RSV preF protein provided as a single-dose, preservative-free, white to off-white, liquid suspension in a PFS for intramuscular use. Each 0.5 mL dose of MRESVIA contains 50 mcg of nucleoside modified mRNA encoding the RSV preF protein and the following additional ingredients: a total lipid content of 1.02 mg (SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate), polyethylene glycol 2000 dimyristoyl glycerol [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.25 mg tromethamine, 1.2 mg tromethamine hydrochloride, 0.021 mg acetic acid, 0.10 mg sodium acetate trihydrate, 44 mg sucrose, and water for injection.

Manufacturing Overview

The manufacturing process for the DS consists of (b) (4) main steps: (b) (4) [redacted]. The DP (MRESVIA) is manufactured by adjusting the concentration of the LNP-100-AR02 to the target RNA dose and formulation with a cryoprotectant, followed by sterile filtration, filling into syringes, labeling and packaging.

Drug Substance

Manufacture of RNA-100-AR02 mRNA DS intermediate

(b) (4) [redacted]

3 pages have been determined to be not releasable: (b)(4)

Drug Product (DP)

Drug Product (DP) is a white to off-white suspension of nanoparticles composed of four lipids: SM-102, (a custom, ionizable lipid), cholesterol, DSPC (1,2 distearoyl-sn-glycero-3-phosphocholine) and PEG2000-DMG (1,2-dimyristoyl-rac-glycerol-3-methoxypolyethylene glycerol 2000) that protect and deliver mRNA that encodes for the RSV-F protein stabilized in the prefusion conformation in a 20 mM Tris buffer containing 87 g/L sucrose as a cryoprotectant and (b) (4) acetate buffer at (b) (4). MRESVIA DP is supplied as sterile, single-dose, ready-to-use liquid solution in a 1mL PFS for intramuscular (IM) injection. Each PFS contains approximately (b) (4) to ensure delivery of a 0.5mL dose containing 50 mcg of mRNA with approximately 1 mg of total lipids. DP composition per mL and per unit dose and properties of the PFS are shown in Table 2.

Table 2. MRESVIA DP Composition (50 mcg RNA per Dose)

Component (UNII Code)	Grade	Function	Unit formula mg/mL	Unit Formula mg/dose (0.5mL)
RNA-100-AR02 (2ZKG2M978D)	Custom	Encodes of RSVpreF protein	0.10	0.050
SM-102 (T7OBQ65G2I)	Custom (b) (4)	Component of LNP	(b) (4)	(b) (4)
Cholesterol (97C5T2UQ7J)	(b) (4)	Component of LNP	(b) (4)	(b) (4)
DSPC (043IPI2M0K)	(b) (4)	Component of LNP	(b) (4)	(b) (4)
PEG2000-DMG (9X2596CIE0)	Custom (b) (4)	Component of LNP	(b) (4)	(b) (4)
Tris /Tromethamine (023C2WHX2V)	(b) (4)	Component of Tris buffer	0.50	0.25
Tris HCL (383V75M34E)	(b) (4)	Component of Tris buffer	2.5	1.2

Acetic Acid (Q40Q9N063P)	(b) (4)	Components from acetate buffer in RNA and LNP	0.043	0.021
Sodium acetate (4550K0SC9B)	(b) (4)	Components from acetate buffer in RNA and LNP	0.20	0.10
Sucrose (C151H8M554)	(b) (4)	Cryoprotection	87	44
WFI (059QF0KO0R)	(b) (4)	Diluent	q.s. to 1.0mL	q.s. to 0.5mL

b. Testing Specifications

The tests and specifications applied for routine release of MRESVIA are shown in Table 3.

Table 3. Tests and Specifications Applied for Routine Release of MRESVIA

Quality Attribute	Analytical Procedure	Release Acceptance Criteria	Shelf Life Acceptance Criteria
Appearance	Visual inspection	White to off- white dispersion; may contain visible white or translucent product-related particulates.	Same
Identity	(b) (4)	Matches description	NA
Total RNA content	(b) (4)	(b) (4)	Same
mRNA purity	(b) (4)	(b) (4)	(b) (4)
Product related impurities RNA (b) (4)	(b) (4)	(b) (4)	(b) (4)
Product related impurities (b) (4) (b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) (b) (4)	(b) (4)	(b) (4)	Same
(b) (4)	(b) (4)	(b) (4)	Same
(b) (4)	(b) (4)	(b) (4)	Same

Quality Attribute	Analytical Procedure	Release Acceptance Criteria	Shelf Life Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)	Same
Lipid Identity SM102	(b) (4)	(b) (4)	NA
Lipid Identity Cholesterol	(b) (4)	(b) (4)	NA
Lipid Identity DSPC	(b) (4)	(b) (4)	NA
Lipid Identity PEG2000-DMG	(b) (4)	(b) (4)	NA
Lipid Content SM-102	(b) (4)	(b) (4)	Same
Lipid Content Cholesterol	(b) (4)	(b) (4)	Same
Lipid Content DSPC	(b) (4)	(b) (4)	Same
Lipid Content PEG2000-DMG	(b) (4)	(b) (4)	Same
Lipid related impurities	(b) (4)	RRT Individual impurities (b) (4) Total impurities (b) (4)	Same
(b) (4)	(b) (4)	(b) (4)	Same
Deliverable volume	(b) (4)	≥ 0.5mL; each of 5 PFS	NA
(b) (4)	(b) (4)	(b) (4)	Same
(b) (4)	(b) (4)	(b) (4)	Same
(b) (4)	(b) (4)	(b) (4)	Same
(b) (4)	(b) (4)	(b) (4)	NA
Bacterial endotoxin	(b) (4)	(b) (4)	Same
Sterility	(b) (4)	No growth	Same
Container Closure Integrity Test	In-house test	NA	PASS

Abbreviations: (b) (4) RS, Reference Standard; (b) (4) ; LOQ, limit of quantitation, (b) (4) ; ppm, parts per million; (b) (4) SOP, standard operating procedure; (b) (4)

Assays of "Total RNA Content" ((b) (4) DP), Lipid Nano-Particle (LNP) (b) (4) DP), Appearance ((b) (4) DP), (b) (4) (b) (4) (DP) and Deliverable Volume (DP) are found to be adequate for the intended use.

The bioburden, sterility, and bacterial endotoxin analytical methods and their qualifications reviewed for (b) (4) drug product were found to be adequate for their intended use.

The analytical methods and their validations and/or qualifications for the MRESVIA DS and DP were found to be adequate for their intended use.

c. CBER Lot Release

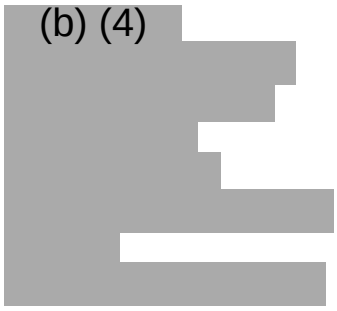
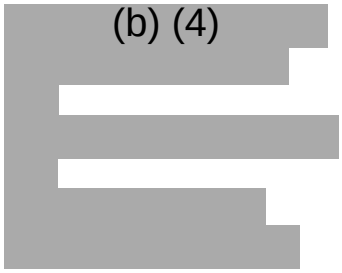
The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of MRESVIA are listed in Table 4 below. The activities performed and inspectional histories are also noted in Table 4 and are further described in the paragraphs that follow.

Table 4. Facilities Involved in the Manufacture of MRESVIA

Manufacturing Facility	FEI Number	DUNS Number	Inspection/ Waiver	Results/ Justification
(b) (4) Manufacture of (b) (4) for mRNA	(b) (4)	(b) (4)	Waiver	(b) (4) PLI CBER/DMPQ NAI
ModernaTX, Inc. (b) (4) Drug Substance DS intermediate manufacturing	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance ORA/OBPO NAI (b) (4) Surveillance ORA/OBPO VAI

Manufacturing Facility	FEI Number	DUNS Number	Inspection/ Waiver	Results/ Justification
(b) (4)  DS intermediate manufacturing DS manufacturing	(b) (4)	(b) (4)	Pre-License Inspection (PLI)	CBER/DMPQ (b) (4) CBER NAI
(b) (4)  Drug Product DP manufacturing, and final release testing	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance ORA/OPQO NAI (b) (4) Surveillance MRA/(b) (4) VAI
(b) (4)  DP primary labeling, packaging, and release testing	(b) (4)	(b) (4)	Waiver	(b) (4) PAI ORA/OPQO VAI

Manufacturing Facility	FEI Number	DUNS Number	Inspection/ Waiver	Results/ Justification
(b) (4) Drug Product DP (b) (4) ; storage	(b) (4)	(b) (4)	Waiver	(b) (4) Records request CBER/DMPQ Acceptable

Acronym key: (b) (4) ; DS – drug substance; DP – drug product; CBER – Center for Biologics Evaluation and Research; DMPQ – Division of Manufacturing and Product Quality; MRA – Mutual Recognition Agreement; OBPO – Office of Biological Products Operations; OPQO – Office of Pharmaceutical Quality Operations; ORA – Office of Regulatory Affairs; NAI – No Action Indicated; PLI – Pre-license Inspection; PAI: Pre-approval Inspection; VAI – Voluntary Action Indicated; (b) (4)

CBER/DMPQ conducted a PLI of (b) (4) contract manufacturing facility in (b) (4) for the Spikevax BLA. No Form FDA 483 was issued, and the inspection was classified NAI.

ORA/OBPO conducted a surveillance inspection of ModernaTX (b) (4) in (b) (4) and no Form FDA 483 was issued and the inspection will be classified as NAI. Previously, ORA/OBPO conducted a surveillance inspection of ModernaTX (b) (4) in (b) (4) . A Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER/DMPQ conducted a PLI of (b) (4) contract manufacturing facility in (b) (4) . No Form FDA 483 was issued, and the inspection was classified NAI.

ORA/OPQO conducted a surveillance inspection of (b) (4) contract manufacturing facility in (b) (4) . No Form FDA 483 was issued, and the inspection was classified NAI. The (b) (4) conducted a surveillance inspection at (b) (4) in (b) (4) . In accordance with the MRA confidentiality commitment between the U.S. FDA and European regulators, ORA assessed the inspection report and determined the inspection was VAI.

ORA/OPQO for CDER conducted a PAI of (b) (4) contract manufacturing facility in (b) (4) . A Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

In lieu of an on-site inspection for the DP contract manufacturing facility, (b) (4) , a review of requested manufacturing site records under Section 704(a)(4) was conducted by CBER/DMPQ in (b) (4) . The records review was found to be acceptable.

e. Container/Closure System

The DP is supplied as a sterile, single-dose, ready-to-use liquid solution at 0.10 mg/mL for intramuscular administration in a 1mL PFS. Each PFS is intended to deliver 50 mcg of RNA in a dose volume of 0.5 mL.

The primary container closure system consists of 1 mL cyclic olefin copolymer (COC) syringe, 1-mL rubber plunger stopper and a polypropylene plunger rod. The DP is manufactured at (b) (4) (formulation, filling), (b) (4), and (b) (4) (thawing) CMOs. The MRESVIA DP PFS primary container closure system (CCS), including syringe, plunger, and plunger rod, is summarized in Table 5.

Table 5. Prefilled Syringe (PFS) Primary Container Closure System (CCS)

Container Closure Component	Manufacturer	Description/Materials of Construction	Standards
Syringe	(b) (4)	1 mL long, halobutyl rubber tip-cap in rigid plastic cover	(b) (4)
Plunger	(b) (4)	1 mL long halobutyl rubber plunger with fluoropolymer coating on product contact surface	(b) (4)
Plunger rod	(b) (4)	1 mL long polypropylene plunger rod (non-product contact)	(b) (4)

Abbreviations: COC: cyclic olefin copolymer; (b) (4)

The sterile filtered solution is filled into ready-to-use syringes (RTU). Pre-sterilized, RTU plungers are placed in the syringes after filling. The PFS then undergo 100% manual or automated visual inspection. The (b) (4) prefilled, inspected syringes undergo an (b) (4) prior to assembly (plunger rod insertion), label, and packaging activities. The (b) (4) step is included to allow flexibility in the scale of label and packaging operations. A (b) (4) is performed, and the (b) (4) syringes are transferred to long-term storage.

Container Closure Integrity Testing (CCIT) was performed using the (b) (4) method with (b) (4), and by (b) (4) analysis. CCIT methods ((b) (4)) were established at temperatures pertinent to MRESVIA DP PFS storage conditions. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The concentration or distribution of MRESVIA RNA and/or the associated lipids, metabolites and degradation products do not significantly

impact the environment. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Non-GLP Repeat Dose Toxicity and Immunogenicity Study
The report from a non-good laboratory practice (GLP) repeat-dose toxicity and immunogenicity study of IM injection of different dose levels of MRESVIA in rats was submitted and reviewed under the BLA. In this study, rats received two tri-weekly IM administrations of 2 IM injections of a single dose level (98 mcg/dose). Antibodies to RSV pre-F protein were demonstrated in sera on Day 23 prior to termination and a dose-dependent neutralizing antibody response was observed. Findings from the IM repeat dose rat toxicity study demonstrated that vaccine dose of up to 98 mcg was well-tolerated.

Developmental Assessment and Reproductive Toxicology (DART) Study
In a developmental toxicity study, 0.2 mL of a vaccine formulation containing 96 mcg of nucleoside-modified mRNA per dose (a full human dose of MRESVIA contains 50 mcg of nucleoside modified mRNA) and other ingredients that are included in a 0.5-mL single human dose of MRESVIA was administered IM to female rats on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related fetal malformations or variations and no adverse effect on postnatal development were observed in the study. Immunoglobulin G (IgG) responses to the pre-fusion stabilized spike protein antigen following immunization were observed in maternal samples and F1 generation rats indicating transfer of antibodies from mother to fetus and from mother to nursing pups.

Other Supportive Toxicology Studies
The safety of MRESVIA is further supported by the aggregate rat repeat-dose toxicity profiles observed in six GLP toxicity studies of five vaccines formulated in SM-102 lipid particles containing mRNAs encoding various viral glycoprotein antigens, demonstrating tolerance of repeat doses of these vaccines without any detrimental effects. Three other toxicology studies were also reviewed in support of safety of MRESVIA. A study report from an (b) (4) assay evaluating the genotoxic potential of (b) (4) mRNA in SM-102 LNP revealed no genotoxic effects of SM-102 LNP. In addition, study reports from a (b) (4) test and an (b) (4) test of PEG2000-DMG were also reviewed. No genotoxic effects of PEG2000-DMG were observed in these studies.

Biodistribution Study
A biodistribution study was not performed with MRESVIA. Results from the biodistribution study of a different vaccine, (b) (4) for an (b) (4), manufactured using the same procedure as MRESVIA and formulated with (b) (4) mcg mRNA in SM-102-containing LNPs, were submitted in support of MRESVIA. Because biodistribution and retention is a property of the LNP rather than the mRNA, results from this study were considered supportive for the approval of MRESVIA BLA.

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral immune responses to MRESVIA, were obtained in the clinical studies. The data demonstrated that MRESVIA induces a humoral immune response against the RSV pre-F protein. The exact immunologic mechanism that confers protection against RSV is unknown.

6. Clinical/Statistical

a. Clinical Program

The Applicant included data from two clinical studies in the BLA. The clinical studies which will be discussed in this SBRA are shown in Table 6.

Table 6. Overview of Clinical Studies in Support of Efficacy and Safety Determinations of MRESVIA

Parameter	mRNA-1345-P301	mRNA-1345-P101
NCT ID	05127434	04528719
Phase	2/3	1
Countries	Argentina, Australia, Bangladesh, Belgium, Canada, Chile, Colombia, Costa Rica, Finland, Germany, Japan, Mexico, New Zealand, Panama, Poland, Singapore, South Africa, South Korea, Spain, Taiwan, the United Kingdom, and the U.S.	United States
Enrollment	N=18,290 n=18,231	N=260 n=47
Age	Individuals ≥60 years with or without underlying medical conditions	Healthy individuals 65 to 79 years; Healthy individuals of Japanese descent ≥60 years
Purpose	Randomized, observer-blind, placebo-controlled, multicenter, case-driven study to evaluate efficacy and safety	Randomized, observer-blind, placebo-controlled, dose-escalation multicenter study to evaluate safety and immunogenicity
Control	Saline Placebo	None
Groups	2 groups, 1:1 to receive 50 mcg IM MRESVIA or Placebo (0.9% normal saline	6 groups, randomized received MRESVIA IM 12.5 µg or 25 µg or 50 µg or 100 µg or 200 µg or placebo (0.9% normal saline)
Total follow-up	Median follow-up for efficacy was 8.6 months and median follow-up for safety was 10.2 months (follow-up ongoing)	5 groups: 14 Months (follow-up ongoing) 1 group: 6 months

Abbreviations: N=number of participants who received at least 1 dose of MRESVIA; n=number of participants who received the final dose level of MRESVIA

For these studies, MRESVIA was supplied as a sterile liquid in a glass vial. The Applicant intends for the licensed product to include a suspension in a PFS that is shipped frozen and thawed, according to instructions in the full prescribing information, before use. Administration of MRESVIA using a PFS was supported by data from a use-related risk analysis (URRA) for a plastic PFS and a HF validation study previously reviewed by Division of Medication Error Prevention and Analysis 1 (DMEPA 1) for a PFS used with Moderna's US-licensed mRNA-based vaccine product (SPIKEVAX). This approach was determined to be acceptable based on a consultation with DMEPA.

The studies used an Internal Safety Team, comprised of internal, medically qualified employees of the Applicant who were not directly involved in the study or development program, to review interim and cumulative blinded safety data on a regular basis and to escalate concerns to the Data and Safety Monitoring Board (DSMB) as needed.

A blinded and independent Cardiac Event Adjudication Committee (CEAC), comprised of cardiologists and other medically qualified personnel, reviewed suspected cases of myocarditis and pericarditis using the Centers for Disease Control and Prevention Working Case Definitions (Gargano et al., 2021) as a guidance.

Safety Monitoring
All participants in Study mRNA-1345-P301 (P301) had a safety follow-up (via telephone, email, text message, or other electronic means) on Day 8, Day 15 (for Phase 3), Day 60, and then monthly through Month 24. Reactogenicity issues, symptoms of RSV-like illness, or new or ongoing AEs were assessed with additional unscheduled study visits.

For Study mRNA-1345-P101 (P101), all participants had postvaccination safety phone calls approximately 1 day after receiving each vaccination. Unscheduled visits may have been prompted by reactogenicity issues, new or ongoing AEs, or symptoms of RSV-like illness.

Data cutoff date for safety analyses was June 24, 2023.

Solicited local adverse reactions (injection site pain, injection site erythema [redness], injection site swelling/induration [hardness], and axillary [underarm] swelling or tenderness ipsilateral to the side of injection) and solicited systemic ARs (headache, fatigue, myalgia [muscle aches all over the body], arthralgia [joint aches in several joints], nausea/vomiting, fever [oral temperature], and chills) were monitored and recorded daily using electronic diaries (eDiaries) during the 7 days following vaccination (i.e., the day of vaccination and 6 subsequent days).

Unsolicited adverse events (AEs) occurring within 28 days of vaccination (i.e., the day of vaccination and 27 subsequent days) were recorded. AEs leading to discontinuation from study participation, medically attended adverse events (MAAEs), adverse event of special interests (AESIs) and serious adverse events (SAEs) were monitored and recorded from Day 1 through end of study (EOS) or withdrawal from study. AESIs were thrombocytopenia, anaphylaxis, myocarditis/pericarditis, and new onset or worsening of the following neurologic diseases: Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), idiopathic peripheral facial nerve palsy (Bell's palsy), and

seizures. All AEs and SAEs were followed until resolution, stabilization, the event was otherwise explained, or the participant was lost to follow-up.

Efficacy Monitoring
Starting 14 days after study vaccination (Study Day 15), participants were actively and passively monitored for respiratory disease. eDiaries were used for weekly surveillance of new or worsening symptoms of RSV-like illness and known exposure to RSV. In the case of new or worsening symptoms, an unscheduled visit was arranged within 5 days (if possible) for medical evaluation and nasopharyngeal (NP) swabs collection for detection of respiratory pathogens by RT-PCR. If a NP swab was not collected within 5 days of symptom onset, swabs were collected as soon as possible. If a participant visited a healthcare provider outside the study, study personnel were encouraged to obtain any clinical or diagnostic information associated with the external visit. Results from specimens obtained outside the study using an assay compliant with state and federal regulations (e.g., Clinical Laboratory Improvement Amendment (CLIA)-certified or a regulated laboratory) could be included as a study endpoint. Participants continued to complete eDiaries to monitor respiratory symptom status and were contacted weekly to document resolution, return to baseline, or worsening of symptoms until resolution or 30 days from the onset or worsening of RSV-like illness, whichever came first.

Data cutoff date for interim efficacy analyses was November 30, 2022. Data cutoff date for additional efficacy analyses was April 30, 2023.

Immunogenicity Monitoring
Immunogenicity data for Study mRNA-1345-P301 (P301) were not available at the time of BLA submission. Sera to assess RSV neutralizing antibody levels were collected from a subset of participants at protocol-defined timepoints at baseline, Day 15 (Phase 2 only), Day 29, Month 6, Month 12, Month 18, and Month 24.

For Study P101, following the screening visit, Cohorts 7 through 11 had scheduled visits for sera collection for immunogenicity assessments on Days 29, 57, 85, 169, 365 after each dose (Day 1, Month 12) administered in Cohorts 7 through 11; and after the single dose administered in Cohort 15.

Study mRNA-1345-P301
Study mRNA-1345-P301 (P301) is a multi-country study designed to evaluate the efficacy and safety of MRESVIA for the prevention of lower respiratory tract disease due to RSV (RSV-LRTD) in healthy older individuals ≥60 years. The study took place in 268 sites, including 136 sites in the U.S. Study P301 was initiated November 17, 2021, and is planned to be conducted through 2 RSV seasons with blinded follow-up of participants until 24 months after vaccination. To support the submission of this original BLA, the primary efficacy analysis was conducted based on the protocol-specified interim analysis of clinical RSV disease cases accrued through November 30, 2022 (3.7 months median follow-up). Additional efficacy data through April 30, 2023 (8.6 months median follow-up) and safety data to support primary safety objectives through June 24, 2023 (10.2 months median follow-up) were collected in a blinded manner. Participants in both segments in both phases were randomized 1:1 to receive a single IM injection of MRESVIA or placebo and stratified by age (80% as 60 to 74 years of age and 20% as ≥75 years of age) and risk factors for LRTD (present or absent). The total planned study enrollment

included approximately 37,000 participants across both study phase segments and the target age enrollment goals were 60% of participants 60 to 69 years of age, 30% of participants 70 to 79 years of age, and 10% of participants ≥80 years of age.

In this Study, the median age of the participants was 67 years, with 61.9% of participants 60-69 years, 30.1% of participants 70-79 years, and 7.9% of participants ≥80 years of age at baseline. Overall, most participants were White (61.8%), non-Hispanic/Latino (65.3%), and located in the US (53.5%). The demographic characteristics were similar between the vaccine and placebo groups.

Safety Analysis

Solicited Adverse Reactions
Solicited local and systemic adverse reactions (ARs) with onset within 7 days after vaccination were assessed in 18,160 MRESVIA recipients and 18,098 placebo recipients. Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling/induration, and axillary swelling/tenderness) and systemic reactions (headache, fatigue, myalgia, arthralgia, nausea/vomiting, fever, and chills).

The percentage of participants who reported solicited local and systemic adverse reactions are presented in Table 7 and Table 8. Among those who received MRESVIA, the median day of onset for solicited local reactions and solicited systemic reactions was 2 to 3 days post-vaccination. Solicited local reactions had a median duration of 1 day; solicited systemic reactions had a median duration of 1 to 2 days.

Table 7. Percentage of Participants With Solicited Local Adverse Reactions Any Grade and ≥Grade 3 Starting Within 7 Days* of Vaccination

Local Adverse Reactions‡	**MRESVIA N=18,154 – 18,156 %**	**Placebo† N=18,093 – 18,094 %**
Injection Site Pain, Any Grade§	55.9	13.8
Injection Site Pain, Grade 3§	1.7	1.1
Erythema (Redness), ≥2.5 cm	2.0	0.6
Erythema (Redness), Grade 3, >10 cm	0.6	0.3
Swelling (Hardness), ≥2.5 cm	3.7	0.3
Swelling (Hardness), Grade 3, >10 cm	0.9	<0.1
Axillary (underarm) swelling or tenderness, Any Grade¶	15.2	6.1
Axillary (underarm) swelling or tenderness, Grade 3¶	0.8	0.6

Abbreviations: Any=Grade 1 or above; Percentages were based on the number of exposed participants who submitted any data for the event.
N = number of vaccinated participants with available data for the events listed.
* 7 days included day of vaccination and the subsequent 6 days. Adverse reactions and use of pain medication were collected in the electronic diary (e-diary).
† Placebo is 0.9% sodium chloride (normal saline) injection.
‡ No Grade 4 solicited local adverse reactions were reported.

§ Injection site pain grading scale: Does not interfere with activity (Grade 1); repeated use of over-the-counter pain reliever >24 hours or interferes with activity (Grade 2); any use of prescription pain reliever or prevents daily activity (Grade 3).
¶ Axillary (underarm) swelling or tenderness grading scale: No interference with activity (Grade 1); repeated use of over-the-counter pain reliever >24 hours or some interference with activity (Grade 2); any use of prescription pain reliever or prevents daily activity (Grade 3).

Table 8. Percentage of Participants With Solicited Systemic Adverse Reactions Any Grade and ≥Grade 3 Starting Within 7 Days* of Vaccination

Systemic Adverse Reactions‡	MRESVIA (N=18,146 – 18,153) %	Placebo† (N=18,092 – 18,093) %
Fever, Any Grade (≥38°C / ≥100.4°F)	2.7	1.3
Fever, Grade 3 (39.0°C – 40.0°C / 102.1°F – 104.0°F)	0.4	0.2
Fever, Grade 4 (>40.0°C / >104.0°F)	0.2	0.2
Headache, Any Grade§	26.7	18.8
Headache, Grade 3§	1.5	1.1
Fatigue, Any Grade¶	30.8	20.0
Fatigue, Grade 3¶	1.7	1.2
Myalgia, Any Grade#	25.6	14.4
Myalgia, Grade 3#	1.4	0.8
Arthralgia, Any Grade#	21.7	14.0
Arthralgia, Grade 3#	1.1	0.7
Nausea/vomiting, Any Grade♠	7.0	5.2
Nausea/vomiting, Grade 3♠	0.4	0.4
Chills, Any Grade♥	11.6	6.8
Chills, Grade 3♥	0.6	0.4

Abbreviations: Any = Grade 1 or above; Percentages were based on the number of exposed participants who submitted any data for the event.
N = number of vaccinated participants with available data for the events listed.
* 7 days included day of vaccination and the subsequent 6 days. Adverse reactions and use of pain medication were collected in the electronic diary (e-diary).
† Placebo is 0.9% sodium chloride (normal saline) injection.
‡ With the exception of fever, no Grade 4 solicited systemic adverse reactions were reported.
§ Headache grading scale: No interference with activity (Grade 1); repeated use of over-the-counter pain reliever >24 hours or some interference with activity (Grade 2); significant, any use of prescription pain reliever or prevents daily activity (Grade 3).
¶ Fatigue grading scale: No interference with activity (Grade 1); some interference with activity (Grade 2); significant, prevents daily activity (Grade 3).
# Myalgia and arthralgia grading scales: No interference with activity (Grade 1); some interference with activity (Grade 2); significant, prevents daily activity (Grade 3).
♠ Nausea/vomiting grading scale: No interference with activity or 1-2 episodes per 24 hours (Grade 1); some interference with activity or >2 episodes per 24 hours (Grade 2); prevents daily activity, requires outpatient intravenous hydration (Grade 3).
♥ Chills grading scale: No interference with activity (Grade 1); some interference with activity not requiring medical intervention (Grade 2); prevents daily activity and requires medical intervention (Grade 3).

Unsolicited Adverse Events

The proportion of participants who reported unsolicited AEs within 1 month after vaccination were similar across groups (20.8% MRESVIA and 19.0% placebo). AEs that were assessed as related to study vaccination per the Investigator were reported for 5.7% of MRESVIA recipients and 4.4% of placebo recipients. These AEs primarily represented reactogenicity events. Most events were mild to moderate in severity, with severe AEs considered to be related to study vaccination per the Investigator reported for 0.3% of participants in each group. Most of these severe AEs were associated with reactogenicity events.

There was a numerically higher incidence of urticaria in the vaccine group than in the placebo group. Within 7 days of study vaccination, there were 9 events of urticaria

reported in 8 participants (<0.1%) in the MRESVIA group compared to 2 events in 2 participants (<0.1%) in the placebo group, and within 1 month of study vaccination, there were 17 events of urticaria reported in 15 participants (<0.1%) in the MRESVIA group compared to 5 events in 5 participants (<0.1%) in the placebo group.

Serious Adverse Events
The median duration of safety follow-up was 311 days (range 1 to 585 days), and 96.6% of participants had at least a 6-month follow-up duration after vaccination. SAEs throughout the study were reported at similar rates in 7.8% of the participants in the MRESVIA group and 7.9% of the placebo group. One participant in the MRESVIA group had an SAE of facial paralysis with onset four days after vaccination assessed as related to MRESVIA. Within 28 days and 42 days post vaccination, there was no imbalance in reports of facial paralysis (including Bell's palsy) between treatment groups. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (SAEs) that would suggest a causal relationship to MRESVIA.

Efficacy Analyses

Primary Efficacy Objective:

- To evaluate the efficacy of a single dose of MRESVIA vaccine for the prevention of a first episode of RSV-associated lower respiratory tract disease (RSV-LRTD) as compared with placebo within the period of 14 days post-injection up to 12 months post-injection.

Two interim analyses (IA1 and IA2), one primary analysis, a potential analysis at 12 months, and one final analysis were planned.

- IA1 was performed when approximately 50% of the total target cases (at least 43 RSV-LRTD cases with ≥2 symptoms and 16 RSV-LRTD cases with ≥3 symptoms) occurred.
- IA2 was to be performed when approximately 85% of the total target cases (at least 74 RSV-LRTD cases with ≥2 symptoms and 28 RSV-LRTD cases with ≥3 symptoms) occurred.
- The primary analysis was to be performed when approximately 100% of the total target cases (86 RSV-LRTD cases with ≥2 symptoms and 32 RSV-LRTD cases with ≥3 symptoms) occurred.
- An analysis at 12 months may be conducted for some secondary and exploratory endpoints, as appropriate.
- The final analysis will be performed when all participants have completed Month 24 follow-up.

The BLA submission includes data from the pre-specified interim analysis of the primary efficacy endpoints which includes cases of first episode of RSV-LRTD through the data cutoff date of November 30, 2022. Since efficacy was demonstrated for both primary endpoints, IA1 was considered the primary analysis of efficacy and subsequent analyses were considered supportive. In the PPE Set, the study population used for the primary efficacy analyses, the median follow-up time for analysis of the primary endpoints was

approximately 3.7 months. For the 35,064 participants included in the PPE Set, 99.7% (N=34,961) completed at least 28 days, 20.2% (N=7,096) completed at least 6 months, and 0.2% (N=63) completed at least 12 months since study vaccination. Additional supportive efficacy data were submitted to the BLA using a data cutoff date of April 30, 2023, with a median of 8.6 months of follow-up.

The two primary efficacy endpoints, tested sequentially, were (1) VE in preventing first-episode RSV-LRTD with 2 or more symptoms within the period of 14 days post-vaccination up to 12 months post-vaccination and (2) VE in preventing first-episode RSV-LRTD with 3 or more symptoms within the period of 14 days postvaccination up to 12 months postvaccination.

Primary Endpoint 1: RSV-LRTD with ≥2 Symptoms
As of the data cutoff date of November 30, 2022, there were 85 cases of first-episode RSV-LRTD with ≥2 symptoms starting between 14 days and up to 12 months after vaccination. The case split was 15 cases in the MRESVIA group compared to 70 cases in the placebo group, with a VE of 78.7% (95.04% CI: 62.8, 87.9), which met the pre-specified success criterion (Table 9).

Primary Endpoint 2: RSV-LRTD with ≥3 Symptoms
As of the data cutoff date of November 30, 2022, there were 31 cases of first-episode RSV-LRTD with ≥3 symptoms starting between 14 days and up to 12 months after vaccination. The case split was 5 cases in the MRESVIA group compared to 26 cases in the placebo group, with a VE of 80.9% (95.1% CI: 50.1, 92.7), which met the pre-specified success criterion (Table 9).

Table 9. Vaccine Efficacy of MRESVIA Against First Episode of RSV-LRTD With ≥2 or ≥3 Symptoms Starting 14 Days After Vaccination up to 12 Months After Vaccination, PPE Set, Study mRNA-1345-P301 (30 NOV 2022; Median Follow-Up 3.7 Months)

Efficacy Endpoint	MRESVIA N=17561 Cases, n (%)	Placebo N=17503 Cases, n (%)	VE[a] % (alpha-adjusted% CI)[b]
First episode of RSV-LRTD with ≥2 symptoms	15 (0.09)	70 (0.40)	78.7 (62.8, 87.9)[c]
First episode of RSV-LRTD with ≥3 symptoms	5 (0.03)	26 (0.15)	80.9 (50.1, 92.7)[d]

Source: Adapted from STN 125796/0.45, mRNA-1345-P301 IR29 Ad hoc Tables 10.11.1.1 and 10.11.2.1 (data cutoff 30 Nov 2022; data extraction 13 Feb 2024)
Abbreviations: CI=confidence interval; N=total number of participants in each vaccination group; n=number of cases of the specified endpoint from 14 days after study vaccination through 12 months after study vaccination; PPE=Per- Protocol Efficacy; RSV=respiratory syncytial virus; RSV-LRTD=RSV-associated lower respiratory tract disease; RT-PCR=reverse transcriptase polymerase chain reaction; VE=vaccine efficacy.
[a]VE is defined as 100% x (1 - hazard ratio (MRESVIA vs. placebo)).
[b]CI is obtained using a stratified Cox proportional hazard model with Efron's method of tie handling and with stratification factors at randomization as covariates, adjusted by Lan-Demets Pocock approximation spending function. Vaccine efficacy is demonstrated if the lower bound of the two-sided alpha adjusted CI exceeds 20%.
[c]95.04% CI, two-sided adjusted alpha=4.96%.
[d]95.1% CI, two-sided adjusted alpha=4.9%.
Note: Case definition was based on eligible symptoms onset within a timeframe of +/- 14 days from positive RSV RT-PCR collection date. RT-PCR test results from the specialty laboratory were used; if not available, results from a certified laboratory (CLIA or CLIA equivalent) with a regulatory approved (FDA or other agency) RT-PCR test kit were used instead.

Analyses of the primary endpoints based on the mITT Set yielded similar results to those shown above in Table 9.

Supportive Analyses [April 30, 2023 data cutoff]
Additional supportive efficacy data was submitted to the BLA using a cutoff date of April 30, 2023, after a median follow-up duration of 8.6 months. For the 36,084 participants included in the PPE Set as of the April 2023 cutoff date, 94.2% (N=33,974) completed at least 6 months, and 12.7% (N=4,595) completed at least 12 months since study vaccination.

There were 175 cases of first-episode RSV-LRTD with ≥2 symptoms starting between 14 days and up to 12 months after vaccination. The case split was 48 cases in the MRESVIA group compared to 127 cases in the placebo group, with a VE of 62.5% (95% CI: 47.7, 73.1). For first episode of RSV-LRTD with ≥3 symptoms starting between 14 days and up to 12 months after vaccination, there were 71 cases with a case split of 20 cases in the MRESVIA group compared to 51 cases in the placebo group. The VE was 61.1% (95% CI: 34.7, 76.8) (Table 10). While this analysis was descriptive, both primary endpoints met the pre-specified success criterion of LB CI of VE >20%.

Table 10. Vaccine Efficacy of MRESVIA Against First Episode of RSV-LRTD With ≥2 or ≥3 Symptoms Starting 14 Days After Vaccination up to 12 Months After Vaccination, PPE Set, Study mRNA-1345-P301 (30 APR 2023; Median Follow-Up 8.6 Months)

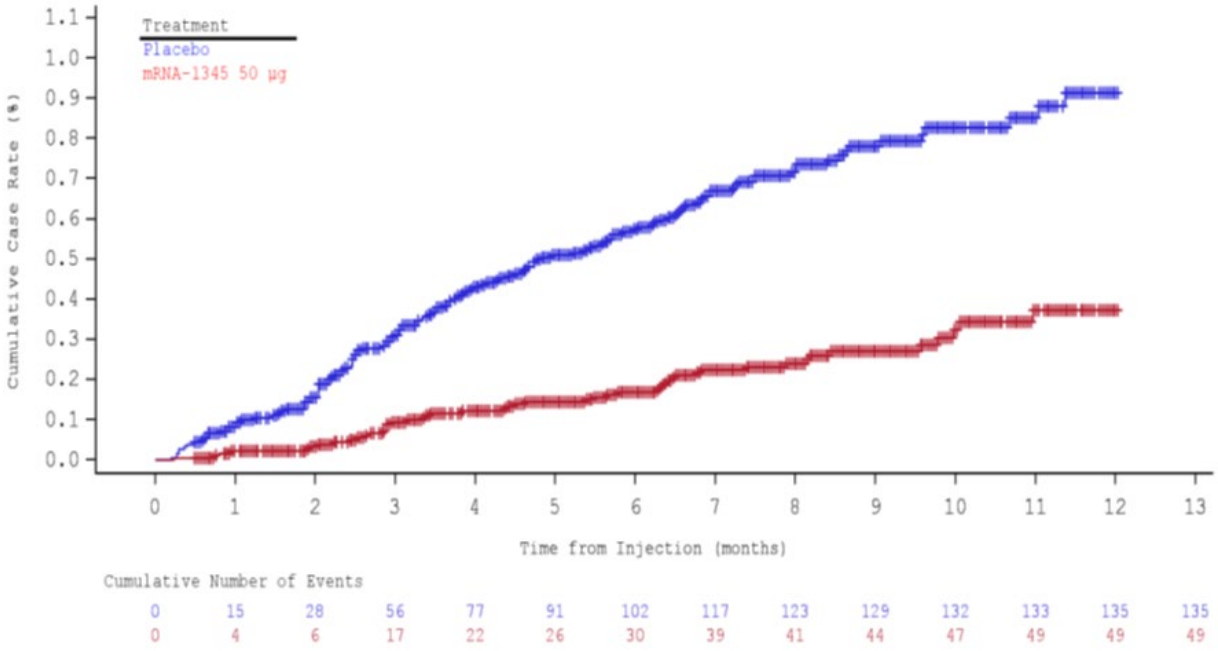
Efficacy Endpoint	MRESVIA N=18074 Cases, n (%)	Placebo N=18010 Cases, n (%)	VE % (95% CI)[a]
First episode of RSV-LRTD with ≥2 symptoms	48 (0.27)	127 (0.71)	62.5 (47.7, 73.1)
First episode of RSV-LRTD with ≥3 symptoms	20 (0.11)	51 (0.28)	61.1 (34.7, 76.8)

Source: Adapted from STN 125796/0.38, mRNA-1345-P301 IR19 Ad hoc Tables 10.11.7 and 10.11.8. (data cutoff 30 Apr 2023; data extraction 13 Feb 2024)
Abbreviations: CI=confidence interval; N=total number of participants in each study vaccine group; n=number of cases of the specified endpoint from 14 days after study vaccination through 12 months after study vaccination; PPE=Per-Protocol Efficacy; RSV=respiratory syncytial virus; RSV-LRTD=RSV-associated lower respiratory tract disease; RT-PCR=reverse transcriptase polymerase chain reaction; VE=vaccine efficacy.
[a]VE is defined as 100% × (1 - hazard ratio (MRESVIA vs. placebo)). The CI for VE is based on a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a fixed effect, adjusting for stratification factors at randomization.
Note: Case definition was based on eligible symptoms onset within a timeframe of +/- 14 days from positive RSV RT-PCR collection date. RT-PCR test results from the specialty laboratory were used; if not available, results from a certified laboratory (CLIA or CLIA equivalent) with a regulatory approved (FDA or other agency) RT-PCR test kit were used instead.

While the study met its prespecified success criteria at the first interim analysis with a November 30, 2022, data cutoff date and a median follow-up duration of approximately 3.7 months, data from the supportive efficacy analyses at the April 30, 2023, data cutoff date, with a median follow-up duration of approximately 8.6 months, provide important clinical information regarding vaccine efficacy through a longer time period. Over the longer duration of follow-up, VE point estimates for both RSV-LRTD with ≥2 symptoms and RSV-LRTD with ≥3 symptoms declined.

Cumulative Case Accrual Curve [April 30, 2023 data cutoff]
The cumulative case accrual curve for RSV-LRTD with ≥2 symptoms starting the day of vaccination up to 12 months post-vaccination, in the mITT Set, is shown in Figure 1. With this April 30, 2023 data cutoff, median follow-up was 8.6 months following vaccination. The curves start to diverge prior to 14 days after vaccination, with more cases accumulating in the placebo group than the MRESVIA group. The cumulative case accrual curve for RSV-LRTD with ≥3 symptoms (not shown) generally followed a similar pattern as that for RSV-LRTD with ≥2 symptoms but was based on fewer cases.

Figure 1. Cumulative Case Accrual Curve From Day of Vaccination, First Episode of RSV-LRTD With ≥2 Symptoms, mITT Set, Study mRNA-1345-P301 (30 APR 2023; Median Follow-Up 8.6 Months)



Source: Adapted from STN 125796/0.46 and 0.53, mRNA-1345-P301 IRs30 and 33 Ad hoc figure 10.2.1 (data cutoff 30 Apr 2023; data extraction 13 Feb 2024)
Abbreviations: RSV-LRTD=RSV associated lower respiratory tract disease; mITT=modified Intent-To-Treat
Note: First episode of RSV-LRTD cases with symptom onset from Day 1 (vaccination date) through 12 months after vaccination were included.

The cumulative case accrual curve above, with a median follow-up duration of 8.6 months, demonstrates an increase of cases in the placebo group as compared to the MRESVIA group following vaccination. Interpretation regarding the durability of vaccine effectiveness is limited to the 12-month period after study vaccination as defined in the primary efficacy objective. The cumulative case accrual curves for the primary analyses with a median follow-up of 3.7 months following vaccination showed the same trend of more cases accumulating in the placebo group compared to the MRESVIA group through the 12-month period after vaccination.

Subpopulation Analyses of Vaccine Efficacy [April 30, 2023 data cutoff]
By age group, the VE point estimate was higher for the 70 through 79 years age subgroup compared to the 60 through 69 years age subgroup, although the confidence intervals overlapped. For the ≥80 years age subgroup, there was a case split of 6 to 5 for the MRESVIA group compared to the placebo group, with a negative VE and a wide confidence interval that included zero, limiting the interpretability of the results.

For the subgroup analysis for the prespecified risk factors of CHF and COPD, the VE point estimate was similar to the overall study population for those without risk factors. The VE point estimate was higher for those with at least one risk factor compared to those without risk factors, although the confidence interval for the higher risk group was wider than for the overall study population due to the small sample size. The VE point estimates were generally similar to the overall study population regardless of the presence or absence of prespecified comorbidities (chronic cardiopulmonary conditions [CHF, COPD, asthma], chronic respiratory conditions, diabetes, advanced liver disease, and advanced kidney disease). The relatively small numbers of enrolled participants and low RSV case counts in the vulnerable and frail subgroups for frailty status led to wide confidence intervals that included zero.

Study mRNA-1345-P101
Study mRNA-1345-P101 was a Phase 1 study to evaluate the safety, reactogenicity, and immunogenicity of MRESVIA in healthy younger individuals 18 through 49 years of age, healthy older individuals 65 through 79 years of age, and Japanese older individuals ≥60 years of age. MRESVIA elicited RSV neutralizing antibody responses across all dose levels of MRESVIA for both the first and second dose. Solicited local and systemic ARs were reported by a higher proportion of MRESVIA recipients compared to placebo, and these ARs are adequately described in Study mRNA-1345-P301 for the purposes of labeling. There were no serious safety findings from this study that merited inclusion in labeling. Based on these results, the 50-mcg dose of MRESVIA was chosen for further clinical development. The data reviewed from this study support the overall findings of Study mRNA-1345-P301.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance
Bioresearch Monitoring (BIMO) inspections were issued for four clinical study sites that participated in the conduct of Study mRNA-1345-P301. Two clinical investigators were cited for inadequate study monitoring reporting. A corrective action plan was submitted by the investigators and accepted by the Applicant and FDA. The validity of the data from these study sites was not impacted. BIMO inspections of the remaining two study sites did not reveal substantive issues.

c. Pediatrics
The Applicant submitted a request for partial waiver for pediatric individuals 0 to <2 months of age as the product does not represent a meaningful therapeutic benefit over existing therapies for this age group and is not likely to be used by a substantial number of patients in this age group.

The Applicant also submitted a request for deferral of studies (see list of studies below) in pediatric individuals 2 months to <18 years of age because MRESVIA would be ready for approval for use before such studies could be completed. The partial waiver and

deferral requests were accepted without revisions by the Pediatric Review Committee on April 9, 2024. The pediatric study plans were subsequently modified to specify that efficacy would be studied in infants and children 2 months to <24 months of age and 2 years to <5 years of age.

7. Safety and Pharmacovigilance

The data cutoff date for safety analyses was June 24, 2023. A total of 36,412 vaccinated participants (18,231 MRESVIA recipients and 18,181 placebo recipients), the majority (96.6%) of whom had at least 6 months of follow-up for safety. The median of the durations of follow-up from Day 1 to June 24, 2023 data cutoff date for safety analyses was 10.2 months (311 days).

Safety evaluation included the following parameters: Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) up to 7 days postvaccination; Unsolicited adverse events (AEs) up to 28 days postvaccination; Medically attended adverse events (MAAEs), adverse events of special interest (AESIs), SAEs, and AEs leading to withdrawal up to 24 months postvaccination. All participants recorded unsolicited AEs in an eDiary.

Through the June 24, 2023 data cutoff (10.2 months median follow-up), deaths were reported in 0.6% MRESVIA recipients, none of which were judged to be related to MRESVIA vaccination.

There were no meaningful imbalances in the overall rates of unsolicited AEs within 1 month following vaccination between MRESVIA and placebo recipients in the Safety Set; however, a numerical imbalance was noted in events of urticaria within 7 days following vaccination (9 events in 8 MRESVIA recipients and 2 events in 2 placebo recipients) and within 1 month following vaccination (17 events in 15 MRESVIA recipients and 5 events in 5 placebo recipients). All events of urticaria within 1 month of vaccination were mild or moderate in severity and all resolved. This imbalance has been included under Adverse Reactions in the USPI.

SAEs were balanced across groups (7.8% of MRESVIA recipients and 7.9% of placebo recipients). One SAE of facial paralysis reported 4 days after vaccination was assessed by the Investigator, Applicant, and FDA as related to MRESVIA and has been included under Adverse Reactions in the USPI. SAEs of chills, dehydration, and superficial vein thrombosis were assessed by FDA as possibly related to MRESVIA due to a temporal relationship; however, there were other biologically plausible explanations for these events. No postmarketing assessments will be required by FDA based on clinical study safety findings.

Overall, the mRNA-1345-P301 data support the safety of MRESVIA for its intended use for the prevention of RSV-LRTD in individuals 60 years of age and older.

Pharmacovigilance

The Applicant submitted a pharmacovigilance plan (PVP) (version 1.0, September 7, 2023) to include routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80. The PVP includes the Applicant’s assessment of important potential risks and missing information. There are no important identified risks associated with the

product and there are no Postmarketing Requirements or Postmarketing Commitments associated with this product. The Applicant plans to conduct two voluntary proposed post-authorization safety studies mRNA-1345-P902 and mRNA-1345-P903 to assess the postmarketing safety of MRESVIA. The Applicant will provide interim study reports for both voluntary studies, including updates of AESIs and an assessment of the cases, in the quarterly periodic safety reports for the first 3 years after approval.

8. Labeling

The proprietary name, MRESVIA, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) and found to be acceptable. CBER communicated this decision to the Applicant on December 22, 2023.

The Review Committee negotiated revisions to the PI, including modifying the proposed proper name from "RSV Vaccine, mRNA" to "Respiratory Syncytial Virus Vaccine." All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the Applicant. The PI, and carton and container labels submitted in amendments 71 (received on May 29, 2024) were considered final for approval.

9. Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee (VRBPAC) committee meeting was not convened for this BLA based on the following: 1) a VRBPAC meeting was convened February 28 to March 1, 2023 to discuss the safety and effectiveness of two candidate RSV vaccines (ABRYSVO and AREXVY) with requested indications for active immunization for the prevention of RSV-LRTD in individuals ≥60 years of age and addressed issues relevant to FDA's review of MRESVIA; 2) there are two RSV vaccines (ABRYSVO and AREXVY) and two mRNA-platform vaccines (SPIKEVAX and COMIRNATY) currently licensed for use in the US; and 3) during FDA review of MRESVIA under the BLA, no concerns were identified that would benefit from a discussion with the VRBPAC.

10. Other Relevant Regulatory Issues

The submission was granted priority review status on November 9, 2023, as the Applicant redeemed a Material Threat Medical Countermeasure Priority Review Voucher (tracking number - PRV BLA 125752, dated January 31, 2022).

Upon consideration of new data and information included in the amendment of February 26, 2024, and as documented in the internal late cycle meeting of March 4, 2024, the review team and Division and Office management determined that designation as a major amendment was appropriate to allow time for a meaningful review, with a corresponding 3-month extension of the review clock. The applicant objected to this review clock extension after issuance of the Major Amendment Letter on March 7, 2024. The Center Director disagreed with review team on the major amendment designation, as described in the memo of April 10, 2024. The review clock was reset to the original PDUFA goal date of May 12, 2024; however, the review team was unable to complete the review of the file and take action by the May 12, 2024, goal date.

The pre-license inspection (PLI) of five facilities for the DS and DP manufacturing and the final release testing facility are waived based on their inspection histories and compliance status. The basis for waiving the inspection of these facilities is documented in a separate inspection waiver memo dated April 23, 2024.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in this original BLA submission, the Review Committee recommends approval of MRESVIA for the labeled indication and usage.

b. Benefit/Risk Assessment

The Review Committee is in agreement that there are more benefits than risks associated with administering a single dose of MRESVIA to individuals 60 years of age and older. However, there are still some uncertainties regarding the long-term immunogenicity and efficacy of MRESVIA, its use in immunocompromised populations and concomitant use with relevant vaccines.

The Review Committee has determined that MRESVIA does not require a REMS or safety Postmarketing Requirement studies under FDCA section 505(o).

c. Requirements and Recommendation for Postmarketing Activities

The Applicant has committed to conduct the following postmarketing activities, which are specified in the approval letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

The required studies are listed below.

1. Deferred pediatric study, mRNA-1345-P101, to evaluate the safety and immunogenicity of MRESVIA in RSV-seropositive children 12 months to 59 months of age.
   Final Protocol Submission: July 31, 2020
   Study Completion: January 31, 2025
   Final Report Submission: December 31, 2025

2. Deferred pediatric study, mRNA-1365-P101, to evaluate the safety and immunogenicity of MRESVIA in infants and children 5 months to < 24 months of age.
   Final Protocol Submission: December 31, 2022
   Study Completion: July 31, 2027
   Final Report Submission: February 28, 2028

3. Deferred pediatric study, mRNA-1345-P202, to evaluate the safety and immunogenicity of MRESVIA in healthy children 2 years to <5 years of age, and

children and adolescents at high risk of severe RSV disease 2 years to <18 years of age.
Final Protocol Submission: September 30, 2023
Study Completion: June 30, 2026
Final Report Submission: December 31, 2026

4. Deferred pediatric study to evaluate the safety and immunogenicity of MRESVIA in infants and children 2 months to <24 months of age.
Final Protocol Submission: March 31, 2026
Study Completion: September 30, 2028
Final Report Submission: March 31, 2029

5. Deferred pediatric study to evaluate the safety and efficacy of MRESVIA in infants and children 2 months to <24 months of age.
Final Protocol Submission: October 31, 2028
Study Completion: May 31, 2031
Final Report Submission: December 31, 2031

6. Deferred pediatric study to evaluate the safety and efficacy of MRESVIA in children 2 years to <5 years of age who are healthy or at risk of severe RSV disease.
Final Protocol Submission: June 30, 2024
Study Completion: June 30, 2027
Final Report Submission: December 31, 2027

The Applicant agreed to conduct two voluntary post-authorization safety studies mRNA-1345-P902 and mRNA-1345-P903.

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