

BLA Clinical Review Memorandum

Application Type	Biologics License Application
STN	125796/0
CBER Received Date	September 12, 2023
PDUFA Goal Date	May 10, 2024
Division / Office	DCTR/OVRR
Priority Review (Yes/No)	Yes
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Review Completion Date / Stamped Date	May 29, 2024
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Applicant	ModernaTX, Inc.
Proper Name	Respiratory Syncytial Virus Vaccine
(Proposed) Trade Name	mResvia
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	Each 0.5-mL dose contains 50 µg of mRNA encoding the RSV stabilized prefusion F protein formulated in lipid nanoparticles composed of 4 lipids (SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol -2,3-dimyristylglycerol)
Dosage Form(s) and Route(s) of Administration	Sterile liquid for intramuscular injection
Dosing Regimen	Single 0.5-mL dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of RSV-associated lower respiratory tract disease (LRTD) in adults ≥60 years of age
Orphan Designated (Yes/No)	No

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GLOSSARY

ADEM	acute disseminated encephalomyelitis
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARD	acute respiratory disease
BLA	Biologics License Application
BIMO	bioresearch monitoring
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendment
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DCTR	Division of Clinical and Toxicology Review
DMEPA	Division of Medication Error Prevention and Analysis
DSMB	Data and Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ERD	enhanced respiratory disease
FDA	United States Food and Drug Administration
FI-RSV	formalin-inactivated RSV
GBS	Guillain-Barré syndrome
HF	human factors
HR	hazard ratio
IM	intramuscular
IR	information request
IP	investigational product
LB	lower bound
LRTD	lower respiratory tract disease
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified Intent-to-Treat
NP	nasopharyngeal
PCR	polymerase chain reaction
PFS	pre-filled syringe
PPE	Per-Protocol Efficacy
PREA	Pediatric Research Equity Act
PT	preferred term
PV	pharmacovigilance
RSV	respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
SAE	serious adverse event
SMQ	standardized MedDRA query
SOC	system organ class
STN	submission tracking number
URRA	use-related risk analysis

USPI	United States Prescribing Information
VE	vaccine efficacy

1. EXECUTIVE SUMMARY

On September 12, 2023, ModernaTX, Inc. (the Applicant) submitted a Biologics License Application (BLA) to the United States Food and Drug Administration (FDA) to support licensure of an mRNA RSV vaccine (proposed trade name: mResvia)¹, with the proposed indication for “active immunization for the prevention of lower respiratory tract disease (LRTD) (b) (4) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older.” mResvia is an mRNA vaccine encoding a stabilized prefusion F glycoprotein from RSV A strain formulated in lipid nanoparticles. The proposed dosing regimen is a single intramuscular injection at the dose level of 50 µg of mRNA.

Data from 2 clinical studies were submitted in support of the BLA. The primary data to support the safety and efficacy of mResvia in individuals 60 years of age and older are from Study mRNA-1345-P301 (referred to as Study P301 throughout this document), a multi-national, randomized, observer-blind, and placebo-controlled trial conducted in sequential Phase 2 and Phase 3 study segments in 36,412 participants who received a dose of mResvia (n=18,230) or placebo (n=18,182). Phase 1 Study mRNA-1345-P101 (referred to as Study P101) provides data to support dose selection, as well as additional supportive safety data.

On January 25, 2024, due to inconsistencies in the datasets submitted for Study P301, FDA requested that the Applicant complete all data cleaning activities up to the June 24, 2023 data cutoff and submit updated datasets for FDA review. The updated data were used in the primary and additional efficacy analyses and identified additional RSV cases with onset prior to data cutoff which met the study case definition. The additional identified cases were incorporated into the estimates of vaccine efficacy in this review memorandum.

Efficacy

The primary objective of Study P301 evaluated the efficacy of mResvia for the prevention of RSV-associated LRTD (RSV-LRTD) up to 12 months postvaccination. Efficacy of mResvia was demonstrated in Study P301 based on a successful protocol-specified interim analysis (considered the primary analysis), performed when approximately 50% of the planned cases had accrued, as per the statistical analysis plan. This analysis occurred after a median follow-up of 3.7 months postvaccination and evaluated primary efficacy endpoints of laboratory-confirmed RSV-LRTD with ≥2 symptoms and ≥3 symptoms with onset at least 14 days postvaccination. Vaccine efficacy (VE) to prevent laboratory-confirmed RSV-LRTD with ≥2 symptoms was 78.7% (95.04% confidence interval [CI]: 62.8, 87.9), with 15 cases in the vaccine group and 70 cases in the placebo group. VE to prevent laboratory-confirmed RSV-LRTD with ≥3 symptoms was 80.9% (95.1% CI: 50.1, 92.7), with 5 cases in the vaccine group and 26 cases in the placebo group.

The hypothesis-tested secondary objective to evaluate the efficacy of mResvia for the prevention of RSV-associated ARD (RSV-ARD) up to 12 months postvaccination met the protocol-specified success criterion based on the endpoint of laboratory-confirmed RSV-ARD with onset at least 14 days postvaccination. However, upon FDA review it

¹ Throughout this review memo, the proposed trade name, mResvia, will be used to identify the vaccine formulation used in clinical studies and intended for licensure.

was noted that most RSV-ARD cases also met criteria for RSV-LRTD, (b) (4)

A meaningful analysis of the hypothesis-tested secondary objective to evaluate efficacy of mResvia for the prevention of first hospitalization associated with RSV-LRTD or RSV-ARD could not be performed due to too few hospitalizations reported.

Additional analyses of the primary and select secondary objectives were performed after a median follow-up of 8.6 months postvaccination. VE to prevent laboratory-confirmed RSV-LRTD with ≥ 2 symptoms was 62.5% (95% CI: 47.7, 73.1), with 48 cases in the vaccine group and 127 cases in the placebo group. VE to prevent laboratory-confirmed RSV-LRTD with ≥ 3 symptoms was 61.1% (95% CI: 34.7, 76.8), with 20 cases in the vaccine group and 51 cases in the placebo group. As previously noted, most participants who met criteria for RSV-ARD also met the criteria for RSV-LRTD, (b) (4).

Safety

Safety data from Study P301 with a median follow-up of 10.2 months postvaccination included 36,412 vaccinated participants (18,231 mResvia recipients and 18,181 placebo recipients), of which 35,169 participants (96.6%) had at least 6 months of follow-up post-vaccination. Data on solicited local and systemic adverse reactions (ARs) within 7 days following vaccination were collected from a Solicited Safety Set of 36,258 participants. The most reported ($\geq 10\%$) solicited ARs among mResvia recipients were injection site pain (55.9%), fatigue (30.8%), headache (26.7%), myalgia (25.6%), arthralgia (21.7%), axillary swelling or tenderness (15.2%), and chills (11.6%); these were predominately mild and moderate, with 3.1% and 4.0% of local and systemic solicited ARs, respectively, reported as severe (Grade 3 or Grade 4).

Unsolicited adverse events (AEs) were followed for the entire Safety Set (N=36,412) through 1 month following vaccination. There were no meaningful imbalances in the overall rates of unsolicited adverse events within 1 month following vaccination between vaccine and placebo recipients in the Safety Population. A numerical imbalance was noted in the specific adverse event of urticaria, with 17 events in the mResvia group and 5 events in the placebo group. These events of urticaria were all mild or moderate in severity and all resolved.

At 10.2 months median follow-up, serious adverse events (SAEs) were balanced between study groups (7.8% in the mResvia group and 7.9% in the placebo group). One SAE of facial paralysis was assessed by FDA as possibly related to mResvia, in agreement with the Investigator's assessment. SAEs of chills, dehydration, and superficial vein thrombosis assessed as related by the Investigator were assessed by FDA as possibly related to mResvia due to a temporal relationship; however, there were other biologically plausible explanations for these events. Deaths occurred in 106 (0.6%) mResvia recipients and 125 (0.7%) placebo recipients. None of the deaths were considered related to study intervention.

In Study P101, approximately 260 adult participants ≥ 60 years of age received varying dose levels of an investigational formulation of mResvia given in a 1 or 2 dose schedule. Review of the safety data from this study did not reveal any safety concerns. In Study P101, there were no SAEs and no deaths assessed as related to study vaccine.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed.

Efficacy

Study P301 was conducted in multiple regions and countries. In descriptive analyses of the primary endpoints by subgroup at a median follow-up time of 8.6 months post-vaccination, VE point estimates were generally consistent with VE in the overall study population by age, sex, race, ethnicity, and comorbidities of interest. VE estimates for participants in the United States (U.S.) were comparable to those of the overall study population. Interpretation of these subgroup analyses; however, is limited by small sample sizes and low case numbers for many of these subgroups.

Safety

In Study P301, descriptive summaries of safety data were reported by age, sex, race, ethnicity, region, comorbidities of interest, and frailty status. In general, there were no clinically relevant differences in local and systemic adverse reactions based on sex, comorbidities of interest, or frailty status. In general, solicited ARs were reported more commonly in the younger age subgroup (60 through 69 years) compared to the older age subgroups (70 through 79 years and ≥80 years). By race, ethnicity, and region, solicited ARs were reported more commonly by participants in the White race subgroup, the not Hispanic or Latino subgroup, and in the U.S., respectively.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input checked="" type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Respiratory syncytial virus (RSV) is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. The severity of RSV disease increases with age in adults and comorbidities (e.g., chronic obstructive pulmonary disease, congestive heart failure, asthma) ([Falsey et al., 2005](#)). RSV disease among adults 65 years of age and older results in an average of 177,000 hospitalizations in the United States (U.S.) each year; during 1999-2018, the highest mortality among all age groups was seen in among adults 65 years of age and older with a mortality rate of 14.7 per 100,000 ([CDC, 2022](#); [Hansen et al., 2022](#)).

RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans. There is currently no immune marker or antibody threshold widely accepted as predictive of protection against RSV. The durability of naturally acquired immunity after RSV infection is also not well understood. Studies of immune responses after RSV infection indicate an initial rise in serum antibody levels, with a return to baseline by 16-20 months post-infection ([Falsey et al., 2006](#)). Although high rates of re-infection and short durability of protection after infection were observed in an RSV human challenge study in young adults ([Hall et al., 1991](#)), another study among elderly individuals suggests that natural re-infection with RSV was rarely observed over two consecutive years ([Johnson et al., 1962](#)).

RSV strains are grouped within a single serotype but are separated into 2 major phylogenetic lineages (subgroups RSV A and RSV B) originally determined by cross neutralization studies and confirmed to be due mainly to antigenic differences in the RSV glycoprotein G. Currently, RSV A and RSV B strains are differentiated by sequences within the N-terminal 270 nucleotides of the RSV glycoprotein G gene. Glycoprotein G and glycoprotein F are the primary targets of neutralizing antibodies. While glycoprotein G shows significant genetic diversity between the two subgroups, glycoprotein F is relatively antigenically conserved. Both subgroups tend to co-circulate during each season, however, the prevalence of the RSV subgroup dominating local annual outbreaks is variable and unpredictable.

RSV is transmitted by large droplets, replicates exclusively in the respiratory epithelium, and causes a wide spectrum of clinical disease, from mild upper respiratory illness to life threatening bronchiolitis and pneumonia. Symptomatic RSV infections and re-infections can manifest as acute upper and/or lower respiratory tract infections. Symptoms

consistent with an upper respiratory tract infection include rhinorrhea, pharyngitis, cough, headache, fatigue, and fever.

High-risk populations include infants and young children, elderly, immunocompromised individuals (hematologic malignancies, hematopoietic stem cell transplant recipients, lung transplant recipients), and those with underlying cardiopulmonary conditions. In older adults, RSV infections can lead to severe disease, requiring hospitalization for respiratory support, including supplemental oxygen, intubation, and/or mechanical ventilation.

2.2 Currently Available, Pharmacologically Unrelated Treatments/Interventions for the Proposed Indication

Treatment for RSV infection is limited to supportive care.

Palivizumab (Synagis; MedImmune), is a monoclonal antibody approved by the FDA for prevention of severe RSV disease in high-risk infants.

Nirsevimab-alip (Beyfortus; AstraZeneca and Sanofi) is a monoclonal antibody approved by the FDA for prevention of RSV disease and LRTD in neonates, infants, and children up to 24 months of age.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, two vaccines have been approved by FDA for prevention of lower respiratory tract disease caused by RSV. On May 3, 2023, FDA approved an adjuvanted RSV vaccine (trade name Arexvy) manufactured by GlaxoSmithKline Biologicals, SA for use in adults 60 years of age and older. Information regarding the safety and effectiveness of Arexvy is described in the [U.S. Prescribing Information](#) (USPI). On May 31, 2023, FDA approved an RSV vaccine (trade name Abrysvo) manufactured by Pfizer, Inc for use in adults 60 years of age and older. On August 21, 2023, this RSV vaccine was also approved for use in pregnant individuals 32 through 36 weeks gestation to prevent RSV in infants. Information regarding the safety and effectiveness of Abrysvo is described in the [USPI](#).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N/A

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Regulatory Pathway to Licensure:

The basis of the licensure approach relied on establishing acceptable safety and efficacy in preventing lower respiratory tract disease due to RSV after administration of mResvia as compared with placebo.

Major Regulatory Activity:

The following timeline provides the major regulatory activity associated with this BLA:

- July 30, 2021: Received Fast Track Designation
- January 25, 2023: Received Breakthrough Therapy Designation
- March 21, 2023: FDA Response to pre-BLA Clinical Questions

- FDA provided guidance on the required size of the safety database and duration of follow-up postvaccination
- January 19, 2023: Notification of Intent to use Priority Review Voucher
- May 17, 2023: FDA agreement on Rolling Review of BLA
- November 9, 2023: Received Priority Review

2.6 Vaccine-Associated Enhanced Respiratory Disease

In the late 1960's, evaluation of a formalin-inactivated RSV vaccine (FI-RSV) in RSV-naïve infants was associated with enhanced respiratory disease (ERD) following subsequent natural RSV infection ([Kim et al., 1969](#)). The mechanisms responsible for FI-RSV vaccine associated ERD are still not fully understood, however studies suggest that inadequate production of neutralizing antibody despite an increase in overall antibody titer and an exaggerated Th2 response after subsequent infection may be implicated ([Chin et al., 1969](#); [Kapikian et al., 1969](#); [Fulginiti et al., 1969](#)). The risk of ERD in older children and adults is low, due to immunity induced by prior natural RSV infection ([Acosta et al., 2016](#)).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. However, presentation of the submitted safety datasets for Study P301 did not initially align with the data standards outlined in Clinical Data Interchange Standards Consortium. Following CBER's request, the Applicant submitted revised datasets that were considered sufficient to permit full review and verification of available safety data. Additionally, updated data for the analyses of safety and efficacy were submitted for a later data cutoff point as Study P301 is ongoing at the time of this review. These updated data were obtained in a timely manner for review through an information request. Please see memorandum by Dr. Brenda Baldwin, PhD, Consult Reviewer, and Dr. Ross Peterson, PhD, Statistical Reviewer.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Safety, efficacy, and immunogenicity data from two studies were provided in this application to support licensure of mResvia. All clinical trials were approved by Ethics Committees; followed the International Council on Harmonization's Good Clinical Practice (GCP) guidelines [E6(R2)]; and informed, written consent was obtained from all participants as per GCP guidelines and contained all the essential elements of informed consent as stated in 21 CFR 50.25. Issues regarding the conduct of the study were investigated and corrective and preventive actions were taken.

Bioresearch Monitoring (BIMO) inspections were issued for four clinical study sites that participated in the conduct of Study 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. Please see memorandum by the BIMO Reviewer.

3.3 Financial Disclosures

Not applicable.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing, pharmacology non-clinical testing, and clinical assays used for case confirmation and to assess vaccine immunogenicity were reviewed by CBER CMC reviewers and determined to support licensure.

4.2 Assay Validation

All analytical procedures used for the in-process, release and stability testing of mRNA-1345 were reviewed and determined adequate to support licensure. All platform analytical methods were validated as proper to confirm suitability for their intended use. Clinical assays used for case confirmation and to assess vaccine immunogenicity were adequate to support licensure as determined by CBER Product and Assay reviewers.

4.3 Nonclinical Pharmacology/Toxicology

The Applicant of this BLA submitted sufficient nonclinical toxicology studies and considered by the CBER Toxicology reviewer to be adequate to support licensure.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

mResvia is an LNP-encapsulated mRNA-based vaccine encoding the membrane-anchored RSV F glycoprotein derived from an RSV-^{(b)(4)} strain ((b) (4)) and stabilized in the prefusion conformation. The F protein exists in 2 primary conformational states, prefusion and postfusion. The prefusion state facilitates entry into the host cell through a conformational change to the postfusion state. The prefusion conformation displays the epitopes that are the primary targets of a neutralizing antibody response following RSV infection. mResvia induces an immune response against RSV pre-F protein that protects against LRTD caused by RSV.

4.5 Statistical

The CBER Clinical Statistical reviewer confirmed the statistical analyses for both the efficacy and safety endpoints by reproducing the results using datasets submitted in the Study Data Tabulation Model format by the Applicant. No major statistical issues were identified that would impact the interpretation of the data and conclusions.

4.6 Pharmacovigilance

The CBER Pharmacovigilance (PV) reviewer had no safety concerns and agree with the Applicant's proposed pharmacovigilance plans to include routine pharmacovigilance in accordance with 21 CFR 600.80. The PV team will be requesting the Applicant to provide updates of adverse events of special interest (AESIs) from both voluntary studies, along with an assessment of the cases, in the quarterly periodic safety reports for the first 3 years after approval. The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy at this time.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This BLA included clinical data from Study P301 to support efficacy and safety of mResvia in adults 60 years of age and older. Supportive data from Study P101 were also submitted to the BLA and are outlined in [Table 1](#). Data from each study are individually summarized in Section [6](#).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following amendments were reviewed in support of this application (listed by modules):

- Amendment 0: Modules 1, 2, and 5
- Amendment 1: Modules 1, 2, and 5
- Amendment 4: Modules 1 and 5
- Amendment 5: Modules 1 and 5
- Amendment 6: Modules 4 and 5
- Amendment 7: Modules 1 and 5
- Amendment 8: Modules 1 and 5
- Amendment 10: Modules 1 and 5
- Amendment 11: Modules 1 and 5
- Amendment 12: Module 1
- Amendment 13: Modules 1 and 5
- Amendment 19: Modules 1 and 5
- Amendment 20: Modules 1 and 5
- Amendment 21: Modules 1 and 5
- Amendment 22: Modules 1 and 5
- Amendment 27: Modules 1 and 5
- Amendment 28: Module 1
- Amendment 30: Module 1
- Amendment 31: Module 1
- Amendment 32: Module 1
- Amendment 34: Module 1
- Amendment 36: Modules 1 and 5
- Amendment 37: Module 1
- Amendment 38: Modules 1 and 5
- Amendment 40: Modules 1 and 5
- Amendment 41: Modules 1 and 5
- Amendment 44: Modules 1 and 5
- Amendment 45: Modules 1 and 5
- Amendment 46: Module 1
- Amendment 47: Module 1
- Amendment 48: Module 1
- Amendment 51: Module 1 and 5
- Amendment 52: Module 1 and 5
- Amendment 53: Module 1 and 5
- Amendment 56: Module 1
- Amendment 65: Module 1
- Amendment 67: Module 1

5.3 Table of Studies/Clinical Trials

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of mResvia

Study Number	Study Description	Total Randomized (N) Total Final mResvia ^a (n) Age Group	Test Product(s) ^b
P301	Sequential Phase 2 and Phase 3 randomized, observer-blind, placebo-controlled, multicenter, case-driven study to evaluate efficacy and safety	N=18,290 n=18,231 Adults ≥60 years with or without underlying medical conditions	mResvia 50 µg
P101	Phase 1 randomized, observer-blind, placebo-controlled, dose-escalation multicenter study to evaluate safety and immunogenicity	N=260 n=47 Healthy adults 65 through 79 years; Healthy adults of Japanese descent ≥60 years	mResvia 12.5 µg mResvia 25 µg mResvia 50 µg mResvia 100 µg mResvia 200 µg

Source: STN 125796/0. Synopses of Individual Studies; P101 CSR, Tables 14.1.2.2.1 and 14.1.2.5; Amendment 38, Table 14.1.2.1.

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

a. Final dose and formulation of mResvia (50 µg)

b. Only the active vaccine is listed. Each study also included a placebo group.

5.4 Consultations

A consultation with the Division of Medication Error Prevention and Analysis (DMEPA) at the Center for Drug Evaluation and Research (CDER) of the FDA was requested to review use-related risks and human factors data to support the use of a prefilled syringe (PFS) presentation. DMEPA evaluated the use-related risk analysis (URRA) submitted for a plastic PFS and did not identify any new or unique risks when compared with similar marketed products intended for use by healthcare providers. DMEPA also considered that human factors (HF) validation data from the plastic PFS used with US-licensed Spikevax COVID-19 vaccine manufactured by Moderna and previously reviewed by DMEPA to be supportive.

5.4.1 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 adults ≥60 years of age and addressed issues relevant to FDA's review of mResvia; 2) with 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 VRBPAC.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed (if applicable)

Gargano, JW, 2021 Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021, *MMWR Morb Mortal Wkly Rep*, 70(27):977-982.

Acosta, P et al. (2016). Brief history and characterization of enhanced respiratory syncytial virus disease. *Clinical and Vaccine Immunology*. March 7;23(3):189-195. doi: 10.1128/CVI.00609-15

Centers for Disease Control and Prevention (CDC). (2022). RSV Research and Surveillance. Accessed October 10, 2022.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study P301

NCT05127434

Title: “A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Adults ≥60 Years of Age”

Study Overview: Study 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 adults ≥60 years. The Phase 2 segment was designed to assess the safety of mResvia in approximately 2,000 participants prior to enrollment of approximately 35,000 participants in the Phase 3 segment. 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. Only study objectives and results available at the time of BLA submission are described below.

6.1.1 Objectives

Primary Objectives

1. *Efficacy:* 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

Endpoints: RSV-LRTD cases (see [Table 2](#) for case definitions)

- a. Vaccine efficacy (VE) of mResvia to prevent a first episode of RSV-LRTD with 2 or more symptoms within the period of 14 days post-injection up to 12 months post-injection
 - **Statistical Criterion for Success:** The lower bound (LB) of the 2-sided confidence interval (CI) adjusted for interim hypothesis testing for VE to prevent protocol-defined RSV-LRTD with 2 or more symptoms is >20%, with VE defined as the percent of reduction in the hazard of the primary endpoint, estimated by $VE = 100 \times (1 - \text{hazard ratio (HR) [mResvia vs placebo]}) \%$.
- b. Vaccine efficacy (VE) of mResvia to prevent a first episode of RSV-LRTD with 3 or more symptoms within the period of 14 days post-injection up to 12 months post-injection
 - **Statistical Criterion for Success:** The LB of the 2-sided CI adjusted for interim hypothesis testing for VE to prevent protocol-defined RSV-LRTD with 3 or more symptoms is >20%, with VE defined as the percent of reduction in the hazard of the primary endpoint, estimated by $VE = 100 \times (1 - \text{HR [mResvia vs placebo]}) \%$.

2. **Safety:** To evaluate the safety and tolerability of the mResvia vaccine

Endpoints:

- a. Numbers and percentages of participants with solicited local and systemic adverse reactions (ARs) up to 7 days post-injection.
- b. Unsolicited adverse events (AEs) up to 28 days post-injection.
- c. Medically attended adverse events (MAAEs), adverse events of special interest (AESIs), serious adverse events (SAEs), and AEs leading to withdrawal up to 24 months post-injection (see definitions [below](#)).

Hypothesis-Tested Secondary Efficacy Objectives

1. To evaluate the efficacy of a single dose of mResvia vaccine in the prevention of a first episode of RSV-associated acute respiratory disease (RSV-ARD) as compared with placebo within the period of 14 days post-injection up to 12 months post-injection

Endpoint: RSV-ARD cases

- VE of mResvia to prevent a first episode of RSV-ARD within the period of 14 days post-injection up to 12 months post-injection
 - **Statistical Criterion for Success:** The LB of the 2-sided 95% CI for VE to prevent the first episode of RSV-ARD is >20%.

2. To evaluate the efficacy of a single dose of mResvia vaccine in the prevention of first hospitalization associated with RSV-ARD or RSV-LRTD as compared with placebo within the period of 14 days post-injection up to 12 months post-injection

Endpoint: prevention of RSV-ARD or RSV-LRTD associated hospitalization

- VE of mResvia to prevent first hospitalization associated with RSV-ARD or RSV-LRTD within the period of 14 days post-injection up to 12 months post-injection
 - **Statistical Criterion for Success:** The LB of the 2-sided 95% CI for VE to prevent first hospitalization associated with RSV-ARD or RSV-LRTD is >20%.

Additional secondary efficacy objectives for this BLA submission include evaluation of VE to prevent a first episode of RSV-LRTD (with ≥ 2 symptoms and with ≥ 3 symptoms) and RSV-ARD by RSV subtype A and subtype B. Additional exploratory efficacy objectives evaluated specific clinical disease endpoints according to defined parameters. Secondary objectives evaluating immunogenicity endpoints were included in the study design; however, immunogenicity data were not available for review at the time of the BLA submission.

6.1.2 Design Overview

Study P301 is a multicenter, randomized, observer-blind, placebo-controlled, case-driven study conducted in sequential Phase 2 and Phase 3 segments to evaluate the safety and efficacy of mResvia vaccine as compared with placebo in adults ≥ 60 years of age. The Phase 2 segment was conducted at U.S. sites only with the primary purpose to provide a preliminary assessment of the safety of mResvia in adults ≥ 60 years of age prior to enrollment in the Phase 3 segment conducted at sites in multiple countries. Enrollment in the Phase 3 segment was initiated following a satisfactory review by the independent Data and Safety Monitoring Board (DSMB) of Day 29 safety data from the first 400 Phase 2 segment participants. Participants in both segments were randomized 1:1 to receive a single intramuscular (IM) injection of mResvia or placebo and stratified

by age (80% 60 through 74 years of age and 20% ≥ 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 through 69 years of age, 30% of participants 70 through 79 years of age, and 10% of participants ≥ 80 years of age. Participants from both study Phase segments contributed to the planned safety, efficacy, and immunogenicity analyses. Study P301 is designed to follow participants in a blinded fashion until 24 months after vaccination.

6.1.3 Population

Key Inclusion Criteria

- Adults ≥ 60 years of age who are primarily responsible for self-care and activities of daily living. Those with one or more chronic medical diagnoses could be included if medically stable, defined as:
 - No changes in medical therapy within 1 month due to treatment failure or toxicity
 - No medical events qualifying as serious adverse events (SAEs) within 1 month of the planned study vaccination
 - No known, current, and life-limiting diagnoses which could continue during the primary efficacy period and could make completion of the protocol unlikely
- Body mass index (BMI) from ≥ 18 kg/m² to ≤ 35 kg/m²

Key Exclusion Criteria

- Reported history of congenital or acquired immunodeficiency, immune-suppressive condition, or immune-mediated disease.
Note: Participants with stable autoimmune diseases that do not require systemic immunosuppressants were permitted.
- Reported history of anaphylaxis or severe hypersensitivity reaction after receipt of the mResvia vaccine or any components of the mResvia vaccine.
- History of a serious reaction to any prior vaccination, or Guillain-Barré syndrome within 6 weeks of any prior influenza immunization.
- Received or plans to receive any non-study vaccine (including authorized or approved vaccines for the prevention of COVID-19 regardless of type of vaccine) within 28 days before or after study injection.
- 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.
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of the study injection or during the study.
- Acute disease at the time of enrollment (defined as the presence of moderate or severe illness with or without fever, or an oral temperature $\geq 37.8^{\circ}\text{C}$ (100.0°F) on the planned day of vaccine administration).
- 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.

- Known history of hypotension, or systolic blood pressure <85 mmHg at the screening or baseline (Day 1) visit.
- Diastolic blood pressure >90 mmHg at the screening or baseline (Day 1) visit.
- Known uncontrolled disorder of coagulation.
Note: Participants receiving aspirin, clopidogrel, prasugrel, dipyridamole, dabigatran, apixaban, rivaroxaban, or warfarin for cardiovascular prophylaxis or prophylaxis of thromboembolic disease or stroke in the setting of atrial fibrillation and under good control will NOT be excluded.
- History of myocarditis, pericarditis, or myopericarditis within 2 months prior to screening. Participants who have not returned to baseline after their convalescent period will also be excluded.

6.1.4 Study Treatments or Agents Mandated by the Protocol

mResvia (investigational RSV vaccine):

- Dose and route of administration: 0.5 mL IM
- Formulation: 50 µg of mRNA encoding the RSV stabilized prefusion F protein formulated in lipid nanoparticles composed of 4 lipids (SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1 monomethoxypolyethyleneglycol-2,3-dimyristylglycerol)
- Presentation: sterile liquid for injection, white to off-white dispersion
 - Phase 2 - concentration of 0.4 mg/mL (diluted 1:4 with 0.9% sodium chloride to achieve a concentration of 0.1 mg/mL) in 20 mM Tris buffer containing 87 mg/mL sucrose and (b) (4) mM sodium acetate at (b) (4)
 - Phase 3 – concentration of 0.1 mg/mL in 20 mM Tris containing 87 mg/mL sucrose and (b) (4) mM acetate at (b) (4)
- Lots: 6011021001 and 6012521001

Placebo:

- Dose and route of administration: 0.5 mL IM
- Formulation: 0.9% normal saline
- Presentation: sterile, clear solution
- Lots: 6028290, 20QGF026, 20QHH025, 20QIF006, 20QKH007, 20QKH026, 20QMF012, 21102DK, and EG1869

6.1.5 Directions for Use

For this study, mResvia was supplied as a sterile liquid in a glass vial.

Reviewer Comment

The Applicant intends for the licensed product to include a suspension in a pre-filled syringe (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 URRA for a plastic PFS and a HF validation study previously reviewed by DMEPA for a PFS used with Moderna's U.S.-licensed mRNA-based vaccine product (Spikevax). This approach was determined to be acceptable based on a consultation with DMEPA, as discussed above in Section 5.4. For further information, please refer to DMEPA's consultation review memo.

6.1.6 Sites and Centers

Phase 2 was conducted at 55 sites in the United States (U.S.) only. Phase 3 was conducted at 268 sites in the following 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.

6.1.7 Surveillance/Monitoring

Study oversight included Institutional Review Board or Independent Ethics Committee review and approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents.

The study 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. The DSMB, comprised of external independent subject matter experts and an unblinded statistician, held regular meetings to periodically review blinded and unblinded safety data, cases of respiratory disease, and ad hoc reviews of safety events from Study P301, as well as information from other nonclinical and clinical studies related to mResvia.

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. Cases were adjudicated as either a CEAC-confirmed event (i.e., acute myocarditis, acute pericarditis, or myopericarditis), not a charter-defined event per CEAC (i.e., does not meet any of the categories above), or undecided (i.e., not enough information). CEAC determinations were based on clinical history, laboratory testing, imaging findings, and consultation reports and did not include causality adjudication. Probable or confirmed cases were referred to the Applicant to make a final decision on whether to suspend further enrollment and/or study dosing.

Following the screening visit, all participants will complete up to 7 scheduled visits, with the following major study activities:

- Visit 1: Day 1
Blood collection (serum antibodies), single IM injection of mResvia or placebo, eDiary training and activation for solicited adverse reactions, frailty status assessment
- Visit 2: Day 15 (Phase 2 participants only)
Blood collection (serum antibodies), eDiary activation for RSV-like symptoms
- Visits 3 and 4: Days 29 and 181, respectively
Blood collection (serum antibodies)
- Visit 5: Day 365
Blood collection (serum antibodies), frailty status assessment
- Visit 6: Day 546
Blood collection (serum antibodies)

- Visit 7: Day 730
Blood collection (serum antibodies), frailty status assessment

All participants 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.

Safety Monitoring

Solicited local ARs (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).

The grading scales for solicited local ARs were as follows:

- Pain and axillary swelling/tenderness
 - Grade 1: no interference with activity
 - Grade 2: repeated use of over-the-counter pain reliever >24 hours or interferes with activity
 - Grade 3: any use of prescription pain reliever or prevents daily activity
 - Grade 4 requires emergency room visit or hospitalization
- Erythema and swelling
 - Grade 1: 2.5 cm to 5.0 cm
 - Grade 2: 5.1 cm to 10.0 cm
 - Grade 3: >10.0 cm
 - Grade 4: necrosis

The grading scales for solicited systemic ARs were as follows:

- Headache
 - Grade 1: no interference with activity
 - Grade 2: repeated use of over-the-counter pain reliever >24 hours or some interference with activity
 - Grade 3: significant; any use of prescription pain reliever or prevents daily activity
 - Grade 4: requires emergency room visit or hospitalization
- Fatigue, myalgia, and arthralgia
 - Grade 1: no interference with activity
 - Grade 2: some interference with activity
 - Grade 3: significant; prevents daily activity
 - Grade 4: requires emergency room visit or hospitalization
- Nausea/vomiting
 - Grade 1: no interference with activity or 1-2 episodes/ 24 hours
 - Grade 2: some interference with activity or >2 episodes/ 24 hours
 - Grade 3: prevents daily activity, requires outpatient intravenous hydration
 - Grade 4: requires emergency room visit or hospitalization for hypotensive shock

- Chills
 - Grade 1: no interference with activity
 - Grade 2: some interference with activity not requiring medical intervention
 - Grade 3: prevents daily activity and requires medical intervention
 - Grade 4: requires emergency room visit or hospitalization
- Fever
 - Grade 1: 38.0-38.4°C
 - Grade 2: 38.5-38.9°C
 - Grade 3: 39.0-40.0°C
 - Grade 4: >40.0°C

Unsolicited AEs occurring during the 28 days following vaccination (i.e., the day of vaccination and 27 subsequent days) were recorded. AEs leading to discontinuation from study participation, MAAEs, AESIs and 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) swab collection for detection of respiratory pathogens by reverse transcription polymerase chain reaction (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. Clinical symptomology to support the study case definitions for RSV-LRTD and RSV-ARD could be participant reported and/or from a clinical assessment.

Immunogenicity Monitoring

Immunogenicity data were not available at the time of BLA submission. Sera to assess RSV neutralizing antibody levels and RSV binding antibody levels were to be collected in 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.

6.1.8 Endpoints and Criteria for Study Success

See Section [6.1.1](#) above and Section [6.1.9](#) below.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

Sample size was estimated by the total number of cases to demonstrate VE (mResvia vs. placebo) to prevent protocol-defined RSV-LRTD disease. Target enrollment was approximately 37,000 participants to be randomized in a 1:1 ratio to receive either mResvia or placebo.

Methods

A hierarchical statistical testing procedure was used to control the overall type I error rate at 2.5% (1-sided) over the primary efficacy endpoints and hypothesis-tested secondary efficacy endpoints.

For the primary and hypothesis-tested secondary efficacy objectives, mResvia was compared with placebo, testing the following null hypotheses sequentially:

1. H^1_0 : VE $\leq 20\%$ for RSV-LRTD cases with ≥ 2 symptoms within the period of 14 days post-injection up to 12 months post-injection
2. H^2_0 : VE $\leq 20\%$ for RSV-LRTD cases with ≥ 3 symptoms within the period of 14 days post-injection up to 12 months post-injection or ≥ 75 years of age and risk factors for LRTD (present versus absent), was used to estimate the hazard ratio (HR).

The primary efficacy objectives were considered met if the lower bound of the 2-sided CI adjusted for interim hypothesis testing of VE ruled out 20% either at an interim analysis or the primary analysis, as discussed below under [Analysis Timing](#).

Hypothesis-tested secondary efficacy endpoints were to be tested at the planned analysis at 12 months or the final analysis, whichever was applicable, after both primary efficacy endpoints achieved statistical significance. If efficacy was demonstrated for the 2 primary efficacy endpoints at an earlier interim analysis, secondary efficacy endpoints could be analyzed at that interim analysis if data were available.

Case Definitions

The case definitions for the efficacy endpoints for Study P301 are shown in [Table 2](#). Case definitions required the onset of eligible symptoms occur either before or after 14 days of a positive RSV RT-PCR nasopharyngeal swab specimen collection date. The primary analysis required that cases be confirmed by RT-PCR conducted in a CLIA-certified or CLIA-equivalent laboratory using a validated PCR assay. VE sensitivity analyses were conducted using all PCR-confirmed cases, including those derived from noncertified laboratories.

Table 2. Case Definitions, Study P301

Term	Case Definition
RSV-LRTD with ≥ 2 (or ≥ 3) symptoms	RT-PCR-confirmed RSV infection PLUS new or worsening of ≥ 2 (or ≥ 3) of the following symptoms, lasting for at least 24 hours: <ul style="list-style-type: none">• shortness of breath• cough and/or fever ($\geq 37.8^\circ\text{C}$ [100.0°F])• wheezing and/or rales and/or rhonchi• sputum production

Term	Case Definition
	<ul style="list-style-type: none"> tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline measurement in those who have baseline tachypnea) hypoxemia (new oxygen saturation $\leq 93\%$ or new or increasing use of supplemental oxygen) pleuritic chest pain
RSV-ARD	<p>RT-PCR-confirmed RSV infection PLUS an acute symptomatic respiratory disease manifesting as new or worsening of ≥ 1 of the following symptoms, lasting for at least 24 hours:</p> <ul style="list-style-type: none"> stuffy nose runny nose sore throat hoarseness sinus pain chills cough fever ($\geq 37.8^{\circ}\text{C}$ [100.0°F]) shortness of breath observed tachypnea (≥ 20 breaths per minute or increase of ≥ 2 breaths per minute from baseline in those who have baseline tachypnea), hypoxemia (new oxygen saturation $\leq 93\%$ or new or increasing use of supplemental oxygen) wheezing sputum production pleuritic chest pain

Source: Adapted from STN 125796/0, P301 Clinical Study Report, Table 4

RSV=respiratory syncytial virus; RSV-ARD=respiratory syncytial virus-acute respiratory disease; RSV-LRTD=respiratory syncytial virus-lower respiratory tract disease; RT-PCR=reverse transcriptase polymerase chain reaction

Reviewer Comment

The majority of symptoms in the case definition for RSV-ARD are the same symptoms used to define RSV-LRTD (i.e., cough, fever, shortness of breath, tachypnea, hypoxemia, wheezing, sputum production, and pleuritic chest pain). Symptoms unique to the RSV-ARD case definition are generally upper respiratory tract symptoms (i.e., stuffy nose, runny nose, sore throat, hoarseness, sinus pain, and chills).

Analysis Timing

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.

Reviewer Comment

IA1 was conducted when at least 50% of targeted RSV-LRTD cases had accrued. This analysis was conducted using a data cutoff date of November 30, 2022 with a median of 3.7 months of follow-up. Since efficacy was demonstrated for both primary endpoints, IA1 was considered the primary analysis of efficacy and subsequent analyses were considered supportive. 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.

Sensitivity Analyses/Subgroup Analyses

For each primary efficacy endpoint, the following sensitivity analyses were performed:

1. Analyses of primary endpoints using the actual stratification factors derived from the electronic case report form (eCRF) in the stratified Cox model based on the Per-Protocol Efficacy (PPE) Set
2. Analyses of the primary endpoints based on the modified Intent to Treat (mITT) Set
3. Analyses of the primary endpoints based on the PPE Set following the alternative definition of the primary efficacy endpoint (i.e., RT-PCR results to detect RSV infection from specialty laboratory, results with a verified RT-PCR test kit from a certified laboratory [CLIA or CLIA equivalent] or results with a test kit from a non-certified laboratory).

For each primary efficacy endpoint, the following supportive analyses were performed:

1. Incidence rate for each group in the PPE Set
2. Farrington and Manning's score method to estimate VE with a 2-sided 95% CI in the PPE Set.

The primary efficacy endpoint was analyzed by the following subgroups based on risk factors for LRTD:

- Sex
- Race
- Ethnicity
- Age groups (≥ 60 and < 75 years vs. ≥ 75 years and ≥ 60 and < 70 years, ≥ 70 and < 80 years, or ≥ 80 years)
- Congestive heart failure [CHF]/chronic obstructive pulmonary disease [COPD] absent or present)
- Comorbidities of interest
- Frailty status (based on Edmonton Frail Score),
- World Bank region and country classifications by income level 2022
- History of COVID-19 and hospitalization due to COVID-19.

Protocol Amendments and Changes to Planned Analyses

The original protocol was dated October 7, 2021.

Protocol Amendment 1.0 (dated September 22, 2022) included the following substantial changes:

- Update to primary efficacy endpoints: Added RSV-LRTD case definition requiring ≥ 3 symptoms of LRTD to be present. This endpoint (corresponding to the second case definition) was tested in a hierarchical fashion after RSV-LRTD with ≥ 2 LRTD symptoms.
- Increase in planned study sample size to 37,000 participants to provide adequate power for the endpoint assessing RSV-LRTD with 3 or more symptoms.
- Futility analysis removed because study enrollment would have been nearly complete when the DSMB reviewed the futility analysis results.

Protocol Amendment 2.0 (dated November 16, 2022) was implemented to harmonize the efficacy success criteria with other candidate RSV vaccines. In addition, the amendment clarified that visits due to surveillance for RSV (per-protocol illness visits) that would normally have not resulted in consultation of a healthcare provider were not to be reported as MAAEs.

6.1.10 Study Population and Disposition

This BLA submission consists of data from the study start on November 17, 2021 through the primary efficacy analysis data cutoff date of November 30, 2022, the supportive efficacy analysis data cutoff date of April 30, 2023 and the safety analysis data cutoff date of June 24, 2023. As of the November 30, 2022 data cutoff, there were 35,519 participants randomized, and as of the April 30, 2023 and June 24, 2023 data cutoffs, there were 36,540 participants randomized.

6.1.10.1 Populations Enrolled/Analyzed

Populations used for the study analyses are defined in [Table 3](#). The Per-protocol Efficacy Population was the primary population used for the analyses of efficacy.

Table 3. Analysis Populations

Population	Description
Randomization Set	All randomized participants regardless IP administration status.
Full Analysis Set (FAS)	All randomized participants who received any IP.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who completed at least 1 visit or surveillance 14 days after the IP administration.
Per-protocol Efficacy (PPE) Set	All participants in the mITT Set who received the assigned IP dose according to protocol, completed at least 1 visit or surveillance contact 14 days after the IP administration, and had no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding.
Solicited Safety Set	All randomized participants who received any IP and contributed any solicited AR data.
Safety Set	All randomized participants who received any IP; used for all analyses of safety.

Source: Adapted from STN 125796/0, P301 Clinical Study Report, Table 5.

Abbreviations: AR=adverse reactions; IP=investigational product; RSV=respiratory syncytial virus.

6.1.10.1.1 Demographics

The demographics of participants in the Safety Set are shown in [Table 4](#). The median age of participants at enrollment in the Safety Population was 67 years, with 61.9% of

participants 60 through 69 years, 30.1% of participants 70 through 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 U.S. (53.5%). The demographic characteristics were similar between the vaccine and placebo groups.

Table 4. Demographic and Baseline Characteristics, Safety Set, Study P301 (24 JUN 2023)

Characteristic	mResvia N=18231 n (%)	Placebo N=18181 n (%)
Sex, n (%)	--	--
Male	9343 (51.2)	9238 (50.8)
Female	8888 (48.8)	8943 (49.2)
Age, years	--	--
Mean age (SD)	68.5 (6.60)	68.5 (6.62)
Median age (minimum, maximum)	67.0 (60, 108)	67.0 (60, 105)
60-69 years	11304 (62.0)	11250 (61.9)
70-79 years	5490 (30.1)	5482 (30.2)
≥80 years	1437 (7.9)	1449 (8.0)
Race, n (%)	--	--
African American/Black	2197 (12.1)	2158 (11.9)
American Indian or Alaska Native	905 (5.0)	892 (4.9)
Asian	2013 (11.0)	1995 (11.0)
Native Hawaiian or other Pacific Islander	27 (0.1)	19 (0.1)
White	11266 (61.8)	11252 (61.9)
Multiracial	760 (4.2)	751 (4.1)
Unknown	10 (<0.1)	20 (0.1)
Not reported	59 (0.3)	85 (0.5)
Other	994 (5.5)	1009 (5.5)
Ethnicity, n (%)	--	--
Hispanic/Latino	6091 (33.4)	6147 (33.8)
Not Hispanic/Latino	11955 (65.6)	11825 (65.0)
Not reported	158 (0.9)	187 (1.0)
Unknown	27 (0.1)	22 (0.1)

Characteristic	mResvia N=18231 n (%)	Placebo N=18181 n (%)
Country, n (%)	--	--
United States	9742 (53.4)	9725 (53.5)
Argentina	1794 (9.8)	1786 (9.8)
Australia	127 (0.7)	129 (0.7)
Bangladesh	1212 (6.6)	1209 (6.6)
Belgium	206 (1.1)	206 (1.1)
Canada	354 (1.9)	352 (1.9)
Chile	333 (1.8)	337 (1.9)
Colombia	1309 (7.2)	1312 (7.2)
Costa Rica	102 (0.6)	105 (0.6)
Finland	49 (0.3)	46 (0.3)
Germany	237 (1.3)	234 (1.3)
Japan	413 (2.3)	405 (2.2)
Mexico	370 (2.0)	361 (2.0)
New Zealand	146 (0.8)	152 (0.8)
Panama	773 (4.2)	773 (4.3)
Poland	171 (0.9)	173 (1.0)
Singapore	4 (<0.1)	4 (<0.1)
South Africa	493 (2.7)	489 (2.7)
South Korea	13 (<0.1)	14 (<0.1)
Spain	112 (0.6)	108 (0.6)
Taiwan	43 (0.2)	41 (0.2)
United Kingdom	228 (1.3)	220 (1.2)

Source: Adapted from STN 125796/0.38, P301 IR19 Table 14.1.3.6 and ad hoc Table 10.1.2 (DCO 24 Jun 2023; data extraction 13 Feb 2024).

Abbreviations: DCO=data cutoff; N=total number of participants in the specified group, or the total sample; n=number of participants with the specified characteristic; SD=standard deviation

The Safety Set included all randomized participants who received any study vaccine.

The demographics of the PPE Set (not shown) for the primary efficacy endpoint analyses (November 30, 2022 data cutoff) generally reflected what was observed in the Safety Set, except for a lower percentage of participants ≥80 years of age (5.5% vs. 7.9%) and a smaller proportion of Asian participants (8.7% vs. 11.0%) in the PPE Set compared to the Safety Set, respectively.

Reviewer Comment

The data cutoff date for the primary efficacy endpoint analyses was November 30, 2022, and the data cutoff date for the safety analyses was June 24, 2023. The higher proportion of participants ≥80 years in the Safety Set is likely due to enrollment enriched for older and high-risk participants between November 30, 2022 and December 23, 2022. The higher proportion of Asian participants in the Safety Set compared to the PPE Set likely reflects greater participant enrollment at sites in Bangladesh (6.6% vs. 4.3%, respectively) during the same time period following the data cutoff for the primary efficacy endpoint analyses. Due to the relatively small number of participants in these subgroups, the differences did not impact the demographic and baseline characteristics of the overall study population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Approximately 29% of participants in the Safety Set had at least one pre-specified comorbidity, as described in [Table 5](#). The most common comorbidity was diabetes (17.6%), and protocol-defined risk factors for LRTD of CHF and COPD were present in 1.5% and 6.0% of participants, respectively. Based on the Edmonton Frail Scale, most participants, 73.8%, were considered fit, with 15.8% of participants in the vulnerable range and 5.6% of participants considered frail. The proportions and types of at-risk conditions were balanced between the mResvia and placebo groups.

Table 5. Baseline Comorbidities, Safety Set, Study P301 (24 JUN 2023)

	mResvia N=18231 n (%)	Placebo N=18181 n (%)
Prespecified Comorbidities		
With ≥1 prespecified comorbidity ^a	5407 (29.7)	5295 (29.1)
Diabetes ^b	3249 (17.8)	3160 (17.4)
Lung disease ^c	2441 (13.4)	2366 (13.0)
Heart disease ^d	273 (1.5)	267 (1.5)
Liver disease	48 (0.3)	42 (0.2)
Renal disease	111 (0.6)	125 (0.7)
With ≥1 chronic cardiopulmonary condition	2575 (14.1)	2504 (13.8)
Asthma	1401 (7.7)	1357 (7.5)
Chronic obstructive pulmonary disease (COPD)	1091 (6.0)	1103 (6.1)
Congestive heart failure (CHF)	273 (1.5)	267 (1.5)
Frailty status ^e	--	--
Score 0-3: fit	13501 (74.1)	13359 (73.5)
Score 4-5: vulnerable	2834 (15.5)	2902 (16.0)
Score 6-7: mild frailty	812 (4.5)	826 (4.5)
Score 8-9: moderate frailty	169 (0.9)	160 (0.9)
Score ≥10: severe frailty	25 (0.1)	39 (0.2)
Missing	890 (4.9)	895 (4.9)

Source: Adapted from STN 125796/0.38, P301 IR19 Table 14.1.3.6 and ad hoc Table 10.2.1 (DCO 24 Jun 2023; data extraction 13 Feb 2024).

Abbreviations: DCO=data cutoff; N=total number of participants in the specified group, or the total sample; n=number of participants with the specified characteristic.

a. Participants may have more than one prespecified comorbid condition at baseline but were only counted once for summary rows.

b. Participants with Diabetes at baseline included 155 with Type 1 Diabetes (82 in mResvia and 73 in placebo), 6240 with Type 2 Diabetes (3157 in mResvia and 3083 in placebo), and 21 without discrimination between Type 1 or Type 2 recorded (12 in mResvia, 9 in placebo).

c. Includes Asthma, Chronic respiratory disease, and COPD.

d. Includes CHF.

e. Frailty status according to the Edmonton Frail Scale defined as follows: 0-3: Fit, 4-5: Vulnerable, 6-7: Mild Frail, 8-9: Moderate Frail, 10 or More: Severe Frail.

6.1.10.1.3 Participant Disposition

Primary Efficacy Analyses [November 30, 2022 data cutoff]

Disposition of Study P301 participants who contributed to the analyses of efficacy as of the November 30, 2022 data cutoff is presented in [Table 6](#). A total of 35,519 participants were randomized to receive mResvia (n=17,777) or placebo (n=17,742). The PPE Set, used for the primary analyses of efficacy, included a total of 35,064 participants, with 17,561 mResvia recipients and 17,503 placebo recipients. Of these participants, 99.7% (17,516 in the mResvia group and 17,445 in the placebo group) completed at least 28 days of efficacy follow-up post vaccination; 20.2% (3,557 in the mResvia group and 3,539 in the placebo group) completed at least 6 months of efficacy follow-up post

vaccination; and 0.2% (34 in the mResvia group and 29 in the placebo group) completed at least 12 months of efficacy follow-up postvaccination. The median duration of follow-up postvaccination was 3.7 months. The percentages of participants excluded and reasons for exclusion from the PPE Set were similar across groups. The most common reason for exclusion (0.6% in both groups) was the participant did not complete any visit or surveillance contact starting 14 days after study vaccination.

Table 6. Participant Disposition, Randomization Set, Study P301 (30 NOV 2022; Median Follow-Up 3.7 Months)

Population	mResvia N=17777 n (%)	Placebo N=17742 n (%)
Randomization Set	17777	17742
Full Analysis Set (FAS) ^a	17717 (99.7)	17674 (99.6)
Modified Intent-To-Treat (mITT) Set ^b	17634 (99.2)	17592 (99.2)
Excluded from mITT Set	143 (0.8)	150 (0.8)
Reason for exclusion	--	--
Did not receive study vaccine	60 (0.3)	68 (0.4)
Did not complete any visit or surveillance contact starting 14 days after IP administration	83 (0.5)	82 (0.5)
Per-Protocol Efficacy (PPE) Set ^c	17561 (98.8)	17503 (98.7)
Excluded from PPE Set	216 (1.2)	239 (1.3)
Reason for exclusion ^d	--	--
Did not receive study injection	60 (0.3)	68 (0.4)
Did not receive assigned IP dose according to protocol	1 (<0.1)	2 (<0.1)
Did not complete any visit or surveillance contact starting 14 days after IP administration	83 (0.5)	82 (0.5)
Had prohibited medication/vaccination affecting efficacy outcomes	29 (0.2)	33 (0.2)
Had other major protocol deviations affecting efficacy outcomes ^e	43 (0.2)	54 (0.3)

Source: Adapted from STN 125796/0.53, P301 IR34 Table 14.1.2.1 and Ad hoc Tables 10.1.4 and 10.1.7.

Abbreviations: FAS=full analysis set; IP=investigational product; mITT=modified intent-to-treat; PPE=per-protocol efficacy; N=total number of participants randomized to the group; n=number of participants with the specified characteristic; percentages based on Randomization Set.

a. The FAS included all randomized participants who received any IP.

b. The mITT Set included all participants in the FAS who completed at least 1 visit or surveillance 14 days after the IP administration.

c. The PPE Set included all participants in the mITT Set who received the assigned IP dose according to protocol, completed at least 1 visit or surveillance contact 14 days after the IP administration and had no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding.

d. Participants may have been excluded for more than 1 reason. A participant who has multiple reasons was counted only once based on the order of the reasons for exclusion listed.

e. Of the 97 total participants with "other major protocol deviations affecting efficacy outcomes," 50 were excluded from the PPE Set due to being dosed twice (within or external to Study P301).

Supportive Efficacy Analyses [April 30, 2023 data cutoff]

As of the April 30, 2023 data cutoff, the PPE Set included a total of 36,084 participants, with 18,074 mResvia recipients and 18,010 placebo recipients. Of these participants, 94.2% (17,040 in the mResvia group and 16,934 in the placebo group) completed at least 6 months of follow-up post vaccination and 12.7% (2,312 in the mResvia group and 2,283 in the placebo group) completed at least 12 months of follow-up postvaccination. The median duration of follow-up postvaccination was 8.6 months.

Safety Analyses [June 24, 2023 data cutoff]

Disposition of Study P301 participants who contributed to the analyses of safety are presented in [Table 7](#). A total of 36,412 (99.6%) of the randomized participants received study intervention and were included in the Safety Set, consisting of 18,231 participants in the mResvia group and 18,181 participants in the placebo group. Of these participants, 96.6% (17,635 in the mResvia group and 17,534 in the placebo group) completed at least 6 months of safety follow-up post vaccination. The Solicited Safety Set, used for the analyses of solicited safety, included 18,160 and 18,098 participants in the mResvia and placebo groups, respectively.

A total of 2,195 participants (6.0%) withdrew from the study after receipt of study intervention. The reasons for withdrawal and proportions of participants withdrawn were similar across groups. The most common reasons for withdrawal from the study after vaccination were withdrawal by the participant (2.5%) and lost to follow-up (2.4%). Death during the study led to the withdrawal of 0.6% of participants. Study withdrawal due to non-fatal adverse events was rare and occurred in <0.1% of participants in each group. Details about these AEs leading to withdrawal are further discussed in [Section 6.1.12.7](#).

Table 7. Participant Disposition, Safety Set, Study P301 (24 JUN 2023)

Population	mResvia N=18231 n (%)	Placebo N=18181 n (%)
Safety Set	18231	18181
Completed 6 months safety follow-up	17635 (96.7)	17534 (96.4)
Completed 12 months safety follow-up	4657 (25.5)	4647 (25.6)
Participants withdrawn after vaccination	1070 (5.9)	1125 (6.2)
Reason for withdrawal	--	--
Withdrawal by participant	445 (2.4)	480 (2.6)
Lost to follow-up	459 (2.5)	433 (2.4)
Death	97 (0.5)	116 (0.6)
Physician decision	36 (0.2)	57 (0.3)
Protocol deviation ^a	8 (<0.1)	7 (<0.1)
Adverse event	8 (<0.1)	13 (<0.1)
Other ^b	16 (<0.1)	18 (<0.1)
Non-compliance with study drug	1 (<0.1)	1 (<0.1)
Solicited Safety Set ^c	18160 (99.6)	18098 (99.5)
Excluded from Solicited Safety Set ^d	71 (0.4)	83 (0.5)
Did not contribute any solicited adverse reaction data	71 (0.4)	83 (0.5)

Source: Adapted from STN 125796/0.38 and 0.40, P301 IR19 Table 14.1.7.1 and ad hoc Tables 10.1.1 and 10.1.5 (DCO 24 Jun 2023; data extraction 13 Feb 2024).

Abbreviations: DCO=data cutoff; IP=investigational product; N=number of participants in Safety Set; n=number of participants with the specified characteristic; percentages based on the Safety Set.

a. Source ad hoc Table 10.1.1 terms a protocol deviation a "protocol violation."

b. Other reasons included: Investigator's decision, moving/relocation, non-compliance with study procedures/eDiary, incarceration, financial reasons, withdrawal of consent, personal reasons, lost ability to cognitively give informed consent or complete study requirements, participant enrolled in another mRNA trial, lost to follow-up.

c. The Solicited Safety Set included all randomized participants who receive any IP and contribute any solicited ARs data. The values in this row are the denominators for the percentage calculations for the rows below.

d. Excluded due to reason in the row below.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Primary Analyses [November 30, 2022 data cutoff]

The BLA submission includes data from the pre-specified interim analysis of the primary efficacy endpoints (considered the primary analysis) which includes cases of first episode of RSV-LRTD through the data cutoff date of November 30, 2022. 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.

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 postvaccination 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 8](#)).

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 8](#)).

Table 8. 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 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, 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; CLIA=Clinical Laboratory Improvement Amendment; FDA=US Food and Drug Administration; IP=investigational product; 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 $100\% \times (1 - \text{hazard ratio (mResvia vs. placebo)})$.

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 7](#).

Supportive Analyses [April 30, 2023 data cutoff]

Additional supportive efficacy data were 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 9](#)). While this analysis was descriptive, both primary endpoints met the pre-specified success criteria of LB CI of VE >20%.

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 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, 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; CLIA=Clinical Laboratory Improvement Amendment; FDA=US Food and Drug Administration; IP=investigational product; 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 $100\% \times (1 - \text{hazard ratio (mResvia vs. placebo)})$. 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 RTPCR 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.

The median duration of symptoms of RSV-LRTD cases with ≥ 2 symptoms was 20 days in the mResvia group, with a range 5 to 72 days, and 18 days in the placebo group, with a longer range 5 to 84 days. For RSV-LRTD cases with ≥ 3 symptoms, the median

duration of symptoms was 22 days in the mResvia group, with a range of 6 to 57 days, compared with 23 days in the placebo group, with a longer range of 8 to 84 days.

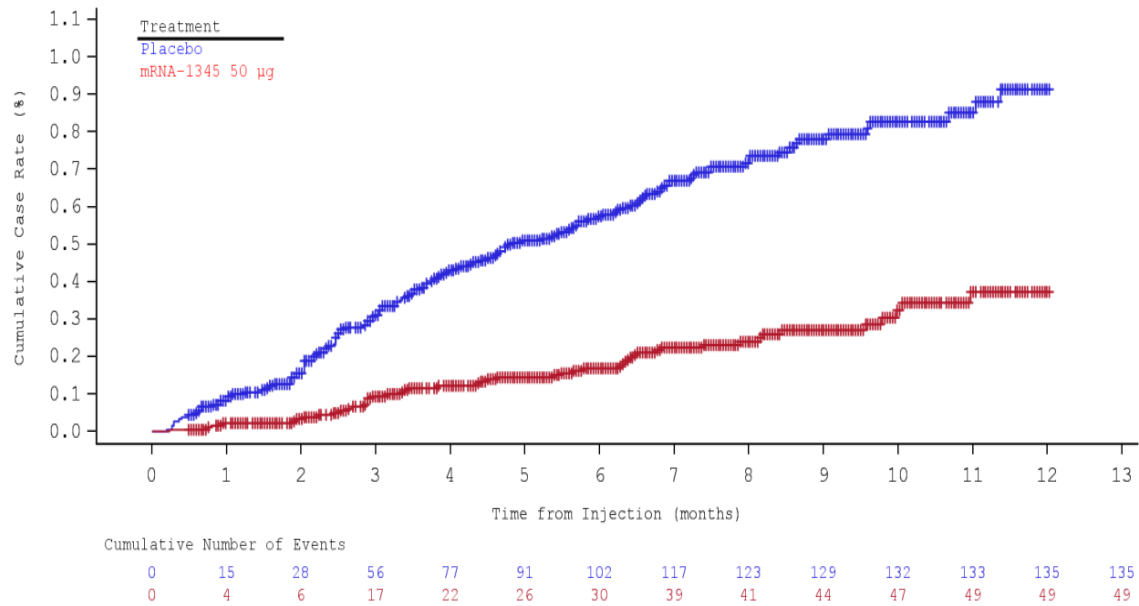
Reviewer Comment

1. 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.
2. The applicant initially submitted preliminary results from their interim analysis of Study P301, citing VEs of 83.7% (95.88% CI: 66.0, 92.2) and 82.4% (96.36% CI: 34.8, 95.3) for prevention of LRTD with ≥ 2 symptoms and LRTD with ≥ 3 symptoms, respectively. Due to inconsistencies noted in the original datasets submitted to the BLA, FDA requested that the Applicant complete all data cleaning activities up to the June 24, 2023 data cutoff and submit updated datasets. The updated datasets, submitted to the BLA on February 26, 2024, identified additional RSV cases with onset prior to data cutoff which met the study case definition. The primary efficacy analyses reflecting the updated datasets are presented in [Table 8](#) and [Table 9](#) above.

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 postvaccination, 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 P301 (30 APR 2023; Median Follow-Up 8.6 Months)



Source: Adapted from STN 125796/0.46 and 0.53, 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.

Reviewer Comment

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.

6.1.11.2 Subpopulation Analyses of Vaccine Efficacy [April 30, 2023 data cutoff]

The study was not powered to assess VE by demographic subgroups. The estimation of VE by demographic subgroups was limited by the small number of cases and group sizes for many of the subgroups. VE against RSV-LRTD with ≥ 2 symptoms by subgroups were generally similar when compared with the overall study population, however some confidence intervals were wide, non-estimable, or included a lower bound that crossed zero. [Table 10](#) below shows VE by subgroup at the time of the supportive analysis data cutoff with a median follow-up of 8.6 months after vaccination.

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 with 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.

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

Subgroup	mResvia Cases n/N	Placebo Cases n/N	VE % (95% CI) ^a
Age at study vaccination	--	--	--
60-69 years	32/11193 (0.29)	77/11146 (0.69)	58.8 (37.8, 72.7)
70-79 years	10/5455 (0.18)	45/5431 (0.83)	78.0 (56.3, 88.9)
≥80 years	6/1426 (0.42)	5/1433 (0.35)	-20.0 (-293.3, 63.4)
Sex	--	--	--
Male	22/9248 (0.24)	57/9134 (0.62)	61.9 (37.6, 76.7)
Female	26/8826 (0.29)	70/8876 (0.79)	63.0 (41.9, 76.4)
Race	--	--	--
White	44/11172 (0.39)	105/11144 (0.94)	58.4 (40.8, 70.7)
Black or African American	1/2157 (0.05)	3/2112 (0.14)	68.1 (-207.1, 96.7)
Asian	1/2007 (0.05)	9/1988 (0.45)	89.0 (13.5, 98.6)
Ethnicity	--	--	--
Hispanic/Latino	6/6054 (0.10)	24/6118 (0.39)	74.7 (38.2, 89.7)
Non-Hispanic/non-Latino	40/11838 (0.34)	103/11687 (0.88)	61.9 (45.1, 73.6)
Country	--	--	--
United States	28/9619 (0.29)	68/9581 (0.71)	59.1 (36.5, 73.7)
Argentina	2/1785 (0.11)	10/1782 (0.56)	80.0 (8.9, 95.6)
Australia	2/126 (1.59)	1/129 (0.78)	-103.1 (-2140.7, 81.6)
Bangladesh	0/1211	7/1207 (0.58)	100.0 (NE, 100.0)
Belgium	3/205 (1.46)	6/206 (2.91)	50.6 (-97.7, 87.6)
Canada	1/352 (0.28)	3/349 (0.86)	67.0 (-217.8, 96.6)
Chile	0/330	2/334 (0.60)	100.0 (NE, 100.0)
Colombia	1/1305 (0.08)	5/1310 (0.38)	79.9 (-71.9, 97.7)
Costa Rica	1/100 (1.00)	0/105	NE (NE, NE)
Finland	1/49 (2.04)	3/46 (6.52)	69.6 (-192.7, 96.8)
Germany	3/237 (1.27)	7/233 (3.00)	58.4 (-61.0, 89.3)
Japan	0/410	0/402	NE (NE, NE)
Mexico	0/369	1/360 (0.28)	100.0 (NE, 100.0)
New Zealand	0/145	2/150 (1.33)	100.0 (NE, 100.0)
Panama	0/771	4/770 (0.52)	100.0 (NE, 100.0)
Poland	2/170 (1.18)	1/173 (0.58)	-89.1 (-1988.5, 82.9)
Singapore	0/4	0/4	NE (NE, NE)
South Africa	3/492 (0.61)	2/487 (0.41)	-48.0 (-786.0, 75.3)

Subgroup	mResvia Cases n/N	Placebo Cases n/N	VE % (95% CI) ^a
South Korea	0/13	0/14	NE (NE, NE)
Spain	0/112	1/107 (0.93)	100.0 (NE, 100.0)
Taiwan	0/43	0/41	NE (NE, NE)
United Kingdom	1/226 (0.44)	4/220 (1.82)	76.0 (-114.6, 97.3)
Prespecified at-risk condition	--	--	--
With no prespecified comorbidity ^b	31/12709 (0.24)	76/12766 (0.60)	59.5 (38.5, 73.3)
With ≥1 prespecified comorbidity ^b	17/5365 (0.32)	51/5244 (0.97)	67.4 (43.6, 81.2)
CHF/COPD absent	45/16773 (0.27)	113/16703 (0.68)	60.6 (44.3, 72.1)
CHF/COPD present	3/1301 (0.23)	14/1307 (1.07)	78.3 (24.3, 93.8)
Frailty status ^c	--	--	--
Score 0-3: fit	37/13382 (0.28)	104/13246 (0.79)	65.0 (49.0, 75.9)
Score 4-5: vulnerable	8/2810 (0.28)	10/2861 (0.35)	18.9 (-105.6, 68.0)
Score 6-7: mild frailty	1/800 (0.13)	5/813 (0.62)	79.7 (-73.8, 97.6)
Score 8-9: moderate frailty	1/169 (0.59)	1/157 (0.64)	-4.0 (-1565.7, 93.5)
Score ≥10: severe frailty	0/25	1/39 (2.56)	100.0 (NE, 100.0)
Missing	1/888 (0.11)	6/894 (0.67)	83.1 (-40.3, 98.0)

Source: Adapted from STN 125796/0.41 and 0.51, P301 IRs 27 and 33 Ad hoc Tables 14.2.2.1.10.1 and 10.2.2. (data cutoff 30 Apr 2023; data extraction 13 Feb 2024)

Abbreviations: CHF=congestive heart failure; CI=confidence interval; CLIA=Clinical Laboratory Improvement Amendment; COPD=chronic obstructive pulmonary disease; EFS=Edmonton Frail Scale; IP=investigational product; N=total number of participants in each vaccination group; n=number of participants meeting the efficacy endpoint case definition from 14 days after study vaccination through 12 months after study vaccination; NE=not estimable; 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 $100\% \times (1 - \text{hazard ratio (mResvia vs placebo)})$. CI is obtained using 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 as applicable.

b. Includes diabetes, lung disease (asthma, chronic respiratory disease, and COPD), heart disease (includes CHF), liver disease, and renal disease.

c. Frailty status according to the Edmonton Frail Scale defined as follows: 0-3: Fit, 4-5: Vulnerable, 6-7: Mild Frail, 8-9: Moderate Frail, 10 or More: Severe Frail.

Due to fewer participants meeting the criteria for RSV-LRTD with ≥3 symptoms than for RSV-LRTD with ≥2 symptoms, results of subgroup analyses based on this endpoint yielded wider confidence intervals and less reliable vaccine effectiveness estimates, though subgroup analysis by participant age and demographics generally followed similar trends as observed for subgroup analysis of RSV-LRTD with ≥2 symptoms.

Reviewer Comment

As discussed in Section 6.1.9 above, additional sensitivity analyses were performed and did not identify any meaningful differences compared with the primary analyses.

6.1.11.3 Analyses of Secondary Endpoints

Primary Analysis of First Episode of RSV-ARD [November 30, 2022 data cutoff]

As of the November 30, 2022 data cutoff, after a median follow-up duration of 3.7 months, there were 139 cases of first-episode RSV-ARD reported occurring between 14 days and 12 months postvaccination, with 33 cases in the mResvia group compared to 106 cases in the placebo group. The VE point estimate for this endpoint was 69.1% (95% CI: 54.3, 79.1), which met the pre-specified success criterion (see Table 11).

Table 11. Vaccine Efficacy of mResvia Against First Episode of RSV-ARD, PPE Set, Study P301 (30 NOV 2022; Median Follow-Up 3.7 Months)

Efficacy Endpoint	mResvia N=17561 Cases, n (%)	Placebo N=17503 Cases, n (%)	VE % (95% CI)^a
First episode of RSV-ARD	33 (0.19)	106 (0.61)	69.1 (54.3, 79.1)
First hospitalization associated with RSV-ARD or RSV-LRTD	0	0	NE (NE, NE)

Source: Adapted from STN 125796/0.38 and 0.51, P301 IRs 19 and 33 Ad hoc Tables 10.11.3 and 14.2.2.4.1. (data cutoff 30 Nov 2022; data extraction 13 Feb 2024)

Abbreviations: AE=adverse event; CI=confidence interval; CLIA=Clinical Laboratory Improvement Amendments; 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; NE=not estimable; PPE=Per-Protocol Efficacy; RSV=respiratory syncytial virus; RT-PCR=reverse transcription polymerase chain reaction; RSV-ARD=RSV-associated acute respiratory disease; RSV-LRTD=RSV-associated lower respiratory tract disease; VE=vaccine efficacy.

a. VE is defined as $100\% \times (1 - \text{hazard ratio (mResvia vs placebo)})$. 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.

Supportive Analysis of First Episode of RSV-ARD [April 30, 2023 data cutoff]

Through the April 30, 2023 data cutoff, after a median follow-up duration of 8.6 months, there were 275 cases of first episode of RSV-ARD reported, with 87 cases in the mResvia group compared to 188 cases in the placebo group. The VE point estimate was 54.1% (95% CI: 40.8, 64.4).

Reviewer Comment

As described above in Section 6.1.9 (Table 2), many of the clinical symptoms used to support the ARD case definition were also used to support the LRTD case definition. As a result, most participants who met criteria for RSV-ARD also met the case definition for RSV-LRTD with ≥ 2 symptoms, confounding the interpretation of efficacy of mResvia against all cases of acute respiratory disease caused by RSV, particularly those that involve upper respiratory tract symptoms.

FDA requested a post hoc analysis to evaluate RSV-ARD without any symptoms of RSV-LRTD to provide a more clinically meaningful assessment of vaccine efficacy to prevent RSV upper respiratory symptoms. In this analysis, as of the November 30, 2022 data cutoff (median follow-up 3.7 months), there were 8 cases in total, with 2 cases in the mResvia group and 6 cases in the placebo group, resulting in a VE of 66.9% (95% CI: -63.9, 93.3). With a longer 8.6 months median duration of follow-up (April 30, 2023 data cutoff), there were 16 cases in total, with 6 cases in the mResvia group and 10 cases in the placebo group, resulting in a VE of 40.5% (95% CI: -63.8, 78.4).

This post hoc analysis demonstrated that when LRTD symptoms were excluded from the ARD definition, the remaining case count was low and resulted in a VE estimate with a negative lower bound and a wide confidence interval that included zero. Therefore, the indication for prevention of RSV-ARD in product labeling is not supported by these results.

Prevention of First Hospitalization [April 30, 2023 data cutoff]

The secondary objective to evaluate the efficacy of mResvia in preventing first hospitalization associated with RSV-LRTD or RSV-ARD could not be analyzed due to too few hospitalizations reported, with one RSV-associated hospitalization reported in the placebo group up to the April 30, 2023 data cutoff (median 8.6 months follow-up). There were no participants in the mResvia group who were hospitalized in association with RSV-LRTD or RSV-ARD up to the April 30, 2023 data cutoff.

Vaccine Efficacy by RSV Subtype [April 30, 2023 data cutoff]

Vaccine efficacy to prevent RSV-LRTD and RSV-ARD by RSV subtype A and B was descriptively assessed as a secondary objective. VE point estimates were consistently numerically higher against RSV-A compared to RSV-B; however, the confidence intervals were overlapping for each of the RSV subtypes. In addition, the low number of cases for some endpoints resulted in wide confidence intervals. The results as of the April 30, 2023 data cutoff (median follow-up 8.6 months) are shown below in [Table 12](#).

Table 12. Vaccine Efficacy of mResvia Against First Episode of RSV-LRTD With ≥2 or ≥3 Symptoms and RSV-ARD Starting 14 Days after Vaccination, By RSV Subtype, PPE Set, Study P301 (30 APR 2023; Median Follow-Up 8.6 Months)

Endpoint	mResvia N=18074 Cases n (%)	Placebo N=18010 Cases n (%)	VE ^a % (95% CI) ^b
First episode of RSV-LRTD with ≥2 symptoms	--	--	--
RSV-A	25 (0.14)	78 (0.43)	68.2 (50.0, 79.7)
RSV-B	22 (0.12)	50 (0.28)	56.3 (27.9, 73.5)
First episode of RSV-LRTD with ≥3 symptoms	--	--	--
RSV-A	11 (0.06)	30 (0.17)	63.6 (27.3, 81.7)
RSV-B	9 (0.05)	22 (0.12)	59.3 (11.7, 81.3)
First episode of RSV-ARD	--	--	--
RSV-A	44 (0.24)	108 (0.60)	59.5 (42.5, 71.5)
RSV-B	42 (0.23)	81 (0.45)	48.5 (25.3, 64.5)

Source: Adapted from STN 125796/0.41, P301 IR27 Ad hoc Tables 14.2.2.9.1, 14.2.2.10.1, 14.2.2.10.3 (data cutoff 30 Apr 2023; data extraction 13 Feb 2024)

Abbreviations: CI=confidence interval; CLIA=Clinical Laboratory Improvement Amendments; IP=investigational product; N=number of participants (at risk) in the specified vaccine group. These values are the denominators for the percentage calculations; n=total number of cases of the specified endpoint from 14 days after vaccination through 12 months after vaccination; PPE=Per-Protocol Efficacy; RSV=respiratory syncytial virus; RT-PCR=reverse transcription polymerase chain reaction; RSV-ARD=RSV-associated acute respiratory disease; RSV-LRTD=RSV-associated lower respiratory tract disease; VE=vaccine efficacy.

The PPE Set included all randomized participants who received the assigned IP dose according to protocol, complete at least 1 visit or surveillance contact 14 days after the IP administration and have no major protocol deviations affecting the efficacy outcomes as determined prior to database lock and unblinding.

a. VE is defined as $100\% \times (1 - \text{hazard ratio (mResvia vs placebo)})$.

b. CI is obtained using a stratified Cox proportional hazard model with Efron's method of tie handling and with 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 RTPCR 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.

No participants in the mResvia group and one participant in the placebo group tested positive for RSV-A and RSV-B concurrently.

6.1.11.4 Exploratory and Post Hoc Analyses

Exploratory analyses to assess severity [April 30, 2023 data cutoff]

Select exploratory efficacy objectives were included in this BLA submission using the April 30, 2023 data cutoff with a median follow-up duration of 8.6 months to evaluate specific clinical disease endpoints (e.g., hypoxia, tachypnea) according to predefined parameters to explore the possibility that these endpoints might represent measures of disease severity. For most of the exploratory endpoints, there were too few cases to conduct a meaningful analysis. A descriptive analysis of VE of mResvia to prevent first occurrence of protocol-defined RSV-LRTD with shortness of breath and at least one other symptom as a surrogate severity measure demonstrated a VE of 74.6% (95% CI: 50.7, 86.9) with 11 cases in the mResvia group and 43 cases in the placebo group.

Post hoc analysis to Assess RSV-ARD excluding RSV-LRTD Symptoms

As discussed in the [Reviewer Comment](#) above, FDA requested a post hoc analysis to evaluate RSV-ARD without any symptoms of RSV-LRTD to provide a more clinically meaningful assessment of vaccine efficacy to prevent RSV upper respiratory symptoms.

Post hoc analysis of Medically Attended RSV-LRTD [April 30, 2023 data cutoff]

A medically attended RSV case was defined as an event for which a participant seeks medical attention outside normal study procedures and scheduled assessments, including unscheduled study visits to a study site, mobile site, or at home visit and visits to health care providers external to the study site (e.g., emergency room, urgent care, or primary care physician). The VE point estimates were similar to those obtained in the primary efficacy analyses for the two RSV-LRTD endpoints. In both the mResvia and placebo groups, most RSV-LRTD cases (with ≥ 2 and ≥ 3 symptoms) were medically attended. In the mResvia group, 87.5% of RSV-LRTD cases with ≥ 2 symptoms and 90.0% of RSV-LRTD cases with ≥ 3 symptoms were medically attended. In the placebo group, 88.2% of RSV-LRTD cases with ≥ 2 symptoms and 96.1% of RSV-LRTD cases with ≥ 3 symptoms were medically attended.

6.1.12 Safety Analyses

There were 36,412 participants included in the Safety Set, of whom 35,169 (96.6%) completed at least 6 months of safety follow-up postvaccination (17,635 mResvia recipients and 17,534 placebo recipients) by the June 24, 2023 data cutoff date (10.2 months median follow-up).

6.1.12.1 Methods

See Section [6.1.7](#) above.

6.1.12.2 Overview of Adverse Events

Safety Overview

[Table 13](#) provides an overview of the rates of adverse events in the mResvia group compared with the placebo group during the study period up to the June 24, 2023 data cutoff. The rates of solicited reactions were higher among mResvia recipients compared to placebo recipients, with a more pronounced difference for solicited local reactions compared to solicited systemic reactions. The rates of unsolicited adverse events were similar across groups (20.8% in the mResvia group and 19.0% in the placebo group). The proportion of AEs leading to withdrawal from the study was also similar across groups (0.6% in the mResvia group and 0.8% in the placebo group). AESIs occurred in 0.3% of participants in each group. SAEs were reported by 7.8% of participants in the

mResvia group and 7.9% of participants in the placebo group, with 5 participants in the mResvia group and 4 participants in the placebo group experiencing SAEs considered by Investigators to be related to the study intervention (see Section 6.1.12.4 for details). At the time of the June 24, 2023 data cutoff, AEs that led to death were balanced across groups, occurring in 106 (0.6%) mResvia recipients and 125 (0.7%) placebo recipients. None of these deaths were considered related to study intervention by FDA, in agreement with the Investigators' assessments.

Table 13. Proportion of Participants Reporting at Least One Adverse Event Following Vaccination, Safety Set, Study P301 (24 JUN 2023)

AE Type: Monitoring Period^a	mResvia % (n/N)	Placebo % (n/N)
Immediate (solicited and unsolicited) ^b : 60 minutes	6.7 (1228/18231)	6.6 (1205/18181)
Solicited immediate AEs	6.6 (1195/18231)	6.5 (1177/18181)
Unsolicited immediate AEs	0.3 (56/18231)	0.2 (44/18181)
Solicited local reaction at the injection site ^c : Day 1-7	58.3 (10584/18157)	16.2 (2936/18094)
Grade 3 or above solicited local	3.1 (560/18157)	1.7 (309/18094)
Solicited systemic reaction ^d : Day 1-7	47.4 (8608/18157)	32.9 (5956/181097)
Grade 3 or above solicited systemic	4.0 (718/18157)	2.8 (511/18097)
Unsolicited: Day 1-28 ^e	17.4 (3170/18231)	16.4 (2977/18181)
Severe unsolicited AEs ^e	0.5 (88/18231)	0.5 (93/18181)
Related unsolicited AEs ^{e,f}	0.9 (155/18231)	0.7 (130/18181)
Severe and related unsolicited AEs ^{e,f}	<0.1 (4/18231)	<0.1 (7/18181)
MAAEs: Entire study period	44.8 (8161/18231)	44.0 (8002/18181)
Severe unsolicited MAAEs	5.0 (905/18231)	5.1 (930/18181)
Related unsolicited MAAEs ^f	0.4 (75/18231)	0.3 (55/18181)
Severe and related MAAEs ^f	<0.1 (9/18231)	<0.1 (5/18181)
AESIs: Entire study period	0.3 (54/18231)	0.3 (51/18181)
Severe unsolicited AESIs	<0.1 (8/18231)	<0.1 (11/18181)
Related unsolicited AESIs ^f	<0.1 (3/18231)	<0.1 (2/18181)
Severe and related unsolicited AESIs ^f	<0.1 (1/18231)	<0.1 (1/18181)
AEs leading to withdrawal: Entire study period	0.6 (118/18231)	0.8 (143/18181)
SAEs: Entire study period	7.8 (1414/18231)	7.9 (1438/18181)
Related SAEs ^f : Entire study period	<0.1 (5/18231)	<0.1 (4/18181)
Deaths: Entire study period	0.6 (106/18231)	0.7 (125/18181)
Related deaths ^f	0.0 (0/18231)	0.0 (0/18181)

Source: Adapted from STN 125796/0.38 and 0.52, P301 IRs19 and 33 Tables 14.3.1.1.1, 14.3.2.1.1.1, and 14.3.1.2.1 and ad hoc Tables 10.1.6 and 10.8.3 (data cutoff 24 Jun 2023; data extraction 13 Feb 2024).

Abbreviations: AE=Adverse Event; MAAE=medically attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; IP=investigational product; N=number of exposed participants who submitted any data for the event for solicited adverse reactions, or number of participants in the Safety Set for unsolicited AEs; n=number of participants who experienced the event.

The Safety Set included all randomized participants who receive any IP. The Solicited Safety Set included all randomized participants who receive any IP and contribute any solicited ARs data. Note: Participants were allocated to the vaccine groups as received.

a. Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.

b. There were 23 participants in the mResvia group and 16 participants in the placebo group who reported both solicited and unsolicited immediate AEs and were included in both of the following two rows for solicited immediate AEs and unsolicited immediate AEs.

c. Solicited local reactions included pain, erythema (redness), swelling (hardness), axillary (underarm) swelling or tenderness.

d. Solicited systemic reactions included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills.

e. Reactogenicity events are not included.

f. Relatedness to study vaccine as determined by the Principal Investigator.

Solicited Adverse Reactions

Solicited local and systemic ARs with onset within 7 days after vaccination were assessed using the Solicited Safety Set which included all randomized participants who received any study vaccine and contributed any solicited AR data. The Solicited Safety Set included 36,258 participants, consisting of 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 (as described above in Section 6.1.7).

Solicited Local Adverse Reactions

Table 14 includes the proportions of mResvia and placebo participants who reported any solicited local AR, by maximum severity. Within 7 days postvaccination, the proportion of participants reporting any local reaction was higher in the mResvia group (58.3%) compared to the placebo group (16.2%). The most frequently reported local reaction in both groups was pain at the injection site, reported by 55.9% of participants in the mResvia group and 13.8% of participants in the placebo group, followed by axillary swelling or tenderness (15.2% mResvia; 6.1% placebo). Severe (Grade 3) solicited local reactions were reported by 3.1% and 1.7% of participants in the mResvia and placebo groups, respectively. There were no reported Grade 4 local ARs in either group.

Among those who received mResvia, the median day of onset for solicited local reactions was 2 to 3 days postvaccination. Solicited local reactions had a median duration of 1 day.

Table 14. Proportion of Participants Reporting at Least One Solicited Local Adverse Reaction Within 7 Days Following Vaccination, by Maximum Severity, Solicited Safety Set, Study P301 (24 JUN 2023)

Solicited Local Adverse Reaction	mResvia % (n/N)	Placebo % (n/N)
Any local reaction	58.3 (10584/18157)	16.2 (2936/18094)
Grade 1	50.9 (9244/18157)	13.7 (2470/18094)
Grade 2	4.3 (780/18157)	0.9 (157/18094)
Grade 3	3.1 (560/18157)	1.7 (309/18094)
Grade 4	0.0 (0/18157)	0.0 (0/18094)
Pain ^a	--	--
Any	55.9 (10155/18156)	13.8 (2497/18094)
Grade 1	51.0 (9262/18156)	12.1 (2183/18094)
Grade 2	3.2 (585/18156)	0.7 (120/18094)
Grade 3	1.7 (308/18156)	1.1 (194/18094)
Grade 4	0.0 (0/18156)	0.0 (0/18094)
Erythema (redness)	--	--
Any	2.0 (363/18154)	0.6 (103/18093)
Grade 1 (2.5 cm to 5.0 cm)	1.0 (186/18154)	0.2 (33/18093)
Grade 2 (5.1 cm to 10.0 cm)	0.4 (72/18154)	<0.1 (12/18093)
Grade 3 (>10.0 cm)	0.6 (105/18154)	0.3 (58/18093)
Grade 4 (necrosis or exfoliative dermatitis)	0.0 (0/18154)	0.0 (0/18093)

Solicited Local Adverse Reaction	mResvia % (n/N)	Placebo % (n/N)
Swelling/induration (hardness)	--	--
Any	3.7 (674/18155)	0.3 (60/18093)
Grade 1 (2.5 cm to 5.0 cm)	2.1 (374/18155)	0.2 (32/18093)
Grade 2 (5.1 cm to 10.0 cm)	0.8 (144/18155)	<0.1 (10/18093)
Grade 3 (>10.0 cm)	0.9 (156/18155)	<0.1 (18/18093)
Grade 4 (necrosis)	0.0 (0/18155)	0.0 (0/18093)
Axillary (underarm) swelling or tenderness ^{a,b}	--	--
Any	15.2 (2761/18154)	6.1 (1105/18093)
Grade 1	13.2 (2401/18154)	5.2 (933/18093)
Grade 2	1.2 (222/18154)	0.3 (55/18093)
Grade 3	0.8 (138/18154)	0.6 (117/18093)
Grade 4	0.0 (0/18154)	0.0 (0/18093)

Source: Adapted from STN 125796/0, P301 IR19 Table 14.3.1.2.1 (data cutoff 24 Jun 2023; data extraction 13 Feb 2024).

Abbreviations: N=Number of participants with any solicited AR data for the specific solicited local/systemic AR in the group; n=Number of participants who experienced the event, or with maximum severity of grade 1, grade 2, or grade 3.

Note: Participants were allocated to the vaccine groups as received.

a. For pain and axillary swelling or tenderness – Grade 1: Does not interfere with activity; Grade 2: Repeated use of over-the-counter pain reliever >24 hours or interferes with activity; Grade 3: Any use of prescription pain reliever or prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.

b. Axillary swelling/tenderness ipsilateral to the side of injection.

Solicited Systemic Adverse Reactions

[Table 15](#) includes the percentages of mResvia and placebo participants who reported any solicited systemic AR, by maximum severity. Within 7 days postvaccination, the proportion of participants reporting any systemic reaction was higher in the mResvia group (47.4%) compared to the placebo group (32.9%). Fatigue was the most frequently reported systemic AR (30.8% mResvia; 20.0% placebo), followed by headache (26.7% mResvia; 18.8% placebo), myalgia (25.6% mResvia; 14.4% placebo), arthralgia (21.7% mResvia; 14.0% placebo), and chills (11.6% mResvia; 6.8% placebo). Fever was reported in 2.7% of mResvia recipients compared to 1.3% of placebo recipients. Grade 3 fever (maximum temperature between 39.0°C to 40.0°C) was reported in 0.4% of mResvia recipients and 0.2% of placebo recipients. Fever was the only solicited AR reported in any participant at Grade 4 (defined as maximum temperature >40.0°C) and was reported by 0.2% of participants in each group. Overall, severe (Grade 3 or Grade 4) systemic ARs were reported in 4.0% of mResvia recipients and 2.8% of placebo recipients.

Among those who received mResvia, the median day of onset for solicited systemic reactions was 2 to 3 days postvaccination. Solicited systemic reactions had a median duration of 1 to 2 days.

Table 15. Proportion of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days Following Vaccination, by Maximum Severity, Solicited Safety Set, Study P301 (24 JUN 2023)

Solicited Systemic Adverse Reaction	mResvia % (n/N)	Placebo % (n/N)
Any systemic reaction	47.4 (8608/18157)	32.9 (5956/18097)
Grade 1	28.9 (5254/18157)	21.6 (3915/18097)
Grade 2	14.5 (2636/18157)	8.5 (1530/18097)
Grade 3	3.8 (683/18157)	2.7 (482/18097)
Grade 4 (fever >40.0°C) ^b	0.2 (35/18157)	0.2 (29/18097)

Solicited Systemic Adverse Reaction	mResvia % (n/N)	Placebo % (n/N)
Headache^a	--	--
Any	26.7 (4854/18153)	18.8 (3404/18093)
Grade 1	20.8 (3773/18153)	15.4 (2789/18093)
Grade 2	4.4 (804/18153)	2.3 (408/18093)
Grade 3	1.5 (277/18153)	1.1 (207/18093)
Grade 4	0 (0/18153)	0 (0/18093)
Fatigue^b	--	--
Any	30.8 (5586/18153)	20.0 (3616/18093)
Grade 1	19.3 (3506/18153)	13.4 (2424/18093)
Grade 2	9.7 (1765/18153)	5.4 (975/18093)
Grade 3	1.7 (315/18153)	1.2 (217/18093)
Grade 4	0 (0/18153)	0 (0/18093)
Myalgia (muscle aches all over body)^b	--	--
Any	25.6 (4652/18153)	14.4 (2607/18093)
Grade 1	16.5 (2993/18153)	9.8 (1779/18093)
Grade 2	7.7 (1400/18153)	3.7 (675/18093)
Grade 3	1.4 (259/18153)	0.8 (153/18093)
Grade 4	0 (0/18153)	0 (0/18093)
Arthralgia (joint aches in several joints)^b	--	--
Any	21.7 (3945/18153)	14.0 (2538/18092)
Grade 1	14.4 (2608/18153)	9.6 (1731/18092)
Grade 2	6.3 (1136/18153)	3.7 (674/18092)
Grade 3	1.1 (201/18153)	0.7 (133/18092)
Grade 4	0 (0/18153)	0 (0/18092)
Nausea/vomiting^c	--	--
Any	7.0 (1273/18153)	5.2 (949/18092)
Grade 1	5.1 (923/18153)	3.8 (695/18092)
Grade 2	1.5 (270/18153)	1.0 (180/18092)
Grade 3	0.4 (80/18153)	0.4 (74/18092)
Grade 4	0 (0/18153)	0 (0/18092)
Fever (oral temperature $\geq 38^{\circ}\text{C}$)	--	--
Any	2.7 (499/18146)	1.3 (235/18092)
Grade 1: $38.0\text{--}38.4^{\circ}\text{C}$	1.5 (267/18146)	0.6 (100/18092)
Grade 2: $38.5\text{--}38.9^{\circ}\text{C}$	0.7 (121/18146)	0.4 (66/18092)
Grade 3: $39.0\text{--}40.0^{\circ}\text{C}$	0.4 (76/18146)	0.2 (40/18092)
Grade 4: $>40.0^{\circ}\text{C}$	0.2 (35/18146)	0.2 (29/18092)

Solicited Systemic Adverse Reaction	mResvia % (n/N)	Placebo % (n/N)
Chills ^d	--	--
Any	11.6 (2113/18153)	6.8 (1226/18092)
Grade 1	7.7 (1391/18153)	4.9 (883/18092)
Grade 2	3.4 (612/18153)	1.5 (265/18092)
Grade 3	0.6 (110/18153)	0.4 (78/18092)
Grade 4	0 (0/18153)	0 (0/18092)

Source: Adapted from STN 125796/0, P301 IR19 Table 14.3.1.2.1 (data cutoff 24 Jun 2023; data extraction 13 Feb 2024).
Abbreviations: N=number of participants with at least 1 day of e-diary data for the specific solicited local/systemic AR;
n=number of participants who experienced the event, or with maximum severity of grade 1, grade 2, or grade 3.
Temperature 38.0°C=100.4°F.

Note: Participants were allocated to the vaccine groups as received.

- a. For headache – Grade 1: No interference with activity; Grade 2: Repeated use of over-the-counter pain reliever >24 hours or some interference with activity; Grade 3: Significant; any use of prescription pain reliever or prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
b. For fatigue, myalgia, and arthralgia – Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
c. For nausea/vomiting – Grade 1: No interference with activity or 1-2 episodes/ 24 hours; Grade 2: Some interference with activity or >2 episodes/ 24 hours; Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires emergency room visit or hospitalization for hypotensive shock.
d. For chills – Grade 1: No interference with activity; Grade 2: Some interference with activity not requiring medical intervention; Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires emergency room visit or hospitalization.

Subgroup Analyses for Solicited Adverse Reactions

Solicited local and systemic ARs were reported more frequently among female mResvia recipients (63.4% and 52.1%, respectively) compared to male mResvia recipients (53.4% and 42.9%, respectively). This trend was also observed in the placebo group.

Among mResvia recipients, solicited local and systemic ARs were reported more frequently among White participants (65.3% and 52.0%, respectively) compared to any other race subgroup (Asian: 56.3% and 45.2%, respectively; Black: 44.9% and 42.8%, respectively). By ethnicity, solicited local and systemic ARs were reported more frequently among those who reported ethnicity as not Hispanic or Latino (62.2% and 50.9%, respectively) compared to those who reported ethnicity as Hispanic or Latino (50.3% and 40.3%, respectively). The trends observed in the mResvia group based on race and ethnicity subgroups were not observed in the placebo group.

Among mResvia recipients, the proportions of participants reporting solicited ARs were inversely related to increasing age, with a higher rate of solicited local and systemic reactions reported in the 60 through 69 years of age group (61.2% and 48.8%, respectively) as compared to the 70 through 79 (55.4% and 46.4%, respectively) and ≥80 (46.3% and 40.1%, respectively) years of age groups.

There were no notable differences observed in incidence of solicited ARs based on presence or absence of comorbidities of interest or frailty status (see Section [6.1.10.1.2](#) for details on comorbidities of interest and frailty status).

Unsolicited AEs

Immediate Adverse Events

Unsolicited adverse events within 60 minutes of vaccination were reported infrequently across groups (0.3% mResvia and 0.2% placebo). These events consisted primarily of events associated with reactogenicity and increased blood pressure/hypertension.

There was one mild serious adverse event of visual impairment in a 76-year-old male participant in the mResvia group that resolved without treatment after 24 minutes. The event was considered serious based on the criterion of being a medically important event and was assessed by the Investigator as not related to study vaccine due to the participant's history that included ongoing hypertension and type 2 diabetes mellitus, a history of subarachnoid hematoma, and tobacco use. FDA agrees with the Investigator's assessment that the event was likely unrelated to study vaccine with other vascular etiologies being more likely.

Unsolicited Adverse Events Within 1 Month After Vaccination

The proportion of participants who reported unsolicited AEs within 1 month after vaccination were similar across groups (20.8% mResvia and 19.0% placebo). Unsolicited AEs reported by $\geq 2\%$ of participants in the mResvia group were under the following Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC): *Infections and infestations* (7.8% mResvia and 7.2% placebo), *General disorders and administration site conditions* (4.4% mResvia and 3.3% placebo), *Musculoskeletal and connective tissue disorders* (4.2% mResvia and 4.1% placebo), and *Nervous system disorders* (2.3% mResvia and 2.1% placebo). By MedDRA preferred term (PT), the most frequently reported AEs were fatigue (2.7% mResvia and 2.2% placebo) and arthralgia (2.3% mResvia and 2.2% placebo).

Within 1 month of vaccination, AEs assessed as severe (\geq Grade 3) were reported in 0.7% of participants in the mResvia group and 0.8% of participants in the placebo group. By MedDRA SOC, the most frequently reported severe AEs among participants in both groups were in the SOC *General disorders and administration site conditions*, reported by 40 mResvia recipients (0.2%) and 34 placebo recipients (0.2%). By MedDRA PT, the most frequently reported severe AEs were the same among mResvia recipients and placebo recipients: fatigue (28 mResvia recipients and 28 placebo recipients), arthralgia (13 mResvia recipients and 19 placebo recipients), headache (12 mResvia recipients and 9 placebo recipients), and myalgia (11 mResvia recipients and 15 placebo recipients).

Adverse events 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.

Subgroup Analyses for Unsolicited Adverse Events

Analyses of unsolicited adverse events in the mResvia group by demographic subgroups, including by age, sex, race, comorbidities of interest, and frailty status, were similar in participants in the mResvia group compared with participants in the placebo group; however, small sample sizes limit the interpretability of these analyses.

Standard MedDRA Queries

FDA conducted standardized MedDRA queries (SMQs) using FDA-developed software to evaluate the Safety Set for constellations of unsolicited adverse events with onset following vaccination through the June 24, 2023, data cutoff. The SMQs were conducted on adverse event PTs that could represent various conditions, including but not limited to

allergic, cardiac, neurologic, inflammatory, immune-mediated, and autoimmune disorders.

Under the SMQ for *Angioedema*, there was a numerical imbalance observed with 11 events reported by 10 participants in the mResvia group and 2 events reported by 2 participants in the placebo group (each <0.1%) within 7 days of study vaccination, and 24 events reported by 22 participants in the mResvia group (0.1%) and 8 events reported by 8 participants in the placebo group (<0.1%) within 1 month of study vaccination. This imbalance primarily reflected higher rates of urticaria. 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. All events of urticaria within 1 month were mild or moderate in severity and all resolved. Urticaria events considered to be related to study vaccine by the Investigator were reported for 6 mResvia recipients, with onset between 1- and 17-days postvaccination and lasting from 7 to 70 days, and for 1 placebo recipient, with onset 1 day postvaccination and lasting 2 days. Events of urticaria occurring greater than 1 month after study vaccination were balanced across groups, reported in 35 participants in the mResvia group and 40 participants in the placebo group (each 0.2%) up to the June 24, 2023 data cutoff, and all of these events were considered unrelated to study vaccine by the Investigator.

Under the SMQ for *Hypersensitivity*, the overall rate of events within 1 month of vaccination was balanced across groups with 115 events reported by 107 participants (0.6%) in the mResvia group and 106 events reported by 101 participants (0.6%) in the placebo group. The most frequently reported events were allergic rhinitis with 17 events in 17 participants (<0.1%) in the mResvia group and 30 events in 30 participants (0.2%) in the placebo group; contact dermatitis with 16 events in 16 mResvia recipients and 15 events in 15 placebo recipients (<0.1% in each group); and urticaria with 17 events reported in 15 participants (<0.1%) in the mResvia group compared to 5 events in 5 participants (<0.1%) in the placebo group, as previously discussed under the SMQ for *Angioedema*.

Under the SMQs for *Immune-mediated/autoimmune disorders* and *Vasculitis*, within 1 month of study vaccination, there was 1 event of nonserious polymyalgia rheumatica in an mResvia recipient and 3 events of nonserious dermatitis (2 events in 2 mResvia recipients and 1 event in a placebo recipient) considered related to study vaccine by the Investigator. Within 1 month of study vaccination, there were no other events of polymyalgia rheumatica. Overall, the rate of events under the *Immune-mediated/autoimmune disorders* SMQ was balanced across groups with 7 events reported in 7 participants in the mResvia group and 5 events in 5 participants in the placebo group up to 1 month after study vaccination. Under the *Vasculitis* SMQ, there were 2 events reported in the mResvia group and 0 events in the placebo group up to 1 month after study vaccination.

No other notable imbalances were observed in other queries, including for the SMQ *Cardiac arrhythmias*, with 24 events reported in 23 participants in the mResvia group and 20 events in 20 participants in the placebo group up to 1 month after study vaccination. The most frequently reported PT under this SMQ was atrial fibrillation, with 0 events in the mResvia group and 3 events in 3 participants in the placebo group reported within 7

days of study vaccination. Within 1 month of study vaccination, there were 9 events reported in 9 participants in the mResvia group and 10 events in 10 participants in the placebo group, of which 1 event in each group was considered related to study vaccine by the Investigator. In the mResvia group, a 69-year-old male with a history of hypertension and type 2 diabetes mellitus had a nonserious event of atrial fibrillation with rapid ventricular response on Day 13 that was assessed as related to study vaccine by the Investigator and was resolving at data cutoff. Up to the June 24, 2023 data cutoff, 113 events of atrial fibrillation were reported in 102 mResvia recipients (0.6%) and 129 events were reported in 115 placebo recipients (0.6%). None of the events that occurred greater than 1 month after study vaccination were considered related to study vaccine per the Investigator.

6.1.12.3 Deaths

Up to the June 24, 2023 data cutoff, there were 106 (0.6%) deaths among mResvia recipients and 125 (0.7%) among placebo recipients. In general, the causes of death among study participants were consistent with the leading causes of death among elderly adult populations. The most frequently reported causes of death were in the SOC *Cardiac disorders* for participants in both the mResvia group (28 participants, 0.2%) and the placebo group (40 participants, 0.2%). The most frequently reported PTs for fatal events in the mResvia group were death (11 mResvia recipients and 15 placebo recipients), myocardial infarction (6 mResvia recipients and 8 placebo recipients), and acute myocardial infarction and pneumonia (each with 6 mResvia recipients and 3 placebo recipients). None of the deaths were assessed as related to study vaccine by the study Investigators.

Reviewer Comment

Based on independent review of event narratives, the Clinical Reviewer agrees with the Investigators' assessments that none of the deaths were related to study vaccination.

6.1.12.4 Nonfatal Serious Adverse Events

With 10.2 months median follow-up, SAEs were reported in 7.8% of participants (n=1414) in the mResvia group and 7.9% of participants (n=1438) in the placebo group. SAEs were most frequently reported in the SOC *Infections and infestations* (1.6% mResvia and 1.7% placebo) and *Cardiac disorders* (1.3% mResvia and 1.6% placebo). There were 5 participants in the mResvia group and 4 participants in the placebo group who experienced SAEs that were assessed as related to study vaccination by the Investigator. The case narratives for the 5 SAEs in the mResvia group considered related to study vaccination include the following:

- A 75-year-old female with a medical history that includes COPD, hypertension, and hypothyroidism experienced an SAE of severe chills on Day 1 that was assessed as related to study vaccine by the Investigator. She experienced additional solicited ARs of headache on Day 1, fatigue on Day 2, and arthralgia and myalgia on Day 6. On Day 8 she was diagnosed and hospitalized with an SAE of pneumonia with symptoms of chills and shortness of breath. The chills resolved on Day 10 and the pneumonia on Day 19. The Applicant considered the event of chills unrelated to study vaccine. Both the Investigator and Applicant considered the event of pneumonia unrelated to study vaccine.

- A 64-year-old female with a history of diabetes mellitus type 2 and diabetic gastroenteropathy experienced a severe SAE of dehydration on Day 2 assessed as related to study vaccine by the Investigator. She concurrently experienced non-serious solicited ARs of nausea and vomiting with dizziness and was diagnosed in the emergency department with a urinary tract infection (no urine culture was performed). The event of dehydration resolved the same day following intravenous hydration. The Applicant considered the event of dehydration unrelated to study vaccine.
- A 69-year-old female with a history of hypertension experienced a moderate SAE/AESI of facial paralysis on Day 5 in which she was not able to completely close her eye on the affected side and experienced ipsilateral tearing and difficulty smiling. Treatment included acyclovir, dexamethasone, and cyanocobalamin/pyridoxine hydrochloride/thiamine hydrochloride. The event resolved on Day 118. The Investigator and Applicant considered the event of facial paralysis related to study vaccine.
- A 72-year-old male with a history of lower limb varicose veins experienced a moderate SAE of superficial vein thrombosis on Day 11 requiring hospitalization for thrombectomy. The event resolved on Day 44. The Investigator assessed the event as related to study vaccine while the Applicant considered the event of superficial vein thrombosis unrelated to study vaccine.
- A 73-year-old male with a history of aortic, mitral, and tricuspid valve regurgitation, bradycardia, and Factor V deficiency experienced an SAE of thrombocytopenia on Day 153 assessed as related to study vaccine by the Investigator. He previously experienced two SAEs of aortic incompetence on Day 115 and cardiac failure congestive on Day 140 that were assessed by the Investigator as not related to study vaccine. On Day 146, he was admitted to the hospital for planned heart valve and pacemaker replacements and started on heparin. He underwent surgery on Day 153 and was noted to have low platelet counts peri-operatively that decreased further post-operatively. He received a platelet transfusion on Day 154, and the event of thrombocytopenia resolved on Day 158. The Applicant considered the event of thrombocytopenia unrelated to study vaccine.

Reviewer Comment

While in general, given the temporal association and biological plausibility, the Clinical Reviewer agrees with the Investigators' assessments that the 5 SAEs described above in mResvia recipients have a reasonable possibility of a relationship to study vaccine, the following caveats and exceptions are noted:

- The SAEs of chills on Day 1 in a 75-year-old, dehydration on Day 2 in a 64-year-old, and superficial vein thrombosis on Day 11 in a 72-year-old had a temporal relationship to study vaccine administration; however, there were other possible explanations for the events, as described above in the case narratives.
- The Clinical Reviewer does not agree with the Investigator's assessment that the event of thrombocytopenia on Day 153 was related to study vaccine due to the long duration of time between study vaccine administration and the event of thrombocytopenia, as well as due to the presence of temporally related risk factors for low platelets. The Clinical Reviewer agrees with the

Applicant's assessment that this event was not causally associated with study vaccination.

Due to the presence of biologically plausible alternative explanations for the above 4 SAEs, only the SAE of facial paralysis will be recommended for inclusion in product labeling.

6.1.12.5 Adverse Events of Special Interest (AESI)

Protocol-defined AESIs were thrombocytopenia, anaphylaxis, myocarditis/pericarditis, and new onset or worsening of neurologic diseases including Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), idiopathic peripheral facial nerve palsy (Bell's palsy), and seizures. Up to the June 24, 2023 data cutoff, AESIs were reported in 0.3% of participants in both the mResvia (n=54) and placebo (n=51) groups.

Thrombocytopenia

Among AESIs, thrombocytopenia was the most frequently reported PT. There were no reported AESIs of thrombocytopenia within 28 days of study vaccination in the mResvia group. Up to the June 24, 2023 data cutoff, thrombocytopenia and associated PTs were reported as AESIs in 0.1% of participants in both the mResvia group (n=25) and placebo group (n=26). Of those AESIs, thrombocytopenia was reported in 25 participants in the mResvia group and 22 participants in the placebo group. Three events of thrombocytopenia were assessed as related to study vaccine by the Investigator: 2 events in mResvia recipients (decreased platelet count on Day 144 and thrombocytopenia on Day 153 [discussed above in Section 6.1.12.4]) and 1 event in a placebo recipient (decreased platelet count on Day 22). The following is the case narrative for the mResvia recipient with decreased platelet count on Day 144:

- A 79-year-old female with a history including COPD, HTN, hyperthyroidism, autoimmune peripheral neuropathy, and diabetes mellitus type 2 experienced a moderate AESI of platelet count decreased, assessed by the Investigator as related, concurrently with an unrelated severe SAE of pneumonia on Day 144, for which she was hospitalized. The pneumonia resolved on Day 156. She was hospitalized again on Day 165 for another SAE of pneumonia and discharged on Day 166 with the pneumonia reported as resolved. The low platelet count was not treated and was reported as resolved on Day 509. The Applicant considered both the low platelet count and the events of pneumonia as unrelated to study vaccine.

Reviewer Comment

The Clinical Reviewer does not agree with the Investigator's assessment that the event of decreased platelet count on Day 144 was related to study vaccine due to the long duration of time between study vaccine administration and the event, as well as due to the presence of other factors that more likely contributed to the event. The Clinical Reviewer agrees with the Applicant's assessment of causality for this event.

Anaphylaxis

There were no reported vaccine-associated events of anaphylactic reaction through the June 24, 2023 data cutoff.

Myocarditis and pericarditis

There were no CEAC-confirmed cases of acute myocarditis or acute pericarditis within 42 days after study vaccination in either group. Within 42 days of study vaccination, there was 1 AESI of pericarditis in a 68-year-old female placebo recipient on Day 8 that was adjudicated as not charter-defined per CEAC and was considered unrelated to study vaccine per the Investigator.

Up to the June 24, 2023 data cutoff, in addition to the above event, there were 2 mResvia recipients with 3 CEAC-confirmed AESIs of acute pericarditis, 1 placebo recipient with an AESI of pericarditis that was adjudicated as not charter-defined per CEAC, and 1 mResvia recipient with an AESI of myocarditis that was adjudicated as not charter-defined per CEAC. The Investigator assessed the events as not related to study vaccine.

The following are narratives of the myocarditis and pericarditis events that occurred in the mResvia group:

- A 65-year-old male with a viral upper respiratory tract infection from Day 8 to 13 after vaccination experienced mild pleuritic chest pain on Day 48 that was diagnosed as acute pericarditis. An electrocardiogram (ECG) on Day 52 showed mild ST elevation with normal troponin values. The event resolved on Day 60. On Days 145 and 153 the participant tested positive for COVID-19, on Day 220 he received a first dose of Pfizer bivalent mRNA COVID-19 vaccine and a second dose of Jynneos (Smallpox and Monkeypox Vaccine, Live, Non-Replicating), and on Day 223 he experienced a second episode of acute pericarditis with an ECG reported as consistent with pericarditis and an echocardiogram demonstrating a small pericardial effusion. He was treated with anti-inflammatories and colchicine for both episodes. The second event was ongoing at the time of data cutoff.
- A 67-year-old female with a non-serious AE of right bundle branch block on Day 75 experienced fatigue, dyspnea at rest, and acute sternal chest pain with inspiration on Day 81 that was diagnosed as acute pericarditis. Echocardiogram demonstrated mild pericardial effusion. The event resolved Day 89.
- A 70-year-old male experienced an event of intermittent mild palpitations on Day 62 that was reported as myocarditis. Testing demonstrated normal cardiac function and no pericardial fluid. Holter monitoring recorded atrial and ventricular extrasystoles and episodes of atrial and ventricular tachycardia on Day 67 for which he was treated with amiodarone. The event resolved on Day 199.

Reviewer Comment

There were no CEAC-confirmed cases of acute myocarditis up to the June 24, 2023 data cutoff (see Section [6.1.7](#)). There were 3 CEAC-confirmed cases of acute pericarditis in 2 participants in the mResvia group up to the June 24, 2023 data cutoff, none considered related to study vaccine by the Investigator. The Clinical Reviewer agrees with the Investigators' assessments that these events were likely not related to study vaccination. Therefore, it is recommended that product labeling will not include warnings and precautions for myocarditis/pericarditis.

New onset of or worsening of neurologic diseases

GBS and ADEM

There were no reported events of GBS or ADEM through the June 24, 2023 data cutoff.

Bell's palsy and facial paralysis

Within 42 days of study vaccination, there were AESIs of Bell's palsy/facial paralysis reported for 2 participants in each group (<0.1%). In the mResvia group:

- A 69-year-old female with a history of hypertension experienced an AESI (and SAE) of facial paralysis on Day 5 (as discussed above in Section [6.1.12.4](#)). The event was assessed by the Investigator as related to study vaccine and resolved on Day 118.
- A 60-year-old female with a history of Bell's palsy experienced an AESI of Bell's palsy on Day 27 with preceding COVID-19 disease on Days 20 to 27. The event was assessed as not related to study vaccine by the Investigator and resolved on Day 62.

Up to the June 24, 2023 data cutoff, AESIs of Bell's palsy were reported for 5 participants in the mResvia group and 3 participants in the placebo group, and AESIs of facial paralysis were reported for 3 participants in the mResvia group and 2 participants in the placebo group. Events were balanced across groups (each <0.1%). None of the additional events were assessed as related to study vaccine by the Investigator.

Reviewer Comment

The Clinical Reviewer agrees with the Investigators' assessments of relatedness to study vaccine for the reported AESIs of Bell's palsy and facial paralysis. The events in the mResvia group assessed as not related to study vaccine occurred in participants with risk factors for the event other than age (i.e., hypertension, diabetes mellitus, viral illness, and/or prior history of Bell's palsy) and most occurred with a long duration of time between study vaccination and the event.

Seizure

There were no reported AESIs of seizure (or seizure-like PTs) within 28 days after study vaccination in the mResvia group. Up to the June 24, 2023 data cutoff, there were AESIs with PTs indicative of seizure reported for 14 participants in the mResvia group and 15 participants in the placebo group (each <0.1%). None of the events in the mResvia group were considered related to study vaccine per the Investigator.

Reviewer Comment

The Clinical Reviewer agrees with the Investigators' assessments that these AESIs were not related to study vaccine.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

Up to the June 24, 2023 data cutoff, AEs leading to study discontinuation were reported in 0.6% of participants (n=118) in the mResvia group and 0.8% of participants (n=143) in the placebo group. By PT, the most reported AE leading to study discontinuation was death, reported in <0.1% of participants in both groups (see Section [6.1.12.3](#)). There were no study participants who experienced an AE leading to study discontinuation that was assessed as related to study vaccination per the Investigator. See Section [6.1.10.1.3](#) for a complete overview of participants included in the Safety Set and reasons for study withdrawal.

6.1.13 Study Summary and Conclusions

Study P301 contributed the primary evidence to support the safety and efficacy of mResvia in individuals 60 years of age and older. Data submitted to the BLA are based on the primary analysis (data cutoff November 30, 2022) with a median follow-up for efficacy of approximately 3.7 months. The VE of mResvia to prevent first-episode RSV-associated lower respiratory tract disease (RSV-LRTD) with ≥ 2 and ≥ 3 symptoms was 78.7% (95.04% CI: 62.8, 87.9) and 80.9% (95.1% CI: 50.1, 92.7), respectively. The supportive analysis (data cutoff of April 30, 2023) with a median follow-up for efficacy of approximately 8.6 months demonstrated VE of 62.5% (95% CI: 47.7, 73.1) to prevent RSV-LRTD with ≥ 2 symptoms and 61.1% (95% CI: 34.7, 76.8) to prevent RSV-LRTD with ≥ 3 symptoms. In general, the point estimates for VE of mResvia against RSV-LRTD by RSV subtype were numerically higher for RSV-A compared to RSV-B. Due to the overlap in case definitions between RSV-ARD and RSV-LRTD, FDA determined that the RSV-ARD data did not contribute meaningfully to the overall efficacy analysis.

Descriptive subgroup analyses of efficacy estimates based on baseline demographic characteristics were generally consistent with the overall findings of the primary and supportive analyses but were limited by small subpopulation sizes. In total, the P301 data support the effectiveness of mResvia for the prevention of RSV-LRTD in adults 60 years of age and older.

Safety data from Study P301 are available from 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. Solicited local and systemic ARs within 7 days after vaccination were reported by a higher proportion of mResvia recipients compared to placebo recipients. The most frequently reported ($\geq 10\%$) solicited ARs among mResvia recipients were injection site pain (55.9%), fatigue (30.8%), headache (26.7%), myalgia (25.6%), arthralgia (21.7%), axillary swelling or tenderness (15.2%), and chills (11.6%).

The majority of reported solicited ARs were considered mild in severity. Grade 3 solicited local ARs and solicited systemic ARs were reported by 3.1% and 3.8% of mResvia recipients, respectively. The only Grade 4 solicited AR was fever, reported in 0.2% of mResvia recipients. In general, solicited ARs among mResvia recipients were reported more frequently among individuals who were White and among the younger age subgroup (60 through 69 years) compared to the older subgroups (70 through 79 years and ≥ 80 years). There were no notable differences in reported rates of solicited ARs based on the presence or absence of comorbidities of interest or frailty status.

There were no meaningful imbalances in the overall rates of unsolicited adverse events 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. 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. 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. Overall, the P301 data support the safety of mRESVIA for its intended use for the prevention of RSV-LRTD in adults 60 years of age and older.

6.2 Study P101

NCT04528719

Title: “A Phase 1, Randomized, Observer-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Healthy Younger Adults Aged 18 to 49 Years, Women of Child-Bearing Potential Aged 18 to 40 Years, Healthy Older Adults Aged 65 to 79 Years, Japanese Older Adults Aged ≥60 Years, and RSV-Seropositive Children Aged 12 to 59 Months.”

Study Overview: Study P101 is a Phase 1 ongoing, multicenter study designed to describe the safety and immunogenicity of different dose levels of mResvia (12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg) in multiple age cohort populations. The study was initiated in September 2020 and was conducted at 21 clinical sites in the United States. Because the study is ongoing for the older adult cohorts at the time of this review, an interim analysis of data was conducted in October 2022 (Month 14), and the results were submitted to the BLA. Only study objectives and data evaluating different dose levels in older adult cohorts were reviewed to support the proposed indication for use in elderly individuals (≥60 years).

6.2.1 Objectives

Primary Objective

1. To evaluate the tolerability and reactogenicity of a single injection of up to 5 dose levels of mResvia in younger adults, women of child-bearing potential, and older adults, including Japanese adults

Endpoints:

- a. Solicited local and systemic adverse reactions (ARs) through 7 days after each injection
- b. Unsolicited AEs through 28 days after each injection
- c. SAEs and MAAEs throughout the entire study period

Secondary Objective

1. To evaluate the antibody response to a vaccine booster injection given approximately 12 and 24 months after the primary injection in older adults

Endpoints:

- a. Geometric metric titer (GMT) of serum RSV-neutralizing antibodies and geometric mean concentration (GMC) of serum RSV-binding antibodies across prespecified study time points
- b. Geometric mean fold rise (GMFR) of postbaseline/baseline antibody titers
- c. Proportion of participants with ≥2-fold and ≥4-fold increases in antibody titers from baseline

All endpoints were descriptive with no hypothesis testing conducted.

Reviewer Comment

1. Clinical disease efficacy endpoints were not included in the study.
2. Study objectives and data evaluating the investigational vaccine in younger adults, women of childbearing potential, children are not presented or reviewed in this memo.

6.2.2 Design Overview

Study P101 is an ongoing Phase 1, randomized, observer-blind, placebo-controlled dose escalation, multicenter study designed to describe the safety, reactogenicity, and immunogenicity of different doses of mResvia in younger adults, women of child-bearing potential, older adults (including Japanese older adults), and pediatric populations. The duration of follow-up for the Cohorts 7 through 11 was 24 months, and for the Japanese Cohort 15 was 6 months. The table below provides an overview of study cohorts, including cohort planned sample size, dose level, and number of doses.

Table 16. Study Groups, Study P101

Cohort	mResvia Dose Level, µg	Number of Doses	mResvia N	Placebo N
Healthy adults 18 through 49 years ^a	--	--	--	--
Cohort 1	50	1	20	5
Cohort 2	100	1	20	5
Cohort 3	100	3	20	5
Cohort 4	200	1	20	5
Total	--	--	80	20
Healthy adults 65 through 79 years ^{b,c}	--	--	--	--
Cohort 7	50	2	48	12
Cohort 8	100	2	48	12
Cohort 9	200	2	48	12
Cohort 10	12.5	2	48	12
Cohort 11	25	2	48	12
Total	-	-	240	60
Healthy Japanese adults ≥60 years	--	--	--	--
Cohort 15 ^d	100	1	20	5
Total	--	--	20	5

Source: FDA information request: Shell Tables for Study P101, Table E

Dose (µg)=dose given to each cohort as per study design; N=total number of participants in the specified group

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

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

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

d. Data submitted for the Japanese older adult cohort were collected through the end of study, September 2022.

Healthy older adult participants 65 through 79 years of age were enrolled into Cohorts 7 through 11 and were randomized to receive mResvia at 5 escalating dose levels of 12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg or placebo. All participants in these cohorts received the same study vaccine dose 12 months after the first dose. Enrollment of participants in older adult cohorts with higher doses (50 µg, 100 µg, 200 µg) were based on the review of safety data from younger age cohorts receiving the 100-µg dose.

Japanese older adult participants ≥ 60 years of age were enrolled in Cohort 15 and were randomized to receive a single 100- μg dose of mResvia or placebo. This cohort did not receive a second dose.

Reviewer Comment

Clinical data from the older adult cohorts (Cohorts 7 through 11, Cohort 15) are reviewed in this memo. The duration of follow-up for the Japanese Cohort 15 was 6 months as the participants received a single dose while the older adult Cohorts 7-11 received a 2nd dose, which increased their duration of follow-up.

6.2.3 Population

Eligibility Criteria

Inclusion Criteria (in summary): Healthy male and female participants 65 through 79 years of age for older adults and ≥ 60 years of age for older Japanese adults who were able to provide informed consent.

- Specific inclusion criteria for Japanese older adults: Japanese participants are defined as individuals born in Japan, with both parents and 4 grandparents who were born in Japan.

Exclusion Criteria (in summary): Pregnant or lactating; febrile; significant or poorly controlled preexisting disease or laboratory abnormality; previous vaccination with any licensed or investigational vaccine (including COVID-19 vaccines) 28 days before enrollment or throughout the study; history of myocarditis, pericarditis, or myopericarditis; known systemic hypersensitivity to vaccine components; history of or active autoimmune disease; congenital or acquired immunodeficiency or immunosuppression; receipt of blood/plasma products within 3 months of investigational product administration.

- Specific exclusion criteria for older adults (in summary): Poorly controlled hypertension or diabetes mellitus, history of hypotension, significant chronic pulmonary disease or chronic cardiovascular disease, residence in a nursing home, diagnosis of malignancy within previous 10 years

6.2.4 Study Treatments or Agents Mandated by the Protocol

mResvia (mResvia as an investigational formulation):

- Dose and route of administration: 0.5 mL intramuscular (IM) injection
- Formulation: 12.5- μg , 25- μg , 50- μg , 100- μg , or 200- μg total dose of mRNA encoding the RSV stabilized prefusion F protein formulated in lipid nanoparticles composed of 4 lipids (SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1 monomethoxypolyethyleneglycol-2,3-dimyristylglycerol)
- Presentation: sterile liquid for injection, white to off-white dispersion
 - (b) (4) with 0.6 mL of 0.9% sodium chloride injection [(b) (4)] to a concentration of 0.8 mg/mL, then the reconstituted mResvia drug product was further diluted with (b) (4) to concentrations required for clinical dose level.
- Lots: AN2848, 6033922001

Placebo:

- Dose and route of administration: 0.5 mL IM injection
- Formulation: 0.9% sodium chloride
- Presentation: sterile, clear solution
- Lots: 21102DK, FK8455, 6026604

6.2.5 Directions for Use

For this study, mResvia was supplied as a sterile liquid in a glass vial.

6.2.6 Sites and Centers

The study was conducted at 21 clinical sites in the United States only.

6.2.7 Surveillance/Monitoring

Surveillance/Study Monitoring

Study oversight included Institutional Review Board (IRB) or Independent Ethics Committee (IEC) review and approval of the study protocol, protocol amendments, informed consent forms, investigational brochure, and other relevant documents. Study centers were monitored by the Applicant or its representatives. This study used a blinded Internal Safety Team (IST) and an unblinded independent Data and Safety Monitoring Board (DSMB).

An independent Cardiac Event Adjudication Committee (CEAC), comprised of medically qualified personnel, used the CDC Working Case Definitions ([Gargano, 2021](#)) as a guidance to review suspected cases of myocarditis, pericarditis, and myopericarditis. The CEAC members are blinded to study treatment.

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. 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.

Safety Monitoring

Electronic diaries (eDiaries) were used to record and monitor the solicited local ARs (injection site pain, injection site erythema, and injection site swelling/induration) and solicited systemic ARs (headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, fever, and lymphadenopathy [axillary swelling or tenderness]) during the 7 days following vaccination (i.e., the day of injection and 6 subsequent days).

The grading scale for solicited local ARs were as follows:

- Pain:
 - Grade 0: None
 - Grade 1: Does not interfere with activity
 - Grade 2: Repeated use of over-the-counter (nonnarcotic) pain reliever >24 hours or some interference with activity
 - Grade 3: Any use of prescription pain reliever or prevents daily activity
 - Grade 4: Requires emergency room visit or hospitalization

- Erythema and Swelling/Induration
 - Grade 0: ≤ 2.5 cm
 - Grade 1: 2.5 – 5.0 cm
 - Grade 2: 5.1 – 10.0
 - Grade 3: >10.0 cm
 - Grade 4: necrosis

The grading scales for solicited systemic ARs were as follows:

- Headache:
 - Grade 1: No interference with activity
 - Grade 2: Repeated use of over-the-counter pain reliever >24 hours or some interference with activity
 - Grade 3: Significant; any use of prescription pain reliever or prevents daily activity
 - Grade 4: Requires emergency room visit or hospitalization
- Fatigue, Myalgia, and Arthralgia:
 - Grade 1: No interference with activity
 - Grade 2: Some interference with activity
 - Grade 3: Significant; prevents daily activity
 - Grade 4: Requires emergency room visit or hospitalization
- Nausea/Vomiting:
 - Grade 1: No interference with activity or 1-2 episodes/24 hours
 - Grade 2: Some interference with activity >2 episodes/24 hours
 - Grade 3: Prevents daily activity, requires outpatient intravenous hydration
 - Grade 4: Requires emergency room visit or hospitalization for hypotensive shock
- Chills:
 - Grade 1: No interference with activity
 - Grade 2: Some interference with activity not requiring medical intervention
 - Grade 3: Prevents daily activity and requires medical intervention
 - Grade 4: Requires emergency room visit or hospitalization
- Fever
 - Grade 1: 38.0-38.4°C;
 - Grade 2: 38.5-38.9°C;
 - Grade 3: 39.0-40.0°C;
 - Grade 4: $>40.0^\circ\text{C}$
- Axillary Swelling/Tenderness:
 - Grade 1: No interference with activity
 - Grade 2: Repeated use of over the counter (nonnarcotic) pain reliever >24 hours or some interference with activity
 - Grade 3: Any use of prescription pain reliever or prevents daily activity
 - Grade 4: Emergency room visit or hospitalization

Unsolicited AEs occurring during the 28 days following the last dose were recorded. AEs leading to discontinuation from study participation, MAAEs, AESIs, and SAEs were monitored and recorded from Day 1 through end of study (EOS) or withdrawal from study. Investigators followed participants with SAEs or participants who were withdrawn as result of an AE until the event had resolved, stabilized, or until the event was

otherwise explained, or the participant was lost to follow-up. Those with other non-serious AEs were followed until resolution, study end, or loss to follow-up.

Immunogenicity Monitoring

Serum samples were collected prior to vaccination on Visit #1 for all cohorts and at multiple timepoints following each administered study dose. Serum samples were assayed for RSV A and RSV B serum neutralizing antibodies titers by (b) (4) assay and RSV F protein binding antibodies (in PreF and PostF conformation) as measured by (b) (4) assay. Testing was performed in laboratories designated by the Applicant.

6.2.8 Endpoints and Criteria for Study Success

See Section [6.2.1](#) above and Section [6.2.9](#) below.

6.2.9 Statistical Considerations & Statistical Analysis Plan

All study analyses were descriptive without formal hypothesis testing.

6.2.10 Study Population and Disposition

In Cohorts 7 through 11, 300 participants were randomized to receive mResvia (n=240) or placebo (n=60); 239 participants received the initial dose of mResvia and 59 received placebo. Of the participants who received the first dose of mResvia, 195 (81.3%) completed the 12-month follow-up visit and received a second dose, as of the data cutoff date (October 3, 2022). In Cohort 15, 25 participants were randomized to receive mResvia (n=20) or placebo (n=5); all 25 participants received the vaccination and completed the study.

6.2.10.1 Populations Enrolled/Analyzed

The safety analyses were conducted on the Safety Set population for first and second vaccination. The Safety Set for the first vaccination consists of all randomized participants who received the first dose of study vaccine or placebo. The Safety Set for the second vaccination consists of all randomized participants who received both first and second doses of study vaccine or placebo.

The population used for the immunogenicity analyses was the Per-Protocol Set (PPS). The Per-Protocol Set consists of participants who:

- Complied with the vaccination schedule
- Complied with timings of immunogenicity blood sampling to have baseline and postvaccination results available for at least one assay component that corresponds to an immunogenicity objective
- Had no major protocol violations that impact immune response during the period corresponding to the immunogenicity analysis objective

6.2.10.1.1 Demographics

Demographic characteristics of participants in the Safety Set are summarized in [Table 17](#). In the overall safety population for Cohorts 7 through 11, the median age was 69 years, and most participants were White and non-Hispanic. Demographic characteristics were generally similar across all the cohorts. For Cohort 15, the median age was 66 years of age, and all participants were of Japanese descent.

Table 17. Demographic and Baseline Characteristics, Safety Set, Adults 65 Through 79 Years of Age, Study P101, Single Dose

Characteristic	Placebo N=59	Cohort 7 mResvia 50 µg N=47	Cohort 8 mResvia 100 µg N=48	Cohort 9 mResvia 200 µg N=48	Cohort 10 mResvia 25 µg N=48	Cohort 11 mResvia 12.5 µg N=48
Sex, n (%)	--	--	--	--	--	--
Male	27 (45.8)	23 (48.9)	23 (47.9)	20 (41.7)	22 (45.8)	19 (39.6)
Female	32 (54.2)	24 (51.1)	25 (52.1)	28 (58.3)	26 (54.2)	29 (60.4)
Age (years)	--	--	--	--	--	--
Mean age (SD)	69.9 (3.75)	70.1 (3.85)	70.2 (3.88)	69.9 (3.94)	70.7 (3.71)	69.9 (3.23)
Median age (minimum, maximum)	69.0 (65, 78)	69.0 (65, 78)	69.0 (65, 78)	69.0 (65, 79)	71.0 (65, 79)	69.0 (65, 78)
65-69 years	31 (52.5)	29 (61.7)	26 (54.2)	27 (56.3)	20 (41.7)	25 (52.1)
70-79 years	28 (47.5)	18 (38.3)	22 (45.8)	21 (43.8)	28 (58.3)	23 (47.9)
Race, n (%)	--	--	--	--	--	--
African American/Black	7 (11.9)	1 (2.1)	6 (12.5)	1 (2.1)	2 (4.2)	4 (8.3)
American Indian/Alaska Native	0	0	0	1 (2.1)	0	0
Asian	1 (1.7)	1 (2.1)	0	0	2 (4.2)	0
Native Hawaiian/other Pacific Islander	1 (1.7)	0	0	0	0	0
White	49 (83.1)	44 (93.6)	42 (87.5)	46 (95.8)	43 (89.6)	44 (91.7)
Multiracial	0	1 (2.1)	0	0	0	0
Other ^a	1 (1.7)	0	0	0	1 (2.1)	0
Unknown	0	0	0	0	0	0
Not reported	0	0	0	0	0	0
Ethnicity, n (%)	--	--	--	--	--	--
Hispanic/Latino	4 (6.8)	3 (6.4)	0	4 (8.3)	2 (4.2)	2 (4.2)
Not Hispanic/Latino	55 (93.2)	44 (93.6)	48 (100.0)	44 (91.7)	46 (95.8)	44 (91.7)
Not reported	0	0	0	0	0	2 (4.2)

Source: FDA information request: Shell Tables for Study P101, Table B

Abbreviations: N=total number of participants in the specified group, or the total sample; n=number of participants with the specified characteristic; SD=standard deviation
The Randomized Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study. The Safety Set consists of all randomized participants who receive any study injection.

a. Other included East Indian.

Reviewer Comment

Across Cohorts 7 through 11, 41.7% - 61.7% of participants were 65 through 69 years of age 38.3% to 58.3% were 70 through 79 years of age, and over half the participants were female (52.1% to 60.4%). The proportion of participants who were White and non-Hispanic was 83.1% to 95.8%, which is not representative of the current demographic characteristics of the United States.

6.2.10.1.2 Participant Disposition

Disposition of participants in the Safety Set after first vaccination is summarized in [Table 18](#). The number of participants who withdrew from the study after vaccination was higher in 200-µg cohort (33.3%) than in the placebo cohort (15.3%) and the 50-µg cohort (17.0%). The most common reason for withdrawal was withdrawal by the participant. One participant in the 12.5-µg cohort withdrew due to a serious adverse event of gunshot wound, which the Investigator assessed as not related to the study vaccination.

A total of 290 (96.6%) randomized participants were included in the Per Protocol Set for immunogenicity analyses, of whom 58 (20.0%) participants received placebo and 232 (80.0%) participants received mResvia. The proportion of participants excluded from the Per Protocol Set was similar between participants who received vaccine and placebo. The reasons for exclusion included: did not receive the first vaccination (n=2), missing immunogenicity result at corresponding visit (n=2), no post-baseline immunogenicity value (n=2), and other study deviations (n=4).

Table 18. Disposition, Safety Set, Adults 65 Through 79 Years of Age, Study P101, Single Dose

Population	Placebo N=59 n (%)	Cohort 7 mResvia 50 µg N=47 n (%)	Cohort 8 mResvia 100 µg N=48 n (%)	Cohort 9 mResvia 200 µg N=48 n (%)	Cohort 10 mResvia 25 µg N=48 n (%)	Cohort 11 mResvia 12.5 µg N=48 n (%)
Safety Set	59 (100.0)	47 (100.0)	48 (100.0)	48 (100.0)	48 (100.0)	48 (100.0)
Completed 6 months safety follow up	53 (89.8)	42 (89.4)	39 (81.3)	39 (81.3)	45 (93.8)	44 (91.7)
Participants withdrawn after vaccination ^a	9 (15.3)	8 (17.0)	13 (27.1)	16 (33.3)	5 (10.4)	6 (12.5)
Reason for withdrawal	--	--	--	--	--	--
Withdrawal by participant	4 (6.8)	5 (10.6)	3 (6.3)	12 (25.0)	3 (6.3)	2 (4.2)
Lost to follow up	5 (8.5)	2 (4.3)	9 (18.8)	3 (6.3)	1 (2.1)	1 (2.1)
Death	0	0	0	0	1 (2.1)	1 (2.1)
Physician decision	0	1 (2.1)	1 (2.1)	0	0	0
Pregnancy	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	1 (2.1)
Study terminated by Sponsor	0	0	0	0	0	0
Refused further study procedures	--	--	--	--	--	--
Adverse event	0	0	0	0	0	1 (2.1)
No longer meets eligibility criteria	--	--	--	--	--	--
Other ^b	0	0	0	1 (2.1)	0	0
Solicited Safety Set ^c	58 (98.3)	47 (100.0)	48 (100.0)	47 (97.9)	48 (100.0)	46 (95.8)
Excluded from Solicited Safety Set	1 (1.7)	0	0	1 (2.1)	0	2 (4.3)
Reason for exclusion	--	--	--	--	--	--
Participant did not receive study vaccination	0	0	0	0	0	0
Participant did not have at least 1 postbaseline solicited safety [eDiary] assessment	1 (1.7)	0	0	1 (2.1)	0	2 (4.3)

Source: Adapted from STN 125796/0, P101 Clinical Study Report, Table 14.1.7.2.1, and ad hoc Table I. Data cutoff: M14 – refer to shell table D.

Abbreviations: N=number of participants in Safety Set; n=number of participants with the specified characteristic; percentages based on the Safety Set

a. Study discontinuation

b. Other reasons included participant found no longer able to make informed consent.

c. The Solicited Safety Set consists of all participants who are randomized and receive any study injection, and contribute any solicited AR data (i.e., have at least 1 postbaseline solicited safety [eDiary] assessment). The values in this row are the denominators for the percentage calculations for the rows below.

Reviewer Comment

A total of 57 participants withdrew after first vaccination with 29 participants (50.8%) who withdrew themselves and 21 participants (36.8%) who were lost to follow-up. The 200-µg and 100-µg cohorts had the highest number of withdrawals from the study. Although a specific reason for the withdrawals was not provided, the 200-µg and 100 µg-doses were also associated with higher rates of reactogenicity, which may have impacted participant retention. The disposition of participants in the 50-µg dose cohort was similar to those participants who received placebo.

6.2.11 Immunogenicity Analyses

Adults 65 Through 79 years of Age: First Dose of mResvia

[Table 19](#) shows the RSV neutralizing titer (NT) GMFRs data for study participants 65 through 79 years of age who received the first dose of mResvia or placebo. One month post-first dose, the immune responses of mResvia recipients increased across all dose levels when compared to placebo recipients. The GMFRs for the mResvia recipients peaked one month post first dose and remained elevated above baseline through Month 12.

Table 19. RSV Neutralizing Titer GMFRs, Per-Protocol Set, Adults 65 Through 79 Years of Age, Study P101, First Dose

Subgroup and Timepoint	Placebo N=58 GMFR (n) (95% CI)	Cohort 7 mResvia 50 µg N=47 GMFR (n) (95% CI)	Cohort 8 mResvia 100 µg N=46 GMFR (n) (95% CI)	Cohort 9 mResvia 200 µg N=47 GMFR (n) (95% CI)	Cohort 10 mResvia 25 µg N=46 GMFR (n) (95% CI)	Cohort 11 mResvia 12.5 µg N=46 GMFR (n) (95% CI)	Cohort 15 mResvia 100 µg N=20 GMFR (n) (95% CI)
RSV A Neutralizing Antibody (IU/mL) ^a	-	-	-	-	-	-	-
Baseline (Day 1)	-	-	-	-	-	-	-
Month 1 (Day 29)	1.15 (56) (0.99, 1.34)	12.03 (44) (8.78, 16.47)	14.14 (43) (10.23, 19.54)	16.54 (47) (12.25, 22.33)	12.17 (45) (8.90, 16.64)	10.19 (44) (7.17, 14.48)	11.15 (20) (7.76, 16.01)
Month 2 (Day 57)	1.12 (58) (0.95, 1.33)	9.16 (46) (6.73, 12.47)	9.31 (39) (6.65, 13.04)	12.70 (44) (9.53, 16.92)	10.03 (42) (7.17, 14.02)	6.61 (44) (4.92, 8.89)	9.75 (20) (7.17, 13.27)
Month 3 (Day 85)	1.11 (55) (0.98, 1.26)	7.53 (44) (5.54, 10.24)	7.73 (42) (5.95, 10.05)	9.35 (46) (6.76, 12.92)	7.54 (45) (5.57, 10.22)	5.27 (43) (3.82, 7.29)	7.77 (19) (5.61, 10.76)
Month 6 (Day 169)	1.00 (54) (0.87, 1.17)	5.05 (43) (3.77, 6.76)	4.05 (42) (2.96, 5.54)	5.74 (44) (4.54, 7.25)	4.10 (44) (3.04, 5.54)	3.08 (44) (2.33, 4.08)	4.16(20) (2.96, 5.83)
Month 12 (Day 365)	1.15 (49) (0.96, 1.38)	3.00 (39) (2.18, 4.13)	2.66 (33) (1.94, 3.66)	3.16 (37) (2.38, 4.20)	2.96 (41) (2.22, 3.94)	2.39 (40) (1.84, 3.10)	-

Subgroup and Timepoint	Placebo N=58 GMFR (n) (95% CI)	Cohort 7 mResvia 50 µg N=47 GMFR (n) (95% CI)	Cohort 8 mResvia 100 µg N=46 GMFR (n) (95% CI)	Cohort 9 mResvia 200 µg N=47 GMFR (n) (95% CI)	Cohort 10 mResvia 25 µg N=46 GMFR (n) (95% CI)	Cohort 11 mResvia 12.5 µg N=46 GMFR (n) (95% CI)	Cohort 15 mResvia 100 µg N=20 GMFR (n) (95% CI)
RSV B Neutralizing Antibody (IU/mL) ^b	-	-	-	-	-	-	-
Baseline (Day 1)	-	-	-	-	-	-	-
Month 1 (Day 29)	1.12 (56) (0.98, 1.29)	8.96 (44) (6.79, 11.84)	9.60 (43) (7.31, 12.61)	12.49 (47) (9.10, 17.16)	6.56 (45) (4.86, 8.87)	5.29 (44) (3.74, 7.49)	6.60 (20) (4.90, 8.88)
Month 2 (Day 57)	1.27 (58) (1.12, 1.44)	7.08 (46) (5.40, 9.28)	8.87 (39) (6.71, 11.73)	9.77 (44) (7.34, 13.00)	5.66 (42) (4.35, 7.36)	4.02 (44) (3.08, 5.23)	6.60 (20) (4.90, 8.88)
Month 3 (Day 85)	1.27 (55) (1.12, 1.44)	5.62 (44) (4.24, 7.45)	7.02 (42) (5.35, 9.20)	7.99 (46) (6.00, 10.64)	4.57 (45) (3.54, 5.90)	3.51 (43) (2.58, 4.78)	3.82 (19) (2.97, 4.91)
Month 6 (Day 169)	1.35 (54) (1.16, 1.57)	4.38 (43) (3.37, 5.70)	4.60 (42) (3.69, 5.73)	5.50 (44) (4.39, 6.89)	3.20 (44) (2.36, 4.34)	2.87 (44) (2.24, 3.70)	2.67 (20) (2.04, 3.50)
Month 12 (Day 365)	1.07 (49) (0.89, 1.29)	2.27 (39) (1.77, 2.91)	2.78 (33) (2.10, 3.69)	2.92 (37) (2.32, 3.68)	1.61 (41) (1.25, 2.06)	1.52 (40) (1.23, 1.88)	-

Source: Adapted from STN 125796/0, P101 Clinical Study Report, Tables 27, 28, 29, 32 and 33. Data cutoff: M14 – refer to shell table D. Abbreviations: AU=arbitrary units; CI=confidence interval; IU=international units; GMFR=geometric mean fold-rise, comparing postbaseline to baseline titer values; LLOQ=lower limit of quantitation; RSV=respiratory syncytial virus; ULOQ=upper limit of quantitation.

Notes: N=number of participants in any Per Protocol set. 95% CI was calculated based on the t-distribution of the log-transformed values for GMFR, then back transformed to the original scale for presentation; n=Number of participants with valid and determinate assay results both before vaccination (Day 1) and at the specified time point. For GMFR calculation, comparing postbaseline to baseline titer values, antibody values reported as below LLOQ at baseline were replaced by LLOQ.

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

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

Reviewer Comment

As shown in [Table 17](#) above, the GMFR point estimates were higher for RSV-A than for RSV-B across all dose levels, and higher doses of mResvia were associated with greater GMFRs for RSV-A and RSV-B. Although participants who received higher dose levels of mResvia generally had higher GMFR point estimates, the confidence intervals for most vaccine cohorts overlapped across all time points for RSV-A and RSV-B NTs, likely due to the small number of participants enrolled into each cohort. By Month 12, the GMFRs were generally similar across all dose levels, suggesting that the increased GMFRs that were observed in participants who received higher dose levels of mResvia are transient. All vaccine recipients demonstrated higher GMFRs without overlapping confidence intervals when compared to placebo recipients for RSV-A and RSV-B.

Second Dose of mResvia of 50 µg Following First Dose of 50 µg (Adults 65 Through 79 Years):

Though the Applicant is seeking licensure of mResvia when administered as single dose, the immunogenicity findings for 18 mResvia recipients who received a second dose of mResvia are presented to provide additional information to inform future assessments of 2nd vaccination doses at least 12 months after the first dose. Study participants who received mResvia for their first dose were randomized to receive either placebo or mResvia for the second dose. For participants who received 2 doses of mResvia, the same dose level was administered for both the first and second doses. All placebo recipients were administered placebo for their second dose. [Table 20](#) shows the RSV NT GMFRs for the second dose recipients, specifically the 50-µg cohort compared to placebo.

Table 20. RSV Neutralizing Titer GMFRs, Adults 65 Through 79 Years of Age, Study P101, 2nd Dose Subset

Subgroup and Timepoint	Placebo Day 1 Placebo Month 12 N=51 GMFR (n) (95% CI)	mResvia Day 1 Placebo Month 12 N=21 GMFR (n) (95% CI)	mResvia Day 1 mResvia Month 12 N=18 GMFR (n) (95% CI)
RSV A Neutralizing Antibody (IU/mL) ^a	--	--	--
Baseline (Day 1)	--	--	--
Month 1 post Dose 1 (Day 29)	1.16 (49) (0.98, 1.38)	13.05 (19) (8.43, 20.21)	10.05 (17) (5.47, 18.45)
Month 2 post Dose 1 (Day 57)	1.13 (51) (0.93, 1.36)	10.67 (21) (6.59, 17.27)	6.87 (17) (3.99, 11.84)
Month 12 post Dose 1 (Day 365)	1.15 (49) (0.96, 1.38)	3.29 (21) (1.96, 5.52)	2.69 (18) (1.81, 4.00)
Month 1 post Dose 2 (Day 393)	1.24 (48) (0.96, 1.58)	2.92 (21) (1.79, 4.74)	7.29 (17) (4.25, 12.51)
Month 2 post Dose 2 (Day 421)	1.35 (46) (1.08, 1.70)	3.05 (21) (1.84, 5.07)	6.98 (14) (4.35, 11.18)

Subgroup and Timepoint	Placebo Day 1 Placebo Month 12 N=51 GMFR (n) (95% CI)	mResvia Day 1 Placebo Month 12 N=21 GMFR (n) (95% CI)	mResvia Day 1 mResvia Month 12 N=18 GMFR (n) (95% CI)
RSV B Neutralizing Antibody (IU/mL) ^b	-	-	-
Baseline (Day 1)	-	-	-
Month 1 post Dose 1 (Day 29)	1.11 (49) (0.95, 1.30)	11.25 (19) (7.59, 16.68)	6.36 (17) (3.85, 10.52)
Month 2 post Dose 1 (Day 57)	1.25 (51) (1.09, 1.45)	7.20 (21) (4.63, 11.20)	6.80 (17) (4.17, 11.09)
Month 12 post Dose 1 (Day 365)	1.07 (49) (0.89, 1.29)	2.11 (21) (1.42, 3.13)	2.46 (18) (1.78, 3.41)
Month 1 post Dose 2 (Day 393)	1.13 (48) (0.92, 1.38)	2.13 (21) (1.58, 2.87)	5.20 (17) (3.42, 7.92)
Month 2 post Dose 2 (Day 421)	1.24 (46) (1.01, 1.53)	2.32 (21) (1.75, 3.09)	4.52 (14) (2.82, 7.23)

Source: Adapted from STN 125796/0, P101 Clinical Study Report, Table 30 and 31. Data cutoff: 03 Oct 2022 (Month 14; Interim analysis).

Abbreviations: AU=arbitrary units; CI=confidence interval; IU=international units; GMFR=geometric mean fold-rise, comparing postbaseline to baseline titer values; LLOQ=lower limit of quantitation; RSV=respiratory syncytial virus; ULOQ=upper limit of quantitation.

Notes: N=number of participants in any Per Protocol set. 95% CI was calculated based on the t-distribution of the log-transformed values for GMFR, then back transformed to the original scale for presentation; n=Number of participants with valid and determinate assay results both before vaccination (Day 1) and at the specified time point. For GMFR calculation, antibody values reported as below LLOQ at baseline were replaced by LLOQ.

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

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

Reviewer Comment

While an increase in the RSV neutralizing antibody GMFRs was observed in participants who received a second 50-µg dose of mResvia, the point estimates for the GMFRs post-second dose were numerically lower than those observed after the first 50-µg dose. The rate of decline of the RSV NT GMFRs appeared to be slower after the second dose, when compared to the rate of decline after the first dose. However, immunogenicity data following the second dose was limited by only two months post-second dose data, while immunogenicity data following the first dose included GMFRs up to 12 months after the first dose. As such, any conclusions regarding the durability of increased GMFRs following a second dose are limited.

6.2.12 Safety Analyses

Three hundred participants between 65 through 79 years of age were randomized to receive a first dose of mResvia at varying dose levels (48 participants per cohort) or placebo (60 participants). Each cohort received one of five dose levels (12.5 µg, 25 µg, 50 µg, 100 µg, or 200 µg) of mResvia. There were 298 participants who received the first dose, and 247 participants who received the second dose as of the data cutoff date (October 3, 2022). The final dose selected for the Phase 3 study, P301, was 50 µg, and the review of safety data will be focused on this cohort.

Reviewer Comment

Per the Applicant, the safety and immunogenicity data from this Phase 1 study supported dose selection and further clinical evaluation of a single injection of 50 µg of mResvia for subsequent clinical development in adults, based on the safety

and tolerability profile observed with a favorable immune response. FDA agrees that the dose selection was reasonable.

6.2.12.1 Methods

See Section [6.2.7](#) above.

6.2.12.2 Overview of Adverse Events

Safety Overview: Cohort 7 (50-µg dose)

[Table 21](#) summarizes rates of adverse events after the first dose. The rates of solicited local ARs, solicited systemic ARs, immediate AEs and unsolicited AEs were higher in the 50 µg cohort when compared to placebo recipients. There were no AEs leading to withdrawal from the study reported in either group. SAEs were reported by 8.5% of the 50 µg cohort and 1.7% of the placebo group. No SAEs were reported within 28 days after the first dose, and none were considered related to the study vaccination per Investigator. There were no deaths reported in either group as of the data cutoff date (October 3, 2022).

Table 21. Proportion of Participants Reporting at Least One Adverse Event Following Vaccination, Safety Set, Adults 65 Through 79 Years of Age, Study P101, First Dose

AE Type: Monitoring Period ^a	Placebo % (n/N)	Cohort 7 mResvia 50 µg % (n/N)
Immediate: 1 hour	7.3 (4/55)	17.0 (8/47)
Solicited local reaction ^b at the injection site: Day 1-7	12.7 (7/55)	61.7 (29/47)
Grade 3 or above solicited local	5.5 (3/55)	0.0 (0/47)
Solicited systemic reaction ^c : Day 1-7	45.5 (25/55)	53.3 (25/47)
Grade 3 or above solicited systemic	1.8 (1/55)	10.6 (5/47)
Unsolicited: Day 1-28	18.6 (11/59)	25.5 (12/47)
Severe unsolicited AEs	0.0 (0/59)	6.4 (3/47)
Related unsolicited AEs	10.2 (6/59)	4.3 (2/47)
Severe and related unsolicited AEs ^d	0.0 (0/59)	4.3 (2/47)
Serious AEs	1.7 (1/59)	8.5 (4/47)
Deaths	0.0 (0/59)	0.0 (0/47)

Source: FDA information request: Shell Tables for Study P101, Table O

Abbreviations: AE=Adverse Event; MAAE=medically attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; N=total number of participants in the specified group, or the total sample; for solicited local/systemic, N=number of participants in the Solicited Safety Set who submitted any data for the event; n=number of participants who experienced the event.

The Safety Set consists of all randomized participants who received any study injection.

The Solicited Safety Set consists of all participants who are randomized and receive any study injection, and contribute any solicited AR data (i.e., have at least 1 postbaseline solicited safety [eDiary] assessment).

Note: Participants were allocated to the vaccine groups as received.

a. Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.

b. Solicited local reactions included injection site pain, erythema (redness), and swelling/induration (hardness).

c. Solicited systemic reactions included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, underarm swelling or tenderness on same side as injection (solicited term; coded to "lymphadenopathy" in raw data and summarized as such in data tables), and chills.

d. Relatedness to study vaccine as determined by the Principal Investigator

Note: SAEs, MAAEs, fatal TEAEs, and AESIs were summarized from the first injection up to the booster injection, or to EOS if participant did not receive booster injection.

Solicited Local Adverse Reactions: Cohort 7 (50-µg dose)

[Table 22](#) includes the proportions of study participants who reported any solicited local AR, by maximum severity. Within 7 days postvaccination, the proportion of participants

reporting any local reaction was higher in the 50 µg cohort (61.7%) compared to the placebo group (12.7%). The most frequently reported local AR in both groups was injection site pain, reported by 61.7% of participants in the 50 µg cohort and 12.7% of participants in the placebo group. Severe (Grade 3 or higher) solicited local ARs were reported by 3 participants (5.5%) in the placebo group, and no participants in the 50 µg cohort. The median onset of injection site pain was 1-2 days and the median onset for swelling was 1 day across both groups. No participants in either group reported erythema.

Table 22. Proportion of Participants Reporting at Least One Solicited Local Adverse Reaction Within 7 Days Following Vaccination, by Maximum Severity, Solicited Safety Set, Adults 65 Through 79 Years of Age, Study P101, First Dose

Solicited Local Adverse Reaction	Placebo %(n/N)	Cohort 7 mResvia 50 µg % (n/N)
Any local reaction	12.7 (7/55)	61.7 (29/47)
Grade 1	7.3 (4/55)	59.6 (28/47)
Grade 2	0.0 (0/55)	2.1 (1/47)
Grade 3	5.5 (3/55)	0.0 (0/47)
Grade 4	0.0 (0/55)	0.0 (0/47)
Pain ^a	--	--
Any	12.7 (7/55)	61.7 (29/47)
Grade 1	7.3 (4/55)	59.6 (28/47)
Grade 2	0.0 (0/55)	2.1 (1/47)
Grade 3	5.5 (3/55)	0.0 (0/47)
Grade 4	0.0 (0/55)	0.0 (0/47)
Erythema (Redness)	--	--
Any	0.0 (0/55)	0.0 (0/47)
Grade 1 (2.5 cm to 5.0 cm)	0.0 (0/55)	0.0 (0/47)
Grade 2 (5.1 cm to 10.0 cm)	0.0 (0/55)	0.0 (0/47)
Grade 3 (>10.0 cm)	0.0 (0/55)	0.0 (0/47)
Grade 4 (Necrosis or exfoliative dermatitis)	0.0 (0/55)	0.0 (0/47)
Swelling/Induration (Hardness)	--	--
Any	0.0 (0/55)	2.1 (1/47)
Grade 1 (2.5 cm to 5.0 cm)	0.0 (0/55)	2.1 (1/47)
Grade 2 (5.1 cm to 10.0 cm)	0.0 (0/55)	0.0 (0/47)
Grade 3 (>10.0 cm)	0.0 (0/55)	0.0 (0/47)
Grade 4 (Necrosis)	0.0 (0/55)	0.0 (0/47)
Axillary swelling/tenderness ^{a,b}	--	--
Any	--	--
Grade 1	--	--
Grade 2	--	--
Grade 3	--	--
Grade 4	--	--

Source: Source: FDA information request: Shell Tables for Study P101, Table S Adapted from STN 125796/0, P101 Clinical Study Report, Table 15. Data cutoff: M14 – refer to shell table D. Abbreviations: N=Number of participants with any solicited AR data for the specific solicited local/systemic AR in the group; n=Number of participants who experienced the event, or with maximum severity of grade 1, grade 2, grade 3, or grade 4.

Note: Participants were allocated to the vaccine groups as received.

a. For pain and axillary swelling/tenderness – Grade 1: Does not interfere with activity; Grade 2: Repeated use of over the counter (nonnarcotic) pain reliever >24 hours or some interference with activity; Grade 3: Any use of prescription pain reliever or prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.

b. Axillary swelling/tenderness ipsilateral to the side of injection

Reviewer Comment

Although data from the other study cohorts were not presented (12.5-µg, 25-µg, 100-µg, and 200-µg cohorts), solicited local ARs were reported more frequently in the 100-µg and 200-µg cohorts than in the 12.5-µg, 25-µg, and 50-µg cohorts. The most frequently reported local AR across all cohorts was injection site pain, reported by 74.5% of participants in the 100-µg cohort, 78.7% of participants in the 200-µg cohort, 65.9% of participants in the 25-µg cohort, and 50.0% of participants in the 12.5-µg cohort. Severe (Grade 3 or above) solicited local ARs were reported by 2.1% of participants in the 200-µg cohort and 6.8% of participants in the 25-µg cohort. Episodes of axillary swelling/tenderness are reported in [Table 23](#) below as lymphadenopathy.

Solicited Systemic Adverse Reactions: Cohort 7 (50-µg dose)

[Table 23](#) summarizes solicited systemic ARs, by maximum severity. Overall, the rates of solicited systemic ARs within 7 days postvaccination were higher in the 50 µg cohort (53.2%) when compared to the placebo group (45.5%). Among participants in the 50 µg cohort, the most frequently reported systemic AR was headache (31.9%), followed by fatigue (29.8%), then followed by myalgia (27.7%) and arthralgia (27.7%). For placebo recipients, fatigue (36.4%) was the most frequently reported solicited systemic AR, followed by arthralgia (23.6%) then myalgia (18.2%). Fever was reported in 2.1% of participants in the 50 µg cohort and 1.9% of participants in the placebo group. Grade 3 systemic ARs were reported in 10.6% of participants in the 50 µg cohort and 1.8% of participants in the placebo group and generally followed the same distribution as the overall proportions of solicited systemic ARs.

Table 23. Proportion of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 days Following Vaccination, by Maximum Severity, Solicited Safety Set, Adults 65 Through 79 Years of Age, Study P101, First Dose

Solicited Systemic Adverse Reaction	Placebo % (n/N)	Cohort 7 mResvia 50 µg % (n/N)
Any systemic reaction	45.5 (25/55)	53.2 (25/47)
Grade 1	29.1 (16/55)	34.0 (16/47)
Grade 2	14.5 (8/55)	8.5 (4/47)
Grade 3	1.8 (1/55)	10.6 (5/47)
Grade 4 (fever >40.0°C)	0.0 (0/55)	0.0 (0/47)
Headache ^a	--	--
Any	14.5 (8/55)	31.9 (15/47)
Grade 1	9.1 (5/55)	19.1 (9/47)
Grade 2	3.6 (2/55)	6.4 (3/47)
Grade 3	1.8 (1/55)	6.4 (3/47)
Grade 4	0.0 (0/55)	0.0 (0/47)
Fatigue ^b	--	--
Any	36.4 (20/55)	29.8 (14/47)
Grade 1	21.8 (12/55)	19.1 (9/47)
Grade 2	14.5 (8/55)	4.3 (2/47)
Grade 3	0.0 (0/55)	6.4 (3/47)
Grade 4	0.0 (0/55)	0.0 (0/47)

Solicited Systemic Adverse Reaction	Placebo % (n/N)	Cohort 7 mResvia 50 µg % (n/N)
Myalgia^b	--	--
Any	18.2 (10/55)	27.7 (13/47)
Grade 1	10.9 (6/55)	14.9 (7/47)
Grade 2	7.3 (4/55)	8.5 (4/47)
Grade 3	0.0 (0/55)	4.3 (2/47)
Grade 4	0.0 (0/55)	0.0 (0/47)
Arthralgia^b	-	-
Any	23.6 (13/55)	27.7 (13/47)
Grade 1	18.2 (10/55)	19.1 (9/47)
Grade 2	5.5 (3/55)	4.3 (2/47)
Grade 3	0.0 (0/55)	4.3 (2/47)
Grade 4	0.0 (0/55)	0.0 (0/47)
Nausea/Vomiting^c	--	--
Any	9.1 (5/55)	6.4 (3/47)
Grade 1	7.3 (4/55)	4.3 (2/47)
Grade 2	1.8 (1/55)	0.0 (0/47)
Grade 3	0.0 (0/55)	2.1 (1/47)
Grade 4	0.0 (0/55)	0.0 (0/47)
Fever (temperature ≥38°C)	--	--
Any fever	1.9 (1/54)	2.1 (1/47)
Grade 1: ≥38.0-38.4°C	1.9 (1/54)	0.0 (0/47)
Grade 2: 38.5-38.9°C	0.0 (0/54)	2.1 (1/47)
Grade 3: 39-40.0°C	0.0 (0/54)	0.0 (0/47)
Grade 4: >40.0°C	0.0 (0/54)	0.0 (0/47)
Chills^d	--	--
Any	5.5 (3/55)	8.5 (4/47)
Grade 1	1.8 (1/55)	2.1 (1/47)
Grade 2	3.6 (2/55)	4.3 (2/47)
Grade 3	0.0 (0/55)	2.1 (1/47)
Grade 4	0.0 (0/55)	0.0 (0/47)
Lymphadenopathy^{e,f}	--	--
Any	5.5 (3/55)	6.4 (3/47)
Grade 1	5.5 (3/55)	6.4 (3/47)
Grade 2	0.0 (0/55)	0.0 (0/47)
Grade 3	0.0 (0/55)	0.0 (0/47)
Grade 4	0.0 (0/55)	0.0 (0/47)

Source: Adapted from STN 125796/0, P101 Clinical Study Report, Table 15. Data cutoff: M14 – refer to shell table D.
Abbreviations: N=number of participants with at least 1 day of e-diary data for the specific solicited local/systemic AR in

the group; n=number of participants who experienced the event, or with maximum severity of grade 1, grade 2, grade 3 or grade 4.

Temperature 38.0°C = 100.4°F.

Note: Participants were allocated to the vaccine groups as received.

- a. For headache – Grade 1: No interference with activity; Grade 2: Repeated use of over-the-counter pain reliever >24 hours or some interference with activity; Grade 3: Significant; any use of prescription pain reliever or prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
- b. For fatigue, myalgia, and arthralgia – Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; Grade 4: Requires emergency room visit or hospitalization.
- c. For nausea/vomiting – Grade 1: No interference with activity or 1-2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires emergency room visit or hospitalization for hypotensive shock.
- d. For chills – Grade 1: No interference with activity; Grade 2: Some interference with activity not requiring medical intervention; Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires emergency room visit or hospitalization.
- e. For axillary swelling/tenderness – Grade 1: No interference with activity; Grade 2: Repeated use of over the counter (nonnarcotic) pain reliever >24 hours or some interference with activity; Grade 3: Any use of prescription pain reliever or prevents daily activity; Grade 4: Emergency room visit or hospitalization.

Data from the other study cohorts were not presented (12.5-µg, 25-µg, 100-µg, and 200-µg cohorts) in the table above. Solicited systemic ARs were reported more frequently in the 100 µg-and 200-µg cohorts than in the 12.5-µg, 25-µg, and 50-µg cohorts. A larger proportion of study participants who received 100 µg or 200 µg of mResvia experienced solicited systemic ARs (78.7% and 66.0%, respectively) than participants who received 12.5 µg, 25 µg or 50 µg of mResvia (50 - 53.2%). The most frequently reported solicited systemic AR in the 100-µg and 200-µg cohorts was fatigue observed in 59.6% and 57.4% of participants, respectively. The most frequently reported solicited systemic AR in participants who received 12.5 µg or 25 µg of mResvia was headache occurring in 28.3% and 36.4% of participants, respectively. Most solicited systemic ARs were reported as Grade 1 or Grade 2 in severity, regardless of dose.

Though the Applicant is seeking licensure of mResvia when administered as single dose, the safety findings for the 247 participants who received a second dose of mResvia or placebo following a first dose of mResvia are included:²

- Solicited local ARs after the second dose were reported for 76.3% of mResvia/mResvia participants, 8.5% of mResvia/placebo participants, and 9.8% of placebo/placebo participants. The most frequently reported solicited local AR was injection site pain. The proportion of solicited local ARs after the second dose in the mResvia/mResvia participants (71.9%) was higher than that after the first dose in this group (61.7%).
- Solicited systemic ARs after the second dose were reported for 64.9% of the mResvia/mResvia participants, 34.0% of the mResvia/placebo participants, and 23.5% of the placebo/placebo participants. The most frequently reported solicited systemic ARs were headache and fatigue. The proportion of solicited systemic ARs after the second dose in the mResvia/mResvia participants (55.2%) was higher than that of the first dose in this group (53.2%); however, severity, onset time, and duration of solicited systemic ARs were similar between the first and second dose.

² **Note:** mResvia/mResvia indicate participants who received the study vaccination for both doses, mResvia/placebo indicate participants who received the study vaccination for the first dose and placebo for the second dose, and placebo/placebo indicate participants who received placebo for both doses

Reviewer Comment

Based on the available data, the safety profile of a second dose of mResvia are similar to those after the first dose. New or concerning safety findings were not identified following this additional dose.

Unsolicited Adverse Events

The proportion of participants who reported unsolicited AEs within 28 days of the first dose were 63.8% in the 50-µg cohort and 35.6% in the placebo group. The highest proportion of unsolicited AEs were reported under the MedDRA SOC of *musculoskeletal and connective tissue disorders* (19.1%) for the 50-µg cohort and *infections and infestations* (18.6%) for the placebo group. There were two unsolicited AEs that were Grade 3 in severity and were assessed by the Investigator as related to the study dose (1 event of hypertension and 1 event of prothrombin time prolonged).

Reviewer Comment

The review team sent the Applicant an information request regarding the two Grade 3 unsolicited AEs that were assessed as related by the Investigator. Per the Applicant's response, the event of prothrombin time prolonged occurred on Day 10 post first dose, no treatment was reported, and repeat coagulation labs on Day 29 post first dose had normalized. The event of hypertension was a worsening of pre-existing disease, occurred on Day 1 post first dose and resolved on Day 8 post first dose. The participants hypertensive medications were adjusted following the AE.

6.2.12.3 Deaths

Adults 65 Through 79 Years of Age: First Dose of mResvia

No deaths were reported by the data cutoff date (October 3, 2022) in participants who received 12.5 µg, 25 µg, 50 µg, 100 µg, 200 µg of mResvia or placebo after the first dose.

Adults 65 Through 79 Years of Age: Second Dose of mResvia

There were two fatal events (which also led to premature discontinuation from the study) reported after the second dose. Both participants had received a second dose of placebo after a first dose of mResvia and neither event was considered related to the study injection per the Investigator:

- One participant in the 12.5 µg mResvia/placebo group died due to bone sarcoma on Day 162 after the second dose.
- One participant in the 25 µg mResvia/placebo group died due to a road traffic accident on Day 63 after the second dose.

Cohort 15: Japanese Older Adults ≥60 Years

No deaths were reported by the end of the study in participants who received 100 µg of mResvia or placebo.

Adults 18 Through 49 Years of Age

No deaths were reported by the end of the study in participants who received a single dose of 50 µg, 100 µg, 200 µg of mResvia or placebo. No deaths were reported by the end of the study in participants who received three injections of 100 µg or placebo.

Reviewer Comment

No deaths were reported for any dose level of mResvia. Two deaths were reported following placebo, and based on independent review of event narratives, FDA agrees with the Investigators' assessments of causality.

6.2.12.4 Nonfatal Serious Adverse Events

Adults 65 Through 79 Years of Age: First Dose of mResvia

SAEs were reported in 12.5%, 6.3%, 8.5%, 0%, and 2.1% of participants in the 12.5-µg, 25-µg, 50-µg, 100-µg, and 200-µg cohorts, respectively, and 1.7% of participants in the placebo cohort. While the incidence of SAEs was higher in the mResvia cohorts than the placebo cohort, no SAEs were reported within 28 days after first dose and no SAEs were related to study vaccine per Investigator assessment. Events of potential clinical interest in the older adult cohorts include:

- Atrial fibrillation and congestive cardiac failure: A 69-year-old white female participant with medical history including systolic cardiac murmur received 12.5 µg of mResvia. The participant had atrial fibrillation (moderate) on Day 352 post first dose. The events required hospitalization and resolved on Day 369. The participant experienced life-threatening congestive cardiac failure on Day 372. The congestive cardiac failure was ongoing at the time of data cutoff date (October 3, 2022). The patient did not receive a second dose as she was lost to follow-up.
- Cerebrovascular accident: A 76-year-old white male participant received 50 µg of mResvia. The participant had a cerebrovascular accident (severe) on Day 235 post first dose and was hospitalized and treated with tissue plasminogen activator. The event resolved on Day 238. The patient received a second dose of mResvia without experiencing any additional SAEs.
- Coronary artery disease: A 69-year-old white male participant with medical history including coronary artery disease received 50 µg of mResvia. The participant had coronary artery disease (severe) on Day 103 post first dose and was hospitalized. The event resolved on Day 110.
- Subarachnoid hemorrhage: A 70-year-old white male participant received 25 µg of mResvia. The participant had subarachnoid hemorrhage (moderate) on Day 115 post first dose and was hospitalized. The event resolved on Day 117.
- Upper gastrointestinal hemorrhage: A 73-year-old white male participant received 25 µg of mResvia. The participant had upper gastrointestinal hemorrhage (severe) on Day 161 post first dose and was hospitalized. The event resolved on Day 163.

Reviewer Comment

None of the SAEs were assessed as related to study intervention by the study Investigators. Based on independent review of event narratives, FDA agrees with the Investigators' assessments of causality.

Adults 65 Through 79 Years of Age: Second Dose of mResvia

SAEs were reported in 3.0% of study participants who received two doses of mResvia, 4.2% of study participants who received mResvia and placebo, and 1.9% of study participants who received two doses of placebo. The reported SAEs were sporadic without any predominant MedDRA SOC and were not assessed as related to study vaccine.

Japanese Adults ≥60 Years of Age

No SAEs were reported by the end of the study in study participants who received a single 100-µg dose of mResvia or placebo.

Adults 18 Through 49 Years of Age

No SAEs were reported by the end of the study in study participants who received a single dose of 50 µg, 100 µg, 200 µg of mResvia or placebo. Similarly, no SAEs were reported by the end of the study in study participants who received three doses of 100 µg mResvia or placebo.

6.2.12.5 Adverse Events of Special Interest (AESI)

No AESIs were reported by the data cutoff date (October 3, 2022) in Cohorts 1-4, Cohorts 7-11, and Cohort 15.

6.2.12.6 Adverse Events Leading to Study Withdrawal

There were no AEs leading to study withdrawal reported in any study participants (adults 18 through 49 years of age, adults 65 through 79 years of age, and adults of Japanese descent ≥60 years of age) through the end of study or by the data cutoff date (October 3, 2022).

6.2.13 Study Summary and Conclusions

Study P101 was a Phase 1 study to evaluate the safety, reactogenicity, and immunogenicity of mResvia in healthy younger adults 18 through 49 years of age, healthy older adults 65 through 79 years of age and Japanese older adults ≥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 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-µg dose of mResvia was chosen for further clinical development. The data reviewed from this study support the overall findings of Study P301.

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated summary of efficacy is not applicable to this review as Study P301 was the only study with clinical efficacy evaluation of mResvia in the relevant age population.

8. INTEGRATED OVERVIEW OF SAFETY

Study P301 contributed most of the study participant safety data for the final mResvia 50 µg formulation in the target population for licensure (adult participants ≥60 years of age). In the remaining study submitted to this BLA, P101, only 48 participants ≥60 years of age received the final dose level and formulation of mResvia. The overall safety conclusions for mResvia are sufficiently characterized by data from Study P301 and reflect the safety findings from the other supportive study.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The application did not contain data from clinical studies specifically addressing whether the vaccine is safe for use in pregnancy, and it is not known if there is a vaccine-associated risk with use of mResvia in pregnancy.

9.1.2 Use During Lactation

The application did not contain data from clinical studies specifically addressing whether the vaccine is safe for use during lactation. It is not known whether mResvia is excreted in human milk. No human or animal data are available to assess the effects of mResvia on the breastfed infant or on milk production/excretion.

9.1.3 Pediatric Use and PREA Considerations

Safety and effectiveness of mResvia in individuals younger than 18 years of age have not been established.

To address PREA requirements, 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 the following studies 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 deferred pediatric studies are:

- Phase 1 P101, to evaluate the safety and immunogenicity of mResvia in RSV-seropositive children 12 months to <60 months of age
- Phase 1 mRNA-1365-P101, to evaluate the safety and immunogenicity of mResvia in infants 5 to <24 months of age
- Phase 2 mRNA-1345-P202, to evaluate the safety, tolerability, and immunogenicity of mResvia in healthy children 2 to <5 years of age, and children and adolescents at high risk of severe RSV disease 2 to <18 years of age
- Proposed Phase 2 study to evaluate the safety and immunogenicity of mResvia in infants and children 2 to <24 months of age
- Proposed Phase 3 study to evaluate the safety and efficacy of mResvia in infants and children 2 to <24 months of age
- Proposed Phase 3 study to evaluate the safety and efficacy of mResvia in children 2 to <5 years of age who are healthy or at risk of severe RSV disease

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.

9.1.4 Immunocompromised Patients

Immunocompromised individuals, including those receiving immunosuppressive therapy, may have a diminished immune response to mResvia.

9.1.5 Geriatric Use

Of the total number of participants (n=36,412) who received mResvia or placebo in Study P301, 22,554 (61.9%) were 60 through 69 years of age, 10,972 (30.1%) were 70 through 79 years of age, and 2,886 (7.9%) were 80 years of age and older.

10. CONCLUSIONS

The data submitted to this BLA provide evidence to support the safety and effectiveness of a single 50- μ g dose of mResvia vaccine for prevention of RSV-associated lower respiratory tract disease in adults \geq 60 years of age.

The clinical data submitted to the BLA include results from multi-country, randomized, observer-blind, placebo-controlled clinical trial P301 that evaluated the safety and efficacy of mResvia vaccine in >36,000 participants (>18,000 mResvia recipients) 60 years of age and older. The primary efficacy analysis, with a data cutoff of November 30, 2022 and a median follow-up of 3.7 months postvaccination, demonstrated a vaccine efficacy to prevent laboratory-confirmed RSV-LRTD with \geq 2 and \geq 3 symptoms of 78.7% (95.04% CI: 62.8, 87.9) and 80.9% (95.1% CI: 50.1, 92.7), respectively. At the April 30, 2023 data cutoff (median follow-up of 8.6 months postvaccination), vaccine efficacy to prevent laboratory-confirmed RSV-LRTD with \geq 2 and \geq 3 symptoms was 62.5% (95% CI: 47.7, 73.1) and 61.1% (95% CI: 34.7, 76.8), respectively. Efficacy outcomes across demographic subgroups were generally consistent with the overall findings of the primary and supportive analyses but were limited by small subpopulation sizes.

An analysis of the secondary endpoint of vaccine efficacy to prevent RSV-ARD demonstrated a VE of 69.1% at the median follow-up of 3.7 months postvaccination and 54.1% at the median follow-up of 8.6 months postvaccination; however, most participants who met criteria for ARD also met the case definition for LRTD, confounding the interpretation of efficacy of mResvia against ARD alone. (b) (4)

The safety database for this BLA included >18,000 mResvia recipients, of whom 96.6% completed at least 6 months of safety follow-up postvaccination, with a median follow-up of 10.2 months. In Study P301, local and/or systemic solicited reactions following vaccination were generally of short duration and occurred more commonly in the mResvia vaccine group than in the placebo group. Overall, deaths and SAEs were reported by similar proportions of participants in each treatment group. An observed numerical imbalance in events of urticaria within 7 days and within 1 month after vaccination supports inclusion of urticaria in labeling. One SAE of facial paralysis assessed as related to mResvia will be included in labeling due to the close temporal relationship to vaccination. Review of safety data from Study P101 did not reveal any safety concerns and supported the overall safety findings of Study P301.

Clinical data to support selection of a single 50- μ g dose of mResvia came from Study P101.

Based on the totality of data and the risk-benefit considerations as described in Section [11](#) below, the clinical review team concludes that the clinical trial data submitted in this application support approval of a single 50-µg dose of mResvia vaccine for the indication of prevention of LRTD caused by RSV in individuals 60 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 24. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> RSV is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. Among adults 65 years of age and older, RSV disease results in an average of 177,000 hospitalizations in the U.S. per year with a mortality rate of 14.7 per 100,000. RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans. 	<ul style="list-style-type: none"> LRTD due to RSV infection in older adults is a serious and life-threatening condition and can be associated with significant morbidity and mortality.
Unmet Medical Need	<ul style="list-style-type: none"> Treatment for RSV infection is limited to supportive care. Currently, there are two licensed vaccines for the prevention of LRTD caused by RSV in individuals ≥60 years of age. 	<ul style="list-style-type: none"> Currently, there are two licensed vaccines for the prevention of LRTD caused by RSV. With an aging global population, it is important to have multiple RSV vaccines available to the public to avoid potential vaccine shortages.
Clinical Benefit	<ul style="list-style-type: none"> In a population of >36,000 participants 60 years of age and older enrolled in a randomized, placebo-controlled trial conducted in sequential Phase 2 and Phase 3 segments, vaccine efficacy against LRTD associated with RSV with at least 2 and at least 3 symptoms was 62.5% (95% CI: 47.7, 73.1) and 61.1% (95% CI: 34.7, 76.8), respectively, with the median duration of follow-up for efficacy of 8.6 months. Subgroup analyses of vaccine efficacy suggest that VE is, in general, preserved across demographic subgroups, including among participants with co-morbidities associated with increased risk of more severe RSV disease. Uncertainties in clinical benefit include: the duration of vaccine effectiveness; VE in frail elderly individuals and those ≥80 years of age; VE in immunocompromised individuals; concomitant administration with vaccines recommended for use in this population. 	<ul style="list-style-type: none"> The effectiveness of mResvia was supported by the demonstration of vaccine efficacy against LRTD associated with RSV in Study P301. The Applicant's studies ongoing at the time of this review evaluate the durability of protection up to 24 months postvaccination, vaccine effectiveness after re-vaccination, vaccine effectiveness in immunocompromised and high-risk individuals, and concomitant administration of mResvia with seasonal influenza vaccine, high-dose seasonal influenza vaccine, and mRNA COVID-19 vaccine.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	<ul style="list-style-type: none"> The most commonly reported ($\geq 10\%$) solicited ARs among mResvia recipients were injection site pain (55.9%), fatigue (30.8%), headache (26.7%), myalgia (25.6%), arthralgia (21.7%), axillary swelling or tenderness (15.2%), and chills (11.6%); The rates of severe (Grade 3 or 4) reactions were 3.1% and 4.0% of local and systemic solicited adverse reactions, respectively. A numerical imbalance was noted between the mResvia group and the placebo group for events of urticaria within 7 days following vaccination (8 and 2 participants, respectively) and within 28 days following vaccination (15 and 5 participants, respectively); All events were mild or moderate in severity and resolved. One case of facial paralysis with onset 4 days following administration of mResvia was reported as an SAE and assessed by the Investigator, Applicant, and FDA as possibly related to study vaccine in Study P301. 	<ul style="list-style-type: none"> The data submitted adequately characterize the reactogenicity of mResvia in adults ≥ 60 years of age. Available information on urticaria indicates a potential causal relationship with the vaccine. The case of facial paralysis does not establish a causal relationship to vaccination. The safety of mResvia is acceptable for its intended use.
Risk Management	<ul style="list-style-type: none"> The most substantial risks of vaccination with mResvia are associated with solicited injection site and systemic adverse reactions (see "Risk" section above). However, most injection site and systemic reactions are mild in severity and resolve within 1 to 2 days. Anaphylaxis and myocarditis/pericarditis are important potential risks. Missing safety information includes interaction with coadministered vaccines, use in immunocompromised individuals, use in those with autoimmune or inflammatory disorders, and long-term safety. 	<ul style="list-style-type: none"> The safety data provided in the prescribing information adequately describes the risks. The Applicant's proposed plan for routine pharmacovigilance and active surveillance in studies ongoing at the time of this review and in planned studies would be adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of mResvia in individuals 60 years of age and older in preventing RSV-associated LRTD is favorable compared to the risks associated with vaccination. Data submitted to this BLA establish the safety and effectiveness of mResvia among individuals 60 years of age and older. The safety of mResvia is adequately described in the prescribing information, and the Applicant's pharmacovigilance plan is adequate for monitoring AEs post-marketing.

11.3 Discussion of Regulatory Options

The Applicant originally proposed an indication of prevention of (b) (4) lower respiratory tract disease. Due to the overlap in case definitions between the lower respiratory tract disease (b) (4) endpoints, FDA determined that the available data would most appropriately support the more clinically relevant indication limited to prevention of lower respiratory tract disease due to RSV (see Section [6.1](#) and in Section [10](#)).

Efficacy data provided in the application did not adequately address the duration of vaccine effectiveness, VE in immunocompromised individuals, and concomitant administration with vaccines routinely recommended for use in this population. The interpretation of efficacy in individuals ≥80 years of age, those with risk factors (COPD/CHF), and those with frailty status of vulnerable or frail was limited by the small number of individuals and low case numbers in these subgroups. Missing information identified in the Applicant's Core Risk Management Plan for mResvia includes interaction with other vaccines, use in immunocompromised individuals, use in those with autoimmune or inflammatory disorders, and long-term safety.

Overall, the data provided in the application support the safety and effectiveness of mResvia for the indication of prevention of LRTD caused by RSV in individuals 60 years of age and older.

11.4 Recommendations on Regulatory Actions

Based on the clinical data provided in the application, the Clinical Reviewer recommends approval of mResvia for the prevention of lower respiratory tract disease caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older.

11.5 Labeling Review and Recommendations

The proprietary name mResvia was reviewed by the Advertising and Promotional Labeling Branch and found acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

No postmarketing requirements or postmarketing commitments are needed or recommended. The Clinical Reviewer agrees with the pharmacovigilance activities as proposed by the Applicant in the pharmacovigilance plan which include routine pharmacovigilance through signal detection and adverse event reporting as required under 21 CFR 600.80.

The Applicant has identified two important potential risks: anaphylaxis and myocarditis/pericarditis, and four areas of missing information: interaction with other vaccines, use in immunocompromised individuals, use in individuals with autoimmune or inflammatory disorders, and long-term safety. To address these potential risks and areas of missing information, and to further characterize the risk of pre-defined AESIs, the Applicant plans two large-scale active surveillance studies in older adults overall and within subgroups defined by age, sex, immunocompromised status, coadministration of other vaccine(s), and status of autoimmune or inflammatory disorder using administrative healthcare databases in the U.S. and Europe as follows:

- Study 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
- Study mRNA-1345-P903: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1345 Vaccine for respiratory syncytial virus (RSV) in Europe

In addition to routine pharmacovigilance activities and the active surveillance studies, anaphylaxis, myocarditis/pericarditis, interaction with other vaccines, use in immunocompromised individuals, and long-term safety will continue to be evaluated and monitored in the following trials ongoing at the time of this review.

- P101: A Phase 1 Randomized, Observer-blind, Placebo-controlled, Dose Escalation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Healthy Younger Adults Aged 18 through 49 Years, Women of Child-bearing Potential Aged 18 to 40 Years, Healthy Older Adults Aged 65 through 79 Years, Japanese Older Adults Aged ≥ 60 Years, and RSV-seropositive Children Aged 12 to 59 Months
- mRNA-1345-P201: A Phase 2 Randomized, Observer-blind, Placebo-controlled, Dose Escalation Study to Evaluate the Reactogenicity, Safety, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, in Pregnant Women, and Safety, and Immunogenicity in Infants Born to Vaccinated Mothers.
- 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
- 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, When Given Alone or Coadministered with a Seasonal Influenza Vaccine or SARS-CoV-2 Vaccine in Adults ≥ 50 Years of Age
- 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
- mRNA-1345-P304: A Phase 3 Randomized, Observer-blind Study to Evaluate Safety, Tolerability, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus, When Coadministered with a High-dose, Quadrivalent Seasonal Influenza Vaccine in Adults ≥ 65 Years of Age