**Report on the Deliberation Results**

April 25, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

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|---|---|
| **Brand Name** | mRESVIA Intramuscular Injection Syringes |
| **Non-proprietary Name** | Respiratory Syncytial Virus RNA Vaccine |
| **Applicant** | Moderna Japan Co., Ltd. |
| **Date of Application** | May 30, 2024 |

**Results of Deliberation**

In its meeting held on April 21, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The vaccine product and its active substance are both classified as powerful drugs.

**Approval Condition**

The applicant is required to develop and appropriately implement a risk management plan.

Latest Corrected Version**

# Review Report

April 8, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

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|---|---|
| **Brand Name** | mRESVIA Intramuscular Injection Syringes |
| **Non-proprietary Name** | Respiratory Syncytial Virus RNA Vaccine |
| **Applicant** | Moderna Japan Co., Ltd. |
| **Date of Application** | May 30, 2024 |
| **Dosage Form/Strength** | Injection: Each syringe contains 0.050 mg of mRNA encoding the respiratory syncytial virus F glycoprotein stabilized in the prefusion conformation. |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |
| **Items Warranting Special Mention** | None |
| **Reviewing Office** | Office of Vaccines and Blood Products |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of disease caused by respiratory syncytial virus (RSV) infection, and that the product has acceptable safety in view of its benefits (see Attachment). The product is not classified as a biological product or a specified biological product. The vaccine product and its active substance are both classified as powerful drugs.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

**Indication**

Prevention of disease caused by respiratory syncytial virus (RSV) infection

**Dosage and Administration**

A single dose of 0.5 mL is injected intramuscularly in individuals aged ≥60 years.



** The English translation has been corrected to reflect the corrections listed in the latest errata sheet (dated February 3, 2026) for the Japanese original.

**Approval Condition**

The applicant is required to develop and appropriately implement a risk management plan.

Latest Corrected Version

**Attachment**

# Review Report (1)

February 18, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

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|---|---|
| **Brand Name** | mRESVIA Intramuscular Injection Syringes |
| **Non-proprietary Name** | Respiratory Syncytial Virus RNA Vaccine |
| **Applicant** | Moderna Japan Co., Ltd. |
| **Date of Application** | May 30, 2024 |
| **Dosage Form/Strength** | Injection: Each syringe contains 0.050 mg of mRNA encoding the respiratory syncytial virus F glycoprotein stabilized in the prefusion conformation. |

**Proposed Indication**

Prevention of disease caused by RSV infection

**Proposed Dosage and Administration**

A single dose of 0.5 mL is injected intramuscularly in individuals aged ≥60 years.

**Table of Contents**



**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Respiratory syncytial virus (RSV) is an RNA virus that belongs to the pneumovirus family and is classified into 2 subgroups of respiratory syncytial virus A subtype (RSV-A) and respiratory syncytial virus B subtype (RSV-B). RSV infects the human respiratory tract. The infection in healthy non-elderly adults causes only flulike symptoms, which mostly resolve spontaneously, while the elderly, who are immunocompromised with aging and likely to have underlying diseases such as chronic heart disease and chronic lung disease, are at a high risk of disease caused by RSV infection and even a fatal outcome (*Clin Microbiol Rev.* 2000;13:371-84, etc.). According to a report in 2019, acute respiratory disease (ARD) caused by RSV (RSV-ARD) was estimated to have occurred in approximately 5.2 million adults aged ≥60 years in advanced countries, resulting in 470,000 hospitalizations and 30,000 in-hospital deaths (*Influenza Other Respir Viruses.* 2023;17:e13031).

In Japan, research conducted during the 2011/2012 and 2012/2013 seasons reports that of 817 adult pneumonia cases, 5.3% received a diagnosis of RSV-related disease (*The Journal of the Japanese Association for Infectious Diseases.* 2016;90:645-51). A prospective observational cohort study in adults aged ≥65 years conducted in the 2019/2020 season reports that RSV-ARD was detected in 24 of 1,000 participants and lower respiratory tract disease (LRTD) caused by RSV infection (RSV-LRTD) was detected in 8 of 1,000 participants (*Influenza Other Respir Viruses.* 2022;16:298-307).

As of January 2025, no drugs for the treatment of disease caused by RSV infection in adults have been approved in Japan. To treat disease caused by RSV infection in adults, symptomatic therapies are mainly provided, including antipyretics, antitussives/expectorants, bronchodilators, and infusions as well as, for severe diseases, oxygen inhalation and mechanical ventilation. To prevent disease caused by RSV infection in adults aged ≥60 years, recombinant RSV vaccine products have been marketed under the brand names of Abrysvo Intramuscular Injection and Arexvy Intramuscular Injection.

mRESVIA Intramuscular Injection Syringes (hereinafter also referred to as mRESVIA), is a lipid nanoparticle (LNP)-encapsulated messenger ribonucleic acid (mRNA)-based vaccine, and an active substance is mRNA encoding the membrane-anchored RSV F glycoprotein, derived from RSV subtype A strain (RSV-A A2 variant), and stabilized in the prefusion conformation. As of December 2024, mRESVIA has been granted a marketing approval for immunization in adults aged ≥60 years in 5 counties or regions including the US and European countries.

The applicant has submitted an application for drug marketing approval of mRESVIA with the proposed indication of “Prevention of disease caused by RSV infection” based on the results from a global phase II/III study (Study mRNA-1345-P301 [Study P301]) in adults aged ≥60 years.

## 2. Quality and Outline of the Review Conducted by PMDA

### 2.1 Active substance

The active substance (RNA-100-AR02) is the mRNA encoding RSV F glycoprotein stabilized in the prefusion conformation by genetical modification. On RSV, F glycoprotein forms a trimer, which promotes intracellular invasion of the virus via membrane fusion. The RNA-100-AR02 mRNA sequence includes a 5’-Cap1 structure, the 5’-untranslated region, the open reading frame encoding F glycoprotein

stabilized in the prefusion conformation, 3'-untranslated region, and 3' poly A tail. Instead of UTP, N1-Me-ΨTP is used to avoid activation of Toll-like receptors (TLRs) and to dampen innate immune response.

### 2.1.1 Generation and control of cell substrate

Linear plasmid deoxyribonucleic acid (DNA), one of the raw materials for mRESVIA, is prepared from an *Escherichia coli* (*E. coli*) cell bank. The master cell bank (MCB) of an *E. coli* cell bank was prepared from *E. coli* ( strain) transfected with plasmid DNA that contains , , sequences, and a gene encoding F glycoprotein stabilized in the prefusion conformation and poly A tail. The working cell bank (WCB) was prepared from the MCB via passages.

The MCB has been subjected to purity tests, , viable cell count, , identification of host cells, sequencing of the plasmid, restriction enzyme analysis, and . The WCB has been subjected to the same tests as those for the MCB except for the identification of host cells.

### 2.1.2 Manufacturing process

The manufacturing process for the active substance consists of *in vitro* transcription, tangential flow filtration, chromatography, tangential flow filtration, capping, tangential flow filtration, chromatography, final tangential flow filtration, clarification, testing, and storage.

and have been defined as critical steps.

The manufacturing process for the active substance has been subjected to process validation at a commercial scale.

### 2.1.3 Manufacturing process development

Main changes made to the process during development of the active substance include a change that , , and (the post-change process is defined as the proposed process). The vaccine product using active substance (RNA-100-AR01) manufactured in the pre-change process was supplied to non-clinical and clinical studies of mRESVIA.

In response to the process changes, a comparability assessment on quality attributes was performed, and comparability of the pre- and post-change active substances has been demonstrated. When the active substance was changed from RNA-100-AR01 to RNA-100-AR02, in addition to the comparability assessment on quality attributes, an immunogenicity study was conducted in mice, and has been demonstrated to have no impact on immunogenicity or safety profile.

### 2.1.4 Characterization

#### 2.1.4.1 Structure and characterization

The active substance was subjected to characterization as shown in Table 1.

**Table 1. Parameters for Characterization**

| Attributes | | Test method |
|---|---|---|
| Primary structure | RNA sequence | Sanger sequencing, oligonucleotide mapping ([redacted], [redacted]), identification of N1-Me-ΨTP ([redacted], [redacted]), next-generation sequencing |
| | 5'-Cap1 structure | RP-HPLC/ESI-MS after RNase H digestion |
| | Poly A tail length and dispersity | [redacted], [redacted] |
| | Percent Poly A tail adducts | [redacted] |
| Higher order structure | Secondary structure | Circular dichroism spectroscopy |
| | Higher order structure | Differential scanning calorimetry |
| Physicochemical properties | Extinction coefficient | UV |
| Biological properties | *In vitro* translation | SDS-PAGE, Western blotting |

The biological properties of the active substance were evaluated using an *in vitro* translation assay, in which the mRNA sequence encoding RSV F glycoprotein stabilized in the prefusion conformation, in the active substance, was translated into a protein in a cell-free system, and the molecular weight of the protein was confirmed by SDS-polyacrylamide gel electrophoresis (SDS-PAGE). A band indicative of the same molecular weight as that of the desired protein separated by SDS-PAGE was identified as the RSV F glycoprotein by Western blotting.

#### 2.1.4.2 Product-related substances/Product-related impurities

Product-related impurities specified were short mRNA species, high-molecular-weight mRNA, double-stranded RNA, Cap variants, variants with a point mutation, and variants with insertions/deletions. Short mRNA species and Cap variants are controlled by the active substance specifications. High-molecular-weight mRNA represents reversible multimers of desired mRNA or mRNA longer than the desired sequence length and has been demonstrated to have no impact on protein expression. Double-stranded RNA may be formed in the step for *in vitro* transcription, but its level is consistently controlled at a level comparable to that in the clinically qualified lots by optimization of parameters of the step for *in vitro* transcription. Variants with a point mutation and variants with insertions/deletions have been demonstrated to be consistently below the detection limit throughout the manufacturing process.

#### 2.1.4.3 Process-related impurities

Process-related impurities were template DNA, residual proteins (Process-related Impurity A, Process-related Impurity B, Process-related Impurity C, Process-related Impurity D, Process-related Impurity E), low-molecular-weight impurities (Process-related Impurity F, Process-related Impurity G, Process-related Impurity H, Process-related Impurity I, Process-related Impurity J), residual solvents (Process-related Impurity K and Process-related Impurity L), and residual [redacted]. All the process-related impurities have been demonstrated to be adequately removed in the manufacturing process.

### 2.1.5 Control of active substance

The proposed specifications for the active substance consist of content, description, identification (base sequence), pH, purity (mRNA purity and product-related impurities [ion-paired reversed-phase high

performance liquid chromatography (RP-IP-HPLC)]), percent 5'-Cap1 adduct (RP-IP-HPLC), percent Poly A tail adducts (reversed-phase high performance liquid chromatography [RP-HPLC]), bacterial endotoxins, microbial limits, and assay (ultraviolet-visible spectroscopy [UV]).

### 2.1.6 Stability of active substance

Main stability studies of the active substance are outlined in Table 2.

**Table 2. Main stability studies of the active substance**

| Study | Manufacturing process | No. of batches | Temperature | Storage period | Storage package |
|---|---|---|---|---|---|
| Long-term | Proposed process | 3 | -80°C to -60°C | 18 months[a)] | [redacted] |
| Accelerated | Proposed process | 3 | 2°C to 8°C | 6 months | [redacted] bag |

a) Planned to be continued for up to 60 months.

Under the long-term condition, no clear change with time was observed in any test item performed during the storage period.

Under the accelerated condition, a decrease in mRNA purity and an increase in product-related impurities were observed at Month [redacted].

Based on the above, a shelf life of 18 months has been proposed for the active substance when stored in the [redacted] bag at −90°C to −60°C.

## 2.2 Vaccine product

### 2.2.1 Description and composition of vaccine product and formulation development

The vaccine product is a suspension for injection containing 0.050 mg of the active substance (RNA-100-AR02) per syringe (0.5 mL). In the vaccine product, the active substance (RNA-100-AR02) is encapsulated in lipid nanoparticles composed of 4 lipids (heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate [SM-102], cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC], and 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG]). The vaccine product contains the following excipients: SM-102, cholesterol, DSPC, PEG2000-DMG, trometamol, trometamol hydrochloride, glacial acetic acid, sodium acetate hydrate, sucrose, and water for injection. The vaccine product is a combination product classified as a drug and presented as a prefilled syringe in which the active substance suspension is filled in a syringe for prefilling with the tip cap. For the syringe for prefilling, notification has been submitted (Medical Device Marketing Notification No. 13B2X10352000002).

### 2.2.2 Manufacturing process

The manufacturing process for the vaccine product consists of the manufacturing process for lipid nanoparticles and that for a vaccine product intermediate in which the active substance (RNA-100-AR02) is encapsulated in lipid nanoparticles followed by the processes for thawing and pooling of the vaccine product intermediate, dilution, clarification, sterile filtration, filling and inspection, freezing and storage of unlabeled intermediate vaccine product (UDP), thawing of UDP, assembly, labeling and packaging, testing, freezing and storage of packaged vaccine product, and testing and storage of frozen packaged vaccine product. Of note, a process shortened by omitting the processes for freezing and

storage of UDP and its thawing and allowing direct proceeding to the process for assembly and subsequent process is also established.

[redacted], [redacted], and [redacted] have been defined as critical steps.

The commercial scale manufacturing process has been subjected to process validation.

### 2.2.3 Manufacturing process development

Main changes are described below.

- First Generation to Second Generation: License-in of the preparation process for lipid nanoparticles, change from lyophilized formulation to suspension formulation, change of manufacturing scale, changes of composition and active substance concentration
- Second Generation to Third Generation: Change of manufacturing scale, changes of composition and active substance concentration
- Third Generation to proposed process: Change of active substance (from RNA-100-AR01 to RNA-100-AR02), change of manufacturing scale, change of filled container from vial to syringe

The First Generation vaccine product was used in a phase I study, and the Second Generation and Third Generation vaccine products were used in a phase III study.

In response to the process changes, a comparability assessment on quality attributes was performed, and comparability of the pre- and post-change products has been demonstrated.

### 2.2.4 Control of vaccine product

The proposed specifications for the vaccine product consist of strength, description, identification (mRNA [base sequence]), lipids [SM-102, cholesterol, DSPC, and PEG2000-DMG (high performance liquid chromatography/charged aerosol detection [HPLC/CAD])]), purity tests (mRNA purity and product-related impurities [RP-IP-HPLC], lipid impurities [HPLC/CAD]), percent RNA encapsulation (UV), *in vitro* translation (SDS-PAGE), pH, osmolality, mean particle size and polydispersity index (dynamic light scattering), foreign insoluble matter, insoluble particulate matter, extractable volume, bacterial endotoxins, sterility, break-loose force and glide force, lipid content (SM-102, cholesterol, DSPC, and PEG2000-DMG [HPLC/CAD]), and assay (anion exchange high performance liquid chromatography [AEX-HPLC]/UV).

### 2.2.5 Stability of vaccine product

Main stability studies of the vaccine product are outlined in Table 3.

**Table 3. Main stability studies of the vaccine product**

| Study | Manufacturing process | No. of batches | Temperature | Storage period | Storage package |
|---|---|---|---|---|---|
| Long-term | Proposed process | 3 | -25°C to -15°C | 6 months[a)] | Cyclic olefin copolymer syringe with a bromobutyl rubber tip cap and a plunger stopper |
| Accelerated | Proposed process | 3 | 2°C to 8°C | 9 months[b)] | |
| | Proposed process | 3 | 23°C to 27°C | 3 months | |
| Photostability | Proposed process[c)] | 1 | Overall illumination of ≥1.2 million lx·hr, an integrated near ultraviolet energy of ≥200 W·h/m$^2$, 25°C | | |

a) The study will be continued for up to [redacted] months.
b) The study will be continued for up to [redacted] or [redacted] months.
c) The batch was manufactured at a pilot scale.

Under the long-term condition, no clear change with time was observed in any test item performed during the storage period.

Under the accelerated condition at 2°C to 8°C, a decreasing trend in mRNA purity and an increasing trend in product-related impurities were observed.

Under the accelerated condition at 23°C to 27°C, a decrease in mRNA purity and an increase in product-related impurities were observed at Month [redacted].

Photostability data showed that the vaccine product is sensitive to light.

Based on the above, a shelf life of 6 months has been proposed for the vaccine product when stored in a cyclic olefin copolymer syringe with a bromobutyl rubber tip cap and a plunger stopper packaged in a carton to protect from light at −40°C to −15°C.

### 2.3 Quality control strategy

Quality control strategy was established based on the following investigations:

- Identification of critical quality attributes (CQAs)

As quality attributes affecting the efficacy and safety of mRESVIA, the following CQAs were identified:

CQAs for active substance: Description, identification (mRNA sequence), mRNA purity and product-related impurities, percent 5'-Cap1 adducts, percent Poly A tail adduct, Poly A variants, template DNA, residual protein, pH, bacterial endotoxins, and microbial limits

CQAs for vaccine product: Description, identification (mRNA sequence, lipids), RNA content, mRNA purity and product-related impurities, percent RNA encapsulation, particle size, polydispersity index, *in vitro* translation (SDS-PAGE), lipid content, lipid impurities, pH, osmolality, insoluble particulate matter, extractable volume, bacterial endotoxins, sterility, break-loose force and glide force

- Process characterization

Each process was subjected to characterization using a small-down model and a failure mode and effects analysis approach. Based on the results, of process parameters, critical process parameters (CPPs) that would affect the CQAs were identified, and an acceptable control range was studied for each process parameter.

- Development of control method

Control methods of quality attributes for mRESVIA were developed using the process parameter control and specifications in combination, based on the above process characterization, process knowledge including manufacturing results for Spikevax Intramuscular Injection (hereinafter also referred to as Spikevax), which is manufactured in a similar process to that for mRESVIA, and risk assessment on quality attributes [for control of product-related impurities and process-related impurities for the active substance, see Sections 2.1.4.2 and 2.1.4.3].

**2.R Outline of the review conducted by PMDA**

Based on the submitted data and the following review, PMDA concluded that the quality of the active substance and vaccine product has been appropriately controlled.

**2.R.1 Control of potency**

In view of the mechanism of action of mRESVIA, PMDA considers it important, from a viewpoint of control strategy, to verify that the antigen protein is expressed to a certain level as a result of intracellular delivery of the vaccine product. [redacted] included in the specifications for the vaccine product is a test to check expression of the antigen protein qualitatively using [redacted] active substance but does not cover the test system including the intracellular distribution process of the active substance encapsulated in lipid nanoparticles. PMDA thus considered that the applicant should develop the control strategy of the vaccine product for antigen protein expression, for example, including the *in vitro* relative protein expression (IVRPE) assay using Hep3B cells, which was a quantitative test performed for the characterization of the vaccine product, in the specifications for the vaccine product. The applicant's response is reported in the Review Report (2).

**2.R.2 Novel excipients**

The vaccine product contains SM-102, PEG2000-DMG, and DSPC as excipients that are permitted only for use in specific products in accordance with the "Handling of excipients that are permitted only for use in specific drug products or under specific conditions" (Administrative Notice dated June 23, 2009).

Based on the submitted data, PMDA concluded that no problems are found in the specifications for these excipients or their stability or the safety of them used according to the proposed dosage and administration. These excipients may be accepted for use in vaccine products to prevent infections, but data on the long-term safety have not been obtained. The use of these excipients should be limited to mRESVIA used according to the dosage regimen and should not be deemed as a general precedent.

**3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA**

The applicant submitted primary pharmacodynamic data of mRESVIA, in the form of the results from an immunogenicity study in mice and a protective efficacy study in cotton rats.

### 3.1 Primary pharmacodynamics

The applicant's explanation:

Results in Sections 3.1.1 and 3.1.2 demonstrated immunogenicity of mRESVIA. mRESVIA vaccination is expected to protect the vaccine recipients from RSV infection or exert the protective efficacy, without causing immunological and pathological changes related to enhanced respiratory disease (ERD).

#### 3.1.1 Antibody production ability and T-cell response (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.4)

In serum samples from mice treated with mRESVIA,[1)] RSV-specific neutralizing antibodies (micro neutralizing assay) as well as immunoglobulin G (IgG) antibodies specific to RSV F protein in the prefusion conformation (prefusion F protein [preF]) and in the postfusion conformation (postfusion F protein [postF]) (enzyme-linked immunoassay [ELISA]) were measured. Using splenocytes, T-cell response (after stimulation with a pool of overlapping peptides that cover the RSV F protein, cytokine responses were evaluated by flow cytometry) was measured. As a comparator in assessment of the ERD risk associated with mRESVIA treatment, formalin-inactivated RSV was used.

In mice treated with 2 or 3 doses of mRESVIA, RSV-A neutralizing antibodies as well as preF- and postF-specific IgG antibodies were induced. Induced IgG antibodies were IgG 1 and IgG 2a in terms of the subclass, and Class I cytokine producing CD4-positive T cells and CD8-positive T cells were induced, indicating that immune response to mRESVIA is T helper 1 (Th1)-directed response. This immune response was different from that induced by treatment with the formalin-inactivated RSV, which was Th2-directed response.

#### 3.1.2 Protective efficacy study (CTD 4.2.1.1.3)

In cotton rats treated with 2 doses of mRESVIA,[2)] protection from RSV infection was investigated. Five days after RSV challenge, the nasal and lung tissues were subjected to RSV viral load assay, and the lung tissue was subjected to histopathological examination and cytokine mRNA expression assay by real-time PCR. As a comparator in assessment of the ERD risk associated with mRESVIA treatment, formalin-inactivated RSV was used.

The viral loads in the nasal and lung tissues after RSV challenge were lower in rats treated with mRESVIA (3 or 30 μg) than in control rats (formalin mock, control LNPs, phosphate buffered saline [PBS]), showing the protection from infection. The histopathological examination on the lung tissue presented findings indicative of enhanced lung inflammation in rats treated with formalin-inactivated RSV, but rats treated with mRESVIA had histopathological scores similar to those in control rats and presented no findings indicative of enhanced lung inflammation.

In the rats treated with formalin-inactivated RSV, the viral challenge led to an increase in mRNA expression level of Th2 cytokines, which is a finding representative of ERD. On the other hand, in rats

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1) Vaccine product containing [redacted] active substance (RNA-100-AR01) or [redacted] active substance (RNA-100-AR02) encoding conformationally stabilized RSV preF, LNPs with the same composition as that in Spikevax Intramuscular Injection, and 20 mM Tris, 87 mg/mL sucrose, and [redacted] mM sodium acetate ([redacted])

2) Vaccine product containing [redacted] active substance (RNA-100-AR01) encoding conformationally stabilized RSV preF, LNPs with the same composition as that in Spikevax, and 20 mM Tris, 87 mg/mL sucrose, and [redacted] mM sodium acetate ([redacted])

treated with mRESVIA, mRNA expression levels of Th2 cytokines were lower than those in rats treated with formalin-inactivated RSV.

### 3.2 Safety pharmacology

Although no independent safety pharmacology studies of mRESVIA have been conducted, the safety pharmacology of mRESVIA was evaluated based on clinical signs and histopathological findings in a repeated-dose toxicity study in rats (CTD 4.2.3.2.7). The applicant explained that there were no findings raising concerns about effects on physiological functions in the cardiovascular, respiratory, or central nervous system.

### 3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the non-clinical pharmacology data of mRESVIA had no particular problems. The risk of ERD in humans is continuously reviewed in Section 7.R.2.2.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted non-clinical pharmacokinetic data of mRESVIA in the form of results from a biodistribution study in rats using mRNA-1647 encapsulated in LNPs with the same composition as that in mRESVIA. The mRNA-1647 contained 6 mRNAs that encoded cytomegalovirus glycoproteins (CTD 4.2.2.3.1). The applicant also submitted data on metabolism and excretion of SM-102, a constituent lipid of LNP contained in mRESVIA in the form of study results (CTD 4.2.2.4.1 and 4.2.2.4.2).

The LNP used in mRESVIA has the same composition as that used in Spikevax, which is approved in Japan. The study results submitted in the present application were originally submitted in the initial marketing application and partial change application of Spikevax (previously COVID-19 Vaccine Moderna Intramuscular Injection) and were reviewed (Report on Special Approval for Emergency on COVID-19 Vaccine Moderna Intramuscular Injection dated May 17, 2021 and Report on Special Approval for Emergency on Spikevax Intramuscular Injection dated September 7, 2022).

### 4.R Outline of the review conducted by PMDA

The applicant’s explanation about biodistribution of mRESVIA:
The biodistribution study of mRNA-1647 in rats revealed that mRNA was mainly distributed at the injection site, proximal (popliteal) lymph node, distal (axillary) lymph node, and spleen and then eliminated with the half-lives of 14.9, 34.8, 31.1, and 63.0 hours, respectively. In the other tissues, mRNA was also detected but all found below the detection limit in 1 to 3 days.

The test article, mRNA-1647, is a vaccine product with mRNA encapsulated in LNPs that have been manufactured as done for those used in mRESVIA in terms of the process and composition. When administered into the body, generally, mRNA not encapsulated in LNPs is rapidly metabolized as with nucleic acids in the body, but mRNA encapsulated in LNPs is not metabolized and is delivered into the cells, enabling protein expression in the cytoplasm. The biodistribution of vaccine products with mRNA encapsulated in LNPs is not influenced by the mRNA itself but is expected to be dependent primarily on characteristics of the LNP such as the composition and particle size (*Mol Ther Nucleic Acids.* 2019;15:1-11, *Nanomedicine (Lond).* 2016;11:673-92). Results from a biodistribution study with

mRNA-1647, of which LNPs have the same composition and size as those of LNPs of mRESVIA, can be extrapolated to mRESVIA.

PMDA accepted the applicant's explanation.

## 5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data of mRESVIA in the form of the results from a repeated-dose toxicity study and reproductive and developmental toxicity study of mRESVIA.[2)] The LNP used in mRESVIA has the same composition as that used in Spikevax, which is approved in Japan. The evaluation data submitted in the present application (repeated-dose toxicity studies, CTD 4.2.3.2.1 to 4.2.3.2.6; genotoxicity studies, CTD 4.2.3.3.1.1 to 4.2.3.3.1.4, 4.2.3.3.2.1) were originally submitted in the initial marketing application of Spikevax (previously COVID-19 Vaccine Moderna Intramuscular Injection) and reviewed (Report on Special Approval for Emergency on COVID-19 Vaccine Moderna Intramuscular Injection dated May 17, 2021).

### 5.1 Single-dose toxicity

Acute toxicity of mRESVIA was evaluated based on the results after the first dose in a repeated-dose toxicity study of mRESVIA[2)] in rats (CTD 4.2.3.2.7). Neither death nor changes in clinical signs were observed.

### 5.2 Repeated-dose toxicity

A repeated-dose toxicity study of mRESVIA[2)] in rats was conducted (Table 4). Principal findings include inflammatory reaction at the injection site and effects on lymphoid tissues (inflammation in the tissue surrounding the lymph node, decreased cellularity in the spleen, etc.). The applicant explained that the recovery group was not included in the study, but these findings are all reversible in view of results from repeated-dose toxicity studies of the other mRNA-LNP vaccine products containing LNPs with the same composition as that of the LNPs in mRESVIA.

**Table 4. Repeated-dose toxicity study**

| Test system | Route of administration | Duration of dosing | Dose (μg/body) | Principal findings | NOAEL (μg/body) | Attached document CTD |
|---|---|---|---|---|---|---|
| Male and female rats (SD) | Intramuscular | 3 weeks (2 doses[a)]) | Vehicle[b)] or mRESVIA : 98 | mRESVIA group[c)] (male and female): Inflammatory reaction at the injection site[d)] (swelling and erythema; inflammatory cell infiltration in the subcutaneous, myofiber, and sciatic perineural tissues; myofiber degeneration and necrosis, etc.); changes in leukocyte parameters (high neutrophil and eosinophil counts; low lymphocyte and monocyte counts); high red cell distribution width; low reticulocyte and platelet counts; high fibrinogen value; prolonged aPTT; high serum creatinine, globulin, and triglyceride values; low serum albumin value and albumin/globulin ratio; effects on the iliac, inguinal, and popliteal lymph nodes (swelling, induration, inflammatory cell infiltration in the surrounding tissue, increased sinus macrophages); increased spleen weight, decreased cellularity, and lymphocytic cell apoptosis/necrosis[e)]<br><br>mRESVIA group (male only): Low body weight, body weight gain, and food consumption; low serum glucose value; high serum calcium value<br><br>mRESVIA group (female only): Prolonged prothrombin time; high serum urea value<br><br>* No recovery group included. | 98 | 4.2.3.2.7 |

a) On Days 1 and 22, the dosing fluid was injected into the left and right thighs at 200 μL/site.
b) An aqueous solution containing 20 mM Tris, 87 mg/mL sucrose, and [redacted] mM sodium acetate ([redacted]).
c) In the mRESVIA group, antibodies against RSV F protein were detected on Day 23.
d) Accompanied by transient hindlimb disorder
e) The applicant explained that the finding is of little toxicological significance because it is slight in severity, and no similar findings were obtained in the other lymphoid tissues.

## 5.3 Genotoxicity

No genotoxicity studies of mRESVIA have been conducted. The applicant explained that mRESVIA vaccination is considered to have a low genotoxicity risk, in view of results from *in vivo* genotoxicity studies of the other mRNA-LNP vaccine products (CTD 4.2.3.3.2.1 and 4.2.3.3.2.2) and *in vitro* studies of excipients (SM-102 and PEG2000-DGM) that constitute LNPs of mRESVIA (CTD 4.2.3.3.1.1 to 4.2.3.3.1.4).

## 5.4 Carcinogenicity

No carcinogenicity studies of mRESVIA have been conducted.

## 5.5 Reproductive and developmental toxicity

A reproductive and developmental toxicity study of mRESVIA[2)] in rats was conducted. No effects on the dams, embryo-fetuses, or offspring were observed.

**Table 5. Reproductive and developmental toxicity**

| Type of study | Test system | Route of administration | Duration of dosing | Dose (μg/body) | Principal findings | NOAEL (μg/body) | Attached document CTD |
|---|---|---|---|---|---|---|---|
| Fertility and early embryonic development to implantation, embryo-fetal development, prenatal and postnatal development, including maternal function | Female rats (SD) | Intramuscular | From 28 days prior to mating through Gestation Day 13 (4 doses[a]) | Vehicle[b] or mRESVIA: 96 | Dams[c]<br>mRESVIA group: Swelling at the injection site and hindlimb disorder[d]; low body weight gain and food consumption[e]<br><br>Embryos/fetuses[f]<br>None<br><br>F1 offspring[g]<br>None | Dams (general toxicity, reproductive performance): 96<br><br>Embryos/fetuses: 96<br><br>F1 offspring: 96 | 4.2.3.5.3-1 |

a) The dosing fluid was injected into the left or right thigh alternately at 200 μL/site at 28 and 14 days prior to mating and on Gestation Days 1 and 13.
b) An aqueous solution containing 20 mM Tris, 87 mg/mL sucrose, [redacted] mM sodium acetate ([redacted]).
c) Anti-RSV antibodies were detected in serum samples collected on Day 15, on Gestation Days 1, 13, and 21 (cesarean section) as well as on 13 and 21 days post-partum. Anti-RSV antibodies were detected in milk samples collected on 13 and 21 days post-partum.
d) The finding was continued for approximately 2 days post-vaccination and generally resolved within 1 week.
e) The applicant explained that the finding was transient and a change related to the injection site reaction.
f) Anti-RSV antibodies were detected in serum samples collected on Gestation Day 21 (cesarean section).
g) Anti-RSV antibodies were detected in serum samples collected on 13 and 21 days post-partum.

### 5.6 Local tolerance

Local tolerance of mRESVIA intramuscularly vaccinated was evaluated based on the results from the repeated-dose toxicity study of mRESVIA[2)] [Section 5.2]. The vaccine product used in the concerned study and mRESVIA share the quality attributes related to local irritation potential (pH, osmolality, etc.), and mRESVIA was expected to be well tolerated when intramuscularly vaccinated.

### 5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the toxicity of mRESVIA was acceptable.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

For humoral immunity evaluation, anti-RSV preF and postF IgG antibody titers in serum samples were determined by a fluorescent antibody method (assay ranges, 35-580,553 and 57-847,551 AU/mL), and RSV-A and RSV-B neutralizing antibody titers in serum samples were determined by virus neutralization assay (assay ranges of RSV-A and RSV-B neutralizing antibodies, 13-259,061 IU/mL and 10-112,476 IU/mL). RSV and the other respiratory infectious agents were detected by nucleic acid test.

### 6.2 Clinical pharmacology

In the present application, no clinical pharmacology data are included.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results from clinical studies listed in Table 6.

**Table 6. Summary of clinical studies**

| Region | Study ID | Phase | Study population | No. of participants enrolled | Dosage regimen | Main endpoints |
|---|---|---|---|---|---|---|
| Foreign | mRNA-1345-P101 | I | Non-Japanese young adults (18-49 years) | 100 (4 cohorts)<br>25 per cohort | Single intramuscular administration of placebo or mRESVIA 50, 100, or 200 µg or 3 intramuscular administrations of placebo or mRESVIA 100 µg, 56 days apart | Safety<br>Immunogenicity |
| | | | Non-Japanese elderly (65-79 years) | 300 (5 cohorts)<br>60 per cohort | The first intramuscular administration of placebo or mRESVIA 12.5, 25, 50, 100, or 200 µg, and 12 months later the second intramuscular administration of mRESVIA at the same dose level or placebo. For the second dose, participants were randomized in a 1:2:2 ratio to receive the 2 doses in the combination of placebo/placebo, mRESVIA/placebo, or mRESVIA/mRESVIA. | |
| | | | Japanese elderly (≥60 years) | 25 (5 in the placebo group, 20 in the mRESVIA group) | Single intramuscular administration of placebo or mRESVIA 100 µg | |
| Global | mRNA-1345-P301 | II/III | Elderly (≥60 years) | 36,557<br>Placebo group: 18,253<br>RESVIA group: 18,304 | Single intramuscular administration of placebo or mRESVIA 50 µg | Safety<br>Efficacy<br>Immunogenicity |

## 7.1 Phase I study

### 7.1.1 Foreign phase I study (CTD 5.3.5.1.2; Study mRNA-1345-P101; study period, ongoing since September 2020; data cut-off on September 27, 2021 for non-Japanese healthy young adults, on October 3, 2022 for non-Japanese healthy elderly, on September 13, 2022 for Japanese healthy elderly)

A randomized, observer-blind, parallel-group study[3)] was conducted at 21 study sites in the US to evaluate safety and immunogenicity of mRESVIA in non-Japanese healthy young adults (18-49 years), non-Japanese healthy elderly (65-79 years), and Japanese healthy elderly (≥60 years)[4)] (target sample size, 100 participants in the non-Japanese young adult part, 300 participants in the non-Japanese elderly part, 25 participants in the Japanese elderly part; in each part, participants were randomized to receive placebo or mRESVIA in a 1:4 ratio in each dose cohort).

In the non-Japanese young adult part, a single dose of placebo or mRESVIA (50, 100, or 200 µg) was intramuscularly administered at 0.5 mL/dose or placebo or mRESVIA 100 µg was intramuscularly administered at 0.5 mL/dose 3 times, 56 days apart; in the non-Japanese healthy elderly part, placebo or mRESVIA (12.5, 25, 50, 100, or 200 µg) was intramuscularly administered, and 12 months later, placebo or mRESVIA at the same dose level[5)] as that for the first dose was intramuscularly administered; and in the Japanese healthy elderly part, a single dose of placebo or mRESVIA 100 µg was intramuscularly administered.

In the single dose cohort in the non-Japanese young adult part, of 75 randomized participants (25 in each dose cohort, consisting of 5 in the placebo group and 20 in the mRESVIA group), 74 participants

3) Investigators, participants or participants' parents/legal guardians, site monitors, and sponsor were blinded, while only the designated study personnel in charge of preparation, administration, or control of the study vaccine were unblinded.
4) Data from cohorts of RSV-seropositive non-Japanese child (aged 12-59 months) and non-Japanese women of child-bearing potential (18-40 years) were not submitted in the present application.
5) For the second dose, participants were randomized in a 1:2:2 ratio to receive the 2 doses in the combination of placebo/placebo, mRESVIA/placebo, or mRESVIA/mRESVIA.

received at least 1 dose of the study vaccine and were included in the safety analysis population, and the remaining 1 participant in the mRESVIA 50 µg group who did not receive the study vaccine was excluded. Of 74 participants, 71 participants (15 in the placebo group, 18 in the mRESVIA 50 µg group, 19 in the mRESVIA 100 µg group, 19 in the mRESVIA 200 µg group) were included in the per-protocol (PP) population at Day 30 of the first dose and in the immunogenicity analysis population, and the remaining 3 participants[6)] were excluded. In the 3-dose cohort, all of 25 randomized participants (5 in the placebo group and 20 in the mRESVIA group) received at least 1 dose of the study vaccine and were included in the safety analysis population. Of 25 participants, 23 participants (4 in the placebo group and 19 in the mRESVIA group) were included in the PP population and in the immunogenicity analysis population, and the remaining 2 participants[7)] were excluded.

In the non-Japanese elderly part, of 300 randomized participants for the first dose (60 in each dose cohort, consisting of 12 in the placebo group and 48 in the mRESVIA group), 298 participants (59 in the placebo group, 48 in the mRESVIA 12.5 µg group, 48 in the mRESVIA 25 µg group, 47 in the mRESVIA 50 µg group, 48 in the mRESVIA 100 µg group, 48 in the mRESVIA 200 µg group) received at least 1 dose of the study vaccine and were included in the safety analysis population for the first dose, and the remaining 2 participants[8)] were excluded. Of 298 participants, 290 participants (58 in the placebo group, 46 in the mRESVIA 12.5 µg group, 46 in the mRESVIA 25 µg group, 47 in the mRESVIA 50 µg group, 46 in the mRESVIA 100 µg group, 47 in the mRESVIA 200 µg group) were included in the PP population for the first dose and in the immunogenicity analysis population, and the remaining 8 participants[9)] were excluded. Of 298 participants who received the first dose, 247 participants received the second dose of the study vaccine (52 in the placebo/placebo group, 96 in the mRESVIA/placebo group, 99 in the mRESVIA/mRESVIA group) and were included in the safety analysis population for the second dose. Of 247 participants, 243 participants (51 in the placebo/placebo group, 94 in the mRESVIA/placebo group, 98 in the mRESVIA/mRESVIA group) were included in the PP population for the second dose and in the immunogenicity analysis population, and the remaining 4 participants[10)] were excluded.

In the Japanese elderly part, all of 25 randomized participants (5 in the placebo group and 20 in the mRESVIA 100 µg group) received the study vaccine, but 1 participant randomized to the placebo group actually received mRESVIA 100 µg. The concerned participant was counted as a participant in the mRESVIA group in the safety analysis population (4 in the placebo group and 21 in the mRESVIA 100 µg group), and other 24 participants (4 in the placebo group and 20 in the mRESVIA 100 µg group) were included in the PP population and in the immunogenicity analysis population.

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6) Reason for the exclusion: Missing data on immunogenicity in 3 participants (1 each in the mRESVIA 50 µg group, 100 µg group, and 200 µg group)

7) Reason for the exclusion: Missing data on immunogenicity in 2 participants (1 each in the placebo group and mRESVIA group)

8) Reason for the exclusion: Consent withdrawal in 1 participant in the placebo group and discontinuation of vaccination in 1 participant in the mRESVIA 50 µg group

9) Reason for the exclusion: Missing data on immunogenicity in 4 participants (1 each in the mRESVIA 12.5, 25, 100, and 200 µg groups) and other protocol deviations in 4 participants (1 each in the placebo group and mRESVIA 12.5, 25, and 100 µg groups)

10) Reason for the exclusion: Missing data on immunogenicity in 2 participants (1 each in the mRESVIA 25 µg/placebo group and mRESVIA 100 µg/placebo group) and other protocol deviations in 2 participants (1 each in the placebo/placebo group and mRESVIA 100 µg/mRESVIA 100 µg group)

The main safety endpoints and follow-up period are as follows:

- Solicited adverse reactions through 7 days after each dose of the study vaccine[11]: Local (injection site pain, injection site erythema and injection site swelling) and systemic (pyrexia [≥38°C[12]], headache, fatigue, myalgia, arthralgia, nausea/vomiting, axillary swelling/tenderness[13] and chills)
- Unsolicited adverse events through 28 days after each dose of the study vaccine
- Serious adverse events, adverse events leading to discontinuation of vaccination, adverse events leading to study discontinuation throughout the study period

Non-Japanese young adult part:

(a) Single dose group

Table 7 shows incidences of solicited adverse reactions through 7 days after the study vaccination.

**Table 7. Solicited adverse reactions through 7 days after the study vaccination (Study mRNA-1345-P101 [Study P101], single dose group in the non-Japanese young adult part, safety analysis population)**

| | Placebo (n = 15) | | mRESVIA 50 µg (n = 19) | | mRESVIA 100 µg (n = 20) | | mRESVIA 200 µg (n = 20) | |
|---|---|---|---|---|---|---|---|---|
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Local (overall) | 0 | 0 | 73.7 (14) | 5.3 (1) | 90.0 (18) | 0 | 100.0 (20) | 10.0 (2) |
| Injection site pain | 0 | 0 | 73.7 (14) | 5.3 (1) | 90.0 (18) | 0 | 100.0 (20) | 10.0 (2) |
| Injection site swelling | 0 | 0 | 10.5 (2) | 0 | 15.0 (3) | 0 | 5.0 (1) | 0 |
| Injection site erythema | 0 | 0 | 5.3 (1) | 0 | 15.0 (3) | 0 | 15.0 (3) | 0 |
| Systemic (overall) | 40.0 (6) | 0 | 57.9 (11) | 5.3 (1) | 70.0 (14) | 5.0 (1) | 100.0 (20) | 30.0 (6) |
| Headache | 26.7 (4) | 0 | 36.8 (7) | 5.3 (1) | 30.0 (6) | 0 | 95.0 (19) | 10.0 (2) |
| Fatigue | 20.0 (3) | 0 | 31.6 (6) | 0 | 50.0 (10) | 5.0 (1) | 90.0 (18) | 25.0 (5) |
| Myalgia | 13.3 (2) | 0 | 31.6 (6) | 0 | 35.0 (7) | 5.0 (1) | 90.0 (18) | 20.0 (4) |
| Nausea/vomiting | 13.3 (2) | 0 | 15.8 (3) | 0 | 25.0 (5) | 0 | 55.0 (11) | 0 |
| Chills | 0 | 0 | 26.3 (5) | 0 | 25.0 (5) | 0 | 95.0 (19) | 0 |
| Arthralgia | 0 | 0 | 10.5 (2) | 0 | 30.0 (6) | 0 | 75.0 (15) | 10.0 (2) |
| Axillary swelling/tenderness | 0 | 0 | 10.5 (2) | 0 | 20.0 (4) | 0 | 30.0 (6) | 5.0 (1) |
| Pyrexia | 0 | 0 | 10.5 (2) | 0 | 0 | 0 | 30.0 (6) | 0 |

Incidence % (number of participants with event)

Unsolicited adverse events occurred in 33.3% (5 of 15) of participants in the placebo group, 10.5% (2 of 19) of participants in the mRESVIA 50 µg group, 10.0% (2 of 20) of participants in the mRESVIA 100 µg group, and 75.0% (15 of 20) of participants in the mRESVIA 200 µg group. Adverse events reported by ≥2 participants in any group were headache (4 participants in the placebo group, 2 participants in the mRESVIA 200 µg group), injection site pain (2 participants in the mRESVIA 50 µg group, 1 participant in the mRESVIA 200 µg group), aphthous ulcer (2 participants in the mRESVIA 200 µg group), nasopharyngitis (2 participants in the mRESVIA 200 µg group), and dyspnoea (2 participants in the mRESVIA 200 µg group). Adverse reactions occurred in 2 participants in the mRESVIA 50 µg group (injection site pain in 2 participants), 1 participant in the mRESVIA 100 µg group (injection site induration), and 3 participants in the mRESVIA 200 µg group (injection site pruritus, arthralgia, and musculoskeletal stiffness in 1participant each).

None of the Grade ≥3 unsolicited adverse events, deaths, serious adverse events, and adverse events leading to study discontinuation occurred.

11) Severity grading of adverse events was specified with reference to the FDA guidance “Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (September 2007) and applied to assessment.
12) Oral thermometry recommended
13) Axillary swelling/tenderness was tabulated as a solicited local reaction.

(b) 3-dose group

Table 8 shows incidences of solicited adverse reactions through 7 days after each dose of the study vaccine.

Grade ≥3 solicited adverse reactions did not occur in the placebo group after any dose, but in the mRESVIA 100 µg group, Grade ≥3 solicited local adverse reactions occurred in 1 participant each after the first and third doses (injection site pain), and Grade ≥3 solicited systemic adverse reactions occurred in 1 participant after the first dose (myalgia), in 3 participants after the second dose (headache in 2 participants, myalgia and arthralgia in 1 participant each [some participants had multiple events]), and in 1 participant after the third dose (fatigue, myalgia, and arthralgia).

**Table 8. Solicited adverse reactions through 7 days after each dose (Study P101, 3-dose group in the non-Japanese young adult part, safety analysis population)**

| | First dose | | Second dose | | Third dose | |
|---|---|---|---|---|---|---|
| | Placebo (n = 5[a)]) | mRESVIA 100 µg (n = 20[a)]) | Placebo (n = 4[a)]) | mRESVIA 100 µg (n = 16[a)]) | Placebo (n = 3[a)]) | mRESVIA 100 µg (n = 14[a)]) |
| Local (overall) | 0 | 95.0 (19) | 0 | 87.5 (14) | 0 | 85.7 (12) |
| Injection site pain | 0 | 95.0 (19) | 0 | 87.5 (14) | 0 | 85.7 (12) |
| Injection site swelling | 0 | 20.0 (4) | 0 | 6.3 (1) | 0 | 7.1 (1) |
| Injection site erythema | 0 | 15.0 (3) | 0 | 12.5 (2) | 0 | 0 |
| Systemic (overall) | 40.0 (2) | 90.0 (18) | 0 | 81.3 (13) | 33.3 (1) | 64.3 (9) |
| Fatigue | 20.0 (1) | 60.0 (12) | 0 | 62.5 (10) | 0 | 35.7 (5) |
| Headache | 20.0 (1) | 55.0 (11) | 0 | 68.8 (11) | 33.3 (1) | 50.0 (7) |
| Myalgia | 20.0 (1) | 55.0 (11) | 0 | 68.8 (11) | 0 | 42.9 (6) |
| Arthralgia | 20.0 (1) | 35.0 (7) | 0 | 56.3 (9) | 0 | 35.7 (5) |
| Chills | 0 | 50.0 (10) | 0 | 43.8 (7) | 0 | 42.9 (6) |
| Pyrexia | 0 | 35.0 (7) | 0 | 6.3 (1) | 0 | 0 |
| Nausea/vomiting | 0 | 30.0 (6) | 0 | 43.8 (7) | 33.3 (1) | 28.6 (4) |
| Axillary swelling/tenderness | 0 | 30.0 (6) | 0 | 31.3 (5) | 0 | 0 |

Incidence % (number of participants with event)

a) Number of participants who provided data on solicited adverse reactions via electronic diary

No unsolicited adverse events occurred in the placebo group after any dose but in the mRESVIA 100 µg group, such events occurred in 30.0% (6 of 20) of participants after the first dose, 6.3% (1 of 16) of participants after the second dose, and 20.0% (3 of 15) of participants after the third dose. The events reported by ≥2 participants after any dose were headache in 2 participants (after the first dose) and nausea in 2 participants (after the third dose). Unsolicited adverse reactions occurred in 10.0% (2 of 20) of participants after the first dose and 6.3% (1 of 16) of participants after the second dose in the mRESVIA 100 µg group, and no such reactions reported by ≥2 participants occurred.

None of the Grade ≥3 unsolicited adverse events, deaths, serious adverse events, and adverse events leading to study discontinuation occurred.

Non-Japanese healthy elderly part:

(a) First dose

Table 9 shows incidences of solicited adverse reactions through 7 days after the first dose of the study vaccine.

**Table 9. Solicited adverse reactions through 7 days after the first dose (Study P101, non-Japanese elderly part, safety analysis population)**

| | Placebo (n = 58[a]) | mRESVIA 12.5 μg (n = 46[a]) | mRESVIA 25 μg (n = 44[a]) | mRESVIA 50 μg (n = 47[a]) | mRESVIA 100 μg (n = 47[a]) | mRESVIA 200 μg (n = 47[a]) |
|---|---|---|---|---|---|---|
| Local (overall) | 12.7 (7) | 50.0 (23) | 65.9 (29) | 61.7 (29) | 74.5 (35) | 78.7 (37) |
| Grade ≥3 | 5.5 (3) | 0 | 6.8 (3) | 0 | 0 | 2.1 (1) |
| Injection site pain | 12.7 (7) | 50.0 (23) | 29 (65.9) | 61.7 (29) | 74.5 (35) | 78.7 (37) |
| Grade ≥3 | 5.5 (3) | 0 | 6.8 (3) | 0 | 0 | 2.1 (1) |
| Injection site erythema | 0 | 4.3 (2) | 2.3 (1) | 0 | 4.3 (2) | 2.1 (1) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Injection site swelling | 0 | 0 | 0 | 2.1 (1) | 4.3 (2) | 4.3 (2) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Systemic (overall) | 45.5 (25) | 50.0 (23) | 52.3 (23) | 53.2 (25) | 78.7 (37) | 60.0 (31) |
| Grade ≥3 | 1.8 (1) | 4.3 (2) | 2.3 (1) | 10.6 (5) | 8.5 (4) | 14.9 (7) |
| Fatigue | 36.4 (20) | 23.9 (11) | 34.1 (15) | 29.8 (14) | 59.6 (28) | 57.4 (27) |
| Grade ≥3 | 0 | 0 | 0 | 6.4 (3) | 4.3 (2) | 12.8 (6) |
| Arthralgia | 23.6 (13) | 13.0 (6) | 13.6 (6) | 27.7 (13) | 34.0 (16) | 34.0 (16) |
| Grade ≥3 | 0 | 0 | 0 | 4.3 (2) | 0 | 6.4 (3) |
| Myalgia | 18.2 (10) | 19.6 (9) | 25.0 (11) | 27.7 (13) | 36.2 (17) | 48.9 (23) |
| Grade ≥3 | 0 | 0 | 0 | 4.3 (2) | 0 | 8.5 (4) |
| Headache | 14.5 (8) | 28.3 (13) | 36.4 (16) | 31.9 (15) | 44.7 (21) | 40.4 (19) |
| Grade ≥3 | 1.8 (1) | 4.3 (2) | 2.3 (1) | 6.4 (3) | 6.4 (3) | 2.1 (1) |
| Nausea/vomiting | 9.1 (5) | 4.3 (2) | 6.8 (3) | 6.4 (3) | 14.9 (7) | 10.6 (5) |
| Grade ≥3 | 0 | 0 | 0 | 2.1 (1) | 0 | 0 |
| Axillary swelling/tenderness | 5.5 (3) | 6.5 (3) | 11.4 (5) | 6.4 (3) | 14.9 (7) | 8.5 (4) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chills | 5.5 (3) | 6.5 (3) | 4.5 (2) | 8.5 (4) | 19.1 (9) | 36.2 (17) |
| Grade ≥3 | 0 | 0 | 0 | 2.1 (1) | 0 | 0 |
| Pyrexia | 1.9 (1)[b] | 2.2 (1) | 4.5 (2) | 2.1 (1) | 12.8 (6) | 4.3 (2) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |

Incidence % (number of participants with event)

a) Number of participants who provided data on solicited adverse reactions via electronic diary

b) The denominator is 54 (participants).

Table 10 shows unsolicited adverse events reported by ≥2 participants in any group after the first dose of the study vaccine. Unsolicited adverse reactions occurred in 10.2% (6 of 59) of participants in the placebo group, 10.4% (5 of 48) of participants in the mRESVIA 12.5 μg group, 4.2% (2 of 48) of participants in the mRESVIA 25 μg group, 4.3% (2 of 47) of participants in the mRESVIA 50 μg group, 10.4% (5 of 48) of participants in the mRESVIA 100 μg group, and 10.4% (5 of 48) of participants in the mRESVIA 200 μg group. Unsolicited adverse reactions reported by ≥2 participants in any group were arthralgia (2 participants in the placebo group, 3 participants in the mRESVIA 12.5 μg group, 1 participant in the mRESVIA 100 μg group, 2 participants in the mRESVIA 200 μg group), fatigue (2 participants in the placebo group, 2 participants in the mRESVIA 12.5 μg group, 2 participants in the mRESVIA 100 μg group, 1 participant in the mRESVIA 200 μg group), myalgia (1 participant in the placebo group, 1 participant in the mRESVIA 12.5 μg group, 1 participant in the mRESVIA 100 μg group, 2 participants in the mRESVIA 200 μg group), and headache (2 participants in the mRESVIA 100 μg group).

Grade ≥3 unsolicited adverse events occurred in 0% (0 of 59) of participants in the placebo group, 12.5% (6 of 48) of participants in the mRESVIA 12.5 μg group, 6.3% (3 of 48) of participants in the mRESVIA 25 μg group, 10.6% (5 of 47) of participants in the mRESVIA 50 μg group, 8.3% (4 of 48) of participants in the mRESVIA 100 μg group, and 6.3% (3 of 48) of participants in the mRESVIA 200 μg group, and there were no such events reported by ≥2 participants in any group. Grade ≥3 unsolicited adverse reactions occurred in 4.3% (2 of 47) of participants in the mRESVIA 50 μg group (prothrombin time prolonged and hypertension in 1 participant each).

Serious unsolicited adverse events occurred in 1.7% (1 of 59) of participants in the placebo group, 12.5% (6 of 48) of participants in the mRESVIA 12.5 μg group, 6.3% (3 of 48) of participants in the mRESVIA 25 μg group, 8.5% (4 of 47) of participants in the mRESVIA 50 μg group, and 2.1% (1 of 48) of participants in the mRESVIA 200 μg group. The event reported by ≥2 participants in any group was only pneumonia in 2 participants in the mRESVIA 12.5 μg group. A causal relationship to the study vaccine was ruled out for all the events.

Neither deaths nor adverse events leading to study discontinuation occurred.

**Table 10. Unsolicited adverse events reported by ≥2 participants in any group (Study P101, non-Japanese elderly part, safety analysis population)**

| | Placebo (n = 59) | mRESVIA 12.5 μg (n = 48) | mRESVIA 25 μg (n = 48) | mRESVIA 50 μg (n = 47) | mRESVIA 100 μg (n = 48) | mRESVIA 200 μg (n = 48) |
|---|---|---|---|---|---|---|
| Overall | 35.6 (21) | 66.7 (32) | 50.0 (24) | 63.8 (30) | 41.7 (20) | 60.4 (29) |
| Arthralgia | 5.1 (3) | 6.3 (3) | 4.2 (2) | 4.3 (2) | 2.1 (1) | 6.3 (3) |
| Hypertension | 3.4 (2) | 4.2 (2) | 6.3 (3) | 2.1 (1) | 0 | 4.2 (2) |
| Fatigue | 3.4 (2) | 4.2 (2) | 0 | 0 | 8.3 (4) | 4.2 (2) |
| Tooth infection | 3.4 (2) | 0 | 2.1 (1) | 0 | 0 | 0 |
| Hordeolum | 3.4 (2) | 0 | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 1.7 (1) | 4.2 (2) | 0 | 0 | 2.1 (1) | 2.1 (1) |
| Upper respiratory tract infection | 1.7 (1) | 4.2 (2) | 0 | 0 | 0 | 0 |
| Dermatitis contact | 1.7 (1) | 4.2 (2) | 0 | 0 | 0 | 0 |
| Osteoarthritis | 1.7 (1) | 2.1 (1) | 2.1 (1) | 2.1 (1) | 2.1 (1) | 4.2 (2) |
| Myalgia | 1.7 (1) | 2.1 (1) | 0 | 0 | 2.1 (1) | 4.2 (2) |
| Bronchitis | 1.7 (1) | 2.1 (1) | 0 | 0 | 0 | 6.3 (3) |
| Back pain | 1.7 (1) | 0 | 2.1 (1) | 2.1 (1) | 6.3 (3) | 2.1 (1) |
| Urinary tract infection | 1.7 (1) | 0 | 2.1 (1) | 2.1 (1) | 2.1 (1) | 4.2 (2) |
| Actinic keratosis | 1.7 (1) | 0 | 0 | 2.1 (1) | 4.2 (2) | 0 |
| Dizziness | 1.7 (1) | 0 | 0 | 0 | 2.1 (1) | 4.2 (2) |
| Headache | 0 | 4.2 (2) | 2.1 (1) | 0 | 6.3 (3) | 0 |
| Pneumonia | 0 | 4.2 (2) | 0 | 0 | 2.1 (1) | 0 |
| Type 2 diabetes mellitus | 0 | 4.2 (2) | 0 | 0 | 0 | 0 |
| Tendonitis | 0 | 4.2 (2) | 0 | 0 | 0 | 0 |
| Basal cell carcinoma | 0 | 4.2 (2) | 0 | 0 | 0 | 0 |
| COVID-19 | 0 | 0 | 6.3 (3) | 2.1 (1) | 2.1 (1) | 8.3 (4) |
| Ventricular extrasystoles | 0 | 0 | 4.2 (2) | 0 | 0 | 0 |
| Anxiety | 0 | 0 | 2.1 (1) | 0 | 0 | 4.2 (2) |
| Skin laceration | 0 | 0 | 0 | 4.3 (2) | 2.1 (1) | 0 |
| Neck pain | 0 | 0 | 0 | 4.3 (2) | 0 | 0 |
| Arthritis | 0 | 0 | 0 | 2.1 (1) | 0 | 4.2 (2) |
| Trigger finger | 0 | 0 | 0 | 2.1 (1) | 0 | 4.2 (2) |
| Hypothyroidism | 0 | 0 | 0 | 0 | 0 | 4.2 (2) |
| Atrophic vulvovaginitis | 0 | 0 | 0 | 0 | 0 | 4.2 (2) |

Incidence % (number of participants with event)
Medical dictionary for regulatory activities (MedDRA) version 25.0

(b) Second dose

As the second dose of the study vaccine, placebo or mRESVIA at the same dose level as that for the first dose was administered 12 months after the first dose (participants who had received placebo as the first dose also received placebo as the second dose). A group of participants who received placebo as the second dose was referred to as the second-dose placebo group, while a group of participants who received mRESVIA as the second dose was referred to as the second-dose mRESVIA group.

Table 11 shows incidences of solicited adverse reactions through 7 days after the second dose in the second-dose placebo group.

**Table 11. Solicited adverse reactions through 7 days after the second dose (Study P101, non-Japanese elderly part, second-dose placebo group, safety analysis population)**

| | Placebo/ Placebo (n = 51[a)]) | mRESVIA 12.5 µg/ Placebo (n = 19[a)]) | mRESVIA 25 µg/ Placebo (n = 20[a)]) | mRESVIA 50 µg/ Placebo (n = 21[a)]) | mRESVIA 100 µg/ Placebo (n = 18[a)]) | mRESVIA 200 µg/ Placebo (n = 16[a)]) |
|---|---|---|---|---|---|---|
| Local (overall) | 9.8 (5) | 5.3 (1) | 5.0 (1) | 9.5 (2) | 16.7 (3) | 6.3 (1) |
| Grade ≥3 | 2.0 (1) | 0 | 0 | 0 | 5.6 (1) | 0 |
| Injection site pain | 9.8 (5) | 5.3 (1) | 5.0 (1) | 9.5 (2) | 16.7 (3) | 6.3 (1) |
| Grade ≥3 | 2.0 (1) | 0 | 0 | 0 | 5.6 (1) | 0 |
| Injection site erythema | 0 | 0 | 0 | 0 | 0 | 0 |
| Injection site swelling | 0 | 0 | 0 | 0 | 0 | 0 |
| Systemic (overall) | 23.5 (12) | 31.6 (6) | 50.0 (10) | 28.6 (6) | 44.4 (8) | 12.5 (2) |
| Grade ≥3 | 0 | 5.3 (1) | 0 | 4.8 (1) | 11.1 (2) | 0 |
| Fatigue | 19.6 (10) | 15.8 (3) | 25.0 (5) | 14.3 (3) | 27.8 (5) | 12.5 (2) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 5.6 (1) | 0 |
| Headache | 13.7 (7) | 10.5 (2) | 25.0 (5) | 23.8 (5) | 27.8 (5) | 0 |
| Grade ≥3 | 0 | 5.3 (1) | 0 | 4.8 (1) | 5.6 (1) | 0 |
| Arthralgia | 13.7 (7) | 5.3 (1) | 15.0 (3) | 19.0 (4) | 22.2 (4) | 6.3 (1) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Myalgia | 7.8 (4) | 10.5 (2) | 15.0 (3) | 19.0 (4) | 16.7 (3) | 0 |
| Grade ≥3 | 0 | 0 | 0 | 0 | 5.6 (1) | 0 |
| Chills | 5.9 (3) | 0 | 10.0 (2) | 0 | 5.6 (1) | 0 |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pyrexia | 3.9 (2) | 0 | 0 | 0 | 0 | 0 |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphadenopathy | 0 | 0 | 5.0 (1) | 4.8 (1) | 0 | 0 |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nausea/vomiting | 0 | 0 | 5.0 (1) | 0 | 16.7 (3) | 0 |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |

Incidence % (number of participants with event)

a) Number of participants who provided data on solicited adverse reactions via electronic diary

After the second dose of the study vaccine, unsolicited adverse events occurred in 19.2% (10 of 52) of participants in the placebo/placebo group, 50.0% (10 of 20) of participants in the mRESVIA 12.5 µg/placebo group, 30.0% (6 of 20) of participants in the mRESVIA 25 µg/placebo group, 19.0% (4 of 21) of participants in the mRESVIA 50 µg/placebo group, 11.1% (2 of 18) of participants in the mRESVIA 100 µg/placebo group, and 23.5% (4 of 17) of participants in the mRESVIA 200 µg/placebo group. Such events reported by ≥2 participants in any group were the coronavirus disease 2019 (COVID-19) (1 participant in the placebo/placebo group, 2 participants in the mRESVIA 12.5 µg/placebo group, and 1 participant in the mRESVIA 200 µg/placebo group) and arthralgia (1 participant in the placebo/placebo group, 1 participant in the mRESVIA 12.5 µg/placebo group, and 2 participants in the mRESVIA 25 µg/placebo group).

Unsolicited adverse reactions occurred in 3.8% (2 of 52) of participants in the placebo/placebo group, 5.0% (1 of 20) of participants in the mRESVIA 12.5 µg/placebo group, 10.0% (2 of 20) of participants in the mRESVIA 25 µg/placebo group, 0% (0 of 21) of participants in the mRESVIA 50 µg/placebo group, 0% (0 of 18) of participants in the mRESVIA 100 µg/placebo group, and 0% (0 of 17) of participants in the mRESVIA 200 µg/placebo group. Reported unsolicited adverse reactions were arthralgia (1 participant each in the placebo/placebo group, mRESVIA 12.5 µg/placebo group, and mRESVIA 25 µg/placebo group), fatigue (1 participant each in the placebo/placebo group and mRESVIA 25 µg/placebo group), myalgia (1 participant in the mRESVIA 12.5 µg/placebo group), and headache (1 participant in the mRESVIA 25 µg/placebo group).

Grade ≥3 unsolicited adverse events occurred in 1.9% (1 of 52) of participants in the placebo/placebo group, 5.0% (1 of 20) of participants in the mRESVIA 12.5 µg/placebo group, 5.0% (1 of 20) of

participants in the mRESVIA 25 μg/placebo group, 4.8% (1 of 21) of participants in the mRESVIA 50 μg/placebo group, 0% (0 of 18) of participants in the mRESVIA 100 μg/placebo group, and 5.9% (1 of 17) of participants in the mRESVIA 200 μg/placebo group. There were no events reported by ≥2 participants in any group. A causal relationship to the study vaccine was ruled out for all the events.

Deaths occurred in 1 participant each in the mRESVIA 12.5 μg/placebo group (bone sarcoma) and mRESVIA 25 μg/placebo group (road traffic accident). A causal relationship to the study vaccine was ruled out for both events.

Serious unsolicited adverse events occurred in 1.9% (1 of 52) of participants in the placebo/placebo group, 5.0% (1 of 20) of participants in the mRESVIA 12.5 μg/placebo group, 5.0% (1 of 20) of participants in the mRESVIA 25 μg/placebo group, 4.8% (1 of 21) of participants in the mRESVIA 50 μg/placebo group, and 5.9% (1 of 17) of participants in the mRESVIA 200 μg/placebo group. There were no serious events reported by ≥2 participants in any group. A causal relationship to the study vaccine was ruled out for all the events.

No adverse events leading to study discontinuation occurred.

Table 12 shows incidences of solicited adverse reactions through 7 days after the second dose in the second-dose mRESVIA group.

**Table 12. Solicited adverse reactions through 7 days after the second dose (Study P101, non-Japanese healthy elderly part, second-dose mRESVIA group, safety analysis population)**

| | mRESVIA 12.5 μg/ mRESVIA 12.5 μg (n = 21[a]) | mRESVIA 25 μg/ mRESVIA 25 μg (n = 22[a]) | mRESVIA 50 μg/ mRESVIA 50 μg (n = 18[a]) | mRESVIA 100 μg/ mRESVIA 100 μg (n = 18[a]) | mRESVIA 200 μg/ mRESVIA 200 μg (n = 18[a]) |
|---|---|---|---|---|---|
| Local (overall) | 71.4 (15) | 68.2 (15) | 77.8 (14) | 77.8 (14) | 88.9 (16) |
| Grade ≥3 | 4.8 (1) | 4.5 (1) | 5.6 (1) | 5.6 (1) | 11.1 (2) |
| Injection site pain | 71.4 (15) | 68.2 (15) | 77.8 (14) | 77.8 (14) | 88.9 (16) |
| Grade ≥3 | 4.8 (1) | 4.5 (1) | 5.6 (1) | 5.6 (1) | 11.1 (2) |
| Injection site swelling | 0 | 13.6 (3) | 0 | 11.1 (2) | 11.1 (2) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 |
| Injection site erythema | 0 | 4.5 (1) | 5.6 (1) | 11.1 (2) | 16.7 (3) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 |
| Systemic (overall) | 52.4 (11) | 50.0 (11) | 50.0 (9) | 83.3 (15) | 94.4 (17) |
| Grade ≥3 | 0 | 18.2 (4) | 5.6 (1) | 22.2 (4) | 33.3 (6) |
| Fatigue | 47.6 (10) | 40.9 (9) | 38.9 (7) | 66.7 (12) | 88.9 (16) |
| Grade ≥3 | 0 | 9.1 (2) | 0 | 5.6 (1) | 16.7 (3) |
| Headache | 33.3 (7) | 45.5 (10) | 44.4 (8) | 72.2 (13) | 77.8 (14) |
| Grade ≥3 | 0 | 4.5 (1) | 5.6 (1) | 5.6 (1) | 11.1 (2) |
| Myalgia | 28.6 (6) | 40.9 (9) | 44.4 (8) | 66.7 (12) | 77.8 (14) |
| Grade ≥3 | 0 | 9.1 (2) | 0 | 5.6 (1) | 11.1 (2) |
| Arthralgia | 28.6 (6) | 31.8 (7) | 38.9 (7) | 44.4 (8) | 61.1 (11) |
| Grade ≥3 | 0 | 4.5 (1) | 0 | 0 | 11.1 (2) |
| Chills | 14.3 (3) | 18.2 (4) | 11.1 (2) | 44.4 (8) | 66.7 (12) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 5.6 (1) |
| Nausea/vomiting | 4.8 (1) | 18.2 (4) | 11.1 (2) | 27.8 (5) | 16.7 (3) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 |
| Lymphadenopathy | 4.8 (1) | 4.5 (1) | 5.6 (1) | 5.6 (1) | 16.7 (3) |
| Grade ≥3 | 0 | 0 | 0 | 0 | 0 |
| Pyrexia | 0 | 13.6 (3) | 0 | 16.7 (3) | 11.1 (2) |
| Grade ≥3 | 0 | 0 | 0 | 11.1 (2) | 0 |

Incidence % (number of participants with event)
a) Number of participants who provided data on solicited adverse reactions via electronic diary

After the second dose of the study vaccine, unsolicited adverse events occurred in 19.0% (4 of 21) of participants in the mRESVIA 12.5 μg/mRESVIA 12.5 μg group, 40.9% (9 of 22) of participants in the mRESVIA 25 μg/mRESVIA 25 μg group, 16.7% (3 of 18) of participants in the mRESVIA 50 μg/mRESVIA 50 μg group, 16.7% (3 of 18) of participants in the mRESVIA 100 μg/mRESVIA 100 μg group, and 35.0% (7 of 20) of participants in the mRESVIA 200 μg/mRESVIA 200 μg group. Such event reported by ≥2 participants in any group was COVID-19 (2 participants in the mRESVIA 25 μg/mRESVIA 25 μg group, 1 participant in the mRESVIA 200 μg/mRESVIA 200 μg group).

Unsolicited adverse reactions occurred in 0% (0 of 21) of participants in the mRESVIA 12.5 μg/mRESVIA 12.5 μg group, 4.5% (1 of 22) of participants in the mRESVIA 25 μg/mRESVIA 25 μg group, 5.6% (1 of 18) of participants in the mRESVIA 50 μg/mRESVIA 50 μg group, 5.6% (1 of 18) of participants in the mRESVIA 100 μg/mRESVIA 100 μg group, and 10.0% (2 of 20) of participants in the mRESVIA 200 μg/mRESVIA 200 μg group. Reported unsolicited adverse reactions were injection site erythema (1 participant each in the mRESVIA 50 μg/mRESVIA 50 μg group and mRESVIA 200 μg/mRESVIA 200 μg group), nausea (1 participant in the mRESVIA 25 μg/mRESVIA 25 μg group), fatigue (1 participant in the mRESVIA 25 μg/mRESVIA 25 μg group), injection site pain (1 participant in the mRESVIA 100 μg/mRESVIA 100 μg group), dehydration (1 participant in the mRESVIA 200 μg/mRESVIA 200 μg group), myalgia (1 participant in the mRESVIA 25 μg/mRESVIA 25 μg group), and headache (1 participant in the mRESVIA 25 μg/mRESVIA 25 μg group).

Grade ≥3 unsolicited adverse events occurred in 0% (0 of 21) of participants in the mRESVIA 12.5 μg/mRESVIA 12.5 μg group, 9.1% (2 of 22) of participants in the mRESVIA 25 μg/mRESVIA 25 μg group, 0% (0 of 18) of participants in the mRESVIA 50 μg/mRESVIA 50 μg group, 5.6% (1 of 18) of participants in the mRESVIA 100 μg/mRESVIA 100 μg group, and 0% (0 of 18) of participants in the mRESVIA 200 μg/mRESVIA 200 μg group. There were no events reported by ≥2 participants in any group. A causal relationship to the study vaccine was ruled out for all the events.

Serious unsolicited adverse events occurred in 9.1% (2 of 22) of participants in the mRESVIA 25 μg/mRESVIA 25 μg group and 5.6% (1 of 18) of participants in the mRESVIA 100 μg/mRESVIA 100 μg group. There were no serious events reported by ≥2 participants in any group. A causal relationship to the study vaccine was ruled out for all the events.

Neither deaths nor adverse events leading to study discontinuation occurred.

Japanese elderly part:
Table 13 shows incidences of solicited adverse reactions through 7 days after the study vaccination. No Grade ≥3 solicited adverse reactions occurred in any group.

**Table 13. Solicited adverse reactions through 7 days after the study vaccination (Study P101, Japanese elderly part, safety analysis population)**

| | Placebo (n = 4) | mRESVIA 100 μg (n = 21) |
|---|---|---|
| Local (overall) | 0 | 85.7 (18) |
| Injection site pain | 0 | 85.7 (18) |
| Injection site erythema | 0 | 28.6 (6) |
| Injection site swelling | 0 | 19.0 (4) |
| Systemic (overall) | 75.0 (3) | 71.4 (15) |
| Fatigue | 50.0 (2) | 52.4 (11) |
| Headache | 25.0 (1) | 28.6 (6) |
| Myalgia | 0 | 38.1 (8) |
| Arthralgia | 0 | 28.6 (6) |
| Chills | 0 | 23.8 (5) |
| Axillary swelling/tenderness | 0 | 19.0 (4) |
| Pyrexia | 0 | 4.8 (1) |
| Nausea/vomiting | 0 | 4.8 (1) |

Incidence % (number of participants with event)

Unsolicited adverse events occurred in 50.0% (2 of 4) of participants in the placebo group (vertigo and headache in 1 participant each) and 4.8% (1 of 21) of participants in the mRESVIA 100 μg group (diplopia, injection site swelling, and intracranial aneurysm in 1 participant each [1 participant had multiple events]), and injection site swelling in the mRESVIA 100 μg group was assessed as an adverse reaction. A Grade ≥3 unsolicited adverse event occurred in 4.8% (1 of 21) of participants in the mRESVIA 100 μg group (diplopia), and a causal relationship to the study vaccine was ruled out for the event.

None of the deaths, serious adverse events, and adverse events leading to study discontinuation occurred.

## 7.2 Phase II/III study

### 7.2.1 Global phase II/III study (CTD 5.3.5.1.1, Study mRNA-1345-P301, study period, ongoing since November 2021; data cut-off on November 30, 2022 for primary efficacy analysis and on April 30, 2023 for additional efficacy analysis and safety analysis)

A randomized, observer-blind,[14)] placebo-controlled, parallel-group study was conducted at 55 study sites in the US (the phase II part) and at a total of 269 study sites in 22 countries including Japan[15)] (the phase III part) to evaluate efficacy, immunogenicity, and safety of mRESVIA in adults aged ≥60 years (including those with medically stable underlying diseases) (target sample size,[16)] approximately 2,000 participants for the phase II part and approximately 35,000 participants for the phase III part[17)]).

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14) Investigators, participants or participants' parents/legal guardians, site monitors, and sponsor were blinded, while previously designated pharmacists and independent team members in charge of preparation of the study vaccine, administration, and support of the analyses performed by unblinded DSMB were unblinded.

15) Argentina, Australia, Bangladesh, Belgium, Canada, Chile, Colombia, Costa Rica, Finland, Germany, Japan, Mexico, New Zealand, Panama, Poland, Singapore, South Africa, South Korea, Spain, Taiwan, UK, and the US

16) This study was conducted in a phase II/III seamless design, and data pooled from the phase II and III parts were used in the primary efficacy and safety evaluation. The phase II part (conducted only in the US) was planned as follows: The target sample size is 2,000 participants; when the first 400 participants have completed ≥28-day follow-up, the safety data will be evaluated by the Data Safety Monitoring Board (DSMB) in an open-label manner; if the DSMB finds no concerns in the data, enrollment in the phase III part may be initiated.

17) To RSV-LRTD with ≥2 signs or symptoms and RSV-LRTD with ≥3 signs or symptoms, employed in the primary endpoints, the following assumptions were applied:

- RSV-LRTD with ≥2 symptoms: Expected vaccine efficacy (VE) is 65%, and the incidence rate in the placebo group is 0.5%.
- RSV-LRTD with ≥3 symptoms: Expected VE is 80%, and the incidence rate in the placebo group is 0.2%.

The nNull hypothesis is VE ≤20%, and 10% of participants are to be unevaluable. With a significance level of 2.5% (1-sided) for the study overall, multiplicity associated with an interim analysis on efficacy was adjusted using the Lan-DeMets spending function (Pocock-type). Based on the log-rank test, 86 cases of RSV-LRTD with ≥2 symptoms would provide a power of at least 90%, and 32 cases of RSV-LRTD with ≥3 symptoms would provide a power of approximately 89%. The number of participants required for the above evaluation was specified as approximately 37,000.

In this study, a single dose of placebo or mRESVIA 50 μg (0.5 mL) was intramuscularly administered.

Of 35,541 participants randomized up to the primary efficacy analysis (data cut-off on November 30, 2022)[18] (17,748 in the placebo group, 17,793 in the mRESVIA group), 35,413 participants (17,680 in the placebo group, 17,733 in the mRESVIA group) received the study vaccine and were included in the full analysis set (FAS). Of the FAS, 35,088 participants (17,516 in the placebo group, 17,572 in the mRESVIA group) were included in the per-protocol efficacy (PPE) population and also the primary efficacy analysis population, while 325 participants (164 in the placebo group, 161 in the mRESVIA group) were excluded.[19] Of 36,557 participants randomized up to the additional analysis (data cut-off on April 30, 2023) (18,253 in the placebo group, 18,304 in the mRESVIA group), 36,429 participants (18,185 in the placebo group, 18,244 in the mRESVIA group) received the study vaccine and were included in the FAS. Because 3 participants (2 in the placebo group, 1 in the mRESVIA group) received a study vaccine different from the assigned vaccine, 36,429 participants (18,184 in the placebo group, 18,245 in the mRESVIA group) were included in the safety analysis population. Of the above population, 36,276 participants (18,102 in the placebo group, 18,174 in the mRESVIA group) were included in the solicited adverse reaction analysis population.

The primary endpoint was defined as vaccine efficacy (VE) in prevention of the first episode of lower respiratory tract disease caused by RSV infection[20] (RSV-LRTD) confirmed by reverse transcription polymerase chain reaction (RT-PCR) test during a period from 14 days to 12 months post-vaccination. The first primary endpoint was VE using “RSV-LRTD with ≥2 signs or symptoms” as an event, and the second primary endpoint was VE using “RSV-LRTD with ≥3 signs or symptoms” as an event (VE = 100 × [1 – hazard ratio (HR) of mRESVIA to placebo], %). RSV-LRTD was defined as follows:

- RSV infection is confirmed by RT-PCR test and at least 2 (or 3) of the symptoms and signs listed in (a) to (g) below newly occur or worsen and last for ≥24 hours.
  (a) Shortness of breath; (b) either or both of cough and pyrexia (≥37.8°C [100.0°F]); (c) any or combination of wheezing, rales, and rhonchi; (d) expectoration; (e) tachypnea (≥20 breaths/min or increase of ≥2 breaths/min from baseline measurement in those who have baseline tachypnea); (f) hypoxemia (oxygen saturation newly decreased to ≤93%, new or increasing use of supplemental oxygen); and (g) pleuritic chest pain.

Of the 2 primary endpoints, VE against the first episode of RSV-LRTD with ≥2 signs or symptoms was first tested followed by that of RSV-LRTD with ≥3 signs or symptoms in a hierarchical order. To demonstrate superiority of mRESVIA over placebo, the lower limit of confidence interval (CI) of VE was required to exceed 20%. This study was an event-driven study, requiring “RSV-LRTD with ≥2 signs or symptoms” and “RSV-LRTD with ≥3 signs or symptoms” to occur in 86 and 32 participants (the same order applies hereinafter), respectively, (number of participants with the event required

[18] Randomization was performed using age category (60-74 years, ≥75 years) and presence or absence of risk factors for LRTD (congestive heart failure or chronic obstructive pulmonary disease) as stratification factors. Enrollment was implemented to ensure that participants aged 70 to 79 years and those aged ≥80 years would constitute 30% and 10%, respectively, of the study population.

[19] Reasons for the exclusion: Failure to visit or be followed up at Day 14 after the study vaccination and afterward in 209 participants (108 in the placebo group, 101 in the mRESVIA group), major protocol deviation in 72 participants (30 participants, 42 participants), use of prohibited drugs in 41 participants (24 participants, 17 participants), and receipt of the study vaccine different from assigned vaccine in 3 participants (2 participants, 1 participant)

[20] According to the definitions of RSV-LRTD, target symptoms or signs were required to occur within 14 days after the day of collecting a sample for RT-PCR, which tested positive for RSV.

statistically). The statistical analysis plan was as follows: When the events employed in the 2 primary endpoints have occurred in approximately 50% (43 participants and 16 participants) and 85% (74 participants and 28 participants) of the number of participants with the event required statistically, interim efficacy analyses[21)] should be performed by independent statisticians; if an interim analysis on the 2 primary endpoints demonstrates the efficacy, the concerned interim analysis should be deemed as the primary analysis, and the subsequent analyses on the primary endpoints should be deemed as supplemental analyses.

The first interim analysis was performed when RSV-LRTD with ≥2 signs or symptoms and RSV-LRTD with ≥3 signs or symptoms were reported by 64 and 20 participants, respectively. As of the first data cut-off (November 30, 2022), the follow-up period after the study vaccination in the PPE population (35,088 participants) was ≥28 days in 35,006 participants (99.8%), ≥6 months in 7,152 participants (20.4%), and ≥12 months in 63 participants (0.2%), and the median follow-up period in this population was 112 days (range, 15-379 days).

For efficacy, Table 14 shows the number of participants with the first episode of RSV-LRTD, incidence rate, and VE as of the first interim analysis. VE [2-sided 95.88% CI] against RSV-LRTD with ≥2 signs or symptoms was 83.7% [66.0%, 92.2%], and VE [2-sided 96.36% CI] against RSV-LRTD with ≥3 signs or symptoms was 82.4% [34.8%, 95.3%]. The lower limits of the CI of VE for both events exceeded the pre-defined threshold (20%), leading to the conclusion that efficacy was demonstrated. The concerned interim analysis was thus deemed as the primary analysis.

**Table 14. VE in prevention of the first episode of RSV-LRTD with ≥2 or ≥3 signs or symptoms during a period from 14 days to 12 months after the study vaccination (Study P301, PPE population, as of the first interim analysis [primary analysis], data cut-off on November 30, 2022)**

| | Placebo (n = 17,516) | mRESVIA (n = 17,572) |
|---|---|---|
| RSV-LRTD with ≥2 signs or symptoms | | |
| Number of participants with episode of RSV-LRTD (%) | 55 (0.31) | 9 (0.05) |
| Incidence rate of RSV-LRTD/1,000 person-years [2-sided 95% CI][a)] | 8.795 [6.626, 11.448] | 1.435 [0.656, 2.724] |
| VE [2-sided 95.88% CI][b)] (%) | 83.7 [66.0, 92.2] | |
| RSV-LRTD with ≥3 signs or symptoms | | |
| Number of participants with episode of RSV-LRTD (%) | 17 (0.10) | 3 (0.02) |
| Incidence rate of RSV-LRTD/1,000 person-years [2-sided 95% CI][a)] | 2.716 [1.582, 4.348] | 0.478 [0.099, 1.398] |
| VE [2-sided 96.36% CI][b)] (%) | 82.4 [34.8, 95.3] | |

a) The 2-sided 95% CI was calculated using the exact method (Poisson distribution) with adjustment for person-years.
b) VE was calculated based on a stratified Cox proportional hazard model using the vaccination group as a fixed effect and adjusted for stratification factors at randomization (age category and presence or absence of risk factors of LRTD) (tie data were handled according to the Efron's method). The confidence coefficient was calculated by approximation according to the Lan-DeMets spending function (Pocock type) based on the total number of participants with episode of the event as of the analysis.

The main safety endpoints and follow-up period are as follows:

- Solicited adverse reactions through 7 days after the study vaccination[11)]: Local (injection site pain, injection site erythema [redness], and injection site swelling [induration], and axillary swelling/tenderness); and systemic (pyrexia [≥38°C[12)]], headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills)

[21)] Multiplicity associated with the interim analysis was adjusted using the Lan-DeMets spending function (Pocock-type), and a type-I error rate of 2.5% (1-sided) was applied to the study overall.

- Unsolicited adverse events through 28 days after the study vaccination
- Serious adverse events and adverse events leading to study discontinuation up to data cut-off (April 30, 2023)

Table 15 shows incidences of solicited adverse reactions through 7 days after the study vaccination.

**Table 15. Solicited adverse reactions through 7 days after the study vaccination (Study P301, solicited adverse reaction analysis population, data cut-off on April 30, 2023)**

| | Placebo (n = 18,102) | | mRESVIA (n = 18,174) | |
|---|---|---|---|---|
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Solicited adverse reactions overall | 38.5 (6,975/18,102) | 4.0 (723/18,102) | 68.1 (12,383/18,174) | 6.1 (1,115/18,174) |
| Local (overall) | 16.2 (2,939/18,097) | 1.7 (310/18,097) | 58.7 (10,591/18,171) | 3.1 (561/18,171) |
| Injection site pain | 13.8 (2,498/18,097) | 1.1 (194/18,097) | 55.9 (10,161/18,170) | 1.7 (308/18,170) |
| Axillary swelling/tenderness | 6.1 (1,105/18,096) | 0.6 (116/18,096) | 15.2 (2,764/18,168) | 0.8 (138/18,168) |
| Injection site erythema (redness) | 0.6 (103/18,096) | 0.3 (59/18,096) | 2.0 (364/18,168) | 0.6 (106/18,168) |
| Injection site swelling (induration) | 0.3 (61/18,096) | <0.1 (18/18,096) | 3.7 (673/18,169) | 0.9 (156/18,169) |
| Systemic (overall) | 32.9 (5,959/18,101) | 2.8 (513/18,101) | 47.4 (8,613/18,171) | 4.0 (719/18,171) |
| Fatigue | 20.0 (3,618/18,096) | 1.2 (218/18,096) | 30.8 (5,589/18,167) | 1.7 (316/18,167) |
| Headache | 18.8 (3,406/18,096) | 1.2 (209/18,096) | 26.7 (4,856/18,167) | 1.5 (277/18,167) |
| Myalgia | 14.4 (2,610/18,096) | 0.9 (154/18,096) | 25.6 (4,655/18,167) | 1.4 (260/18,167) |
| Arthralgia | 14.0 (2,541/18,095) | 0.7 (134/18,095) | 21.7 (3,948/18,167) | 1.1 (201/18,167) |
| Chills | 6.8 (1,228/18,095) | 0.4 (79/18,095) | 11.6 (2,114/18,167) | 0.6 (110/18,167) |
| Nausea/vomiting | 5.3 (950/18,095) | 0.4 (75/18,095) | 7.0 (1,274/18,167) | 0.4 (80/18,167) |
| Pyrexia | 1.3 (235/18,096) | 0.4 (69/18,096) | 2.8 (502/18,160) | 0.6 (111/18,160) |

Incidence (%) (number of participants with the event/number of participants analyzed)

Through 28 days after the study vaccination, unsolicited adverse events and adverse reactions occurred in 18.8% (3,412 of 18,184) and 4.4% (795 of 18,184) of participants, respectively, in the placebo group and 20.5% (3,749 of 18,245) and 5.7% (1,035 of 18,245) of participants, respectively, in the mRESVIA group. Table 16 shows unsolicited adverse events and adverse reactions reported by ≥1% of participants in either group.

**Table 16. Unsolicited adverse events and adverse reactions reported through 28 days after the study vaccination by ≥1% of participants in either group (Study P301, safety analysis population, data cut-off on April 30, 2023)**

| | Adverse events | | Adverse reactions | |
|---|---|---|---|---|
| | Placebo (n = 18,184) | mRESVIA (n = 18,245) | Placebo (n = 18,184) | mRESVIA (n = 18,245) |
| All events | 18.8 (3,412) | 20.5 (3,749) | 4.4 (795) | 5.7 (1,035) |
| Arthralgia | 2.2 (408) | 2.3 (424) | 1.9 (339) | 2.0 (359) |
| Fatigue | 2.2 (405) | 2.7 (492) | 2.1 (388) | 2.6 (466) |
| COVID-19 | 1.8 (321) | 2.1 (381) | 0 | <0.1 (1) |
| Myalgia | 1.6 (294) | 1.7 (307) | 1.5 (266) | 1.5 (281) |
| Headache | 1.4 (254) | 1.7 (307) | 1.1 (200) | 1.3 (235) |
| Upper respiratory tract infection | 1.1 (200) | 1.2 (210) | <0.1 (1) | <0.1 (1) |

Incidence % (number of participants with event)
MedDRA ver.25.0

Through 28 days after the study vaccination, Grade ≥3 unsolicited adverse events and adverse reactions occurred in 0.7% (135 of 18,184) and 0.3% (52 of 18,184) of participants, respectively, in the placebo group and 0.7% (129 of 18,245) and 0.3% (53 of 18,245) of participants, respectively, in the mRESVIA group. Grade ≥3 unsolicited adverse events reported by ≥5 participants in either group were fatigue (27 participants in the placebo group, 28 participants in the mRESVIA group), arthralgia (17 participants, 13 participants), headache (9 participants, 12 participants), myalgia (14 participants, 11 participants), hypertension (5 participants, 6 participants), and chronic obstructive pulmonary disease (5 participants, 4 participants). Grade ≥3 unsolicited adverse reactions were fatigue (27 participants in the placebo group,

28 participants in the mRESVIA group, the same order applies hereinafter), arthralgia (16 participants, 13 participants), myalgia (14 participants, 11 participants), headache (9 participants, 11 participants), and hypertension (0 participants, 2 participants).

Up to data cut-off, adverse events leading to death occurred in 0.5% (83 of 18,184) of participants in the placebo group (mainly including death in 10 participants; myocardial infarction in 8 participants; cardio-respiratory arrest in 6 participants; septic shock and cerebrovascular accident in 5 participants each; cardiac arrest in 4 participants; brain injury, cardiopulmonary failure, and chronic obstructive pulmonary disease in 3 participants each; acute myocardial infarction, pneumonia, haemorrhagic stroke, and road traffic accident in 2 participants each) and 0.5% (84 of 18,245) of participants in the mRESVIA group (mainly including death in 11 participants; pneumonia in 7 participants; myocardial infarction in 6 participants; acute myocardial infarction in 5 participants; cardiac arrest, chronic obstructive pulmonary disease, and respiratory failure in 3 participants each; sepsis, lung neoplasm malignant, cerebrovascular accident, ischaemic stroke, acute coronary syndrome, cardiac failure, cardio-respiratory arrest, cardiopulmonary failure, and multiple organ dysfunction syndrome in 2 participants each). A causal relationship to the study vaccine was ruled out for all the events.

Up to data cut-off, serious adverse events occurred in 6.0% (1,092 of 18,184) of participants in the placebo group and 6.1% (1,114 of 18,245) of participants in the mRESVIA group. Serious adverse events reported by >0.1% of participants in either group were pneumonia (56 participants in the placebo group [0.3%], 64 in the mRESVIA group [0.4%]), chronic obstructive pulmonary disease (41 participants [0.2%], 51 participants [0.3%]), osteoarthralgia (28 participants [0.2%], 29 participants [0.2%]), urinary tract infection (33 participants [0.2%], 29 participants [0.2%]), and atrial fibrillation (35 participants [0.2%], 23 participants [0.1%]). Serious adverse events for which a causal relationship to the study vaccine could not be ruled out occurred in 5 participants in the placebo group (pyrexia, seizure, chronic obstructive pulmonary disease, transient ischaemic attack, and myelodysplastic syndrome in 1 participant each) and 4 participants in the mRESVIA group (chills, dehydration, facial paralysis, and superficial vein thrombosis in 1 participant each). For outcome, except for the myelodysplastic syndrome, which was resolving, all the events resolved.

Up to data cut-off, adverse events leading to study discontinuation occurred in 0.6% (105 of 18,184) of participants in the placebo group and 0.5% (99 of 18,245) of participants in the mRESVIA group, and most of the events were involved in death. An adverse event leading to study discontinuation for which a causal relationship to the study vaccine could not be ruled out occurred in 1 participant in the mRESVIA group (fatigue), but the event resolved.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy

#### 7.R.1.1 Efficacy of mRESVIA

The applicant’s explanation:

(a) Efficacy

For efficacy, mRESVIA’s prevention of disease caused by RSV infection was evaluated in the global phase II/III study (Study P301) in adults aged ≥60 years (including those with medically stable

underlying diseases). Before participation of Japanese individuals in Study P301, intrinsic and extrinsic ethnic factors were investigated, and no factors potentially affecting the efficacy evaluation were identified as described below. The applicant thus considered it possible to evaluate efficacy of mRESVIA in Japanese population by enrolling them in Study P301.

- Intramuscular vaccination of mRESVIA is designed to result in intracellular delivery of mRNA, which would lead to transient expression of the protein and undergo metabolism in the body as with intrinsic mRNA. Thus the effect of food is not involved. The efficacy of mRESVIA is unlikely to be affected by race.
- Based on multiple published literature in and outside Japan, prevalence, clinical course, disease burden, and other characteristics of RSV infection in Japan are not considered to be largely different from those outside Japan (*Influenza Other Respir Viruses.* 2022;16:298-307, *N Engl J Med.* 2005;352:1749-59, etc.).
- When Study P301 was initiated, no products indicated for treatment or prevention of disease caused by RSV infection in the elderly were approved for marketing either in or outside Japan, and the medical environment surrounding disease caused by RSV infection in Japan was considered similar to that outside Japan.
- In the foreign phase I study (Study P101) [see Section 7.1.1], Japanese elderly living outside Japan (≥60 years) participated, formed a cohort, and intramuscularly received a single dose of mRESVIA 100 μg. No large differences were observed in the safety profile between this cohort and non-Japanese elderly vaccinated at the same dose level. Immunogenicity data in this cohort had a generally similar trend to those observed in non-Japanese elderly vaccinated with mRESVIA 25, 50, and 100 μg.

Primary endpoints:

The primary endpoints of Study P301 were defined as VE in prevention of the first episode of RSV-LRTD confirmed by RT-PCR test during a period from 14 days to 12 months after the study vaccination, using “RSV-LRTD with ≥2 signs or symptoms” and “RSV-LRTD with ≥3 signs or symptoms” as the events. To demonstrate the efficacy, both lower limits of CIs of VE using these events were required to exceed 20%. To perform a test for the efficacy with an adequate statistical power, “RSV-LRTD with ≥2 signs or symptoms” and “RSV-LRTD with ≥3 signs or symptoms” were required to occur in 86 and 32 participants, respectively, (number of participants with the event required statistically). To evaluate the efficacy, 2 interim analyses on the 2 primary endpoints were planned as follows: The first interim analysis should be performed after the above events have occurred in approximately 50% (43 and 16 participants) of the number of participants with the event required statistically; and the second interim analysis should be performed after they have occurred in approximately 85% (74 and 28 participants). To the study overall with the interim analyses and final analysis taken into account, a type-I error rate of 2.5% (1-sided) was applied based on the Lan-DeMets spending function (Pocock-type).

In the first interim analysis (data cut-off on November 30, 2022), the lower limits of CI of VE in prevention of the first episode of both events exceeded 20%, demonstrating efficacy of mRESVIA. The concerned interim analysis was deemed as the primary analysis [see Section 7.2.1].

Figure 1 and Figure 2 show cumulative incidence rates of RSV-LRTD with ≥2 signs or symptoms and RSV-LRTD with ≥3 signs or symptoms.

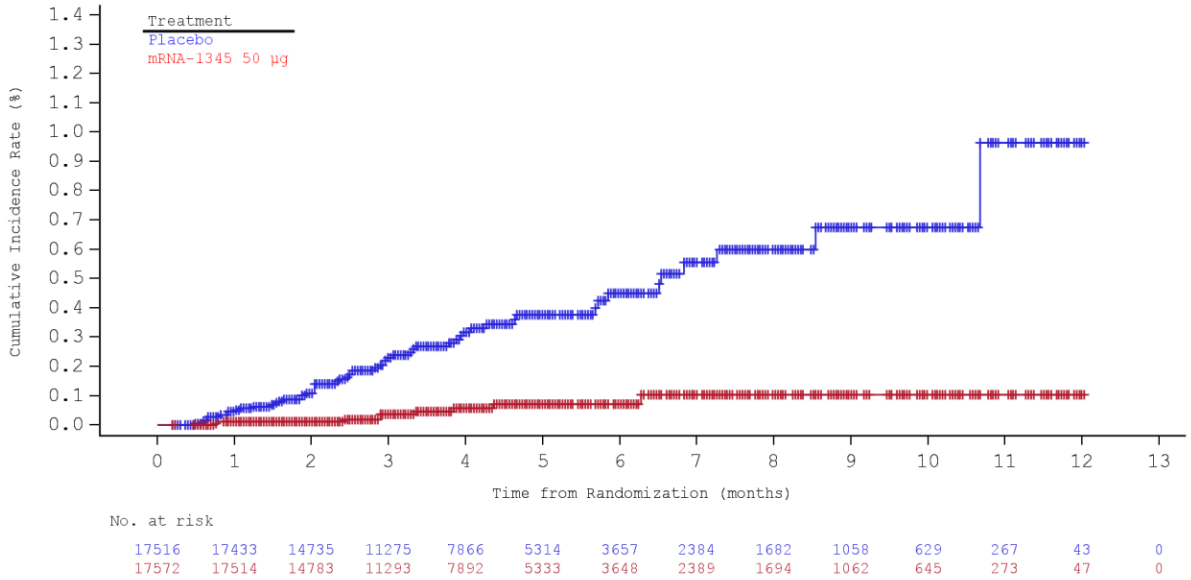


**Figure 1. Cumulative incidence rate of the first episode of RSV-LRTD with ≥2 signs or symptoms during a period from 14 days to 12 months after the study vaccination**
**(Study P301, PPE population, as of the first interim analysis [primary analysis], data cut-off on November 30, 2022)**

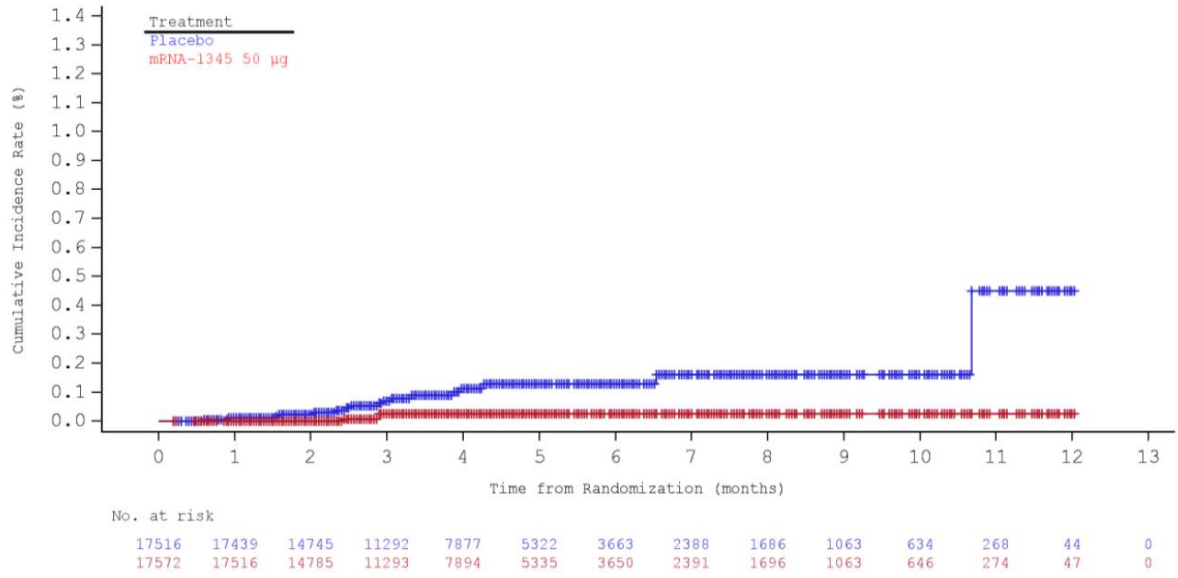


**Figure 2. Cumulative incidence rate of the first episode of RSV-LRTD with ≥3 signs or symptoms during a period from 14 days to 12 months after the study vaccination**
**(Study P301, PPE population, as of the first interim analysis [primary analysis], data cut-off on November 30, 2022)**

Secondary endpoints:

Table 17 shows VE in prevention of the first episode of RSV-ARD,[22] the secondary endpoint, and Figure 3 shows the cumulative incidence rate.

**Table 17. VE in prevention of the first episode of RSV-ARD during a period from 14 days to 12 months post-vaccination**
**(Study P301, PPE population, as of the first interim analysis [primary analysis], data cut-off on November 30, 2022)**

| | Placebo (n = 17,516) | mRESVIA (n = 17,572) |
|---|---|---|
| Number of participants with episode of RSV-ARD (%) | 82 (0.47) | 26 (0.15) |
| Incidence rate of RSV-ARD/1,000 person-years [2-sided 95% CI][a)] | 13.119 [10.434, 16.285] | 4.148 [2.710, 6.078] |
| VE [2-sided 95% CI][b)] (%) | 68.4 [50.9, 79.7] | |

a) The 2-sided 95% CI was calculated using the exact method (Poisson distribution) with adjustment for person-years.
b) VE was calculated based on a stratified Cox proportional hazard model using the vaccination group as a fixed effect and adjusted for stratification factors at randomization (age category and presence or absence of risk factors of LRTD) (tie data were handled according to the Efron's method).

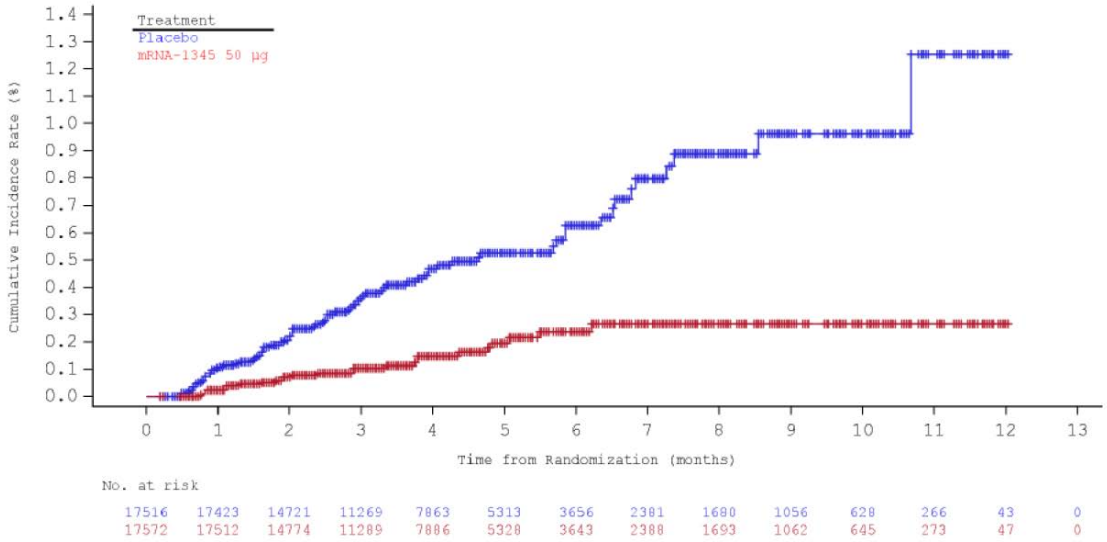


**Figure 3 Cumulative incidence rate of the first episode of RSV-ARD during a period from 14 days to 12 months after the study vaccination**
**(Study P301, PPE population, as of the first interim analysis [primary analysis], data cut-off on November 30, 2022)**

Efficacy by RSV subtype:

Table 18 shows subgroup analysis results on VE in prevention of the first episode of RSV-LRTD with ≥2 or ≥3 signs or symptoms by RSV subtype, which have similar trends to that in the overall population.

**Table 18. VE in prevention of the first episode of RSV-LRTD during a period from 14 days to 12 months after the study vaccination by RSV subtype**

[22] Definition of ARD case: RSV infection is documented by RT-PCR test (the target signs or symptoms occur within 14 days after the day of collecting a sample for RT-PCR, which tested positive for RSV) and an acute symptomatic respiratory disease develops with at least 1 of the following signs and symptoms newly occurring or being worsened and lasting for ≥24 hours: Cough, nasal congestion, nasal discharge, pharyngeal pain, pyrexia (≥37.8°C [100.0°F]), shortness of breath, tachypnea (≥20 breaths/min or if tachypnea is present at baseline, an increase from baseline by ≥2 breaths/min), hypoxemia (oxygen saturation newly decreased to ≤93%, new or increased use of supplemental oxygen), wheezing, expectoration, hoarseness, sinus pain, chills, and pleural chest pain

**(Study P301, PPE population, as of the first interim analysis [primary analysis], data cut-off on November 30, 2022)**

| | Placebo (n = 17,516) | mRESVIA (n = 17,572) | VE [2-sided 95% CI][a] (%) |
|---|---|---|---|
| | No. of participants (%) | No. of participants (%) | |
| RSV-LRTD with ≥2 signs or symptoms | | | |
| RSV-LRTD overall | 55 (0.31) | 9 (0.05) | 83.7 [66.0, 92.2] |
| RSV-A | 36 (0.21) | 3 (0.02) | 91.7 [73.0, 97.4] |
| RSV-B | 19 (0.11) | 6 (0.03) | 68.5 [21.1, 87.4] |
| RSV-LRTD with ≥3 signs or symptoms | | | |
| RSV-LRTD overall | 17 (0.10) | 3 (0.02) | 82.4 [34.8, 95.3] |
| RSV-A | 10 (0.06) | 1 (0.01) | 90.0 [22.0, 98.7] |
| RSV-B | 7 (0.04) | 2 (0.01) | 71.5 [-37.0, 94.1] |

a) VE was calculated based on a stratified Cox proportional hazard model using the vaccination group as a fixed effect and adjusted for stratification factors at randomization (age category and presence or absence of risk factors of LRTD).

Efficacy by patient characteristic:

Table 19 shows subgroup analysis results on VE in prevention of the first episode of RSV-LRTD with ≥2 signs or symptoms by patient characteristic. RSV-LRTD with ≥3 signs or symptoms occurred only in 20 participants in total. VE in prevention of the first episode of RSV-LRTD with ≥2 signs or symptoms in each subgroup mostly showed a similar trend to that in the overall population, although interpretation of the subgroup analysis results on items with the small number of events or in subgroups with small sample size has limitations.

**Table 19. VE in prevention of the first episode of RSV-LRTD with ≥2 signs or symptoms during a period from 14 days to 12 months after the study vaccination by subgroup (Study P301, PPE population, as of the first interim analysis [primary analysis], data cut-off on November 30, 2022)**

| | | Placebo | | mRESVIA | | VE [2-sided 95% CI] (%)[a] |
|---|---|---|---|---|---|---|
| | | No. of participants | No. of RSV-LRTD cases | No. of participants | No. of RSV-LRTD cases | |
| Age | 60-69 years | 11,118 | 33 | 11,168 | 8 | 76.0 [48.0, 88.9] |
| | 70-79 years | 5,416 | 22 | 5,440 | 1 | 95.4 [65.9, 99.4] |
| | ≥80 years | 982 | 0 | 964 | 0 | NE [NE, NE] |
| Sex | Male | 8,875 | 25 | 8,974 | 4 | 84.1 [54.4, 94.5] |
| | Female | 8,641 | 30 | 8,598 | 5 | 83.4 [57.3, 93.6] |
| Race | White | 11,121 | 39 | 11,144 | 8 | 79.5 [56.1, 90.4] |
| | Black | 2,111 | 2 | 2,163 | 0 | 100.0 [NE, 100.0] |
| | Asian | 1,521 | 6 | 1,533 | 1 | 83.6 [-36.0, 98.0] |
| | Other races | 2,661 | 8 | 2,665 | 0 | 100.0 [NE, 100.0] |
| Ethnicity | Hispanic or Latino | 6,105 | 15 | 6,043 | 1 | 93.3 [48.9, 99.1] |
| | Non-Hispanic or non-Latino | 11,203 | 40 | 11,347 | 6 | 85.2 [65.0, 97.3] |
| Comorbidity | None | 12,431 | 38 | 12,377 | 7 | 81.6 [58.8, 91.8] |
| | Yes | 5,085 | 17 | 5,195 | 2 | 88.4 [49.9, 97.3] |
| Frailty status | Fit (score 0-3) | 13,250 | 45 | 13,396 | 8 | 82.3 [62.5, 91.7] |
| | Vulnerable/Frailty (score ≥4) | 3,858 | 6 | 3,781 | 0 | 100.0 [NE, 100.0] |
| Region | North America/Europe | 10,896 | 34 | 10,945 | 7 | 79.5 [53.7, 90.9] |
| | Central and South America, Africa | 5,139 | 14 | 5,148 | 1 | 92.9 [45.9, 99.1] |
| | Asia | 1,481 | 7 | 1,479 | 1 | 85.7 [-16.3, 98.0] |

NE, Not evaluable

a) VE was calculated based on a stratified Cox proportional hazard model using the vaccination group as a fixed effect and adjusted for stratification factors at randomization (age category and presence or absence of risk factors of LRTD).

(b) Immunogenicity

Immunogenicity was investigated in the per-protocol immunogenicity (PPI) population of 1,848 participants (333 in the placebo group, 1,515 in the mRESVIA group) who received the study vaccine assigned according to the protocol, provided results on immunogenicity at baseline and 28 days after the study vaccination, and had no major protocol deviations in Study P301. Table 20 and Table 21 show RSV-A and RSV-B neutralizing antibody titers and RSV preF binding antibody concentrations after the

study vaccination, respectively. In the placebo group, no changes were observed in neutralizing antibody titer or RSV preF binding antibody concentration from baseline to 28 days after the study vaccination, while in the mRESVIA group, evident increases were observed in both RSV-A and RSV-B neutralizing antibody titers and RSV preF binding antibody concentration from baseline to 28 days after the study vaccination.

In the subgroup analysis, increases were observed in RSV-A and RSV-B neutralizing antibody titers and RSV preF binding antibody concentration in all subgroups by any of age, sex, race, ethnicity, underlying disease, and region, as observed in the overall population.

**Table 20. RSV-A and RSV-B neutralizing antibody titers (Study P301, PPI population)**

| | | RSV-A | | RSV-B | |
|---|---|---|---|---|---|
| | | Placebo (n = 333) | mRESVIA (n = 1,515) | Placebo (n = 333) | mRESVIA (n = 1,515) |
| Baseline | No. of participants[a)] | 333 | 1,513 | 333 | 1,512 |
| | GMT [2-sided 95% CI][b)] | 2403.72 [2136.01, 2704.98] | 2552.82 [2414.25, 2699.35] | 1350.25 [1203.25, 1515.20] | 1425.35 [1352.69, 1501.91] |
| 28 days after vaccination | No. of participants[a)] | 332 | 1,511 | 332 | 1,509 |
| | GMT [2-sided 95% CI][b)] | 2417.17 [2155.94, 2710.04] | 21475.40 [20273.94, 22748.05] | 1304.74 [1159.97, 1467.58] | 7245.98 [6864.75, 7648.38] |
| | No. of participants[c)] | 332 | 1,509 | 332 | 1,506 |
| | GMFR [2-sided 95% CI][b)] | 1.00 [0.95, 1.05] | 8.44 [7.98, 8.92] | 0.96 [0.90, 1.03] | 5.11 [4.87, 5.37] |
| | SRR [2-sided 95% CI][d)e)] | 0.6 [0.1, 2.2] | 74.2 [71.9, 76.3] | 1.5 [0.5, 3.5] | 56.5 [54.0, 59.0] |

RSV-A (lower limit of quantitation [LLOQ], 13 IU/mL; upper limit of quantitation [ULOQ], 259,061 IU/mL), RSV-B (LLOQ, 10 IU/mL; ULOQ, 112,476 IU/mL)
Seroresponse rate (SRR) was defined as a proportion of participants in whom the neutralizing antibody titer increased to ≥4 fold the LLOQ after vaccination if the baseline value was below the LLOQ, or ≥4 fold the baseline value if it was equal to or higher than the LLOQ.

a) Number of participants with a neutralizing antibody titer measured
b) The 2-sided 95% CI was calculated by assuming log-transformed values of neutralizing antibody titers or fold-rise values in antibody titer in t-distribution and back transforming the results obtained on this assumption.
c) Number of participants with a neutralizing antibody titer measured at baseline and 28 days after vaccination
d) The denominator is the number of participants with a neutralizing antibody titer measured at baseline and 28 days after vaccination.
e) The 2-sided 95% CI was calculated using the Clopper-Pearson method.

**Table 21. RSV preF binding antibody concentrations (Study P301, PPI population)**

| | | Placebo (n = 333) | mRESVIA (n = 1,515) |
|---|---|---|---|
| Baseline | No. of participants[a)] | 333 | 1,513 |
| | GMC [2-sided 95% CI][b)] | 10194.25 [9374.48, 11085.69] | 10729.51 [10310.57, 11165.47] |
| 28 days after vaccination | No. of participants[a)] | 332 | 1,511 |
| | GMC [2-sided 95% CI][b)] | 10060.15 [9258.94, 10930.70] | 81884.16 [78644.23, 85257.58] |
| | No. of participants[c)] | 332 | 1,510 |
| | GMFR [2-sided 95% CI][b)] | 0.99[0.96, 1.01] | 7.65[7.33, 7.98] |
| | SRR [2-sided 95% CI][d)e)] | 0.3[0.0, 1.7] | 79.1[77.0, 81.2] |

SRR was defined as a proportion of participants in whom RSV preF binding antibody concentration increased to ≥4 fold LLOQ after vaccination if the baseline value was below the LLOQ (35 AU/mL), or ≥4 fold the baseline value if it was equal to or higher than the LLOQ.

a) Number of participants with RSV preF binding antibody concentration measured
b) The 2-sided 95% CI was calculated by assuming log-transformed values of RSV preF binding antibody concentrations or fold-rise values in antibody concentration in t-distribution and back transforming the results obtained on this assumption.
c) Number of participants with RSV preF binding antibody concentration measured at baseline and 28 days after vaccination
d) The denominator is the number of participants with RSV preF binding antibody concentration measured at baseline and 28 days after vaccination.
e) The 2-sided 95% CI was calculated using the Clopper-Pearson method.

In a foreign phase I study in healthy adults (Study CRID-001), cellular immune response was exploratorily investigated. After vaccination of mRESVIA (50 μg), the count of RSV preF-specific CD4-positive and CD8-positive T cells increased and peaked within 2 weeks and then decreased with time but remained above the baseline value until 3 months post-vaccination.

As shown above, mRESVIA vaccination led to increases in RSV-A and RSV-B neutralizing antibody titers and RSV preF binding antibody concentrations as well as an increase in count of RSV preF-specific CD4-positive and CD8-positive T cells, which is considered to have contributed to the efficacy of mRESVIA.

PMDA's view:
Based on the results on the primary endpoints in Study P301, PMDA has confirmed that mRESVIA has efficacy in prevention of RSV-LRTD with ≥2 and ≥3 signs or symptoms in adults aged ≥60 years [see Section 7.2.1]. PMDA descriptively evaluated results on VE in the prevention of the first episode of RSV-ARD, the secondary endpoint, and results on VE in prevention of the first episode of RSV-LRTD by RSV subtype and confirmed that these results were consistent with results on the primary endpoints. The efficacy in subgroups was also confirmed to have a similar trend to that in the overall population. Based on the results on immunogenicity in Studies P301 and CRID-001, mRESVIA was confirmed to induce humoral immune response and cellular immune response, although a correlation between prevention of disease caused by RSV infection and immunogenicity has not been established at the present time, and discussion of the efficacy of mRESVIA based on the extent of immune response has difficulty.

Based on the above results, PMDA considers that the efficacy of mRESVIA can be expected in adults aged ≥60 years.

#### 7.R.1.2 Efficacy in Japanese population

The applicant's explanation:
In Study P301, enrollment in Japan with the target sample size of 700 Japanese individuals[23)] was implemented from September 1 to October 31, 2022, and 822 participants (408 in the placebo group, 414 in the mRESVIA group) were enrolled. However, no cases of RSV-LRTD with ≥2 or ≥3 signs or symptoms or RSV-ARD in Japanese individuals during a period of 14 days to 12 months after vaccination were reported as of April 30, 2023.

Although the enrollment period in Japan should have been before a usual RSV epidemic period but was actually after the RSV epidemic in 2022 in Japan where the reported number of patients with RSV infection peaked in July 2022, according to the Infectious Disease Trend Surveillance in fixed pediatrics in Japan (https://www.niid.go.jp/niid/en/10/2096-weeklygraph/1661-21rsv.html [last accessed on February 18, 2025]). The RSV seasonal epidemic pattern after COVID-19 pandemic was different from that before COVID-19 pandemic. Implementation of government-recommended strict infection control measures against COVID-19 (use of face mask, avoidance of close contact, hand hygiene) may have affected accumulation of episodes of RSV-LRTD and RSV-ARD.

Although VE in the Japanese population was not calculated due to the absence of episodes of RSV-LRTD and RSV-ARD in Study P301, the efficacy similar to that in the overall population can be expected in the Japanese population as well, because VE in the subgroup of Asia region including Japan

[23)] In view of the feasibility of the study in Japan, the target sample size of 700 Japanese individuals was specified. In 700 Japanese individuals enrolled, approximately 2 cases and 1 case of RSV-LRTD were assumed to occur in the placebo group and mRESVIA group, respectively.

and subgroups by the other characteristics (age, sex, race, ethnicity, comorbidity, frailty status, region) was similar to that in the overall population [see Section 7.R.1.1].

Table 22 shows results on immunogenicity in non-Japanese population[24)] and Japanese population[25)] in Study P301. RSV-A and RSV-B neutralizing antibody titers at baseline and 28 days after vaccination in the Japanese population were lower than those in the non-Japanese population, but the geometric mean fold rise (GMFR) was similar to that in the non-Japanese population. Seroresponse rate (SRR) 28 days after vaccination in the Japanese population was also similar to that in the non-Japanese population. Although a correlation between prevention of disease caused by RSV infection and immunogenicity has not been established, in view of the literature reports, immune response induced by mRESVIA may contribute to prevention of disease caused by RSV infection [see Section 7.R.1.1], and the results on immunogenicity after vaccination of mRESVIA can support the efficacy as well.

In view of no clear differences in intrinsic and extrinsic ethnic factors between Japanese and non-Japanese populations [see Section 7.R.1.1] in addition to discussion based on the above clinical study results, the efficacy demonstrated in the overall population in Study P301 can be similarly expected in Japanese population as well.

**Table 22. RSV-A and B neutralizing antibody titers in the non-Japanese population and Japanese population (Study P301, PPI population, PPISJ population)**

| | | RSV-A neutralizing antibody titer | | RSV-B neutralizing antibody titer | |
|---|---|---|---|---|---|
| | | Non-Japanese population (n = 1,502) | Japanese population (n = 406) | Non-Japanese population (n = 1,502) | Japanese population (n = 406) |
| **GMT** | | | | | |
| Baseline | No. of participants | 1,500 | 406 | 1,499 | 406 |
| | GMT [2-sided 95% CI][a)] | 2556.92 [2417.43, 2704.45] | 1505.62 [1354.48, 1673.63] | 1431.77 [1358.51, 1508.97] | 1080.11 [980.68, 1189.61] |
| 28 days after vaccination | No. of participants | 1,498 | 406 | 1,496 | 406 |
| | GMT [2-sided 95% CI][a)] | 21575.77 [20364.30, 22859.31] | 10833.09 [9731.90, 12058.89] | 7296.92 [6911.96, 7703.32] | 4526.18 [4110.74, 4983.62] |
| | GMFR [2-sided 95% CI][a)] | 8.47 [8.00, 8.95] | 7.20 [6.55, 7.90] | 5.12 [4.88, 5.38] | 4.19 [3.87, 4.54] |
| **SRR** | | | | | |
| SRR [2-sided 95% CI] (%)[b)] | | 74.3 [72.0, 76.5] | 71.4 [66.8, 75.8] | 56.7 [54.1,59.2] | 46.3 [41.4, 51.3] |

RSV-A (LLOQ, 13 IU/mL; ULOQ, 259,061 IU/mL), RSV-B (LLOQ, 10 IU/mL; ULOQ, 112,476 IU/mL)
SRR was defined as a proportion of participants in whom the neutralizing antibody titer increased to ≥4 fold the LLOQ after vaccination if the baseline value was below the LLOQ, or ≥4 fold the baseline value if it was equal to or higher than the LLOQ.

a) The 2-sided 95% CI was calculated by assuming log-transformed values of neutralizing antibody titers or fold-rise values in antibody titer in t-distribution and back transforming the results obtained on this assumption.
b) The 2-sided 95% CI was calculated using the Clopper-Pearson method.

PMDA's view:

Although VE in Japanese population has not been evaluated due to the absence of episodes of RSV-LRTD in Japanese participants in Study P301, PMDA accepts the applicant's explanation that the

24) The PPI population includes participants who were randomized on and before October 31, 2022, received the study vaccine, and were included in subgroups when stratified by age (60-74 years or ≥75 years), presence or absence of risk factors for LRTD, region (Northern or Southern Hemisphere), and includes 1,848 participants (333 in the placebo group and 1,515 in the mRESVIA group) who had effective immunogenicity data on anti-RSV antibody titer at baseline and at one or more time points post-vaccination, and did not have major protocol deviations that would affect the primary immunogenicity evaluation. RSV-A and B neutralizing antibody titers in the mRESVIA group in the non-Japanese population were obtained from data in 1,502 participants in the PPI population excluding 13 Japanese participants.

25) The per-protocol immunogenicity subgroup Japanese (PPISJ) population includes 801 participants (395 in the placebo group and 406 in the mRESVIA group) who were randomized at study sites in Japan, received the study vaccine, had effective immunogenicity data on anti-RSV antibody titer at baseline and at one or more time points post-vaccination, and did not have major protocol deviations that would affect the primary immunogenicity evaluation (including 15 Japanese participants in the PPI population [2 in the placebo group and 13 in the mRESVIA group]). RSV-A and B neutralizing antibody titers in the mRESVIA group in the Japanese population were obtained from data in the PPISJ population.

efficacy similar to that in the overall population can be expected in Japanese population as well, considering the efficacy analysis results in the overall population and subgroups in Study P301, results on immunogenicity, and descriptions about the intrinsic and extrinsic ethnic factors comprehensively.

### 7.R.1.3 Efficacy persistence of mRESVIA

The applicant's explanation:

Efficacy persistence of mRESVIA was investigated based on the results as of the latest data cut-off in Study P301.

Table 23 shows VE in prevention of the first episode of RSV-LRTD with ≥2 signs or symptoms in the PPE population as of the data cut-off on March 8, 2024 (the median follow-up period [minimum, maximum], 18.8 months [1 day, 830 days]), and Figure 4 shows the cumulative incidence rate. Similar results were also obtained for VE in prevention of the first episode of RSV-LRTD with ≥3 signs or symptoms and RSV-ARD in the PPE population.

**Table 23. VE in prevention of the first episode of RSV-LRTD with ≥2 signs or symptoms during a period from 14 days to 12 and 24 months post-vaccination (Study P301, PPE population, data cut-off on March 8, 2024)**

| | From 14 days to 12 months post-vaccination | | From 14 days to 24 months post-vaccination | |
|---|---|---|---|---|
| | Placebo (n = 18,132) | mRESVIA (n = 18,181) | Placebo (n = 18,132) | mRESVIA (n = 18,181) |
| Number of RSV-LRTD cases (%) | 165 (0.91) | 73 (0.40) | 248 (1.37) | 132 (0.73) |
| Incidence rate of RSV-LRTD/1,000 person-years [2-sided 95% CI][a)] | 9.433 [8.049, 10.988] | 4.136 [3.242, 5.200] | 9.098 [8.001, 10.304] | 4.789 [4.007, 5.679] |
| VE [2-sided 95% CI][b)] (%) | 56.1 [42.2, 66.7] | | 47.4 [35.0, 57.4] | |

a) The 2-sided 95% CI was calculated using the exact method (Poisson distribution) with adjustment for person-years.
b) VE was calculated based on a stratified Cox proportional hazard model using the vaccination group as a fixed effect and adjusted for stratification factors at randomization (age category and presence or absence of risk factors of LRTD) (tie data were handled according to the Efron's method).

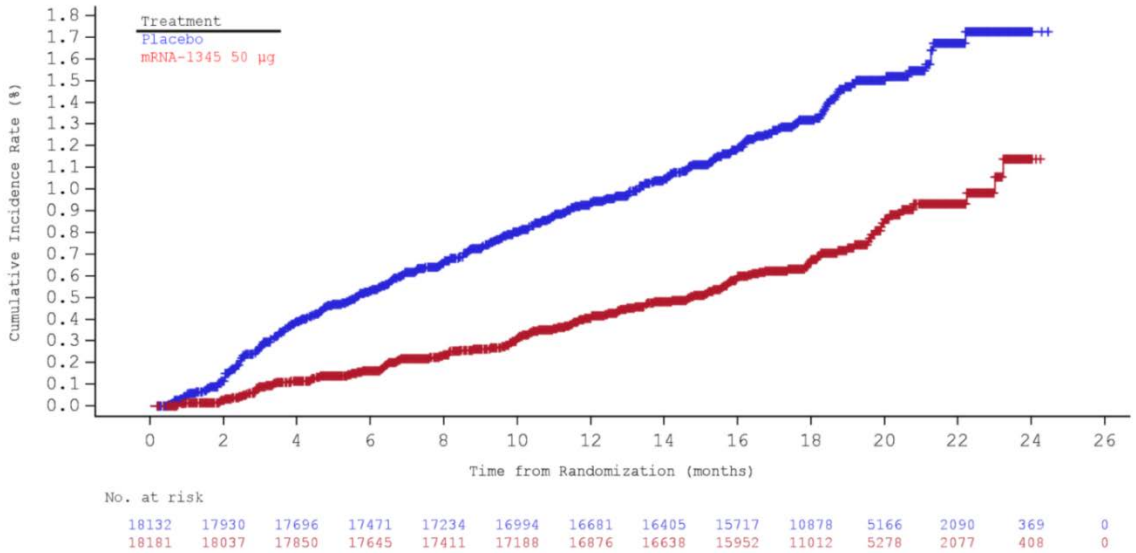


**Figure 4. Cumulative incidence rate of the first episode of RSV-LRTD with ≥2 signs or symptoms during a period from 14 days post-vaccination to data cut-off (Study P301, PPE population, data cut-off on March 8, 2024)**

For long-term efficacy of mRESVIA, results from Study P301 demonstrated that VE persisted throughout a period from 14 days to 12 and 24 months post-vaccination. Efficacy can be expected during a period including 2 RSV seasons. For the approved RSV vaccine for the elderly, single-dose vaccination is currently recommended outside Japan, requiring no consideration of a specific season for vaccination (*MMWR.* 2024;73:32:696-702), but the applicant will consider appropriate actions to prevent diseases related to RSV including necessity and timing of mRESVIA booster dose in view of results from currently ongoing Study P301 and Study mRNA-1345-P302 (Study P302: a foreign phase III study to investigate co-administration with the other vaccines) [see Section 7.R.5.2].

PMDA accepted the applicant's explanation.

### 7.R.2 Safety

Based on the review in Sections 7.R.2.1 and 7.R.2.2, PMDA has concluded that mRESVIA has acceptable safety.

#### 7.R.2.1 Safety profile of mRESVIA

The applicant's explanation about safety of mRESVIA:

Table 24 shows a summary of the safety in Study P301. Table 15 shows incidences of solicited adverse reactions through 7 days after the study vaccination.

**Table 24. Summary of safety (Study P301, safety analysis population, data cut-off on April 30, 2023)**

| | Overall population | | Japanese population | |
|---|---|---|---|---|
| | Placebo (n = 18,184) | mRESVIA (n = 18,245) | Placebo (n = 405) | mRESVIA (n = 413) |
| Solicited adverse reactions overall[a)] | 38.5 (6,975/18,102) | 68.1 (12,383/18,174) | 25.6 (103/403) | 83.5 (343/411) |
| Grade ≥3 solicited adverse reactions overall | 4.0 (723/18,102) | 6.1 (1,115/18,174) | 1.0 (4/403) | 2.7 (11/411) |
| Local reactions | 16.2 (2,939/18,097) | 58.3 (10,591/18,171) | 12.7 (51/403) | 79.8 (328/411) |
| Grade ≥3 local reactions | 1.7 (310/18,097) | 3.1 (561/18,171) | 0.2 (1/403) | 1.7 (7/411) |
| Systemic reactions | 32.9 (5,959/18,101) | 47.4 (8,613/18,171) | 18.9 (76/403) | 44.8 (184/411) |
| Grade ≥3 systemic reactions | 2.8 (513/18,101) | 4.0 (719/18,171) | 0.7 (3/403) | 1.2 (5/411) |
| Unsolicited adverse events[b)] | 18.8 (3,412) | 20.5 (3,749) | 9.1 (37) | 10.7 (44) |
| Unsolicited adverse reactions | 4.4 (795) | 5.7 (1,035) | 3.0 (12) | 5.1 (21) |
| Grade ≥3 unsolicited adverse events | 0.7 (135) | 0.7 (129) | 0.2 (1) | 0 |
| Grade ≥3 unsolicited adverse reactions | 0.3 (52) | 0.3 (53) | 0 | 0 |
| Death[c)] | 0.5 (83) | 0.5 (84) | 0 | 0 |
| Adverse reactions leading to death | 0 | 0 | 0 | 0 |
| Serious adverse events[c)] | 6.0 (1,092) | 6.1 (1,114) | 2.7 (11) | 2.9 (12) |
| Serious adverse reactions | <0.1 (5) | <0.1 (4) | 0 | 0 |
| Adverse events leading to discontinuation | 0.6 (105) | 0.5 (99) | 0 | 0 |
| Adverse reactions leading to discontinuation | 0 | <0.1 (1) | 0 | 0 |

Incidence % (number of participants with event). For solicited adverse reactions, incidence (%) (number of participants with the event/number of participants analyzed)

a) Through 7 days after the study vaccination
b) Through 28 days after the study vaccination
c) Up to data cut-off

(a) Safety in the overall population in Study P301

The incidence of solicited adverse reactions through 7 days after the study vaccination was 16.2% in the placebo group and 58.3% in the mRESVIA group for local reactions and 32.9% in the placebo group and 47.4% in the mRESVIA group for systemic reactions. Either incidence was higher in the mRESVIA group than in the placebo group. The solicited adverse reactions with a higher incidence in the

mRESVIA group were injection site pain for local reactions, and fatigue, headache, myalgia, and arthralgia for systemic reactions [see Section 7.2.1]. In both groups, most of the solicited adverse reactions were Grade 1, and Grade ≥3 solicited adverse reactions occurred in 4.0% of the participants in the placebo group and 6.1% of the participants in the mRESVIA group. No Grade 4 local solicited adverse reactions were reported, and Grade 4 systemic solicited adverse reactions were limited to pyrexia, of which the incidence was similar in both groups (0.2% in each group). Most of the local and systemic solicited adverse reactions occurred within 1 to 2 days after vaccination and resolved within 1 to 2 days after onset. Solicited adverse reactions lasting beyond 7 days after vaccination occurred in 5.1% of the participants in the placebo group and 6.7% of the participants in the mRESVIA group. Local solicited adverse reactions occurred in 0.7% of the participants in the placebo group and 1.7% of the participants in the mRESVIA group, and systemic solicited adverse reactions occurred in 4.8% and 5.8%. Local solicited adverse reactions lasting beyond 7 days after vaccination were injection site pain (0.5% and 1.0%). Of systemic solicited adverse reactions lasting beyond 7 days after vaccination, fatigue (2.8% and 3.4%), arthralgia (2.6% and 2.8%), and myalgia (2.1% and 2.3%) were commonly reported.

Incidences of unsolicited adverse events through 28 days after vaccination and unsolicited adverse events for which a causal relationship to the study vaccine could not be ruled out were similar in both groups. The most commonly reported unsolicited adverse events through 28 days after vaccination in both groups were events related to reactogenicity or general infections.

An adverse event leading to death through 7 days after vaccination occurred only in 1 participant in the placebo group (road traffic accident), and incidences of such events through 28 days after vaccination and up to data cut-off were <0.1% and 0.5%, respectively, in both groups; the incidence during either period was similar in both groups. A causal relationship to the study vaccine was ruled out for all the events.

Incidences of serious adverse events through 7 and 28 days after vaccination were 0.1% and 0.6% in both groups, and the incidence up to data cut-off was 6.0% in the placebo group and 6.1% in the mRESVIA group; the incidence during any period was similar in both groups. Up to data cut-off, serious adverse events for which a causal relationship to the study vaccine could not be ruled out occurred in 5 participants in the placebo group (pyrexia, seizure, chronic obstructive pulmonary disease, transient ischaemic attack, and myelodysplastic syndrome in 1 participant each) and 4 participants in the mRESVIA group (chills, dehydration, facial paralysis, and superficial vein thrombosis in 1 participant each). Except for the myelodysplastic syndrome, which was resolving, all the events resolved.

Incidences of adverse events leading to study discontinuation through 28 days after vaccination were <0.1% in both groups, and the incidence up to data cut-off was 0.6% in the placebo group and 0.5% in the mRESVIA group; the incidence during either period was similar. Up to data cut-off, study discontinuation was mostly caused by adverse events leading to death. Up to data cut-off, an adverse event leading to study discontinuation for which a causal relationship to the study vaccine could not be ruled out was fatigue in 1 participant in the mRESVIA group, and for outcome, it resolved.

(b) Safety in the Japanese population in Study P301

Table 25 shows solicited adverse reactions through 7 days after the study vaccination.

**Table 25. Solicited adverse reactions through 7 days after the study vaccination (Study P301, solicited adverse reaction analysis population, Japanese population, data cut-off on April 30, 2023)**

| | Placebo (n = 403) | | mRESVIA (n = 411) | |
|---|---|---|---|---|
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Solicited adverse reactions overall | 25.6 (103) | 1.0 (4) | 83.5 (343) | 2.7 (11) |
| Local (overall) | 12.7 (51) | 0.2 (1) | 79.8 (328) | 1.7 (7) |
| Injection site pain | 10.9 (44) | 0 | 77.6 (319) | 0.2 (1) |
| Axillary swelling/tenderness | 3.2 (13) | 0 | 22.1 (91) | 0 |
| Injection site erythema (redness) | 0.5 (2) | 0.2 (1) | 2.7 (11) | 0.2 (1) |
| Injection site swelling (induration) | 0.5 (2) | 0 | 10.2 (42) | 1.2 (5) |
| Systemic (overall) | 18.9 (76) | 0.7 (3) | 44.8 (184) | 1.2 (5) |
| Fatigue | 12.4 (50) | 0 | 29.2 (120) | 0.5 (2) |
| Headache | 10.7 (43) | 0 | 25.8 (106) | 0.7 (3) |
| Myalgia | 6.0 (24) | 0 | 25.3 (104) | 0.2 (1) |
| Arthralgia | 6.0 (24) | 0 | 15.1 (62) | 0 |
| Chills | 3.0 (12) | 0 | 9.2 (38) | 0.2 (1) |
| Nausea/vomiting | 2.2 (9) | 0.2 (1) | 1.9 (8) | 0 |
| Pyrexia | 0.5 (2) | 0.5 (2) | 1.9 (8) | 0 |

Incidence (%) (number of participants with the event/number of participants analyzed)

The incidence of solicited adverse reactions through 7 days after the study vaccination was 12.7% in the placebo group and 79.8% in the mRESVIA group for local reactions and 18.9% in the placebo group and 44.8% in the mRESVIA group for systemic reactions. Either incidence was higher in the mRESVIA group than in the placebo group. The incidence of local solicited adverse reactions in the Japanese population was higher than that in the overall population, and the incidence of systemic solicited adverse reactions in the Japanese population was similar to that in the overall population.

The common local solicited adverse reaction in the mRESVIA group was injection site pain (77.6%) as observed in the overall population. Local solicited adverse reactions in the mRESVIA group of which incidence in the Japanese population was ≥5% higher than that in the overall population were injection site pain (77.6% in the Japanese population and 55.9% in the overall population), axillary swelling or tenderness (22.1% and 15.2%), and injection site swelling (induration) (10.2% and 3.7%). The incidence of Grade 3 local solicited adverse reactions in the mRESVIA group was lower in the Japanese population (1.7% and 3.1%). In the Japanese population, no Grade 4 local solicited adverse reactions occurred.

The most commonly reported systemic solicited adverse reactions were fatigue (29.2% in the Japanese population and 30.8% in the overall population), headache (25.8% and 26.7%), myalgia (25.3% and 25.6%), and arthralgia (15.1% and 21.7%), and the incidences in the Japanese population were similar to those in the overall population. The incidence of Grade 3 systemic solicited adverse reactions in the mRESVIA group was lower in the Japanese population (1.2% and 3.8%). In the Japanese population, no Grade 4 systemic solicited adverse reactions occurred.

Time to onset of and duration of local and systemic solicited adverse reactions in the Japanese population were similar to those in the overall population.

The incidence of unsolicited adverse events through 28 days after the study vaccination in the Japanese population was similar in both groups (9.1% in the placebo group and 10.7% in the mRESVIA group)

and lower than that in the overall population (18.8% in the placebo group and 20.5% in the mRESVIA group). A profile of unsolicited adverse events in the Japanese population was similar to that in the overall population.

In the Japanese population up to data cut-off, no adverse events leading to death or study discontinuation occurred, and the incidence of serious adverse events was lower than that in the overall population.

PMDA's view:
For safety of mRESVIA, most of the adverse events reported after vaccination of mRESVIA in the clinical studies were events generally reported with the other vaccination (injection site pain, fatigue, headache, myalgia, etc.) and resolved in a short term, and adverse events in the Japanese population had a similar trend to that in the overall population. In view of the above, PMDA confirmed that no safety concerns specific to Japanese individuals were recognized. In view of limited vaccination experience in Japanese individuals, the applicant should provide information to healthcare professionals promptly if any new safety concern is recognized.

**7.R.2.2 Events of special interest**

The applicant's explanation:
The following events were defined as events of special interest: Shock and anaphylaxis, Guillain-Barre syndrome, Bell's palsy and facial paralysis, myocarditis and pericarditis, and vaccine associated enhanced respiratory disease (VAERD) and vaccine associated enhanced disease (VAED). Data on these events in Study P301 (data cut-off on April 30, 2023) and Study P101 (data cut-off on September 27, 2021 for the non-Japanese young adult cohort; October 3, 2022 for the non-Japanese elderly cohort; September 13, 2022 for the Japanese elderly cohort) were investigated for incidences. The investigation results are shown below.

(a) Shock and anaphylaxis
Events of preferred terms (PTs) coded to Medical dictionary for regulatory activities (MedDRA) "Anaphylactic reaction (Standardized MedDRA query [SMQ])" and "Anaphylactic/anaphylactoid shock conditions (SMQ)" (narrow) were tabulated.

In Study P301, the concerned events occurred in 5 participants in the placebo group (acute respiratory failure and dyspnoea in 2 participants; pruritus, eye pruritus, rash, hypotension, wheezing, cardiac arrest, and circulatory collapse in 1 participant each; some participants had multiple events) and 4 participants in the mRESVIA group (anaphylactic reaction in 2 participants[26)]; circulatory collapse, eye pruritus and cough in 1 participant each, some participants had multiple events). Serious events occurred in 2 participants in the placebo group (cardiac arrest, acute respiratory failure, and circulatory collapse in 1 participant each, some participants had multiple events) and 2 participants in the mRESVIA group (anaphylactic reaction in 2 participants). All the events occurred beyond 7 days after the study vaccination, and a causal relationship to the study vaccine was ruled out for all events. For outcome, in the placebo group, all the events resolved except for the cardiac arrest and acute respiratory failure in 1

26) In both participants, insect bite was deemed responsible for anaphylactic reaction.

participant, which led to death, as well as dyspnoea in 1 participant, which did not resolve. All the events in the mRESVIA group resolved.

In Study P101, the concerned events did not occur in any group.

Based on the above, a risk of anaphylactic shock and anaphylactic reaction related to mRESVIA is considered extremely low, but generally vaccines have a risk of shock and anaphylactic reaction, which may be life-threatening if they occur. The applicant will continue safety monitoring of these events in post-marketing settings as well by defining them as important potential risks for mRESVIA.

(b) Guillain-Barre syndrome
Events of PTs coded to MedDRA “Guillain-Barre syndrome (SMQ)” (narrow) were tabulated.

Up to data cut-off in Studies P301 and P101, the concerned event did not occur in any group.

Based on clinical study data in Studies P301 and P101 as well as mRNA vaccine safety data from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine data of the applicant, there is no information enough to support a potential causal relationship for Guillain-Barre syndrome to mRESVIA at the present time.

The applicant has defined the concerned event as an adverse event of special interest (AESI) in the currently ongoing clinical studies of mRESVIA and will continue safety monitoring in post-marketing settings as well.

(c) Bell’s palsy and facial paralysis
Events of PTs coded to MedDRA PT “Bell’s palsy” and “Facial paralysis” were tabulated.

In Study P301, the concerned events occurred in 5 participants in the placebo group (Bell’s palsy in 3 participants, facial paralysis in 2 participants) and 9 participants in the mRESVIA group (Bell’s palsy in 6 participants, facial paralysis in 3 participants). Serious events occurred in 2 participants in the placebo group (facial paralysis in 2 participants) and 2 participants in the mRESVIA group (facial paralysis in 2 participants). A causal relationship to the study vaccine could not be ruled out for facial paralysis in 1 participant (serious) in the mRESVIA group, and for outcome, the event resolved.

In Study P101, the concerned events did not occur in any group.

In Study P301, facial paralysis in 1 participant in the mRESVIA group for which a causal relationship to the study vaccine could not be ruled out occurred 5 days after vaccination of mRESVIA and was deemed serious, but the concerned participant had a medical history of hypertension, a risk factor of Bell’s palsy. Incidences of Bell’s palsy and facial paralysis were similar in the mRESVIA group and placebo group in Study P301. Data at the present time are not enough for bases that support a causal relationship for Bell’s palsy and facial paralysis to mRESVIA, and thus no particular safety concerns are raised.

(d) Myocarditis and pericarditis

Events of PTs coded to MedDRA “Noninfectious myocarditis/pericarditis (SMQ)” (narrow) were tabulated.

In Study P301, the concerned events occurred in 1 participant in the placebo group (pericarditis in 1 participant) and 3 participants in the mRESVIA group (pericarditis in 2 participants, myocarditis in 1 participant). Serious events occurred in 1 participant in the placebo group (pericarditis in 1 participant) and 1 participant in the mRESVIA group (myocarditis in 1 participant). A causal relationship to the study vaccine was ruled out for all the events, and for outcome, all were resolving or resolved.

In Study P101, the concerned events did not occur in any group.

At the present time, information about risks of myocarditis and pericarditis is not enough to support a causal relationship for onset of myocarditis or pericarditis to mRESVIA. Nevertheless, myocarditis and pericarditis are considered as important potential risks, because onset of myocarditis and pericarditis after the mRNA vaccination against SARS-CoV-2 have been reported although such onset is very infrequent (*Lancet Respir Med.* 2022;10:679-88, etc.); and myocarditis and pericarditis, if occur, would have critical outcome clinically. The applicant has defined the concerned event as an AESI in the currently ongoing clinical studies of mRESVIA and will continue safety monitoring in post-marketing settings as well.

(e) VAERD and VAED

In Study P301 that included ≥36,000 adults aged ≥60 years, mRESVIA reduced the incidence rate of RSV-LRTD compared with placebo at any timepoint of analyses performed. Furthermore, there were no reports that cases of RSV-LRTD in the mRESVIA group were severer than those in the placebo group.

In clinical studies conducted in 1960s, infants without a history of RSV infection received formalin-inactivated RSV vaccine, and some experienced RSV-vaccine-associated ERD after natural infection with RSV (*Am J Epidemiol.* 1969;89:449-63, *Am J Epidemiol.* 1969;89:422-34). Disease pathogenesis of the RSV-vaccine-associated ERD remains to be elucidated completely. In view of clinical study results of mRESVIA and the WHO guideline for RSV vaccines (WHO Technical Report Series No.1024 Annex 2 Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines. WHO; 2020), however, risks of VAERD and VAED after vaccination of mRESVIA are considered extremely low, because mRESVIA is intended for use in adults aged ≥60 years, corresponding to the population with a history of RSV infection.

PMDA’s view:

PMDA largely accepted the applicant’s explanation about the events of special interest. For shock and anaphylaxis, no serious adverse events for which the causal relationship could not be ruled out occurred However, cautions are raised with the other approved vaccines, and mRESVIA is considered to have the risk similarly. PMDA concluded that similar cautions should be raised. For Bell’s palsy and facial paralysis, serious adverse events for which a causal relationship to mRESVIA could not be ruled out

occurred, although the number of cases is extremely limited. Cautions should be provided appropriately in the package insert. Details of post-marketing surveillance are discussed in Section 7.R.6.

### 7.R.3 Clinical positioning

The applicant's explanation:

RSV is a highly contagious virus, prevalent across the world, and the primary cause of respiratory diseases in all age categories. Natural infection induces only a transient and incomplete immune response to RSV, leaving individuals with a history of the infection still susceptible to RSV infection throughout their life (*J Med Virol.* 2006;78:1493-7, *Am J Respir Crit Care Med.* 2015;191:1040-9). The elderly are likely to have decreased immunocompetence with aging and underlying diseases such as chronic heart diseases and chronic lung diseases, and they are at a high risk of disease caused by RSV infection including fatal one (*CDC OLDER ADULTS.* 2022, *Clin Microbiol Rev.* 2000;13:371-84). However, no drugs indicated for disease caused by RSV infection in adults are available. In the global phase II/III study in adults aged ≥60 years with diverse characteristics (Study P301), the efficacy of mRESVIA against disease caused by RSV infection was evaluated, and mRESVIA was demonstrated to be effective in prevention of RSV-LRTD with ≥2 signs or symptoms and with ≥3 signs or symptoms compared with placebo and have acceptable safety. Accordingly, mRESVIA is considered to be clinically meaningful as a vaccine product to prevent disease caused by RSV infection in adults aged ≥60 years.

In Japan, recombinant RS vaccine products under the brand names of Arexvy Intramuscular Injection and Abrysvo Intramuscular Injection have been approved for marketing as vaccines indicated for prevention of RSV-LRTD in adults aged ≥60 years. On the other hand, mRESVIA is a mRNA vaccine product that can be produced promptly and thus has a potential to offer a new option in prevention of RSV infection. While Arexvy Intramuscular Injection and Abrysvo Intramuscular Injection are presented in vials at the present time, mRESVIA is intended to be provided as a pre-filled syringe vaccine product, which can facilitate vaccination practices.

Based on the clinical study results, which show that mRESVIA can be expected to have the efficacy and has acceptable safety, PMDA has concluded that mRESVIA is clinically meaningful as one of RSV vaccine products in adults aged ≥60 years.

### 7.R.4 Indication

The applicant's explanation about the indication of mRESVIA:

Results from the global phase II/III study (Study P301) demonstrated the efficacy of mRESVIA in adults aged ≥60 years [see Section 7.R.1] and indicated acceptable safety [see Section 7.R.2]. In view of the indication of the approved RSV vaccine products, the indication of mRESVIA should be proposed as "Prevention of disease caused by RSV infection."

PMDA's view:

In view of the indication of the RSV vaccine products approved in Japan in addition to the clinical study results on mRESVIA, the indication of mRESVIA may be specified as prevention of disease caused by RSV infection. RSV is classified into 2 subtypes (RSV-A, RSV-B), but symptoms caused by RSV

infection did not largely differ between these subtypes, and which subtype will be predominantly prevalent is not known at the time of vaccination. Furthermore, based on the mechanism of action of mRESVIA, the efficacy can be expected against either subtype, and results on the efficacy of mRESVIA did not clearly differ between the subtypes [see Section 7.R.1.1]. In view of the above points, specifying the target RSV subtype in the indication of mRESVIA is considered of little significance.

Study P301 is still ongoing. Based on evidence to be obtained in the future, the applicant is required to consider appropriate measures on prevention of disease caused by RSV infection, including necessity and timing of a booster dose of mRESVIA [see Section 7.R.1.3].

PMDA thus considers that the indication of mRESVIA may be specified as follows as proposed by the applicant, and the "Precautions Concerning Indication" section in the package insert should include a statement that data on efficacy persistence of mRESVIA have not been obtained.

**Indication:**
Prevention of disease caused by RSV infection

**Precautions Concerning Indication:**
Data on efficacy persistence of mRESVIA have not been obtained

### 7.R.5 Dosage and administration

#### 7.R.5.1 Dosage and administration of mRESVIA

The applicant's explanation about dosage and administration of mRESVIA:
In the non-Japanese elderly part (aged 65-79 years) in the foreign phase I study (Study P101), a single dose of mRESVIA (12.5, 25, 50, 100, or 200 μg) (0.5 mL) was intramuscularly administered, and the safety and immunogenicity were evaluated. At 1 month after the first dose of the study vaccine, increases in neutralizing antibody titers against RSV-A and RSV-B were observed in any dose group (Table 26). The neutralizing antibody titers at 1 month post-vaccination were similar in the mRESVIA 25, 50 and 100 μg groups but tended to be lower in the 12.5 μg group and higher in the 200 μg group. Besides the immunogenicity, the safety profiles were compared among the dose groups, and incidences of solicited adverse reactions in the mRESVIA 100 and 200 μg groups were higher than those in the mRESVIA 12.5, 25, and 50 μg groups [see Section 7.1.1]. Based on evaluation for a balance between the immunogenicity and safety profile, a single intramuscular administration of mRESVIA 50 μg (0.5 mL) was selected as the dosage regimen of mRESVIA in the global phase II/III study (Study P301).

In the global phase II/III study (Study P301), the efficacy of mRESVIA intramuscularly administered at 50 μg (0.5 mL) as a single dose was demonstrated [see Section 7.R.1], and the safety was considered acceptable [see Section 7.R.2]. The applicant considers that the dosage and administration of mRESVIA may be proposed as "A single dose of 0.5 mL is injected intramuscularly in individuals aged ≥60 years."

**Table 26. RSV-A and RSV-B neutralizing antibody titers before and after the first dose of the study vaccine**
**(Study P101, non-Japanese elderly part, PP population)**

| | Placebo (n = 58) | mRESVIA 12.5 µg (n = 46) | mRESVIA 25 µg (n = 46) | mRESVIA 50 µg (n = 47) | mRESVIA 100 µg (n = 46) | mRESVIA 200 µg (n = 47) |
|---|---|---|---|---|---|---|
| **RSV-A neutralizing antibody titer** | | | | | | |
| **Baseline (before the first dose)** | | | | | | |
| No. of participants | 58 | 46 | 46 | 47 | 46 | 47 |
| GMT [2-sided 95% CI][a)] | 1590.7 [1141.8, 2215.9] | 1329.8 [969.1, 1824.8] | 1519.0 [1128.8, 2044.0] | 1204.7 [918.5, 1580.0] | 1224.9 [877.7, 1709.4] | 1879.9 [1403.5, 2517.9] |
| **1 month after the first dose** | | | | | | |
| No. of participants | 56 | 44 | 45 | 44 | 43 | 47 |
| GMT [2-sided 95% CI][a)] | 1827.2 [1306.1, 2556.2] | 13619.5 [9340.7, 19858.3] | 19008.4 [14470.5, 24969.5] | 13739.0 [9875.5, 19113.8] | 17053.4 [12486.8, 23289.9] | 31084.4 [24302.8, 39758.5] |
| GMFR [2-sided 95% CI][a)] | 1.15 [0.99, 1.34] | 10.19 [7.17, 14.48] | 12.17 [8.90, 16.64] | 12.03 [8.78, 16.47] | 14.14 [10.23, 19.54] | 16.54 [12.25, 22.33] |
| SRR [2-sided 95% CI] (%)[b)] | 5.4 [1.1, 14.9] | 75.0 [59.7, 86.8] | 88.9 [75.9, 96.3] | 84.1 [69.9, 93.4] | 93.0 [80.9, 98.5] | 93.6 [82.5, 98.7] |
| **RSV-B neutralizing antibody titer** | | | | | | |
| **Baseline (before the first dose)** | | | | | | |
| No. of participants | 58 | 46 | 46 | 47 | 46 | 47 |
| GMT [2-sided 95% CI][a)] | 1450.8 [1053.2, 1998.7] | 1437.5 [1015.1, 2035.4] | 1507.7 [1055.3, 2153.9] | 1135.3 [833.2, 1547.0] | 941.0 [681.6, 1299.1] | 1455.4 [1008.2, 2100.9] |
| **1 month after the first dose** | | | | | | |
| No. of participants | 56 | 44 | 45 | 44 | 43 | 47 |
| GMT [2-sided 95% CI][a)] | 1579.9 [1102.0, 2265.2] | 8154.1 [5568.1, 11941.1] | 10235.2 [7445.9, 14069.5] | 9432.1 [6706.2, 13266.0] | 9319.9 [6754.5, 12859.7] | 18183.8 [13206.2, 25037.5] |
| GMFR [2-sided 95% CI][a)] | 1.12 [0.98, 1.29] | 5.29 [3.74, 7.49] | 6.56 [4.86, 8.87] | 8.96 [6.79, 11.84] | 9.60 [7.31, 12.61] | 12.49 [9.10, 17.16] |
| SRR [2-sided 95% CI] (%)[b)] | 1.8 [0.0, 9.6] | 54.5 [38.8, 69.6] | 66.7 [51.0, 80.0] | 79.5 [64.7, 90.2] | 79.1 [64.0, 90.0] | 80.9 [66.7, 90.9] |

SRR was defined as a proportion of participants in whom the antibody titer increased to ≥4 fold the LLOQ after vaccination if the baseline value was below the LLOQ, or ≥4 fold the baseline value if it was equal to or higher than the LLOQ.
a) The 2-sided 95% CI was calculated by assuming log-transformed values of antibody titers or fold-rise values in antibody titer in t-distribution and back transforming the results obtained on this assumption.
b) The 2-sided 95% CI was calculated using the Clopper-Pearson method.

PMDA accepted the applicant's explanation and considers that the dosage and administration of mRESVIA may be specified as follows as proposed by the applicant.

**Dosage and Administration:**
A single dose of 0.5 mL is injected intramuscularly in individuals aged ≥60 years.

### 7.R.5.2 Coadministration of other vaccines

The applicant's explanation about coadministration of mRESVIA with the other vaccines:
To investigate coadministration of mRESVIA with influenza vaccine or SARS-CoV-2 vaccine, a foreign phase III study (Study P302) is being conducted in the US.

Study P302 is a randomized, observer-blind, parallel-group study to evaluate the immunogenicity and safety of mRESVIA coadministered with influenza vaccine or SARS-CoV-2 vaccine in adults aged ≥50 years (including those with medically stable underlying diseases). In Part A, mRESVIA was coadministered with seasonal inactivated influenza vaccine (SIIV) (quadrivalent influenza vaccine; brand name, AFLURIA). In Part B, mRESVIA was coadministered with Spikevax (bivalent vaccine of SARS-CoV-2 original strain and Omicron BA.1 variant). In this study, non-inferiority of the

coadministration to single administration was investigated based on serum neutralizing antibody titers (RSV-A, SARS-CoV-2) or hemagglutination inhibition (HAI) antibody titer (influenza virus)[27)].

In Part A, coadministration of mRESVIA and SIIV or single administration of mRESVIA or SIIV was implemented, and in Part B, coadministration of mRESVIA and Spikevax or single administration of mRESVIA or Spikevax was implemented. A total of 3,304 participants (1,623 in Part A, 1,681 in Part B) were vaccinated. The study is ongoing, and an interim analysis was performed (database lock on March 8, 2023 for Part A and June 21, 2023 for Part B).

For the immunogenicity, the primary endpoints in Part A are ratios of geometric mean titers (GMRs) of RSV-A neutralizing antibody titer and HAI antibody titers against 4 influenza strains as well as a difference in SRR against RSV-A at 1 month after the study vaccination, and the primary endpoints in Part B are GMRs of RSV-A neutralizing antibody and neutralizing antibodies against 2 SARS-CoV-2 strains as well as a difference in SRR against RSV-A at 1 month after the study vaccination. Table 27 shows GMRs of antibodies against each target antigen[28)] in the coadministration group to the single administration group as well as differences in SRR or seroconversion rate (SCR) between the single administration and coadministration groups in Parts A and B.

Of the primary endpoints, the GMRs of RSV-A neutralizing antibody titer and HAI antibody titers against 4 influenza strains as well as GMRs of RSV-A neutralizing antibody titer and neutralizing antibody titers against 2 SARS-CoV-2 strains met the non-inferiority criteria. Of the primary endpoints, the difference in SRR against RSV-A met the non-inferiority criteria in Part B but not in Part A. This failure in Part A is potentially attributable to relatively high RSV-A neutralizing antibody titers at baseline in Part A in which all participants had RSV-A neutralizing antibodies at baseline, making it difficult to achieve a 4-fold increase in antibody titer. Whether the 4-fold increase in neutralizing antibody titer in participants with pre-existing neutralizing antibodies has benefit remains unclear, the efficacy can be expected for coadministration with mRESVIA.

27) In each of Part A and Part B, meeting the following 2 criteria was required to demonstrate non-inferiority of the coadministration to single administration.
(i) GMR: The lower limit of 95% CI >0.667; (ii) Difference in SRR or SCR: The lower limit of 95% CI >−10%

28) Comparisons of RSV-A and RSV-B neutralizing antibody titers were performed between the mRESVIA + SIIV or mRESVIA + Spikevax coadministration group and mRESVIA alone group. Comparisons of HAI titers against 4 influenza strains were performed between the mRESVIA + SIIV coadministration group and SIIV alone group. Comparisons of neutralizing antibody titers against 2 SARS-CoV-2 strains were performed between the mRESVIA + Spikevax coadministration group and Spikevax alone group.

**Table 27. GMR, SRR,[a] or SCR[b] against each target antigen in the coadministration group to the single administration group at 1 month after the study vaccination (Study P302, PP population)**

| **Part A (639 participants in the coadministration group, 232 in the mRESVIA single administration group, 626 in the SIIV single administration group)** | | **Part B (514 participants in the coadministration group, 513 in the mRESVIA single administration group, 519 in the Spikevax single administration group)** | |
|---|---|---|---|
| **GMR** | | | |
| Target antigen | GMR [2-sided 95% CI][c] | Target antigen | GMR [2-sided 95% CI][c] |
| RSV-A | 0.81 [0.67, 0.97] | RSV-A | 0.80 [0.70, 0.90] |
| RSV-B | 0.85 [0.73, 1.00] | RSV-B | 0.89 [0.79, 1.00] |
| Influenza A/H1N1 | 0.89 [0.77, 1.03] | SARS-CoV-2 original strain | 0.96 [0.87, 1.06] |
| Influenza A/H3N2 | 0.97 [0.86, 1.09] | SARS-CoV-2 Omicron BA.1 variant | 1.00 [0.89, 1.14] |
| Influenza B/Victoria | 0.93 [0.82, 1.05] | | |
| Influenza B/Yamagata | 0.91 [0.81, 1.02] | | |
| **Difference in SRR or SCR** | | | |
| Target antigen | Difference in SRR or SCR [2-sided 95% CI][d] (%) | Target antigen | Difference in SRR [2-sided 95% CI][d] (%) |
| RSV-A | -11.2 [-17.9, -4.1] | RSV-A | -4.4 [-9.9, 1.0] |
| RSV-B | -14.3 [-21.5, -6.9] | RSV-B | -5.9 [-11.9, 0.3] |
| Influenza A/H1N1 | -2.7 [-8.2, 2.9] | SARS-CoV-2 original strain | 0.2 [-6.0, 6.3] |
| Influenza A/H3N2 | -0.9 [-6.3, 4.4] | SARS-CoV-2 Omicron BA.1 variant | -0.9 [-6.6, 4.7] |
| Influenza B/Victoria | -0.9 [-6.2, 4.3] | | |
| Influenza B/Yamagata | -1.2 [-6.3, 3.9] | | |

a) SRRs of RSV-A/RSV-B and SARS-CoV-2 neutralizing antibodies were defined as a proportion of participants in whom the antibody titer increased to ≥4 fold the LLOQ after vaccination if the baseline value was below the LLOQ, or ≥4 fold the baseline value if it was equal to or higher than the LLOQ.

b) SCR was defined as a proportion of participants in whom the antibody titer increased to ≥1:40 after vaccination if the baseline value was <1:10, or increased to ≥4 fold the baseline value if it was ≥1:10

c) The values were calculated by back transforming the least mean square values and 2-sided 95% CI estimated by the analysis of covariance using neutralizing antibody titer (log-transformed value) at 29 days after vaccination as response variable, dose group, neutralizing antibody titer (log-transformed value) at baseline, and age category (50-59 years/60-74 years/≥75 years) as factors.

d) The 2-sided 95% CI was calculated using the Miettinen-Nurminen method.

Tables 28 and 29 show solicited adverse reactions through 7 days after the study vaccination. In the mRESVIA + SIIV or mRESVIA + Spikevax coadministration group, some solicited adverse reactions more frequently occurred than those in the single administration group, but many of the solicited adverse reactions overall were mild or moderate. In Study P302, the follow-up period (median) was approximately 6 months in Part A and approximately 7 months in Part B. Thers were no serious adverse events for which a causal relationship to the study vaccine could not be ruled out, AESI, or adverse events leading to study discontinuation or death in any group. The safety profile of coadministration of mRESVIA with SIIV or Spikevax was acceptable, raising no additional safety concerns.

**Table 28. Solicited adverse reactions through 7 days after the study vaccination (Study P302, Part A, solicited adverse reaction analysis population)**

| | mRESVIA + SIIV (n = 678) | | mRESVIA alone (n = 249) | | SIIV alone (n = 683) | |
|---|---|---|---|---|---|---|
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Solicited adverse reactions overall | 58.4 (396/678) | 5.9 (40/678) | 59.0 (147/249) | 7.6 (19/249) | 42.8 (292/683) | 3.5 (24/683) |
| Local (overall) | 49.7 (337/678) | 2.1 (14/678) | 49.0 (122/249) | 3.6 (9/249) | 29.0 (198/683) | 0.7 (5/683) |
| Injection site pain | 47.9 (325/678) | 1.2 (8/678) | 46.6 (116/249) | 1.6 (4/249) | 25.8 (176/683) | 0.1 (1/683) |
| Axillary swelling/tenderness | 12.2 (83/678) | 0.7 (5/678) | 15.3 (38/249) | 1.6 (4/249) | 9.2 (63/683) | 0.3 (2/683) |
| Injection site swelling (induration) | 1.9 (13/678) | 0.4 (3/678) | 2.8 (7/249) | 0.4 (1/249) | 1.0 (7/683) | 0.3 (2/683) |
| Injection site erythema (redness) | 1.2 (8/678)) | 0.4 (3/678) | 1.2 (3/249) | 0 | 1.6 (11/683) | 0.3 (2/683) |
| Systemic (overall) | 41.3 (280/678) | 4.1 (28/678) | 40.2 (100/249) | 4.4 (11/249) | 31.6 (216/683) | 2.8 (19/683) |
| Fatigue | 25.8 (175/678) | 2.1 (14/678) | 24.9 (62/249) | 1.2 (3/249) | 22.0 (150/683) | 1.3 (9/683) |
| Myalgia | 24.3 (165/678) | 0.6 (4/678) | 23.3 (58/249) | 0.8 (2/249) | 13.6 (93/683) | 0.3 (2/683) |
| Headache | 23.2 (157/678) | 1.0 (7/678) | 24.5 (61/249) | 0.8 (2/249) | 17.1 (117/683) | 0.6 (4/683) |
| Arthralgia | 19.6 (133/678) | 0.7 (5/678) | 20.9 (52/249) | 1.6 (4/249) | 14.3 (98/683) | 0.1 (1/683) |
| Chills | 9.0 (61/678) | 0 | 11.2 (28/249) | 0 | 6.6 (45/683) | 0.1 (1/683) |
| Nausea/vomiting | 8.0 (54/678) | 0 | 6.8 (17/249) | 0.4 (1/249) | 3.4 (23/683) | 0 |
| Pyrexia | 3.1 (21/674) | 1.3 (9/674) | 6.9 (17/248) | 2.4 (6/248) | 2.1 (14/682) | 0.9 (6/682) |

Incidence (%) (number of participants with the event/number of participants analyzed)

**Table 29. Solicited adverse reactions through 7 days after the study vaccination (Study P302, Part B, solicited adverse reaction analysis population)**

| | mRESVIA + Spikevax (n = 558) | | mRESVIA alone (n = 555) | | Spikevax alone (n = 557) | |
|---|---|---|---|---|---|---|
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Solicited adverse reactions overall | 70.6 (394/558) | 8.4 (47/558) | 64.5 (358/555) | 3.2 (18/555) | 64.8 (361/557) | 5.7 (32/557) |
| Local (overall) | 62.9 (351/558) | 2.2 (12/558) | 57.1 (317/555) | 1.1 (6/555) | 56.7 (316/557) | 1.1 (6/557) |
| Injection site pain | 61.3 (342/558) | 1.8 (10/558) | 54.4 (302/555) | 0.7 (4/555) | 55.3 (308/557) | 0.7 (4/557) |
| Axillary swelling/tenderness | 19.4 (108/558) | 0.5 (3/558) | 16.8 (93/555) | 0 | 15.3 (85/557) | 0.4 (2/557) |
| Injection site erythema (redness) | 2.7 (15/558) | 0.4 (2/558) | 2.9 (16/555) | 0.4 (2/555) | 2.5 (14/557) | 0 |
| Injection site swelling (induration) | 2.5 (14/558) | 0 | 2.7 (15/555) | 0 | 2.5 (14/557) | 0.2 (1/557) |
| Systemic (overall) | 57.3 (320/558) | 6.8 (38/558) | 46.3 (257/555) | 2.9 (16/555) | 47.6 (265/557) | 5.2 (29/557) |
| Fatigue | 40.5 (226/558) | 4.1 (23/558) | 30.1 (167/555) | 0.9 (5/555) | 32.5 (181/557) | 2.3 (13/557) |
| Myalgia | 40.0 (223/558) | 3.0 (17/558) | 26.7 (148/555) | 1.3 (7/555) | 30.7 (171/557) | 1.6 (9/557) |
| Arthralgia | 34.6 (193/558) | 1.4 (8/558) | 22.3 (124/555) | 0.9 (5/555) | 25.7 (143/557) | 1.3 (7/557) |
| Headache | 31.9 (178/558) | 1.4 (8/558) | 26.7 (148/555) | 1.1 (6/555) | 29.6 (165/557) | 1.6 (9/557) |
| Chills | 21.9 (122/558) | 0.2 (1/558) | 12.8 (71/555) | 0.5 (3/555) | 16.5 (92/557) | 0.4 (2/557) |
| Nausea/vomiting | 10.0 (56/558) | 0 | 7.0 (39/555) | 0 | 9.0 (50/557) | 0 |
| Pyrexia | 7.6 (42/556) | 0.5 (3/556) | 2.0 (11/555) | 0.5 (3/555) | 3.2 (18/555) | 1.1 (6/555) |

Incidence (%) (number of participants with the event/number of participants analyzed)

In view of the above results, the applicant considers that coadministration of mRESVIA with influenza vaccine or SARS-CoV-2 vaccine is allowed.

PMDA accepted the applicant's explanation that coadministration of mRESVIA with influenza vaccine or SARS-CoV-2 vaccine is possible.

### 7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigations of mRESVIA:

Based on clinical study results on mRESVIA, common adverse reactions of mRESVIA were events generally observed with vaccination (injection site pain, fatigue, headache, myalgia, etc.), indicating favorable safety profile of mRESVIA [see Section 7.R.2.1].

The post-marketing safety specification of mRESVIA includes “Myocarditis and pericarditis” and “Shock and anaphylaxis” as important potential risks. These events were observed in clinical studies, but a causal relationship to the study vaccine was ruled out for all of them [see Section 7.R.2.2]. However, “Myocarditis and pericarditis,” which is defined as an important identified risk or a risk warranting caution for SARS-CoV-2 mRNA vaccine, is also considered to warrant the continued attention for mRESVIA, sharing the same mRNA platform. Considering that there are no definitive evidence supporting a relationship of mRESVIA to onset of “Myocarditis and pericarditis” at the present time, the applicant plans to conduct a specified use-results survey in individuals aged ≥60 years (target sample size, 800 individuals; observation period, 28 days after vaccination) as a part of additional pharmacovigilance activities. In this survey, the safety specification of mRESVIA including these events will be monitored to investigate their incidence in post-marketing clinical use of mRESVIA and risk factors. If safety information from the above survey in addition to spontaneous reports collected as a part of routine pharmacovigilance activities raises a safety concern for mRESVIA, the applicant will consider conducting new additional safety pharmacovigilance activities where necessary.

PMDA’s view:
Based on the submitted clinical study results, PMDA has concluded that mRESVIA has acceptable safety [see Section 7.R.2]. In view of the limited post-marketing experience with mRESVIA outside Japan, PMDA considers the applicant’s policy appropriate to continue safety pharmacovigilance activities in post-marketing settings with attention paid to the important potential risk, safety specification of mRESVIA.

In view of the points presented below, however, PMDA considered that the applicant might not have to conduct post-marketing surveillance in the limited number of individuals immediately after the approval, if they ensure that the following actions are taken: Provision to healthcare professionals with information about “Myocarditis and pericarditis” and “Shock and anaphylaxis” collected through early post-marketing phase vigilance and routine pharmacovigilance activities; collection of the safety information on mRESVIA; and taking safety measures based on the information up to now and to be obtained in the future.

- In Study P301 where approximately 20,000 participants received mRESVIA, the events corresponding to “Myocarditis and pericarditis” and “Shock and anaphylaxis” occurred only in the limited number of participants, and a causal relationship to the study vaccine was ruled out for all of them [see Section 7.R.2.2]. The proposed specified use-results survey is considered unlikely to achieve the investigation of their incidence in post-marketing clinical use of mRESVIA and risk factors.
- The safety information in the clinical study results of mRESVIA available up to now has not raised mRESVIA-specific safety concerns.

The above post-marketing actions will be finalized, taking account of comments from the Expert Discussion.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issue in CTD 3.2.P.8.3, which had no significant impact on the overall assessment of the study. The applicant was notified of the issue as the finding requiring corrective action.

Finding requiring corrective action:
3.2.P.8.3
Applicant

- Because the application documents were not appropriately subjected to quality control, some errors in writing were found in the documents.

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, the clinical studies were conducted in accordance with the GCP overall, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The following issues were observed at some of the study sites and the sponsor, although they had no significant impact on the overall assessment of the study. The relevant study sites and sponsor were notified of the issues as the findings requiring corrective action.

Finding requiring corrective action:
5.3.5.1.1
Sponsor

- Monitoring activities failed to identify inconsistencies between case reports and source data for some participants.

Study sites

- Inconsistencies between case reports and source data (failures to enter medical history/comorbidities, adverse events [including serious adverse events], and concomitant medication)

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that mRESVIA has efficacy in the prevention of disease caused by RSV infection, and that mRESVIA has acceptable safety in view of its benefits. The vaccine product and its active substance are both classified as powerful drugs. mRESVIA is clinically meaningful because it offers a new option to prevent disease caused by RSV infection in adults aged ≥60 years.

PMDA has concluded that mRESVIA may be approved if mRESVIA is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

April 7, 2025

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | mRESVIA Intramuscular Injection Syringes |
| **Non-proprietary Name** | Respiratory Syncytial Virus RNA Vaccine |
| **Applicant** | Moderna Japan Co., Ltd. |
| **Date of Application** | May 30, 2024 |

**List of Abbreviations**
See Appendix.

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusions in Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.3 Clinical positioning," "7.R.4 Indication," "7.R.5 Dosage and administration," and "7.R.6 Post-marketing investigations" presented in the Review Report (1).

### 1.1 Risk management plan (draft)

In view of the comments from the Expert Discussion, PMDA has concluded that the risk management plan (draft) for mRESVIA should include the safety specification presented in Table 30, and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 31.

**Table 30. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| None | • Shock and anaphylaxis<br>• Myocarditis and pericarditis | None |
| Efficacy specification | | |
| None | | |

**Table 31. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance | • Disseminate data gathered during early post-marketing phase vigilance |

### 1.2 Others

#### 1.2.1 Quality

The applicant's explanation about control of the potency in the vaccine product, in response to the request during preparation of the Review Report (1):

In view of the comment of PMDA, IVRPE assay using Hep3B cells is specified as a process control testing for the vaccine product to control the potency. In this assay, Hep3B cells are incubated with mRESVIA, and the antigen protein expressed from intracellularly delivered mRNA (RNA-100-AR02) is quantitatively measured by ELISA. The applicant plans to collect measured values from additional vaccine product batches, continue assessing analytical performance of the test method, and re-consider appropriateness of the control value when manufacturing results are obtained.

PMDA accepted the applicant's explanation, and based on the submitted data and above review, has concluded that the quality of the active substance and vaccine product is appropriately controlled.

## 2. Overall Evaluation

As a result of the above review, PMDA has concludes that the product may be approved for the indication and the dosage and administration shown below, with the following condition. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The vaccine product and its active substance are both classified as powerful drugs.

**Indication**

Prevention of disease caused by RSV infection

**Dosage and Administration**

A single dose of 0.5 mL is injected intramuscularly in individuals aged ≥60 years.

**Approval Condition**

The applicant is required to develop and appropriately implement a risk management plan.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| AESI | Adverse event of special interest |
| AEX-HPLC | Anion exchange high performance liquid chromatography |
| aPTT | Activated partial thromboplastin time |
| ARD | Acute respiratory disease |
| [redacted] | [redacted] |
| CAD | Charged aerosol detection |
| CI | Confidence interval |
| COVID-19 | Coronavirus disease 2019 |
| CQA | Critical quality attribute |
| DNA | Deoxyribonucleic acid |
| DSPC | 1,2-Distearoyl-sn-glycero-3-phosphocholine |
| dsRNA | Double-stranded RNA |
| ERD | Enhanced respiratory disease |
| ESI-MS | Electrospray ionization-MS |
| GMC | Geometric mean concentration |
| GMFR | Geometric mean fold rise |
| GMR | Ratio of geometric mean titers |
| GMT | Geometric mean titer |
| HAI | Hemagglutination inhibition |
| HR | Hazard ratio |
| [redacted] | [redacted] |
| IVRPE | In vitro relative protein expression |
| IVT | In vitro transcription |
| LLOQ | Lower limit of quantitation |
| LNP | Lipid nanoparticle |
| LRTD | Lower respiratory tract disease |
| MCB | Master cell bank |
| MedDRA/J | Medical dictionary for regulatory activities Japanese version |
| mRESVIA | mRESVIA Intramuscular Injection Syringe |
| mRNA | Messenger ribonucleic acid |
| PDE1 | Phosphodiesterase I |
| PEG2000-DMG | 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| postF | Postfusion F protein |
| PPE | Per-protocol efficacy |
| PPI | Per-protocol immunogenicity |
| preF | Prefusion F protein |
| PT | Preferred term |
| [redacted] | [redacted] |
| RP-HPLC | Reversed-phase high performance liquid chromatography |
| RP-IP-HPLC | Ion-paired reversed-phase high performance liquid chromatography |
| RSV | Respiratory syncytial virus |
| RSV-A | Respiratory syncytial virus A subtype |
| RSV-B | Respiratory syncytial virus B subtype |
| RT-PCR | Reverse transcription polymerase chain reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SCR | Seroconversion rate |
| SDS-PAGE | SDS-polyacrylamide gel electrophoresis |
| SIIV | Seasonal inactivated influenza vaccine |
| SM-102 | Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate |

| | |
|---|---|
| SMQ | Standardized MedDRA query |
| SRR | Seroresponse rate |
| Study P101 | Study mRNA-1345-P101 |
| Study P301 | Study mRNA-1345-P301 |
| Study P302 | Study mRNA-1345-P302 |
| UV | Ultraviolet-visible spectroscopy |
| VAED | Vaccine associated enhanced disease |
| VAERD | Vaccine associated enhanced respiratory disease |
| VE | Vaccine efficacy |
| WCB | Working cell bank |