Amsterdam, 29 January 2026
EMADOC-1700519818-2863720
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abrysvo

Common name: Respiratory syncytial virus vaccine (bivalent, recombinant)

Procedure No. EMA/X/0000258051

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviations	Term
2-PE	2-Phenoxyethanol
AE	Adverse event
AESI	Adverse event of special interest
AET	Anti-microbial effectiveness test
AS	Active substance
AVI	Automated visual inspection
BMI	Body mass index
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CPP	Critical process parameters
CQA	Critical quality attribute
CRF	Case report form
CRO	Contract research organisation
CSR	Clinical study report
DCT	Data collection tools
DS	Drug Substance
EC	Ethics committee
ECG	Electrocardiogramme
e-diary	Electronic diary
EU	European Union
Eudra-CT	European clinical trials database
FDA	Food and Drug Administration
FPFV	First participant first visit
FP	Finished product
GBS	Guillain-Barre syndrome
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMP	Good Manufacturing Practices
GMR	Geometric mean ration
GMT	Geometric mean titer
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodefidiency virus
ICD	Informed consent document
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee

Abbreviations	Term
IgG	Immunoglobulin G
IRB	Institutional review board
IRT	Interactive response technology
LLOQ	Lower limit of quantitation
LMIC	Low- and middle-income country
LPLV	Last participant last visit
MAE	Medically attended event
MCAR	Missing completely at random
MAH	Marketing Authorisation Holder
MDV	Multidose vial
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MVI	Manual visual inspection
NCT	National clinical trial
NI	Non-inferiority
NOR	Normal operating range
NT	Neutralising titer
NMR	Nuclear magnetic resonance
PACL	Protocol administrative change letter
PD	Protocol deviation
PDE	Permitted daily exposure
PFS	Prefilled syringe
Ph. Eur.	European Pharmacopeia
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	Preferred term
QTL	Quality tolerance limit
RCDC	Reverse cumulative distribution curve
rHBsAg	Recombinant hepatitis B surface antigen
RSV	Respiratory syncytial virus
RSV A	Respiratory syncytial virus subgroup A
RSV B	Respiratory syncytial virus subgroup B
RSVpreF	Respiratory syncytial virus stabilized prefusion F subunit vaccine
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCT	Safety concern threshold
SD	Standard deviation
SDS	Single-dose syringe
SDV	Single dose vial
SoA	Schedule of activities
SOC	System organ class
SRSD	Single reerence safety document
TDI	Total daily intake

Abbreviations	Term
US	United States
USUBJID	Unique subject identifier
VC3	Vaccine Cell 3
WFI	Water for injection

1. Executive Summary

On 29 January 2026, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the extension of the marketing authorisation for the medicinal product Abrysvo.

The CHMP recommended the approval of one new presentation of Abrysvo (Powder and solvent for solution for injection in multidose container; packaged as 10 multidose antigen vials (30 doses) + 10 multidose solvent vials (30 doses)), for use in pregnant individuals or adults and the associated grouped variations.

The indication for Abrysvo (Powder and solvent for solution for injection, Powder and solvent for solution for injection in multidose container) remains unchanged and is provided in the summary of product characteristics (SmPC).

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

2. Administrative/regulatory information and recommendations on the procedure

2.1. Submission of the dossier

On 7 March 2025, Pfizer Europe MA EEIG submitted an extension of the marketing authorisation application to introduce a new pharmaceutical form (Powder and solvent for solution for injection in multidose container; packaged as 10 multidose antigen vials (30 doses) + 10 multidose solvent vials (30 doses)).

2.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) - Extensions of marketing authorisations.

2.3. Scientific advice and protocol assistance

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
26 January 2023	Non-clinical	EMA/SA/0000119459	Repeat-dose toxicity and developmental and reproductive toxicity studies for the preservative containing vaccine formulation of RSVpreF in multidose vials.

2.4. Information on orphan market exclusivity

2.4.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Ruth Kieran

The application was received by the EMA on	10 March 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was received on	16 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 July 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 September 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 October 2025
The Biologics Working Party agreed on the Assessment Overview during their meeting on	05 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	13 November 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	15 December 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 January 2026
The Biologics Working Party agreed on the Assessment Overview during their meeting on	21 January 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting the extension of the marketing authorisation for Abrysvo on	29 January 2026

2.6. Final CHMP outcome

2.6.1. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Abrysvo powder and solvent for solution for injection in multidose container (packaged as 10 multidose antigen vials (30 doses) + 10 multidose solvent vials (30 doses) is favourable in the following indications:

- Active immunisation of pregnant individuals to protect infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV). See sections 4.2 and 5.1.
- Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the extension of the marketing authorisation for Abrysvo, subject to the conditions described in the following sections.

2.6.2. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

2.6.3. Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory, or a laboratory designated for that purpose.

2.6.4. Other conditions and requirements of the marketing authorisation

2.6.4.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

2.6.5.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

2.6.6. Proposed list of recommendations

Table 2: Proposed list of recommendations

Description of Recommendation(s)
The MAH should submit a variation to remove the 2-phenoxyethanol preservative within 6 months of authorisation. Supporting data should include process validation and release data for three batches of preservative-free multi-dose sterile water diluent vials and confirmatory stability data. In accordance with Ph. Eur. 0153, the MAH should also provide in-use stability data to support the proposed in-use period for this preservative free-formulation.

3. Introduction

Therapeutic Context

Abrysvo (also referred to as RSVpreF) was approved in the European Union on 23 August 2023.

Abrysvo is indicated:

- Active immunisation of pregnant individuals to protect infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV). See sections 4.2 and 5.1.
- Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

RSV is a major cause of respiratory infection in both infants and older adults. Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall. RSV has two subgroups, A and B, which co-circulate and either can cause severe disease. RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in very young infants, in infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems. RSV disease in older adults is associated with increased morbidity and mortality either caused by the virus itself, due to bacterial superinfection, or deterioration of already existing chronic medical conditions. Older adults hospitalized due to RSV infection have a high morbidity and health-resource utilisation.

In infants, treatment of RSV disease consists primarily of supportive care (e.g., nutrition/hydration for infants who cannot maintain hydration, and supplemental oxygen). The benefit of antiviral therapy (e.g., ribavirin) for RSV is unclear and therefore, it is rarely used to treat RSV. Paracetamol and OTC cold medications may be used to relieve milder symptoms. There is a prophylactic humanised monoclonal antibody against the RSV F glycoprotein, palivizumab, with demonstrated safety and efficacy against severe disease in high-risk infants. Nirsevimab, a next-generation single dose, extended half-life prefusion F-specific monoclonal antibody for preventative use in infants has received marketing authorisation in the EU in October 2022. In older adults, treatment of RSV disease consists primarily of supportive care (e.g., fluids, supplemental oxygen, or mechanical ventilation). Paracetamol OTC cold medications may be used to relieve milder symptoms.

As noted in the recent WHO SAGE on immunisation document published online, September 2024, RSV is a leading cause of LRTI, such as bronchiolitis and pneumonia, in children globally. Nearly all children in the world are infected with RSV by their second birthday, and it is responsible for a substantial number of hospitalisations among infants under 1 year of age. A recent global burden analysis estimated 101,400 RSV-attributable deaths globally in children under 5 years of age in the year 2019, representing 2.0% of all global childhood deaths and 3.6% of all deaths in children 28 days to 6 months of age. Overall, 51% of all RSV deaths occurred in children 0-6 months of age and 97% in low- and middle-income country (LMICs).

Most (approximately 80%) of RSV deaths in LMICs occur in the community, before the infant can access medical care. Additionally, an estimated 3.6 million RSV-LRTI hospitalizations and 33 million RSV-LRTI episodes occur annually in children. RSV occurs in seasonal epidemics in temperate and semi-temperate settings, usually in the cooler season, but can cause year-round disease in countries closer to the equator.

Currently, RSVpreF is available preservative free as an SDV presentation. It is also currently the only licensed vaccine for maternal immunisation (there are no other maternal vaccines available, including for use in LMICs).

Vaccines are often offered in an MDV presentation for use in LMICs to meet the supply needs of national immunisation program requirements. The MAH has partnered with the Gates Foundation to increase access to immunisation in LMICs by developing an MDV presentation of RSVpreF (3 doses per vial). In SDV presentations, each dose remains sealed and protected until it is ready for administration, decreasing chances for wastage and contamination. Because each dose needs its own container, single-dose presentations typically occupy a greater volume per dose with regard to supply chain storage and medical waste disposal. This issue is a significant problem when storage and transport space are limited. The advantage of multidose vials is that they generally allow the vaccine to occupy less cold-chain capacity than single-dose presentations, therefore reducing cold-chain and storage costs. Unlike SDVs that are discarded immediately after single use, MDVs are used more than once after the vial is opened. As the vaccine vial is repeatedly used a preservative not present in single-dose syringes was added to the MDV formulation: 2-Phenoxyethanol (2-PE). This preservative is a phenolic derivative used as a preservative in a number of commercially available vaccines.

MDV RSVpreF aims to support the clinical development of the vaccine and improve RSVpreF availability and accessibility in resource-limited countries.

3.1. Aspects of development

The efficacy and effectiveness of RSVpreF against RSV disease has been demonstrated in older adult (Study C3671013) and maternal immunisation (Studies C3671003, C3671008) clinical trials. RSVpreF (Abrysvo) was approved for marketing in the US for the older adult population on 31 May 2023 and for pregnant individuals on 21 August 2023. On 23 August 2023, RSVpreF (Abrysvo) was granted marketing authorization within the EU for the older adult population and for pregnant individuals.

To support the addition of the MDV formulation, a single pharmacological study was conducted in non-human primates to evaluate the immunogenicity of Abrysvo with or without the 2-PE preservative and a clinical Study C4841001 - "A Phase 3, Randomised, Open-Label Trial to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine Formulated in Multidose Vials in Healthy Female Adults" was conducted. This is a completed Phase 3, randomised, open-label study to evaluate the safety, tolerability, and immunogenicity of RSVpreF vaccine with 2-Phenoxyethanol (2-PE) formulated in multi-dose vial (MDV) compared to RSVpreF vaccine without 2-PE formulated in single-dose vial.

3.2. Description of the product

Abrysvo (RSVpreF) is comprised of equal quantities of 2 recombinant RSV F antigens representing the 2 major subgroups A and B, each structurally engineered for enhanced stability in the prefusion conformation. The RSV vaccine consists of 60 micrograms RSV subgroup A stabilised prefusion F protein and 60 micrograms of RSV subgroup B stabilised prefusion F protein for a total RSV drug product dose of 120 micrograms.

Prefusion F is the primary target of neutralising antibodies that block RSV infection. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects

against RSV-associated lower respiratory tract disease. In infants born to mothers who were vaccinated with Abrysvo between weeks 24 and 36 of gestation, protection against RSV-associated lower respiratory tract disease is due to transplacental transfer of RSV neutralising antibodies.

In the EU, Abrysvo is a vaccine indicated for:

- Active immunisation of pregnant individuals to protect infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV). See sections 4.2 and 5.1.
- Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

The use of this vaccine should be in accordance with official recommendations.

3.3. Inspection issues

3.3.1. GMP inspection(s)

The CHMP is of the view that no GMP inspection is required.

3.3.2. GLP inspection(s)

The CHMP is of the view that no GLP inspection is required.

3.3.3. GCP inspection(s)

As per the MAH, this study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents. The MAH has confirmed that no inspections by a regulatory authority are planned or were carried out during the course of this study.

Study centres were monitored by the CRO. Centres were visited at regular intervals, and a visit log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study-specific CRFs.

Two investigator audits of this study were included as part of the independent sponsor quality assessment performed by an independent contractor under the direction of the sponsor. The audit certificates for this study are partially provided. The MAH has confirmed the findings of the audits and that they have been addressed through the CAPA plan process and closed.

Based on the review of clinical data, the CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier.

The CHMP is of the view that no GCP inspection is required.

4. Quality aspects

4.1. Introduction

The finished product is presented as powder and solvent for solution for injection containing 60 mcg 847A antigen and 60 mcg 847B antigen as active substances.

Other ingredients are trometamol, trometamol hydrochloride, sucrose, mannitol (E421), polysorbate 80 (E433), sodium chloride, hydrochloric acid, 2-phenoxyethanol (2-PE).

The product is available in a three-dose multidose vial of antigens for Abrysvo (powder) and vial of solvent (three-dose multidose) in a pack containing 10 vials of power and solvent.

With this line extension application, the MAH also submitted a grouped variation:

-

Variation(s) requested		**Product Information affected**
A.4	A. ADMINISTRATIVE CHANGES - Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)	
B.II.z	B.II. FINISHED PRODUCT - B.II.z Other variation	
A.5.b	A.5 Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) - A.5.b The activities for which the manufacturer/importer is responsible do not include batch release	
A.7	A. ADMINISTRATIVE CHANGES - A.7 Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)*	Annex II and the Package Leaflet are updated to delete a batch release site.

4.2. Active substance

No changes have been made to the active substances as part of this line extension.

4.3. Finished medicinal product – RSV Multidose Vial (MDV)

4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product (FP) is a sterile lyophilised powder for injection that consists of equal amounts of two stabilised active substance antigens, 847A and 847B. The authorised lyophilised FP is presented in a 2 mL clear glass vial sealed with a 13 mm lyophilisation stopper and an aluminium overseal with flip-off plastic cap.

This line extension is to introduce powder and solvent for solution for injection in a multidose container. The multi-dose vial (MDV) FP is designed to deliver three 60 µg doses of each prefusion protein, equivalent to three total doses of 120 µg protein per 0.5 mL injection. There is no overfill. The MDV FP vial contains no preservatives; however, is provided with a diluent vial containing a preservative. It is intended for multi-use after reconstitution with the bacteriostatic diluent, hereafter referred to as the RSV MDV Diluent. The RSV MDV Diluent will be addressed in the subsequent section.

The composition of the lyophilised finished product is provided in Table 3. There are no novel excipients used and excipients are either pharmacopeial or controlled to an in-house standard. There is no manufacturing overage.

Table 3 Composition of Lyophilised Finished product Vial

Name of Ingredients	Grade/Quality Standard	Function
847A	In-house specification	Active Ingredient
847B	In-house specification	Active Ingredient
Tromethamine (Tris base)[a]	USP-NF, Ph. Eur., JP	Buffer component
Tris (hydroxymethyl) aminomethane hydrochloride (Tris-HCl) [b c]	In-house specification	Buffer component
Sucrose	USP-NF, Ph. Eur., JP	Cryoprotectant
Mannitol	USP-NF, Ph. Eur., JP	Bulking agent
Polysorbate 80	USP-NF, Ph. Eur., JP	Surfactant
Sodium Chloride	USP-NF, Ph. Eur., JP	Tonicifier

a. Also known as Trometamol
b. Also known as Tromethamine HCl and Trometamol HCl
c. Hydrochloric acid (HCl) (NF, Ph. Eur., JP) is used for pH adjustment in drug substance formulation

Pharmaceutical development

The formulation has been updated as part of this line extension to include a preservative, 2-phenoxyethanol, in the final finished product. The preservative-free formulation has been previously authorised as a single dose vial (SDV) as part of EMA procedure number EMEA/H/C/6027/0000.

The MAH has provided data to demonstrate that three complete doses can be obtained from each MDV vial at both the upper and lower fill weights in the manufacturing process. No other substantial changes have been made to the manufacturing process and the information provided was considered acceptable.

The control strategy has been adequately described. It is largely the same as the control strategy used for the SDV and relevant information has been updated for the MDV. Comparability has been demonstrated between the SDV and MDV. The statistical approach for setting comparability acceptance criteria was acceptable and was generated based on a suitable number of batches. All results were within the proposed comparability acceptance criteria, and the two presentations are considered comparable.

The only major difference between the SDV manufacturing process and the MDV manufacturing process is the fill volume into the final container closure system. The lyophilisation process has not changed. Data is provided demonstrating that the lyophilisation cycle for the SDV is also suitable for the MDV.

The proposed container closure is a 2 mL Type I borosilicate glass vial with a synthetic bromobutyl rubber stopper. The choice of container closure system has been adequately justified. The proposed container is considered a standard container for biological medicines and is considered appropriate for the finished product form. In-use studies have been provided to support suitable delivery of three independent doses.

The MAH has provided preservative efficacy testing for the diluent (see below), however did not provide data supporting that a preservative is required in the final finished product in the context of the proposed in-use period of 8 hours, in accordance with Ph. Eur. 0153.

However, as no safety concerns are raised regarding the MDV presentation RSVpreF with 2-phenoxyethanol based on the preclinical and clinical data, this issue, in itself, does not preclude approval of this presentation.

Nevertheless, the MAH is recommended to generate in-use data, in accordance with Ph. Eur. 0153, to determine if the preservative is required. Should the data demonstrate that the preservative is not adding benefit, the MAH should commit to removing the preservative from the formulation:

The MAH should submit a variation to remove the 2-phenoxyethanol preservative within 6 months of authorisation. Supporting data should include process validation and release data for three batches of preservative-free multi-dose sterile water diluent vials and confirmatory stability data. In accordance with Ph. Eur. 0153, the MAH should also provide in-use stability data to support the proposed in-use period for this preservative free-formulation **(Recommendation 1)**.

4.3.2. Manufacture of the product and process controls

Manufacture

Manufacture and batch release are conducted by Pfizer Manufacturing Belgium N.V. (Pfizer Puurs) at Rijksweg 12, 2870 Puurs-Sint-Amands, Belgium. Valid GMP certificates have been provided for sites involved in the manufacture and testing of the finished product.

The finished product manufacturing process is relatively straightforward consisting of thaw, compounding, mix, sterile filtering and fill/finish. The only changes required for the MDV compared to the previously authorised SDV FP manufacturing process are an increase in batch size, which

necessitates an increase in the amount of dilution buffer manufactured and an increase in fill weights to accommodate multiple doses per vial. The target finished product batch size is defined. As the batch formula for the dilution buffer is provided as constituent per kg, there are no updates required to the description of the manufacturing process to address the increased scale. The registered in-process controls for the dilution buffer remain unchanged. The fill weight controls have been updated to reflect the MDV FP presentation. The final bulk weight of the formulation step has been updated to include reference to the increased MDV batch size. All proposed hold times have been adequately supported. A maximum of two AS batches will be used to manufacture the MDV FP.

Process controls

There are no changes to the control of critical steps and intermediates. Reference to the MDV FP has been added where relevant. The information provided was considered adequate.

Process validation / verification

Validation has been performed on 3 consecutive commercial scale finished product batches. The batch genealogy has been provided demonstrating that the FP validation batches were prepared with 3 independent 847A AS batches and 3 independent 847B AS batches. No issues were identified during the process validation. All test results met predefined acceptance criteria, and the validation demonstrates that a product of consistent quality can be manufactured. No additional media fill data has been provided with this line extension. The media fill data was previously provided during a variation to add the VC3 line. The vials used during this media fill study are considered representative of the proposed final container closure system for the MDV FP presentation, and the filling duration challenged during the media fill validation exceeds the maximum filling time proposed for the MDV FP presentation; therefore, the media fill data is considered acceptable and no additional media fill information is required. The sterile filter has been adequately validated following the increase in batch size.

4.3.3. Control of Finished Product

Specifications

The finished product specification includes appropriate physicochemical and microbiological tests and tests for identity, purity and potency.

The MAH proposes to apply the specifications from the SDV for the MDV. As comparability has been demonstrated between the SDV and MDV, and the differences in the manufacturing process between both are considered minor, the MAH's proposal to apply the release specifications from the SDV to the MDV is considered acceptable.

In accordance with ICH Q3D, elemental impurities were investigated. A risk assessment identified all potential elemental impurities that could be present. All potential elemental impurities were investigated, and the calculated total daily intake (TDI) were below their respective permitted daily exposure (PDE). All elemental impurities tested were also below the quantitation limit of the test. Therefore, the elemental impurities levels are considered acceptable. The MAH identified no risk for small molecule nitrosamine formation based on a risk assessment of the active substance and multidose antigen vial finished product.

Analytical procedures and reference standards

As there are no changes to the specifications between the authorised SDV and MDV, the analytical method descriptions and validation are applicable. MDV specific methods and verification have been adequately addressed. Analytical procedures were validated according to ICH Q2(R1) and compendial methods verified for use.

Batch analysis

The batch analysis data has been provided and supports that the manufacturing process can produce a product of consistent quality. The batches presented consist of a suitable number of clinical batches and validation batches manufactured at commercial scale.

4.3.4. Stability of the product

Container closure

The primary container closure system is a clear, Type I borosilicate glass vial with a 2 mL volume that has a thickness of either 0.85 mm or 1.2 mm. Both vial variations were included in process validation. The vials are stoppered with a synthetic 13 mm bromobutyl rubber stopper. Compliance with Ph. Eur. 3.2.1 for vials, and Ph. Eur. 3.2.9 for stoppers have been declared. The name and address of manufacturers, dimensions, representative schematic drawings have been provided for the vials and stoppers. Quality control tests and acceptance criteria have been provided for both the vials and stoppers, which are considered acceptable.

Vials and stoppers are sterilised. Vials are sterilised by depyrogenation in accordance with Ph. Eur. 5.1.1, which has been appropriately verified. Stoppers are sterilised by steam sterilisation in accordance with Ph. Eur. 5.1.1 and a sterility assurance level of 10-6 is achieved. Further information on sterilisation is provided in Module 3.

The information provided on the container closure system is acceptable.

Stability

The MAH proposes a shelf-life of 18 months of the multidose antigen vial when stored at 2 ºC - 8 ºC.

Stability for the MDV FP has been studied under long-term conditions (5 ± 3°C), accelerated conditions (30 ± 2°C/75 ± 5%), stressed conditions (40 ± 2°C/75 ± 5%), thermal cycling and photostability determined. All studies are performed in accordance with ICH Q1A and ICH Q5C. Photostability studies were performed in accordance with ICH Q1B. All samples are stored in the primary container closure that is the intended container for the commercial product. In-use stability has been adequately addressed during pharmaceutical development. The approved in-use conditions as described in the Product information are: the unopened vial of antigens is stable for 5 days when stored at temperatures from 8 °C to 30 °C. At the end of this period Abrysvo should be used or discarded. This information is used to guide healthcare professionals in case of temporary temperature excursions only. After reconstitution, store in a refrigerator (2 °C to 8 °C). Abrysvo should be administered within 8 hours with no more than 4 hours stored at room temperature (up to 30 °C). Do not freeze.

Sufficient data has been provided to support an 18-month shelf-life of the finished product multidose antigen vial at 2 ºC - 8 ºC.

4.4. Finished medicinal product – RSV MDV Diluent

4.4.1. Description of the product and pharmaceutical development

Description of the product

The RSVpreF multidose vial (MDV) diluent is designed to reconstitute lyophilised finished product to obtain the final RSVpreF MDV vaccine. The diluent is supplied in a glass vial. The volume of MDV diluent ensures the reconstituted vaccine meets the required volume of injection for three, 0.5 mL doses. The diluent vial description is summarised in Table 4. The constituents of the solvent comply with Ph. Eur. standards.

Table 4 Composition of MDV Diluent Vial

Ingredient	Function	Grade/Quality Standard
2- Phenoxyethanol (2-PE)	Anti-microbial Preservative	USP-NF, Ph. Eur.
Water for Injection (WFI)	Solvent	USP-NF, Ph. Eur., JP

Abbreviations: USP = United States Pharmacopeia; N/A = not applicable; NF = National Formulary; Ph. Eur. = European Pharmacopoeia; JP = Japanese Pharmacopeia; q.s. = quantum satis

Pharmaceutical development

The diluent proposed for the MDV vial is composed of water for injection (WFI) with a preservative excipient. The choice of preservative, 2-PE, was based on previous clinical experience, as it is also used in the multidose presentation of Prevenar 13.

To support the choice of 2-PE in the Abrysvo multidose presentation, the MAH performed both a single- and multi-challenge anti-microbial effectiveness test (AET) to establish a suitable concentration. The AET was run in accordance with Ph. Eur. 5.1.3 and the MAH has justified the use of applying acceptance criteria B on the basis that all three doses will be administered within 8 hours while the acceptance criteria B ensures microbial control for up to 28 days. This justification is considered acceptable to apply acceptance criteria B.

The MAH tested three concentrations of 2-PE. Results from the AET showed the minimum concentration of 2-PE was required to achieve microbial control. The final concentration of 2-PE chosen accounted for dilution during reconstitution, manufacturing variability and testing variability. This proposed concentration is considered suitably justified. However, whether a preservative is required remains unclear, see recommendation.

Manufacturing process development

Process characterisation data for compounding of WFI with 2-PE, bioburden reduction filtration, filling, terminal sterilisation and visual inspection has been provided.

For compounding, the minimum mixing speed for the minimum time was sufficient to achieve homogeneity. For the bioburden reduction filtration, the proposed PDVF filter was investigated for compatibility with 2-PE and potential adsorption of 2-PE. No negative impact was observed when the filter was challenged with varying levels of 2-PE. No adsorption of 2-PE to the bioburden reduction filter was observed. The data supports the choice of bioburden reduction filter for the manufacturing process.

The MDV diluent vial is terminally sterilised. Nuclear magnetic resonance (NMR) data has been provided demonstrating that no new degradation peaks were observed following the steam sterilisation cycle that will be used for terminal sterilisation.

Container Closure

The extractables and leachables study for the proposed primary container of the MDV diluent. For the extractables study, it is stated that the safety concern threshold (SCT) is set at 5 µg/day for compounds without a mutagenic concern and 1.5 µg/day for those compounds with a mutagenic concern. Numerous compounds are above at least the maximum threshold of 5 µg/day in the alkaline water solvent. A toxicological risk assessment was provided for these extractable compounds and demonstrated that they pose a negligible risk to humans. Therefore, the information provided is considered to be adequate.

4.4.2. Manufacture of the product and process controls

Manufacture

Manufacture and QA release are conducted by Pfizer Manufacturing Belgium N.V. (Pfizer Puurs) at Rijksweg 12, 2870 Puurs-Sint-Amands, Belgium. The site is appropriately GMP certified.

The information provided for manufacturing of the MDV diluent is considered quite high-level, however, this is acceptable as it is a straightforward process. The process begins with a compounding step where a target weight of 2-PE is added to water for injection while mixing. The WFI is then q.s. to the final volume and mixed to homogeneity. The MDV diluent is then filtered, filled into vials, stoppered, capped and terminally sterilised. All proposed hold times have been adequately validated during process validation and are acceptable. A variation has been submitted with this line extension to correct the filter flush volume (acceptable range and normal operating range), cartridge filter filtration pressure (target), lyophilization hold time at annealing temperature (target) for the freeze driers used in the Vaccine Cell building, and the number of test vials required for drug product dye ingress testing. The proposed changes are acceptable to the CHMP.

Process controls

The process parameters and in-process testing associated with the MDV diluent have been adequately outlined. The assignment of criticality to process parameters is considered suitable for manufacture of the MDV diluent to a consistent quality. NORs, targets and acceptance criteria were provided in process characterisation. The proposed acceptance criteria for critical process parameters (CPPs), non-CPPs and in-process tests are considered suitable to ensure control of the product.

The overall control strategy has been adequately outlined. The control elements associated with each critical quality attribute (CQA) has been outlined. The elements used to control all CQAs are in-process monitoring, process parameters, finished product specifications, finished product stability testing and control of raw materials. For the MDV diluent, CQAs have been provided, which are considered appropriate to ensure a consistent MDV diluent is manufactured. There was no risk assessment performed for assignment of criticality to the quality attributes as they were all assigned in accordance with compendial requirements. This is considered acceptable. Upper and lower process ranges were established using a bracketing approach during process validation and this approach was considered acceptable.

Process validation / verification

Process validation has been performed on 3 consecutive commercial scale batches of the MDV diluent. All 3 batches met all release criteria. The validation covers compounding, bioburden reduction filtration, terminal sterilisation and visual inspection. All process parameters and in-process tests met acceptance criteria throughout process validation. Mixing time and speed were validated at the maximum and minimum registered limits across the 3 validation batches. Overall, the data provided supports that the process is capable of consistently manufacturing the MDV diluent of suitable quality.

4.4.3. Control of Finished Product

Specifications

The finished product specification includes appropriate physicochemical tests, microbiological, 2-PE content test and tests for purity.

The release tests are considered suitable to ensure the quality of the MDV diluent. Suitable justification for the proposed release specification has been provided. The justifications cover compendial requirements, historical data and information from process characterisation on the required concentration of 2-phenoxyethanol required to have preservative function.

The MAH identified no risk for small molecule nitrosamine formation based on a risk assessment of the multidose vial diluent.

Elemental impurities have been addressed previously in Section 4.3.3 of the RSV MDV finished product.

Analytical procedures and reference standards

The compendial analytical methods consist of clarity, colouration, visible particles, subvisible particles, extractable volume, endotoxin and sterility. No description has been provided for these methods; however, this is acceptable as they are compendial. The non-compendial methods have been adequately described.

No validation has been provided for compendial methods. Reference to the Ph. Eur. method has been provided, which is considered sufficient. Method validation has been provided for the non-compendial methods. The non-compendial methods are considered adequately validated for their intended purpose. Sterility testing and endotoxin testing have been verified for the MDV diluent.

No reference standards are registered for the MDV diluent.

Batch analysis

To date, multiple batches of the MDV diluent have been manufactured. This consists of a suitable number of clinical MDV diluent and process validation batches manufactured at commercial scale. Batch data has been provided for all batches.

All release results provided were within the proposed release specification and demonstrate that the process can produce the MDV diluent to a consistent quality.

4.4.4. Stability of the product

Container closure system

The container closure system consists of a 2 mL, type I borosilicate glass vial with a 13 mm rubber stopper that is sealed with a 20 mm aluminium cap. The description of the components is brief but adequate. All contact materials comply with Ph. Eur. 3.2.1 (glass vial) and Ph. Eur. 3.2.9 (rubber stopper). The vial is sterilised and depyrogenated by dry heat and the stoppers are sterilised by steam. Both sterilisation cycles comply with the conditions outlined in Ph. Eur. 5.1.1.

Representative technical drawings with dimensions of the glass vial and stopper have been provided. The suppliers of the vials and stoppers have been listed in the dossier. The quality control of the vial and stopper have been provided in the dossier and are considered sufficient.

The container closure systems provide adequate protection from microbial contamination as demonstrated during stability where container closure integrity and sterility are included within the stability studies.

Overall, the information provided on the container closure system is acceptable.

Stability data

The MAH proposes a shelf-life for the multidose solvent vial of 18 months when stored under long-term conditions at either 5 ±3°C or 30 ± 2°C/75 ± 5%.

Stability studies for the MDV diluent have been performed under 2 long-term conditions (5 ± 3°C and 30 ± 2°C/75 ± 5%), accelerated conditions (40 ± 2°C/75 ± 5%), thermal cycling and photostability. All studies are performed in accordance with ICH Q1A and ICH Q5C. Photostability studies were performed in accordance with ICH Q1B. All samples are stored in the primary container closure. All results met stability acceptance criteria with data available for up to 12 months. When extrapolation is applied in accordance with ICH Q1E, a maximum shelf-life of 18 months can be granted.

A shelf-life of 18 months for the multidose solvent vial when stored under long-term conditions at either 5 ±3°C or 30 ± 2°C/75 ± 5% is accepted.

4.4.5. Adventitious agents

There are no changes to the adventitious agents' considerations as part of this line extension.

4.5. *Discussion and conclusions on quality aspects*

Active substance

There are no changes to the active substance as part of this line extension.

Finished product

The manufacturing process of the multi-dose vial is considered highly similar to the previously authorised single dose vial, with the only major change being an increase in fill volume of the final container to accommodate three complete doses. Therefore, the description of the product, pharmaceutical development, manufacturing process controls, control of the product, container

closure are considered to be adequately described for both the multi-dose finished product and the multi-dose diluent.

A recommendation is proposed. Data supporting the additional benefit of including a preservative in the reconstituted product formulation has not been provided. While the MAH has adequately addressed all safety concerns related to the preservative, they are recommended to generate in-use data, in accordance with Ph. Eur. 0153, to determine if the preservative is required. Should the data demonstrate that the preservative is not adding benefit, the MAH should commit to removing the preservative from the formulation (**Recommendation 1**).

As part of this line extension, the MAH submitted four grouped variations as referred to in section 4.1 Three are administrative and one impacts minor changes to the finished product manufacturing process. These are all accepted by the CHMP.

4.5.1. Recommendation(s) for future quality development

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

1. The MAH should submit a variation to remove the 2-phenoxyethanol preservative within 6 months of authorisation. Supporting data should include process validation and release data for three batches of preservative-free multi-dose sterile water diluent vials and confirmatory stability data. In accordance with Ph. Eur. 0153, the MAH should also provide in-use stability data to support the proposed in-use period for this preservative free-formulation.

5. Non-clinical aspects

Introduction

Respiratory syncytial virus (RSV) is a negative sense, single stranded RNA orthopneumovirus that causes infections of the human respiratory tract.

RSV is a major cause of respiratory infection in both infants and older adults. Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall. RSV has 2 subgroups, A and B, which co-circulate and either can cause severe disease. RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in very young infants, in infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems. RSV disease in older adults is associated with increased morbidity and mortality either caused by the virus itself, due to bacterial superinfection, or deterioration of already existing chronic medical conditions. Older adults hospitalized due to RSV infection have a high morbidity and health-resource utilisation.

This is an Extension Application (EA) for Abrysvo powder and solvent for solution for injection (respiratory syncytial virus stabilized prefusion F subunit vaccine [bivalent, recombinant]) to add an alternative pharmaceutical form – 'powder and solvent for solution for injection in multidose container'.

To support the EA, a single pharmacological study (VR-VTR-11153) was conducted in non-human primates to evaluate the immunogenicity of Abrysvo with or without the 2-PE preservative. This is an immunogenicity study to evaluate the effect on the immune responses of 2-PE. Since it is not a toxicology study, it was therefore not run under GLP practices. This is acceptable.

The MAH received Scientific Advice on the development of respiratory syncytial virus prefusion F subunit vaccine (PF-06928316) for the prevention of RSV-associated lower respiratory tract disease from the CHMP on 26 January 2023 (EMA/SA/0000119459). The Scientific Advice pertained to the following non-Clinical aspects:

- Repeat-dose toxicity and developmental and reproductive toxicity studies for the preservative containing vaccine formulation of RSVpreF in multidose vials.

The CHMP concluded that that safety of 2-PE was sufficiently addressed by the data cited by the MAH and further non-clinical repeat-dose toxicity, or DART studies are not needed for 2-PE containing vaccines intended for immunization of pregnant women, such as RSVpreF.

5.1. Pharmacology

5.1.1. Pharmacodynamics

Primary pharmacodynamics

The pharmacology of RSVpreF was previously assessed and described in Module 2.4 of EMEA/H/C/006027/0000 for the MAA of Abrysvo® (SDV). To support the EA, a single pharmacological

study was conducted in non-human primates to evaluate the immunogenicity of Abrysvo with or without the 2-PE preservative.

The MDV RSVpreF vaccine is reconstituted similarly to the SDV vaccine, except the diluent contains a preservative, 2-phenoxyethanol (2-PE), to prevent microbial growth following reconstitution.

Two dose levels of 2-PE were evaluated, 5 mg (10 mg/mL) and 1 mg (2 mg/mL). The highest dose, 5 mg, was representative of the concentration evaluated in the MDV RSVpreF safety and immunogenicity study (C4841001). The lower 1 mg dose was chosen to determine if even a small amount of 2-PE would have a detrimental effect on immunogenicity. To achieve this, NHPs were immunised on Day 0 and Day 21. Sera collected post dose 1 and post dose 2 were tested in RSV A and RSV B neutralisation assays. Intramuscular vaccination of RSVpreF induced robust RSV neutralising antibody responses in NHPs that were comparable between formulations, both with and without 2-PE preservative. These data suggest that the addition of 2-PE does not negatively impact the immunogenicity of RSVpreF. The study results provide non-clinical data to support RSVpreF multi-dose vial (MDV) development.

5.1.2. Pharmacokinetics

No new data was submitted. Information on pharmacokinetics of RSVpreF can be found in Module 2.4 of EMEA/H/C/006027/0000.

5.2. Toxicology

No new toxicology studies have been performed. Information on the toxicology of RSVpreF can be found in Module 2.4 of EMEA/H/C/006027/0000.

The MAH received Scientific Advice on the development of respiratory syncytial virus prefusion F subunit vaccine (PF-06928316) for the prevention of RSV-associated lower respiratory tract disease from the CHMP on 26 January 2023 (EMA/SA/0000119459). The Scientific Advice related to the requirement to perform repeat-dose toxicity and developmental and reproductive toxicity studies for the preservative containing vaccine formulation of RSVpreF in multidose vials.

The CHMP concluded that that safety of 2-PE was sufficiently addressed by the data cited by the MAH and further non-clinical repeat-dose toxicity, or DART studies are not needed for 2-PE containing vaccines intended for immunisation of pregnant women, such as RSVpreF.

5.2.1. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, RSV PreF (RSV A and RSV B PreF) is not expected to pose a risk to the environment.

5.3. Overall discussion and conclusions on non-clinical aspects

5.3.1. Discussion

To support the EA, a single pharmacological study was conducted in non-human primates to evaluate the immunogenicity of Abrysvo with or without the 2-PE preservative.

The MDV vaccine is reconstituted similarly to the SDV vaccine, except the diluent contains a preservative, 2-phenoxyethanol (2-PE), to prevent microbial growth. The pharmacological study in non-human primates (NHPs) evaluated RSV neutralising responses conferred by MDV RSVpreF and SDV RSVpreF. Two dose levels of 2-PE were evaluated, 5 mg (10 mg/mL) and 1 mg (2 mg/mL), and compared to a formulation containing no 2-PE. The highest dose, 5 mg, was representative of the concentration evaluated in the MDV RSVpreF safety and immunogenicity study (C4841001).

The MAH received Scientific Advice on the development of respiratory syncytial virus prefusion F subunit vaccine (PF-06928316) for the prevention of RSV-associated lower respiratory tract disease from the CHMP on 26 January 2023 (EMA/SA/0000119459). The Scientific Advice related to the requirement to perform repeat-dose toxicity and developmental and reproductive toxicity studies for the preservative containing vaccine formulation of RSVpreF in multidose vials.

The CHMP concluded that that safety of 2-PE was sufficiently addressed by the data cited by the MAH and further non-clinical repeat-dose toxicity, or DART studies are not needed for 2-PE containing vaccines intended for immunization of pregnant women, such as RSVpreF.

The MAH provided a justification for the absence of ERA studies. Vaccines without adjuvants are unlikely to result in a risk to the environment and the justification for not submitting ERA studies on this basis is acceptable. In addition, the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, RSV PreF (RSV A and RSV B PreF) is not expected to pose a risk to the environment.

5.3.2. Conclusions

These data submitted suggest that the addition of 2-PE does not negatively impact the immunogenicity of RSVpreF. The CHMP is of the opinion that the study results provide non-clinical data to support RSVpreF multi-dose vial (MDV) development from a nonclinical perspective.

6. Clinical aspects

Introduction

6.1.1. GCP aspects

The MAH has confirmed that no inspections by a regulatory authority are planned or were carried out during the course of this study.

Study centres were monitored by the CRO. Centres were visited at regular intervals and a visit log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study-specific CRFs.

Two investigator audits of this study were included as part of the independent sponsor quality assessment performed by an independent contractor under the direction of the sponsor. The audit certificates for this study are partially provided. The MAH has confirmed the findings of the audits, and that they have been addressed through the CAPA plan process and closed.

Based on the review of clinical data, the CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier (see section 3.3.3.).

6.1.2. Tabular overview of clinical trials

Table 5: Tabular overview of main clinical studies

Study	Enrolment status Start date Total enrolment/ enrolment goal	Design, control type	Treatment	Population Main inclusion/ exclusion criteria (No. of Participants)
C4841001 (United States)	Completed. Initiated: 24 Jun 2024. LPLV date: 20 September 2024. Duration 6weeks. Number of participants As Randomized: MDV RSVpreF R/T/C: 224/223/220 SDV RSVpreF R/T/C: 229/227/218	A Phase 3, Randomized, Open-label Trial to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine Formulated in Multidose Vials in Healthy Female Adults	MDV RSVpreF Route: Intramuscular Dose Regimen: 120 µg) RSVpreF with 2-PE SDV RSVpreF Route: Intramuscular Dose Regimen: 120 µg) RSVpreF	**Safety Population (As Administered):** MDV RSVpreF Sex: 0 M/223 F Mean/Median Age (min, max): 33.8/34.0 (18, 49) years Race (W/B/O): 161/55/7 SDV RSVpreF Sex: 0 M/227 F Mean/Median Age (min, max): 34.4/35.0 (18, 49) years Race: W/B/O: 152/63/12 **Evaluable Immunogenicity Population (As Administered):** MDV RSVpreF Sex: 0 M/218 F Mean/Median Age (min, max): 33.9/34.0 (18, 49) years

Abbreviations: 2-PE = 2-phenoxyethanol; AE = adverse event; B = Black or African American; F = Female; M = Male; MDV = multidose vial; No = Number; O = Other; RSV = respiratory syncytial virus; RSVpreF = respiratory syncytial virus prefusion F subunit vaccine; SAE = serious adverse event; SDV = single dose vial; W = White.

6.2. Clinical pharmacology

No new data was submitted. As per the MAH, for the clinical development of vaccines, pharmacodynamic studies are essentially composed of the immunogenicity studies that characterise the immune response to the vaccine.

6.3. Clinical efficacy

6.3.1. Dose response study

Not applicable.

6.3.2. Main study

6.3.2.1. Study C4841001.

6.3.2.1.1. Study title

A Phase 3, Randomised, Open-label Trial to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine Formulated in Multidose Vials in Healthy Female Adults

6.3.2.1.2. Study design

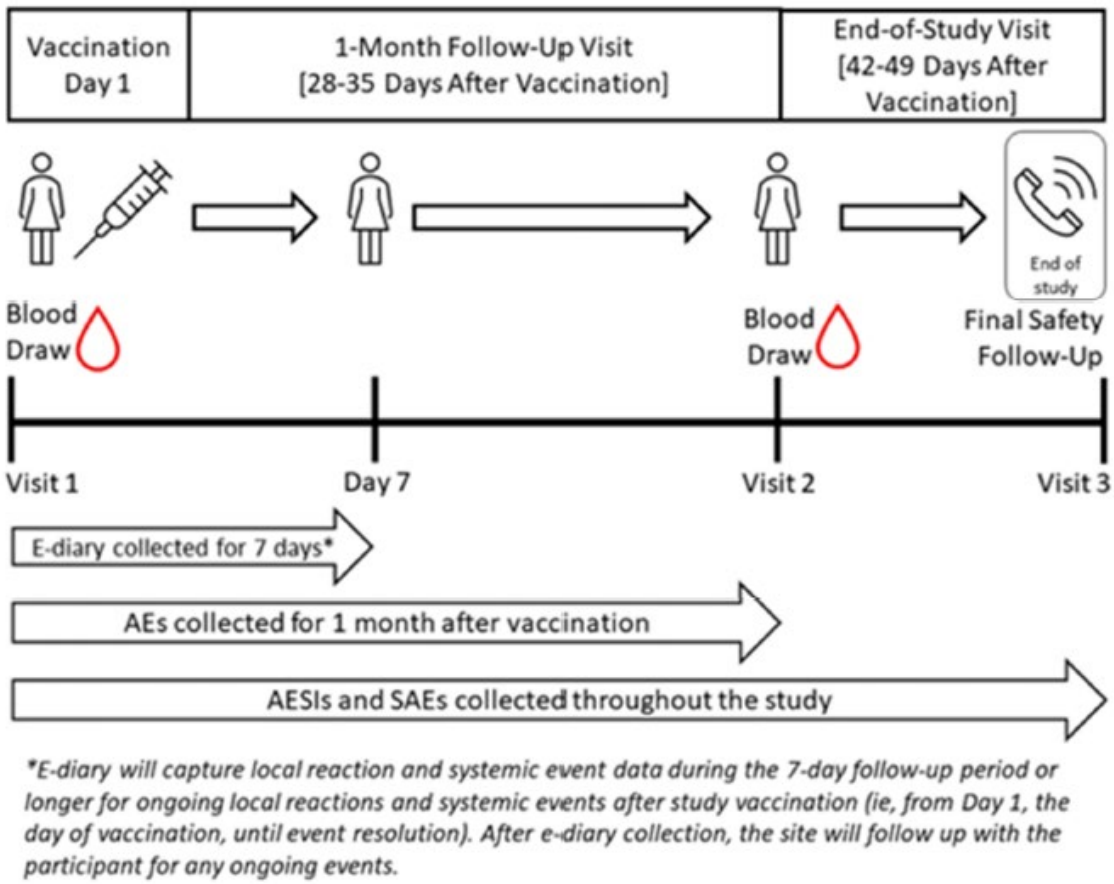
This was a Phase 3, randomised, open-label study to evaluate the safety, tolerability, and immunogenicity of RSVpreF with 2-PE formulated in MDVs compared to SDV RSVpreF. A total of 453 healthy nonpregnant, non-breastfeeding female participants 18 through 49 years of age in the US were randomised in a 1:1 ratio. The total duration for each participant on the study was approximately 6 weeks.

For the immunogenicity analyses presented, serum samples (collected prior to study vaccination [Visit 1] and 1 month after vaccination [Visit 2]) were assayed for RSV A and RSV B–neutralizing antibody titres and RSVpreF-binding IgG levels.

An e-diary was used to collect local and systemic reactogenicity event data for 7 days following study vaccination (Days 1 through 7, where Day 1 was the day of vaccination). Any reactogenicity events ongoing on the last day that the e-diary was completed, were followed up until resolution. Reported Grade 3 reactogenicity event was assessed by the study site to determine if an unscheduled visit was required.

AEs were collected from informed consent through 1 month following study intervention administration, and AESIs and SAEs were collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that were related to study procedures were collected.

Figure 1 Study Schema



Bioanalytical methods

All immunological assays used for assessment of the immune response to MDV RSVpreF are summarized in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods and fully described in Module 5.3.1.4 Reports of Bioanalytical Methods for Human Studies of EMEA/H/C/006027/0000.

6.3.2.1.2.1. Treatment

The vaccine candidate selected for this study was RSVpreF 120 µg, via a single injection, either with the preservative 2-PE (MDV RSVpreF) or without the preservative 2-PE (SDV RSVpreF). Study intervention (RSVpreF) was supplied as a lyophilized white cake in a glass vial. For MDV reconstitution, a sterile water diluent consisting of 2-PE in a separate glass vial was used; for SDV reconstitution, a PFS containing diluent of sterile water and a vial adapter was used. All study interventions were administered intramuscularly in the deltoid muscle of the upper arm. For the purposes of this study, only a single 0.5-mL dose (120 µg) was administered from each of the MDVs; the rest was discarded.

6.3.2.1.2.2. Randomisation

All participants were centrally assigned to randomised study intervention using an IRT system.

6.3.2.1.2.3. Blinding

This was an open-label study.

6.3.2.1.2.4. Patient population

This study enrolled healthy nonpregnant, non-breastfeeding female participants aged 18 through 49 years of age. Participants were required to meet the following key inclusion criteria and none of the exclusion criteria.

Key Inclusion Criteria:

- Healthy nonpregnant, non-breastfeeding females 18 through 49 years of age at Visit 1 (Day 1).

Key Exclusion Criteria:

- Any medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality, that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the vaccines being administered in the study.
- History or active autoimmune disease, including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).
- Previous vaccination with any licensed or investigational RSV vaccine or planned receipt of a non-study RSV vaccine throughout the study.
- Receipt of chronic systemic treatment with immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment through conclusion of the study
- Individuals who were pregnant or breastfeeding.

6.3.2.1.3. Objectives and estimands

6.3.2.1.3.1. Primary objective

Table 6 Primary Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Immunogenicity:		
To demonstrate that the immune responses elicited by MDV RSVpreF are noninferior to the immune response in adults vaccinated with SDV RSVpreF.	• RSV A and RSV B serum NTs.	In participants who received the study intervention and in compliance with the key protocol criteria (evaluable immunogenicity population): • GMT ratio (GMR), estimated by the ratio of the GMTs, for RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF in MDV participants to that of SDV participants.
Primary Safety:		
To describe the safety profile of RSVpreF (MDV and SDV) as measured by the percentage of participants reporting local reactions, systemic events, AEs, and SAEs following study intervention administration.	• Local reactions (pain at the injection site, redness, and swelling). • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain). • AEs. • SAEs.	In participants receiving the study intervention: • The proportion of participants reporting local reactions within 7 days following study intervention administration. • The proportion of participants reporting systemic events within 7 days following study intervention administration. • The proportion of participants reporting AEs through 1 month following study intervention administration. • The proportion of participants reporting SAEs throughout the study.

6.3.2.1.3.2. Estimands for the primary objective

Table 7: Estimands for primary objective- Immunogenicity

Population	Participants receiving 1 dose of study intervention and in compliance with the key protocol criteria (evaluable participants).
Treatment condition	The randomised MDV group or SDV group.
Endpoint (variable)	• Functional antibody levels estimated by the GMT for RSV A and RSV B serum NTs before vaccination and at 1 month after vaccination. • GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum NTs of the MDV group to the SDV group before vaccination and at 1 month after vaccination.
Population-level summary	GMR of the GMTs for RSV A and RSV B serum NTs of the MDV group to the SDV group.
Intercurrent events and strategy to handle them	

Intercurrent event 1	The participants with major protocol violation who received a prohibited vaccine. The immunogenicity data after intercurrent events will be excluded (hypothetical strategy). Major protocol violations will be determined by clinical review.
Intercurrent event 2	Treatment that may alter the immune response and subsequently impact the vaccine protection. The immunogenicity data after intercurrent events will be excluded (hypothetical strategy). Major protocol violations will be determined by clinical review.

Table 8 Estimands for primary objective- Safety

Population	Participants receiving 1 dose of study intervention
Treatment condition	The administered MDV group or SDV group. The immunogenicity data after intercurrent events will be excluded (hypothetical strategy).
Endpoint (variable)	• Local reactions within 7 days after vaccination. • Systemic events within 7 days after vaccination. • The percentage of participants having AEs through 1 month after vaccination. • The percentage of participants reporting SAEs throughout the study.
Population-level summary	The percentage of participants reporting local reactions, systemic events, AEs, and SAEs in each group.
Intercurrent events and strategy to handle them	
Intercurrent event	There are no intercurrent events to be considered. All data collected after discontinuation or major protocol deviation would be included. Missing e-diary data will not be imputed; missing AE dates and missing AE intensity data will be handled according to MAH safety rules.

For all the immunogenicity endpoints, the analysis will be primarily based on the evaluable immunogenicity population. An additional analysis will be performed based on the mITT population if there is a large enough difference in the number of participants included between the mITT and the evaluable immunogenicity populations. Participants will be summarised according to the study intervention group to which they were randomised. Missing laboratory results will not be imputed.

Statistical methods for estimation and sensitivity analysis on primary estimands

Immunogenicity Statistical Analysis Plan

For the immunogenicity analyses presented, serum samples (collected prior to study vaccination [Visit 1] and 1 month after vaccination [Visit 2]) were assayed for RSV A and RSV B–neutralizing antibody titers and RSVpreF-binding IgG levels. RSV A– and RSV B–neutralizing antibody titres were determined for each serum sample and reported as the GMTs, GMRs, and GMFRs. The primary objective of the study was the evaluation of noninferiority of immune responses at 1 month after vaccination in the MDV group compared to the SDV group.

Noninferiority criteria were met for the GMRs of those receiving MDV RSVpreF as compared to those participants who received SDV RSVpreF, if the lower bounds of the 2-sided 95% Cis >0.67 (1.5-fold noninferiority margin) for both RSV A and RSV B NTs. The secondary objective of the study was the seroresponse rates, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the prevaccination titer; or ≥4 times the LLOQ if the pre-vaccination titre was below the LLOQ. IgG

levels were determined against both RSV A and RSV B prefusion F antigens and reported as GMCs, GMRs, and GMFRs of RSVpreF-binding IgG concentrations.

Table 9 Statistical Analysis Plan – Immunogenicity

Endpoints	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary Immunogenicity:			
• Functional antibody levels estimated by the GMT for RSV A and RSV B serum NTs before vaccination and at 1 month after vaccination. • GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum NTs of the MDV group to the SDV group before vaccination and at 1 month after vaccination.	• Evaluable immunogenicity • mITT	The following intercurrent event could have impacted the interpretation or the measurement of the immune response: The participant's having major protocol violations (eg, receiving a prohibited vaccine or treatment) that may alter the immune response and subsequently impact the vaccine protection. The immunogenicity data after intercurrent events were excluded (hypothetical strategy). The intercurrent events were determined by clinical review of major protocol violations. Missing serology results were not imputed, as MCAR was assumed.	• Two-sample t-test.
Secondary Immunogenicity:			
• Seroresponse rates, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the prevaccination titer; or ≥4 times the LLOQ if the prevaccination titer is below the LLOQ.	• Evaluable immunogenicity • mITT	The following intercurrent event could have impacted the interpretation or the measurement of the immune response: The participant's having major protocol violations (eg, receiving a prohibited vaccine or treatment) that may alter the immune response and subsequently impact the vaccine protection. The immunogenicity data after intercurrent events were excluded (hypothetical strategy). The intercurrent events were determined by clinical review of major protocol violations. Missing serology results were not imputed, as MCAR was assumed.	• Descriptive statistics

Source: Appendix 16.1.9, SAP Section 2.2.1.1, 2.2.2.1, 3.1.1, and 3.1.2.

Hypothesis testing was used to assess the primary objective of NI of the immune responses for RSV A and RSV B of the MDV group to the SDV group.

For the primary objective, the null hypotheses (H0) for both RSV A and RSV B were:

- RSV A: H0A: $\ln(\mu MDV) - \ln(\mu SDV) \leq -\ln(1.5)$,
- RSV B: H0B: $\ln(\mu MDV) - \ln(\mu SDV) \leq -\ln(1.5)$,

where ln(μMDV) was the mean of natural logarithm–transformed antibody concentration at 1 month after vaccination from participants in the MDV group, and ln(μSDV) was the mean of natural logarithm–transformed antibody concentration at 1 month after vaccination from participants in the SDV group. The antibody titer data was logarithmically transformed for analysis of GMT ratios along with 95% CIs, and results were presented on the original scale.

The NI of RSVpreF of the MDV group with respect to the SDV group was evaluated at 1 month after vaccination for RSV A and RSV B NTs. The primary objective of NI was met if:

- The lower bounds of the 2-sided 95% CI for the GMT ratio (MDV group divided by SDV group) were greater than the predefined limit of 0.67 (NI margin of 1.5-fold) for both RSV A and RSV B NTs.

Safety Statistical Analysis Plan

The safety analyses were based on the safety population. Participants were summarized by vaccine group according to the study intervention they received. Descriptive statistics including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method will be presented for each vaccine group.

Table 10 Statistical Analysis Plan – Safety

Endpoints	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary Safety:			
• Local reactions within 7 days after vaccination. • Systemic events within 7 days after vaccination. • The percentage of participants having AEs through 1 month after vaccination. • The percentage of participants reporting SAEs throughout the study.	• Safety	There were no intercurrent events to be considered. All data collected after discontinuation or major protocol deviation were included. Missing e-diary data were not imputed. Missing AE dates and missing AE intensity data were handled according to Pfizer Safety rules.	• Descriptive statistics

Source: Appendix 16.1.9, SAP Section 2.2.1.2.

6.3.2.1.3.3. Secondary objectives

Table 11 Secondary Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Secondary Immunogenicity:		
To describe the immune response elicited by MDV RSVpreF compared to the immune response elicited by SDV RSVpreF.	• RSV A and RSV B serum NTs.	In participants who received the study intervention and in compliance with the key protocol criteria (evaluable immunogenicity population): • Seroresponse rates, by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the prevaccination titer; or ≥4 times the LLOQ if the prevaccination titer is below the LLOQ.
Exploratory Immunogenicity:		
To further describe the immune responses induced by MDV RSVpreF following vaccination.	• RSV A and RSV B prefusion F–binding IgG.	Not applicable.

The secondary objective of the study was the seroresponse rates, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the pre-vaccination titre; or ≥4 times the LLOQ if the pre-vaccination titre was below the LLOQ. IgG levels were determined against both RSV A and RSV B prefusion F antigens and reported as GMCs, GMRs, and GMFRs of RSVpreF-binding IgG concentrations.

6.3.2.1.3.4. Estimands for the secondary objective

Secondary Immunogenicity:

Estimand strategy: Hypothetical.

Population: Evaluable immunogenicity

Statistical method/test: Hypothesis testing.

Method of handling intercurrent events and missing values: The immunogenicity data after intercurrent events will be censored. Missing serology results will not be imputed, as MCAR is assumed.

Seroresponse rates by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the pre-vaccination titre; or ≥4 times the LLOQ if the pre-vaccination titre is below the LLOQ.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

See above.

6.3.2.1.4. Results

6.3.2.1.4.1. Participant flow and numbers analysed

A total of 453 participants were randomised and 450 were vaccinated; 223 participants received MDV RSVpreF and 227 participants received SDV RSVpreF. In total, 438 participants completed the end of study visit (89.8%).

A total of 12 participants withdrew after vaccination: 10 participants withdrew before the 1- month postvaccination visit (2.0%) and 2 participants withdrew after the 1-month postvaccination visit (0.4%). The reasons for withdrawal before the 1-month postvaccination visit were lost to follow-up (1.0%) and withdrawal by subject (1.0%), and withdrawal after the 1-month postvaccination visit was due to lost to follow-up (0.4%).

1 participant missed Visit 2 due to an unrelated SAE of motor vehicle accident and resulting hospitalisation but completed Visit 3.

Analysis Sets

Of the 453 participants randomised to study intervention, there were 3 participants excluded from the safety population due to study intervention not received (0.7%).

There was a total of 19 participants excluded from the evaluable immunogenicity population (4.2%). The most common reasons for exclusion were: Did not have 1 month after vaccination blood draw or had 1 month after vaccination blood draw but was not within 27 to 42 days after vaccination (19 participants [4.2%]) and did not have at least 1 valid and determinate assay result at the 1-month follow-up visit (14 participants [3.1%]).

A total of 14 participants were excluded from the mITT population (3.1%). The most common reason for exclusion was: Did not have a valid and determinate assay result at the 1- month follow-up visit (11 participants [2.4%]).

The majority of randomised participants that were vaccinated had blood samples obtained prior to vaccination at Visit 1, per the protocol (99.3%). At Visit 2 (1 month after vaccination), the majority of randomized participants had blood samples drawn within the protocol-specified time frame of 27 to 42 days after vaccination (95.8%).

Table 12 Analysis Populations – All Randomized Participants

	Vaccine Group (as Randomized)		
	RSVpreF(MDV) (N^a=224) n^b (%)	RSVpreF(SDV) (N^a=229) n^b (%)	Total (N^a=453) n^b (%)
Safety population	223 (99.6)	227 (99.1)	450 (99.3)
Excluded from safety population	1 (0.4)	2 (0.9)	3 (0.7)
Not vaccinated	1 (0.4)	2 (0.9)	3 (0.7)
mITT immunogenicity population	220 (98.2)	219 (95.6)	439 (96.9)
Excluded from mITT immunogenicity population[c]	4 (1.8)	10 (4.4)	14 (3.1)
Did not receive vaccine	1 (0.4)	2 (0.9)	3 (0.7)
Did not have a valid and determinate assay result after vaccination	3 (1.3)	8 (3.5)	11 (2.4)
Evaluable immunogenicity population	218 (97.3)	216 (94.3)	434 (95.8)
Excluded from evaluable immunogenicity population[c]	6 (2.7)	13 (5.7)	19 (4.2)
Not eligible for the study*	0	1 (0.4)	1 (0.2)
Did not receive study vaccine at Visit 1 as randomized	1 (0.4)	2 (0.9)	3 (0.7)
Did not have 1 month after vaccination blood draw or Had 1 month after vaccination blood draw but was not within 27 to 42 days after vaccination	6 (2.7)	13 (5.7)	19 (4.2)
Had major protocol violation(s) from randomization through the 1 month after vaccination blood draw	0	0	0
Did not have at least 1 valid and determinate assay result at the 1-month follow-up visit	4 (1.8)	10 (4.4)	14 (3.1)

Abbreviations: mITT= modified intent-to-treat; NT = neutralizing titer; RSV = respiratory syncytial virus.
*Note: 1 participant was erroneously randomized in the study but withdrew consent without eligibility criteria completion.
a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
c. Participants could be excluded for more than 1 reason.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adsl Table Generation: 26DEC2024 (08:15)
(Database snapshot date : 11NOV2024) Output File: ./nda_mdv/C4841001_CSR/adsl_sx01_anal

6.3.2.1.4.2. Deviations from study plan

In total, there were 7 participants with important PDs. The most common important PDs were related to participants not meeting inclusion/exclusion criteria (6 participants [1.3%]). Upon review of all important PDs on the study, there was no impact to immunogenicity or safety population analyses. Thus, no participants were excluded from the evaluable immunogenicity or safety population due to an important PD.

6.3.2.1.4.3. Baseline data

Demographic characteristics for all participants in the safety and evaluable immunogenicity population were similar between the participants who received MDV RSVpreF or SDV RSVpreF.

Overall, most participants in the evaluable immunogenicity population were White (69.8%), with 25.8% Black or African American participants, 1.4% Asian participants, and 21.2% Hispanic/Latino participants. The median age at the time of study vaccination was 34.0 years. All study participants were enrolled in the US and were female.

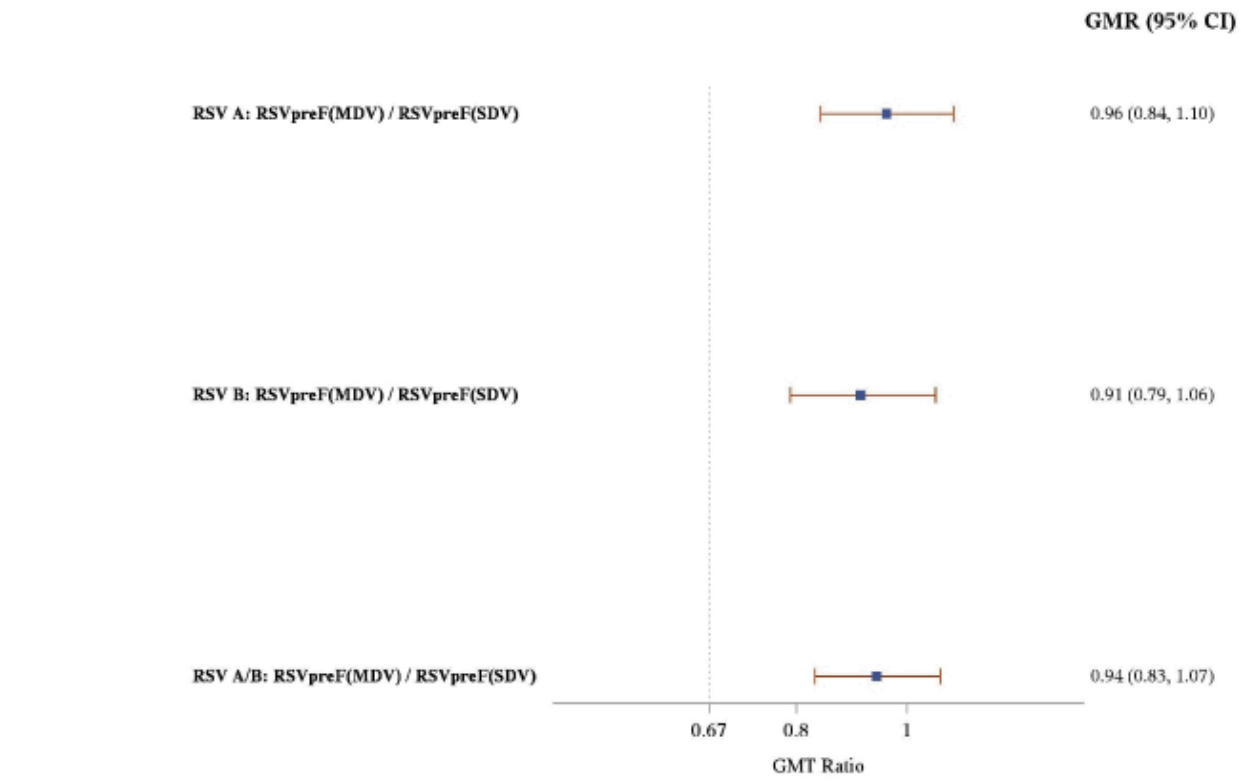
6.3.2.1.4.4. Outcomes and estimation

One month after vaccination with RSVpreF, the noninferiority criteria were met for the RSV NTs GMRs of healthy female adults 18 through 49 years of age who received MDV RSVpreF compared to those who received SDV RSVpreF, with the lower bounds of the 2- sided 95% CIs >0.67 (1.5-fold noninferiority margin) for both RSV A and RSV B NTs.

In the evaluable immunogenicity population, the GMRs (RSVpreF (MDV)/RSVpreF (SDV)) at 1 month after vaccination were 0.96 (0.84,1.10) for RSV A and 0.91 (0.79,1.06) for RSV B. The combined RSV A/B serum NTs, of the MDV group to the SDV group at 1 month after vaccination was 0.94 (0.83,1.07).

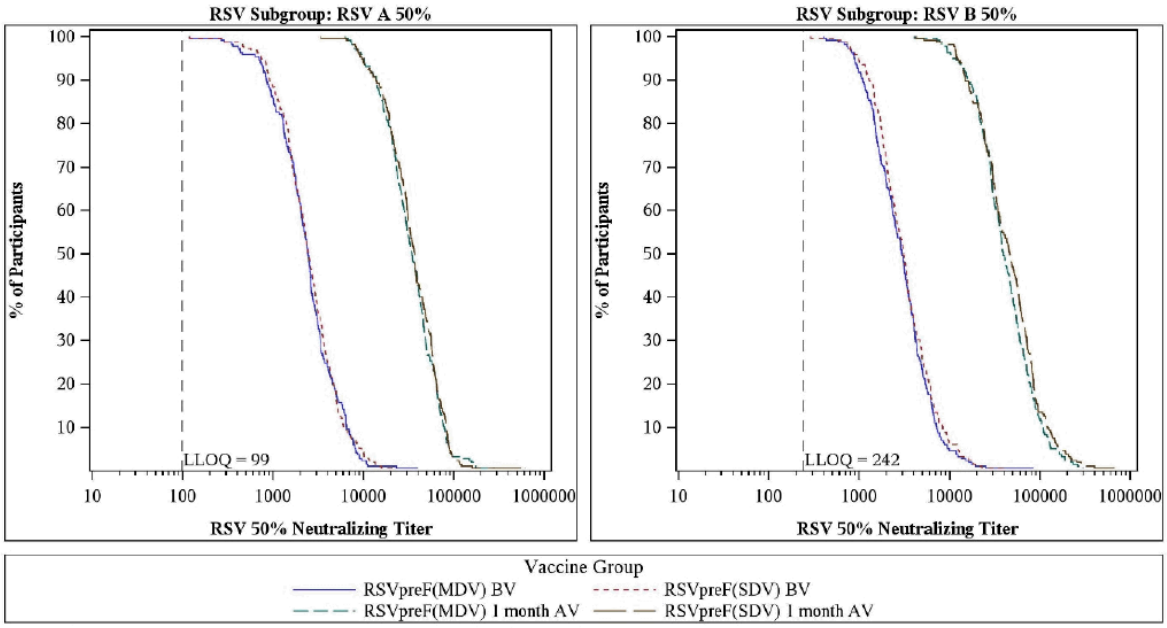
For both RSV A and RSV B subgroups, the lower bounds of the 2-sided 95% CIs for the GMRs at 1 month after vaccination for the MDV group compared to the SDV group were greater than the predefined limit of 0.67, demonstrating noninferiority of MDV RSVpreF compared to SDV RSVpreF.

Figure 2 Forest Plot, Geometric Mean Ratios with 95% CIs Between RSVpreF (MDV) and RSVpreF (SDV) Comparison, by RSV subgroup – Evaluable Immunogenicity Population



Abbreviation: GMR =Geometric mean ratio.

Figure 3 Reverse Cumulative Distribution Curves: RSV Neutralizing Titre 1 Month After Vaccination – Evaluable Immunogenicity Population



Abbreviations: LLOQ = lower limit of quantitation; BV = Before Vaccination; AV = After Vaccination.
PFIZER CONFIDENTIAL SDTM Creation: 27NOV2024 (02:10) Source Data: adva Table Generation: 13JAN2025 (09:44)Output File: ./nda mdv/C4841001 CSR/adva f001 rcdc

For the evaluable immunogenicity population, the GMTs for RSV A, RSV B, and the combined RSV A/B serum NTs, at 1 month after vaccination were similar across the MDV group (33715, 41471, and 37393, respectively) and the SDV group (35131, 45374, and 39883, respectively). Results were similar in the mITT population.

Figure 4 RSV Neutralizing Titer GMTs and GMR before Vaccination and 1 Month after Vaccination for RSVpreF (MDV) to RSVpreF (SDV) – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)						Comparison
		RSVpreF (MDV)			RSVpreF (SDV)			RSVpreF (MDV)/RSVpreF (SDV)
RSV Subgroup	Time Point [a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	GMR[d] (95% CI[e])
A	Before vaccination	218	2362	(2118.7, 2634.0)	215	2472	(2226.2, 2744.8)	0.96 (0.82,1.11)
	1 Month after vaccination	218	33715	(30737.7, 36981.4)	215	35131	(31949.4, 38630.0)	0.96 (0.84,1.10)
B	Before vaccination	218	2926	(2637.1, 3245.7)	216	3172	(2866.2, 3509.8)	0.92 (0.80,1.07)
	1 Month after vaccination	218	41471	(37505.0, 45856.0)	215	45374	(40664.0, 50628.8)	0.91 (0.79,1.06)
A/B	Before vaccination	218	2629	(2387.6, 2894.6)	215	2799	(2551.0, 3070.9)	0.94 (0.82,1.07)
	1 Month after vaccination	218	37393	(34285.2, 40781.5)	214	39883	(36293.6, 43828.1)	0.94 (0.83,1.07)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation.
Note: The LLOQ values were 242 for RSV A and 99 for RSV B neutralizing titers. Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. n = number of participants with valid and determinate assay results for the specified time point in the specified analysis population.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution).
d. GMRs were calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units.
e. CIs were back transformations of CIs based on the Student t distribution for the mean difference of logarithm of the titers.
PFIZER CONFIDENTIAL SDTM Creation: 27NOV2024 (02:10) Source Data: adva Table Generation: 26DEC2024 (08:29)
(Database snapshot date : 11NOV2024) Output File: ./nda_mdv/C4841001_CSR/adva_s001a_2

Results were similar in the mITT population. The GMRs, estimated by the ratio of the GMTs for RSV A, RSV B (mITT population) at 1 month after vaccination were 0.96 (0.84,1.10) for RSV A and 0.90 (0.78,1.05) for RSV B. The combined RSV A/B serum NTs, of the MDV group to the SDV group at 1 month after vaccination was 0.93 (0.82,1.06).

Figure 5 RSV Neutralizing Titer GMTs and GMR before Vaccination and 1 Month after Vaccination for RSVpreF (MDV) to RSVpreF (SDV) – mITT Immunogenicity Population

		Vaccine Group (as Randomized)						Comparison
		RSVpreF (MDV)			RSVpreF (SDV)			RSVpreF (MDV)/RSVpreF (SDV)
RSV Subgroup	Time Point [a]	n[b]	GMT[c]	(95% CI[c])	n[b]	GMT[c]	(95% CI[c])	GMR[d] (95% CI[e])
A	Before vaccination	220	2368	(2125.1, 2637.9)	218	2461	(2218.5, 2729.6)	0.96 (0.83,1.12)
	1 Month after vaccination	220	33815	(30851.7, 37062.6)	218	35116	(31969.5, 38572.4)	0.96 (0.84,1.10)
B	Before vaccination	220	2930	(2643.7, 3248.3)	219	3178	(2873.0, 3516.4)	0.92 (0.80,1.06)
	1 Month after vaccination	220	41463	(37531.0, 45806.3)	218	45906	(41105.5, 51266.4)	0.90 (0.78,1.05)
A/B	Before vaccination	220	2634	(2393.9, 2898.3)	218	2796	(2549.6, 3065.4)	0.94 (0.83,1.08)
	1 Month after vaccination	220	37444	(34358.8, 40806.3)	217	40109	(36514.7, 44058.0)	0.93 (0.82,1.06)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation.
Note: The LLOQ values were 242 for RSV A and 99 for RSV B neutralizing titers. Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. n = number of participants with valid and determinate assay results for the specified time point in the specified analysis population.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution).
d. GMRs were calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units.
e. CIs were back transformations of CIs based on the Student t distribution for the mean difference of logarithm of the titers.
PFIZER CONFIDENTIAL SDTM Creation: 27NOV2024 (02:10) Source Data: adva Table Generation: 26DEC2024 (08:48)
(Database snapshot date : 11NOV2024) Output File: ./nda mdv/C4841001 CSR/adva s001b 2

Secondary Endpoint

The secondary immunogenicity endpoint aimed to describe the immune response elicited by MDV RSVpreF compared to the immune response elicited by SDV RSVpreF. The secondary endpoint is defined as seroresponse rates, by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the pre-vaccination titre; or ≥4 times the LLOQ if the pre-vaccination titre is below the LLOQ.

For the evaluable immunogenicity population, the seroresponse rates at 1 month after vaccination were similar across the MDV and SDV groups for RSV A (91.7% and 91.6%, respectively), RSV B (96.8% and 90.7%, respectively), and the combined RSV A/B (96.3% and 93.9%, respectively) serum NTs. n = Number of participants meeting the seroresponse definition. Results were similar in the mITT population.

Table 13 RSV Neutralizing Titer Seroresponse Rates 1 Month After Vaccination with RSVpreF (MDV) compared to RSVpreF (SDV) – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)					
	RSVpreF (MDV)			RSVpreF (SDV)		
RSV Subgroup	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
A	218	200 (91.7)	(87.3, 95.0)	214	196 (91.6)	(87.0, 94.9)
B	218	211 (96.8)	(93.5, 98.7)	215	195 (90.7)	(86.0, 94.2)
A/B	218	210 (96.3)	(92.9, 98.4)	213	200 (93.9)	(89.8, 96.7)

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation.
Note: The LLOQ values were 242 for RSV A and 99 for RSV B neutralizing titers.
Note: Seroresponse is defined as achieving a ≥4-fold rise from baseline (before vaccination) if the baseline measurement is above the LLOQ. If the baseline measurement is below the LLOQ, a postvaccination assay result ≥4 × LLOQ is considered a seroresponse.
a. N = number of participants with valid and determinate assay results for the specified assay at both before vaccination and 1 month after vaccination timepoints in specified immunogenicity population. This value is the denominator for the percentage calculations.
b. n = Number of participants meeting the seroresponse definition.
c. Exact 2-sided CI calculated using the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 27NOV2024 (02:10) Source Data: adva Table Generation: 26DEC2024 (08:48) (Database snapshot date : 11NOV2024) Output File: ./nda mdv/C4841001 CSR/adva s007 sero comp evim

Exploratory Immunogenicity Endpoints

GMCs, GMRs, and GMFRs for RSVpreF-binding IgG

Geometric mean concentration- For the evaluable immunogenicity population, the GMCs of RSVpreF-binding IgG for RSV A and RSV B, were substantially increased from before vaccination to 1 month after vaccination for the MDV group (RSV A: 1811 to 35643; RSV B: 2153 to 40166, respectively) and the SDV group (RSV A: 1996 to 38722; RSV B: 2415 to 42913, respectively). Results were similar in the mITT population.

Geometric mean ratio- For the evaluable immunogenicity population, the GMR of RSVpreF-binding IgG estimated by the ratio of the GMCs of RSVpreF-binding IgG for RSV A and RSV B, of the MDV group compared to the SDV group at 1 month after vaccination for RSV A was 0.92 and for RSV B was 0.94. Results were similar in the mITT population.

Geometric mean fold rise- For the evaluable immunogenicity population, the GMFRs of RSVpreF-binding IgG at 1 month after vaccination were similar across the MDV and SDV groups for RSV A (19.7 and 19.4, respectively) and RSV B (18.7 and 17.8, respectively). Results were similar in the mITT population.

6.3.3. Overall discussion and conclusions on clinical efficacy

6.3.3.1. Discussion

The present submission seeks to add the MDV presentation of RSVpreF to the EU marketing authorisation for Abrysvo, the results from the Phase 3, C4841001 study demonstrating safety and tolerability are supportive (LPLV date: 20 September 2024). Results demonstrated that RSV A and RSV B neutralising responses elicited following a dose of MDV RSVpreF are noninferior (by GMR) to responses following a dose of SDV RSVpreF.

A total of 453 healthy nonpregnant, non-breastfeeding female participants 18 through 49 years of age in the US were randomised in a 1:1 ratio. The total duration for each participant on the study was approximately 6 weeks.

For the immunogenicity analyses presented, serum samples (collected prior to study vaccination [Visit 1] and 1 month after vaccination [Visit 2]) were assayed for RSV A and RSV B–neutralising antibody titres and RSVpreF-binding IgG levels.

In the MDV group, noninferiority of immune responses was demonstrated for RSV A and RSV B serum NTs based on the protocol-specified 1.5-fold margin. NI was evaluated using a 1.5-fold margin as the criterion. With the assumption of SD (ln scale) from the historical study, the overall power to demonstrate NI for both RSV A and RSV B is 90.0%.

The statistical aspect of the 1.5-fold non-inferiority margin has been adequately described and is consistent with other relevant publicly available vaccine trials.

In the evaluable immunogenicity population, the GMRs (RSVpreF (MDV)/RSVpreF (SDV)) at 1 month after vaccination were 0.96 (0.84,1.10) for RSV A and 0.91 (0.79,1.06) for RSV B. The combined RSV A/B serum NTs, of the MDV group to the SDV group at 1 month after vaccination was 0.94 (0.83,1.07). Results were similar in the mITT population.

For both RSV A and RSV B subgroups, the lower bounds of the 2-sided 95% CIs for the GMRs at 1 month after vaccination for the MDV group compared to the SDV group were greater than the predefined limit of 0.67, demonstrating noninferiority of MDV RSVpreF compared to SDV RSVpreF.

The secondary immunogenicity endpoint aimed to describe the immune response elicited by MDV RSVpreF compared to the immune response elicited by SDV RSVpreF. The secondary endpoint is defined as seroresponse rates, by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the pre-vaccination titre; or ≥4 times the LLOQ if the pre-vaccination titre is below the LLOQ.

For the evaluable immunogenicity population, the seroresponse rates at 1 month after vaccination were similar across the MDV and SDV groups for RSV A (91.7% and 91.6%, respectively), RSV B (96.8% and 90.7%, respectively), and the combined RSV A/B (96.3% and 93.9%, respectively) serum NTs. Results were similar in the mITT population.

Exploratory immunogenicity endpoints (GMCs, GMRs, and GMFRs for RSVpreF-binding IgG) for the evaluable immunogenicity population, were comparable for the MDV group and the SDV group, results were similar in the mITT population.

The multidose vial group elicited immune responses that were considered noninferior to those of the single dose vial group, meeting the 1.5-fold noninferiority criteria for both RSV A and RSV B based on geometric mean ratios of neutralising titres.

6.3.3.2. Conclusions on the clinical efficacy

The CHMP is of the view that the multidose vial group elicited immune responses that were considered noninferior to those of the single dose vial group, meeting the 1.5-fold noninferiority criteria for both RSV A and RSV B based on geometric mean ratios of neutralising titres.

6.4. Clinical safety

For the purpose of this section, whilst cross referring to the table of studies in section 6.3.2, the following definitions apply:

- 'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
- 'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
- 'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

6.4.1. Safety data collection

Safety Assessments

Planned time points for all safety assessments are in the SoA as Visit 1 (prior to study vaccination), Visit 2 (1 month after vaccination) and Visit 3 (End-of-Study Visit, 42-49 days after vaccination). Unscheduled safety measurements could be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including significant medical history, were performed on all participants at their first visit to establish a baseline. Significant medical history and observations from any physical examination and vital sign assessments, if performed, were documented in the CRF.

The time period for actively eliciting and collecting:

- Prespecified local reactions (pain at the injection site, redness, and swelling) occurring at the RSVpreF injection site and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhoea, muscle pain, and joint pain) occurring within 7 days after vaccination were recorded daily by the participant in an e-diary,
- Any reactogenicity events ongoing on the last day that the e-diary was completed, were followed up until resolution.
- Nonserious AEs were from the time of informed consent through and including Visit 2 (1 month after study vaccination);

- SAEs and AESIs was from the time of informed consent through study completion (Visit 3, 42-49 days after vaccination);
- Any AEs occurring within 30 minutes after vaccination were recorded and defined as immediate AEs.

Adverse Events of Special Interest

AESIs were collected from informed consent until the participant completed the study. The following events are considered AESIs:

- Diagnosis of Guillain-Barré syndrome
- Diagnosis of acute polyneuropathy without an underlying aetiology
- Diagnosis of atrial fibrillation
- Preterm delivery (delivery at <37 0/7 weeks' gestation)
- Diagnosis of hypertensive disorder of pregnancy

A 3-tier approach was used to summarize AEs. Under this approach, AEs were classified into 1 of 3 tiers. Different analyses were performed for different tiers.

- Tier 1 events: These were prespecified events of clinical importance, and they were maintained in a list in the product's Safety Review Plan. The AESIs were considered Tier 1 events for RSVpreF and were analysed for the entire study period.
- Tier 2 events: These were events that were not Tier 1 but were "common". A MedDRA PT was defined as a Tier 2 event if there were at least 1% of participants with the AE term in at least 1 vaccine group.
- Tier 3 events: These were events that were neither Tier 1 nor Tier 2 events.

E-Diary Compliance

Transmission of e-diary data was similar across the MDV and SDV groups. Almost all participants had at least 1 day of e-diary data transmitted within 24 hours (98.2%) and 72 hours (99.1%) of the e-diary reporting day. For all participants, the overall transmission of e-diary data within 24 and 72 hours of the e-diary reporting day for each day was ≥82.4% and ≥94.7%, respectively, and for all 7 days was 60.7% and 91.6%, respectively.

Note: Site 1004 experienced an e-diary system malfunction which impacted 25 of 60 participants at the site. Site 1004 captured all known missing e-diary data in the CRF. All CRF data reported and captured during the study were included in the safety analysis.

6.4.2. Patient exposure

The safety analyses were based on the safety population. Participants were summarized by vaccine group according to the study intervention they actually received.

A total of 453 participants were randomized and 450 were vaccinated; 223 participants received MDV RSVpreF and 227 participants received SDV RSVpreF. In total, 438 participants completed the end of study visit (89.8%).

A total of 12 participants withdrew after vaccination: 10 participants withdrew before the 1- month postvaccination visit (2.0%) and 2 participants withdrew after the 1-month postvaccination visit (0.4%). The reasons for withdrawal before the 1-month postvaccination visit were lost to follow-up (1.0%) and withdrawal by subject (1.0%), and withdrawal after the 1-month postvaccination visit was due to lost to follow-up (0.4%).

Note: 1 participant missed Visit 2 due to an unrelated SAE of motor vehicle accident and resulting hospitalization, but completed Visit 3.

Overall, most participants in the safety population were White (69.6%), with 26.2% Black or African American participants, 1.3% Asian participants, and 22.2% Hispanic/Latino participants. The median age at the time of study vaccination was 34.0 years. All study participants were enrolled in the US and were female.

Table 14 Demographic and Baseline Characteristics – Safety Population

	Vaccine Group (as Administered)		
	RSVpreF (MDV) (N[a]=223) n[b] (%)	RSVpreF (SDV) (N[a]=227) n[b] (%)	Total (N[a]=450) n[b] (%)
Sex			
Female	223 (100.0)	227 (100.0)	450 (100.0)
Race			
White	161 (72.2)	152 (67.0)	313 (69.6)
Black or African American	55 (24.7)	63 (27.8)	118 (26.2)
Asian	3 (1.3)	3 (1.3)	6 (1.3)
American Indian or Alaska Native	0	3 (1.3)	3 (0.7)
Native Hawaiian or Other Pacific Islander	0	1 (0.4)	1 (0.2)
Unknown	0	1 (0.4)	1 (0.2)
Multiracial	2 (0.9)	3 (1.3)	5 (1.1)
Not reported	2 (0.9)	1 (0.4)	3 (0.7)
Ethnicity			
Non-Hispanic/non-Latino	174 (78.0)	168 (74.0)	342 (76.0)
Hispanic/Latino	46 (20.6)	54 (23.8)	100 (22.2)
Not reported	3 (1.3)	5 (2.2)	8 (1.8)
Age at vaccination (years)			
n	223	227	450
Mean (SD)	33.8 (9.3)	34.4 (8.8)	34.1 (9.1)
Median	34.0	35.0	34.0
(Min, max)	(18, 49)	(18, 49)	(18, 49)

a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants in the specified category.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adsl Table Generation: 26DEC2024 (08:15)
(Database snapshot date : 11NOV2024) Output File: ./nda_mdv/C4841001_CSR/adsl_s005

6.4.3. Adverse events

Overview of Adverse Events

Most AEs were mild or moderate. From vaccination through study completion, 3 participants reported 6 SAEs, of which, only 1 SAE was considered by the investigator to be related to study intervention; the related, immediate, and Grade 3 SAE of anaphylactic reaction was reported by 1 participant in the SDV group. The participant was treated and fully recovered by the following day. One participant (0.4%) in the SDV group reported a life-threatening SAE of appendicitis, which was not considered by the investigator to be related to study intervention.

The number of participants reporting any AEs from vaccination through 1 month after vaccination were similar between the MDV and SDV groups (9.0% and 8.4%, respectively).

Through 1 month after vaccination:

- 6 participants reported related AEs (3 participants [1.3%] in each of the MDV and SDV groups),
- 1 participant reported an immediate AE (0.4% of the SDV group),
- 1 participant reported an SAE (0.4% of the SDV group),
- 1 participant reported a severe AE (0.4% of the SDV group),
- No participant reported a life-threatening AE or AESI.

From vaccination through 1 month after vaccination, participants in the MDV group, most frequently reported AEs in the SOCs of infections and infestations (3.6%) and nervous system disorders (2.2%). Among participants in the SDV group, AEs were most frequently reported in the SOCs of infections and infestations (3.1%), and nervous system disorders and investigations (each 0.9%). There were 7 AEs reported in 6 participants that were considered by the investigator to be related to study intervention.

No deaths or AEs leading to withdrawal were reported in the study.

There were no AESIs (including any Tier 1 events) reported in the study or Tier 2 events reported through 1 month after vaccination.

Table 15 Number (%) of Participants Reporting at Least 1 Adverse Event for Each Analysis Interval After Vaccination – Safety Population

Interval Adverse Event Type	Vaccine Group (as Administered) RSVpreF (MDV) (N[a]= 223) n[b] (%)	 (95% CI[c])	 RSVpreF (SDV) (N[a]= 227) n[b] (%)	 (95% CI[c])
Any AEs reported from vaccination through 1 month follow-up visit	20 (9.0)	(5.6, 13.5)	19 (8.4)	(5.1, 12.8)
Related	3 (1.3)	(0.3, 3.9)	3 (1.3)	(0.3, 3.8)
Immediate[d]	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
SAE	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Severe	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Life-threatening	0	(0.0, 1.6)	0	(0.0, 1.6)
AESI[e]	0	(0.0, 1.6)	0	(0.0, 1.6)
Any SAEs reported from vaccination throughout the study	1 (0.4)	(0.0, 2.5)	2 (0.9)	(0.1, 3.1)
Related	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Severe	1 (0.4)	(0.0, 2.5)	1 (0.4)	(0.0, 2.4)
Life-threatening	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Any AEs leading to withdrawal after vaccination	0	(0.0, 1.6)	0	(0.0, 1.6)
Related	0	(0.0, 1.6)	0	(0.0, 1.6)
Serious	0	(0.0, 1.6)	0	(0.0, 1.6)
Severe	0	(0.0, 1.6)	0	(0.0, 1.6)
Life-threatening	0	(0.0, 1.6)	0	(0.0, 1.6)
Any AEs leading to death after vaccination	0	(0.0, 1.6)	0	(0.0, 1.6)
Related	0	(0.0, 1.6)	0	(0.0, 1.6)
Severe	0	(0.0, 1.6)	0	(0.0, 1.6)
Any AESIs reported from vaccination throughout the study[e]	0	(0.0, 1.6)	0	(0.0, 1.6)
Related	0	(0.0, 1.6)	0	(0.0, 1.6)
Severe	0	(0.0, 1.6)	0	(0.0, 1.6)

Abbreviation: AESI = adverse events of special interest; CI = confidence interval.
Note: The classification of adverse events (AE) is based on MedDRA (v27.1).
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting the specified AE type during the analysis interval.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. AE reported within the first 30 minutes after vaccination.
e. AESI refers to protocol-specified adverse events of special interest.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adae Table Generation: 26DEC2024 (09:18)
(Database snapshot date : 11NOV2024) Output File: ./nda_mdv/C4841001_CSR/adae_s015_tov

Adverse Events by System Organ Class and Preferred Term

The proportions of participants with any AEs reported within 1 month after vaccination were similar across the MDV and SDV groups (9.0% and 8.4%, respectively). Among participants in the MDV and SDV groups, AEs were most frequently reported in the SOCs of infections and infestations (3.6% and 3.1%, respectively) and nervous system disorders (2.2% and 0.9%, respectively). By PT, the most frequently reported AE in both groups was upper respiratory tract infection (each 0.9%).

Table 16 Adverse Events Reported From Vaccination Through 1 Month Follow-up Visit, by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) RSVpreF (MDV) (N[a]=223) n[b] (%)	 (95% CI[c])	 RSVpreF (SDV) (N[a]=227) n[b] (%)	 (95% CI[c])
Any event	20 (9.0)	(5.6, 13.5)	19 (8.4)	(5.1, 12.8)
Blood and lymphatic system disorders	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Iron deficiency anaemia	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Gastrointestinal disorders	1 (0.4)	(0.0, 2.5)	1 (0.4)	(0.0, 2.4)
Eosinophilic oesophagitis	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Gastrooesophageal reflux disease	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
General disorders and administration site conditions	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Face oedema	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Oedema peripheral	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Immune system disorders	1 (0.4)	(0.0, 2.5)	1 (0.4)	(0.0, 2.4)
Anaphylactic reaction	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Milk allergy	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Infections and infestations	8 (3.6)	(1.6, 6.9)	7 (3.1)	(1.2, 6.3)
COVID-19	2 (0.9)	(0.1, 3.2)	1 (0.4)	(0.0, 2.4)
Nasopharyngitis	0	(0.0, 1.6)	2 (0.9)	(0.1, 3.1)
Onychomycosis	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Postoperative wound infection	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Sinusitis	1 (0.4)	(0.0, 2.5)	1 (0.4)	(0.0, 2.4)
Upper respiratory tract infection	2 (0.9)	(0.1, 3.2)	2 (0.9)	(0.1, 3.1)
Urinary tract infection	2 (0.9)	(0.1, 3.2)	0	(0.0, 1.6)
Viral infection	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Injury, poisoning and procedural complications	3 (1.3)	(0.3, 3.9)	1 (0.4)	(0.0, 2.4)
Animal bite	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Hand fracture	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Ligament sprain	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Muscle strain	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Road traffic accident	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Investigations	0	(0.0, 1.6)	2 (0.9)	(0.1, 3.1)
Blood pressure increased	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
SARS-CoV-2 test positive	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Metabolism and nutrition disorders	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Iron deficiency	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)

System Organ Class Preferred Term	Vaccine Group (as Administered) RSVpreF (MDV) (N[a]=223) n[b] (%)	 (95% CI[c])	 RSVpreF (SDV) (N[a]=227) n[b] (%)	 (95% CI[c])
Musculoskeletal and connective tissue disorders	2 (0.9)	(0.1, 3.2)	1 (0.4)	(0.0, 2.4)
Arthritis	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Joint Pain	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Pain in extremity	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Nervous system disorders	5 (2.2)	(0.7, 5.2)	2 (0.9)	(0.1, 3.1)
Brain fog	2 (0.9)	(0.1, 3.2)	0	(0.0, 1.6)
Dizziness	0	(0.0, 1.6)	2 (0.9)	(0.1, 3.1)
Hypoaesthesia	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Paraesthesia	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Syncope	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Psychiatric disorders	2 (0.9)	(0.1, 3.2)	0	(0.0, 1.6)
Attention deficit hyperactivity disorder	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Insomnia	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Renal and urinary disorders	1 (0.4)	(0.0, 2.5)	1 (0.4)	(0.0, 2.4)
Nephrolithiasis	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Pollakiuria	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Reproductive system and breast disorders	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Breast disorder	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Skin and subcutaneous tissue disorders	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Hyperkeratosis	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)

Abbreviation: CI = confidence interval.
Note: The classification of adverse events (AE) is based on MedDRA (v27.1)
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified AE.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adae Table Generation: 26DEC2024 (09:18)
(Database snapshot date : 11NOV2024) Output File: ./nda mdv/C4841001 CSR/adae all s150

6.4.4. Adverse drug reactions

The proportions of participants who reported AEs from vaccination to 1 month after vaccination that were considered by the investigator to be related to study intervention were low for all participants in the MDV and SDV groups (each 3 participants [1.3%]).

Table 17 Related Adverse Events Reported From Vaccination Through 1 Month Follow-up Visit, by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) RSVpreF (MDV) (N[a]=223) n[b] (%)	 (95% CI[c])	 RSVpreF (SDV) (N[a]=227) n[b] (%)	 (95% CI[c])
Any event	3 (1.3)	(0.3, 3.9)	3 (1.3)	(0.3, 3.8)
General disorders and administration site conditions	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Face oedema	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Oedema peripheral	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Immune system disorders	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Anaphylactic reaction	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Nervous system disorders	3 (1.3)	(0.3, 3.9)	1 (0.4)	(0.0, 2.4)
Brain fog	2 (0.9)	(0.1, 3.2)	0	(0.0, 1.6)
Dizziness	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Paraesthesia	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)

Abbreviation: CI = confidence interval.
Note: The classification of adverse events (AE) is based on MedDRA (v27.1)
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified AE.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adae Table Generation: 26DEC2024 (09:18)
(Database snapshot date : 11NOV2024) Output File: ./nda_mdv/C4841001_CSR/adae_rel_s150

The related AEs reported in the MDV group were brain fog (0.9%) and paraesthesia (0.4%) and in the SDV group were facial oedema, peripheral oedema, anaphylactic reaction, and dizziness (each 0.4%).

- Of note, 1 participant in the SDV group reported a related, immediate, and Grade 3 SAE of anaphylactic reaction. The participant had a history of allergic reactions to multiple medications. The participant was treated at the site with improvement of symptoms, sent to the emergency room for observation, and fully recovered by the following day.
- One (1) participant in the SDV group reported related and mild events of left facial oedema and peripheral oedema after receiving vaccination in the left deltoid muscle. This participant had a history of similar adverse reactions to COVID-19 vaccine in the past.
- Both events started on Day 2 and resolved in 5 days.
- One (1) participant in the SDV group reported a related and mild event of dizziness, which started on Day 3 and resolved in 3 days.
- Two (2) participants in the MDV group reported related, mild and moderate events of brain fog, which started on Day 3 and 2, respectively, and resolved in 2 and 4 days, respectively.
- One (1) participant in the MDV group reported a related and mild event of paresthesia, which started on Day 2 and resolved in 2 days. This participant had experienced similar reactions to influenza vaccine in the past.

6.4.5. AEs of special interest, serious adverse events and deaths, other significant events

Severe and Life-Threatening Adverse Events

From vaccination through 1 month after vaccination, 1 participant (0.4%) in the SDV group reported a severe SAE (Grade 3 events) of anaphylactic reaction, which was considered to be related to the study intervention by the investigator. No participant in the MDV group reported a severe AE through 1 month after vaccination.

There were no life-threatening AEs (Grade 4 event) reported from vaccination through 1 month after vaccination. From vaccination through study completion, 1 participant (0.4%) in the SDV group reported a life-threatening SAE of appendicitis, which was not considered to be related to the study intervention by the investigator. No participant in the MDV group reported a life-threatening AE from vaccination through study completion.

Deaths

No deaths were reported during the study.

Other Serious Adverse Events

From the time of informed consent through study completion, 6 SAEs were reported in 3 participants:

- 1 participant in the MDV group (0.4%) reported 4 SAEs of road traffic accident, ankle fracture, rib fracture, and tibia fracture, of which, none of the events were considered to be related to the study intervention by the investigator.
- 2 participants in the SDV group (0.9%), each reported 1 SAE (anaphylactic reaction and appendicitis) of which, 1 of the events (anaphylactic reaction, 0.4%) was considered to be related to the study intervention by the investigator.

Table 18 Serious Adverse Events Reported From Vaccination Throughout the Study, by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) RSVpreF (MDV) (N[a]=223) n[b] (%)	 (95% CI[c])	 RSVpreF (SDV) (N[a]=227) n[b] (%)	 (95% CI[c])
Any event	1 (0.4)	(0.0, 2.5)	2 (0.9)	(0.1, 3.1)
Immune system disorders	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Anaphylactic reaction	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Infections and infestations	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Appendicitis	0	(0.0, 1.6)	1 (0.4)	(0.0, 2.4)
Injury, poisoning and procedural complications	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Ankle fracture	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Rib fracture	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Road traffic accident	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)
Tibia fracture	1 (0.4)	(0.0, 2.5)	0	(0.0, 1.6)

Abbreviation: CI = confidence interval.
Note: The classification of adverse events (AE) is based on MedDRA (v27.1).
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified AE.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adae Table Generation: 26DEC2024 (09:18)
(Database snapshot date : 11NOV2024) Output File: ./nda_mdv/C4841001_CSR/adae_ser_s150

Reactogenicity

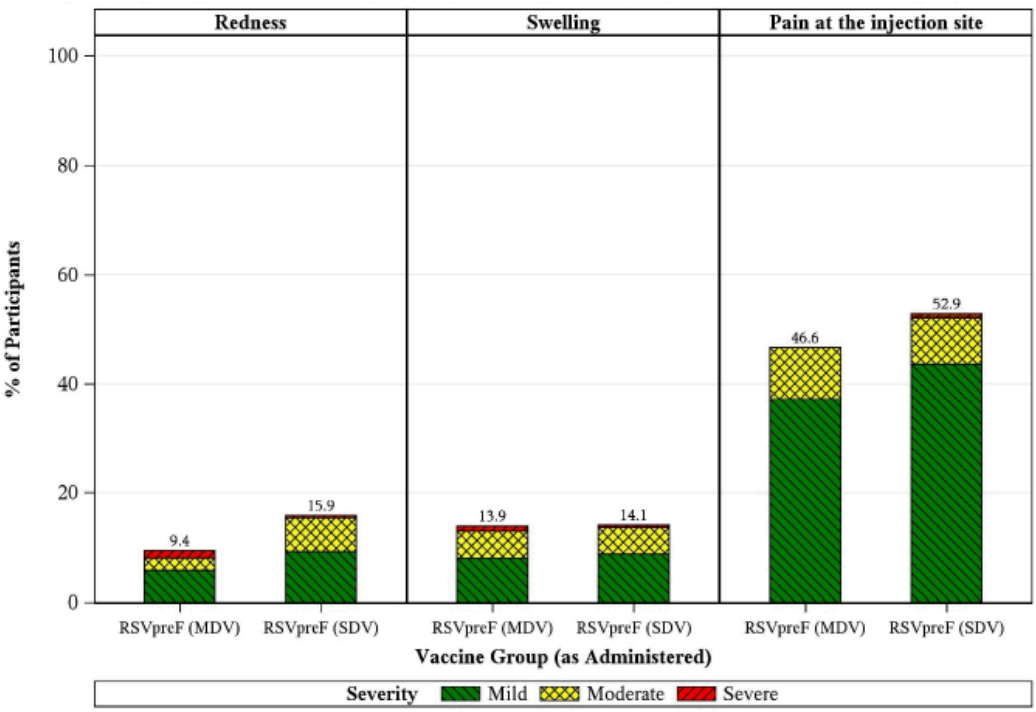
Local Reactions

The percentages of participants in the safety population who reported any local reactions within 7 days after vaccination were similar for the MDV group (50.2%), compared to the SDV group (55.1%).

For both groups, most local reactions were mild or moderate; severe local reactions were infrequently reported by the MDV and SDV groups (each 1.3%). The most frequently reported local reaction in the MDV and SDV groups was pain at injection site (46.6% and 52.9%, respectively).

In the MDV and SDV groups, local reactions had a median onset of Day 2 (Day 1 was the day of vaccination), and reactions resolved with median durations of ≤3 and ≤2 days, respectively.

Figure 6 Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Vaccination – Safety Population



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adfacevd Table Generation: 27DEC2024 (00:07) (Snapshot Date: 11NOV2024) Output File: ./nda_mdv/C4841001_CSR/adce_f001_lr_max

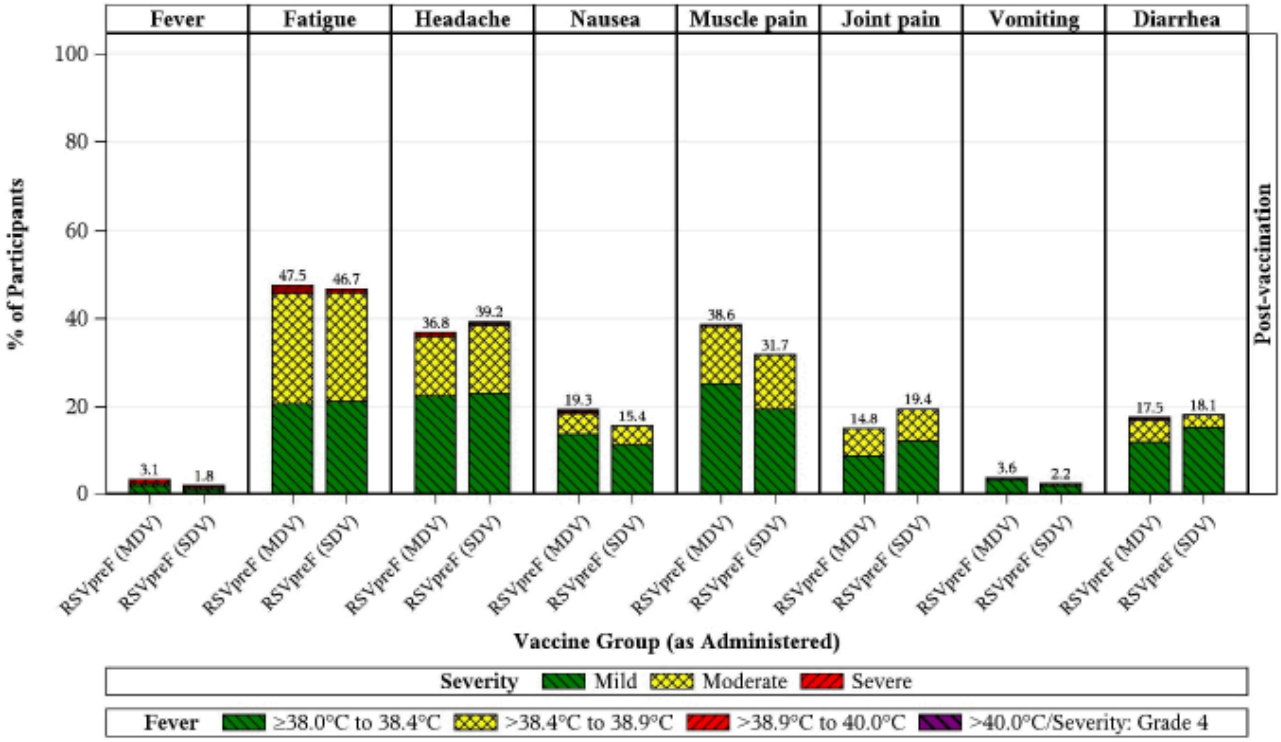
Systemic Events

The percentages of participants in the safety population who reported systemic events within 7 days after vaccination were similar for the MDV and SDV groups (68.6% and 67.4%, respectively).

For both groups, most systemic events were mild or moderate; severe systemic events were reported by 2.7% of the MDV group and 1.8% of the SDV group. Of which, there were 2 participants who reported Grade 4 systemic events: 1 participant in the MDV group reported severe events of diarrhoea and nausea on Day 1, which both escalated to Grade 4 events on Day 2 (for 1 day only), which resolved by Days 5 and 7, respectively. The same participant reported a Grade 4 event of vomiting on Day 2 which resolved in 1 day; 1 participant in the SDV group reported a severe event of headache on Day 2 which escalated to Grade 4 on Day 3 and resolved on Day 4. The most frequently reported systemic event in the MDV and SDV groups was fatigue (47.5% and 46.7%, respectively).

In the MDV and SDV groups, systemic events had a median onset day of Day 2 and Day 1, respectively (Day 1 was the day of vaccination), and events resolved with median durations of ≤2 days and ≤3 days, respectively.

Figure 7 Systemic Events, by Maximum Severity, Within 7 Days After Vaccination – Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adfacevd Table Generation: 27DEC2024 (00:07)
(Snapshot Date: 11NOV2024) Output File: ./nda mdv/C4841001 CSR/adce f001 se max

Grade 4 Reactogenicity Events

For Study C4841001, a medically attended event only refers to Grade 4 reactogenicity events (see the table below) reported during the planned e-diary period.

Medically attended events were reported by 1 participant in the MDV and SDV groups (each 0.4%). No prespecified immediate events, events leading to withdrawal, or SAEs were reported in either group.

Figure 8 Number (%) of Participants Reporting at Least 1 Prespecified Event After Vaccination – Safety Population

Prespecified Event Category	Vaccine Group (as Administered)		
	RSVpreF(MDV) (N^a=223) n^b (%)	RSVpreF(SDV) (N^a=227) n^b (%)	Total (N^a=450) n^b (%)
Immediate event	0	0	0
Event leading to withdrawal	0	0	0
Medically attended event	1 (0.4)	1 (0.4)	2 (0.4)
Serious adverse event	0	0	0

Note: Prespecified events are protocol-specified local reactions and systemic events reported in the Summary of Reactogenicity case report form during the protocol-specified collection period.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the prespecified event category.
PFIZER CONFIDENTIAL SDTM Creation: 13NOV2024 (04:07) Source Data: adsl Table Generation: 26DEC2024 (09:07)
(Database snapshot date : 11NOV2024) Output File: ./nda mdv/C4841001 CSR/adsl rc anal

Immediate AEs

Immediate AEs (onset within 30 minutes after vaccination) were not reported by any participant in the MDV group and by 1 participant (0.4%) in the SDV group (anaphylactic reaction).

Adverse Events of Special Interest

No AESIs/Tier 1 AEs (atrial fibrillation, GBS, and polyneuropathy without underlying aetiology, preterm delivery, hypertensive disorder of pregnancy) were reported during the study.

Exposure During Pregnancy

One (1) participant reported an exposure during pregnancy (pregnancy reported 34 days after receiving SDV RSVpreF, during Visit 2). The participant had a false negative pregnancy test at screening . The participant remained in the safety, evaluable immunogenicity, and mITT analysis sets, and had no protocol deviations. The participant had no systemic events, AEs, or SAEs.

At the time of this submission, the participant was not full-term. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the MAH of the outcome as a follow-up to the initial report.

6.4.6. Discontinuation due to adverse events

There were no discontinuations from the study due to AEs.

6.4.7. Safety in special populations

Not applicable. Study C4841001 enrolled nonpregnant, non-breastfeeding female participants.

6.4.8. Vital signs and laboratory findings

Clinical laboratory evaluations were not performed routinely in Study C4841001. Any abnormal laboratory values of clinical significance that came to the attention of the investigator were to be reported as AEs.

Any signs or symptoms of concern related to vital signs, physical examinations, or other safety assessments that came to the attention of the investigator were to be reported as AEs or SAEs if they occurred within the protocol-specified time frames for collection of safety information.

Vital signs were similar between the MDV and SDV groups.

6.4.9. Post-marketing experience

This section is not applicable. As the MDV presentation has not been marketed yet, there is no post-marketing experience regarding this presentation. Given the similarities of the two presentations (MDV and SDV) both in composition, and in safety and immunogenicity profiles as demonstrated by the C4841001 study, the post-marketing data from SDV RSVpreF could offer insight for MDV RSVpreF, however it is not formally assessed as part of this line extension.

6.4.10. Overall discussion and conclusions on clinical safety

6.4.10.1. Discussion

6.4.10.1.1. Overall assessment of available safety data

The known safety profile of administering a single dose of Abrysvo to pregnant women at 24-36 weeks of gestation (n=3 682) and to individuals 18 years of age and older (n=18 575) was evaluated in phase 3 clinical trials.

In pregnant women at 24-36 weeks of gestation the most frequently reported adverse reactions were vaccination site pain (41%), headache (31%) and myalgia (27%). The majority of local and systemic reactions in maternal participants were mild to moderate in severity and resolved within 2-3 days of onset.

In individuals 18 years of age and older the most frequently reported adverse reactions were fatigue (23%), headache (20%), vaccination site pain (19%) and myalgia (16%). The majority of reactions were mild to moderate in severity and resolved within 1-2 days of onset.

2-PE has been increasingly used as antimicrobial preservative in multidose vaccine formulations since the phasing-out of thiomersal that began in the 1990s, comprising also vaccines recommended for large-scale use in sensitive populations such as young infants and pregnant women (e.g. Tdap vaccine). As mentioned by the MAH, similar safety findings were observed in clinical studies comparing formulations with and without 2-PE in pregnant women (Phase 1 study with Tdap vaccine) and young infants (open-label study with MAH's Prevenar 13 pneumococcal vaccine). It can be added that a larger post-marketing safety dataset has been published for the Adacel vaccine in pregnant women (11 years of data from Adacel pregnancy registry, 1182 women). Finally, 2-PE at up to 1% concentration has been used as antimicrobial preservative in topical pharmaceuticals as well as in cosmetics for more than 10 years (EC regulation 1223/2009 on cosmetics). The preservative is discussed in full as part of

the quality and preclinical assessment, and the safety, tolerability and potential impact on immunogenicity is explored in Study C4841001.

Study C4841001 is a completed Phase 3, randomised, open-label study to evaluate the safety, tolerability, and immunogenicity of RSVpreF with 2-PE formulated in MDVs compared to RSVpreF without 2-PE formulated in SDVs. A total of 453 healthy nonpregnant, non-breastfeeding female participants 18 through 49 years of age in the US were randomized in a 1:1 ratio. The total study duration for each participant was approximately 6 weeks. Planned time points for all safety assessments are Visit 1 (prior to study vaccination), Visit 2 (1 month after vaccination) and Visit 3 (End-of-Study Visit, 42-49 days after vaccination).

In addition to adverse events (AEs, SAEs, deaths, AESI, ADRs, etc.), the MAH presented adverse events in terms of reactogenicity (local reactions, systemic events, medically attended events and immediate events).

Safety results

A total of 453 participants were randomised and 450 were vaccinated; 223 participants received MDV RSVpreF and 227 participants received SDV RSVpreF. In total, 438 participants completed the end of study visit (89.8%). There were no discontinuations from the study due to AEs.

Demographic characteristics for all participants in the safety population were in general similar between the participants who received MDV RSVpreF or SDV RSVpreF and representative of a female US population.

Most AEs were mild or moderate. From vaccination through study completion, 3 participants reported 6 SAEs, of which, only 1 SAE was considered by the investigator to be related to study intervention; the related, immediate, and Grade 3 SAE of anaphylactic reaction was reported by 1 participant in the SDV group. One participant (0.4%) in the SDV group reported a life-threatening SAE of appendicitis, which was not considered by the investigator to be related to study intervention.

The number of participants reporting any AEs from vaccination through 1 month after vaccination were similar between the MDV and SDV groups (9.0% and 8.4%, respectively). No participant reported a life-threatening AE or AESI.

From vaccination through 1 month after vaccination, participants in the MDV group, most frequently reported AEs in the SOCs of infections and infestations (3.6%) and nervous system disorders (2.2%). Among participants in the SDV group, AEs were most frequently reported in the SOCs of infections and infestations (3.1%), and nervous system disorders and investigations (each 0.9%).

There were 7 AEs reported in 6 participants that were considered by the investigator to be related to study intervention (3 participants [1.3%] in each of the MDV and SDV groups). The related AEs reported in the MDV group were brain fog (0.9%) and paraesthesia (0.4%) and in the SDV group were facial oedema, peripheral oedema, anaphylactic reaction, and dizziness (each 0.4%).

Of note, 1 participant in the SDV group reported a related, immediate, and Grade 3 SAE of anaphylactic reaction. The participant had a history of allergic reactions to multiple medications. The participant was treated at the site with improvement of symptoms, sent to the emergency room for observation, and fully recovered by the following day. The SmPC contains instructions that "appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine." Anaphylaxis is a known ADR with frequency "very rare".

Two (2) participants in the MDV group reported related, mild and moderate events of brain fog, which started on Day 3 and 2, respectively, and resolved in 2 and 4 days, respectively. The MAH was

requested to provide a brief summary of the PT brain fog in terms of the pivotal SDV data ± relevant post-marketing data. The PT 'brain fog' was searched in the Phase 3 pivotal studies C3671008 and C3671013; 2 reported AEs of 'brain fog' across these studies were retrieved. Both events were reported in Study C3671013 in older adults: 1 in a placebo recipient (assessed as related) and 1 in an RSVpreF recipient (assessed as not related). Overall in the post-marketing data, a total of 4 cases were reported, all spontaneous reports. These 4 cases are considered in the context of the 27.5 million doses of Abrysvo shipped globally as of 31 July 2025. Based on the totality of reports in a larger population size, the PT brain fog was not identified as related to the drug.

Reactogenicity

Prespecified local reactions (pain at the injection site, redness, and swelling) occurring at the RSVpreF injection site and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhoea, muscle pain, and joint pain) occurring within 7 days after vaccination were recorded daily by the participant in an e-diary.

The percentages of participants in the safety population who reported any local reactions within 7 days after vaccination were similar for the MDV group (50.2%), compared to the SDV group (55.1%). For both groups, most local reactions were mild or moderate; severe local reactions were infrequently reported by the MDV and SDV groups (each 1.3%). The most frequently reported local reaction in the MDV and SDV groups was pain at injection site (46.6% and 52.9%, respectively).

The percentages of participants in the safety population who reported systemic events within 7 days after vaccination were similar for the MDV and SDV groups (68.6% and 67.4%, respectively).

For both groups, most systemic events were mild or moderate; severe systemic events were reported by 2.7% of the MDV group and 1.8% of the SDV group. The most frequently reported systemic event in the MDV and SDV groups was fatigue (47.5% and 46.7%, respectively). Fatigue is a known ADR with an assigned frequency of "Very common".

Severe systemic events were reported by 2 participants: 1 participant in the MDV group reported severe events of diarrhoea, nausea and vomiting. 1 participant in the SDV group reported a severe event of headache. The systemic events of nausea and diarrhoea, inclusive of mild and moderate events, were reported at a frequency of approx. 15-20%. Headache is a known ADR, as outlined in the SmPC with a frequency of "very common". The MAH was requested to clarify their methodology of ADR inclusion/exclusion for these PTs in the pivotal trials to contextualise these reports in Study C4841001, in the absence of a placebo arm.

Following the MAH's review of these PTs in this context and confirmation that no signal has emerged from the post-marketing data regarding the AEs nausea, vomiting, and diarrhoea, it can be concluded that the AEs nausea, vomiting, and diarrhoea reported in Study C4841001 are consistent with the known safety profile for RSVpreF.

Immediate AEs (onset within 30 minutes after vaccination) were not reported by any participant in the MDV group and by 1 participant (0.4%) in the SDV group (anaphylactic reaction).

Reactogenicity and AEs observed in the MDV group were similar to the SDV group. Notably, there were no AESIs (including Tier 1 events of GBS, polyneuropathy, or atrial fibrillation) reported during the study.

The CHMP is of the opinion that the safety profile of MDV RSVpreF is comparable to SDV RSVpreF and consistent with the known safety profile.

6.4.10.1.2. Adverse drug reactions in the SmPC

The MAH was requested by the CHMP to clarify their methodology of ADR inclusion/exclusion for specific PTs in the pivotal trials to contextualise certain TEAE reports in Study C4841001, in the absence of a placebo arm.

Further information was requested for the TEAEs brain fog, diarrhoea, nausea and vomiting, face/peripheral oedema, dizziness and paraesthesia, in terms of the pivotal SDV data ± relevant post-marketing data.

Following the MAH's review of these PTs in this context and confirmation that no signal has emerged from the post-marketing data, the CHMP concluded that the TEAEs reported in Study C4841001 are consistent with the known safety profile for RSVpreF.

6.4.10.2. Conclusions on clinical safety

The preservative 2-phenoxyethanol (2-PE) has well-established clinical use in a number of commercially available MDV vaccines, including use in sensitive populations such as young infants and pregnant women. Study C4841001 further demonstrated that the safety profile for a dose of Abrysvo from the multidose vial with 2-PE was comparable to that from the single dose vial and was consistent with the known safety profile for RSVpreF without 2-PE.

The CHMP notes that the risk of potential of infection due to administration of a contaminated dose was not explored as part of Study C4841001. For the purposes of this study, only a single 0.5-mL dose (120 µg) was administered from each of the MDVs; the rest was discarded.

7. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.1. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

Updates to add the new formulation - multidose vial - are implemented in Sections 1, 2, 3, 4.9, 5.1, 6.1, 6.3, 6.4 and 6.6 including updates to the *Instructions for Preparation for Administration*.

While non-inferiority was pursued, the MDV formulation provides no difference in the efficacy or safety profile compared to the SDV.

8.2. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The PIL submitted as part of the current Extension Application to add the multidose presentation for Abrysvo is substantially the same as that originally tested. Importantly, there are no changes to route of administration, no new safety issues identified, and no new medical terminology requiring explanation.

As there are no significant changes, the initial user test remains valid for this PIL and no further user testing, including bridging, is considered necessary.

9. Benefit-risk assessment

The present submission seeks to add the multidose (MDV) presentation of RSVpreF to the EU marketing authorisation for Abrysvo.

Therapeutic context

Abrysvo (RSVpreF) is comprised of equal quantities of 2 recombinant RSV F antigens representing the 2 major subgroups A and B, each structurally engineered for enhanced stability in the prefusion conformation. The RSV vaccine consists of 60 micrograms RSV subgroup A stabilised prefusion F protein and 60 micrograms of RSV subgroup B stabilized prefusion F protein for a total RSV drug product dose of 120 micrograms.

Prefusion F is the primary target of neutralising antibodies that block RSV infection. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated lower respiratory tract disease. In infants born to mothers who were vaccinated with Abrysvo between weeks 24 and 36 of gestation, protection against RSV-associated lower respiratory tract disease is due to transplacental transfer of RSV neutralising antibodies.

In the EU, Abrysvo is a vaccine indicated for:

- Active immunisation of pregnant individuals to protect infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV). See sections 4.2 and 5.1.
- Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

The use of this vaccine should be in accordance with official recommendations.

9.1.1. Disease or condition, therapeutic indication

Abrysvo (also referred to as RSVpreF) was approved in the European Union on 23 August 2023, with indications for:

- Active immunisation of pregnant individuals to protect infants from birth through 6 months of age against lower respiratory tract disease caused by respiratory syncytial virus (RSV). See sections 4.2 and 5.1.
- Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

RSV is a major cause of respiratory infection in both infants and older adults. Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall. RSV has 2 subgroups, A and B, which co-circulate and either can cause severe disease. RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in very young infants, in infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems. RSV disease in older adults is associated with increased morbidity and mortality either caused by the virus itself, due to bacterial superinfection, or deterioration of already existing

chronic medical conditions. Older adults hospitalised due to RSV infection have a high morbidity and health-resource utilisation.

As noted in the recent WHO SAGE on immunisation document published online, September 2024, RSV is a leading cause of LRTI, such as bronchiolitis and pneumonia, in children globally. Nearly all children in the world are infected with RSV by their second birthday, and it is responsible for a substantial number of hospitalisations among infants under 1 year of age. A recent global burden analysis estimated 101,400 RSV-attributable deaths globally in children under 5 years of age in the year 2019, representing 2.0% of all global childhood deaths and 3.6% of all deaths in children 28 days to 6 months of age. Overall, 51% of all RSV deaths occurred in children 0-6 months of age and 97% in low- and middle-income country (LMICs).

9.1.2. Available therapies and unmet medical need

In infants, treatment of RSV disease consists primarily of supportive care (e.g., nutrition/hydration for infants who cannot maintain hydration, and supplemental oxygen). The benefit of antiviral therapy (e.g., ribavirin) for RSV is unclear, and therefore, it is rarely used to treat RSV. Paracetamol and OTC cold medications may be used to relieve milder symptoms. There is a prophylactic humanised monoclonal antibody against the RSV F glycoprotein, palivizumab, with demonstrated safety and efficacy against severe disease in high-risk infants. Nirsevimab, a next-generation single dose, extended half-life prefusion F-specific monoclonal antibody for preventative use in infants has received marketing authorisation in the EU in October 2022. In older adults, treatment of RSV disease consists primarily of supportive care (e.g., fluids, supplemental oxygen, or mechanical ventilation). Paracetamol OTC cold medications may be used to relieve milder symptoms.

Most (approximately 80%) of RSV deaths in low-middle income countries (LMICs) occur in the community, before the infant can access medical care. Additionally, an estimated 3.6 million RSV-LRTI hospitalizations and 33 million RSV-LRTI episodes occur annually in children.

Currently, RSVpreF is available preservative free as an SDV presentation. It is also currently the only licensed vaccine for maternal immunisation (there are no other maternal vaccines available, including for use in LMICs).

Vaccines are often offered in an MDV presentation for use in LMICs to meet the supply needs of national immunisation program requirements. The MAH has partnered with the Gates Foundation to increase access to immunisation in LMICs by developing an MDV presentation of RSVpreF (3 doses per vial). In SDV presentations, each dose remains sealed and protected until it is ready for administration, decreasing chances for wastage and contamination. Because each dose needs its own container, single-dose presentations typically occupy a greater volume per dose with regard to supply chain storage and medical waste disposal. This issue is a significant problem when storage and transport space are limited. The advantage of multidose vials is that they generally allow the vaccine to occupy less cold-chain capacity than single-dose presentations, therefore reducing cold-chain and storage costs. Unlike SDVs that are discarded immediately after single use, MDVs are used more than once after the vial is opened. As the multidose vaccine vial is intended for repeated use (x3 doses), a preservative, not present in the formulation of single-dose syringes, has been proposed for the multidose vial. 2-Phenoxyethanol (2-PE) is the preservative that was added to the RSVpreF MDV vaccine. This preservative is a phenolic derivative used as a preservative in a number of commercially available vaccines. Typically, the addition of a preservative such as 2-PE can prevent microbial growth,

following breaching of the sterile barrier for up to 28 days. Nevertheless, for the MDV presentation, the MAH is proposing that the vaccine be discarded 8 hr after breaching the sterile barrier.

MDV RSVpreF aims to support the clinical development of the vaccine and improve RSVpreF availability and accessibility in resource-limited countries.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer also to section 6.3.2. of this document.

Study C4841001 was a Phase 3, randomised, open-label study to evaluate the safety, tolerability, and immunogenicity of RSVpreF with 2-PE formulated in MDVs compared to SDV RSVpreF. A total of 453 healthy nonpregnant, non-breastfeeding female participants 18 through 49 years of age in the US were randomized in a 1:1 ratio. The total duration for each participant on the study was approximately 6 weeks.

For the immunogenicity analyses presented, serum samples (collected prior to study vaccination [Visit 1] and 1 month after vaccination [Visit 2]) were assayed for RSV A and RSV B–neutralising antibody titres and RSVpreF-binding IgG levels.

An e-diary was used to collect local and systemic reactogenicity event data for 7 days following study vaccination (Days 1 through 7, where Day 1 was the day of vaccination). Any reactogenicity events ongoing on the last day that the e-diary was completed, were followed up until resolution. Reported Grade 3 reactogenicity event was assessed by the study site to determine if an unscheduled visit was required.

AEs were collected from informed consent through 1 month following study intervention administration, and AESIs and SAEs were collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that were related to study procedures were collected.

A total of 453 participants were randomized and 450 were vaccinated; 223 participants received MDV RSVpreF and 227 participants received SDV RSVpreF. In total, 438 participants completed the end of study visit (89.8%). There were no discontinuations from the study due to AEs.

Demographic characteristics for all participants in the safety population were in general similar between the participants who received MDV RSVpreF or SDV RSVpreF and representative of a female US population.

9.3. Favourable effects

In the evaluable immunogenicity population of Study C4841001, the GMRs (RSVpreF (MDV)/RSVpreF (SDV)) at 1 month after vaccination were 0.96 (0.84,1.10) for RSV A and 0.91 (0.79,1.06) for RSV B. The combined RSV A/B serum NTs, of the MDV group to the SDV group at 1 month after vaccination was 0.94 (0.83,1.07). Results were similar in the mITT population.

For both RSV A and RSV B subgroups, the lower bounds of the 2-sided 95% CIs for the GMRs at 1 month after vaccination for the MDV group compared to the SDV group were greater than the predefined limit of 0.67, demonstrating noninferiority of MDV RSVpreF compared to SDV RSVpreF.

The secondary immunogenicity endpoint aimed to describe the immune response elicited by MDV RSVpreF compared to the immune response elicited by SDV RSVpreF. The secondary endpoint is defined as seroresponse rates, by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the pre-vaccination titre; or ≥4 times the LLOQ if the pre-vaccination titre is below the LLOQ.

For the evaluable immunogenicity population, the seroresponse rates at 1 month after vaccination were similar across the MDV and SDV groups for RSV A (91.7% and 91.6%, respectively), RSV B (96.8% and 90.7%, respectively), and the combined RSV A/B (96.3% and 93.9%, respectively) serum NTs. n = Number of participants meeting the seroresponse definition. Results were similar in the mITT population.

Exploratory immunogenicity endpoints (GMCs, GMRs, and GMFRs for RSVpreF-binding IgG) for the evaluable immunogenicity population, were comparable for the MDV group and the SDV group, results were similar in the mITT population.

Overall, Study C4841001 demonstrated that the multidose vial group elicited immune responses that were noninferior to those of the single dose vial group, meeting the 1.5-fold noninferiority criteria for both RSV A and RSV B based on geometric mean ratios of neutralising titres.

The proposed manufacturing process for the MDV is highly similar to the previously authorised SDV. The only major difference in manufacture between the SDV and MDV is the volume of drug product filled into the final vial. This does not result in any change to the formulation or concentration of active substance per dose in the MDV. Data provided demonstrated that all quality attributes between the SDV and MDV were comparable. Additionally, the same control strategy is applied to both presentations, ensuring a product of consistent quality will be manufactured. Therefore, from a quality perspective, there would be no anticipated differences between an SDV and MDV dose, except for the presence of 2-PE.

To support the preclinical data, a single pharmacological study (VR-VTR-11153) was conducted in non-human primates to evaluate the immunogenicity of Abrysvo with or without the 2-PE preservative. This is an immunogenicity study to evaluate the effect on the immune responses of 2-PE.

The pharmacological study in non-human primates (NHPs) evaluated RSV neutralising responses conferred by MDV RSVpreF and SDV RSVpreF. Two dose levels of 2-PE were evaluated, 5 mg (10 mg/mL) and 1 mg (2 mg/mL), and compared to a formulation containing no 2-PE. The highest dose, 5 mg, was representative of the concentration evaluated in the MDV RSVpreF safety and immunogenicity study (C4841001). The data suggest that the addition of 2-PE does not negatively impact the immunogenicity of RSVpreF. The study results provide non-clinical data to support RSVpreF multi-dose vial (MDV) development.

9.3.1. Uncertainties and limitations about favourable effects

In the MDV group, noninferiority (NI) of immune responses was demonstrated for RSV A and RSV B serum NTs based on the protocol-specified 1.5-fold margin. NI was evaluated using a 1.5-fold margin as the criterion. With the assumption of SD (ln scale) from the historical study, the overall power to demonstrate NI for both RSV A and RSV B is 90.0%.

The statistical aspect of the 1.5-fold non-inferiority margin has been adequately described. The clinical rationale for selection of the non-inferiority margin as per EMA *Guideline on Clinical Evaluation of Vaccines, EMEA/CHMP/VWP/164653/05 Rev. 1* and *EMA Guideline on the Choice of the non-inferiority*

margin, EMEA/CPMP/EWP/2158/99 in not further pursued. The chosen margins are consistent with what is generally used in vaccine trials and can therefore be deemed acceptable.

From a quality perspective, the MDV is highly comparable to the existing, authorised SDV vaccine, with the exception of the presence of a preservative.

Of note, the currently authorised Abrysvo presentation is provided in a single dose vial and sterile format, a preservative is not present and is not required. Multi dose vial vaccines introduce a potential risk of infection if a dose becomes contaminated during administration. To mitigate this potential risk, the MAH has included the preservative 2-PE in the proposed RSVpreF multi-dose vial. The use of a preservative also enables extended storage after the vial's sterile barrier has been breached, reducing product wastage. Typically, the addition of a preservative such as 2-PE can prevent microbial growth, following breaching of the sterile barrier, for up to 28 days. Nevertheless, for the MDV presentation, the MAH is proposing that the vaccine be discarded 8 hr after breaching the sterile barrier.

The choice of preservative has been based on the well-established clinical use and known safety profile of 2-PE in a number of commercially available MDV vaccines, including use in sensitive populations such as young infants and pregnant women. Licensed vaccines containing 2-PE (e.g., poliovirus vaccine inactivated); pneumococcal vaccines [Prevnar 13]; diphtheria, tetanus, and pertussis–containing vaccines [DTP and DTaP]; hexavalent vaccines) have been shown to be immunogenic with a positive benefit-risk profile.

While the MAH has adequately addressed all efficacy and safety concerns related to the 2-phenoxyethanol preservative, they are recommended to perform additional in-use stability studies in the absence of the preservative, and in accordance with Ph. Eur. 0153, to determine if the preservative is required in the context of the proposed 8-hour in-use period. Should the data demonstrate that the preservative is not adding benefit, the MAH should commit to removing the preservative from the formulation. Any proposed in-use period for the preservative free formulation should be supported with data, see recommendation for further details (See Section 2.7.7).

9.4. Unfavourable effects

In Study C4841001, most AEs were mild or moderate. From vaccination through study completion, 3 participants reported 6 SAEs, of which, only 1 SAE was considered by the investigator to be related to study intervention; the related, immediate, and Grade 3 SAE of anaphylactic reaction was reported by 1 participant in the SDV group. One participant (0.4%) in the SDV group reported a life-threatening SAE of appendicitis, which was not considered by the investigator to be related to study intervention. Anaphylaxis is a known ADR with frequency "very rare".

The number of participants reporting any AEs from vaccination through 1 month after vaccination were similar between the MDV and SDV groups (9.0% and 8.4%, respectively). No participant reported a life-threatening AE or AESI.

From vaccination through 1 month after vaccination, participants in the MDV group, most frequently reported AEs in the SOCs of infections and infestations (3.6%) and nervous system disorders (2.2%). Among participants in the SDV group, AEs were most frequently reported in the SOCs of infections and infestations (3.1%), and nervous system disorders and investigations (each 0.9%).

There were 7 AEs reported in 6 participants that were considered by the investigator to be related to study intervention (3 participants [1.3%] in each of the MDV and SDV groups). The related AEs

reported in the MDV group were brain fog (0.9%) and paraesthesia (0.4%) and in the SDV group were facial oedema, peripheral oedema, anaphylactic reaction, and dizziness (each 0.4%).

Of note, 1 participant in the SDV group reported a related, immediate, and Grade 3 SAE of anaphylactic reaction. The participant had a history of allergic reactions to multiple medications. The participant was treated at the site with improvement of symptoms, sent to the emergency room for observation, and fully recovered by the following day. The SmPC contains instructions that "appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine."

Reactogenicity

Prespecified local reactions (pain at the injection site, redness, and swelling) occurring at the RSVpreF injection site and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhoea, muscle pain, and joint pain) occurring within 7 days after vaccination were recorded daily by the participant in an e-diary.

The percentages of participants in the safety population who reported any local reactions within 7 days after vaccination were similar for the MDV group (50.2%), compared to the SDV group (55.1%). For both groups, most local reactions were mild or moderate; severe local reactions were infrequently reported by the MDV and SDV groups (each 1.3%). The most frequently reported local reaction in the MDV and SDV groups was pain at injection site (46.6% and 52.9%, respectively).

The percentages of participants in the safety population who reported systemic events within 7 days after vaccination were similar for the MDV and SDV groups (68.6% and 67.4%, respectively).

For both groups, most systemic events were mild or moderate; severe systemic events were reported by 2.7% of the MDV group and 1.8% of the SDV group. The most frequently reported systemic event in the MDV and SDV groups was fatigue (47.5% and 46.7%, respectively).

Severe systemic events were reported by 2 participants: 1 participant in the MDV group reported severe events of diarrhoea, nausea and vomiting. 1 participant in the SDV group reported a severe event of headache.

Immediate AEs (onset within 30 minutes after vaccination) were not reported by any participant in the MDV group and by 1 participant (0.4%) in the SDV group (anaphylactic reaction).

Reactogenicity and AEs observed in the MDV group were similar to the SDV group. Notably, there were no AESIs (including Tier 1 events of GBS, polyneuropathy, or atrial fibrillation) reported during the study. The safety profile of MDV RSVpreF was comparable to SDV RSVpreF and consistent with the known safety profile.

9.4.1. Uncertainties and limitations about unfavourable effects

Two (2) participants in the MDV group reported related, mild and moderate events of brain fog, which started on Day 3 and 2, respectively, and resolved in 2 and 4 days, respectively. The MAH was requested to provide a brief summary of the PT brain fog in terms of the pivotal SDV data ± relevant post-marketing data. The PT 'brain fog' was searched in the Phase 3 pivotal studies C3671008 and C3671013; 2 reported AEs of 'brain fog' across these studies were retrieved. Both events were reported in Study C3671013 in older adults: 1 in a placebo recipient (assessed as related) and 1 in an RSVpreF recipient (assessed as not related). Overall, in the post-marketing data, a total of 4 cases were reported, all spontaneous reports. These 4 cases are considered in the context of the 27.5 million

doses of Abrysvo shipped globally as of 31 July 2025. Based on the totality of reports in a larger population size, the PT brain fog was not identified as related to the drug.

Severe systemic events were reported by 2 participants: 1 participant in the MDV group reported severe events of diarrhoea, nausea and vomiting. 1 participant in the SDV group reported a severe event of headache. The systemic events of nausea and diarrhoea, inclusive of mild and moderate events, were reported at a frequency of approx. 15-20%. Headache is a known ADR, as outlined in the SmPC with a frequency of "very common".

Following the MAH's review of the PTs nausea, vomiting, and diarrhoea in the context of the pivotal trial data and confirmation that no signal has emerged from the post-marketing data regarding the AEs nausea, vomiting, and diarrhoea, it can be concluded that the AEs nausea, vomiting, and diarrhoea reported in Study C4841001 are consistent with the known safety profile for RSVpreF.

The MAH was requested to clarify their methodology of ADR inclusion/exclusion for specific PTs in the pivotal trials to contextualise certain TEAE reports in Study C4841001, in the absence of a placebo arm. Further information was requested for the TEAEs brain fog, diarrhoea, nausea and vomiting, face/peripheral oedema, dizziness and paraesthesia, in terms of the pivotal SDV data ± relevant post-marketing data.

Following the MAH's review of these PTs in this context and confirmation that no signal has emerged from the post-marketing data, it can be concluded that the TEAEs reported in Study C4841001 are consistent with the known safety profile for RSVpreF.

Study C4841001 demonstrated comparable safety and tolerability profiles between the RSVpreF with 2-PE formulated in MDVs compared to RSVpreF without 2-PE formulated in SDVs.

9.5. Effects Table

Table 19: Effects Table for Abrysvo, RSVpreF (data cut-off: {20 September 2024}).

Effect (short description)	Treatment	Comparison	Uncertainties/ Strength of evidence	Ref
Favourable Effects				
Primary endpoint- the GMR, estimated by the ratio of the GMTs for RSV A, RSV B, and the combined RSV A/B serum NTs, of the MDV group to the SDV group at 1 month after vaccination				
RSV Subgroup (1 month after vaccination)	**Neutralizing Titres, GMR (95% CI) RSVpreF (MDV)/ SVpreF (SDV)**		**SoE:** the lower bounds of the 2-sided 95% CIs for the GMRs at 1 month after vaccination for the MDV group compared to the SDV group were greater than the predefined limit of 0.67, demonstrating noninferiority of MDV RSVpreF compared to SDV RSVpreF. Results were similar in the mITT population. **Unc:** Clinical justification to support the chosen NI margin	Study C4841001
A	0.96 (0.84,1.10)			
B	0.91 (0.79,1.06)			
A/B	0.94 (0.83,1.07)			
Secondary endpoint- Seroresponse Rates for RSV A and B Serum NTs – 1 Month After Vaccination. Seroresponse is defined as achieving a ≥4-fold rise from baseline (before vaccination)				

Effect (short description)	Treatment	Comparison	Uncertainties/ Strength of evidence	Ref
RSV subgroup	**RSVpreF (MDV) (%) (95%CI)**	**RSVpreF (SVD) (%)(95%CI)**	**SoE:** seroresponse definition in line with EMA guidance EMEA/CHMP/VWP/164653 /05 Rev. 1	Study C484 1001
A	91.7% (87.3, 95.0)	91.6% (87.0, 94.9)		
B	96.8% (93.5, 98.7)	90.7% (86.0, 94.2)		
A/B	96.3% (92.9, 98.4)	93.9% (89.8, 96.7)		
Unfavourable Effects				
	MDV group	**SVD group**		
The number of participants reporting any AEs through 1 month after vaccination	9.0%	8.4%	**SoE:** Character and frequency of unfavourable effects are generally comparable between the MDV and SVD groups	Study C484 1001
SAEs	0.4%	0.9%		
AESIs/Tier 1 events/ Deaths	Nil	Nil		
Local reactions	50.2%	55.1%		
Systemic reactogenicity events	68.6%	67.4%		

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; SAE = serious adverse event; ADR = Adverse Drug Reaction; RSVpreF = respiratory syncytial virus stabilized prefusion F subunit vaccine; PT = preferred term

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The present submission seeks to add an MDV presentation of RSVpreF to the EU marketing authorisation for Abrysvo. The aim of multidose vials is to allow the vaccine to occupy less cold-chain capacity than single-dose presentations, thereby reducing cold-chain and storage costs, which is critical for the intended use in low-middle income countries.

Study C4841001, a Phase 3, randomised, open-label study, was submitted in support of the submission. Results demonstrated that the multidose vial group elicited immune responses that were noninferior to those of the single dose vial group, meeting the 1.5-fold noninferiority criteria for both RSV A and RSV B, a comparable safety profile was also demonstrated.

The MAH also submitted a preclinical (VR-VTR-11153) study supporting that the addition of 2-PE does not negatively impact the immunogenicity of RSVpreF.

From a quality perspective, there are no anticipated differences between the SDV and MDV dose, except for the presence of 2-PE. The choice of preservative has been based on the well-established

clinical use and known safety profile of 2-PE in a number of commercially available MDV vaccines, including use in sensitive populations such as young infants and pregnant women.

While the MAH has adequately addressed all efficacy and safety concerns related to the 2-phenoxyethanol preservative, further data is required to demonstrate the additional benefit of the preservative in the context of the proposed in-use storage time of 8 hours.

The MAH is therefore recommended to perform additional in-use stability studies in the absence of the preservative and in accordance with Ph. Eur. 0153, to determine if the preservative is required in the context of the proposed 8-hour in-use period. Should the data demonstrate that the preservative is not adding benefit, the MAH should commit to removing the preservative from the formulation. Any proposed in-use period for the preservative free formulation should be supported with data, see the recommendation for further details.

9.6.2. Balance of benefits and risks

Based on the preclinical, quality and clinical data presented by the MAH, the CHMP is of the opinion that the benefits of the MDV presentation of RSVpreF with 2-phenoxyethanol outweigh the risks, and that the benefit-risk is positive.

9.7. Benefit-risk conclusions

The CHMP is of the opinion that the benefit-risk of the MDV presentation of RSVpreF with 2-PE is positive.