27 February 2025
EMA/109450/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Abrysvo

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

Procedure No. EMEA/H/C/006027/II/0007

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
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
$Al(OH)_3$	aluminum hydroxide
ANCOVA	analysis of covariance
CHF	chronic heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
DS-Cav 1	incompletely stabilized RSV F
ED	emergency department
F1	offspring
FDA	Food and Drug Administration
FIH	first in human
GBS	Guillain-Barre Syndrome
GLP	Good Laboratory Practices
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
GP	general practitioner
IM	intramuscular
LLOQ	lower limit of quantification
LPLV	last participant last visit
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract illness
LRTI-RSV	respiratory syncytial virus associated lower respiratory tract illness
LS	least square
MA-LRTI	medically-attended lower respiratory tract illness
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMWR	Morbidity and Mortality Weekly Report
NDCMC	newly diagnosed chronic medical condition
NIH	National Institutes of Health
NT	neutralizing titer
PCR	polymerase chain reaction
PVP	Pharmacovigilance Plan
RMP	Risk Management Plan
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus bivalent stabilized prefusion F subunit vaccine
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCS	Summary of Clinical Safety
SIIV	seasonal inactivated influenza vaccine
SOC	System Organ Class
SSA	Substudy A
T4	bacteriophage T4
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
Tris	tris(hydroxymethyl)aminomethane
UK	United Kingdom
ULOQ	upper limit of quantification
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe Ma EEIG submitted to the European Medicines Agency on 30 May 2024 an application for a variation:

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The MAH proposes an extension of indication to include active immunisation of individuals 18 through 59 years of age for ABRYSVO, based on final results from C3671023 Substudy A. This is a Phase 3 double-blinded, randomised, placebo-controlled study of safety, tolerability and immunogenicity of Abrysvo in participants ≥18 to <60 years of age at high risk of severe RSV disease due to certain chronic medical conditions. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

In this context, the requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0058/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity and similarity

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Daniela Philadelphy

Timetable	Actual dates
Submission date	30 May 2024
Start of procedure:	22 June 2024
CHMP Rapporteur Assessment Report	2 August 2024
PRAC Rapporteur Assessment Report	20 August 2024
PRAC members comments	28 August 2024
CHMP Co-Rapporteur Assessment	28 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	09 September 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 September 2024
Request for supplementary information (RSI)	19 September 2024
CHMP Rapporteur Assessment Report	7 November 2024
PRAC Rapporteur Assessment Report	19 November 2024
PRAC members comments	20 November 2024
Updated PRAC Rapporteur Assessment Report	21 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	02 December 2024
Updated CHMP Rapporteur Assessment Report	5 December 2024
2nd Request for supplementary information (RSI)	12 December 2024
PRAC Rapporteur Assessment Report	15 January 2025
CHMP Rapporteur Assessment Report	15 January 2025
PRAC members comments	20 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	23 January 2025
Updated PRAC Rapporteur Assessment Report	23 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	11 February 2025
PRAC Rapporteur Assessment Report	12 February 2025
PRAC members comments	17 February 2025
CHMP members comments	17 February 2025
Updated CHMP Rapporteur Assessment Report	20 February 2025
Updated PRAC Rapporteur Assessment Report	20 February 2025
Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

The initial approval of Abrysvo resulted in the following indications for use:

- Passive protection against lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age following maternal immunisation during pregnancy.
- Active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV.

Thus, the current indication covers use in adults aged <60 years only with respect to use in pregnant women to protect their infants in the first 6 months of life.

The MAH proposes to extend use of the licensed vaccine and recommended posology in adults to include all persons aged from 18 years.

The submission is based on safety and immunogenicity data obtained from C3671023 Substudy A, which was a double-blind, randomised, placebo-controlled study that enrolled adults aged 18-59 years at high risk for severe RSV disease due to underlying chronic medical conditions (including COPD, asthma and CHF). In line with the guideline on clinical evaluation of vaccines, efficacy of Abrysvo in this age range is inferred by immunobridging to the C3671013 pivotal efficacy study conducted in participants ≥60 years of age with and without chronic medical conditions.

2.1.1. About the product

The product is unchanged. The approved vaccine is intended for use in all adults.

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not obtain scientific advice specific to this variation application.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

This variation is based on inferring efficacy in adults aged 18-59 years by immunobridging to study C3671013 and provision of safety data in adults aged from 18-59 years in the studies listed below.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. There are statements to this effect in each CSR.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Please note that the new immunogenicity data come from C3671023 Substudy A, which also provides safety data from 678 adults. Comparisons are made with immunogenicity data in C2671013 and 1014.

The dossier includes pooled safety data from 9916 adults aged 18-59 years (including C3671013). The total includes safety data from 9238 such adults included in the other 6 studies listed below (4964 who received RSVpreF 120 µg and 4274 who received placebo, SIIV or Tdap).

Table 1 Studies

Protocol No. (Country)	Study Design and Objective	Study Population	Treatment Groups / No. of Participants (by Treatment Group; R/T/C[a])	Demographics (by Treatment Group)	Study Start/Status	Study Synopsis
C3671023 Substudy A (US Study)	A Phase 3 protocol to evaluate the safety, tolerability, and immunogenicity of respiratory syncytial virus (RSV) prefusion F subunit vaccine in adults at high risk of severe RSV disease **Primary Objectives** • To describe the safety profile of RSVpreF as measured by the percentage of participants 18 through 59 years of age with high-risk chronic medical conditions reporting local reactions, systemic events, AEs, and SAEs following study intervention administration • To demonstrate that the immune responses elicited by RSVpreF in adults 18 through 59 years of age with high-risk chronic medical conditions are noninferior to the immune responses in vaccinated adults ≥60 years of age in Study C3671013 **Secondary Objective** • To describe the immune responses elicited by RSVpreF in adults 18	Immunocompetent male and female participants 18-59 years of age considered to be at high risk of severe RSV disease due to certain chronic medical conditions, including chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus and hyper/hypothyroidism)	• RSVpreF 120 µg R/T/C: 454/453/432 • Placebo R/T/C: 227/225/218	RSVpreF 120 µg Sex: 193 M / 260 F Age [mean/median (min/max)]: 46.8 / 49.0 (18, 59) years Race (W/B/O): 312/106/35 Placebo Sex: 73 M / 152 F Age [mean/median (min/max)]: 46.4 / 49.0 (20, 59) years Race (W/B/O): 152/57/16	11 May 2023 Completed 13 March 2024	C3671023 Substudy A Synopsis
	through 59 years of age with high-risk chronic medical conditions					

C3671014 (US study)	A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of 3 lots of respiratory syncytial virus (RSV) prefusion F subunit vaccine in healthy adults. **Primary Objectives** • To demonstrate that the immune responses induced by 3 RSVpreF lots (Groups 1, 2, and 3) 1 month after vaccination are equivalent. • To evaluate the safety and tolerability profiles of 3 RSVpreF lots (Groups 1, 2, and 3). **Exploratory Objective** • To further evaluate the immune responses induced by 3 RSVpreF lots.	Healthy male and female participants 18 to ≤49 years of age	• Placebo R/T/C: 247/247/243 • RSVpreF 120 µg Lot 1 R/T/C: 249/249/243 • RSVpreF 120 µg Lot 2 R/T/C: 247/247/239 • RSVpreF 120 µg Lot 3 R/T/C: 250/249/245	Placebo Sex: 107 M / 140 F Age [mean/median (min/max)]: 34.5 / 35.0 (18, 49) years Race (W/B/O): 178/48/21 RSVpreF 120 µg Lot 1 Sex: 111 M / 138 F Age [mean/median (min/max)]: 34.2 / 35.0 (18, 49) years Race (W/B/O): 169/53/27 RSVpreF 120 µg Lot 2 Sex: 89 M / 158 F Age [mean/median (min/max)]: 33.8 / 33.0 (18, 49) years Race (W/B/O): 177/53/17 RSVpreF 120 µg Lot 3 Sex: 92 M / 157 F Age [mean/median (min/max)]: 33.9 / 34.0 (18, 49) years Race (W/B/O): 179/50/20	21 October 2021 Completed 04 April 2022	C3671014 Synopsis
WI257521 (UK study)	A Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, immunogenicity and efficacy of a respiratory syncytial virus vaccine (RSVpreF) in a virus challenge model in healthy adults **Primary Objective** • To evaluate the effect of RSVpreF, in reducing the incidence or severity of infection or disease due to RSV-A Memphis 37b when compared to placebo	Healthy male and/or female participants 18-50 years of age	Placebo R/T/Ch/C[b]: 35/35/31/30 RSVpreF 120 µg R/T/Ch/C: 35/35/31/30	Placebo Sex: 25 M / 10 F Age [mean/median (min/max)]: 27.1 / 26.0 (20, 50) years Race (W/B/O): 34/0/1 RSVpreF 120 µg Sex: 25 M / 10 F Age [mean/median (min/max)]: 26.0 / 24.0 (19, 47) years Race (W/B/O): 31/1/3	21 September 2020 Completed 08 April 2021	WI257521 Synopsis
C3671004 (US study)	A Phase 2b, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of a respiratory syncytial virus (RSV) vaccine when administered concomitantly with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy nonpregnant women 18 through 49 years of age. **Primary Objectives** • To demonstrate the immune responses induced by Tdap when administered concomitantly with RSVpreF (RSVpreF/Tdap) are noninferior to the immune responses induced by Tdap alone (placebo/Tdap). • To demonstrate that the immune responses induced by RSVpreF (RSV A and B	Healthy nonpregnant female participants 18-49 years of age	• RSVpreF 120 µg + Placebo R/T/C: 143/141/140 • RSVpreF 120 µg + Tdap R/T/C: 143/141/139 • RSVpreF 240 µg + $Al(OH)_3$ + Placebo R/T/C: 143/143/140 • RSVpreF 240 µg + $Al(OH)_3$ + Tdap R/T/C: 143/143/140 • Placebo + Tdap R/T/C: 141/141/136	Placebo + Tdap Sex: 141 F Age [mean/median (min/max)]: 34.4 / 35.0 (18, 49) years Race (W/B/O): 97/38/6 RSVpreF 120 µg + Placebo Sex: 141 F Age [mean/median (min/max)]: 35.6 / 39.0 (19, 49) years Race (W/B/O): 100/29/12 RSVpreF 120 µg + Tdap Sex: 141 F Age [mean/median (min/max)]: 35.7 / 38.0 (18, 49) years Race (W/B/O): 98/28/15 RSVpreF 240 µg + $Al(OH)_3$ + Placebo Sex: 142 F Age [mean/median (min/max)]: 36.0 / 37.0 (18, 49) years	01 October 2019 Completed 11 December 2019	C3671004 Synopsis

	antigens) when administered concomitantly with Tdap (RSVpreF/Tdap) are noninferior to the immune responses induced by RSVpreF alone (RSVpreF/placebo). • To evaluate the acceptability of the safety and tolerability profile of RSVpreF when administered concomitantly with Tdap and when RSVpreF is administered alone.			Race (W/B/O): 101/25/16 RSVpreF 240 µg + $Al(OH)_3$ + Tdap Sex: 144 F Age [mean/median (min/max)]: 36.1 / 38.0 (18, 49) years Race (W/B/O): 107/29/8		
C3671001 (Final CSR) C3671001 (sCSR) (US study)	A Phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding, first-in-human study to describe the safety, tolerability, and immunogenicity of a respiratory syncytial virus (RSV) vaccine in healthy adults Primary Objective • To describe the safety and tolerability of RSVpreF given alone or concomitantly with SIIV.	Healthy male and female participants 18-85 years of age	Sentinel Cohort (Vaccination 1) 18-49 years of age • RSVpreF 60 µg R/T/C: 12/12/12 • RSVpreF 60 µg + $Al(OH)^3$ R/T/C: 12/12/12 • RSVpreF 120 µg R/T/C: 12/12/11 • RSVpreF 120 µg + $Al(OH)^3$ R/T/C: 12/12/12 • RSVpreF 240 µg R/T/C: 12/12/11 • RSVpreF 240 µg +	Sentinel Cohort (Vaccination 1) 18-49 years of age Sex: 28 M / 56 F Age [mean/median (min/max)]: 35.7 / 37.0 (18, 49) years Race (W/B/O): 61/15/8 50-85 years of age Sex: 32 M / 52 F Age [mean/median (min/max)]: 63.3 / 62.0 (50, 85) years Race (W/B/O): 61/13/10	18 April 2018 Completed 20 November 2019 Expanded Cohort (Revaccination) 18 April 2018 Completed 28 December 2020	C3671001 Final Synopsis C3671001 Suppl Synopsis
C3671008 (Final CSR) (Global study: Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland,	**Primary Objectives (Infant)** • To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV. • To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV. • To describe the safety of RSVpreF.		**Randomized)** Placebo E/C*: 3647/1643 RSVpreF 120 µg E/C*: 3660/1656	RSVpreF 120 µg Sex: 3698 F Age [mean/median (min/max)]: 29.0 / 29.0 (16, 45) years Race (W/B/O): 2397/720/581 **Infant Participants (As Administered)** Placebo		C3671008 Synopsis (Final)
C3671003 (Final CSR) C3671003 (Suppl CSR)	A Phase 2b, randomized, placebo controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of a respiratory syncytial virus (RSV) vaccine in pregnant	Healthy pregnant women 18 through 49 years of age, and between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination	**Maternal Participants** • RSVpreF 120 µg R/T/C: 116/115/107 • RSVpreF 120 µg + $Al(OH)_3$ R/T/C: 117/117/107	**Maternal Participants** RSVpreF 120 µg Sex: 115 F Age [mean/median (min/max)]: 26.9 / 28.0 (18, 36) years Race (W/B/O): 85/25/5	07 August 2019 Completed 30 September 2021	C3671003 Synopsis (Final)
(Global Study: US, Argentina, Chile, South Africa)	women 18 through 49 years of age and their infants. **Primary Objective (Maternal)** • To describe the safety and tolerability of an RSV vaccine.		• RSVpreF 240 µg R/T/C: 116/116/108 • RSVpreF 240 µg + $Al(OH)_3$ R/T/C: 115/114/100 • Placebo R/T/C: 117/117/99	RSVpreF 120 µg + $Al(OH)_3$ Sex: 117 F Age [mean/median (min/max)]: 27.7 / 27.0 (18, 39) years Race (W/B/O): 86/25/6		C3671003 Synopsis (Suppl)

2.4. Clinical efficacy

2.4.1. Main study

C3671023 Substudy A Final Analysis: A Phase 3 Protocol to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults at High Risk of Severe RSV Disease

Methods

C3671023 Substudy A was a Phase 3, multicentre, randomised, double-blind and placebo-controlled study to assess the safety and immunogenicity of RSVpreF in adults aged 18-59 years considered to be at high risk of severe RSV disease due to chronic medical conditions. These conditions included chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic or metabolic disorders (including diabetes mellitus).

Substudy A was conducted at 27 sites in the US with initiation (FPFV) on 11 May 2023. The interim full CSR for Substudy A (Version 1.0) is included in the application dossier. This is dated 12 April 2024, approved 13 April 2024, and it contains data based on a cut-off (LPLV) on 13 March 2024.

The CSR for Substudy A final analysis includes:

- Immune responses at 1 month after vaccination with RSVpreF compared to those in participants aged 60+ years in the C3671013 efficacy study (serology samples were tested concurrently);
- Safety analyses up to 6 months after receipt of RSVpreF, which was the LPLV date.

Study participants

Eligible adults were immunocompetent and aged 18-59 years considered to be at high risk of severe RSV disease by virtue of the following:

- Chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, haematologic or metabolic disorders (including diabetes mellitus and hyper or hypothyroidism).
- Residents of nursing homes and other long-term care facilities.

Chronic medical conditions were defined as:

- Duration greater than 6 months.
- Stable disease not requiring a significant change in therapy in the previous 6 weeks or hospitalisation for worsening disease within 12 weeks before receipt of study intervention.
- Requiring regular medical follow-up or ongoing medication or hospitalisation in the previous year.

Excluded were individuals with a serious chronic disorder (including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease) and immunocompromised individuals with known or suspected immunodeficiency.

Treatments

Study intervention was a single IM injection of either RSVpreF 120 μg vaccine from a single lot or placebo (excipients without antigens), each supplied as a lyophilized white cake in a glass vial.

For reconstitution, a prefilled syringe containing diluent of sterile water and a vial adapter were used.

Objectives

Table 2 C3671023 Substudy A Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary Safety Section 5.2		
• To describe the safety profile of RSVpreF as measured by the percentage of participants 18 through 59 years of age with high-risk chronic medical conditions 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, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) • AEs • NDCMCs • SAEs	In participants receiving 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 NDCMCs throughout the study.
		• The proportion of participants reporting SAEs throughout the study.
Primary Immunogenicity Section 5.1.1		
• To demonstrate that the immune responses elicited by RSVpreF in adults 18 through 59 years of age with high-risk chronic medical conditions are noninferior to the immune responses in vaccinated adults ≥60 years of age in Study C3671013.	RSV A and RSV B serum NTs	In participants who received RSVpreF 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 Study C3671023 participants to that in Study C3671013 adults ≥60 years of age. • Difference in seroresponse rate of RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF between participants in Study C3671023 and in Study C3671013. Seroresponse was defined as a postvaccination NT ≥4 times the LLOQ if baseline titer was below the LLOQ, or a ≥4-fold rise from baseline if the baseline titer was above the LLOQ.

Secondary Immunogenicity Section 5.1.2		
• To describe the immune responses elicited by RSVpreF in adults 18 through 59 years of age with high-risk chronic medical conditions.	RSV A and RSV B serum NTs	In participants in compliance with the key protocol criteria (evaluable immunogenicity population): • GMT of NTs for RSV A and RSV B at each blood sampling visit. • GMFR of NTs for RSV A and RSV B from before vaccination to the postvaccination blood sampling visit.

Outcomes/endpoints

The duration of study participation was 6 months, with 3 scheduled visits at pre-vaccination (Day 1; also day of vaccination), one month post-vaccination and 6 months post-vaccination.

Participants had blood drawn at baseline prior to vaccination and at 1 month after vaccination to assess immunogenicity. The post-vaccination immune responses were used to immunobridge from adults 18-59 years to ~400 randomly selected participants who received RSVpreF in the C3671013 efficacy study and were included in the evaluable immunogenicity population.

The sera from C3671023 Substudy A and the randomly selected RSVpreF recipients in C3671013 were tested concurrently. The assays were previously described and assessed.

An e-diary was used to collect local reaction and systemic event data for 7 days after study vaccination (Days 1 through 7, where Day 1 was the day of vaccination). Reported Grade 3 reactogenicity was assessed by the study site to determine if an unscheduled visit was required. AEs were collected through 1 month following study intervention administration. Adverse events of special interest (AESIs), NDCMCs and SAEs were collected throughout study participation. In addition, AEs occurring up to 48 hours after blood draws that were related to study procedures were collected.

The following events were considered AESIs per protocol and were reported as an AE or SAE: diagnosis of Guillain-Barre syndrome; diagnosis of acute polyneuropathy without an underlying aetiology; diagnosis of atrial fibrillation; preterm delivery; diagnosis of a hypertensive disorder of pregnancy.

Sample size

The sample size of Substudy A was based on demonstrating noninferiority with respect to RSV A and RSV B serum 50% NTs from participants who received RSVpreF compared to RSVpreF-vaccinated older adults from the C3671013 efficacy study. Approximately 675 participants were planned to be enrolled with a comparison of NTs vs. ~400 from the Study C3671013 immunogenicity subset.

Randomisation

There was central randomisation using an IRT system. There was 2:1 randomisation but there was no stratification factor applied at randomisation.

Blinding (masking)

Substudy A was double blind and placebo-controlled.

Statistical methods

Safety Analyses
The AE analyses were based on the safety population (all-treated) and reactogenicity analyses were based on the e-diary safety population (at least 1 day of e-diary data transmitted). A 3-tier approach was used to summarise AEs. Tier 1 events are pre-specified events of clinical importance that are maintained in a list in the product safety review plan. These include Guillain-Barre syndrome, acute polyneuropathy, atrial fibrillation, preterm delivery, preterm birth and hypertensive disorders of pregnancy.

Immunogenicity Analyses
The primary analyses for immunogenicity endpoints were based on the evaluable immunogenicity population. Additionally, some analyses were performed based on the modified intent-to-treat (mITT) population for C3671023 Substudy A. All C3671013 participants included in these analyses were from the evaluable immunogenicity population. Seroresponse at 1 month after vaccination was defined as a postvaccination antibody titre ≥4 times the LLOQ for a baseline titre below the LLOQ, or a ≥4-fold rise from baseline to after vaccination if the baseline titre was above the LLOQ.

Statistical Hypotheses
For the primary immunogenicity objective, there were 4 tests (2 for RSV A and 2 for RSV B). The primary immunogenicity objective was evaluated by the following null hypothesis:

- H_0: $\ln(\mu_1) - \ln(\mu_2) \leq -\ln(1.5)$ or $p_1 - p_2 \leq -10\%$ vs
- H_a: $\ln(\mu_1) - \ln(\mu_2) > -\ln(1.5)$ and $p_1 - p_2 > -10\%$

Where:

- $\ln(1.5)$ corresponds to a 1.5-fold margin for noninferiority in GMR
- $\ln(\mu_1)$ is the mean of the natural logarithm-transformed serum NT at 1 month after vaccination from participants who received the same dose level of RSVpreF in this study
- $\ln(\mu_2)$ is the mean of the natural logarithm-transformed serum NT from participants who received RSVpreF in the C3671013 immunogenicity subset
- 10% is a noninferiority margin for seroresponse rate
- p_1 is the seroresponse rate at 1 month after vaccination who received RSVpreF and have high-risk chronic medical conditions
- p_2 is the seroresponse rate at 1 month after vaccination from participants who received RSVpreF in the C3671013 study immunogenicity subset.

Statistical Analyses

The primary analyses for the comparison of GMT for RSV A and RSV B serum NTs included model-adjusted GMRs at 1 month after vaccination based on ANCOVA model with logarithmically transformed assay results at 1 month after vaccination as dependent variables, including groups (C3671023 Substudy A versus Study C3671013), baseline assay results (in a logarithmic scale) and sex, in order to control for
potential postvaccination immune response variability across participants within C3671023 Substudy A and the C3671013 efficacy study immunogenicity subset.

Seroresponse rate differences were provided with 2-sided 95% confidence intervals (CIs) using the Miettinen and Nurminen method.

Noninferiority would be declared if both the lower bounds of the 95% adjusted GMRs were >0.667 and the lower bounds of the 95% of seroresponse rates differences were >-10% for both RSV A and RSV B. Hence there were 4 co-primary endpoints.

Results

Participant flow

There were 681 participants randomised into the study of which 99.6% received study intervention. In the RSVpreF and placebo groups, 95.2% and 96.0%, respectively, completed the 6-month safety follow-up visit. Across vaccine groups, 4.1% discontinued after vaccination; the most common reason was lost to follow-up (2.9%). Two (1 in each group) had AEs leading to discontinuation and one in the RSVpreF group died (considered unrelated).

Table 3 Disposition of All Participants

Table 3. Disposition of All Participants

	Vaccine Group (as Randomized)		
	RSVpreF n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Enrolled[b]			711
Randomized[c]	454	227	681
Not vaccinated	1 (0.2)	2 (0.9)	3 (0.4)
Vaccinated	453 (99.8)	225 (99.1)	678 (99.6)
Completed the study	432 (95.2)	218 (96.0)	650 (95.4)
Discontinued after vaccination	21 (4.6)	7 (3.1)	28 (4.1)
Reason for discontinuation			
Adverse event	1 (0.2)	1 (0.4)	2 (0.3)
Death	1 (0.2)	0	1 (0.1)
Lost to follow-up	16 (3.5)	4 (1.8)	20 (2.9)
Physician decision	1 (0.2)	0	1 (0.1)
Withdrawal by subject	2 (0.4)	2 (0.9)	4 (0.6)
Completed 6-month safety follow-up visit	432 (95.2)	218 (96.0)	650 (95.4)

a. n = Number of participants with the specified characteristic.
b. Enrolled participants are all who signed an informed consent document.
c. The values in this row are used as the denominators for the percentage calculations.

Conduct of the study

Overall, few important PDs occurred in either vaccine group and all were related to inclusion and exclusion criteria Three participants with important PDs (1 in the RSVpreF group who should have been excluded due to a pre-existing condition and 2 in the placebo group without a qualifying underlying condition) were excluded from the evaluable immunogenicity population.

Baseline data

Overall, demographic and baseline characteristics of the safety population were balanced for the RSVpreF and placebo groups.

Table 4 Demographic and baseline characteristics – Safety Population

	Vaccine Group (as Administered)		
	RSVpreF (N*=453) n[b] (%)	Placebo (N*=225) n[b] (%)	Total (N*=678) n[b] (%)
Sex			
Male	193 (42.6)	73 (32.4)	266 (39.2)
Female	260 (57.4)	152 (67.6)	412 (60.8)
Race			
White	312 (68.9)	152 (67.6)	464 (68.4)
Black or African American	106 (23.4)	57 (25.3)	163 (24.0)
Asian	24 (5.3)	9 (4.0)	33 (4.9)
Not reported	5 (1.1)	5 (2.2)	10 (1.5)
Multiracial	3 (0.7)	1 (0.4)	4 (0.6)
Native Hawaiian or Other Pacific Islander	2 (0.4)	1 (0.4)	3 (0.4)

American Indian or Alaska Native	1 (0.2)	0	1 (0.1)
Ethnicity			
Non-Hispanic/non-Latino	348 (76.8)	175 (77.8)	523 (77.1)
Hispanic/Latino	102 (22.5)	48 (21.3)	150 (22.1)
Not reported	3 (0.7)	2 (0.9)	5 (0.7)
Age at vaccination (years)			
n	453	225	678
Mean (SD)	46.8 (9.9)	46.4 (10.5)	46.7 (10.1)
Median	49.0	49.0	49.0
(Min, max)	(18, 59)	(20, 59)	(18, 59)
18-49 years	240 (53.0)	113 (50.2)	353 (52.1)
50-59 years	213 (47.0)	112 (49.8)	325 (47.9)
With at least 1 prespecified medical condition[c]	453 (100.0)	223 (99.1)	676 (99.7)
Chronic pulmonary conditions	239 (52.8)	116 (51.6)	355 (52.4)
COPD	25 (5.5)	11 (4.9)	36 (5.3)
Asthma	198 (43.7)	88 (39.1)	286 (42.2)
Other lung disease	47 (10.4)	26 (11.6)	73 (10.8)
Cardiovascular conditions	38 (8.4)	16 (7.1)	54 (8.0)
CHF	9 (2.0)	3 (1.3)	12 (1.8)
CAD	19 (4.2)	4 (1.8)	23 (3.4)
Other heart disease	19 (4.2)	12 (5.3)	31 (4.6)
Diabetes	189 (41.7)	101 (44.9)	290 (42.8)
Other	139 (30.7)	68 (30.2)	207 (30.5)
Liver disease	20 (4.4)	13 (5.8)	33 (4.9)
Renal disease	17 (3.8)	4 (1.8)	21 (3.1)
Neurologic disease	16 (3.5)	1 (0.4)	17 (2.5)
Hematologic disease	6 (1.3)	7 (3.1)	13 (1.9)
Other metabolic disease	91 (20.1)	51 (22.7)	142 (20.9)
Tobacco use			
Current	78 (17.2)	39 (17.3)	117 (17.3)
Former	101 (22.3)	39 (17.3)	140 (20.6)
Never	274 (60.5)	147 (65.3)	421 (62.1)
Respiratory rate at baseline (breaths/min)			
n	453	225	678
Mean (SD)	15.6 (1.9)	15.7 (2.0)	15.6 (2.0)
Median	16.0	16.0	16.0

Females comprised 57.4% of the RSVpreF group and 67.6% of the placebo group. The median age at vaccination was 49.0 years, with 52.1% 18-49 years and 47.9% 50-59 years. The prespecified medical conditions that predisposed to an increased incidence rate and risk for severe complications from RSV infection were generally similar between groups. The most common were chronic pulmonary conditions and diabetes. None of the participants were residents of nursing homes or other long-term care facilities.

For the primary immunogenicity analyses, 410 participants in C3671013 were randomly selected among RSVpreF recipients in the evaluable immunogenicity population. The table below compares the data for those included in immunogenicity analyses (C3671023 high-risk adults 18-59 years of age and C3671013 adults ≥60 years). Note 44.4% of controls 60+ years had at least one pre-specified medical condition.

Table 5 Demographic and Baseline Characteristics – Participants 18 Through 59 Years at High Risk (D3671023 SSA) and Participants ⩾60 Years (C3671013) – Evaluable Immunogenicity Population

	Population Group	
	C3671023 SSA RSVpreF 18-59 Years at High Risk (N*=437) n[b] (%)	C3671013 RSVpreF ≥60 Years (N*=410) n[b] (%)
Sex		
Male	185 (42.3)	269 (65.6)
Female	252 (57.7)	141 (34.4)
Race		
White	302 (69.1)	134 (32.7)
Black or African American	102 (23.3)	79 (19.3)
Asian	22 (5.0)	189 (46.1)
Not reported	5 (1.1)	5 (1.2)
Multiracial	3 (0.7)	0
Native Hawaiian or Other Pacific Islander	2 (0.5)	1 (0.2)
American Indian or Alaska Native	1 (0.2)	1 (0.2)
Unknown	0	1 (0.2)
Ethnicity		
Non-Hispanic/non-Latino	335 (76.7)	368 (89.8)
Hispanic/Latino	99 (22.7)	34 (8.3)
Not reported	3 (0.7)	8 (2.0)
Age at vaccination (years)		
n	437	410
Mean (SD)	46.9 (9.8)	67.0 (5.5)
Median	49.0	66.0
(Min, max)	(18, 59)	(60, 87)
18-49 Years	230 (52.6)	0
50-59 Years	207 (47.4)	0
>60 Years	0	410 (100.0)
With at least 1 prespecified medical condition[c]	437 (100.0)	182 (44.4)

Numbers analysed

The safety population included 678 participants who received study intervention (453 RSVpreF and 225 placebo). Of these, 432 and 218 in respective groups completed the 6-month follow-up visit while 451 and 225 had at least 1 day of e-diary data transmitted.

The mITT immunogenicity population included 441 vs. 222 and the evaluable immunogenicity population included 437 and 217 per group. Thus, the proportions excluded were balanced across the RSVpreF and placebo groups (3.7% and 4.4%, respectively) and the most common reason was lack of at least 1 valid and determinate RSV NT assay result (at 1 month after vaccination) (2.6% total). Within 28 days prior to vaccination, 3 (0.4%) received a nonstudy vaccine. From vaccination (Visit 1) onwards, 10.6% received a nonstudy vaccine; most frequently received were influenza (9.0%) and COVID-19 vaccines (6.6%).

Table 6. Immunogenicity Analysis Populations

	Vaccine Group (as Randomized)		
	RSVpreF n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	454 (100.0)	227 (100.0)	681 (100.0)
mITT immunogenicity population	441 (97.1)	222 (97.8)	663 (97.4)
Excluded from mITT immunogenicity population[c]	13 (2.9)	5 (2.2)	18 (2.6)
Did not receive vaccine	1 (0.2)	2 (0.9)	3 (0.4)
Did not have a valid and determinate assay results after vaccination	13 (2.9)	5 (2.2)	18 (2.6)
Evaluable immunogenicity population	437 (96.3)	217 (95.6)	654 (96.0)
Excluded from evaluable immunogenicity population[c]	17 (3.7)	10 (4.4)	27 (4.0)
Not eligible for the study	1 (0.2)	2 (0.9)	3 (0.4)
Did not receive study vaccines at Visit 1	1 (0.2)	2 (0.9)	3 (0.4)
Received study vaccine at Visit 1 but not as randomized	0	0	0
Did not have 1 month after vaccination blood draw	12 (2.6)	3 (1.3)	15 (2.2)
Had 1 month after vaccination blood draw but was not within 27 to 42 days after vaccination	3 (0.7)	4 (1.8)	7 (1.0)
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 RSV NT assay result (at 1 month after vaccination)	13 (2.9)	5 (2.2)	18 (2.6)

Abbreviations: mITT= modified intent-to-treat; NT = neutralizing titer; RSV = respiratory syncytial virus.
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.

Outcomes and estimation

-

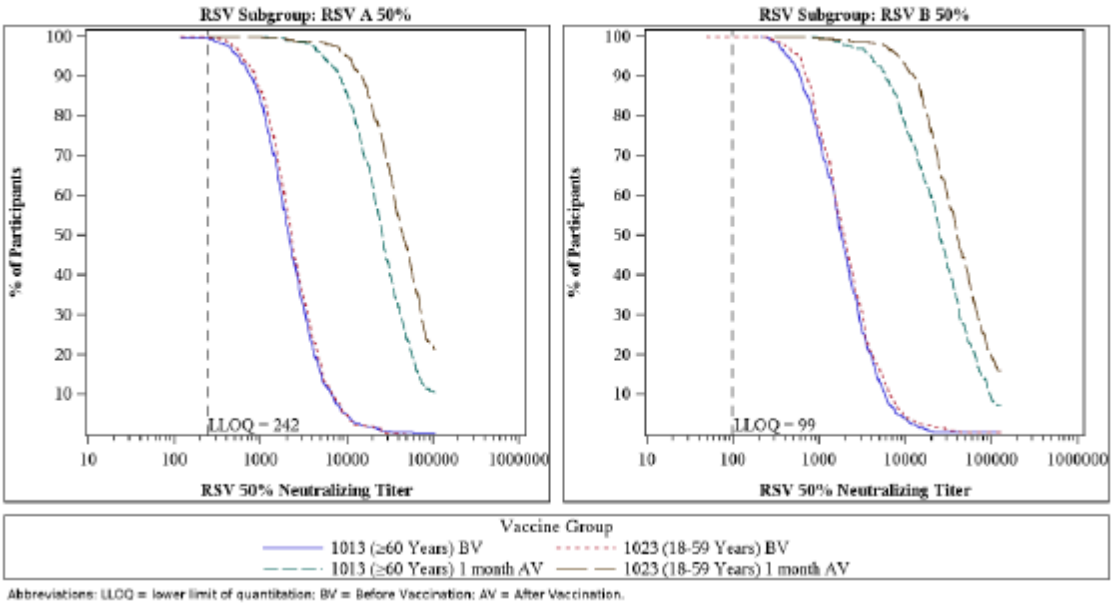
Noninferiority was demonstrated for the primary immunogenicity objective, with the pre-defined criteria met for the four co-primary endpoints. For the immunobridging coprimary estimand as measured by GMRs, due to the known differences for C3671023 Substudy A and C3671013, the analysis is based on the ANCOVA model with sex and baseline titre (in logarithm scale) adjusted to compare the GMTs
(i.e. adjusted GMRs).

Table 7. Comparison of Model Adjusted RSV Neutralizing Titer GMTs at 1 Month After Vaccination with RSVpreF, 18 Through 59 Years at High Risk (C3671023 SSA) vs 60 Years and Older (C3671013) – Evaluable Immunogenicity Population

	Population Group and ANCOVA Adjusted GMTs							
	C3671023-SSA RSVpreF 18-59 Years at High Risk			C3671013 RSVpreF ≥60 Years			ANCOVA Comparison	
RSV Subgroup	n[a]	LS GMT[b]	(95% CI[b])	n[a]	LS GMT[b]	(95% CI[b])	LS GMR[c]	(95% CI[c])
A	435	41097	(37986.1, 44463.4)	408	26225	(24143.1, 28485.7)	1.57	(1.396, 1.759)
B	437	37416	(34277.9, 40842.0)	408	24680	(22504.3, 27065.4)	1.52	(1.333, 1.725)

Abbreviations: ANCOVA = analysis of covariance; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; RSV = respiratory syncytial virus; SSA = Substudy A; ULOQ = upper 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.
Note: The ULOQ values were 108216 for RSV A and 130420 for RSV B neutralizing titers. Assay results from samples with predilution were set to ULOQ.
a. n = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and 1 month after vaccination in the specified analysis population.
b. GMTs and 2-sided CIs were calculated by exponentiating the least square (LS) means and the corresponding CIs based on analysis of log-transformed titers using a regression model with population groups (C3671023 Substudy A versus C3671013 efficacy study), baseline log-transformed titers and sex as covariates.
c. GMRs (ratio of GMTs from C3671023 SSA, compared to C3671013 immunogenicity subset) and 2-sided CIs were calculated by exponentiating the difference in least square (LS) means and the corresponding CIs based on the same regression model as above.

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



As a sensitivity analysis unadjusted GMRs (raw GMT ratios) were summarised. Results from the sensitivity analysis of the unadjusted GMRs of high-risk adults 18 through 59 years of age vs. adults ≥ 60 years of age were consistent with the adjusted GMR results.

Table 8 Comparison of Unadjusted RSV Neutralizing Titer GMTs at 1 Month After Vaccination with RSVpreF, 18 Through 59 Years at High Risk (C3671023 SSA) vs 60 Years and Older (C3671013) – Evaluable Immunogenicity Population

	Population Group							
	C3671023-SSA RSVpreF 18-59 Years at High Risk			C3671013 RSVpreF ≥60 Years			Comparison	
RSV Subgroup	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	GMR[c]	(95% CI[c])
A	436	41595	(38416.6, 45037.5)	409	25673	(23522.2, 28020.0)	1.62	(1.440, 1.823)
B	437	38450	(35187.5, 42014.7)	409	23810	(21477.6, 26396.0)	1.61	(1.410, 1.850)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; RSV = respiratory syncytial virus; SSA = Substudy A; ULOQ = upper 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.
Note: The ULOQ values were 108216 for RSV A and 130420 for RSV B neutralizing titers. Assay results from samples with predilution were set to ULOQ.
a. n = number of participants with valid and determinate assay results for the specified assay in specified immunogenicity population.
b. GMTs and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on Student t distribution).
c. GMRs (ratio of GMTs from C3671023 SSA, compared to C3671013 immunogenicity subset) and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of the titers (RSVpreF C3671023-SSA - RSVpreF C3671013) and the corresponding CIs (based on Student t distribution).

In addition to the above for the evaluable immunogenicity population, the following tables show the model-adjusted and unadjusted analyses for the mITT immunogenicity population. With only small differences in numbers included in each population, the results were highly compatible with those for the evaluable immunogenicity population.

Table 9 Comparison of Model Adjusted RSV Neutralizing Titer GMTs at 1 Month After Vaccination with RSVpreF, 18 Through 59 Years at High Risk (C3671023 SSA) vs 60 Years and Older (C3671013) – mITT Immunogenicity Population

	Population Group and ANCOVA Adjusted GMTs							
	C3671023-SSA RSVpreF 18-59 Years at High Risk			C3671013 RSVpreF ≥60 Years			ANCOVA Comparison	
RSV Subgroup	n[a]	LS GMT[b]	(95% CI[b])	n[a]	LS GMT[b]	(95% CI[b])	LS GMR[c]	(95% CI[c])
A	439	40708	(37632.2, 44036.1)	408	26279	(24186.7, 28551.6)	1.55	(1.380, 1.739)
B	441	37100	(33990.9, 40494.1)	408	24756	(22565.6, 27159.5)	1.50	(1.317, 1.705)

Abbreviations: ANCOVA = analysis of covariance; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; mITT = modified intent-to-treat; RSV = respiratory syncytial virus; SSA = Substudy A; ULOQ = upper 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.
Note: The ULOQ values were 108216 for RSV A and 130420 for RSV B neutralizing titers. Assay results from samples with predilution were set to ULOQ.
a. n = number of participants with valid and determinate assay results for the specified assay at both the prevaccination time point and 1 month after vaccination in the specified analysis population.
b. GMTs and 2-sided CIs were calculated by exponentiating the least square (LS) means and the corresponding CIs based on analysis of log-transformed titers using a regression model with population groups (C3671023 Substudy A versus C3671013 efficacy study), baseline log-transformed titers and sex as covariates.
c. GMRs (ratio of GMTs from C3671023 SSA, compared to C3671013 immunogenicity subset) and 2-sided CIs were calculated by exponentiating the difference in least square (LS) means and the corresponding CIs based on the same regression model as above.

Table 10 Comparison of Unadjusted RSV Neutralizing Titer GMTs at 1 Month After Vaccination with RSVpreF, 18 Through 59 Years at High Risk (C3671023 SSA) vs 60 Years and Older (C3671013) – mITT Immunogenicity Population

	Population Group							
	C3671023-SSA RSVpreF 18-59 Years at High Risk			C3671013 RSVpreF ≥60 Years			Comparison	
RSV Subgroup	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	GMR[c]	(95% CI[c])
A	440	41245	(38100.4, 44650.1)	409	25673	(23522.2, 28020.0)	1.61	(1.428, 1.808)
B	441	38183	(34943.3, 41722.9)	409	23810	(21477.6, 26396.0)	1.60	(1.400, 1.837)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; mITT = modified intent-to-treat; RSV = respiratory syncytial virus; SSA = Substudy A; ULOQ = upper 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.
Note: The ULOQ values were 108216 for RSV A and 130420 for RSV B neutralizing titers. Assay results from samples with predilution were set to ULOQ.
a. n = number of participants with valid and determinate assay results for the specified assay in specified immunogenicity population.
b. GMTs and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on Student t distribution).
c. GMRs (ratio of GMTs from C3671023 SSA, compared to C3671013 immunogenicity subset) and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of the titers (RSVpreF C3671023-SSA - RSVpreF C3671013) and the corresponding CIs (based on Student t distribution).

Furthermore, the results for the pre-planned analysis for GMRs were consistent with those for the primary analysis in the evaluable immunogenicity population. The lower bounds of the 2-sided 95% CIs were >0.667 for both RSV A and RSV B. The model-adjusted GMRs were 1.60 for RSV A and 1.51 for RSV B while the unadjusted GMRs were 1.66 for RSV A and 1.60 for RSV B.

Table 11 Comparison of Model Adjusted RSV Neutralizing Titer GMTs at 1 Month After Vaccination with RSVpreF, 18 Through 59 Years at High Risk (C3671023 SSA) vs 60 Years and Older (C3671013), Based on Assay Results with Predilution – Evaluable Immunogenicity Population

	Population Group and ANCOVA Adjusted GMTs							
	C3671023-SSA RSVpreF 18-59 Years at High Risk			C3671013 RSVpreF ≥60 Years			ANCOVA Comparison	
RSV Subgroup	n[a]	LS GMT[b]	(95% CI[b])	n[a]	LS GMT[b]	(95% CI[b])	LS GMR[c]	(95% CI[c])
A	435	42025	(38699.8, 45635.2)	408	26194	(24021.3, 28563.2)	1.60	(1.421, 1.811)
B	437	37597	(34382.1, 41111.6)	408	24893	(22656.5, 27350.2)	1.51	(1.324, 1.723)

Table 12 Comparison of Unadjusted RSV Neutralizing Titer GMTs at 1 Month After Vaccination with RSVpreF, 18 Through 59 Years at High Risk (C3671023 SSA) vs 60 Years and Older (C3671013) – Based on Assay Results with Predilution – Evaluable Immunogenicity Population

	Population Group							
	C3671023-SSA RSVpreF 18-59 Years at High Risk			C3671013 RSVpreF ≥60 Years			Comparison	
RSV Subgroup	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	GMR[c]	(95% CI[c])
A	436	42574	(39092.8, 46365.1)	409	25599	(23412.0, 27991.0)	1.66	(1.470, 1.881)
B	437	38550	(35198.2, 42220.3)	409	24076	(21659.3, 26761.9)	1.60	(1.393, 1.841)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; RSV = respiratory syncytial virus; SSA = Substudy A.
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. n = number of participants with valid and determinate assay results for the specified assay in specified immunogenicity population.
b. GMTs and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on Student t distribution).
c. GMRs (ratio of GMTs from C3671023 SSA, compared to C3671013 immunogenicity subset) and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of the titers (RSVpreF C3671023-SSA - RSVpreF C3671013) and the corresponding CIs (based on Student t distribution).

One month after vaccination with RSVpreF, the noninferiority criteria were met for the difference in seroresponse rates with the lower bounds of the 2-sided 95% CIs > -10% for both RSV A and RSV B. The seroresponse rates were higher for high-risk adults 18-59 years vs. adults ≥60 years. Similar results were obtained in the mITT immunogenicity population.

Table 13 Comparison of RSV Neutralizing Titer Seroresponse Rates 1 Month After Vaccination – Participants 18 Through 59 Years at High Risk (C3671023 SSA) and Participants ⩾ 60 Years (C3671013) – Evaluable Immunogenicity Population

	Population Group							
	C3671023-SSA RSVpreF 18-59 Years at High Risk			C3671013 RSVpreF ≥60 Years			Comparison	
RSV Subgroup	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	Diff[d]	(95% CI[d])
A	435	405 (93.1)	(90.3, 95.3)	408	359 (88.0)	(84.4, 91.0)	5.1	(1.2, 9.2)
B	437	408 (93.4)	(90.6, 95.5)	408	347 (85.0)	(81.2, 88.4)	8.3	(4.2, 12.6)

Abbreviations: LLOQ = lower limit of quantitation; RSV = respiratory syncytial virus; SSA = Substudy A; ULOQ = upper limit of quantitation.
Note: The LLOQ values were 242 for RSV A and 99 for RSV B neutralizing titers.
Note: The ULOQ values were 108216 for RSV A and 130420 for RSV B neutralizing titers. Assay results from samples with predilution were set to ULOQ.
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 time points 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.
d. Difference (C3671023 SSA, compared to C3671013 immunogenicity subset) in proportions, expressed as a percentage; the 95% CIs for the percentage difference were calculated using the exact method based on Miettinen and Nurminen.

Results for the pre-planned analysis for differences in seroresponse rates were consistent with those for the primary analysis with higher rates in the younger adults (92.9% for RSV A and 93.8% for RSV B) compared to adults ≥60 years (88% and 85%). The differences in seroresponse rates were 4.9% for RSV A and 8.8% for RSV B, with the lower bounds of the 2-sided 95% CIs > -10% for both RSV A and RSV B.

The neutralizing antibody GMTs for RSV A and RSV B increased from before vaccination to 1 month after vaccination for those who received RSVpreF with GMFRs ⩾17.5 vs. 1.0 in the placebo group.

Table 14 RSV Neutralizing Titer GMTs and GMFRs – Evaluable Immunogenicity Population

		Before Vaccination			1 Month After Vaccination			Fold Rise		
Vaccine Group (as Randomized)	RSV Subgroup	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	n[a]	GMFR[c]	(95% CI[c])
RSVpreF	A	436	2388	(2207.7, 2583.3)	436	41595	(38416.6, 45037.5)	435	17.5	(15.88, 19.21)
	B	437	2075	(1899.7, 2265.4)	437	38450	(35187.5, 42014.7)	437	18.5	(16.76, 20.43)
	A/B	437	2223	(2061.6, 2396.6)	437	39904	(36873.7, 43184.2)	437	17.9	(16.34, 19.63)
Placebo	A	217	2797	(2516.8, 3108.9)	217	2660	(2395.2, 2953.9)	217	1.0	(0.90, 1.00)
	B	217	2230	(1988.6, 2501.6)	217	2135	(1905.9, 2391.3)	217	1.0	(0.91, 1.01)
	A/B	217	2498	(2253.6, 2768.4)	217	2383	(2152.8, 2637.7)	217	1.0	(0.91, 1.00)

RSV neutralizing GMTs and GMFRs were evaluated by age group, sex, race, ethnicity and prespecified significant conditions. Observations across subgroups were mostly similar with no clinically meaningful differences in GMTs or GMFRs. Immune responses were similar for high-risk adults aged 18-49 and 50-59 years. Subgroup results for the pre-planned analysis were consistent with those described for the evaluable immunogenicity population.

Table 15 RSV Neutralizing Titer GMTs and GMFRs After Vaccination With RSVpreF, by Demographic Subgroups – Evaluable Immunogenicity Population

		Before Vaccination			1 Month After Vaccination			Fold Rise		
RSV Subgroup	Demographic Subgroup	n[a]	GMT[b]	(95% CI[b])	n[a]	GMT[b]	(95% CI[b])	n[a]	GMFR[c]	(95% CI[c])
A	18-49 Years	229	2363	(2105.8, 2652.2)	230	42214	(37670.1, 47305.9)	229	17.9	(15.67, 20.52)
	50-59 Years	207	2416	(2172.2, 2687.0)	206	40916	(36610.7, 45727.0)	206	17.0	(14.82, 19.40)
	Male	184	2392	(2115.1, 2705.4)	184	41649	(36669.0, 47306.1)	183	17.6	(15.22, 20.33)
	Female	252	2385	(2152.4, 2643.2)	252	41556	(37522.2, 46023.9)	252	17.4	(15.31, 19.72)
	White	302	2374	(2160.3, 2608.7)	301	42078	(38361.2, 46154.0)	301	17.7	(15.78, 19.95)
	Black or African American	102	2280	(1929.8, 2692.7)	102	40815	(33862.6, 49195.9)	102	17.8	(14.69, 21.53)
	Asian	21	2785	(2116.2, 3664.1)	22	43727	(31399.0, 60894.4)	21	17.0	(12.55, 22.99)
	Multiracial	3	1570	(166.9, 14772.5)	3	23572	(1126.3, 493347.8)	3	15.0	(0.67, 335.08)
	Native Hawaiian or Other Pacific Islander	2	4306	Not estimated	2	36176	Not estimated	2	8.4	Not estimated
	American Indian or Alaska Native	1	22167	(NE, NE)	1	27625	(NE, NE)	1	1.2	(NE, NE)
	Hispanic/Latino	99	2784	(2312.7, 3352.2)	98	46075	(38794.5, 54721.3)	98	16.6	(13.36, 20.55)
	Non-Hispanic/non-Latino	334	2283	(2094.4, 2488.8)	335	40579	(37072.7, 44416.3)	334	17.8	(16.02, 19.82)
	Chronic pulmonary conditions	229	2418	(2172.8, 2689.9)	230	40533	(36576.1, 44918.1)	229	16.9	(14.81, 19.24)
	Cardiovascular conditions	36	2275	(1729.9, 2991.6)	35	53903	(41622.3, 69807.0)	35	23.9	(17.57, 32.56)
	Diabetes	184	2445	(2148.2, 2783.5)	184	45662	(40442.9, 51554.5)	184	18.7	(16.09, 21.67)
	Other medical conditions	135	2181	(1893.6, 2511.7)	135	39812	(34069.1, 46523.2)	135	18.2	(15.20, 21.70)
B	18-49 Years	230	2079	(1837.1, 2352.3)	230	38306	(33696.8, 43546.7)	230	18.4	(15.94, 21.18)
	50-59 Years	207	2070	(1824.2, 2348.4)	207	38610	(34157.0, 43643.0)	207	18.7	(16.25, 21.41)
	Male	185	2059	(1800.4, 2355.3)	185	38621	(33635.3, 44346.3)	185	18.8	(16.08, 21.87)
	Female	252	2086	(1854.8, 2345.5)	252	38324	(34116.0, 43052.2)	252	18.3	(16.09, 20.87)
	White	302	2068	(1860.9, 2297.1)	302	37940	(34114.3, 42194.6)	302	18.4	(16.27, 20.70)
	Black or African American	102	1945	(1636.1, 2312.0)	102	40231	(33290.8, 48617.6)	102	20.5	(16.97, 24.88)
	Asian	22	2218	(1591.0, 3092.9)	22	42168	(27991.0, 63525.3)	22	19.0	(13.64, 26.50)
	Multiracial	3	1494	(59.2, 37696.7)	3	24042	(514.3, 1123747.6)	3	16.1	(1.47, 176.42)

Chronic pulmonary conditions	230	2114	(1872.6, 2386.9)	230	39642	(35236.5, 44597.9)	230	18.8	(16.32, 21.55)
Cardiovascular conditions	36	2022	(1483.7, 2754.8)	36	44164	(33490.8, 58239.9)	36	21.8	(14.76, 32.33)
Diabetes	184	2014	(1752.4, 2314.4)	184	41243	(36323.1, 46828.6)	184	20.5	(17.66, 23.74)
Other medical conditions	135	1961	(1695.5, 2267.7)	135	38188	(32326.1, 45113.7)	135	19.4	(16.28, 23.06)

Summary of main study

The following table summarises the immunogenicity results from the main study supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16 Summary of Efficacy for trial C3671023

Title: A Phase 3 Protocol to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults at High Risk of Severe RSV Disease; Substudy A Final Analysis			
Study identifier	C3671023; NCT05842967		
Design	Prospective, randomised and placebo-controlled clinical study, with cross-study immunobridging to adults 60+ years in whom efficacy was shown in C3671013		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		FPFV 11 May 2023 and LPLV 13 March 2024 not applicable not applicable
Hypothesis	Non-inferiority for immune responses vs. adults aged 60+ years enrolled into the pivotal efficacy study in older adults (C3671013)		
Treatments groups	RSVpreF		Single dose Day 1; n=453
	Placebo		Single dose Day 1; n=225
	RSVpreF external control group aged 60+ years in C3671013		Single dose Day 1; n=410
Endpoints and definitions	Primary endpoints	Anti-RSV A and B NT GMTs and SR rates at 1 month	GMT ratio (GMR) for RSV A and B NTs at 1 month after RSVpreF in C3671023 (18-59 years) vs. C3671013 (⩾60 years) Difference in SR rate for RSV A and B NTs at 1 month after RSVpreF in C3671023 vs. C3671013
	Secondary endpoints C3671023 only	Anti-RSV A and B NTs	GMT of NTs for RSV A and B at each blood sampling visit GMFR of NTs for RSV A and B from pre- to postvaccination blood sampling visit
Database lock	13 March 2024		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Evaluable immunogenicity population at 1 months post-vaccination			
Descriptive statistics and estimate variability	Treatment group	RSVpreF 18-50 years	RSVpreF 60+ years	Placebo
	Number of subjects	RSV A 435 RSV B 437	RSV A 408 RSV B 408	RSV A 217 RSV B 217

	GMT A LS GMR (95% CI) GMFR pre/post 95% CI)	41097 1.57 (1.396, 1.759) 17.5 (15.88, 19.21)	26225	2660 GMFR 1.0 (0.91, 1.10)
	GMT B LS GMR (95% CI) GMFR pre/post (95% CI)	37416 1.52 (1.333, 1.725) 18.5 (16.76, 20.43)	24680	2135 GMFR 1.0 (0.91, 1.00)
	RSV A SR rate Diff (95% CI)	93.1 5.1 (1.2, 9.2)	88.0	
	RSV B SR rate Diff (95% CI)	93.4 8.3 (4.2, 12.6)	85.0	
Analysis description	**Subgroup analyses**			
	In the C3671023 RSVpreF recipients, RSV GMTs and GMFRs were evaluated by age group, sex, race, ethnicity and prespecified significant conditions. For most subgroups, observations suggested no clinically meaningful differences in GMTs or GMFRs after a single dose of RSVpreF in high-risk adults 18 through 59 years of age. Immune responses after RSVpreF were similar for high-risk adults 18 through 49 and 50 through 59 years of age.			

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The new data in this application come from C3671023 Substudy A, which was a double-blind and placebo-controlled study intended to generate immunogenicity data in adults aged 18-59 years considered to be at high risk of severe RSV disease to support immunobridging to the efficacy previously shown in C3671013 in adults aged 60+ years, in line with the guideline on clinical evaluation of vaccines. The aim was therefore to demonstrate that immune responses in the generally immunocompetent population enrolled into C3671023 would be non-inferior to immune responses documented in C3671013. The MAH assumed that a demonstration of non-inferiority in C3671023 would support a conclusion that, if studied, there would also be non-inferior immune response in adults aged 18-59 years without the underlying high-risk of severe RSV disease. This is a very reasonable assumption which is endorsed by CHMP. Besides, CHMP notes that substudy A was conducted at 27 sites in the US; the results are considered applicable to similar subjects resident in the EU.

Eligible adults aged 18-59 years had to have at least one of the listed underlying medical conditions, which have all been suggested to predispose to risk for severe RSV disease in published reports. The exclusions from this immunobridging study were appropriate. In particular, subjects with known or suspected immunodeficiency were excluded, which is acceptable to the CHMP for this initial immunobridging exercise noting that the approved SmPC already warns that there are no data and that immune response may be lower in immunodeficient persons.
Although the primary aim was to support the immunobridging exercise, the inclusion of a placebo group (using 2:1 randomisation) was appropriate at the time that the study was conducted and it provides a control for safety as well as background immune response data in this RSV-experienced adult population.

The primary endpoints were the GMTs and seroresponse rates (as defined in the protocol) based on anti-RSV A and anti-RSV B neutralizing antibody titres in sera obtained at 1-month post-vaccination. This is appropriate. It means that effectively there were 4 co-primary endpoints in the study.

In the four co-primary analyses conducted in the evaluable immunogenicity populations, the RSV A and RSV B GMTs and seroresponse rates were compared between 437 adults aged 18-59 years assigned to RSVpreF in C3671023 vs. 410 randomly selected adults aged 60+ years who received RSVpreF in C3671013. It is important to note that the sera from the two studies were tested concurrently using assays that were previously described and assessed. There is no suggestion that the immune response in the randomised subset would have led to bias in favour of showing non-inferiority. Conduct in the evaluable immunogenicity population is acceptable in the setting of immunobridging. However, the applicant also supplied analyses in the mITT immunogenicity population.

Non-inferiority was to be declared if the lower bounds of the 95% adjusted GMRs were >0.667 and the lower bounds of the 95% of seroresponse rates differences were >-10% for both RSV A and RSV B. While there is no immune correlate of protection established for prevention of RSV, these non-inferiority acceptance criteria are acceptable. Moreover, study success required that all four analyses met the applicable criteria, which is appropriate.

Efficacy data and additional analyses

Study C3671023 met the enrolment target, with 681 participants randomised into the study of which 99.6% received study intervention. Study completion rates were very high and comparable between the RSVpreF and placebo groups. In general, conduct of the study appears to have been satisfactory, with only few important protocol deviations.

Within C3671023, demographic and baseline characteristics of the safety population were mostly well balanced for the RSVpreF and placebo groups. Although there were no stratification factors applied at randomisation, approximately half of subjects were in the age groups 18-49 vs. 50-59 years.

The most common prespecified medical conditions were chronic pulmonary conditions and diabetes. None of the participants were residents of nursing homes or other long-term care facilities. With an inevitable difference in age between the test and reference groups included in the primary (immunobridging) analysis, there was no declared aim to attempt to match the populations based on other characteristics.

With the immunodeficient subjects excluded from both studies, and with 44% of the reference population having at least one pre-specified underlying condition, it is unlikely that the differences would have biased the study towards demonstrating non-inferiority.

Non-inferiority was demonstrated for the primary immunogenicity objective, with the pre-defined criteria met for the four co-primary endpoints. The results suggested that greater immune response was achieved in the 18-59 years group with underlying medical conditions vs. the 60+ group including 44% of subjects with underlying conditions, noting that the pre-specified conditions were not necessarily expected to affect the magnitude of the immune response.

For the immunobridging co-primary estimand as measured by GMRs, due to the known differences for C3671023 Substudy A and C3671013, the analysis was based on the ANCOVA model with sex and baseline titre (in logarithm scale) adjusted to compare the GMTs (i.e. adjusted GMRs). The unadjusted analysis provided very similar results. The CSR also provided the model-adjusted and unadjusted analyses for the mITT immunogenicity population. With only small differences in numbers included in each population, the results were compatible with those for the evaluable immunogenicity population.

For the immunobridging coprimary estimand as measured by seroresponse rates, at one month after vaccination with RSVpreF and with noninferiority criteria met, seroresponse rates were higher for adults 18-59 years vs. adults 60+ years. Similar results were obtained in the mITT immunogenicity population. Results for the pre-planned analysis for differences in seroresponse rates were also consistent with those for the primary analysis with higher rates in the adults aged 18-59 years compared to adults 60+ years.

In the placebo group of C3671023 there was no shift in GMTs for RSV A and RSV B from baseline to month 1 compared to GMFRs $\geqslant$17.5 in the RSVpreF group. This finding indicates that natural exposure to RSV during the one-month period was unlikely to have affected the post-vaccination titres observed.

RSV neutralizing GMTs and GMFRs for C3671023 subjects who received RSVpreF were evaluated by age group, sex, race, ethnicity and prespecified significant conditions. Observations across subgroups were mostly similar with no clinically meaningful differences in GMTs or GMFRs. Immune response was similar for adults aged 18-49 and 50-59 years. Subgroup results for the pre-planned analysis were consistent with those described for the evaluable immunogenicity population. Whereas the CSR does not present the immune responses by subgroups compared between C3671023 and C3671013, the summary of efficacy points to the previously reported data suggesting no important effect of age subgroups and underlying conditions on the immune responses documented in C3671023.

2.4.3. Conclusions on the clinical efficacy

With testing of sera in parallel, the comparisons made between adults aged 18-59 with pre-specified underlying conditions in C3671023 and adults aged 60+ years in C3671013 support an overall conclusion that neutralizing antibodies elicited by RSVpreF are at least as high in the former cohort compared to the latter cohort. Although there is no immune correlate of protection established for RSV, the CHMP considers that this immunobridging exercise supports a conclusion that protection against RSV is likely at least as good in adults aged 18-59 years as has been documented in adults aged 60+ years.

While C3671023 was conducted in adults aged 18-59 years with at least one pre-specified underlying medical condition, there was no expectation that the underlying conditions would have an important effect on the immune responses to RSVpreF. Nevertheless, it is presumed that the intent was to conduct the immunobridging exercise such that the applicability of the results across a broadly immunocompetent population aged 18-59 years would not be questioned.

That being the case, the proposed indication statement is not restricted in any way but simply refers to "*Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV"*. The CHMP is of the view that this wording allows National Immunisation Technical Advisory Groups (NITAGs) to determine if and how to recommend use in adults aged from 18 years just as the currently approved indication allows them to do the same from a minimum age of 60 years. In particular, the proposed wording allows NITAGs to select certain adults for vaccination either because they are considered to be at risk of severe disease if they become infected with RSV and/or because they are particularly at risk of acquiring RSV disease due to their employment even if the disease is expected to be mild in severity. For example, NITAGS may choose to target healthcare workers to minimise staff shortages during the RSV season, just as influenza vaccines are targeted in many countries.

Overall, the extension of indication to include active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV is acceptable from an efficacy point of view.

2.5. Clinical safety

Introduction

The initial MAA for Abrysvo included safety data for adults aged 60+ years and for pregnant women, along with some Phase 1 data in healthy and non-pregnant adults aged <60 years. Thus, few data were available from non-pregnant adults aged 18-59 years. Across the adult population, local reactogenicity was common or very common but most reported ADRs were not severe. Other very common ADRs were headache and myalgia. In adults aged 60+ years, one case of Guillain-Barré syndrome and one of Miller Fisher syndrome were reported with onset of 7 and 8 days, respectively, after receiving Abrysvo and were assessed by the investigator as possibly vaccine-related. Both cases had either confounding factors or an alternative aetiology for the clinical picture. One additional case, with onset 8 months after receiving Abrysvo, was assessed as not vaccine-related by the investigator. There was one case of Guillain-Barré syndrome reported in the placebo group 14 months after administration.

In the current application dossier, the new safety data come from C3671023, with follow-up to the 6-month final safety visit. Data from a pooled safety analysis are included under a separate heading below.

Patient exposure

The safety analysis was conducted in the all-treated (allocated single dose) population, comprising 453 in the Abrysvo group and 225 in the placebo group. Of this total 678 persons, 650 (95.4%) completed the study, i.e. completed the 6-month safety follow-up visit (Visit 3).

Table 17 Demographic and Baseline Characteristics – Safety Population

	Vaccine Group (as Administered)		
	RSVpreF (N[a]=453) n[b] (%)	Placebo (N[a]=225) n[b] (%)	Total (N[a]=678) n[b] (%)
Sex			
Male	193 (42.6)	73 (32.4)	266 (39.2)
Female	260 (57.4)	152 (67.6)	412 (60.8)
Race			
White	312 (68.9)	152 (67.6)	464 (68.4)
Black or African American	106 (23.4)	57 (25.3)	163 (24.0)
Asian	24 (5.3)	9 (4.0)	33 (4.9)
Not reported	5 (1.1)	5 (2.2)	10 (1.5)
Multiracial	3 (0.7)	1 (0.4)	4 (0.6)
Native Hawaiian or Other Pacific Islander	2 (0.4)	1 (0.4)	3 (0.4)
American Indian or Alaska Native	1 (0.2)	0	1 (0.1)
Ethnicity			
Non-Hispanic/non-Latino	348 (76.8)	175 (77.8)	523 (77.1)
Hispanic/Latino	102 (22.5)	48 (21.3)	150 (22.1)
Not reported	3 (0.7)	2 (0.9)	5 (0.7)
Age at vaccination (years)			
n	453	225	678
Mean (SD)	46.8 (9.9)	46.4 (10.5)	46.7 (10.1)
Median	49.0	49.0	49.0
(Min, max)	(18, 59)	(20, 59)	(18, 59)
18-49 years	240 (53.0)	113 (50.2)	353 (52.1)
50-59 years	213 (47.0)	112 (49.8)	325 (47.9)
With at least 1 prespecified medical condition[c]	453 (100.0)	223 (99.1)	676 (99.7)
Chronic pulmonary conditions	239 (52.8)	116 (51.6)	355 (52.4)
COPD	25 (5.5)	11 (4.9)	36 (5.3)
Asthma	198 (43.7)	88 (39.1)	286 (42.2)
Other lung disease	47 (10.4)	26 (11.6)	73 (10.8)
Cardiovascular conditions	38 (8.4)	16 (7.1)	54 (8.0)
CHF	9 (2.0)	3 (1.3)	12 (1.8)
CAD	19 (4.2)	4 (1.8)	23 (3.4)
Other heart disease	19 (4.2)	12 (5.3)	31 (4.6)
Diabetes	189 (41.7)	101 (44.9)	290 (42.8)
Other	139 (30.7)	68 (30.2)	207 (30.5)
Liver disease	20 (4.4)	13 (5.8)	33 (4.9)
Renal disease	17 (3.8)	4 (1.8)	21 (3.1)
Neurologic disease	16 (3.5)	1 (0.4)	17 (2.5)
Hematologic disease	6 (1.3)	7 (3.1)	13 (1.9)
Other metabolic disease	91 (20.1)	51 (22.7)	142 (20.9)
Tobacco use			
Current	78 (17.2)	39 (17.3)	117 (17.3)
Former	101 (22.3)	39 (17.3)	140 (20.6)
Never	274 (60.5)	147 (65.3)	421 (62.1)
Respiratory rate at baseline (breaths/min)			
n	453	225	678
Mean (SD)	15.6 (1.9)	15.7 (2.0)	15.6 (2.0)
Median	16.0	16.0	16.0
(Min, max)	(12, 22)	(12, 21)	(12, 22)

Abbreviations: CAD = coronary artery disease; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease.
a. N = number of participants in the specified vaccine group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Two participants were vaccinated but did not have at least one prespecified medical condition (study inclusion criteria).
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2024 (16:37) Source Data: adsl Table Generation: 26MAR2024 (02:36)
(Database snapshot date : 18MAR2024) Output File: ./nda_oa/C3671023_SSA_CSR/adsl_s005_safety

Adverse events

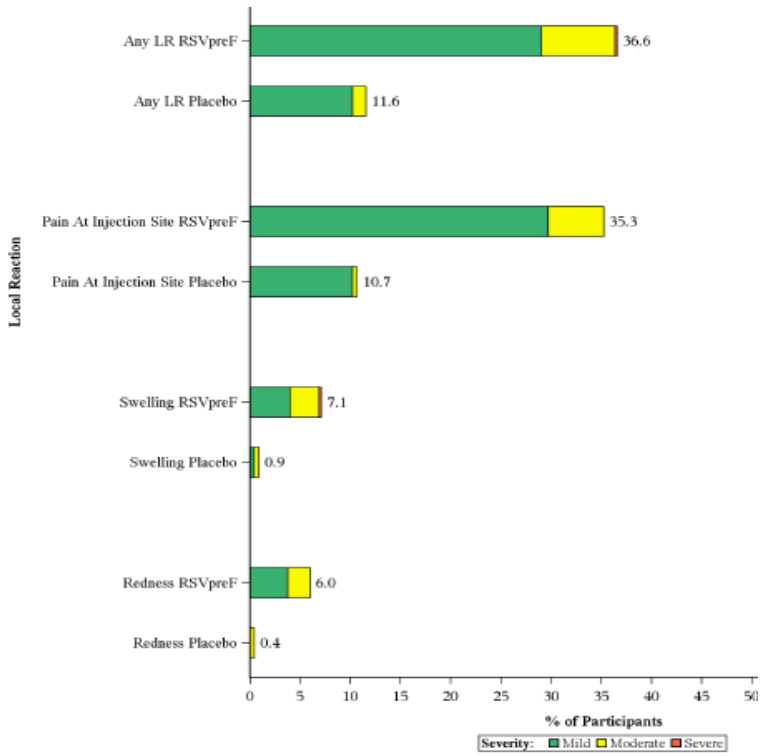
Local reactogenicity

Proportions of participants reporting (e-diary or AE CRF) local reactions within 7 days of vaccination were higher in the RSVpreF group than the placebo group (36.6% vs. 11.6% overall).

As in the initial MAA, the most frequently reported local reaction in both groups was pain at the injection site. Most local reactions were mild or moderate in severity and only 1 (0.2%) participant in the RSVpreF group had a severe local reaction (swelling). The same findings applied to the sensitivity analysis of local reactions from the e-diary only. Across both groups, the median onset for local reactions occurred by Day 3, and median duration was 1 to 2 days.

In the RSVpreF group, reporting of local reactions trended higher for the younger (18-49; 44.2% for RSVpreF vs. 12.4% placebo) vs. older subgroup (50-59; 28% for RSVpreF vs. 10.7% placebo) and for females vs. males (41.3% vs. 30.2% in the RSVpreF group and 10.5% vs. 13.7% in the placebo group).

Figure 2



Systemic reactogenicity

Proportions reporting systemic events within 7 days after vaccination (e-diary or AE CRF) were generally similar between groups (57.4% vs 55.6% overall) and the most frequently reported was fatigue.

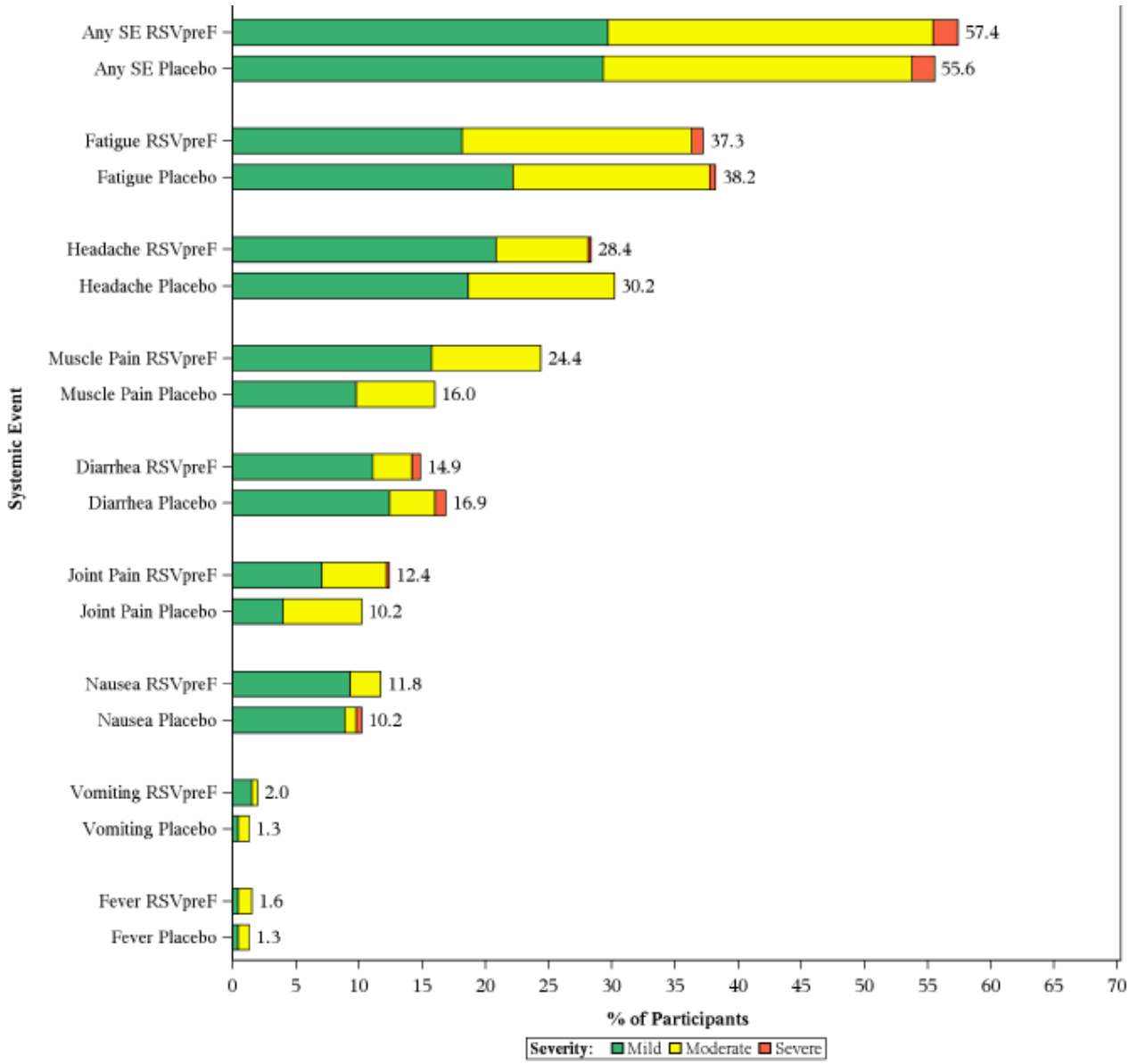
Most systemic events were mild or moderate in severity. The most frequent severe systemic events were fatigue (0.9% vs. 0.4%) and diarrhoea (0.7% vs. 0.9%).

The incidence of fever was low (1.6% vs. 1.3%) and all events were mild (≥38.0 °C to 38.4 °C) or moderate (>38.4 °C to 38.9 °C) in severity. Muscle pain was reported more frequently in the RSVpreF group (24.4%) compared to the placebo group (16.0%).

Similar findings emerged from the sensitivity analysis of systemic events from the e-diary only.

Across both groups, the median onset for most systemic events was Day 2 or Day 3 and median duration was 1 to 2 days.

For the most part, there were no clinically meaningful differences in systemic events by subgroup. In the RSVpreF group, reporting of systemic events trended higher for the younger vs. older subgroup and for females vs. males. Proportions reporting any systemic event were as follows for these subgroups:
☐ age: 62.9% vs. 51.2% for those aged 18-49 vs. 50-59 years in the RSVpreF group, and 54.9% vs. 56.3% for 18-49 vs. 50-59 years in the placebo group;
☐ sex: 61.8% vs. 51.6% for females vs. males in the RSVpreF group, and 59.9% vs. 46.6% for females vs. males in the placebo group.
Figure 3



Overview of AEs

The main analysis of AEs excluded the reactogenicity events that were reported in the AE CRF (except for SAEs) during the 7-day e-diary collection period.

Through the 1-month follow-up visit, the proportions of participants reporting any AEs were similar for the RSVpreF (6.8%) and placebo (7.6%) groups.

Most AEs were mild or moderate in severity; severe AEs were reported in 0.2% of the RSVpreF group and 1.8% of the placebo group. No immediate AEs were reported within 30 minutes and no life-threatening
AEs were reported within 1 month. There was one AE assessed as related by the investigator. This occurred in the RSVpreF group and it was a nonserious event of urticaria (mild severity) that had onset on Day 1 and resolved the next day.

Table 18 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)							
	All AEs From AE CRF				All AEs Excluding Prespecified Events[a]			
	RSVpreF (N[b]= 453)		Placebo (N[b]= 225)		RSVpreF (N[b]= 453)		Placebo (N[b]= 225)	
	n[c] (%)	(95% CI[d])	n[c] (%)	(95% CI[d])	n[c] (%)	(95% CI[d])	n[c] (%)	(95% CI[d])
Any AEs reported from vaccination through 1 month follow-up visit	38 (8.4)	(6.0, 11.3)	18 (8.0)	(4.8, 12.3)	31 (6.8)	(4.7, 9.6)	17 (7.6)	(4.5, 11.8)
Related	8 (1.8)	(0.8, 3.4)	0	(0.0, 1.6)	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Immediate[e]	2 (0.4)	(0.1, 1.6)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)
Severe or life-threatening	1 (0.2)	(0.0, 1.2)	4 (1.8)	(0.5, 4.5)	1 (0.2)	(0.0, 1.2)	4 (1.8)	(0.5, 4.5)
AESI[f]	0	(0.0, 0.8)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)
Any SAEs reported from vaccination throughout the study	5 (1.1)	(0.4, 2.6)	7 (3.1)	(1.3, 6.3)	5 (1.1)	(0.4, 2.6)	7 (3.1)	(1.3, 6.3)
Related	0	(0.0, 0.8)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)
Any NDCMCs reported from vaccination throughout the study	3 (0.7)	(0.1, 1.9)	5 (2.2)	(0.7, 5.1)	3 (0.7)	(0.1, 1.9)	5 (2.2)	(0.7, 5.1)
Related	0	(0.0, 0.8)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)
Any AEs leading to withdrawal after vaccination	1 (0.2)	(0.0, 1.2)	1 (0.4)	(0.0, 2.5)	1 (0.2)	(0.0, 1.2)	1 (0.4)	(0.0, 2.5)
Related	0	(0.0, 0.8)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)
Any AEs leading to death after vaccination	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Related	0	(0.0, 0.8)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)
Any AESIs reported from vaccination throughout the study[f]	0	(0.0, 0.8)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)
Related	0	(0.0, 0.8)	0	(0.0, 1.6)	0	(0.0, 0.8)	0	(0.0, 1.6)

For AEs reported throughout the study, the rates in both groups were low (see table above) for SAEs, NDCMCs and AEs leading to withdrawal. None of the events was assessed as related. One participant (0.2%) in the RSVpreF group had an AE leading to death (cardio-respiratory arrest) on Day 106, which was assessed by the investigator as not related. No AESIs were reported.

AEs were most frequently reported in the SOC of Infections and infestations in both the RSVpreF group (2.9%) and placebo group (4.0%). Across both vaccine groups, the 3 most frequently reported AEs were COVID-19 (0.9% each), upper respiratory tract infection (≤0.9%) and sinusitis (≤0.7%). Observations across subgroups were broadly similar for the RSVpreF and placebo groups.

Table 19 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 (N*=453) n[b] (%)	 (95% CI[c])	 Placebo (N*=225) n[b] (%)	 (95% CI[c])
Any event	31 (6.8)	(4.7, 9.6)	17 (7.6)	(4.5, 11.8)
Cardiac disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Tachycardia	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Ear and labyrinth disorders	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Meniere's disease	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Eye disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Epiretinal membrane	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Ocular hypertension	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Vitreous haemorrhage	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Gastrointestinal disorders	3 (0.7)	(0.1, 1.9)	2 (0.9)	(0.1, 3.2)
Constipation	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Diarrhea	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Food poisoning	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Irritable bowel syndrome	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Nausea	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
General disorders and administration site conditions	0	(0.0, 0.8)	2 (0.9)	(0.1, 3.2)
Non-cardiac chest pain	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Oedema peripheral	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Immune system disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Seasonal allergy	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Infections and infestations	13 (2.9)	(1.5, 4.9)	9 (4.0)	(1.8, 7.5)
Appendicitis	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Bronchitis	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
COVID-19	4 (0.9)	(0.2, 2.2)	2 (0.9)	(0.1, 3.2)
Gastroenteritis	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Localised infection	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Sinusitis	3 (0.7)	(0.1, 1.9)	1 (0.4)	(0.0, 2.5)
Tinea cruris	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Upper respiratory tract infection	2 (0.4)	(0.1, 1.6)	2 (0.9)	(0.1, 3.2)
Urinary tract infection	1 (0.2)	(0.0, 1.2)	2 (0.9)	(0.1, 3.2)
Injury, poisoning and procedural complications	4 (0.9)	(0.2, 2.2)	0	(0.0, 1.6)
Contusion	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Eye contusion	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Eye injury	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)

Table 20 Adverse Events Reported From Vaccination Through 1 Month Follow-up Visit, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF (N=453)		Placebo (N=225)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Fall	2 (0.4)	(0.1, 1.6)	0	(0.0, 1.6)
Hyphaema	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Joint injury	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Muscle rupture	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Metabolism and nutrition disorders	3 (0.7)	(0.1, 1.9)	2 (0.9)	(0.1, 3.2)
Gout	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Hypokalaemia	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Hyponatraemia	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Type 2 diabetes mellitus	2 (0.4)	(0.1, 1.6)	0	(0.0, 1.6)
Musculoskeletal and connective tissue disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Tendonitis	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Nervous system disorders	0	(0.0, 0.8)	3 (1.3)	(0.3, 3.8)
Dizziness	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Migraine	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Seizure	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Psychiatric disorders	1 (0.2)	(0.0, 1.2)	1 (0.4)	(0.0, 2.5)
Attention deficit hyperactivity disorder	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Depression	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Schizophrenia	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Renal and urinary disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Cystitis haemorrhagic	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Respiratory, thoracic and mediastinal disorders	3 (0.7)	(0.1, 1.9)	1 (0.4)	(0.0, 2.5)
Cough	1 (0.2)	(0.0, 1.2)	1 (0.4)	(0.0, 2.5)
Epistaxis	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Oropharyngeal pain	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Respiratory disorder	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Respiratory tract congestion	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Skin and subcutaneous tissue disorders	2 (0.4)	(0.1, 1.6)	0	(0.0, 1.6)
Perioral dermatitis	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Urticaria	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Social circumstances	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Physical assault	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Vascular disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Bleeding varicose vein	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)

Serious adverse event/deaths/other significant events

One AE leading to death occurred in the RSVpreF group that was assessed by the investigator as not related (see above; cardio-respiratory arrest on Day 106 in the 50-59 years group.

Few SAEs were reported throughout the study in the RSVpreF group (1.1%) or placebo group (3.1%) and none was assessed as related.

Table 21 Serious Adverse Events Reported From Vaccination Throughout the study, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF (N*=453)		Placebo (N*=225)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	5 (1.1)	(0.4, 2.6)	7 (3.1)	(1.3, 6.3)
Cardiac disorders	2 (0.4)	(0.1, 1.6)	0	(0.0, 1.6)
Cardio-respiratory arrest	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Tachycardia	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Ear and labyrinth disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Vertigo	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
General disorders and administration site conditions	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Non-cardiac chest pain	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Hepatobiliary disorders	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Cholelithiasis	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Infections and infestations	1 (0.2)	(0.0, 1.2)	1 (0.4)	(0.0, 2.5)
Appendicitis	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Postoperative wound infection	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Injury, poisoning and procedural complications	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Ankle fracture	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Malignant glioma	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Nervous system disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Paraesthesia	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Psychiatric disorders	1 (0.2)	(0.0, 1.2)	1 (0.4)	(0.0, 2.5)
Depression	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Schizophrenia	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Suicidal ideation	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Respiratory, thoracic and mediastinal disorders	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Acute respiratory failure	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Chronic obstructive pulmonary disease	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)

Discontinuation due to adverse events

Throughout the study, 3 AEs leading to discontinuation from study after vaccination were reported in 2 participants, one in each group. These events were not serious and were assessed as not related to study intervention.

Table 22 Adverse Events Leading to Discontinuation After Vaccination, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF (N[a]=453)		Placebo (N[a]=225)	
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any event	1 (0.2)	(0.0, 1.2)	1 (0.4)	(0.0, 2.5)
Eye disorders	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Ocular hypertension	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Vitreous haemorrhage	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Psychiatric disorders	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)
Schizophrenia	0	(0.0, 0.8)	1 (0.4)	(0.0, 2.5)

Pooled safety analysis

The pooled analysis of safety data in adults aged 18-59 years includes data from the trials listed below. The controls include those who received placebo and those who received a non-RSV vaccine (Tdap or SIIV).

Table 23 Number (%) of Participants Who Received at Least 1 Study Vaccination Across All Studies – 18 Through 59 Years Old Safety Population

	Vaccine Group (as Administered)		
	RSVpreF 120 µg (N[a]=4964)	Control (N[a]=4274)	Total (N[a]=9238)
	n[b] (%)	n[b] (%)	n[b] (%)
Total Exposure	4964 (100.0)	4274 (100.0)	9238 (100.0)
Healthy males and nonpregnant females	1160 (23.4)	479 (11.2)	1639 (17.7)

C3671001	98 (2.0)	58 (1.4)	156 (1.7)
C3671004	282 (5.7)	139 (3.3)	421 (4.6)
C3671014	745 (15.0)	247 (5.8)	992 (10.7)
WI257521	35 (0.7)	35 (0.8)	70 (0.8)
Pregnant females	3804 (76.6)	3795 (88.8)	7599 (82.3)
C3671003	115 (2.3)	117 (2.7)	232 (2.5)
C3671008	3689 (74.3)	3678 (86.1)	7367 (79.7)
With at least 6-month follow-up[c]	3844 (77.4)	3780 (88.4)	7624 (82.5)
Healthy males and nonpregnant females	128 (2.6)	87 (2.0)	215 (2.3)
C3671001	94 (1.9)	55 (1.3)	149 (1.6)
C3671004	0	0	0
C3671014	0	0	0
WI257521	34 (0.7)	32 (0.7)	66 (0.7)
Pregnant females	3716 (74.9)	3693 (86.4)	7409 (80.2)
C3671003	111 (2.2)	111 (2.6)	222 (2.4)
C3671008	3605 (72.6)	3582 (83.8)	7187 (77.8)

Note: Participants with age at vaccination between 18 and 59 years old from C3671001 (Dose 1 only), C3671003, C3671004, C3671008, C3671014 and WI257521 are pooled.
Note: "RSVpreF 120 µg" column includes RSVpreF 120 µg administered alone or concomitantly with placebo, SIIV, or Tdap; "Control" column includes placebo administered alone or with SIIV or Tdap.
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.
c. At least 6-month follow-up includes the participants who completed 6-month visit for C3671001 and WI257521 or (date of end of study - date of the first vaccination +1) >182 days for C3671003 and C3671008. C3671004 and C3671014 did not feature 6-month follow-up visits.

Demographic and baseline characteristics were comparable between the RSVpreF and control participants. Overall, there were more female than male participants (94.6% vs. 5.4%). The median age at vaccination was 30.0 years.

Table 24 Integrated Summary of Demographic and Baseline Characteristics – 18 Through 59 Years Old Safety Population

	Vaccine Group (as Administered)		
	RSVpreF 120 µg (N[a]=4964) n[b] (%)	Control (N[a]=4274) n[b] (%)	Total (N[a]=9238) n[b] (%)
Sex			
Male	349 (7.0)	154 (3.6)	503 (5.4)
Female	4615 (93.0)	4120 (96.4)	8735 (94.6)
Race			
White	3304 (66.6)	2810 (65.7)	6114 (66.2)
Black or African American	972 (19.6)	838 (19.6)	1810 (19.6)
Asian	512 (10.3)	480 (11.2)	992 (10.7)
American Indian or Alaskan Native	47 (0.9)	42 (1.0)	89 (1.0)
Native Hawaiian or other Pacific Islander	15 (0.3)	14 (0.3)	29 (0.3)
Multiracial	46 (0.9)	32 (0.7)	78 (0.8)
Other	3 (<0.1)	0	3 (<0.1)
Not reported	55 (1.1)	49 (1.1)	104 (1.1)
Unknown	10 (0.2)	9 (0.2)	19 (0.2)
Ethnicity			
Hispanic/Latino	1333 (26.9)	1196 (28.0)	2529 (27.4)
Non-Hispanic/non-Latino	3585 (72.2)	3042 (71.2)	6627 (71.7)
Not reported	44 (0.9)	36 (0.8)	80 (0.9)
Unknown	2 (<0.1)	0	2 (<0.1)
Age at vaccination (years)			
18-49	4960 (99.9)	4267 (99.8)	9227 (99.9)
50-59	4 (<0.1)	7 (0.2)	11 (0.1)
Mean (SD)	30.2 (6.93)	29.5 (6.40)	29.9 (6.70)
Median	30.0	29.0	30.0
(Min, max)	(18, 59)	(18, 56)	(18, 59)
Country			
United States	2892 (58.3)	2208 (51.7)	5100 (55.2)
South Africa	487 (9.8)	486 (11.4)	973 (10.5)
Argentina	471 (9.5)	467 (10.9)	938 (10.2)
Japan	232 (4.7)	232 (5.4)	464 (5.0)
Taiwan	130 (2.6)	130 (3.0)	260 (2.8)
Spain	117 (2.4)	122 (2.9)	239 (2.6)
Gambia	98 (2.0)	98 (2.3)	196 (2.1)
Netherlands	97 (2.0)	95 (2.2)	192 (2.1)
Chile	90 (1.8)	89 (2.1)	179 (1.9)
Finland	75 (1.5)	73 (1.7)	148 (1.6)
New Zealand	50 (1.0)	49 (1.1)	99 (1.1)
Philippines	40 (0.8)	39 (0.9)	79 (0.9)
Mexico	38 (0.8)	37 (0.9)	75 (0.8)
Brazil	36 (0.7)	37 (0.9)	73 (0.8)
United Kingdom of Great Britain and Northern Ireland	35 (0.7)	35 (0.8)	70 (0.8)
Denmark	31 (0.6)	31 (0.7)	62 (0.7)
Canada	27 (0.5)	28 (0.7)	55 (0.6)
Australia	11 (0.2)	13 (0.3)	24 (0.3)
Korea (the Republic of)	7 (0.1)	5 (0.1)	12 (0.1)

Upon request, the MAH provided reactogenicity data and updated the ADR table (see question 8 in annex 3, below).

Proportions reporting any AEs within 1 month after vaccination were similar in the RSVpreF 120 µg group (12.8%) compared to the control group (13.1%).
Most AEs were mild or moderate; severe AEs were reported in ≤1.5% across both groups. AEs assessed as related by the investigator were slightly higher (mostly due to lymphadenopathy in

C3671008 and C3671014 and Injection site reactions [Erythema, Pruritis, Bruising, Rash and Swelling]) in the RSVpreF 120 µg group (0.6%) compared to the control group (0.1%).

SAEs, AEs leading to death, life-threatening AEs, AEs leading to withdrawal and immediate AEs that occurred within 1 month were reported in ≤3.5% across both groups.

Table 25 Integrated Summary of Adverse Events by Category Reported from AR CRF Within 1 Month After Vaccination – 18 Through 59 Years Old Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=4964)		Control (N[a]=4274)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Any event	634 (12.8)	(11.9, 13.7)	562 (13.1)	(12.1, 14.2)
Serious	162 (3.3)	(2.8, 3.8)	148 (3.5)	(2.9, 4.1)
Immediate[d]	2 (<0.1)	(0.0, 0.1)	1 (<0.1)	(0.0, 0.1)
Severe	76 (1.5)	(1.2, 1.9)	59 (1.4)	(1.1, 1.8)
Life-threatening	19 (0.4)	(0.2, 0.6)	10 (0.2)	(0.1, 0.4)
Related	28 (0.6)	(0.4, 0.8)	6 (0.1)	(0.1, 0.3)
AE leading to withdrawal	2 (<0.1)	(0.0, 0.1)	0	(0.0, 0.1)
Death[e]	0	(0.0, 0.1)	0	(0.0, 0.1)

Note: Data reported from AE CRF from C3671001 (Dose 1 only), C3671003, C3671004, C3671008, C3671014 and WI257521 are pooled.
Note: "RSVpreF 120 µg" column includes RSVpreF 120 µg administered alone or concomitantly with placebo, SIIV, or Tdap; "Control" column includes placebo administered alone or with SIIV or Tdap.

AEs within 1 month after vaccination were reported by 12.8% in the RSVpreF group compared to 13.1% in the control group. The most commonly reported AEs by SOC in the RSVpreF group were Pregnancy, puerperium, and perinatal conditions (5.4% RSVpreF, 5.7% control), Infections and infestations (2.0%vs. 2.4%) and Gastrointestinal disorders (1.0% vs. 0.9%). The most commonly reported AEs by PT in the RSVpreF group were Premature delivery (1.8% RSVpreF, 1.8% control), Preeclampsia (0.7% and 0.8%) and Gestational hypertension (0.7% and 0.6%).

The proportion with related AEs was slightly higher in the RSVpreF 120 µg group (0.6%) compared to the control group (0.1%). The most commonly reported related AEs were Blood and lymphatic system disorders (0.2% RSVpreF, 0% control), General disorders and administration site conditions (0.2% and <0.1%) and Nervous system disorders (<0.1% and <0.1%). The most commonly reported related AE by PT in the RSVpreF 120 µg group was Lymphadenopathy (0.2% vs. 0%) while all other PTs were reported by <0.1% in each group.

AEs were reported within 30 minutes after vaccination in <0.1% in both groups.

Severe or life-threatening AEs were reported within 1 month after vaccination by 1.9% in the RSVpreF group and 1.5% in the control group. Most common were AEs in the SOC Pregnancy, puerperium, and perinatal conditions (1.3% RSVpreF, 1.0% control) and Infections and infestations (0.2% and <0.1%). The most commonly reported severe or life-threatening AEs by PT were Pre-eclampsia (0.3% and 0.2%) and Premature delivery (0.2% and 0.1%).

Throughout the study, SAEs, AEs leading to withdrawal and AEs leading to death were reported in ≤14.0%, <0.1% and <0.1%, respectively, in both groups.

Table 26 Vaccine Group

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=4964)		Control (N[a]=4274)	
Adverse Event Category	**n[b] (%)**	**(95% CI)[c]**	**n[b] (%)**	**(95% CI)[c]**
Any event	1273 (25.6)	(24.4, 26.9)	1161 (27.2)	(25.8, 28.5)
Serious	623 (12.6)	(11.6, 13.5)	597 (14.0)	(12.9, 15.0)
Immediate[d]	2 (<0.1)	(0.0, 0.1)	1 (<0.1)	(0.0, 0.1)
Severe	225 (4.5)	(4.0, 5.1)	222 (5.2)	(4.5, 5.9)
Life-threatening	64 (1.3)	(1.0, 1.6)	44 (1.0)	(0.7, 1.4)
Related	30 (0.6)	(0.4, 0.9)	7 (0.2)	(0.1, 0.3)
AE leading to withdrawal	3 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.1)
Death[e]	2 (<0.1)	(0.0, 0.1)	0	(0.0, 0.1)

Note: Data reported from AE CRF from C3671001 (Dose 1 only), C3671003, C3671004, C3671008, C3671014 and WI257521 are pooled.
Note: "RSVpreF 120 µg" column includes RSVpreF 120 µg administered alone or concomitantly with placebo, SIIV, or Tdap; "Control" column includes placebo administered alone or with SIIV or Tdap.
Note: MedDRA (v26.1) coding dictionary applied.
Note: Any AE reported in AE CRF were included, regardless if it is considered as reactogenicity.
a. N = number of participants who were vaccinated at the age of 18 through 59 years old 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. For "any event", n = number of participants reporting at least 1 occurrence of any AE.
c. Exact 2-sided confidence interval (CI) was calculated using the Clopper and Pearson method.
d. An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product.
e. Refers to AEs leading to deaths.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./mat_1008_bl_eff/RSV_adult/adae_s151_in2 Date of Generation: 14MAR2024 (03:26)

AEs leading to death that occurred throughout the study were reported in 2 (<0.1%) who received RSVpreF and none who received control. In C3671008, there was 1 death of a maternal participant in the RSVpreF group due to postpartum haemorrhage and hypovolaemic shock, which was assessed by the investigator as not related to study intervention. In C3671001, a 48 year old non-pregnant female who received RSVpreF 120 µg died. The cause of death was combined toxic effects of quetiapine and amlodipine use and was considered not related to study intervention.

SAE reporting rates throughout the study by participants with at least 6 months safety follow up after vaccination were 15.8% for the RSVpreF 120 µg group (15.8%) compared to 15.4% for the control group. The most commonly reported SAEs were Pregnancy, puerperium and perinatal conditions (11.7% RSVpreF, 11.2% control), Cardiac disorders (1.6% and 1.7% in control) and Infections and infestations (1.4% and 1.2%). The most commonly reported SAEs by PT in the RSVpreF 120 µg dose group were Foetal distress syndrome (1.7% in each group), Pre-eclampsia (1.7% and 1.4%), Gestational hypertension (1.1% in each group, Arrested labour (1.0% and 1.2%) and Non-reassuring foetal heart rate pattern (1.0% and 0.8%).

AEs leading to withdrawal occurred in <0.1% in each group.

Post marketing experience

No information on post-marketing experience is reported in the application except as summarised and reflected in the updated RMP.

2.5.1. Discussion on clinical safety

The initial MAA for Abrysvo included safety data for adults aged 60+ years and for pregnant women, along with some Phase 1 data in healthy and non-pregnant adults aged <60 years. Thus, few data were available from non-pregnant adults aged 18-59 years. In the current application dossier, the new safety data come from C3671023, with follow-up to the 6-month final safety visit. In this study, the safety analysis was conducted in 453 subjects in the Abrysvo group and 225 in the placebo group. Of this total 678 persons, 650 (95.4%) completed the study, i.e. completed the 6-month safety follow-up visit (Visit 3).

As expected from prior data, the proportions reporting local reactions within 7 days of vaccination were higher in the RSVpreF group than the placebo group (36.6% vs. 11.6% overall) and the most frequently reported local reaction in both groups was pain at the injection site. However, local reactions were mild or moderate in severity and were short-lived. In the RSVpreF group, the reporting rates for local reactions were numerically higher for the younger subgroup (18-49 years) and in females. The CHMP is of the view that this pattern is not unusual for vaccines used in adults.

In contrast, rates for systemic events within 7 days after vaccination were more similar between RSVpreF and placebo groups, the most common one being fatigue. Again, reporting rates in the RSVpreF subgroup were higher for the younger age subgroup and in females.

For all other AEs reported up to the 1-month follow-up visit, rates were low and similar for the RSVpreF and placebo groups. Few were severe and none was immediate and/or life-threatening. The CHMP noted that no AESIs/Tier 1 AEs (including Guillain-Barre syndrome and Miller Fisher syndrome) were reported in the study. There was one case of urticaria with onset on day 1 that was considered related; rash/urticaria was therefore included in the table in section 4.8 (with frequency as "rare"). In addition, a few related AEs from the broad population (high-risk and healthy participants) were added in SmPC section 4.8, with appropriate frequencies assigned (e.g. lymphadenopathy ("rare"), anaphylaxis ("very rare"), arthralgia ("common"), fatigue ("very common"), pyrexia ("uncommon"), vaccination site pruritus ("rare"), vaccination site bruising ("rare") and vaccination site haematoma ("rare")).

2.5.2. Conclusions on clinical safety

The safety profile in the new population is considered in comparable to the two special populations in which the vaccine has already been authorised (pregnant women to passively protect their infants and older adults).

In this light, the CHMP is of the views that there are no new major concerns raised by the safety data for RSVpreF vs. placebo in the study C3671023.

2.5.3. PSUR cycle

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. Risk management plan

The MAH was requested to submit an updated RMP version (1.1) with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.1 with the following content:

Summary of the safety concerns

Table 27 Module SVIII. Summary of the safety concerns

Summary of Safety Concerns	
Important identified risks	Guillain-Barré syndrome
Important potential risks	None
Missing information	Use in immunocompromised pregnant women and high-risk pregnancies
	Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old

Pharmacovigilance plan

Table 28 (from part III.1 of the RMP): On-going and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
A post-authorization safety study (PASS) of Guillain -Barré syndrome (GBS) following Abrysvo among older adults in the United States (C3671031) (Planned)	To evaluate the risk of GBS, other immune-mediated demyelinating conditions and polyneuropathies following Abrysvo administration among older adults	Guillain-Barré syndrome	Submission of final study protocol Submission of final study report	30 November 2023 31 May 2030
A post-authorisation safety study (PASS) of Abrysvo (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK (C3671026) (Planned)	To evaluate the safety of Abrysvo in all pregnant women and their offspring including immunocompromised pregnant women and high-risk pregnancies	Use in immunocompromised pregnant women and high-risk pregnancies. Guillain-Barré syndrome	Submission of study protocol Submission of final study report	31 Mar 2024 28 Sep 2029
A post-authorisation safety study (PASS) of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK (C3671038) (Planned)	To evaluate the safety of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older	Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old. Guillain-Barré syndrome	Submission of study protocol Submission of final study report	31 Mar 2024 28 Sep 2029

Risk minimisation measures

Table 29: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Guillain-Barré syndrome	Routine risk minimisation measures: EU SmPC Section *4.8 Undesirable effects* Medicine's legal status: Medicinal product subject to medical prescription. Additional RMMs: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Abrysvo post-authorisation safety studies in the EU include GBS as a safety outcome among immunocompromised, or renally or hepatically impaired older adults (C3671038) and among pregnant women and their offspring in a real world setting in Europe and UK (C3671026). Post-authorization safety study of GBS following Abrysvo among older adults in United States (C3671031).
Important Potential Risk		
None		
Missing Information		
Use in immunocompromised pregnant women and high-risk pregnancies	Routine risk minimisation measures: EU SmPC Section 4.4 *Special warnings and precautions for use* Medicine's legal status: Medicinal product subject to medical prescription. Additional RMMs: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A post-authorisation safety study (PASS) of Abrysvo (respiratory syncytial virus stabilised prefusion F subunit vaccine) in pregnant women and their offspring in a real world setting in Europe and UK (C3671026).
Use in immunocompromised, or renally or hepatically impaired older adults ≥60 years old	Routine risk minimisation measures: EU SmPC Section 4.4 *Special warnings and precautions for use* Medicine's legal status: Medicinal product subject to medical prescription. Additional RMMs: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A post-authorization safety study of Abrysvo in immunocompromised, or renally or hepatically impaired older adults aged 60 years and older in a real world setting in Europe and UK (C3671038).

2.7. Update of the Product information

As a consequence of this new indication, the sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated, to reflect use from 18 years of age. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

2.7.1. User consultation

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

Readability user testing was performed on the Abrysvo PL submitted for the initial MAA. The package leaflet was found to be readable and comprehensible and only minor editorial revisions were made during MAA assessment. The PIL submitted as part of the current Type II variation is substantially the same as that originally tested. There are no changes to route of administration, no new safety issues identified and no new medical terminology requiring explanation. There have been no changes to layout, style, font or leaflet size. 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In Europe, about 10% of ARI/influenza-like illness or community-acquired pneumonia cases in adults aged ≥50 years are attributable to RSV. Annual RSV attack rates of 4.2% and 7.2% were observed in community-living adults aged ≥60 years in successive seasons. In UK adults aged from 18 years, some authors have estimated of 487,247 outpatient episodes, 17,799 hospitalisations and 8,482 attributable deaths per season. Of these, 36% of GP episodes, 79% of hospitalisations and 93% of deaths were in ≥65-year-olds. There are some recognised risk factors for severe RSV disease in older adults, including the elderly. Immunosenescence can result in a weakened immune response to pathogens and suboptimal response to vaccines. In addition, there may be reduced lung expansion in older adults because of decreased strength of the respiratory muscles and the diaphragm. Older adults may also have decreased protective mucus levels, lung compliance and elastin.

3.1.2. Available therapies and unmet medical need

There are two vaccines approved in the EU for prevention of RSV LRTD in adults aged from 50 years (Arexvy) or 60 years (Abrysvo). Treatment of RSV disease consists primarily of supportive care (e.g. oxygen, hydration and suctioning of secretions). The use of aerosolized ribavirin is usually limited to immunosuppressed persons due to inconvenient administration, questionable benefit, teratogenicity concerns and high cost.

3.1.3. Main clinical studies

In the initial MAA dossier, C3671013 was the pivotal Phase 3 efficacy study in older adults aged from 60 years. This study was double-blind and placebo-controlled. The new data in this application come from C3671023 Substudy A, which was a double-blind and placebo-controlled study intended to generate immunogenicity data in adults aged 18-59 years considered to be at high risk of severe RSV disease to support immunobridging to the efficacy previously shown in C3671013 in adults aged 60+ years. The aim was therefore to demonstrate that immune responses in the generally immunocompetent population enrolled into C3671023 would be non-inferior to immune responses documented in C3671013. The applicant assumed that a demonstration of non-inferiority in C3671023 would support a conclusion that, if studied, there would also be non-inferior immune responses in adults aged 18-59 years without such underlying conditions. This is a very reasonable assumption.

3.2. Favourable effects

The four co-primary primary endpoints were the GMTs and seroresponse rates (as defined in the protocol) based on anti-RSV A and anti-RSV B neutralizing antibody titres in sera obtained at 1-month post-vaccination. In the four co-primary analyses conducted in the evaluable immunogenicity populations, the RSV A and RSV B GMTs and seroresponse rates were compared between 437 adults aged 18-59 years assigned to RSVpreF in C3671023 vs. 410 randomly selected adults aged 60+ years who received RSVpreF in C3671013. Sera from the two studies were tested concurrently. Noninferiority was to be declared if the lower bounds of the 95% adjusted GMRs were >0.667 and the lower bounds of the 95% of seroresponse rates differences were >-10% for both RSV A and RSV B. While there is no immune correlate of protection established for prevention of RSV, these non-inferiority acceptance criteria are acceptable. Moreover, study success required that all four analyses met the applicable criteria, which is appropriate.

Study C3671023 met the enrolment target, with 681 participants randomised into the study of which 99.6% received study intervention. In general, conduct of the study appears to have been satisfactory, with few important protocol deviations. Although there were no stratification factors applied at randomisation, approximately half of subjects were in the age groups 18-49 vs. 50-59 years.

With an inevitable difference in age between the test and reference groups included in the primary (immunobridging) analysis, there was no declared aim to attempt to match the populations based on other characteristics. With the immunodeficient excluded in both studies, and with 44% of the reference population having at least one pre-specified underlying condition, it is unlikely that the differences would have biased the study towards demonstrating non-inferiority.

Noninferiority was demonstrated for the primary immunogenicity objective, with the pre-defined criteria met for the four co-primary endpoints. The results suggested that greater immune responses were achieved in the 18-59 years group with underlying medical conditions vs. the 60+ group including 44% with underlying conditions, noting that the pre-specified conditions were not necessarily expected to affect the magnitude of the immune response.

For the immunobridging coprimary estimand as measured by GMRs, due to the known differences for C3671023 Substudy A and C3671013, the analysis was based on the ANCOVA model with sex and baseline titre (in logarithm scale) adjusted to compare the GMTs (i.e. adjusted GMRs). The unadjusted analysis provided very similar results. The CSR also provided the model-adjusted and unadjusted analyses for the mITT immunogenicity population. With only small differences in numbers included in each population, the results were compatible with those for the evaluable immunogenicity population.

For the immunobridging coprimary estimand as measured by seroresponse rates, at one month after vaccination with RSVpreF and with noninferiority criteria met, seroresponse rates were higher for adults 18-59 years vs. adults 60+ years. Similar results were obtained in the mITT immunogenicity population. Results for the pre-planned analysis for differences in seroresponse rates were also consistent with those for the primary analysis with higher rates in the adults aged 18-59 years compared to adults 60+ years.
In the placebo group of C3671023 there was no shift in GMTs for RSV A and RSV B from baseline to month 1 compared to GMFRs ⩾17.5 in the RSVpreF group. This finding indicates that natural exposure to RSV during the one-month period was unlikely to have affected the post-vaccination titres observed.

Immune responses were similar for adults aged 18-49 and 50-59 years.

3.3. Uncertainties and limitations about favourable effects

In the absence of an immune correlate of protection for RSV disease, this application rests on the principles of immunobridging based on comparing the functional antibody responses to vaccination in subjects aged 18-59 years with those in adults 60+ years in whom efficacy was previously demonstrated against RSV LRTD. Whereas this is a commonly used and broadly acceptable approach, it is not possible to conclude definitively that the immune responses observed in adults 18-59 years, which were actually rather greater in magnitude than those in adults aged 60+ years, will necessarily translate into at least comparable protection. Nevertheless, it is a very reasonable assumption that the vaccine will be efficacious in the younger adults although the risk of severe RSV disease and thus, the clinical benefit of a RSV vaccination, is less clear for healthy adults aged 18-59 years compared to those with factors putting them at high risk of severe RSV disease.

3.4. Unfavourable effects

The initial MAA for Abrysvo included safety data for adults aged 60+ years and for pregnant women, along with some Phase 1 data in healthy and non-pregnant adults aged <60 years. Thus, few data were available from non-pregnant adults aged 18-59 years. In the current application dossier, the new safety data come from C3671023, with follow-up to the 6-month final safety visit. In this study, the safety analysis was conducted in 453 in the Abrysvo group and 225 in the placebo group. Of this total 678 persons, 650 (95.4%) completed the study, i.e. completed the 6-month safety follow-up visit (Visit 3).

As expected from prior data, the proportions reporting local reactions within 7 days of vaccination were higher in the RSVpreF group than the placebo group (36.6% vs. 11.6% overall) and the most frequently reported local reaction in both groups was pain at the injection site. However, local reactions were mild or moderate in severity and were short-lived. In the RSVpreF group, the reporting rates for local reactions were numerically higher for the younger subgroup (18-49 years) and in females. This pattern is not unusual for vaccines used in adults. Compared to older adults (≥60 years), local reactions might be approximately three times more frequent in the younger population 18-59 years, mainly driven by the higher rate for injection site pain.

In contrast, rates for systemic events within 7 days after vaccination were more similar between RSVpreF and placebo groups, the most common being fatigue and with low fever rates. Again reporting rates in the RSVpreF subgroup were higher for the younger age subgroup and in females. Fatigue (37.3%), headache (28.4%) and muscle pain (24.4%) were the most frequently reported

systemic reactions in high-risk individuals. Only muscle pain was reported more frequently in the RSVpreF group in C3671023 Substudy A compared to the placebo group. Similar to the rate in pregnant women, systemic reactions were reported at least twice as frequently compared to older adults (≥60 years). The incidence of fever was low and occurred at a similar frequency in RSVpreF (1.6%) and placebo (1.3%) groups.

For all other AEs reported up to the 1-month follow-up visit, rates were low and similar for the RSVpreF and placebo groups. Few were severe and none was immediate and/or life-threatening.

The proportions reporting any AEs (including reactogenicity) were similar between RSVpreF and placebo groups and also generally similar to rates reported for pregnant women and older adults. Most AEs were mild or moderate in severity. There was one case of urticaria with onset on day 1 that was considered related. The table of ADRs in section 4.8 of the SmPC was amended to note that hypersensitivity reactions include urticaria.

No AESIs/Tier 1 AEs (including Guillain-Barre syndrome and Miller Fisher syndrome) were reported in the study.

Rates for SAEs were comparable between RSVpreF and placebo/control groups in high-risk patients (RSVpreF: 1.1%, Placebo: 3.1%) and in the healthy/pregnant pooled safety set (RSVpreF: 12.6%, Control: 14.0%). The higher rate of SAEs in the pooled set mainly originates from pregnancy-related AEs since most participants of the pooled set were pregnant women.

In C3671023 Substudy A, 1 participant had an AE leading to death in the RSVpreF group due to a cardio-respiratory arrest which was not considered related to vaccination. In the pooled dataset, 2 AEs leading to death were reported in the RSVpreF group (due to postpartum haemorrhage and hypovolemic shock of a maternal participant; and due to toxicity to various agents). Both deaths were not considered related to vaccination.

3.5. Uncertainties and limitations about unfavourable effects

Whereas the total number of adults aged 18-59 years exposed to RSVpreF is relatively modest, the safety database for this vaccine was already extensive pre-licensure and it is expected that routine usage will result in extensive experience derived from routine pharmacovigilance.

3.6. Effects Table

Table 30 ***Effects Table for Abrysvo in C3671023 Substudy A***

Effect	Short description	Unit	Treatment	Control	Strength of evidence	References
Favourable Effects						
NA	RSV A	GMT	RSVpreF 18-59 y 41097	RSVpreF 60+ y 26225	Adj GMR (95% CI) (ANCOVA) 1.57 (1.39, 1.75)	C3671023 vs. C3671013
NA	RSV B	GMT	37416	24680	1.52 (1.33, 1.72)	
  NA	 RSV A	 SR	 93%	 88%	Diff (95% CI) 5.1 (1.2, 9.2)	same
NA	RSV B	SR	93%	85%	8.3 (4.2, 12.6)	
Unfavourable Effects						
			RSVpreF	Placebo		C3671023

Effect	Short description	Unit	Treatment	Control	Strength of evidence	References
Local AE	7 days	%	36.6%	11.6%	Most common was pain	
Systemic AE	7 days		57.4%	55.6%	Most common was fatigue	
AEs	1 month		8.4%	8.0%		
ADRs	1 month		1.8%	0%		
SAEs	study		1.1%	3.1%		
Death	study		1 case	0		
Disc	study		0.2%	0.4%		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy

The humoral immune response upon RSVpreF vaccination was non-inferior in adults 18-59 yoa at increased risk of (severe) RSV disease to response in adults ≥60 yoa for whom efficacy was demonstrated. The results can be considered robust as all 4 coprimary endpoints encompassing neutralizing GMT ratios and difference in seroresponse rates against RSV A and RSV B were met. Sensitivity and supplementary analyses supported primary immunogenicity conclusions.

Although the healthy 18-59 yoa population was not included in the non-inferiority exercise, supportive immunogenicity data suggest that robust immune response is induced by the vaccine. Further, it is considered plausible that immune response upon RSVpreF vaccination is not different between healthy adults and adults with chronic medical conditions or older adults.

Safety

Compared to the already authorized group of older adults (≥60 yoa), especially reactogenicity seems to be more frequent in younger individuals (18-59 yoa), which is the population that should be added to the label via this EOI. Local reactions might be approximately three times more frequent in the younger population (18-59 yoa), mainly driven by vaccination site pain. Similarly, 2-3 times more younger subjects experienced systemic reactions, where fatigue, headache and muscle pain were most frequently reported systemic reactions in high-risk individuals. It is not unexpected that younger individuals experience reactogenicity reactions more frequently than older adults. Reactogenicity data from (non-pregnant) healthy individuals were also provided to complement the data from high-risk patients. Apart from reactogenicity, the overall AE profile seems comparable between the RSVpreF group and placebo/control.

In total, the AE profile seems to be comparable to the two special populations in which the vaccine has already been authorised (pregnant women to passively protect their infants and older adults).

3.7.2. Balance of benefits and risks

With testing of sera in parallel, the comparisons made between adults aged 18-59 with pre-specified underlying conditions in C3671023 and adults aged 60+ years in C3671013 support an overall conclusion that neutralizing antibody elicited by RSVpreF is at least as high in the former cohort compared to the latter cohort. Although there is no immune correlate of protection established for RSV, this immunobridging exercise supports a conclusion that protection against RSV is likely at least

as good in adults aged 18-59 years as has been documented in adults aged 60+ years. Nevertheless, the clinical benefit of a RSV vaccination, is less clear for healthy adults aged 18-59 years compared to those with factors putting them at high risk of severe RSV disease.

While C3671023 was conducted in adults aged 18-59 years with at least one pre-specified underlying medical condition, there was no expectation that the underlying conditions would have an important effect on the immune responses to RSVpreF. Nevertheless, it is presumed that the intent was to conduct the immunobridging exercise such that the applicability of the results across a broadly immunocompetent population aged 18-59 years would not be questioned. That being the case, the final extension of the indication is not restricted in any way, but simply refers to *Active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV*. This wording allows NITAGs to determine if and how to recommend use in adults aged from 18 years just as the currently approved indication allows them to do the same from a minimum age of 60 years.

In particular, the proposed wording allows NITAGs to select certain adults for vaccination either because they are considered to be at risk of severe disease if they become infected with RSV and/or because they are particularly at risk of acquiring RSV disease due to their employment even if the disease is expected to be mild in severity. For example, NITAGS may choose to target healthcare workers (or subgroups most likely to care for RSV cases) to minimize staff shortages during the RSV season just as influenza vaccines are targeted in many countries.

There are no new major concerns raised by the safety data for RSVpreF vs. placebo in C3671023.

Reflecting these considerations, the CHMP agreed with the extended indication statement for active immunisation of adults.

3.8. Conclusions

The overall B/R of Abrysvo for active immunisation of individuals 18 years of age and older for the prevention of lower respiratory tract disease caused by RSV is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include active immunisation of individuals 18 through 59 years of age for ABRYSVO, based on final results from C3671023 Substudy A; this is a Phase 3 double-blinded, randomised, placebo-controlled study of safety, tolerability and immunogenicity of Abrysvo in participants ≥18 to <60 years of age at high risk of severe RSV disease due to certain chronic medical

conditions. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been approved. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

Furthermore, the CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies, as set out in Annex IV.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix" CHMP AR on additional marketing protection").