EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 December 2025
EMADOC-1700519818-2676030
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AREXVY

Common name: Respiratory syncytial virus (RSV) vaccine (recombinant, adjuvanted)

Procedure No. EMA/VR/0000276225

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
AF	Atrial fibrillation
AIR	At increased risk
ANCOVA	Analysis of covariance
AR	Assessment Report
BMI	Body mass index
CAD	Coronary artery disease
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CDC	Centers for Disease Control and Prevention
CHF	Chronic heart failure
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMI	Cell-mediated immunity
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRO	Clinical research organization
CSR	Clinical Study Report
DBL	Database lock
DLP	Data lock point
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
ED60	Estimated Dilution 60
eDiary	Electronic Diary
EoS	End of study
ES	Exposed set
EU	European Union
GBS	Guillain-Barre syndrome
GCP	Good Clinical Practice
GMF	Geometric mean frequency
GMR	Geometric mean titer ratio
GMT	Geometric mean titer
GSK	GlaxoSmithKline Biologicals
GSK	GlaxoSmithKline Biologicals SA
HIPAA	Health Insurance Portability and Accountability Act
HLT	High level term
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICS	Intracellular cytokine staining
ICU	Intensive care unit
ID	Identification
IEC	Independent Ethics Committee

IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular
IRB	Institutional Review Board
IU	International unit
LAR	Legally acceptable representative
LL	Lower limit
LLOQ	Lower limit of quantification
LLT	Lowest Level Term
LRTD	Lower respiratory tract disease
M	Module
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean geometric increase
MPL	Monophosphoryl lipid A
N	Number of participants
NI	Non-inferiority
OA	Older adults
OA	Older adult
PBMC	Peripheral blood mononuclear cell
PD	Protocol deviation
PI	Prescribing Information
PI	Product Information
pIMD	Potential immune-mediated disease
PPS	Per Protocol Set
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred term
QS-21	Quillaja saponaria Molina, fraction 21
RCC	Reverse cumulative distribution curve
RNA	Ribonucleic acid
RSI	Reference safety information
RSV	Respiratory syncytial virus
RSVPreF3	Respiratory Syncytial Virus PreFusion protein F3
RSVPreF3 OA	RSV PreFusion protein F3 Older Adult
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard deviation
SmPC	Summary of product characteristic
SOC	System organ class
SQI	Significant quality issue
SRR	Seroresponse rate
SRT	Safety Review Team
Th	T-helper

TNF	Tumor necrosis factor
UL	Upper limit
US	United States
VE	Vaccine efficacy
YOA	Years of age

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals submitted to the European Medicines Agency on 29 May 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 18 years of age and older for AREXVY, based on results from study 222253 (RSV OA=ADJ-025); this is a Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk of respiratory syncytial virus disease, compared to older adults ≥60 years of age. As a consequence, sections 4.1, 4.6, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The variation requested 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(s) P/0508/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0508/2023 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Scientific advice

The MAH received Scientific Advice from the CHMP on 24 March 2022 EMA/SA/000076659. The Scientific Advice pertained to (non-) clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Daniela Philadelphy

Timetable	Actual dates
Submission date	29 May 2025
Start of procedure:	21 June 2025
CHMP Rapporteur's preliminary assessment report circulated on:	14 August 2025
PRAC Rapporteur's preliminary assessment report circulated on:	25 August 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 September 2025
MAH's responses submitted to the CHMP on:	10 October 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	4 November 2025
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	14 November 2025
PRAC RMP advice and assessment overview adopted by PRAC	27 November 2025
CHMP opinion:	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Respiratory syncytial virus (RSV) is a highly contagious human pathogen that causes respiratory tract infections in people of all ages. RSV infection does not confer long-term immunity. Therefore, re-infection with RSV occurs throughout life and is common in all age groups. Usually, re-infections manifest as common acute upper respiratory tract infections. However, in more vulnerable individuals (e.g. immunocompromised persons, persons with co-morbidities, and older adults), re-infections can also lead to more severe diseases, such as lower respiratory tract disease (LTRD). Although severe disease occurs more commonly in these aforementioned groups, in young healthy individuals an infection can also have a significant health impact. Approximately 22% of influenza-like illness in 25–29-year-olds has been attributed to RSV (Zambon 2001), and such cases have been reported to result

in persistent shortness of breath and fatigue up to 4 weeks following illness (Hall et al 1978). In healthy adults, it has been reported that 38% of the RSV infections result in work absence (Hall, 2000).

State the claimed the therapeutic indication

Arexvy was authorised in June 2023 in adults 60 years of age and older based on efficacy data from an interim analysis of a single pivotal phase 3 trial, supported by multiple phase 3 clinical studies (EMEA/H/C/006054/0000). During a subsequent extension of indication (EMEA/H/C/006054/II/0008), study RSV OA=ADJ-018 was submitted, which was an immune bridging study to include adults 50 through 59 years of age who are at increased risk for RSV disease.

The current indication approved by the EMA for RSVPreF3 Arexvy is:

Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in:

- adults 60 years of age and older
- adults 50 through 59 years of age who are at increased risk for RSV disease.

The sought after indication for RSVPreF3 Arexvy is:

Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 18 years of age and older.

Epidemiology

Incidence rates of RSV disease are frequently derived from population-based influenza surveillance systems in adults ≥65 YOA. Younger adult populations have more limited epidemiological data available. The available epidemiological data for this age group describes a lower incidence of RSV morbidity and mortality than in adults with higher age, and that most hospitalisations in this group occur in patients with pre-existing comorbidities such (e.g. obesity, diabetes, or chronic cardiopulmonary, renal, or immunocompromising conditions). However, the burden of RSV in this younger adult population is most likely underestimated due to a number of factors including undertesting, delayed testing, and lower viral load in adults. (Cong, BMC Med, 2023). Moreover, diagnostic testing is often not performed outside of a hospitalized setting as therapeutic options for RSV is purely supportive for adults.

A retrospective cohort study drew on data from six European databases in order to identify (among others) the hospitalization rates and mortality rates related to RSV (Darwin-EU Age-specific incidence rates of RSV-related disease in Europe). In the general population, the incidence rate of RSV-related hospitalisation was 35 (95% CI, 34 - 36) per 100,000 person-years (PY), with higher incidence rates observed in older adults(≥ 60 years) (28 per 100,000 PY, 95% CI, 27 – 29), and lower in those aged 18 to 59 years, with a rate of 2.1 (95% CI, 1.9 - 2.2) per 100,000 PY.

In younger healthy adults, RSV may cause cold or influenza-like symptoms. Although hospitalization rates are significantly lower than those at opposite ends of the age spectrum, the estimates of RSV infection incidence remain substantial. Approximately 22% of influenza-like illness in 25–29-year-olds has been attributed to RSV (Zambon 2001), and such cases have been reported to result in persistent shortness of breath and fatigue up to 4 weeks following illness (Hall et al 1978). In healthy adults, it has been reported that 38% of the RSV infections result in work absence (Hall, 2000).

Aetiology and pathogenesis

RSV is a single-stranded RNA virus mainly transmitted via contact with aerosols from an infected host. The virus initially replicates in the epithelial cells of the upper respiratory tract and may subsequently migrate to the lower respiratory tract. The incubation period is usually between 3-7 days. Neutrophils infiltrate the airways, leading to complications such as bronchiolitis.

Clinical presentation

Symptomatic RSV usually starts as an upper respiratory tract infection, that can lead to more serious disease by involving the lower respiratory tract. The most common symptoms include nasal congestion/rhinorrhoea, sore throat, cough, sputum, dyspnoea, wheezing, rhonchi, shortness of breath, and decreased oxygen saturation. In addition, systemic signs include fever, fatigue, body aches, headache and decreased appetite

Management

Treatment

Treatment for RSV in adults is limited to supportive care consisting of supplemental oxygen, intravenous fluids and bronchodilators. In addition, inhaled and systemic corticosteroids are often prescribed in patients with asthma or COPD.

Prevention

Since 2023, there have been substantial advances in the prevention of RSV due to the approval of Arexvy and two additional vaccines. mRESVIA is approved for prevention of RSV-LRTD in adults aged ≥ 60 years, and adults 18-59 years who are at increased risk for LRTD caused by RSV. Abrysvo is approved in adults ≥ 18 years regardless of co-morbidity status. In addition, Abrysvo is approved for passive protection in infants following maternal immunization during pregnancy.

Unmet need

Despite new vaccination possibilities for the prevention of RSV, the morbidity and mortality associated with the disease remains high.

2.1.2. About the product

The RSV PreFusion protein F3 Older Adult vaccine (referred to as RSVPreF3 OA, or Arexvy), was developed for prevention of lower respiratory tract disease (LRTD) caused by RSV, A and B in older adults. The RSVPreF3 antigen is an engineered version of the RSV F surface glycoprotein, i.e., a trimeric RSV F protein stabilised in a pre-fusion conformation. The finished product of RSVPreF3 OA vaccine is presented as a preservative-free powder and suspension for injection containing 120µg of RSVPreF3 antigen (powder) adjuvanted with AS01E (suspension).

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

Compliance with CHMP guidance

The most relevant CHMP guidelines applied:

- "Guideline on clinical evaluation of vaccines" (CHMP/VWP/164653/05, Rev.1)

- "Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease" (EMA/CHMP/257022/2017)

Scientific Advice

In EMA/SA/000076659 (24/03/2022) the MAH revealed plans to conduct study RSV OA=ADJ-014, which used an immunobridging approach to support use in 18-59 YOA, both with and without co-morbidities. Although the trial design proposed by the MAH at the time differs slightly from the trial in the current application, the following advice is relevant for ADJ-025.

- if vaccine efficacy is demonstrated in accordance with the predefined criterion in the pivotal efficacy study in subjects aged from 60 years, an approval for a younger adult population could be based on immunobridging accompanied by safety data.
- The focus of the assessment of non-inferiority based on the GMT ratios is appropriate in a population that is expected to have been primed by natural exposure(s) to RSV.
- Comparisons of the percentages with at least a 4-fold increase in NA titre from pre- to post-vaccination should be added as secondary analyses (i.e. in each of HA and AIR and for each of RSV-A and B).

2.1.4. General comments on compliance with GCP

The MAH claims all clinical studies carried out in countries outside the European Union (EU) met the ethical requirements of Directive 2001/20/EC. The clinical studies are conducted by or on behalf of GSK in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines (ICH Harmonised Tripartite Guidelines E6 for Good Clinical Practice, FDA 21CFR parts 50, 56 and 312). During the conduct and reporting of this/these study(s), two independent audits were carried out in accordance with appropriate regulatory requirements and guidelines in order to assess compliance with the study protocol, ICH GCP, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

Table 1 Tabular overview of RSV OA=ADJ- 025 (222253, Completed)

Study Countries	**Study design & Study population**	**Objectives**	**Vaccination schedule Study Groups**	**Number of participants**	
				PPS Day 31	**ES**
Australia, Canada, Germany Japan, South Africa, United States	**Design** Phase 3b, open-label, uncontrolled, non-randomized, multi-country, multi-centre, non-inferiority study with 2 Parts (Part A and Part B). **Study population** <u>Part A includes 2 parallel cohorts (Cohort 1 and Cohort 2):</u> Cohort 1 includes adults 18-49 YOA AIR for RSV disease (RSV-A-AIR Group) who received 1 dose of RSVPreF3 OA vaccine. Cohort 2 includes adults ≥ 60 YOA (RSV-OA Group) who received 1 dose of RSVPreF3 OA vaccine. <u>Part B includes 1 cohort (Cohort 3):</u> Cohort 3 includes adults 18-49 YOA AIR for RSV disease (RSV-A-AIR Group) who received 1 dose of RSVPreF3 OA vaccine.	**Objectives** <u>Primary objectives* (confirmatory) (Part A):</u> To demonstrate the NI** of the humoral immune response in participants 18-49 YOA AIR for RSV disease compared to adults ≥60 YOA for the RSV-A and RSV-B strains after RSVPreF3 OA vaccine administration. <u>Secondary safety objective (descriptive) (Part A and Part B):</u> To evaluate the safety and reactogenicity after the RSVPreF3 OA vaccine administration. Secondary immunogenicity objective (Part A): To evaluate the humoral immune response to RSVPreF3 OA vaccine until 6 months**** after study vaccination for both populations.	**Vaccination schedule** <u>Part A</u> RSV-A-AIR (Cohort 1): RSVPreF3 OA vaccine on Visit 1 (Day 1) RSV-OA (Cohort 2): RSVPreF3 OA vaccine on Visit 1 (Day 1) <u>Part B</u> RSV-A-AIR (Cohort 3): RSVPreF3 OA vaccine on Visit 1 (Day 1)	394*** 417 NA	426 429 603

AIR = at increased risk; NA = not applicable; NI = non-inferiority; OA = older adults; PPS = Per Protocol Set; *Based on hierarchical testing. The analyses of the primary immunogenicity objectives were based on the Visit 2 (Day 31) PPS analysis with a DBL of 17 September 2024 and are considered final. **NI criteria defined as ≤1.5 for the GMT ratio and ≤10% for the SRR difference upper limit of 95% CI. ***This included participants with underlying medical conditions such as chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, chronic liver and renal diseases, and neurologic or neuromuscular conditions. **** The results of the secondary immunogenicity objectives, based on the blood samples collected up to 6 months post-vaccination and the analyses were performed on the PPS (DBL: 26 March 2025). *****There were 394 participants included in the PPS at Visit 2 (Day 31) for the primary analysis. Upon further evaluation during the EoS analysis, one participant was eliminated from the PPS at Visit 2 (Day 31) due to a late reported PD.

2.3.2. Pharmacodynamics

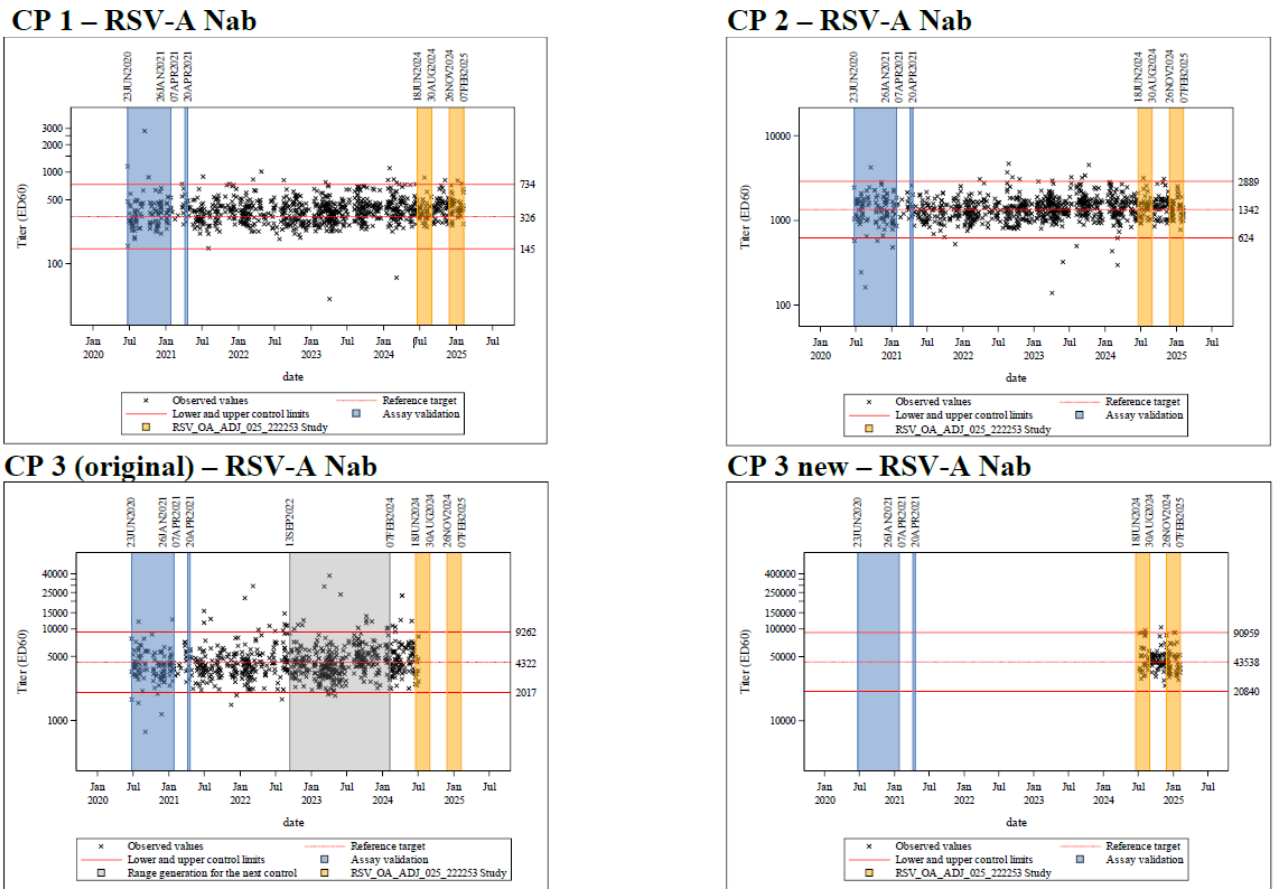
The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

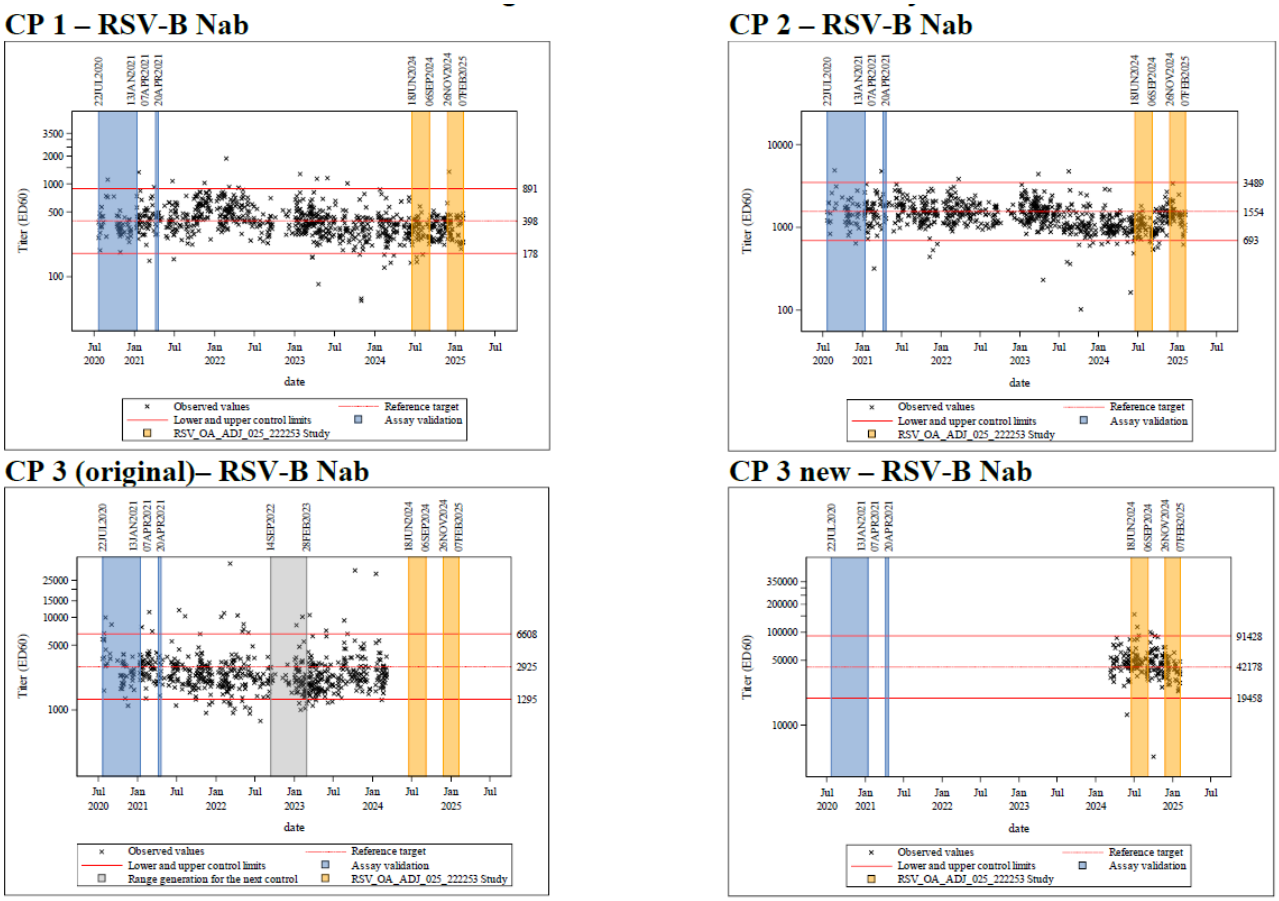
Primary and secondary pharmacology

Laboratory assays used for the assessment of the primary and secondary endpoints (i.e. RSV-A and RSV-B neutralization assays) were considered validated for the purpose of testing in the Phase 3 studies. According to the GlaxoSmithKline Biologicals SA (GSK) assay stability monitoring process, the stability of an assay is routinely monitored over time using in-process testing of quality control (QC) samples and a regular evaluation of a QC panel (proficiency panel) tested at least every 6 months. Compared to previous applications, the current SOP only had minor/editorial changes not impacting the assay experimental procedure.

The MAH provided QC charts for the RSV-A and RSV-B neutralization assays (Figure 1). QC samples are included in each assay run. Data of a given run are validated if all QC sample values are within their respective pre-defined acceptance ranges. If the criterion is not met for at least 1 QC sample, the run is rejected, and testing is repeated according to the assay standard operating procedure (SOP). QC charts are built using all QC sample values generated, from both valid and invalid runs, during non-clinical and clinical testing. These charts allow evaluating assay stability over time and detecting any potential trends.

Figure 1 QC charts for the 4 positive controls used in the RSV-A & B neutralization assay from the validation period until the end of the clinical testing of the RSV OA=ADJ-025 study





ED60, Estimated dilution 60%; Nab, Neutralization antibody corresponding to neutralization titer; QC, Quality control; RSV, Respiratory syncytial virus. The assay validation periods are highlighted in blue, the period of new CP3 control range calculation is highlighted in gray (in the original CP3 control chart) and the periods corresponding to the clinical testing of the RSV OA=ADJ-025 study are highlighted in orange.

2.3.3. Discussion on clinical pharmacology

The RSV-A and RSV-B neutralization assays have previously been found to be fit for purpose of comparative immunogenicity (EMEA/H/C/006054/II/0002/G). The SOP used in the current submission differs only by minor/editorial changes compared to the previous SOPs.

2.3.4. Conclusions on clinical pharmacology

The assays have previously been found fit for purpose.

2.4. Clinical efficacy

Evidence of a single clinical study was submitted, ADJ-025.

2.4.1. Main study

A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults ≥60 years of age.

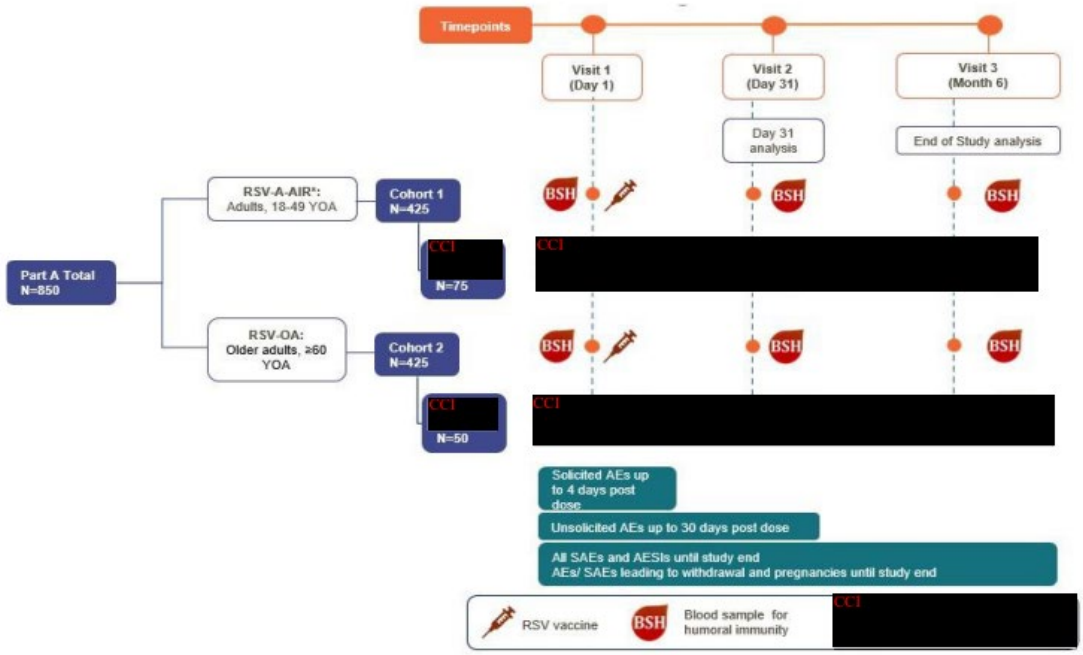
Methods

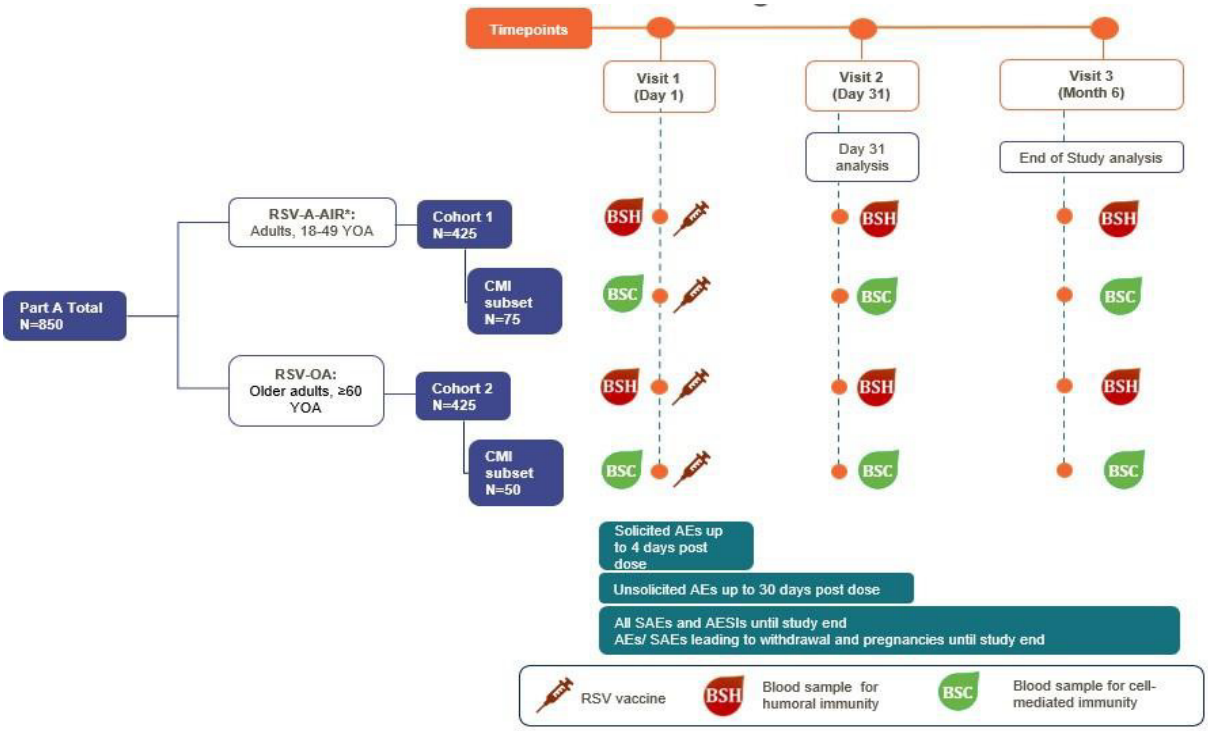
Study ADJ-025 is a completed phase 3, non-blinded, non-randomized, study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk (AIR) for RSV disease, compared to older adults ≥60 years of age from whom efficacy has previously been demonstrated. An overview of the study design is presented in Figure 2 for Part A and Figure 3 for Part B.

The study had three cohorts: Cohort 1 (18-49 YOA AIR for RSV disease), Cohort 2 (≥60 YOA RSV-OA), and Cohort 3 (18-49 YOA AIR for RSV disease), and was divided into two parts (Part A and part B). The primary immunogenicity analyses were only performed for Part A (Cohorts 1 and 2); safety analyses were performed for both Part A and Part B (Cohorts 1, 2, and 3)

The results of the primary immunogenicity objectives were based on the blood samples collected up to Visit 2 (Day 31), with a DBL of 17 September 2024. This CSR also includes the results of the secondary and tertiary immunogenicity objectives, based on the blood samples collected up to 6 months post-vaccination with a DBL of 26 March 2025.

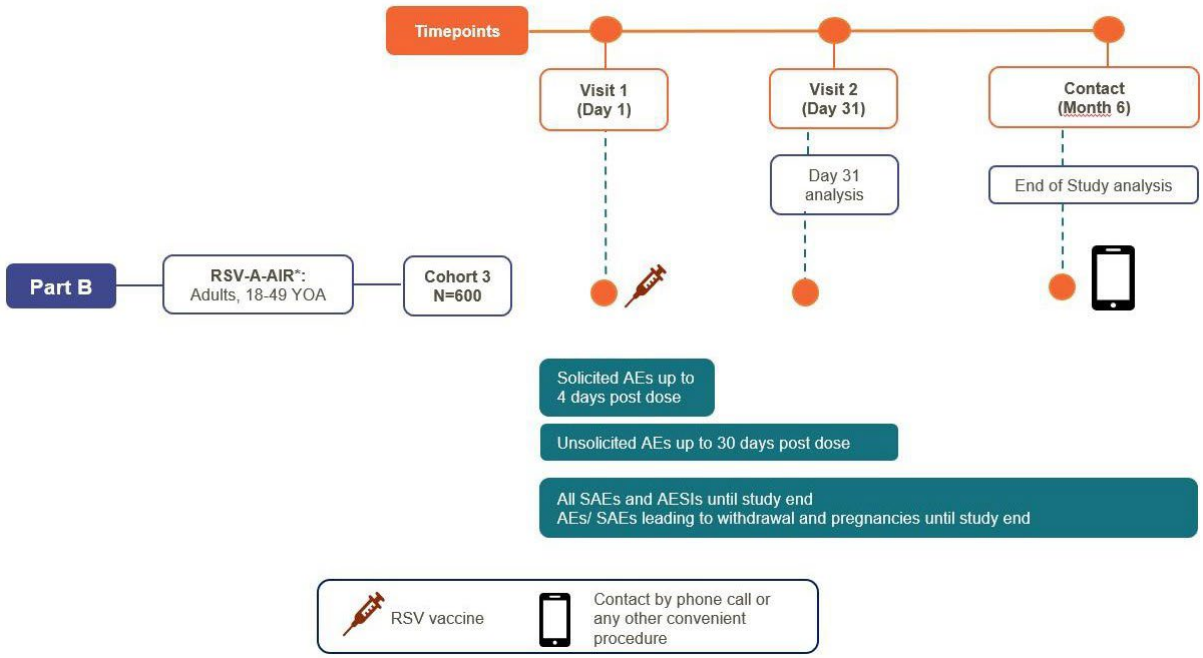
Figure 2 Overview of study design for RSV OA=ADJ-025 Part A





A = Adults; AE=Adverse event; AESI=Adverse events of special interest; AIR=At increased risk; CMI= Cell-mediated immune; N=Number of participants; OA=Older adults; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age. *Participants with underlying medical conditions such as chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, chronic liver and renal diseases, and neurologic or neuromuscular conditions

Figure 3 Overview of study design for RSV OA=ADJ-025 Part B



A = Adults; AE=Adverse event; AESI=Adverse events of special interest; AIR=At increased risk; CMI= Cell-mediated immune; N=Number of participants; OA=Older adults; pIMD=Potential immune-mediated disease;

RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age. *Participants with underlying medical conditions such as chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, chronic liver and renal diseases, and neurologic or neuromuscular conditions

Study participants

Inclusion criteria differed per Cohort.

Cohort 1 & 3 included males and females aged 18-49 years old with at least 1 of the following conditions if considered medically stable: Chronic cardiopulmonary disease, type I or type II diabetes; chronic kidney of liver disease, neurologic or neuromuscular conditions.

Cohort 2 included males and females ≥60 YOA with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease. Enrolment rules were applied to ensure adequate representation by age category within Cohort 2 for participants in 60-69 YOA group and ≥ 70 YOA group.

The main exclusion criteria included suspected immunosuppressive or immunodeficient conditions, unstable chronic illness, history of dementia or any medical condition that may impair cognition, and a history of hypersensitivity which may be exacerbated by the vaccine. Receipt of any RSV vaccine was a further criterion for exclusion.

Treatments

All participants received the RSVPreF3 OA investigational vaccine (120 µg RSVPreF3/AS01E) on day 1 of the study by intramuscular injection in the deltoid of the non-dominant arm. The vaccine formulation and schedule are the same as those used to demonstrate safety and efficacy against confirmed RSV-LRTD in adults ≥60 YOA in study RSV OA=ADJ-006.

Objectives and endpoints

Primary and secondary immunogenicity objectives and endpoints (assessed in part A of the study) are presented in Table 2.

Table 2 Objectives and endpoints (primary, secondary and tertiary)

Objective	Endpoint
Primary* (Part A)	
• To demonstrate the non-inferiority of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to adults ≥60 YOA for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralizing titers expressed as GMT ratio (RSV-OA over RSV-A-AIR) at 1 month (Day 31) after study intervention administration.* • Seroresponse in RSV-A neutralizing titers from Day 1 to Day 31.*
• To demonstrate the non-inferiority of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to adults ≥60 YOA for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralizing titers expressed as GMT ratio (RSV-OA over RSV-A-AIR) at 1 month (Day 31) after study intervention administration.* • Seroresponse in RSV-B neutralizing titers from Day 1 to Day 31.*
Secondary Immunogenicity (Part A)	
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 6 months after study vaccination for both populations.	• RSV-A and RSV-B neutralizing titers, at pre-study intervention administration and 1 month and 6 months after study intervention administration.
Tertiary Immunogenicity (Part A)	
• To evaluate the CMI response after the RSVPreF3 OA investigational vaccine administration until 6 months after study vaccination for both populations.	• CMI response expressed as group geometric mean of the frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least

Objective	Endpoint
	1 cytokine among CD40L, 4-1BB (CD-137), IL-2, TNF-α, IFN-γ, IL-13, IL-17, at pre-study intervention administration 1 month and 6 months after study intervention administration, in a subset of participants.

AIR = at increased risk; CD = cluster of differentiation; CD40L = CD40 ligand; CMI = cell-mediated immunity; GMT = geometric mean titer; IFN = interferon; IL = interleukin; NI = non-inferiority; OA = older adults; RSV = respiratory syncytial virus; RSVPreF3 = Respiratory Syncytial Virus PreFusion protein F3; TNF = tumor necrosis factor; YOA = years of age. *Co-primary endpoints

Seroresponse rate was defined as the proportion of participants with a ≥4-fold increase in neutralizing titers (post-study intervention administration over pre-study intervention administration).

Non-inferiority margins were set at 1.5 for GMT ratio and 10% for difference in seroresponse rate (SRR) for ≥60 YOA compared to 18-49 YOA.

Sample size

The target sample size for part A of the study was approximately 850 participants: 425 participants in Cohort 1 (RSV-A-AIR [18-49 YOA group]) and 425 participants in Cohort 2 (RSV-OA [≥60 YOA group]), to obtain at least 722 evaluable participants (361 participants in the RSV-A-AIR [18-49 YOA] cohort and 361 participants in the RSV-OA [≥60 YOA] cohort) for the evaluation of the primary objectives, assuming that approximately 15% of the enrolled participants would not be evaluable.

This sample size provided 93% global power to demonstrate non-inferiority of immune response in the 18-49 YOA group vs. the ≥60 YOA group for the RSV-A strain (across the co-primary endpoints of GMT ratio and SRR), assuming a standard deviation of 0.45 for the log10 transformed anti-RSV-A Ab GMT and an SRR of 81.6% in the ≥60 YOA group, with a non-inferiority margin of 1.5 for GMT ratio and 10% for SRR. If non-inferiority was demonstrated for RSV-A (using a hierarchical testing sequence, see statistical methods), the sample size would also provide 90% global power for the RSV-B strain, assuming a standard deviation of 0.45 for the log10 transformed anti-RSV-B Ab GMT and an SRR of 78.7% in the ≥60 YOA group, with non-inferiority margins of 1.5 for GMT ratio and 10% for SRR.

For the evaluation of reactogenicity and safety, the sample size of 1025 participants in the combined Cohorts 1 and 3 (18-49 YOA groups) had 64% and 87% probability of observing at least one vaccinated participant with an AE if the true AE incidence rate is 0.1% and 0.2% respectively.

Randomisation

The study was uncontrolled, and no randomisation took place.

Blinding (masking)

The study was conducted as an open-label study.

Statistical methods

Multiple analysis populations were defined:

- the Exposed Set (ES) consisted of all participants who received the study intervention.
- The Per-Protocol Set (PPS) consisted of all eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with

blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

CMI subset was recruited from a selected number of countries and selected number of clinical sites. In the selected sites, the investigator would allocate, if possible, at Visit 1, the first participants in each group to the CMI subset until the allocated target is reached (75 participants from the RSV-A-AIR subset and 50 participants from the RSV-OA subset). Primary immunogenicity analyses were performed in the PPS set of Part A of the study.

The primary analyses for RSV-A and RSV-B GMT ratio at 1-month post-vaccination were performed using ANCOVA, with log10-transformed titer as an outcome and including the factor age group (18-49 YOA vs. ≥60 YOA) and the baseline log10-transformed titer as covariate.

Primary analyses for group differences in RSV-A and RSV-B SRR at 1-month post-vaccination were done by subtracting SRR in the 18-49 YOA group from the SRR in the ≥60 YOA group, with 95% CI derived using the method of Miettinen and Nurminen.

Missing data was not imputed. The primary estimand was defined as shown in Table 3.

Table 3 Primary estimand

Attributes					**Summary measure**
Treatment	**Population**	**Endpoint (variable)**	**Intercurrent events (ICEs)**		
			Description	**Handling strategy**	
RSVPreF3 OA investigational vaccine at Day 1.	Non-immunocompromised adults at increased risk for RSV disease with 18- 49 YOA. OA with ≥60 YOA.	• RSV-A neutralizing titers (expressed in ED60) measured at 1 month (Day 31) after study intervention administration. • Seroresponse in RSV-A neutralizing titers (expressed in ED60) from Day 1 to Day 31. • RSV-B neutralizing titers (expressed in ED60) measured at 1 month (Day 31) after study intervention administration. • Seroresponse in RSV-B neutralizing titers (expressed in ED60) from Day 1 to Day 31.	Taking prohibited medication/vaccine or intercurrent medical condition prior to Day 31.	Data collected after ICEs will be excluded from the analysis at Day 31 (Hypothetical strategy). Rationale: To evaluate the immunogenicity parameters in the absence of ICE.	Ratio of GMTs with 95% CI and difference in seroresponse rate (SRR) with 95% CI for RSV-A and RSV- B neutralizing titers (ED60) at Day 31 between the RSV-OA group (≥60 YOA) and the RSV-A-AIR group (18-49 YOA).

SRR is defined as the proportion of participants having a fold increase in neutralizing titers (1-month post-study intervention administration over pre-study intervention administration)≥4. AIR=At increased risk; CI=Confidence interval; ED60= Estimated dilution 60; GMT=Geometric mean titer; OA=Older adults; YOA=Years of age

Testing of primary endpoints was performed sequentially: in the first sequence, non-inferiority was tested for the GMT ratio and SRR (as co-primary endpoints) for RSV-A. Non-inferiority would be declared if the upper limit of the 95% CI for the GMT ratio was ≤1.5 and the upper limit of the 95% CI for the SRR difference was ≤10%. In the second sequence (only tested if the first sequence was successful), non-inferiority was tested for the RSV-B strain. Non-inferiority would be declared using the same criteria as for RSV-A.

As per the SAP, a second analysis based on the ES would be performed to complement the PPS analysis if the percentage of vaccinated participants with serological results excluded from the PPS was more than 5%. A secondary analysis was also performed using IU/ml for computation of the GMT ratio and SSR instead of titers.

Results

Participant flow

The study was conducted in 52 centres across 6 countries (Australia, Canada, Germany, Japan, South Africa, and the United States). Participants for all three cohorts were included in all countries.

Overall, 1528 participants were screened for parts A and B, and 1459 participants were included in the Enrolled Set, of whom 1458 were included in the Exposed Set. Of these, 426 participants were in cohort 1 (part A, 18-49 YOA), 429 in cohort 2 (part A, ≥60 YOA), and 603 in cohort 3 (part B [safety only], 18-49 YOA). The reasons for withdrawal up to month 6 are presented in Table 4.

Table 4 Summary of study completion up to Month 6 with reasons for withdrawal from exposed set

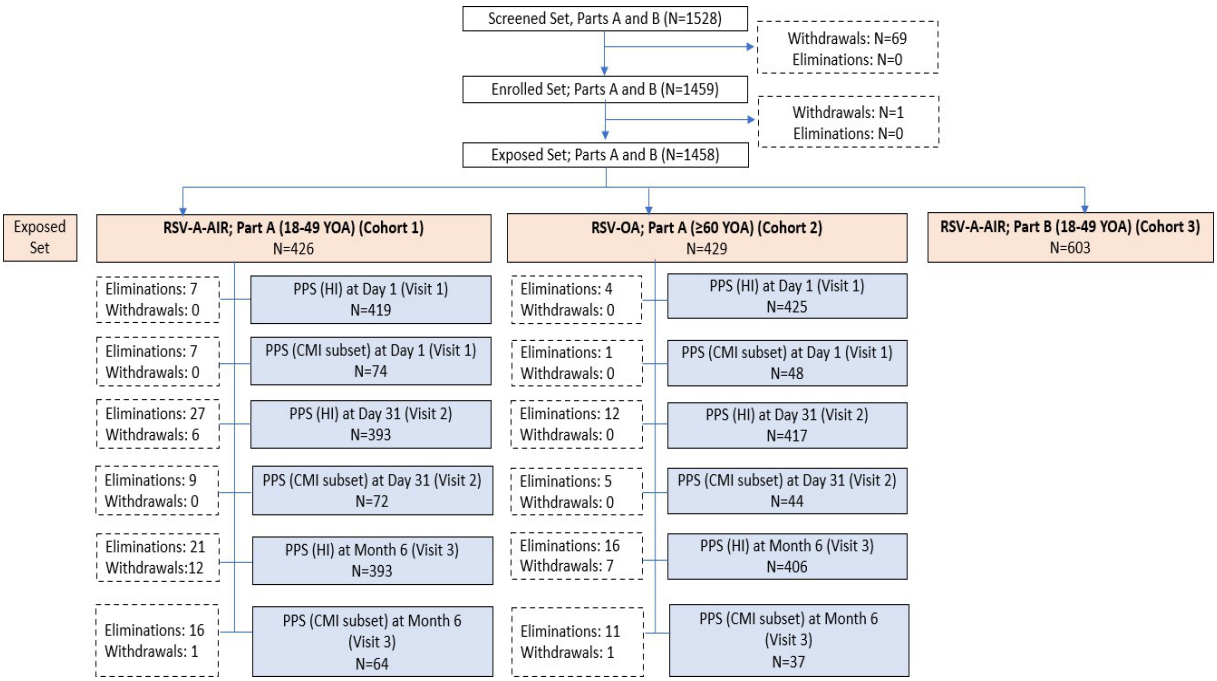
	RSV-A-AIR (Cohort 1) N=426		**RSV-A-AIR (Cohort 3) N=603**		**RSV-A-AIR (Cohort 1 + 3) N=1029**		**RSV-OA (Cohort 2) N=429**		**Total N=1458**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Completed the study	414	97.2	586	97.2	1000	97.2	422	98.4	1422	97.5
Withdrawn from the study	12	2.8	17	2.8	29	2.8	7	1.6	36	2.5
Primary reason for withdrawal										
Lost to follow-up	9	2.1	13	2.2	22	2.1	5	1.2	27	1.9
Protocol deviation	0	0	2	0.3	2	0.2	0	0	2	0.1
Withdrawal by participant	2	0.5	1	0.2	3	0.3	2	0.5	5	0.3
Other	1	0.2	1	0.2	2	0.2	0	0	2	0.1

n/% = number/percentage of participants in a given category; N = number of participants; Withdrawn = number of participants who did not complete their last visit/contact; Completed the study = number of participants who completed the last study visit/contact; RSV-A-AIR = At

increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1; Cohort 3); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2)

Of the part A participants, a total of 810 participants (94.7%) were included in the PPS for the primary analyses (393 [92.3%] in the 18-49 YOA group and 417 [97.2%] in the ≥60 YOA group). The flow of participants is shown in Figure 4.

Figure 4 Participant flow



Recruitment

The study was initiated on April 29th, 2024 (first participant first visit). The last participant for last visit for efficacy at V2 (day 31, time of primary endpoint) was July 30, 2024. The last participant last visit (i.e. month 6 safety data) was March 18th, 2025. Target enrolment was met, as 855 participants were included in the Exposed Set for part A and 1029 18-49 YOA participants were exposed across Part A cohort 1 and Part B cohort 3.

Conduct of the study

Amendments

The original protocol (dated December 18, 2023) of RSV OA=ADJ-025 was amended on May 3, 2024. The purpose of this amendment was to implement a new Cohort 3 as a Part B of this study to collect safety information in an extended sample size to better characterize the safety profile of the RSVPreF3 OA investigational vaccine in a population of individuals at increased risk for RSV disease 18-49 years of age. This extra cohort of approximately 600 adults 18-49 years of age at increased risk for RSV disease, were to be monitored for reactogenicity and safety for a period of 6 months following the administration of one dose of RSVPreF3 OA investigational vaccine at Visit 1. The same inclusion and exclusion criteria as well as enrolment rules as for participants of Cohort 1 applied for Cohort 3.

Protocol deviations

At least 1 important protocol deviation was reported in 89 participants (8.6%) in the RSV-A-AIR group and 28 participants (6.5%) in the RSV-OA group Most of the protocol deviations were related to assessment or timepoint completion, followed by study procedures, and wrong study treatment/administration/dose.

Baseline data

In general, the demographics of the participants, excluding age, were comparable between the RSV-A-AIR and RSV-OA groups (Table 5). The median age of participants at the time of study intervention administration (Visit 1) was 40.0 years (range: 18 to 50 years) in the RSV-A-AIR group and 68.0 years (range: 59 to 89 years) in the RSV-OA group. In the overall study population, a total of 814 participants (55.8%) were female, and 644 participants (44.2%) were male. The percentage of participants with exactly 1 chronic disease of interest was 68.8% in the RSV-A-AIR group and 35.4% in the RSV-OA group.

Table 5 Summary of demography and baseline characteristics – Exposed Set

	RSV-A-AIR Cohort 1 N=426		**RSV-A-AIR Cohort 3 N=603**		**RSV-A-AIR Cohort 1 + 3 N=1029**		**RSV-OA Cohort 2 N=429**		**Total N=1458**	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination										
N with data	426		603		1029		429		1458	
Mean	38.9		38.1		38.4		68.6		47.3	
Standard Deviation	7.8		8.7		8.4		5.7		15.7	
Median	41.0		40.0		40.0		68.0		45.0	
Minimum	19		18		18		59		18	
Maximum	49		50		50		89		89	
Age group										
18-49 YOA	426	*100*	603	*100*	1029	*100*			1029	*70.6*
60-69 YOA							248	*57.8*	248	*17.0*
>=70 YOA							181	*42.2*	181	*12.4*
>=80 YOA							18	*4.2*	18	*1.2*
Sex										
Male	179	*42.0*	256	*42.5*	435	*42.3*	209	*48.7*	644	*44.2*
Race										
American Indian or Alaska Native	8	*1.9*	11	*1.8*	19	*1.8*	0	*0*	19	*1.3*
Asian	60	*14.1*	64	*10.6*	124	*12.1*	50	*11.7*	174	*11.9*
Black Or African American	77	*18.1*	181	*30.0*	258	*25.1*	54	*12.6*	312	*21.4*
Native Hawaiian or Other Pacific Islander	0	*0*	11	*1.8*	11	*1.1*	0	*0*	11	*0.8*
White	255	*59.9*	274	*45.4*	529	*51.4*	302	*70.4*	831	*57.0*
Multiple Race Categories	19	*4.5*	59	*9.8*	78	*7.6*	22	*5.1*	100	*6.9*
Not Reported	3	*0.7*	0	*0*	3	*0.3*	1	*0.2*	4	*0.3*
Unknown	4	*0.9*	3	*0.5*	7	*0.7*	0	*0*	7	*0.5*

	RSV-A-AIR Cohort 1 N=426		RSV-A-AIR Cohort 3 N=603		RSV-A-AIR Cohort 1 + 3 N=1029		RSV-OA Cohort 2 N=429		Total N=1458	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Country										
Australia	20	*4.7*	115	*19.1*	135	*13.1*	40	*9.3*	175	*12.0*
Canada	162	*38.0*	97	*16.1*	259	*25.2*	156	*36.4*	415	*28.5*
Germany	32	*7.5*	17	*2.8*	49	*4.8*	24	*5.6*	73	*5.0*
Japan	42	*9.9*	14	*2.3*	56	*5.4*	41	*9.6*	97	*6.7*
South Africa	58	*13.6*	197	*32.7*	255	*24.8*	53	*12.4*	308	*21.1*
United States	112	*26.3*	163	*27.0*	275	*26.7*	115	*26.8*	390	*26.7*
BMI (kg/m²)										
N with data	426		602		1028		429		1457	
Mean	31.7		31.2		31.4		29.0		30.7	
Standard Deviation	8.6		8.7		8.7		6.2		8.1	
Median	30.7		29.9		30.2		28.1		29.5	
Minimum	16.1		15.0		15.0		16.1		15.0	
Maximum	69.2		70.1		70.1		51.2		70.1	
Chronic disease of interest										
Exactly 1 pre-existing chronic disease	263	*61.7*	445	*73.8*	708	*68.8*	152	*35.4*	860	*59.0*
At least 2 pre-existing chronic disease	163	*38.3*	156	*25.9*	319	*31.0*	128	*29.8*	447	*30.7*
Cardiopulmonary conditions	231	*54.2*	335	*55.6*	566	*55.0*	135	*31.5*	701	*48.1*
Diabetes mellitus	218	*51.2*	285	*47.3*	503	*48.9*	130	*30.3*	633	*43.4*
Other diseases	143	*33.6*	133	*22.1*	276	*26.8*	129	*30.1*	405	*27.8*
Smoking status for tobacco										
Current smoker	84	*19.7*	127	*21.1*	211	*20.5*	55	*12.8*	266	*18.2*
Former smoker	80	*18.8*	106	*17.6*	186	*18.1*	166	*38.7*	352	*24.1*
Never smoker	262	*61.5*	370	*61.4*	632	*61.4*	208	*48.5*	840	*57.6*
Smoking status for e-cigarettes										
Current smoker	26	*6.1*	27	*4.5*	53	*5.2*	6	*1.4*	59	*4.0*
Former smoker	19	*4.5*	19	*3.2*	38	*3.7*	5	*1.2*	43	*2.9*
Never smoker	380	*89.2*	557	*92.4*	937	*91.1*	417	*97.2*	1354	*92.9*
Unknown	1	*0.2*	0	*0*	1	*0.1*	1	*0.2*	2	*0.1*

Numbers analysed

The analysis groups are provided in Table 6. The primary analyses of immunogenicity were performed on the PPS. As the percentage of vaccinated participants with serological results excluded from the PPS was >5% in the 18-49 YOA group, a second analysis based on the ES was also performed.

Immunogenicity analyses were performed for only Part A of the study as planned in the protocol. The overall ES for Part A of the study included 855 participants (426 participants in the RSV-A-AIR group and 429 participants in the RSV-OA group).

At day 31, 417 (97.9%) participants in the RSV-A-AIR group had non-missing serological results for RSV-A and were included in the ES analysis for RSV-A while 416 (97.7%) had non-missing serological results for RSV-B and were included in the ES analysis for RSV-B. Of the ≥60 YOA group, 428 (99.8%) had non-missing serological results for RSV-A and RSV-B and were included in the ES analysis. The PPS at day 31 consisted of 394 participants (for RSV-A) / 393 (for RSV-B) participants in the 18-49 YOA group and 417 participants in the ≥60 YOA group.

At month 6, 799 (93.5%) participants were included in the PPS for humoral immune response (393 participants [92.3%] in the RSV-A-AIR group and 406 participants [94.6%] in the RSV-OA group)

Table 6 Analysis groups in RSV OA = ADJ-025

Analysis set	**RSV-A-AIR (Cohort 1) N (%)**	**RSV-A-AIR (Cohort 3) N (%)**	**RSV-A-AIR (Cohort 1 +3) N (%)**	**RSV-OA (Cohort 2) N (%)**	**Total number N (%)**
Enrolled set **	426	604	1030	429	1459
Exposed set **	426 (100%)	603 (99.8%)	1029 (99.9%)	429 (100%)	1458 (99.9%)
Exposed set for immunogenicity	426 (100%)	NA*	NA*	429 (100%)	855 (100%†)
Per protocol set of immunogenicity (D1)	419 (98.4%)	NA*	NA*	425 (99.1%)	844 (98.7%†)
Per protocol set of immunogenicity (D31)	393 (92.3%)	NA*	NA*	417 (97.2%)	810 (94%†)
Per protocol set of immunogenicity (M6)	393 (92.3%)	NA*	NA*	406 (94.6%)	799 (93.5%†)

D= Day; M=Month; NA*Cohort 3 was used only for the safety analyses in part B; ** enrolled set was used for the safety analyses. †Immunogenicity analyses were only performed in Part A, with cohorts 1 & 2. Percentage provided represents percentage of n=855 (enrolled set for cohort 1 + enrolled set for cohort 2).

Outcomes and estimation

Primary objectives

Non-inferiority of the immune response to RSVPreF3 OA in 18-49 YOA compared to ≥60 YOA was demonstrated in terms of RSV-A neutralizing GMTs (upper limit of the 95% CI on group GMT ratio was 0.81, which was below the pre-defined non-inferiority criterion of 1.5) and SRR (upper limit of the 95% CI on SRR difference was -4.14%, below the pre-defined non-inferiority criterion of **+**10%).

Non-inferiority of the immune response to RSVPreF3 OA in 18-49 YOA compared to ≥60 YOA was also demonstrated in terms of RSV-B neutralizing GMTs (upper limit of the 95% CI on group GMT ratio was 0.82, which was below the pre-defined non-inferiority criterion of 1.5) and SRR (upper limit of the 95% CI on SRR difference was -4.83%, below the pre-defined non-inferiority criterion of 10%). Results are shown in Table 7.

Table 7 Ratio of RSV-A and RSV-B neutralising antibody adjusted GMTs between the 18-49 YOA group and the >60 YOA group at 1 month after vaccination (PPS, First Analysis) measured with the ED60 assay

	RSV-A-AIR			RSV-OA			Adjusted GMT Ratio RSV-OA vs RSV-A-AIR		
		95% CI			95% CI		95% CI		
Assay	**N**	**% or Value**	**LL**	**UL**	**n**	**% or Value**	**LL**	**UL**	**% or Value**	**LL**	**UL**
RSV-A	394				417						
Adjusted GMT (a)		11914.6	10933.2	12984.2		8591.5	7902.7	9340.3	0.72	0.64	0.81
SRR (b): D31/ baseline(D1)	343	87.1	83.3	90.2	324	77.7	73.4	81.6	-9.36	-14.58	-4.14
RSV-B	393				417						
Adjusted GMT (a)		12503.4	11490.5	13605.4		9087.6	8372.1	9864.2	0.73	0.65	0.82
SRR (b): D31/ baseline(D1)	343	87.3	83.6	90.4	322	77.2	72.9	81.2	-10.06	-15.29	-4.83

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1)
N = number of participants with both pre- and post-vaccination results available
n for SRR = number of participants having a fold increase >= 4
a. comparison is done using the group ratio of adjusted GMT (RSV-OA/RSV-A-AIR) (ANCOVA model applied to the log10- transformed titers). The ANCOVA model included the group as fixed effects and the pre-dose log-10 titer as covariate
b. comparison is done using the difference of SRR (RSV-OA - RSV-A-AIR)
CI = Confidence interval; GMT = Geometric mean titer; SRR = Seroresponse rate; LL = Lower limit; UL = Upper limit
PI(D31) = 1 month post RSV vaccination

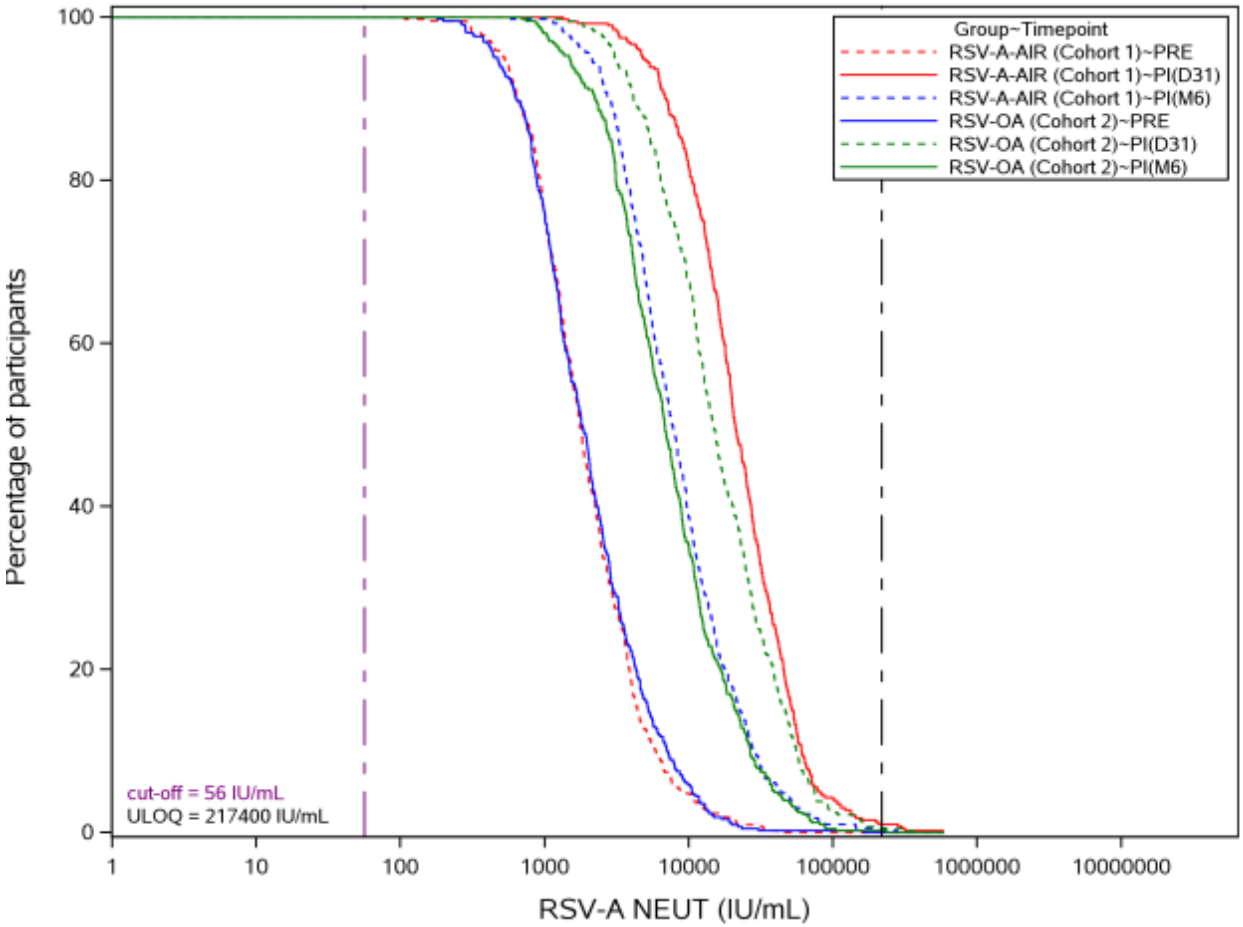
Supplementary analyses

Similar results were also obtained in the ES for the primary objectives. For RSV-A the GMT ratio was estimated as 0.73 (95% CI: 0.64 – 0.82) and SRR difference was estimated as -9.25 (95% CI: -14.37 – -4.15). For RSV-B the GMT ratio was estimated as 0.74 (95% CI: 0.66 – 0.83) and SRR difference was estimated as -9.68 (95% CI: -14.85 – -4.52).

In a sensitivity analysis using IU/ml instead of titer to compute GMT ratio and SRR, similar results were also found. For RSV-A, the GMT ratio was 0.72 (95% CI: 0.63 – 0.81) and the SRR difference was -13.06 (95% CI: -18.61 – -7.48). For RSV-B, the GMT ratio was 0.73 (95% CI: 0.65 – 0.82) and the SRR difference was -9.83 (-14.97 – -4.71).

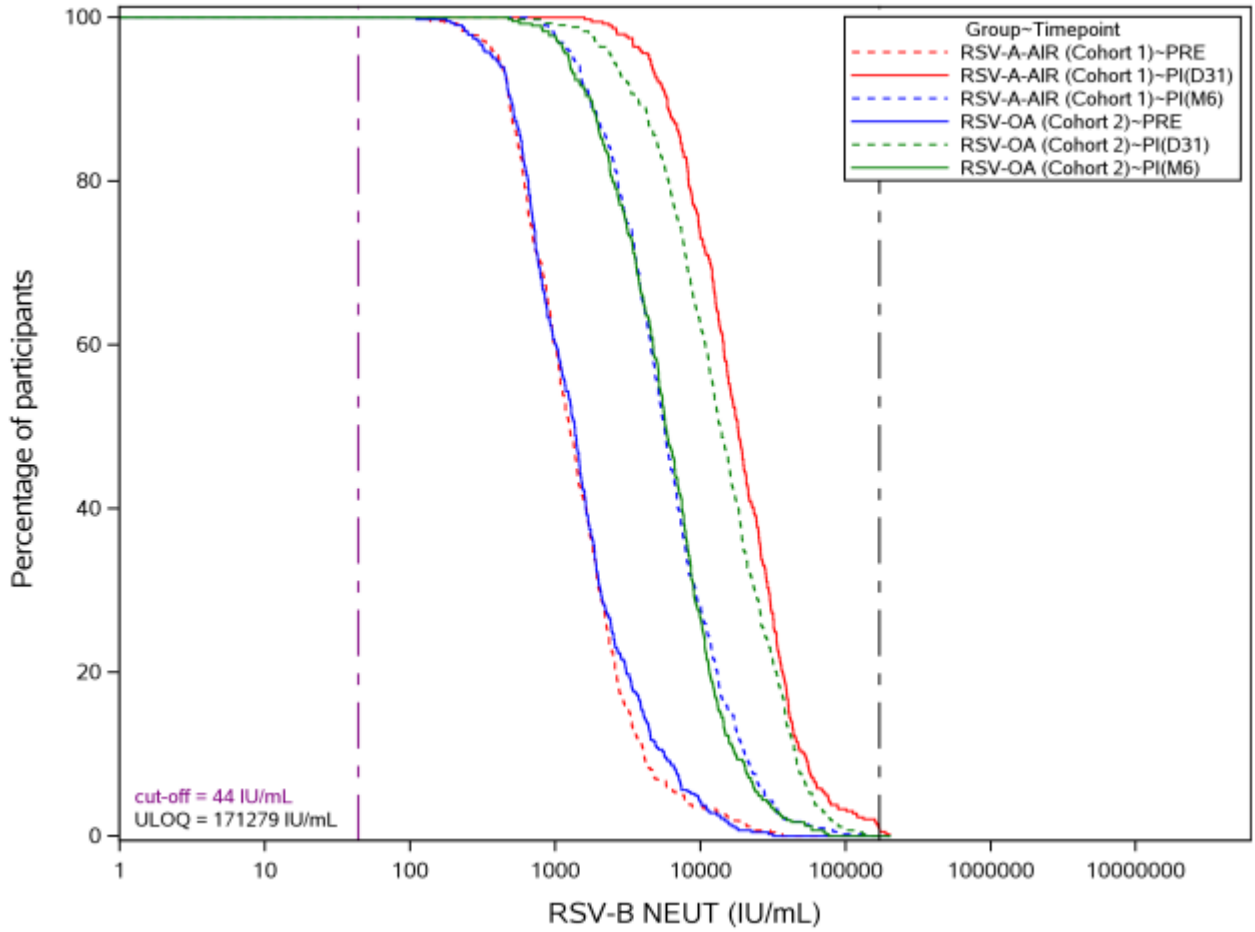
Similar results were obtained when the non-inferiority analysis was performed on the PPS at the End of Study (EoS).

Figure 5 Reverse cumulative distribution curve for RSV-A neutralizing concentrations (IU/mL) per group and timepoint Per Protocol Set for humoral immunogenicity



RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2). PRE = Pre-vaccination; PI(D31) = 1 month post RSV vaccination; PI(M6) = 6 months post RSV vaccination

Figure 6 Reverse cumulative distribution curve for RSV-B neutralizing concentrations (IU/mL) per group and timepoint Per Protocol Set for humoral immunogenicity



RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2). PRE = Pre-vaccination; PI(D31) = 1 month post RSV vaccination; PI(M6) = 6 months post RSV vaccination

Secondary objective: Humoral response after 6 months

Humoral response after 6 months is shown in Table 8 for RSV A and Table 9for RSV-B.

Table 8 Number and percentage of participants with RSV-A neutralizing titers (ED60) equal to or above the cut-off, SRR, GMT and MGI Per-Protocol Set for humoral immunogenicity

		RSV-A-AIR (Cohort 1)				RSV-OA (Cohort 2)			
			95% CI				95% CI		
		n	% or value	LL	UL	n	% or value	LL	UL
PRE	N	419				425			
>= 18 ED60		419	*100*	99.1	100	425	*100*	99.1	100
GMT			*892.6*	821.5	969.9		*913.8*	837.2	997.4

PI(D31)	N	393				417			
>= 18 ED60		393	*100*	99.1	100	417	*100*	99.1	100
GMT			*11853.4*	10875.3	12919.5		*8632.4*	7858.3	9482.6
MGI: D31 / baseline (D1)		393	*13.32*	12.01	14.78	417	*9.45*	8.55	10.45
SRR: D31 / baseline (D1)		342	*87.0*	83.3	90.2	324	*77.7*	73.4	81.6
PI(M6)	N	393				406			
>= 18 ED60		393	*100*	99.1	100	406	*100*	99.1	100
GMT			*4439.8*	4042.1	4876.7		*3917.7*	3553.0	4319.7
MGI: M6 / baseline (D1)		393	*4.98*	4.54	5.47	406	*4.40*	4.04	4.80
SRR: M6 / baseline (D1)		242	*61.6*	56.6	66.4	207	*51.0*	46.0	55.9

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2).

N = number of participants with available results.

n/% = number / percentage of participants with titers within the specified range n for MGI = number of participants with available results at both time points; n for SRR = number of participants with at least a 4-fold increase compared to pre-dose GMT = geometric mean titer; MGI = mean geometric increase; 95% CI = 95% confidence interval; SRR = Seroresponse rate; LL = Lower limit; UL = Upper limit; PRE = Pre-vaccination; PI(D31) = 1 month post RSV vaccination; PI(M6) = 6 months post RSV vaccination

Table 9 Number and percentage of participants with RSV-B neutralizing titers (ED60) equal to or above the cut-off, SRR, GMT and MGI Per-Protocol Set for humoral immunogenicity

		RSV-A-AIR (Cohort 1)				**RSV-OA (Cohort 2)**			
			95% CI				**95% CI**		
		N	**% or value**	**LL**	**UL**	**n**	**% or value**	**LL**	**UL**
PRE	N	418				425			
>= 18 ED60		418	*100*	99.1	100	425	*100*	99.1	100
GMT			*988.1*	905.9	1077.8		*1045.1*	953.7	1145.2
PI(D31)	N	393				417			
>= 18 ED60		393	*100*	99.1	100	417	*100*	99.1	100
GMT			*12337.6*	11334.3	13429.7		*9178.5*	8367.7	10067.8
MGI: D31 / baseline (D1)		392	*12.50*	11.27	13.87	417	*8.75*	7.89	9.69
SRR: D31 / baseline (D1)		342	*87.2*	83.5	90.4	322	*77.2*	72.9	81.2
PI(M6)	N	393				406			
>= 18 ED60		393	*100*	99.1	100	406	*100*	99.1	100
GMT			*4335.6*	3941.7	4769.0		*4355.0*	3971.4	4775.7
MGI: M6 / baseline (D1)		392	*4.40*	4.00	4.85	406	*4.26*	3.87	4.69
SRR: M6 / baseline (D1)		204	*52.0*	47.0	57.1	201	*49.5*	44.5	54.5

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2).

N = number of participants with available results.

n/% = number / percentage of participants with titers within the specified range n for MGI = number of participants with available results at both time points; n for SRR = number of participants with at least a 4-fold increase compared to pre-dose GMT = geometric mean titer; MGI = mean geometric increase; 95% CI = 95% confidence interval; SRR = Seroresponse rate; LL = Lower limit; UL = Upper limit; PRE = Pre-vaccination; PI(D31) = 1 month post RSV vaccination; PI(M6) = 6 months post RSV vaccination

Tertiary objective: CMI response

CMI response expressed as group geometric mean of the frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least 1 cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, at pre-study intervention administration 1 month and 6 months after study intervention administration, in a subset of participants was determined as a tertiary endpoint.

A robust RSVPreF3-specific CD4+ T cell response was elicited post-vaccination in the RSV-A-AIR group and the RSV-OA group as compared to their respective baselines. At Visit 1 (Day 1), results were available for 69 participants in the RSV-A-AIR group and 48 participants in the RSV-OA group.

- The GMF of RSVPreF3-specific CD4+ T cells at baseline, day 31, and month 6 for the RSV-A-AIR versus RSV-OA group were 256.1 versus 121.3, 1883.2 versus 1188.6, and 877.0 versus 620.5.
- The number and percentage of participants with at least 4-fold increase in the frequency of CD4+ T cells expressing at least 2 markers including at least 1 cytokine of interest over baseline at day 31 and month 6 for the RSV-A-AIR versus RSV-OA group were 19 (32.8%) versus 4 (9.3%), and 2 (3.6%) versus 0.
- No RSVPreF3-specific CD8+ T cell response was observed at either day 31 or 6-month post-vaccination.

Ancillary analyses

Subgroup analyses by age at vaccination 18-49 YOA, 60-69 YOA and ≥70 YOA, and by risk-factors were performed. Subgroup analyses were exploratory

Age at vaccination

Table 10 Number and percentage of participants with RSV-A and RSV-B neutralizing titers (ED60) equal to or above the cut-off, SRR, GMT and MGI, by age group (ED60 assay).

		RSV-A-AIR (Cohort 1)				RSV-OA (Cohort 2)							
		18-49 YOA				60-69 YOA				>=70 YOA			
			95% CI				95% CI				95% CI		
Time point		n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL
		RSV A											
PRE	N	419				245				180			
	>= 18 ED60	419	100	99.1	100	245	100	98.5	100	180	100	98.0	100
	GMT		892.6	821.5	969.9		896.7	800.7	1004.1		937.7	816.0	1077.6
PI(D31)	N	393				242				175			

		RSV-A-AIR (Cohort 1)				RSV-OA (Cohort 2)							
		18-49 YOA				60-69 YOA				>=70 YOA			
			95% CI				95% CI				95% CI		
Time point		n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL
	>= 18 ED60	393	100	99.1	100	242	100	98.5	100	175	100	97.9	100
	GMT		11853.4	10875.3	12919.5		8899.4	7903.8	10020.3		8276.3	7098.6	9649.3
	MGI: D31 / baseline (D1)	393	13.32	12.01	14.78	242	9.94	8.70	11.36	175	8.82	7.57	10.27
	SRR: D31 / baseline (D1)	342	87.0	83.3	90.2	191	78.9	73.2	83.9	133	76.0	69.0	82.1
PI(M6)	N	393				235				171			
	>= 18 ED60	393	100	99.1	100	235	100	98.4	100	171	100	97.9	100
	GMT		4439.8	4042.1	4876.7		3912.8	3450.4	4437.1		3924.4	3356.9	4587.8
	MGI: M6 / baseline (D1)	393	4.98	4.54	5.47	235	4.50	4.01	5.05	171	4.27	3.74	4.87
	SRR: M6 / baseline (D1)	242	61.6	56.6	66.4	119	50.6	44.1	57.2	88	51.5	43.7	59.2
		RSV B											
PRE	N	418				245				180			
	>= 30 ED60	418	100	99.1	100	245	100	98.5	100	180	100	98.0	100
	GMT		988.1	905.9	1077.8		1051.9	928.9	1191.1		1035.9	904.5	1186.3
PI(D31)	N	393				242				175			
	>= 30 ED60	393	100	99.1	100	242	100	98.5	100	175	100	97.9	100
	GMT		12337.6	11334.3	13429.7		9821.5	8724.8	11056.0		8358.1	7210.2	9688.9
	MGI: D31 / baseline (D1)	392	12.50	11.27	13.87	242	9.30	8.10	10.67	175	8.04	6.89	9.38
	SRR: D31 / baseline (D1)	342	87.2	83.5	90.4	193	79.8	74.1	84.6	129	73.7	66.5	80.1
PI(M6)	N	393				235				171			
	>= 30 ED60	393	100	99.1	100	235	100	98.4	100	171	100	97.9	100
	GMT		4335.6	3941.7	4769.0		4398.4	3897.8	4963.3		4296.1	3719.7	4961.8
	MGI: M6 / baseline (D1)	392	4.40	4.00	4.85	235	4.31	3.80	4.88	171	4.20	3.62	4.87

		RSV-A-AIR (Cohort 1)				RSV-OA (Cohort 2)							
		18-49 YOA				60-69 YOA				>=70 YOA			
			95% CI				95% CI				95% CI		
Time point		n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL
	SRR: M6 / baseline (D1)	204	52.0	47.0	57.1	121	51.5	44.9	58.0	80	46.8	39.1	54.6

Risk-factors

The MAH submitted a post-hoc subgroup analyses by baseline medical condition (cardiopulmonary conditions, diabetes mellitus, and other diseases) for the primary endpoint analyses for Cohort 1. The subgroup analysis revealed consistent findings across all three RSV-A-AIR subgroups, suggesting no meaningful differences in the immune response based on the specific categories of baseline medical conditions. The GMT ratio (95%CI) for RSV-OA over RSV-A-AIR group for those with cardiopulmonary conditions, diabetes mellitus, other diseases, and overall was 0.71 (0.61, 0.82), 0.67 (0.58, 0.78), and 0.71 (0.60, 0.84), and 0.72 (0.64, 0.81) for RSV A and 0.77 (0.67, 0.89), 0.67 (0.58, 0.77), 0.69 (0.59, 0.82), and 0.73 (0.65, 0.82) for RSV-B.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11 Summary of Efficacy for trial 222253 (RSV OA=ADJ-025)

Title: A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults ≥60 years of age.		
Study identifier	222253 (RSV OA=ADJ-025)	
Design	Phase 3b, open-label, uncontrolled, non-randomized study. The study was conducted in 2 Parts - Part A (immunogenicity and safety evaluation) and Part B (additional safety evaluation).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months not applicable not applicable
Hypothesis	Non-inferiority NI will be claimed if the upper limit of the 95% CI for the RSV-A and RSV B neutralizing group GMT ratio will be ≤1.5 and the upper limit of 95% CI for the group SRR difference will be ≤10% (co-primary endpoints)	

Treatments groups	18–49-year-olds at increased risk of RSV-LRTD (Cohort 1)		1 dose of Arexvy (120 µg RSVPreF3 recombinant antigen adjuvanted with AS01E) administered intramuscularly (IM) N= 426 enrolled N= 426 exposed N= 419 in PPS
	18–49-year-olds at increased risk of RSV-LRTD (Cohort 3)		N= 604 enrolled N= 603 exposed N= NA in PPS (only used for safety endpoints)
	≥60-year-olds with at least 1 chronic stable medical condition (Cohort 2)		1 dose of Arexvy (120 µg RSVPreF3 recombinant antigen adjuvanted with AS01E) administered intramuscularly (IM) N= 429 enrolled N= 429 exposed N= 425 in PPS
Endpoints and definitions	Co-Primary endpoint	**RSV-A neutralization** antibody titers expressed as both **group GMT ratio** (OA-RSV/RSV-A-AIR) and **group SRR difference** (OA-RSV – RSV-A-AIR) 31 days post intervention†	
	Co-Primary endpoint	**RSV-B neutralization** antibody titers expressed as both **group GMT ratio** (OA-RSV/RSV-A-AIR) and **group SRR difference** (OA-RSV – RSV-A-AIR) 31 days post intervention †	
	†NI was claimed if the upper limit of the 95% CI for the GMT ratio was ≤1.5 and the upper limit of 95% CI for the SRR difference was ≤10%. Testing procedure was hierarchical with RSV-A being tested first.		
Database lock	26 March 2025		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Per protocol set:** All eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination 31 days post intervention.		
Descriptive statistics and estimate variability	**Treatment group**	**RSV-AIR**	**OA-RSV**
	Number of subjects	394	417
	Adjusted GMT (RSVA)	11914.6	8591.5
	(95%CI)	10933.2; 12984.2	7902.7;9340.3
	Number of subjects	393	417
	Adjusted GMT (RSVB)	12503.4	9087.6
	(95%CI)	11490.5; 13605.4	8372.1; 9864.2
	Number of subjects	343	324
	Adjusted SRR (RSVA)	87.1	77.7

	(95%CI)	83.3; 90.2	73.4; 81.6
	Number of subjects **Adjusted SRR (RSVB)** **(95%CI)**	343 87.3 83.6; 90.4	322 77.2 72.9; 81.2
Effect estimate per comparison	**RSV-A neutralization group GMT ratio** and **group SRR difference**	Comparison groups	OA-RSV versus RSV-A-AIR
		Ratio of adjusted GMTs (95%CI)	0.72 (0.64;0.81)
		SRR (95%CI)	- 9.36 (-14.58; -4.14)
	RSV-B neutralization group GMT ratio and **group SRR difference**	Comparison groups	OA-RSV versus RSV-A-AIR
		Ratio of adjusted GMTs (95%CI)	0.73 (0.65; 0.82)
		SRR (95%CI)	-10.06 (-15.29; -4.83)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The new data in this application comes from study RSV OA=ADJ-025, which was a phase 3b, open-label, non-randomized study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA vaccine (Arexvy) in adults 18-49 years of age at increased risk for RSV disease, compared to older adults ≥60 years of age for whom efficacy has previously been demonstrated. The open-label, non-randomized design is not expected to affect the comparison of immunogenicity between younger and older adults.

In Part A of the study, the immune response and safety profile of RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease (cohort 1) compared to older adults ≥60 years of age (cohort 2) was investigated. Part B included cohort 3 (same inclusion criteria as cohort 1) and aimed at collecting additional safety data in an extended sample size of individuals at increased risk for RSV disease 18-49 years of age. Overall, the design of the study is acceptable for the immunobridging exercise.

The study included an immunocompetent population 18-49 years of age at increased risk of RSV-LRTD due to the presence of at least 1 stable medical condition (chronic cardiopulmonary disease, diabetes mellitus, chronic kidney disease, chronic liver disease or neurologic/neuromuscular condition) (RSV-A-AIR). An indication is sought for all individuals 18-49 years of age, regardless of co-morbidities. The applicant assumed that a demonstration of non-inferiority for this age group in RSV OA=ADJ-025 would support a conclusion that there would also be non-inferior immune responses in adults aged 18-49 years without such underlying conditions. This is considered a reasonable assumption. This assumption is also supported by the results of RSV OA=ADJ-018 (EMEA/H/C/006054/II/0008) in which

the immune response 1-month post-vaccination with Arexvy for 50–59-year-old both at and not at increased risk of RSV-LRTD was non-inferior to the response seen in ≥60-year-old population (co-primary endpoints). Therefore, the choice of the increased risk population for the immunobridging approach and the broader population sought for in the indication is considered acceptable from an immunogenicity point of view. The four co-primary endpoints were the GMT ratio's and seroresponse rates (SRRs) based on anti-RSV A and anti-RSV B neutralizing antibody titres obtained at 1-month post-vaccination. Non-inferiority margins were set at 1.5 for GMT ratio and 10% for difference in SRR for ≥60 YOA compared to 18-49 YOA. A hierarchical testing strategy was used: in the first sequence, non-inferiority was tested for RSV-A (GMT ratio and SRR as co-primary); in the second sequence, non-inferiority was tested for RSV-B (GMT ratio and SRR as co-primary). The non-inferiority criteria and primary endpoints are appropriate and in line with previous studies involving Arexvy. The per protocol set was used to evaluate the immune response.

Efficacy data and additional analyses

In total, 1528 participants were screened for the study, of which 69 did not meet the inclusion criteria. One participant withdrew before vaccine administration. Therefore 1458 participants were in the exposed set (426 subjects in Cohort 1, 429 subjects in Cohort 2 and 603 subjects in Cohort 3).

Compared to the primary efficacy study ADJ-006, the participants in the OA-RSV group had similar baseline characteristics. In the current study ADJ-025, younger adults had a higher BMI and a greater frequency of tobacco use, which is expected from a younger population with, among others, cardiovascular and pulmonary co-morbidities.

Elimination from the PPS was more common among 18-49 YOA (7.7%) than among ≥60 YOA (2.8%), which might have introduced a slight bias. The main reasons for protocol deviations were "assessment or timepoint completion" followed by "study procedures" and "wrong study treatment/administration/dose". However, overall, a smaller number of participants was eliminated from the PPS than anticipated (~15% anticipated, actual elimination was 5.3%). A sensitivity analyses was performed on the exposed set to address this issue, the result of which did not differ meaningfully from the main PPS analysis.

Regarding the protocol deviation reason "wrong study treatment/administration/dose" due to use of study treatment impacted by temperature excursion (7 participants in cohort 1, 4 participants in cohort 2 and 2 participants in cohort 3), further clarification was requested. According to the Applicant, the monitoring of the study revealed that there was an issue with temperature monitoring of the refrigerator at a Japanese site. At this site, the temperature monitoring device from GSK was not used, but instead a non-calibrated thermometer was used to record temperature. In total, 24 participants were impacted by this issue. Each impacted dose of the Arexvy vaccine was evaluated under a worst-case scenario, assuming continuous exposure to ambient temperature for the duration of the temperature monitoring issue and then compared against the available stability data. The 11 included doses had temperature monitoring gaps shorter than the validated stability limits and were deemed fit for purpose. This is regarded acceptable.

Non-inferiority of the immune response to RSVPreF3 OA in 18-49 YOA compared to ≥60 YOA was demonstrated in terms of RSV-A & B neutralizing GMTs (upper limit of the 95% CI on group GMT ratio was 0.81 and 0.82 respectively, which was below the pre-defined non-inferiority criterion of 1.5) and SRR (upper limit of the 95% CI on SRR difference was -4.14% and -4.83% respectively below the pre-defined non-inferiority criterion of 10%). The neutralising antibody titers for both RSV-A and RSV-B declined over time in both age groups but remained well above baseline levels up till 6 months post vaccination.

Subgroup analyses by baseline medical condition (cardiopulmonary conditions, diabetes mellitus, and other diseases) and age group (18-49 YOA, 60-69 YOA and ≥70 YOA) showed no meaningful differences were found in overall immune response by subgroup. No other subgroup analyses were performed. Based on the known effect of Arexvy and other similar vaccines, no differing immunogenic response between subgroups such as race, gender, or number of co-morbidities would be expected.

In line with results included in the MAA, RSVPreF3 vaccine was able to induce CD4+ T-cells in both 18–49-year-old group, and in the older adults. However, all CMI analyses were exploraty.

2.4.3. Conclusions on the clinical efficacy

Non-inferiority of the immune response to RSVPreF3 OA in 18-49 YOA compared to ≥60 YOA was demonstrated in terms of RSV-A & B neutralizing GMTs and SRR, supporting the inference of efficacy in the younger population.

2.5. Clinical safety

Introduction

The main source of the known safety profile of Arexvy is derived from the pivotal phase 3 study RSV OA=ADJ-006 and is further supported by data from other phase 3 studies (RSV OA=ADJ-004, -007, -009, and -018). The RSVPreF3 OA vaccine was generally well tolerated with an acceptable safety profile across the Phase 3 clinical studies.

The safety data presented for this extension of indication is derived from a phase 3b, open-label, uncontrolled, non-randomized study (RSV OA=ADJ-025). It was conducted in 2 Parts - Part A (immunogenicity and safety evaluation) and Part B (additional safety evaluation). Part A consisted of Cohort 1 which included adults 18-49 YOA AIR for RSV disease and Cohort 2 which included adults ≥60 YOA. Part B included Cohort 3, which had the same inclusion and exclusion criteria as Cohort 1. Safety analyses were performed for both Part A and Part B.

The evaluation of reactogenicity and safety after the RSVPreF3 OA investigational vaccine administration was a secondary objective, with the following descriptive endpoints:

- Percentage of participants reporting each solicited administration site event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days).
- Percentage of participants reporting each solicited systemic event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days).
- Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days) by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Similar tabulation was done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.
- Percentage of participants reporting SAEs and AESIs (including potential immune mediated diseases (pIMDs) and atrial fibrillation (AF)) after study intervention administration (Day 1) up to study end (6 months after study intervention administration) by MedDRA Primary SOC, HLT and PT.

- Percentage of participants reporting SAEs and AESIs (including pIMDs and AF) related to study intervention administration after study intervention administration (Day 1) up to study end (6 months after study intervention administration) by MedDRA Primary SOC, HLT and PT.
- Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (6 months after study intervention administration).

Patient exposure

While presenting safety results in the text within this section, RSV-A-AIR group refers to Cohorts 1+3 and RSV-OA group refers to Cohort 2. The analysis for safety will be performed on the ES, for participants in Parts A and Part B. A total of 1029 participants in RSV AIR group and 429 participants in RSV OA group received 1 dose of RSVPreF3 OA vaccine (Table 12).

Table 12 Number of participants and doses evaluated for safety, exposed set

Study intervention	Study groups	Age (years)	Number of participants	Attendance Month 6
RSVPreF3 OA vaccine	RSV-A-AIR Cohort 1	18-49	426	414 (97.2%)
	RSV-A-AIR Cohort 3		603	586 (97.2%)
	RSV-A-AIR Cohort 1+3		**1029**	**1000 (97.2%)**
	OA-RSV (Cohort 2)	≥60	429	422 (98.4%)
	Total		**1458**	**1422 (97.5%)**

Adverse events

A summary of solicited and unsolicited events occurring within 4- and 30-days following vaccination, respectively, is shown in Table 13.

Table 13 Summary of Solicited and Unsolicited Events - Exposed Set

	RSV-A-AIR/ Cohorts 1+3	**RSV-OA/ Cohort 2**
	N=1027	**N=428**
Solicited events within 4 days following vaccination	n (%)	n (%)
Solicited events (any)	866 (84.3)	297 (69.4)
Solicited events (Grade 3)	66 (6.4)	11 (2.6)
Solicited administration site event (any)	785 (76.4)	249 (58.2)
Solicited administration site event (Grade 3)	16 (1.6)	1 (0.2)
Solicited systemic event (any)	770 (75.0)	235 (54.9)
Solicited systemic event (Grade 3)	60 (5.8)	10 (2.3)
	N=1029	**N=429**
Unsolicited AEs within 30 days following vaccination	n (%)	n (%)
Unsolicited AEs (any)	190 (18.5)	76 (17.7)

Unsolicited AEs (related)	90 (8.7)	13 (3.0)
Unsolicited AEs (Grade 3)	5 (0.5)	5 (1.2)
Unsolicited AEs (related Grade 3)	0 (0)	0 (0)
Unsolicited AEs (medically attended)	58 (5.6)	29 (6.8)

N (for solicited events within 4 days following vaccination) = number of participants with response in the eDiary (Participant entry + Investigator assessment, if applicable and within 36 hours)

N (for unsolicited AEs within 30 days following vaccination) = number of participants

n/% = number/percentage of participants presenting at least one type of symptom/adverse event

Solicited adverse events

Solicited administration site events

Solicited administration site events were reported in 76.4% of participants in the RSV-A-AIR group and 58.2% of participants in the RSV-OA group. The most frequently reported solicited administration site event across both study groups was injection site pain (76.0% of participants in the RSV-A-AIR group and 57.5% of participants in the RSV-OA group). Grade 3 solicited administration site events were reported in 1.6% of participants in the RSV-A-AIR group and 0.2% of participants in the RSV-OA group. The most frequently reported Grade 3 solicited administration site event in both study groups was injection site pain (1.3% of participants in the RSV-A-AIR group and 0.2% of participants in the RSV-OA group). Across all groups, the median duration of each solicited administration site event (pain, erythema, and swelling) was 2-3 days and the median number of days with Grade 3 events was 1-2 days. Table 14 shows the percentage of solicited administration site events within 4 days following vaccination in the exposed set.

Table 14 Percentage of participants with solicited administration site events within 4 days following vaccination – Exposed set

	RSV-A-AIR (Cohort 1)				**RSV-A-AIR (Cohort 3)**				**RSV-A-AIR Cohort 1 + 3**				**RSV-OA**			
			95% CI				**95% CI**				**95% CI**				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Erythema (mm)																
N	425				601				1026				428			
Any	36	8.5	6.0	11.5	52	8.7	6.5	11.2	88	8.6	6.9	10.5	23	5.4	3.4	8.0
>100	1	0.2	0.0	1.3	1	0.2	0.0	0.9	2	0.2	0.0	0.7	0	0	0	0.9
Medically attended visits	3	0.7	0.1	2.0	5	0.8	0.3	1.9	8	0.8	0.3	1.5	3	0.7	0.1	2.0
Pain																
N	425				601				1026				428			
Any	358	84.2	80.4	87.6	422	70.2	66.4	73.8	780	76.0	73.3	78.6	246	57.5	52.6	62.2
Grade 3	7	1.6	0.7	3.4	6	1.0	0.4	2.2	13	1.3	0.7	2.2	1	0.2	0.0	1.3
Medically attended visits	36	8.5	6.0	11.5	53	8.8	6.7	11.4	89	8.7	7.0	10.6	27	6.3	4.2	9.0
Swelling (mm)																
N	425				601				1026				428			
Any	25	5.9	3.8	8.6	47	7.8	5.8	10.3	72	7.0	5.5	8.8	19	4.4	2.7	6.8
>100	1	0.2	0.0	1.3	1	0.2	0.0	0.9	2	0.2	0.0	0.7	0	0	0	0.9
Medically attended visits	4	0.9	0.3	2.4	8	1.3	0.6	2.6	12	1.2	0.6	2.0	1	0.2	0.0	1.3

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1; Cohort 3); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Dy 1) (Cohort 2)

N = number of participants with response in the eDiary (Participant entry + Investigator assessment, if applicable and within 36 hours); n/% = number/percentage of participants presenting at least one type of symptom ; 95% CI = exact 95% confidence interval, LL = Lower limit, UL = Upper limit; For Erythema and Swelling, Grade 3 corresponds to diameter > 100 mm

Solicited systemic adverse events

Solicited systemic events were reported in 75.0% of participants in the RSV-A-AIR group and 54.9% of participants in the RSV-OA group (Table 15). The most frequently reported solicited systemic events were myalgia and fatigue. Myalgia was reported in 59.9% of participants in RSV-A-AIR group and 39.5% of participants in the RSV-OA group. Fatigue was reported in 59.6% of participants in the RSV-A-AIR group and 34.6% of participants in the RSV-OA group. Grade 3 solicited systemic events were reported in 5.8% of participants in the RSV-A-AIR group and 2.3% of participants in the RSV-OA group. The most frequently reported Grade 3 solicited systemic events were fatigue, headache, and myalgia; the incidence of Grade 3 events across all solicited event types was ⩽ 3% in either group. Across all groups, the median duration of each solicited systemic event was 1-2 days and the median number of days with Grade 3 events was 1-2 days.

Table 15 Percentage of participants with solicited systemic administration site events within 4 days following vaccination – Exposed set

		RSV-A-AIR (Cohort 1)				RSV-A-AIR (Cohort 3)				RSV-A-AIR Cohort 1 + 3				RSV-OA			
				95% CI				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Arthralgia																	
	N	425				602				1027				428			
	Any	124	29.2	24.9	33.8	167	27.7	24.2	31.5	291	28.3	25.6	31.2	78	18.2	14.7	22.2
	Grade 3	5	1.2	0.4	2.7	7	1.2	0.5	2.4	12	1.2	0.6	2.0	1	0.2	0.0	1.3
	Medically attended visits	14	3.3	1.8	5.5	27	4.5	3.0	6.5	41	4.0	2.9	5.4	5	1.2	0.4	2.7
Fatigue																	
	N	425				602				1027				428			
	Any	275	64.7	60.0	69.3	337	56.0	51.9	60.0	612	59.6	56.5	62.6	148	34.6	30.1	39.3
	Grade 3	12	2.8	1.5	4.9	19	3.2	1.9	4.9	31	3.0	2.1	4.3	2	0.5	0.1	1.7
	Medically attended visits	21	4.9	3.1	7.5	40	6.6	4.8	8.9	61	5.9	4.6	7.6	8	1.9	0.8	3.6
Fever (°C)																	
	N	425				602				1027				428			
	>= 38.0	25	5.9	3.8	8.6	26	4.3	2.8	6.3	51	5.0	3.7	6.5	11	2.6	1.3	4.6
	> 38.5	7	1.6	0.7	3.4	9	1.5	0.7	2.8	16	1.6	0.9	2.5	6	1.4	0.5	3.0
	> 39.0	3	0.7	0.1	2.0	8	1.3	0.6	2.6	11	1.1	0.5	1.9	6	1.4	0.5	3.0
	> 39.5	2	0.5	0.1	1.7	4	0.7	0.2	1.7	6	0.6	0.2	1.3	5	1.2	0.4	2.7
	> 40.0	0	0	0	0.9	3	0.5	0.1	1.4	3	0.3	0.1	0.9	5	1.2	0.4	2.7
	Medically attended visits	4	0.9	0.3	2.4	6	1.0	0.4	2.2	10	1.0	0.5	1.8	1	0.2	0.0	1.3
Headache																	
	N	425				602				1027				428			
	Any	198	46.6	41.8	51.5	250	41.5	37.6	45.6	448	43.6	40.6	46.7	78	18.2	14.7	22.2
	Grade 3	8	1.9	0.8	3.7	14	2.3	1.3	3.9	22	2.1	1.3	3.2	1	0.2	0.0	1.3

		RSV-A-AIR (Cohort 1)				RSV-A-AIR (Cohort 3)				RSV-A-AIR Cohort 1 + 3				RSV-OA			
				95% CI				95% CI				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Medically attended visits	16	3.8	2.2	6.0	35	5.8	4.1	8.0	51	5.0	3.7	6.5	4	0.9	0.3	2.4
Myalgia																	
	N	425				602				1027				428			
	Any	284	66.8	62.1	71.3	331	55.0	50.9	59.0	615	59.9	56.8	62.9	169	39.5	34.8	44.3
	Grade 3	10	2.4	1.1	4.3	12	2.0	1.0	3.5	22	2.1	1.3	3.2	0	0	0	0.9
	Medically attended visits	29	6.8	4.6	9.7	42	7.0	5.1	9.3	71	6.9	5.4	8.66	15	3.5	2.0	5.7

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1; Cohort 3); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2) N = number of participants with response in the eDiary (Participant entry + Investigator assessment, if applicable and within 36 hours) n/% = number/percentage of participants presenting at least one type of symptom 95% CI = exact 95% confidence interval, LL = Lower limit, UL = Upper limit For Fever, Grade 3 corresponds to temperature > 39.0 C;

Sensitivity analysis for solicited adverse events

A generally high electronic clinical outcomes assessment (eCOA) compliance was observed from Day 1 to Day 4 (98.3%). The compliance for participants who completed the eDiaries for 4 consecutive days (Day 1 to Day 4) was 94.7%. However, a drop in completion of the eDiaries from Day 5 to Day 30 was observed. The overall eDiary compliance (Day 1 to Day 30) was 91.0% (90.6% in the RSV-AIR group [Cohorts 1+3] and 91.9% in the RSV-OA group. From Day 5 onwards, participants had to complete separate daily eDiaries for each ongoing symptom (maximum 8 ongoing solicited events, i.e., maximum 8 eDiaries per day).

As a remedial action, reminders for ongoing solicited events after Day 4 were put in place before the end of the Cohort 3 enrolment, applicable for those enrolled as of 08 August 2024.

To assess the impact of missing data and further complement the main analysis for duration of solicited events, 2 sensitivity analyses were performed.

- Sensitivity Analysis 1: A sensitivity analysis for evaluating the duration of solicited events for those participants from Cohort 3 enrolled as of 08 August 2024, as from then the eDiary alerts for participants from Day 5 onwards were activated in the vendor system.
    - For Cohort 3 participants who received eDiary alerts compliance from Day 5 onwards was 74.5% and compliance from Day 1 to Day 30 was 95.8%.
    - The median duration of solicited administration site events remained 2-3 days.
    - The median duration of solicited systemic events remained 1-2 days.
- Sensitivity Analysis 2: A sensitivity analysis to account for missing eDiary for ongoing symptoms. This analysis was performed for all participants and for those participants enrolled in Cohort 3 as of 08 August 2024. In this analysis a different definition for the duration of an event for the missing data was performed. To account for missing eDiary data as of day 5 onwards (due to non-activation of the eDiary alerts for participants from day 5 onwards in the vendor system), a sensitivity analysis will be performed using the below definition of duration:
    - The duration of a solicited AE with at least one day Grade > 0 is defined as End date– Start date + 1, with Start date defined as the first day with the symptom and End date

defined as the day before the first occurrence of the symptom (in or beyond the solicited period) equals 'N' with no days having occurrence afterwards.

- If a solicited event is still not reported as 'N' at day 30, the end date will be considered equal to vaccination date + 29 days.
- The median duration of solicited administration site events remained 2-3 days.
- The median duration of solicited systemic events remained 1-2 days.

All unsolicited adverse events

Within 30 minutes

No hypersensitivity or anaphylaxis/anaphylactoid reaction to vaccination was reported in any participant. Unsolicited AEs were reported in 4 (0.4%) participants in the RSV-A-AIR group and in none of the participants in the RSV-OA group. The unsolicited AEs were nausea (n=2), lymph node pain (n=1), and feeling hot (n=1). No Grade 3 unsolicited AEs were reported.

Within 30 days

Unsolicited AEs were reported in 18.5% of participants in the RSV-A-AIR group and 17.7% of participants in the RSV-OA group. At the SOC level, the most frequently reported unsolicited AE SOC was "Infections and infestations", reported in 6.2% of participants in the RSV-A-AIR group and 7.0% of participants in RSV-OA group. Table 16 provides a summary of participants by adverse event category, serious and non-serious.

Table 16 Summary of participants by adverse event category, serious and non-serious events – Exposed set

	RSV-A-AIR (Cohort 1) N=426					RSV-A-AIR (Cohort 3) N=60					RSV-A-AIR (Cohort 1 + Cohort 3) N=1029					RSV-OA (Cohort 2) N=429				
	occ	n	%	LL	UL	occ	n	%	LL	UL	occ	n	%	LL	UL	occ	n	%	LL	UL
Any unsolicited adverse event within 30 days of vaccination	110	72	*16.9*	13.5	20.8	181	118	*19.6*	16.5	23.0	291	190	*18.5*	16.1	21.0	100	76	*17.7*	14.2	21.7
Any Grade 3 unsolicited adverse event within 30 days of vaccination	3	3	*0.7*	0.1	2.0	2	2	*0.3*	0.0	1.2	5	5	*0.5*	0.2	1.1	8	5	*1.2*	0.4	2.7
Any related unsolicited adverse event within 30 days of vaccination	41	33	*7.7*	5.4	10.7	81	57	*9.5*	7.2	12.1	122	90	*8.7*	7.1	10.6	15	13	*3.0*	1.6	5.1
Any Grade 3 related unsolicited adverse event within 30 days of vaccination	0	0	*0*	0	0.9	0	0	*0*	0	0.6	0	0	*0*	0	0.4	0	0	*0*	0	0.9
Any medically attended unsolicited adverse event within 30 days of vaccination	32	22	*5.2*	3.3	7.7	51	36	*6.0*	4.2	8.2	83	58	*5.6*	4.3	7.2	39	29	*6.8*	4.6	9.6
Any non-serious unsolicited adverse event within 30 days of vaccination	109	71	*16.7*	13.3 20.6		179	117	*19.4*	16.3 22.8		288	188	*18.3*	16.0 20.8		94	74	*17.2*	13.8 21.2	
Any non-serious Grade 3 unsolicited adverse event within 30 days of vaccination	2	2	*0.5*	0.1	1.7	2	2	*0.3*	0.0	1.2	4	4	*0.4*	0.1	1.0	2	2	*0.5*	0.1	1.7
Any non-serious related unsolicited adverse event within 30 days of vaccination	41	33	*7.7*	5.4	10.7	81	57	*9.5*	7.2	12.1	122	90	*8.7*	7.1	10.6	15	13	*3.0*	1.6	5.1
Any non-serious Grade 3 related unsolicited adverse event within 30 days of vaccination	0	0	*0*	0	0.9	0	0	*0*	0	0.6	0	0	*0*	0	0.4	0	0	*0*	0	0.9
Any non-serious medically attended unsolicited adverse event within 30 days of vaccination	31	21	*4.9*	3.1	7.4	49	35	*5.8*	4.1	8.0	80	56	*5.4*	4.1	7.0	33	27	*6.3*	4.2	9.0
Any adverse events of atrial fibrillation within 30 days of vaccination	0	0	*0*	0	0.9	1	1	*0.2*	0.0	0.9	1	1	*0.1*	0.0	0.5	0	0	*0*	0	0.9
Any serious adverse event within 30 days of vaccination	1	1	*0.2*	0.0	1.3	2	2	*0.3*	0.0	1.2	3	3	*0.3*	0.1	0.8	6	3	*0.7*	0.1	2.0
Any unsolicited adverse event with onset within 30 minutes of vaccination	2	2	*0.5*	0.1	1.7	2	2	*0.3*	0.0	1.2	4	4	*0.4*	0.1	1.0	0	0	*0*	0	0.9
Any Grade 3 unsolicited adverse event with onset within 30 minutes of vaccination	0	0	*0*	0	0.9	0	0	*0*	0	0.6	0	0	*0*	0	0.4	0	0	*0*	0	0.9
Any serious adverse event up to study end	5	4	*0.9*	0.3	2.4	11	10	*1.7*	0.8	3.0	16	14	*1.4*	0.7	2.3	16	13	*3.0*	1.6	5.1
Any serious adverse event of atrial fibrillation up to study end	0	0	*0*	0	0.9	0	0	*0*	0	0.6	0	0	*0*	0	0.4	1	1	*0.2*	0.0	1.3
Any serious related adverse event up to study end	0	0	*0*	0	0.9	0	0	*0*	0	0.6	0	0	*0*	0	0.4	0	0	*0*	0	0.9

	RSV-A-AIR (Cohort 1) N=426					RSV-A-AIR (Cohort 3) N=60					RSV-A-AIR (Cohort 1 + Cohort 3) N=1029					RSV-OA (Cohort 2) N=429				
	occ	n	%	LL	UL	occ	n	%	LL	UL	occ	n	%	LL	UL	occ	n	%	LL	UL
Any fatal serious adverse event up to study end	0	0	*0*	0	0.9	0	0	*0*	0	0.6	0	0	*0*	0	0.4	0	0	*0*	0	0.9
Any pIMD up to study end	1	1	*0.2*	0.0	1.3	1	1	*0.2*	0.0	0.9	2	2	*0.2*	0.0	0.7	1	1	*0.2*	0.0	1.3
Any pIMD related up to study end	1	1	*0.2*	0.0	1.3	0	0	*0*	0	0.6	1	1	*0.1*	0.0	0.5	0	0	*0*	0	0.9

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1; Cohort 3); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2) N = number of participants; occ = number of occurrences = number of unsolicited adverse events reported by a participant for a given category; n/% = number/percentage of participants presenting at least one type of adverse event; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit; pIMD = potential Immune Mediated-Disease; The analysis of unsolicited adverse event includes non-serious and serious adverse events, unless otherwise specified

Unsolicited adverse events related to the vaccination

The percentage of participants reporting unsolicited AEs considered as related to study intervention by the investigator was 8.7% in the RSV-A-AIR group and 3.0% in the RSV-OA group (Table 17).

Table 17 Summary of participants with at least one related unsolicited adverse event with onset within 30 days of vaccination – exposed set

	RSV-A-AIR (Cohort 1) N=426				RSV-A-AIR (Cohort 3) N=603				RSV-A-AIR (Cohort 1 + 3) N=1029				RSV-OA (Cohort 2) N=429			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE) High Level Term (CODE) **Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Any related unsolicited adverse event	33	7.7	5.4	10.7	57	9.5	7.2	12.1	90	8.7	7.1	10.6	13	3.0	1.6	5.1
General disorders and administration site conditions (10018065)	**14**	**3.3**	**1.8**	**5.5**	**28**	**4.6**	**3.1**	**6.6**	**42**	**4.1**	**3.0**	**5.5**	**8**	**1.9**	**0.8**	**3.6**
Feelings and sensations NEC (10068759)	6	1.4	0.5	3.0	15	2.5	1.4	4.1	21	2.0	1.3	3.1	3	0.7	0.1	2.0
Chills (10008531)	5	1.2	0.4	2.7	12	2.0	1.0	3.5	17	1.7	1.0	2.6	2	0.5	0.1	1.7
Feeling hot (10016334)	0	0	0	0.9	3	0.5	0.1	1.4	3	0.3	0.1	0.8	1	0.2	0.0	1.3
Feeling of body temperature change (10061458)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Injection site reactions (10022097)	1	0.2	0.0	1.3	10	1.7	0.8	3.0	11	1.1	0.5	1.9	3	0.7	0.1	2.0
Injection site pruritus (10022093)	0	0	0	0.9	7	1.2	0.5	2.4	7	0.7	0.3	1.4	1	0.2	0.0	1.3
Injection site bruising (10022052)	1	0.2	0.0	1.3	1	0.2	0.0	0.9	2	0.2	0.0	0.7	0	0	0	0.9
Injection site warmth (10022112)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	1.3
Injection site induration (10022075)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Injection site plaque (10073174)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Pain and discomfort NEC (10033372)	4	0.9	0.3	2.4	1	0.2	0.0	0.9	5	0.5	0.2	1.1	0	0	0	0.9
Axillary pain (10048750)	2	0.5	0.1	1.7	1	0.2	0.0	0.9	3	0.3	0.1	0.8	0	0	0	0.9
Pain (10033371)	2	0.5	0.1	1.7	0	0	0	0.6	2	0.2	0.0	0.7	0	0	0	0.9
Asthenic conditions (10003550)	2	0.5	0.1	1.7	0	0	0	0.6	2	0.2	0.0	0.7	1	0.2	0.0	1.3
Malaise (10025482)	2	0.5	0.1	1.7	0	0	0	0.6	2	0.2	0.0	0.7	0	0	0	0.9
Fatigue (10016256)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
General signs and symptoms NEC (10018072)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9
Swelling (10042674)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9
Administration site reactions NEC (10057196)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Administration site pruritus (10075106)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Vaccination site reactions (10068754)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Vaccination site erythema (10059079)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Gastrointestinal disorders (10017947)	**10**	**2.3**	**1.1**	**4.3**	**13**	**2.2**	**1.2**	**3.7**	**23**	**2.2**	**1.4**	**3.3**	**1**	**0.2**	**0.0**	**1.3**
Nausea and vomiting symptoms (10028817)	9	2.1	1.0	4.0	11	1.8	0.9	3.2	20	1.9	1.2	3.0	1	0.2	0.0	1.3
Nausea (10028813)	8	1.9	0.8	3.7	11	1.8	0.9	3.2	19	1.8	1.1	2.9	1	0.2	0.0	1.3

	RSV-A-AIR (Cohort 1) N=426				RSV-A-AIR (Cohort 3) N=603				RSV-A-AIR (Cohort 1 + 3) N=1029				RSV-OA (Cohort 2) N=429			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE) High Level Term (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Preferred Term (CODE)																
Vomiting (10047700)	1	0.2	0.0	1.3	3	0.5	0.1	1.4	4	0.4	0.1	1.0	0	0	0	0.9
Diarrhoea (excl infective) (10012736)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9
Diarrhoea (10012735)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9
Gastrointestinal and abdominal pains (excl oral and throat) (10017926)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Abdominal pain (10000081)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Gastrointestinal atonic and hypomotility disorders NEC (10017933)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Constipation (10010774)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Nervous system disorders (10029205)	**3**	**0.7**	**0.1**	**2.0**	**4**	**0.7**	**0.2**	**1.7**	**7**	**0.7**	**0.3**	**1.4**	**1**	**0.2**	**0.0**	**1.3**
Neurological signs and symptoms NEC (10029306)	2	0.5	0.1	1.7	3	0.5	0.1	1.4	5	0.5	0.2	1.1	0	0	0	0.9
Dizziness (10013573)	1	0.2	0.0	1.3	3	0.5	0.1	1.4	4	0.4	0.1	1.0	0	0	0	0.9
Brain fog (10088940)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Sensory abnormalities NEC (10040021)	0	0	0	0.9	2	0.3	0.0	1.2	2	0.2	0.0	0.7	0	0	0	0.9
Ageusia (10001480)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Dysgeusia (10013911)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Olfactory nerve disorders (10030281)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Parosmia (10034018)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Paraesthesias and dysaesthesias (10033788)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Paraesthesia (10033775)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Respiratory, thoracic and mediastinal disorders (10038738)	**1**	**0.2**	**0.0**	**1.3**	**5**	**0.8**	**0.3**	**1.9**	**6**	**0.6**	**0.2**	**1.3**	**2**	**0.5**	**0.1**	**1.7**
Upper respiratory tract signs and symptoms (10046313)	0	0	0	0.9	4	0.7	0.2	1.7	4	0.4	0.1	1.0	2	0.5	0.1	1.7
Oropharyngeal pain (10068319)	0	0	0	0.9	4	0.7	0.2	1.7	4	0.4	0.1	1.0	2	0.5	0.1	1.7
Rhinorrhoea (10039101)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Nasal congestion and inflammations (10028736)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9
Nasal congestion (10028735)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9

	RSV-A-AIR (Cohort 1) N=426				RSV-A-AIR (Cohort 3) N=603				RSV-A-AIR (Cohort 1 + 3) N=1029				RSV-OA (Cohort 2) N=429			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE) High Level Term (CODE) **Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Coughing and associated symptoms (10011233)	0	0	0	0.9	2	0.3	0.0	1.2	2	0.2	0.0	0.7	0	0	0	0.9
Cough (10011224)	0	0	0	0.9	2	0.3	0.0	1.2	2	0.2	0.0	0.7	0	0	0	0.9
Infections and infestations (10021881)	**1**	**0.2**	**0.0**	**1.3**	**6**	**1.0**	**0.4**	**2.2**	**7**	**0.7**	**0.3**	**1.4**	**0**	**0**	**0**	**0.9**
Upper respiratory tract infections (10046309)	0	0	0	0.9	4	0.7	0.2	1.7	4	0.4	0.1	1.0	0	0	0	0.9
Upper respiratory tract infection (10046306)	0	0	0	0.9	4	0.7	0.2	1.7	4	0.4	0.1	1.0	0	0	0	0.9
Bacterial infections NEC (10004047)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9
Cellulitis (10007882)	0	0	0	0.9	2	0.3	0.0	1.2	2	0.2	0.0	0.7	0	0	0	0.9
Injection site cellulitis (10050057)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Skin and subcutaneous tissue disorders (10040785)	**1**	**0.2**	**0.0**	**1.3**	**5**	**0.8**	**0.3**	**1.9**	**6**	**0.6**	**0.2**	**1.3**	**1**	**0.2**	**0.0**	**1.3**
Apocrine and eccrine gland disorders (10002982)	1	0.2	0.0	1.3	2	0.3	0.0	1.2	3	0.3	0.1	0.8	0	0	0	0.9
Hyperhidrosis (10020642)	1	0.2	0.0	1.3	1	0.2	0.0	0.9	2	0.2	0.0	0.7	0	0	0	0.9
Night sweats (10029410)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Rashes, eruptions and exanthems NEC (10052566)	0	0	0	0.9	2	0.3	0.0	1.2	2	0.2	0.0	0.7	1	0.2	0.0	1.3
Rash (10037844)	0	0	0	0.9	2	0.3	0.0	1.2	2	0.2	0.0	0.7	1	0.2	0.0	1.3
Pruritus NEC (10049293)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Pruritus (10037087)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Blood and lymphatic system disorders (10005329)	**4**	**0.9**	**0.3**	**2.4**	**2**	**0.3**	**0.0**	**1.2**	**6**	**0.6**	**0.2**	**1.3**	**0**	**0**	**0**	**0.9**
Lymphatic system disorders NEC (10025198)	4	0.9	0.3	2.4	2	0.3	0.0	1.2	6	0.6	0.2	1.3	0	0	0	0.9
Lymphadenopathy (10025197)	4	0.9	0.3	2.4	2	0.3	0.0	1.2	6	0.6	0.2	1.3	0	0	0	0.9
Musculoskeletal and connective tissue disorders (10028395)	**3**	**0.7**	**0.1**	**2.0**	**1**	**0.2**	**0.0**	**0.9**	**4**	**0.4**	**0.1**	**1.0**	**1**	**0.2**	**0.0**	**1.3**
Musculoskeletal and connective tissue pain and discomfort (10068757)	2	0.5	0.1	1.7	1	0.2	0.0	0.9	3	0.3	0.1	0.8	1	0.2	0.0	1.3
Limb discomfort (10061224)	1	0.2	0.0	1.3	1	0.2	0.0	0.9	2	0.2	0.0	0.7	0	0	0	0.9

	RSV-A-AIR (Cohort 1) N=426				RSV-A-AIR (Cohort 3) N=603				RSV-A-AIR (Cohort 1 + 3) N=1029				RSV-OA (Cohort 2) N=429			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE) High Level Term (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Preferred Term (CODE)																
Pain in extremity (10033425)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	1	0.2	0.0	1.3
Back pain (10003988)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Joint related signs and symptoms (10023226)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Arthralgia (10003239)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Metabolism and nutrition disorders (10027433)	**0**	**0**	**0**	**0.9**	**1**	**0.2**	**0.0**	**0.9**	**1**	**0.1**	**0.0**	**0.5**	**1**	**0.2**	**0.0**	**1.3**
Appetite disorders (10003022)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	1.3
Decreased appetite (10061428)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	1.3
Reproductive system and breast disorders (10038604)	**1**	**0.2**	**0.0**	**1.3**	**1**	**0.2**	**0.0**	**0.9**	**2**	**0.2**	**0.0**	**0.7**	**0**	**0**	**0**	**0.9**
Menstruation and uterine bleeding NEC (10027335)	1	0.2	0.0	1.3	1	0.2	0.0	0.9	2	0.2	0.0	0.7	0	0	0	0.9
Abnormal uterine bleeding (10085424)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Intermenstrual bleeding (10022559)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Vascular disorders (10047065)	**1**	**0.2**	**0.0**	**1.3**	**1**	**0.2**	**0.0**	**0.9**	**2**	**0.2**	**0.0**	**0.7**	**0**	**0**	**0**	**0.9**
Haemorrhages NEC (10018987)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Haematoma (10018852)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Peripheral vascular disorders NEC (10034638)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Hot flush (10060800)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Ear and labyrinth disorders (10013993)	**0**	**0**	**0**	**0.9**	**1**	**0.2**	**0.0**	**0.9**	**1**	**0.1**	**0.0**	**0.5**	**0**	**0**	**0**	**0.9**
Inner ear signs and symptoms (10022398)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Vertigo (10047340)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Eye disorders (10015919)	**0**	**0**	**0**	**0.9**	**1**	**0.2**	**0.0**	**0.9**	**1**	**0.1**	**0.0**	**0.5**	**0**	**0**	**0**	**0.9**
Lacrimation disorders (10072989)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Dry eye (10013774)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9

	RSV-A-AIR (Cohort 1) N=426				RSV-A-AIR (Cohort 3) N=603				RSV-A-AIR (Cohort 1 + 3) N=1029				RSV-OA (Cohort 2) N=429			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE) High Level Term (CODE) **Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Psychiatric disorders (10037175)	**0**	**0**	**0**	**0.9**	**1**	**0.2**	**0.0**	**0.9**	**1**	**0.1**	**0.0**	**0.5**	**0**	**0**	**0**	**0.9**
Disturbances in initiating and maintaining sleep (10013510)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Insomnia (10022437	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1; Cohort 3); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2) N = number of participants; n/% = number/percentage of participants presenting at least one type of adverse event; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit;

Serious adverse event/deaths/other significant events

SAEs and SAEs with a fatal outcome:

Up to the study end, at least 1 SAE was reported in 14 participants (1.4%) in the RSV-A-AIR group and in 13 participants (3.0%) in the RSV-OA group. None of the SAEs reported in either study group (RSV-A-AIR and RSV-OA) were considered to be related to study intervention by the investigator (*Table 18*). None of the participants in any of the study groups had an SAE leading to withdrawal, treatment discontinuation, or death.

Table 18 Summary of participants with at least one serious adverse event with onset after vaccine administration (Day 1) – exposed set

	RSV-A-AIR COHORT 1 N=426				**RSV-A-AIR Cohort 3 N=603**				**RSV-A-AIR Cohort 1+3 N=1029**				**RSV-OA Cohort 2 N=429**			
High Level Term (CODE) Preferred Term (CODE) Primary System Organ Class (CODE	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	*%*	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Any serious adverse event	4	0.9	0.3	2.4	10	1.7	0.8	3.0	14	*1.4*	0.7	2.3	13	*3.0*	1.6	5.1
Infections and infestations (10021881)	**2**	**0.5**	**0.1**	**1.7**	**5**	**0.8**	**0.3**	**1.9**	**7**	***0.7***	**0.3**	**1.4**	**1**	***0.2***	**0.0**	**1.3**
Bacterial infections NEC (10004047)	0	0	0	0.9	2	0.3	0.0	1.2	2	*0.2*	0.0	0.7	1	*0.2*	0.0	1.3
Cellulitis (10007882)	0	0	0	0.9	1	0.2	0.0	0.9	1	*0.1*	0.0	0.5	1	*0.2*	0.0	1.3

High Level Term (CODE) Preferred Term (CODE) Primary System Organ Class (CODE	RSV-A-AIR COHORT 1 N=426				RSV-A-AIR Cohort 3 N=603				RSV-A-AIR Cohort 1+3 N=1029				RSV-OA Cohort 2 N=429			
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Wound cellulitis (10088486)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Lower respiratory tract and lung infections (10025101)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	1.3
Infective exacerbation of asthma (10088066)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Pneumonia (10035664)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Sepsis, bacteraemia, viraemia and fungaemia NEC (10040054)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	1	0.2	0.0	1.3
Pulmonary sepsis (10051739)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Sepsis (10040047)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Abdominal and gastrointestinal infections (10017967)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Gastroenteritis (10017888)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Bone and joint infections (10005940)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Osteomyelitis (10031252)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Escherichia infections (10015295)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Escherichia bacteraemia (10054258)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Cardiac disorders (10007541)	**1**	**0.2**	**0.0**	**1.3**	**0**	**0**	**0**	**0.6**	**1**	0.1	**0.0**	**0.5**	**2**	**0.5**	**0.1**	**1.7**
Cardiac conduction disorders (10000032)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Atrioventricular block complete (10003673)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Ischaemic coronary artery disorders (10011085)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Acute myocardial infarction (10000891)	1	0.2	0.0	1.3	0	0	0	0.6	1	0.1	0.0	0.5	0	0	0	0.9
Supraventricular arrhythmias (10042600)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Atrial fibrillation (10003658)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	**0**	**0**	**0**	**0.9**	**1**	**0.2**	**0.0**	**0.9**	**1**	**0.1**	**0.0**	**0.5**	**2**	**0.5**	**0.1**	**1.7**
Prostatic neoplasms malignant (10036908)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	2	0.5	0.1	1.7
Prostate cancer (10060862)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Prostate cancer stage II (10036918)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Vulval neoplasms malignant (10047750)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Vulval cancer stage III (10047748)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Nervous system disorders (10029205)	**0**	**0**	**0**	**0.9**	**0**	**0**	**0**	**0.6**	**0**	**0**	**0**	**0.4**	**3**	**0.7**	**0.1**	**2.0**
Memory loss (excl dementia) (10027177)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Transient global amnesia (10044380)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Neurological signs and symptoms NEC (10029306)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Neurological symptom (10060860)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Transient cerebrovascular events (10044376)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
…Transient ischaemic attack (10044390)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Vascular disorders (10047065)	**0**	**0**	**0**	**0.9**	**1**	**0.2**	**0.0**	**0.9**	**1**	**0.1**	**0.0**	**0.5**	**2**	**0.5**	**0.1**	**1.7**
Peripheral embolism and thrombosis (10034572)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	2	0.5	0.1	1.7
Pelvic venous thrombosis (10034272)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Thrombophlebitis (10043570)	0	0	0	0.9	0	0	0	0.6	0	0	0	0.4	1	0.2	0.0	1.3
Vascular hypertensive disorders NEC (10020774)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9
Hypertension (10020772)	0	0	0	0.9	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0	0	0.9

High Level Term (CODE) Preferred Term (CODE) Primary System Organ Class (CODE	RSV-A-AIR COHORT 1 N=426				RSV-A-AIR Cohort 3 N=603				RSV-A-AIR Cohort 1+3 N=1029				RSV-OA Cohort 2 N=429			
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Gastrointestinal disorders (10017947)	**0**	**0**	**0**	**0.9**	**1**	**0.2**	**0.0**	**0.9**	**1**	***0.1***	**0.0**	**0.5**	**1**	***0.2***	**0.0**	**1.3**
Acute and chronic pancreatitis (10033646)	0	0	0	0.9	1	0.2	0.0	0.9	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Alcoholic pancreatitis (10056977)	0	0	0	0.9	1	0.2	0.0	0.9	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Colitis (excl infective) (10009888)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3
Colitis (10009887)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3
Metabolism and nutrition disorders (10027433)	**0**	**0**	**0**	**0.9**	**2**	**0.3**	**0.0**	**1.2**	**2**	***0.2***	**0.0**	**0.7**	**0**	***0***	**0**	**0.9**
Diabetes mellitus (incl subtypes) (10012602)	0	0	0	0.9	2	0.3	0.0	1.2	2	*0.2*	0.0	0.7	0	*0*	0	0.9
Diabetes mellitus inadequate control (10012607)	0	0	0	0.9	1	0.2	0.0	0.9	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Type 1 diabetes mellitus (10067584)	0	0	0	0.9	1	0.2	0.0	0.9	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Skin and subcutaneous tissue disorders (10040785)	1	0.2	0.0	1.3	1	0.2	0.0	0.9	2	*0.2*	0.0	0.7	0	*0*	0	0.9
Angioedemas (10002425)	1	0.2	0.0	1.3	0	0	0	0.6	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Angioedema (10002424)	1	0.2	0.0	1.3	0	0	0	0.6	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Skin and subcutaneous tissue ulcerations (10040796)	0	0	0	0.9	1	0.2	0.0	0.9	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Diabetic foot (10060734)	0	0	0	0.9	1	0.2	0.0	0.9	1	*0.1*	0.0	0.5	0	*0*	0	0.9
Injury, poisoning and procedural complications (10022117)	**0**	**0**	**0**	**0.9**	**0**	**0**	**0**	**0.6**	**0**	***0***	**0**	**0.4**	**1**	***0.2***	**0.0**	**1.3**
Limb fractures and dislocations (10075886)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3
Wrist fracture (10048049)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3
Musculoskeletal and connective tissue disorders (10028395)	**0**	**0**	**0**	**0.9**	**0**	**0**	**0**	**0.6**	**0**	***0***	**0**	**0.4**	**1**	***0.2***	**0.0**	**1.3**
Intervertebral disc disorders NEC (10022635)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3
Intervertebral disc protrusion (10050296)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3
Renal and urinary disorders (10038359)	**0**	**0**	**0**	**0.9**	**0**	**0**	**0**	**0.6**	**0**	***0***	**0**	**0.4**	**1**	***0.2***	**0.0**	**1.3**
Renal failure and impairment (10038443)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3
Acute kidney injury (10069339)	0	0	0	0.9	0	0	0	0.6	0	*0*	0	0.4	1	*0.2*	0.0	1.3

RSV-A-AIR = At increased risk adult participants (18-49 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 1; Cohort 3); RSV-OA = Older adult participants (>= 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) (Cohort 2); N = number of participants; n/% = number/percentage of participants presenting at least one type of adverse event; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

pIMDs and Atrial fibrillation:

pIMDs

- Events of pIMD were reported in 2 participants (0.2%) in the RSV-A-AIR group (hematoma [non-serious AE] and type 1 diabetes mellitus [SAE] in 1 participant each) and in 1 participant (0.2%) in the RSV-OA group (pernicious anaemia [non-serious AE]). The AE of hematoma was considered as related to study intervention by the investigator but not the MAH.

- A non-serious event of AF was reported in 1 participant in the RSV-A-AIR group, and a serious event of AF was reported in 1 participant in the RSV-OA group. Both events were assessed as not related to study intervention by the investigator.

No events of neurological demyelinating pIMDs were reported in any of the participants in RSV-A-AIR group and RSV-OA group up to study end.

Atrial fibrillation

Events of AF were reported in 1 participant each in the RSV-A-AIR group and RSV-OA group. In the RSV-A-AIR group, a >40-year-old participant had a non-serious AF (exacerbation of paroxysmal AF) that occurred 6 days after study intervention administration (the event was not confirmed by electrocardiography). The participant was obese had a relevant medical history of paroxysmal AF, paroxysmal supraventricular tachycardia, hypercholesterolemia, insulin resistance and obstructive sleep apnea. This event was assessed as mild in intensity and as not related to study intervention by the investigator. The event resolved spontaneously after 4 days of its onset.

In the RSV-OA group, a >70-year-old participant had a serious AF that occurred 131 days after study intervention administration and was confirmed by electrocardiography. The participant was obese, had a relevant medical history of benign arrhythmia, obstructive sleep apnoea, and family history of AF. This event was assessed as moderate in intensity and as not related to study intervention by the investigator. The outcome of the event was reported as not resolved; however, the serious AF was reported to be stable by the investigator.

Laboratory findings

No laboratory evaluations were performed in the Phase 3 trials, which is acceptable.

Safety in special populations

Pregnant women

In the study, 3 pregnancies (all in RSV-A-AIR) were reported. All pregnancies resulted in a live infant with no apparent congenital anomaly.

Discontinuation due to adverse events

Up to the study end, no participant discontinued the study due to any AE.

Post marketing experience

Since initial approval on 03 May 2023, and until 02 November 2024 (DLP of the last PSUR), it is estimated that 11 498 281 Arexvy doses have been distributed globally; most doses were distributed in the USA and Canada. The number of Arexvy doses administered since approval is available only for the US. From launch until 02 November 2024, it is estimated that 8.68 million doses were administered in the US, based on IQVIA National Prescription Audit Rapid Weekly Total Prescription data, and included an estimated 2.11 million immunizations in non-retail pharmacy settings. Up to 02 November 2024, a total of 1933 spontaneous reports have been received for Arexvy. These have mostly been non-serious (1659; 86%) and reflect the known safety profile of Arexvy as described in the RSI. The most common AEs reported have been local injection site events such as pain, erythema, swelling, and systemic events such as pyrexia, fatigue, headache, myalgia and arthralgia. The review of the cumulative spontaneous post-marketing data did not

result in any update to the Company's RSI. Two safety signals were assessed following Health Authority Requests; the Company concluded that the available information on these events does not warrant an update of the Company's RSI.

Two safety signals were assessed following Health Authority Requests; the Company concluded that the available information on these events does not warrant an update of the Company's RSI. However, these events were added as ADR in the SmPC/package leaflet.

- In the Assessment for the Arexvy PSUR, covering the reporting period 03 November 2023 to 02 May 2024, the MAH was requested to add injection site necrosis as adverse reaction to the EU PI, based on review of spontaneous reports, including in at least 7 cases a close temporal relationship. It was acknowledged that the mechanism or risk factors for the occurrence of "injection site necrosis" following vaccination with Arexvy remain uncertain: the event could be vaccine, antigen, adjuvant or procedure related. However, a causal association with the vaccine could not be excluded.
- Results from a post-marketing observational study using data from US individuals 65 years and older from the Medicare Fee-For-Service suggest an increased risk of GBS during the 42 days following vaccination with Arexvy, with an incidence rate ratio (GBS cases in the risk window/control window) of 2.46 (95% CI: 1.19, 5.08) and an estimated 7 excess cases of GBS per million doses administered. On 25 October 2024, the US FDA notified GSK that the above-mentioned study results should be included into the US PI for Arexvy. In the PSUR covering the reporting period between 3 May 2024 until 2 November 2024, the PRAC considered that a causal relationship between Arexvy and GBS was at least a reasonable possibility in view of data from clinical trials, the literature, spontaneous reports and the information from the SCCS performed by FDA. Thus, GBS was included as an adverse drug reaction in the SmPC.

The evidence from across the Arexvy development programme and real-world use up to 02 November 2024 does not suggest a causal association with any other pIMD (including neurological demyelinating pIMD) at present.

The review of spontaneous reports from GSK's Global Safety database received up to 02 November 2024 concerning the administration of Arexvy in error in adults 18 through 49 YOA, mostly consisting of reports of exposure in pregnancy, does not highlight any safety issue. To address these vaccination error reports, GSK is strengthening its medical information material to improve awareness of the authorized indication and correct use of Arexvy and is enhancing follow-up of pregnancy exposure cases to support continuous safety surveillance. More details on the post-marketing safety experience will continue to be communicated to regulatory authorities through periodic safety reports.

The post-marketing safety data received up to 02 November 2024 does not alter the overall benefit-risk profile of Arexvy for the active immunization for the prevention of LRTD caused by RSV.

2.5.1. Discussion on clinical safety

The known safety profile of Arexvy is derived from the phase 3 studies RSV OA=ADJ-006, -004, -007, and -009, all of which included participants 60 years of age or older. Study ADJ-018 additionally included participants 50-59 years of age, both with and without co-morbidities leading to an increased risk of RSV-LRTD. In the current variation, evidence from ADJ-025 is submitted, which provides safety data for 1029 participants aged 18–49-year-old AIR of RSV-LRTD, with a follow-up of 6 months. The study had three cohorts: cohort 1 (18-49 YOA AIR for RSV disease),

cohort 2 (≥60 YOA RSV-OA), and cohort 3 (18-49 YOA AIR for RSV disease), all of which participated in the safety endpoints.

Safety endpoints, and methods of collection were comparable to the previous Arexvy trials and collected in an appropriate manner. No subgroup analyses were performed for the safety endpoints. This is acceptable as during the MAA it was observed that gender did not influence the safety profile in older adults >60 years of age and therefore, it is unlikely to be of major influence in the currently evaluated age group.

Proportions reporting any solicited adverse reactions were higher in the younger RSV-A-AIR groups (75.0%) than in the RSV-OA group (54.9%). However, the number of grade 3 events remained low (5.8% versus 2.3%). This is an expected finding. Pain was the most frequently reported solicited administration site event (76%), and fatigue (60%) and myalgia (60%) the most common systemic solicited event. In younger individuals, and the overall frequency of these reactogenicity events did not differ from what was already provided in the SmPC ADR table. These adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.

Between groups, there was no clinically meaningful difference in unsolicited adverse events (both related and unrelated) within 30 days after vaccination (RSV-A-AIR group 18.5%, RSV-OA group 17.7%). Non-serious related unsolicited adverse events within 30 days after vaccination occurred more frequently in RSV-A-AIR (8.7%) group than in RSV-OA (3.0%) group. At PT level, these numerical imbalances were mainly driven by reactogenicity events (chills, injection site reactions, nausea, vomiting) and lymphadenopathy which are recognized ADR in the SmPC of Arexvy.

No new adverse drug reactions have been identified in this application. However, the frequency of adverse reactions in the SmPC was revised considering pooled data from all studies for participants 18 years of age and older (i.e. RSV OA=ADJ-006, -018 and -025). Consequently, the frequency for injection site erythema was revised from very common to common. No other amendments were deemed necessary.

Serious adverse events occurred in similar frequencies in the RSV-A-AIR group and the RSV-OA group. On PT-level 'Infections and infestations' occurred slightly more often in the RSV-A-AIR group than in the RSV-OA group (0.7% versus 0.2%), however there was no indication that this may be a safety signal. Most likely these differences are due to the differing epidemiological factors and baseline characteristics (i.e. greater viral exposure or higher BMI in the younger group). This is aligned with the conclusions in the placebo-controlled trials (-006, -018) where there was no indication that participants receiving Arexvy had a higher rate of infections and infestations than those receiving placebo.

Up to the study end, at least 1 SAE was reported in 14 participants (1.4%) in the RSV-A-AIR group and in 13 participants (3.0%) in the RSV-OA group. None of the SAEs were considered related to Arexvy. There were no SAEs with a fatal outcome reported. Regarding pIMDs, events were reported in 2 participants (0.2%) in the RSV-A-AIR group (hematoma [non-serious AE] and type 1 diabetes mellitus [SAE] in 1 participant each) and in 1 participant (0.2%) in the RSV-OA group (pernicious anaemia [non-serious AE]). The AE of hematoma in a >30-year-old diabetic participant was considered as related to study intervention by the investigator but not the MAH. The participant developed haematoma at the insulin injection site 14 days after vaccination and the condition aggravated over the body. There were no laboratory findings identifying coagulopathy and the haematomas spontaneously resolved within months. The MAH conducted a broad search for haemorrhages in the GSK safety database. The case of exacerbated hematoma in study RSV OA=ADJ-025 is the only case reported across Arexvy clinical studies or post-marketing settings until 27 August 2025. The Company will continue to monitor reports of multiple disseminated

haematomas after administration of Arexvy through routine pharmacovigilance including signal detection activities.

Events of atrial fibrillation were reported in 1 participant each in the RSV-A-AIR group and RSV-OA group. In both reports, this occurred in patients with either pre-existing paroxysmal atrial fibrillation, or with pre-existing risk factors for atrial fibrillation. In addition, the occurrence in one of the participants was not confirmed with an ECG. It is agreed that these episodes of AF were not caused nor aggravated by Arexvy.

There were three pregnancies in the RSV-A-AIR group during the study, which all resulted in a live infant with no apparent congenital anomaly. Arexvy is not recommended during pregnancy, and routine pharmacovigilance activities are sufficient to further characterise this special population.

The available data in post-marketing in 18 years of age and older does not raise any concern.

To conclude, no new safety concern was identified in the submitted data and at this stage, routine pharmacovigilance activities are sufficient to further characterise the safety profile of Arexvy.

2.5.2. Conclusions on clinical safety

Overall, the safety profile in the population 18 years of age and older was similar to the safety profile in the older adults (>60 years) and no new safety signals nor safety concerns have been identified.

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 submitted an updated RMP version 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 3.1 is acceptable.

Safety concerns

Table 19 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

No additional pharmacovigilance activities are required.

Risk minimisation measures

Not applicable

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.6, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

2.7.1. User consultation

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

It is agreed with the applicant that the amendments to the patient leaflet with this extension of the indication are minimal, only one sentence in section 1 of the patient leaflet and a change in section 4.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The intended indication is: Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 18 years of age and older.

RSV is a high attack-rate virus characterized as capable of causing severe disease at opposite ends of life, and in those with co-morbidities. The 18–49-year-old population relevant for this extension of indication has more limited epidemiological data available than those ≥60 years of age and are less likely to be tested for RSV leading to an underestimation of the disease burden. However, existing data does show a disease burden among these individuals. Although hospitalization in healthy adults 18-49 YoA is rare (incidence approximately 2.1 per 100,000 PY), RSV infections are common and may cause cold or influenza-like symptoms. Approximately 22% of influenza-like illness in 25–29-year-olds has been attributed to RSV, and symptomatic illness in adults may be severe enough to result in half or more of effected adults missing work (Zambon 2001). Cases in adults have been reported to result in persistent shortness of breath and fatigue up to 4 weeks following illness (Hall et al 1978). Outbreaks of healthcare-associated respiratory syncytial virus (HA-RSV) infections are well described, particularly in neonatal intensive care units (ICUs), paediatric ICUs, and units caring for immunosuppressed children. HA-RSV is responsible for 20% of RSV-related in-hospital deaths in lower- and middle-income countries (Saiman, 2024, J Pediatric Infect Dis Soc). In such cases, it is plausible that accidental spread due to hospital-workers with a mild RSV-infection contributes to infection of vulnerable children.

3.1.2. Available therapies and unmet medical need

Since 2023, there have been substantial advances in the prevention of RSV due to the approval of Arexvy and two additional vaccines. mRESVIA is approved for prevention of RSV-LRTD in adults aged ≥ 60 years, and adults 18-59 years who are at increased risk for LRTD caused by RSV. Abrysvo is approved in adults ≥ 18 years regardless of co-morbidity status. Abrysvo is also approved for the passive immunization of infants following maternal immunisation during pregnancy. Despite new vaccination possibilities for the prevention of RSV, the morbidity and mortality associated with the disease remains high. Treatment of RSV disease consists primarily of supportive care (e.g. oxygen, hydration and suctioning of secretions). An antiviral agent, ribavirin, is licensed for the treatment of RSV infection in the United States and some EU member states; however, it is not recommended in the United States or EU treatment guidelines.

3.1.3. Main clinical studies

The evidence is provided from a single clinical study: A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for RSV disease (i.e. with pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease such as chronic pulmonary disease, chronic cardiovascular disease, diabetes, chronic kidney or liver disease, or neurological or neuromuscular disease), compared to older adults ≥60 years of age (ADJ-025). The primary objective of the study was to determine non-inferiority of the immune response elicited by Arexvy after 1 month in 18–49-year-old individuals at increased risk of RSV-LRTD compared to ≥60-year-old individuals (i.e. the population for whom efficacy has been established at the time of the initial MA). The study had three cohorts: Cohorts 1 (18-49 YOA AIR for RSV disease), Cohort 2 (≥60 YOA RSV-OA), and Cohort 3 (18-49 YOA AIR for RSV disease), and was divided into two parts (Part A and part B). The primary immunogenicity analyses were only performed for Part A (Cohorts 1 and 2); safety analyses were performed for both Part A and Part B (Cohorts 1, 2, and 3).

3.2. Favourable effects

The primary immunogenicity objective of study ADJ-025 was to demonstrate the non-inferiority of the humoral immune response following the administration of Arexvy in participants 18-49 YOA at increased risk for RSV disease compared to adults ≥60 YOA, in whom vaccine efficacy was demonstrated at the initial application.

The four co-primary endpoints of the pivotal study of this application were met:

The adjusted GMT ratio (95%CI) for (RSV-OA /RSV-A-AIR) was 0.72 (0.64;0.81) and 0.73 (0.65;0.82) for RSV A and B respectively. The SRR difference was -9.36 (-14.58; -4.14) and -10.06 (-15.29; -4.83) for RSV A and B respectively. Thus, the prespecified non-inferiority criteria for the four co-primary endpoints were met. Titers remained well above baseline levels up till 6 months post vaccination for all groups.

An additional analysis was performed on the enrolled set instead of the per protocol set with the same results as in the PPS set.

3.3. Uncertainties and limitations about favourable effects

There is no correlate of protection known for RSV disease. Therefore, the benefit of Arexvy in 18 to 49 years of age and older has been inferred via immunobridging to the e ≥60 YOA population, for

whom vaccine efficacy has been demonstrated in the initial application. This is in alignment with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1.) In studies involving participants 60 years of age and older, vaccine efficacy against RSV-associated LRTD over 3 RSV seasons was 62.9%. It can be inferred that the efficacy in people under 60 years of age is comparable over these three seasons. However, the duration of protection conferred by Arexvy has not been established beyond these three seasons, and it is currently unknown if and when a booster would be beneficial.

3.4. Unfavourable effects

The safety data presented for this extension of indication is derived from the completed study ADJ-025. It includes a total of 1029 participants 18-49 years of age who were followed up to at least 6 months.

Pain (76%) was the most frequently reported solicited administration site event, and fatigue (60%) and myalgia (60%) the most common systemic solicited event followed by headache (44%) and arthralgia (28%). These adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination.

Proportions reporting any solicited adverse reactions were higher in the younger RSV-A-AIR groups (75.0%) than in the RSV-OA group (54.9%). The pattern is also reflected in the number of grade 3 events (5.8% versus 2.3%).

At least 1 SAE was reported in 14 participants (1.4%) in the RSV-A-AIR group and in 13 participants (3.0%) in the RSV-OA group. None of them were considered causally related to vaccination. There were no SAEs with a fatal outcome.

Regarding pIMDs, events were reported in 2 participants (0.2%) in the RSV-A-AIR group (hematoma [non-serious AE] and type 1 diabetes mellitus [SAE] in 1 participant each) and in 1 participant (0.2%) in the RSV-OA group (pernicious anaemia [non-serious AE]). The AE of hematoma was considered as related to study intervention by the investigator but not by the MAH.

No new adverse drug reaction was identified in study ADJ-025. However, the frequency of adverse reactions in the SmPC was revised should be based on pooled data from all studies with Arexvy including participants 18 years of age and older. Consequently, the frequency for injection site erythema was revised from very common to common. No other amendments were deemed necessary.

No new safety concerns were identified.

3.5. Uncertainties and limitations about unfavourable effects

The trial was open-label and not placebo controlled, which could have impacted the reporting of safety endpoints.

The sample size of 1025 participants aged 18-49 had 64% and 87% probability of observing at least one vaccinated participant with an AE if the true AE incidence rate is 0.1% and 0.2% respectively. The known safety profile is based on people ≥50 years.

No additional pharmacovigilance activities are considered necessary to characterise the above uncertainties and limitations.

3.6. Effects Table

Table 20 `Effects Table for Arexvy: adults 18 years of age and older (RSV OA=ADJ-025 Part A)

Effect	Short description	Unit	18–49-year-olds	>=60-year-olds	Uncertainties / Strength of evidence	References
	Favourable Effects					
NA	RSV A	Adj GMT	11914.6	8591.5	Adj GMR (95% CI) (ANCOVA) 0.72 (0.64; 0.81)	RSV OA=ADJ-025
NA	RSV B	Adj GMT	12503.4	77.7	0.73 (0.65;0.82)	
NA	RSV A	SRR	87.1	9087.6	Diff (95% CI) -9.36 (-14.58; -4.14)	
NA	RSV B	SR	87.3	77.2	-10.06 (-15.29;-4.83)	
	Unfavourable Effects					
Solicited Local AE	4 days	%	76.4	58.2	Most common was injection site pain	RSV OA=ADJ-025
Solicited Systemic AE	4 days		75.0	54.9	Most common were myalgia and fatigue	
AEs	30 days		18.5	17.7		
Related AEs	30 days		8.7	3.0		
SAEs	6 months		1.4	3.0		

Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; SR = seroresponse; SRR = seroresponse date; adj = adjusted for group as fixed effects and the pre-dose log-10 titer as covariate; CI = confidence interval

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Non-inferiority of the immune response to RSVPreF3 OA in 18-49 YOA compared to ≥60 YOA was demonstrated in terms of RSV-A & B neutralizing GMTs (upper limit of the 95% CI on group GMT

ratio was 0.81 and 0.82 respectively, below the pre-defined non-inferiority criterion of 1.5) and SRR (upper limit of the 95% CI on SRR difference was -4.14% and -4.83% respectively, below the pre-defined non-inferiority criterion of 10%). Robustness of the results were confirmed with sensitivity analyses. These results support the inference of efficacy in the younger population.

The trial was open label, which potentially impacts the reporting of the safety endpoints. However, as all participants received the vaccination, it is not expected that older and younger individuals would report AEs differently in the open-label setting. Although younger participants had a higher rate of reactogenicity and related adverse events than the older participants (which is an expected observation), in general the frequency and type of events were consistent the known safety profile of Arexvy.

The study population involved 18–49-year-olds at increased risk of RSV LRTD due to co-morbidities. However, the MAH is seeking the indication for all 18–49-year-olds. This is acceptable. In the immune competent population, there is no expectation that the underlying conditions would have a substantial impact on either the immunogenicity or safety results. This assumption is also supported by the results of RSV OA=ADJ-018 in which both the immunogenicity results (as presented by the immune response 1-month post-vaccination with Arexvy for 50–59-year-olds both at and not at increased risk of RSV-LRTD was comparable in both populations) do not suggest differences in outcomes based on the presence of comorbidities.

Although based on the immunogenicity profile it can be inferred that Arexvy is efficacious in younger, healthier populations, the clinical benefit of this efficacy may be less clear than for the older populations in whom severe disease leading to hospitalization occurs more frequently. According to a Darwin-EU study, in the 18–59-year-old population, the rate of RSV-related hospitalization is 2.1 (95% CI, 1.9 - 2.2) per 100,000 PY. However, the clinical benefit of RSV vaccination does not only rest on prevention of hospitalization. RSV infections are common and may cause cold or influenza-like symptoms. Approximately 22% of influenza-like illness in 25–29-year-olds has been attributed to RSV, and symptomatic illness in adults may be severe enough to result in half or more of effected adults missing work (Zambon 2001).

For the safety outcomes, the total number of adults aged 18-49 years exposed to Arexvy is relatively modest. The current study is powered to observe AEs with an incidence of 0.1-0.2% and would therefore not detect AEs with a similar frequency as RSV-related hospitalizations. However, the extensive safety database for Arexvy in older adults (as well as for other AS01 adjuvanted vaccines) does not provide reasons for concern. No new safety concern has been identified.

The uncertainties associated with the level of clinical benefit are not considered significant to impact the extension of indication to this population. Moreover, the current wording of the indication would allow NITAGs to determine if and how to recommend use in adults aged from 18 years 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 minimize staff shortages during the RSV season just as influenza vaccines are so targeted in many countries. Or they may in particular focus on healthcare workers in neonatal intensive care units (ICUs), paediatric ICUs, and units caring for immunosuppressed children to prevent healthcare-associated respiratory syncytial virus infections in these vulnerable populations.

3.7.2. Balance of benefits and risks

The data from study ADJ-025 establish the non-inferiority of immune response in individuals 18-49 years old compared to the population for whom efficacy has been established. There are no new safety concerns. While the study was conducted in adults aged 18-49 years with at least one pre-specified underlying medical condition, there is no expectation that the underlying conditions would have a relevant effect on immunogenicity or safety. From a clinical perspective, a positive benefit/risk balance in the proposed indication is established.

3.8. Conclusions

The overall B/R of Arexvy is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 18 years of age and older for Arexvy, based on results from study 222253 (RSV OA=ADJ-025); this is a Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk of respiratory syncytial virus disease, compared to older adults ≥60 years of age. As a consequence, sections 4.1, 4.6, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

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

The variation leads to amendments to the annex(es) I and IIIB 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.

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

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