EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2024
EMA/354383/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AREXVY

International non-proprietary name: Respiratory syncytial virus, glycoprotein F, recombinant, stabilised in the pre-fusion conformation, adjuvanted with $AS01_E$

Procedure No. EMEA/H/C/006054/II/0008

Note

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

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
AF	Atrial Fibrillation
AIR	At increased risk
ANCOVA	Analysis of covariance
$AS01_E$	Adjuvant system containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
BMI	Body Mass index
CAD	Coronary artery disease
CCI	Charlson Comorbidity Index
CD	Cluster of differentiation
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLS	Clinical laboratory sciences
CMI	Cell-mediated immunity
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
ED60	Estimated Dose: serum dilution giving a 60% reduction of the signal compared to a control without serum
EoS	End of study
ES	Exposed Set
eTMF	Electronic trial master file
FSFV	First subject first visit
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMT	Geometric mean titer
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline Biologicals SA
HA	Healthy adults
ICH	International Council on Harmonization
ICS	Intracellular cytokine staining
IDMC	Independent data monitoring committee
IFN	Interferon
IL	Interleukin
IM	Intramuscular
LRTD	Lower respiratory tract disease
LSLV	Last subject last visit
MAtEx	MATerial EXcellence
MDRD	Modification of Diet in Renal Disease
MGI	Mean geometric increase

NA	Neutralizing antibody
NI	Non-inferiority
OA	Older adults
PCR/NAAT	Polymerase chain reaction / Nucleic Acid Amplification Test
pDiary	Paper diary
pIMD	Potential immune-mediated disease
PPS	Per-Protocol Set
QS-21	Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SBIR	Source data Base for Internet Randomisation
SOP	Standard operating procedure
SRR	Seroresponse rate
SRT	Safety review team
TNF	Tumor necrosis factor
VWP	Vaccine working party
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 S.A. submitted to the European Medicines Agency on 9 January 2024 an application for a variation.

The following variation was requested:

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

Extension of the indication for Arexvy to include vaccination of adults 50-59 years of age who are at increased risk for RSV disease for RSV disease, based on results from study 219238 (RSV OA=ADJ-018); this is a phase 3, observer-blind, placebo-controlled, randomized, multi-country, multi-center, non-inferiority study with 2 cohorts to evaluate immunogenicity, reactogenicity and safety of a single dose of RSVPreF3 OA in adults 50-59 years of age. As a consequence, sections 4.1, 4.6, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 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, to bring it in line with the latest QRD template version 10.3, and to update the list of local representatives in the Package Leaflet. As part of the application, the MAH is requesting a 1-year extension of the market protection.

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 (EMEA-002904-PIP01-20) on the agreement of a paediatric investigation plan (PIP). The PIP included a deferral in accordance with Article 21 and a waiver for infants and toddlers from birth to less than 2 years of age on the grounds that the product is likely to be unsafe in this paediatric population.

On 29 November 2023, a modification to the Paediatric Investigation Plan (PIP) was completed. The modification was set out in the Agency's decision (P/0508/2023) on the basis that the applicant encountered difficulties with its implementation as to render the plan unworkable and no longer appropriate. The submitted modification (concerning timelines and study design of paediatric studies) was accepted (EMA/PDCO/365470/2023).

Information relating to orphan market exclusivity

The product does not have orphan designation.

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.

Derogation(s) of market exclusivity

Not applicable

MAH request for additional market protection

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

Scientific advice

The MAH did not seek Scientific advice at the CHMP specifically for ADJ-018. However, during the course of development for Arexvy, the sponsor sought regulatory and scientific advice from EMA's Committee for Medicinal Products for Human Use (CHMP) on several occasions between 2018 and 2022.

From a clinical perspective, the most important advice pertaining to the current extension of indication is regarding a proposed study (ADJ-014) in Scientific advice EMA/SA/000076659 (24/03/2022). The MAH revealed plans to conduct study RSV OA=ADJ-014, which planned to use an immunobridging approach to support use in younger individuals 18-59 YOA, including those who are at increased risk for RSV LRTD. A comparison would be made to data in adults ≥60 YOA.

The CHMP agreed that if vaccine efficacy is demonstrated in accordance with the predefined criterion in the pivotal efficacy study (RSV OA=ADJ-006) in subjects aged from 60 years, an approval for use from 18 years could be based on immunobridging accompanied by safety data in the younger population. It was further stated that 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 neutralizing antibody (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).

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	9 January 2024
Start of procedure	27 January 2024
CHMP Rapporteur Assessment Report	22 Mar 2024
PRAC Rapporteur Assessment Report	27 Mar 2024
PRAC members comments	03 Apr 2024
Updated PRAC Rapporteur Assessment Report	04 Apr 2024
PRAC Outcome	11 Apr 2024
CHMP members comments	15 Apr 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 April 2024
Request for Supplementary Information (RfSI)	25 April 2024
Re-start of procedure	27 May 2024
CHMP Rapporteur Assessment Report	20 June 2024
PRAC Rapporteur Assessment Report	N/A
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	17 July 2024
PRAC Outcome	11 July 2024
CHMP members comments	18 July 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 July 2024
Opinion	25 July 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

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). Incidence rates of RSV disease are frequently derived from population-based influenza surveillance systems in adults ≥65 YOA. However, several studies underline the high burden of severe RSV-related disease in adults under 60 years of age.

State the claimed therapeutic indication

Arexvy is currently indicated for active immunisation for the prevention of LRTD caused by RSV in adults 60 years of age and older. Arexvy is administered intramuscularly as a single dose of 0.5 mL. It was licensed in June 2023 based on efficacy data from an interim analysis (based on 47 cases) of a single pivotal phase 3 trial, study RSV OA=ADJ-006 (EMEA/H/C/006054/0000). This information was supported by three phase 3 supportive clinical studies using the proposed vaccination regimen mainly investigating immunogenicity and safety and a phase 2 dose-finding study.

With the current type II variation, the MAH is proposing an extension of the indication.

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;*

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

Epidemiology

In temperate climates throughout the world, RSV predictably causes fall-winter epidemics. The RSV-A and RSV-B subtypes co-circulate, and the predominance of one over the other varies by year and geographic location.

RSV is the third most frequent cause (after influenza and rhinovirus, prior to the COVID-19 pandemic) of medically significant respiratory tract disease in adults and is a significant cause of disease burden in the older adult population. The impaired immune response in this population due to the ageing of the immune

system and other risk factors, such as the presence of comorbidities and/or frailty, increase the risk for RSV disease and its complications.

Incidence rates of RSV disease are frequently derived from population-based influenza surveillance systems in adults ≥65 YOA. Younger adult populations (e.g. the 50–59-year-old population relevant for this extension of indication) 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 (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, lower viral load in adults, and the presence of underlying conditions contributing to the clinical picture (Cong, BMC Med, 2023)

In a multiyear Canadian surveillance cohort, RSV was found in 12.9% of patients admitted to the hospital for respiratory infections. The median age of these RSV-patients was 72.0, with an interquartile range of 61.0-82.5, showing that 25% of these RSV admissions were for individuals under the age of 61 (Lee CMAJ 2021). A study conducted in several hospitals during 3 consecutive winter seasons in North America (2006/07 to 2008/09) reported an average annual rate of RSV hospitalisation in patients 50-64 YOA of 82/100 000 PY and 254/100 000 PY in patients ≥65 YOA (Widmer, J Infect Dis, 2012). A separate study showed the pooled reported annual rates of RSV-associated hospitalisation among adults to be 45/100 000 for age 50− 64 and 178/100 000 for ≥65 year olds. (McLaughlin, 2022) Most hospitalisations in younger adults occur among those with chronic medical conditions (e.g., obesity, diabetes, or chronic cardiopulmonary, renal, or immunocompromising conditions). These individuals have rates of RSV-associated illness that are 1.2–28 times higher than those without underlying conditions. (McLaughlin, 2022) Other data suggest that although frequency of deaths increases with age, mechanical ventilation use and length of hospital stay have been reported to be similar in patients within the 45-59 and 50-64 year old range compared to patients 60 years of age and older (Pastula 2017, Choi 2022).

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, diagnosis

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.

The most common method of diagnosis is through demonstrating the presence of RSV virus in the airways of the individual via a PCR/NAAT on a nasopharyngeal swab.

Management

Treatment

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 guidelines. Therefore, there is currently no specific treatment for RSV infections in adults. 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

The RSV vaccines Arexvy and Abrysvo are currently approved in the EU. Both are approved for the active immunization of individuals 60 years and older. Abrysvo is also indicated for the passive immunization of infants through immunization of the mother during pregnancy. No vaccine is currently approved within the EU for adults younger than 60 years of age.

Unmet need

RSV is the third most frequent cause (after influenza and rhinovirus, prior to the COVID-19 pandemic) of medically significant respiratory tract disease in adults and is a significant cause of disease burden in the older adult population. Younger adult populations (e.g. the 50-59 year old population relevant for this extension of indication) have more limited epidemiological data available than older adult populations, and underreporting of RSV-associated morbidity is common.

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, kidney, or immunocompromising conditions). Other data suggest that although frequency of deaths increases with age, mechanical ventilation use and length of stay have been reported to be similar in patients within the 45-59 and 50-64 year old range compared to patients 60 years of age and older (Pastula 2017, Choi 2022).

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 respiratory syncytial virus (RSV, A & 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 suspension for injection containing 120µg of RSVPreF3 antigen (powder) adjuvanted with $AS01_E$ (suspension).

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

Development programme

The extension of indication to individuals 50-59 years is supported by a single phase 3 study OA=ADJ-018.

The clinical development program for Arexvy to support licensure in adults ≥60 years of age consisted of 4 Phase 3 studies, ADJ-006, ADJ-004, ADJ-007 and ADJ-009, and the Phase 2 dose-finding study ADJ-002. The Applicant has stopped the development of a maternal vaccination program using the investigational RSV Maternal (RSVPreF3) vaccine due to imbalances for both preterm birth and neonatal deaths observed in one study.

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

The MAH did not seek scientific advice at the CHMP specifically for ADJ-018. However, during the course of development for Arexvy, the sponsor sought regulatory and scientific advice from EMA’s Committee for Medicinal Products for Human Use (CHMP) on several occasions, and 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 younger individuals albeit in a wide age range of 18-59 YOA. 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-018.

- 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 GLP, 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.

- A routine Sponsor GCP Inspection was conducted by Health Canada at the offices of the Sponsor, this study was selected for the inspection sample. Three findings (no critical, two major and one minor) were identified. The major findings were in relation toSystems and Procedures and temperature monitoring data.

Corrective and preventive actions have been developed to address these findings which have been accepted by Health Canada.

2.2. Non-clinical aspects

2.2.1. Introduction

The purpose of this application is to extend the RSVPreF3 OA vaccine indication to adults 50-59 YOA who are at increased risk for RSV disease. Although pregnancy is unlikely to occur in women ≥50 YOA, with a reported incidence of spontaneous pregnancies of about 4 in 100,000 women [Eijkemans, 2014; Salihu, 2003], considering the applicant’s future plans for studies supporting indication in younger population, a

developmental and reproductive toxicity (DART) study in rabbits has been conducted with RSVPreF3/AS01$_E$.

2.2.2. Pharmacology

No (additional) data on pharmacology have been provided for this type II variation.

2.2.3. Pharmacokinetics

No (additional) data on pharmacokinetics have been provided for this type II variation.

2.2.4. Toxicology

Reproduction toxicity

A GLP nonclinical DART study was conducted in New Zealand White rabbits with RSVPreF3/AS01$_E$ to assess potential effects of RSVPreF3/AS01$_E$ on female fertility, reproductive parameters, embryo-fetal or pre- and post-natal survival, growth or development of the offspring.

Study design.

During the treatment period from 28 days prior to pairing until GD 24 (Caesarean Phase) or LD 7 (Littering Phase), RSVPreF3 OA vaccine (full human dose, 120 µg RSVPreF3 adjuvanted with AS01$_E$) was administered by intramuscular injection to female New Zealand White rabbits (48/group) on Days 1 and 15 (28 and 14 days before pairing, respectively), on gestation days (GD) 3, 9, 16 and 24, and after natural delivery on lactation day (LD) 7. A control group (48/group) was administered sterile physiological saline (0.9% NaCl) under the same conditions as the treated animals. The chosen route of administration was the same as in clinical studies, i.e. intramuscular administration, and the dose volume was a constant 0.5 mL per dose. The frequency of dosing was defined to allow the development of an immune response prior to the gestation phase, and exposure to the antigen and other components of the vaccine formulation during gestation and lactation. The F1 offspring received no direct administration of the vaccine so any exposure to its components was in utero or via lactation.

The following endpoints/parameters were evaluated for females: mortality, clinical observations, body weights, food consumption measurements, dermal scoring, immunogenicity and macroscopic observations.

The following additional endpoints/parameters were observed for Caesarean Phase animals euthanized on GD 29: gravid uterus weights and gravid uterine corrected body weights; maternal performance; placenta weights (en masse); examinations of pregnancies (corpora lutea, implantations, resorptions, live and dead fetuses), fetal examinations (body weights, sex, external, visceral and skeletal abnormalities and the extent of ossification) and fetal immunogenicity.

The following additional endpoints/parameters were observed for Littering Phase animals euthanized on LD 35: gestation length, parturition, observations of females with litters during lactation. The physical development and functional tests of the pups were assessed, and on Postnatal Day (PND) 35, surviving

kits were euthanized, blood was collected for immunogenicity, and a necropsy was performed. Kits that were found dead were examined and a necropsy was performed to the extent possible.

Results

There were no RSVPreF3/AS01$_E$-related effects on mating, fertility, maternal body weights, food consumption, parturition, macroscopic observations, organ weights, embryo-fetal survival, growth, development (external, visceral and skeletal morphology) or on the postnatal growth, physical and reflex development of offspring to LD 35.

Effective vaccine uptake was confirmed in 100% of female rabbits treated with RSVPreF3/AS01$_E$ that developed the expected immune response, and the transfer of antibodies to fetuses and pups was demonstrated.

Conclusion

A GLP DART study in rabbits has been performed with RSVPreF3/AS01$_E$ to assess its' nonclinical safety with regards to reproductive and developmental toxicity. There were no noteworthy findings on this study. The intramuscular administration of RSVPreF3/AS01$_E$ was well tolerated in the rabbit and demonstrated no effects on female fertility, embryo-fetal, pre- and post-natal development when administered to New Zealand White rabbit females 28 and 14 days before pairing, on GD 3, 9, 16 and 24, and on LD 7.

The CHMP notes that for the initial MAA, no reproduction and/or development studies were provided with adjuvanted RSVPreF3, due to the age of the target population. With regard to the potential off-label use in pregnant women, and inclusion of complete information in the SmPC, on request of the RMS, conclusions of the reproductive toxicity studies with unadjuvanted RSVPreF3 were included in section 4.6 and 5.3.

For the current application, and mainly considering the applicant's future plans for studies supporting indication in younger population, a DART study in rabbits with RSVPreF3/AS01$_E$ has been submitted. These results were already submitted in a final report on Reproductive and Development toxicity study with Arexvy during the initial MAA procedure.

In this study, female rabbits were administered a full human dose of RSVPreF3/AS01$_E$ (120 µg RSVPreF3 with 50 µg AS01$_E$ in 0.5 mL) 28 and 14 days before pairing, on GD 3, 9, 16 and 24, and on LD 7. All females developed an anti-RSV PreF3-specific IgG antibody response. No test item-related adverse effects on female fertility, embryo-fetal, pre- and postnatal development were observed.

DART study in rabbits with adjuvanted RSVPreF3 is already mentioned in current SmPC. Within procedure II/008, sections 4.6 and 5.3 are updated providing more clarity.

2.2.5. Ecotoxicity/environmental risk assessment

Environmental Risk Assessment studies are not applicable for RSVPreF3 OA vaccine. Due to the nature of the constituents this vaccine is unlikely to result in a risk to the environment. This is in accordance with the current EMA guideline "Guideline on the environmental risk assessment of medicinal products for human use", EMEA/CHMP/SWP/4447/00 Corr 2, 1 June 2006 (updated 13 January 2015), which states

"In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment. The same applies to vaccines and herbal medicinal products"

In accordance with CHMP guidance EMEA/CHMP/SWP/4447100 entitled "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006, due to their nature, vaccines are unlikely to result in a significant risk to the environment. Therefore, the absence of an environmental risk assessment is agreed with.

2.2.6. Discussion on non-clinical aspects

For this application, a DART study in rabbits with RSVPreF3/AS01$_E$ was submitted. No test item-related adverse effects on female fertility, embryo-fetal, pre- and postnatal development were observed.

Sections 4.6 and 5.3 of the SmPC were updated to reflect the results of the adjuvanted RSVPreF3/AS01E DART study.

2.2.7. Conclusion on the non-clinical aspects

The application is approvable from a non-clinical point of view.

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

Arexvy is currently indicated for the active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 60 years of age and older. The MAH is seeking to extend this indication to include adults 50 through 59 years of age who are at increased risk for RSV disease.

In Table 1, an overview of the (ongoing at the time of the submission) clinical study submitted to support the current application is presented. The trial is an immunogenicity study. No efficacy data is presented here.

Table 1. overview of clinical studies submitted

Study ID Status Location	Study Design	Posology and number of subjects by group	Study population (exposed set)	Primary objectives (confirmatory)
RSV OA=ADJ-018 Ongoing at the time of	Phase 3, observer-blind, placebo-controlled, randomized, multicountry,	IM, single dose at day 1. Cohort 1: Randomisation ratio 2:1 (study intervention or placebo)	Cohort 1:	To demonstrate the NI of the humoral immune response after RSVPreF3 OA administration in

the submission Eight countries 60 centers	multi-center, non-inferiority study with 2 cohorts. Study duration is 12 months after vaccination in all groups.	Adults-HA-RSV: RSVPreF3 OA on Day 1 Exposed: 383 PPS: 329 Adults-HA-Placebo: Placebo on Day 1 Exposed: 192 PPS: 177 Adults-AIR-RSV: RSVPreF3 OA on Day 1 Exposed: 386 PPS: 345 Adults-AIR-Placebo: Placebo on Day 1 Exposed: 191 PPS: 179 <u>Cohort 2:</u> Randomisation ratio 2:1 (study intervention or placebo) OA-RSV: RSVPreF3 OA on Day Exposed: 381 PPS: 347	Median age 55.0 years Median age 55.0 years Median age 55.0 years Median age 56.0 years <u>Cohort 2:</u> Median Age: 69.0 years	-healthy participants 50-59 YOA† compared to OA (≥60 YOA) for the RSV-A strain -healthy participants 50-59 YOA† compared to OA (≥60 YOA) for the RSV-B strain - in participants 50-59 YOA at increased risk of RSV-LRTD* compared to OA (≥60 YOA) for the RSV-A strain - in participants 50-59 YOA at increased risk of RSV-LRTD* compared to OA (≥60 YOA) for the RSV-B strain

AIR = adults at increased risk for RSV LRTD; OA = older adults; PPS = per-protocol set; YOA = years of age; NI= non-inferiority.
* This includes participants with the pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease (chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, and chronic liver and renal diseases).
† This refers to the group of participants without the pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease. Therefore, these participants may either have other underlying conditions or not.

2.3.2. Pharmacokinetics

No pharmacokinetics studies have been conducted for Arexvy. This is because pharmacokinetics studies are generally not needed for vaccines, as detailed in the CHMP guideline “Guideline on Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005).

2.3.3. 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).

Mechanism of action

Arexvy consists of 120 µg of the RSVPreF3 recombinant antigen and the $AS01_E$ adjuvant system administered as a 0.5 mL single dose. 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 F protein is conserved between the RSV A and B subtypes and the main target of RSV neutralising antibodies in human sera. The adjuvant system $AS01_E$ contains QS-21 (i.e. a triterpene glycoside purified from the bark of the tree Quillaja saponaria Molina) and MPL (i.e. 3-O-desacyl-4′-monophosphoryl lipid A), to

enhance the immunogenicity. Currently there is no established correlate of protection for symptomatic disease caused by RSV.

Primary and secondary pharmacology

Three RSV-specific assays were used to support the primary and secondary immunogenicity endpoints in the RSV OA=ADJ-018 study (Table 2).

Table 2 Laboratory values

Component	Assay method	Laboratory	Assay unit	Assay cut-off
Humoral immunity (antibody determination)				
RSV-A neutralization titer*	Neutralization	GSK**	ED60 (IU/mL)	18 (56)
RSV-B neutralization titer*	Neutralization	GSK**	ED60 (IU/mL)	30 (44)
Cell-mediated immunity				
CD40L, 4-1BB, IL-2, TNF-α, IFN- α, IL-13, IL-17 secreting CD4+ and CD8+ T cells	Intracellular cytokine staining	GSK**	Events/1^{60} cells	590***

CD = cluster of differentiation; CD40L = CD40 ligand; ED60 = estimated dilution; IFN = interferon; IL = interleukin; IU/mL = international units per mL; RSV = respiratory syncytial virus; TNF = tumor necrosis factor. * The serum neutralization titers were expressed in Estimated Dilution 60 (ED60) units and converted to concentration in international units per mL (IU/mL). ** GSK laboratory refers to the Vaccines Clinical Laboratory and Assay Portfolio (Vx CL&AP) in Rixensart, Belgium; Wavre, Belgium (formerly referred to as the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium). *** The lower limit of quantification (i.e., 590) was used as assay cut-off to calculate the fold increase.

The laboratory assays used in the assessment for the primary and secondary endpoints of the study were the same as those used in the Phase 3 studies included in the initial file. At the time of the original MAA, some of the assay parameters were only investigated in the assay qualification experiments and not repeated during validation. CHMP concluded that although the assays were not considered fully validated, they were fit for purpose as the parameters most susceptible to change in clinical testing conditions were validated, and the immunogenicity results were not necessary for the benefit/risk assessment (which was based largely on efficacy data), but that the lack of full validation might have implications for (future) claims based on immunogenicity.

The outstanding issues regarding validation were addressed in the type II variation EMEA/H/C/006054/II/0002/G (2024). The application reported on the immune response of Arexvy when administered concomitantly with different seasonal influenza vaccines. At the request of the CHMP, the MAH more thoroughly discussed why the level of assay validation is appropriate to support claims based on comparative immunogenicity. The CHMP agreed that the parameters considered most important to demonstrate the assay appropriateness to quantify the neutralisation response induced in the different study groups had been validated. The impact of not repeating some parameters during assay validation experiments was considered negligible.

Submitted data on RSV-A and RSV-B neutralization assays

All assays supporting primary and secondary endpoints were validated and validation, and qualification reports, as well as SOPs, were submitted along with data supporting assay stability overtime.

2.3.4. Discussion on clinical pharmacology

The laboratory assays used in the assessment for the primary and secondary endpoints of the study were the same as those used in the Phase 3 studies included in the initial file and in the recent EMEA/H/C/006054/II/0002/G submission. These included a serum neutralization assay to evaluate specific neutralising antibodies (NAbs) against RSV-A and RSV-B in human serum, and an intracellular cytokine staining assay to evaluate cell-mediated immunity.

At the time of the initial application, the assays were considered not fully validated. However, as the primary endpoint was efficacy, the issue was not further pursued until EMEA/H/C/006054/II/0002/G which reported on the immune response of Arexvy when administered concomitantly with differing influenza vaccines. In that application the MAH submitted - at the request of the CHMP- a thorough discussion on why the level of assay validation is appropriate to support claims based on comparative immunogenicity. The CHMP agreed that the parameters considered most important had been appropriately validated, and the issue was considered resolved. This decision applies to the current extension of indication as well.

2.3.5. Conclusions on clinical pharmacology

The assays are considered acceptable for immunobridging purposes.

2.4. Clinical efficacy

Evidence of a single clinical study was submitted, ADJ-018.

2.4.1. Main study

Title of Study: A Phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including adults at increased risk for respiratory syncytial virus lower respiratory tract disease, compared to older adults ≥ 60 years of age.

Methods

Design

Study ADJ-018 is a Phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including adults at increased risk of respiratory syncytial virus lower respiratory tract disease, compared to older adults ≥ 60 years of age. An overview of the study design is presented in Figure 1. In the current submission, participants have been followed up until visit 3 (month 6). The total duration of the trial is 12 months.

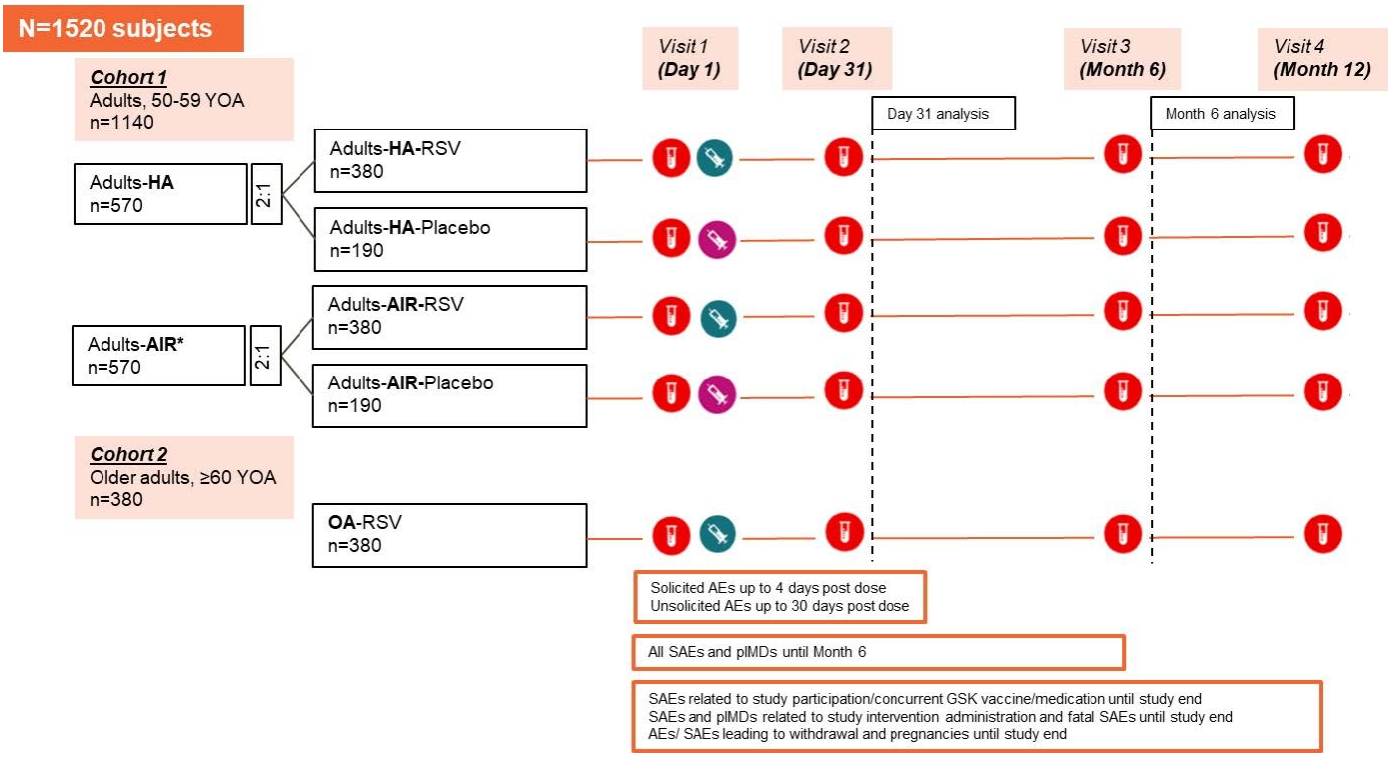
The study was split into two cohorts:

Cohort 1 (adults 50-59 YOA) was subsequently divided into 2 sub-cohorts: Adults-Healthy Adults (Adults-HA) and Adults-Adults at risk for RSV LRTD (Adults-AIR) and assigned to either the vaccine (RSV) or placebo group in a 2:1 ratio:

- Adults-HA-RSV Group
- Adults-HA-Placebo Group
- Adults-AIR-RSV Group
- Adults-AIR-Placebo Group

Cohort 2 (adults ≥60 YOA) was comprises of a single group (OA-RSV Group)

Figure 1 Overview of study design of study RSV OA=ADJ-018



AE=Adverse event; AIR=At increased risk; GSK=GlaxoSmithKline Biologicals SA; HA=Healthy adults; n=Number; 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, and chronic liver and renal diseases

The general study design is acceptable. This submission contains safety data up until 6 months after vaccination and immunogenicity data up until day 31. At the time of submission, the trial was ongoing.
.

Study participants

The study will enrol adult men and women in two differing Cohorts. Cohort 1 will enrol participants ages 50-59 years (new indication) and Cohort 2 will enrol participants >= 60 years of age. Enrolment rules will be applied to ensure equal representation of participants in the healthy adults (Adults-HA) and at

increased risk (Adults-AIR) sub-cohorts in Cohort 1, and adequate representation by age category within Cohort 2.

Cohort 1

- Approximately 50% of healthy participants (Adults-HA-RSV Group and Adults-HA-Placebo Group).
- Approximately 50% of participants at increased risk of RSV-LRTD (Adults-AIR-RSV Group and Adults-AIR-Placebo Group)
    - Since the target population in the Adults-AIR sub-cohort is heterogenous, enrolment will be done to ensure adequate representation of the different diseases. It is therefore intended to enrol:
        - Approximately 25% of participants with chronic pulmonary diseases
        - Approximately 25% of participants with chronic cardiovascular diseases
        - Approximately 25% of participants with diabetes mellitus types 1 and 2
        - The remaining 25% can be distributed freely across the above 3 disease categories as well as include participants with chronic renal or liver disease.

Cohort 2

- Approximately 40% of participants 60-69 YOA
- Approximately 30% of participants 70-79 YOA
- Approximately 10% of participants ≥80 YOA
- The remaining 20% can be distributed freely across the 3 age categories.

Specific inclusion criteria for all participants in Cohort 1

- 50-59 YOA at the time of the study intervention administration.
- Female participants of childbearing potential may be enrolled in the study, if adequate contraception is practiced and the participant has a negative pregnancy test on the day of study intervention administration.

Specific inclusion criteria for participants in the Adults-HA Sub-cohort of Cohort 1

- Healthy participants as established by medical history and clinical examination before entering into the study.
- Participants with chronic stable medical conditions, such as hypertension, hypercholesterolemia, or hypothyroidism, and who are not at increased risk for RSV-LRTD (See “Specific inclusion criteria for participants in the Adults-AIR Sub-cohort of Cohort 1”) are allowed to participate in this study if considered by the investigator as medically stable.

Specific inclusion criteria for participants in the Adults-AIR Sub-cohort of Cohort 1

- Participants should be diagnosed with at least 1 of the following medical conditions and have a stable condition:
    - Chronic pulmonary disease resulting in activity restricting symptoms or use of long-term medication:
        - Chronic Obstructive Pulmonary Disease (GOLD) Grade 2-4

        - Asthma: Patient on regular medication (excluding exercise asthma)
        - Cystic fibrosis
        - Other chronic respiratory diseases: lung fibrosis, restrictive lung disease, interstitial lung disease, emphysema or bronchiectasis
    - Chronic cardiovascular disease
        - Chronic heart failure (CHF)
        - Pre-existing coronary artery disease (CAD not otherwise specified)
        - Cardiac arrhythmia
    - Diabetes mellitus: types 1 and 2
    - Other diseases at increased risk for RSV-LRTD disease
        - Chronic kidney disease
        - Chronic liver disease

Specific inclusion criteria for Cohort 2 (OA-RSV Group)

- ≥60 YOA at the time of the study intervention administration.
- Participants with chronic stable medical conditions, such as diabetes, hypertension or cardiac disease are allowed to participate in this study if considered by the investigator as medically stable.

Main exclusion criteria (applicable to entire study population)

In addition to standard exclusion criteria, subjects presenting with any of the following were ineligible to be included in the study:

- Previous vaccination with an RSV vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy, based on medical history and physical examination.
- Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or administration of long-acting immune-modifying treatments or planned administration at any time up to the end of the study.
    - Up to 3 months prior to the study intervention administration for corticosteroids (prednisone ≥20 mg/day, or equivalent, inhaled and topical steroids are allowed) and immunoglobulins and/or any blood products or plasma derivatives.
    - Up to 6 months prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication

The inclusion and exclusion criteria of the OA study population are similar to the criteria used in study ADJ-006 in which efficacy was demonstrated (EMEA/H/C/006054/0000), and are therefore suitable to use for an immunobridging study. It is noted that study ADJ-018 made the stipulation that medically stable constituted no changes in the treatment or disease severity in the past 3 months. This

stipulation was not made in study ADJ-006 but is not expected to lead to any clinically relevant differences in study population.

The population for which the extension of indication is being sought (i.e. adults 50 through 59 years of age who are at increased risk for RSV disease), is represented by the Adults-AIR sub cohort. The population of the healthy-Adults cohort is not represented in the sought-after indication.

Treatments

Participants will receive a single dose of study intervention (either 0.5 mL RSVPreF3 OA investigational vaccine or 0.7 mL placebo) at Visit 1 (Day 1) by intramuscular injection in the deltoid of the non-dominant arm.

The dosing regimen followed in ADJ-018 is identical to the approved dosing regimen. The use of NaCl in slightly higher volume than the volume of the experimental vaccine is the same as in protocol ADJ-006. The choice for a higher fill volume for the placebo injection is not fully understood, however, as the injections are administered by qualified study personnel who will not participate in the data collection, and the participants remain blinded, the higher administered volume is acceptable. The higher fill volume of 0.2ml is small enough to not expect any differences in pain at the injection site.

The MAH noted in the Clinical Overview that 108 participants may have been administered a higher dose of RSVPreF3 antigen (potential range of 123 to 137 µg), and a lower volume of adjuvant. The potential administered dose falls within the range of Phase 3 acceptance (102-138 µg/dose). Upon request, the MAH provided information, on the number and percentage of participants who received the incorrect dose in each study-group, and the immunogenicity results (GMT, SRR, GMT ratio, SRR difference) per group for those with the higher dose versus those with the normal dose. The number of patients affected by this error is smaller than previously reported (23 participants received incorrect reconstituted placebo) and appears to have the same distribution per randomization group. The descriptive analyses do not suggest differences in immunogenicity between the incorrect reconstitution and the normal reconstitution.

Objectives

Primary objectives

- To demonstrate the non-inferiority of the humoral immune response in healthy participants 50-59 YOA compared to OA **(≥60** YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.
- To demonstrate the non-inferiority of the humoral immune response in healthy participants 50-59 YOA compared to OA **(≥60** YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.
- To demonstrate the non-inferiority of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA **(≥60** YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.
- To demonstrate the non-inferiority of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA **(≥60** YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.

Success criterion: Non-inferiority for each primary objective will be claimed to be successful if the upper limit of the 2-sided CI for the GMT ratio will be **≤1.5** and the upper limit of the 2-sided CI for the sero-response rate (SRR) difference will be **≤0.10**, according to the significance level provided by the graphical testing procedure.

Secondary (safety) objectives

- To evaluate the safety and reactogenicity after the RSVPreF3 OA investigational vaccine administration.

Secondary (Immunogenicity) objectives

- To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 12 months post-study intervention administration.
- To evaluate the CMI response after RSVPreF3 OA investigational vaccine administration until 12 months post-study intervention administration.

Four primary endpoints were defined to assess non-inferiority of the immune response in both healthy and at risk 50-59 YOA adults compared to older adults, in whom Arexvy has been shown to be effective against LRTD caused by RSV. The primary endpoints include assessment of both GMT ratio and SRR. The assessment of non-inferiority based on the GMT ratios is especially 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 neutralising antibody (NA) titre, SRR, from pre- to post-vaccination will further support the analyses of the GMT ratio.

In this application immunogenicity data up to 1 month, and safety data up to 6 months post-vaccination is provided.

Outcomes/endpoints

Primary outcome/endpoint

For the four co-primary objectives, the sampling timepoint will be 1 month post-study intervention administration.

- GMT ratios (OA-RSV Group over Adults-HA-RSV Group and OA-RSV Group over Adults-AIR-RSV Group) will be derived from an ANCOVA model on log10-transformed titers for each neutralization assay. The model will include the group (OA-RSV Group, Adults-HA-RSV Group and Adults-AIR-RSV Group) and the baseline log10-transformed titer as covariate.
- The seroresponse rate (SRR) is defined as the proportion of participants having a fold increase in neutralization titers (1 month post-study intervention administration over pre-study intervention administration) **≥4.**

Secondary (safety) endpoints

Refer to section 5.5 (Safety)

Secondary (immunogenicity) endpoints

To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 12 months post-study intervention administration

- RSV-A and RSV-B neutralization titers expressed as GMT, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration.

To evaluate the CMI response after RSVPreF3 OA investigational vaccine administration until 12 months post-study intervention administration.

- 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, 6 months and at 12 months after study intervention administration, in a subset of participants.

The primary endpoints have been appropriately chosen to fulfil the study objectives. In ADJ-006, in addition to efficacy, immunogenicity was also reported and RSV-A and RSV-B neutralizing antibody titers were determined.

Sample size

The target sample size for the study is approximately 1520 participants: 380 participants each in the Adults-HA-RSV Group and Adults-AIR-RSV Group, 190 participants each in the Adults-HA-Placebo Group and Adults-AIR-Placebo Group and 380 participants in the OA-RSV Group. The sample size in the groups receiving the investigational vaccine is driven by the statistical power to prove the primary NI objectives.

Power was estimated by 10 000 simulations, using SAS 9.4. Assuming 342 evaluable participants in each group receiving the investigational vaccine, the power to demonstrate the primary NI objectives following the graphical testing procedure is presented in Table 3, using a non-inferiority margin of 1.5 for the GMT ratio of OA-RSV over the intervention group and a non-inferiority margin of SRR difference of 10%.

Individual RSV-A and RSV-B neutralization titers at baseline and at 1 month post-study intervention administration were modeled by a multivariate log-normal distribution, means and variance-covariance matrix based on historical data from other RSV OA vaccine clinical trials. The Adults-AIR-RSV Group was assumed to have the same multivariate log-normal distribution of the OA-RSV Group (i.e., same means and variance-covariance matrix), while the Adults-HA-RSV Group was assumed to have a 1.25-fold higher mean at 1 month post-study intervention administration for both neutralization titers (Amended: 25 May 2023).

Raw p-values were obtained from shifted 1-sided t-tests (for group GMT ratios) and using the method of Miettinen and Nurminen (for group SRR difference). The p-value associated to each NI objective is the maximum between the p-values from the GMT ratio and from the SRR difference (co-primary endpoints). P-values associated to each NI objective were compared with the corresponding alpha, as propagated by the graphical testing procedure, to identify which NI objectives were successfully demonstrated at each simulation.

Table 3 Power of primary NI objectives

Objective	Power
NI in the Adults-HA-RSV Group for the RSV-A strain	>99%

NI in the Adults-HA-RSV Group for the RSV-B strain	>99%
NI in the Adults-AIR-RSV Group for the RSV-A strain	93.6%
NI in the Adults-AIR-RSV Group for the RSV-B strain	82.8%
All (power to demonstrate all primary NI objectives simultaneously)	82.7%

NI=Non-inferior

Randomisation

The randomisation of supplies within blocks will be performed at GSK, using MAtEx, a program developed for use in SAS (Cary, NC, US) by GSK. Entire blocks will be shipped to the study centers/warehouse(s).

- Participants in Cohort 1, Adults-HA Sub-cohort will be randomly assigned to the Adults-HA-RSV Group and Adults-HA-Placebo Group in a 2:1 ratio at Visit 1 (Day 1) to receive the RSVPreF3 OA investigational vaccine or placebo, respectively.
- Participants in Cohort 1, Adults-AIR Sub-cohort will be randomly assigned to the Adults-AIR-RSV Group and Adults-AIR-Placebo Group in a 2:1 ratio at Visit 1 (Day 1) to receive the RSVPreF3 OA investigational vaccine or placebo, respectively.
- All participants in Cohort 2 (OA-RSV Group) will be assigned to receive the RSVPreF3 OA investigational vaccine.

The system's randomisation algorithm will use a stratification by healthy/at increased risk status and CMI subset (participant included in the CMI subset or not) and a minimisation procedure accounting for the study and center within each stratum. Minimisation factors will have equal weight in the minimisation algorithm.

Participants contributing to the CMI subset will be recruited from a selected number of countries and selected number of sites. In the selected sites, the investigator will allocate the first participants in each cohort/sub-cohort to the CMI subset until the allocated target is reached. The subsets are detailed below in Table 4.

Table 4 CMI subset recruitment

Cohort	Sub-cohort	Group	Number of participants
Cohort 1	Adults-HA	Adults-HA-RSV	~100
		Adults-HA-Placebo	~50
	Adults-AIR	Adults-AIR-RSV	~100
		Adults-AIR-Placebo	~50
Cohort 2	OA ≥60 YOA	OA-RSV	50
Total			~350

AIR=At increased risk; HA=Healthy adults; OA=Older adults; YOA=Years of age

According to simulations, the study will have >80% power to demonstrate all 4 primary non-inferiority objectives simultaneously. Within each of the 4 primary objectives GMT and SRR are co-primary endpoints, where both non-inferiority for the GMT ratio of OA-RSV over the intervention group (with a non-inferiority margin of 1.5) and non-inferiority of SRR (with a non-inferiority margin of 10%) need to be demonstrated for each objective.

A 2:1 randomisation has been used, which is acceptable. The system's randomisation algorithm will use a stratification by healthy/at increased risk status and CMI subset (participant included in the CMI subset or not), which is understood, given the objective of the study. In addition, it is stated that a minimisation procedure will be used accounting for the study and center within each stratum, with minimisation factors will have equal weight in the minimisation algorithm. The MAH was asked to clarify what was meant by "study", and "study center". "Study" (i.e. RSV-OA=ADJ-018) is the most global characteristic common to all participants and has been added as a minimisation factor in the algorithm to ensure that the groups ratio is respected overall in each stratum defined in the study, in addition to the other minimisation factor "centre" which ensure that the groups ratio is respected by center within each stratum. This minimization factor "study" is added to prevent imbalance in study groups due to small number of subjects enrolled in several centers.

Blinding (masking)

Given the difference in reconstitution and visual appearance of the RSVPreF3 OA investigational vaccine and the saline solution used as placebo, the MAH considered double blinding not possible, and the study will be conducted in an observer-blind manner for Cohort 1 (until Day 31 analysis). The participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. To do so, study intervention(s) will be prepared and administered by qualified study personnel who will not participate in the evaluation and review of any study endpoint (i.e., reactogenicity, safety). Beyond the day 31 analysis, the study will be considered single-blind. The study participants in Cohort 1 will remain blinded up to study end, however, the investigators will receive a copy of the CSR with results of the Day 31 analysis on immunogenicity, reactogenicity and safety data. As a consequence, the investigators could become unblinded to some specific participants through summary results. The individual data listings and participant treatment assignments will not be provided to the investigators until after the conclusion of the study (completion of Visit 4, Month 12 [study end]).

As all participants in Cohort 2 will receive the same study intervention (RSVPreF3 OA investigational vaccine), the study will be conducted in an open-label manner for Cohort 2.

Cohort 1 was observer-blinded, whereas cohort 2 was open-label. The primary outcome of this study is immunogenicity, the observer blinded design is acceptable, also given immunogenicity values are expected to only be to a small extent impacted by a participant's behaviour. The assessor would like to point out that despite the reconstitution and visual appearance double blinding could be possible by having a different investigator administer the vaccine and covering the vial.

Cohort 2 was open-label. This is considered acceptable, as the level of blinding is not expected to alter the immunogenicity results and withholding an approved, effective vaccine from a population for which it was approved would not be desirable.

Statistical methods

Analysis sets

Enrolled Set

- All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure).

Exposed Set (ES)

- All participants who received the study intervention. Analysis per group is based on the administered intervention.

Per Protocol Set (PPS)

- 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. Analysis per group is based on the administered intervention. Contribution of participants to Per Protocol Set was to be defined by timepoint.

CMI assay subset

- Participants contributing to the CMI subset will be recruited from a selected number of countries and selected number of sites. In the selected sites, the investigator will allocate the first participants in each cohort/sub-cohort to the CMI subset until the allocated target is reached.

Hypotheses tested and multiplicity control

Four hypothesis will be tested, where each hypothesis will be a combination of GMT ratio and SSR difference.

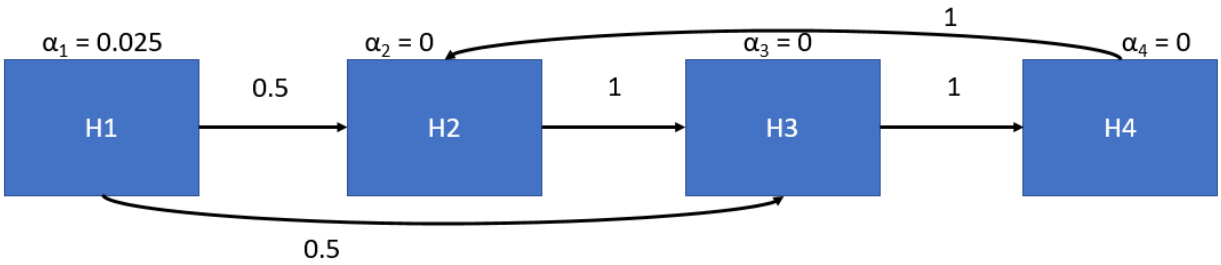
Null hypothesis 1 (H1): The anti-RSV-A GMT ratio (OA-RSV Group over Adults-HA-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-HA-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favour of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

Null hypothesis 2 (H2): The anti-RSV-B GMT ratio (OA-RSV Group over Adults-HA-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-HA-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favour of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

Null hypothesis 3 (H3): The anti-RSV-A GMT ratio (OA-RSV Group over Adults-AIR-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-AIR-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favour of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

Null hypothesis 4 (H4): The anti-RSV-B GMT ratio (OA-RSV Group over Adults-AIR-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-AIR-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favour of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

These four statistical hypotheses (H1, H2, H3 and H4) are associated to the confirmatory primary NI objectives, which will be tested according to the following graphical procedure, controlling type I error at 2.5% (1-sided).



No interim analyses have been performed for the primary endpoint.

Analysis of the primary endpoints

RSV-A and RSV-B neutralizing group GMT ratios at 1 month after the RSVPreF3 OA investigational vaccine administration will be computed for OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group.

RSV-A and RSV-B neutralizing group SRR differences at 1 month after the RSVPreF3 OA investigational vaccine administration will be computed for OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group.

The primary analysis set will be the PPS. If, in any group, the percentage of vaccinated participants with serological results excluded from the PPS is more than 5%, a second analysis based on the ES will be performed to complement the PPS analysis.

For the sampling timepoint at 1-month post-study intervention administration:

- The 2-sided 95% and 97.5% CIs for group GMT ratios (OA-RSV over Adults-HARSV group and OA-RSV over Adults-AIR-RSV group) will be derived from an ANCOVA model on log10-transformed titers for each neutralization assay. The model will include the group and the baseline log10-transformed titer as covariate. The group GMT ratios will be based on a back transformation of group contrast in the ANCOVA model applied to the logarithmically transformed titers. Exact 95% CIs around proportions are derived using the method of Clopper and Pearson [Clopper, 1934].
- The SRR is defined as the proportion of participants having a fold increase in neutralizing titers (1-month post-study intervention administration over prevaccination) ≥4. The 2-sided 95% and 97.5% CIs for group SRR difference (OARSV minus Adults-AIR-RSV group and OA-RSV minus Adults-HA-RSV group) will be derived using the method of Miettinen and Nurminen [Miettinen, 1985].

Success criteria for NI

NI for each primary objective will be claimed if the upper limit of the 2-sided CI for the GMT ratio will be ≤1.5 and the upper limit of the 2-sided CI for the SRR difference will be ≤ 0.10, according to the significance level provided by the graphical testing procedure shown above. The RSV-A and RSV-B neutralizing titer's unit used for computation of the GMT ratio and SRR difference will be ED60.

Missing values

For the purpose of immunogenicity analyses, any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each time point will exclude participants with a missing or non-evaluable measurement.

Titers below the assay cut-off (LLOQ) will be replaced by half the assay cut-off (LLOQ/2) and titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ to compute GMTs, SRRs and MGIs. For the display of reverse cumulative curve, titers below LLOQ and above ULOQ won't be replaced.

Results will be reported using both ED60 and IU/ml units.

Analysis of secondary endpoints

To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 12 months post-study intervention administration, RSV-A and RSV-B neutralization titers will be expressed as GMT, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration.

To evaluate the CMI response after RSVPreF3 OA investigational vaccine administration until 12 months post-study intervention administration, CMI response will be 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, 6 months and at 12 months after study intervention administration, in a subset of participants.

The results of the secondary objectives are based on the PPS.

The analysis will be based on the CMI subset of the PPS. If, in any group, the percentage of vaccinated participants with serological results excluded from the CMI subset of the PPS is more than 5%, a second analysis based on the CMI subset of the ES will be performed to complement the PPS analysis.

Exploratory analysis

Analyses of GMTs were performed per study and overall in subgroups by comorbidity of interest (according to the categories at baseline, according the number of comorbidities of interest (one or multiple comorbidities at baseline), according to the updated Charlson comorbidity index (Low/medium Risk = Participants with comorbidity score at baseline less than 3 and age category; High Risk = Participants with comorbidity score at baseline greater than or equal to 3).

The study was powered to demonstrate the 4 co-primary non-inferiority objectives for the Adults-HA-RSV and Adults-AIR-RSV groups for RSV-A and RSV-B neutralization titers at 1 month post-RSVPreF3 OA investigational vaccine administration compared to the OA-RSV group in terms of GMT ratio and SRR difference.

Within each of the 4 primary objectives GMT and SRR are co-primary endpoints, where both non-inferiority for the GMT ratio of OA-RSV over the intervention group (with a non-inferiority margin of 1.5) and non-inferiority of SRR difference (with a non-inferiority margin of 10%) need to be demonstrated.

Type I error was controlled at 2.5% (1-sided) over all 4 hypotheses, using a graphical testing procedure to construct and compare weighted closed test procedures [Bretz 2009]. For each hypothesis the upper limit of the 2-sided 95% CI or 97.5% CI will be used to according to the significance level provided by the testing procedure. The significance level provided by the testing procedures is not fixed, but will be determined based on results, using the initial allocation of the alpha and the propagation rules. This

adequately controls type I error. Confidence intervals will be derived using the method of Miettinen and Nurminen, this is acceptable.

Based on this testing procedure within each hypothesis both SRR difference and GMT ratio will be evaluated simultaneously (and non-inferiority will be shown for both or none), while for the 4 primary hypothesis different conclusions may be obtained for the population studied or RSV subtype.

The primary analysis set will be the PPS. If, in any group, the percentage of vaccinated participants with serological results excluded from the PPS is more than 5%, a second analysis based on the ES will be performed to complement the PPS analysis. Given the non-inferiority objective of the study this is considered appropriate. Any missing or non-evaluable immunogenicity measurement will not be replaced, which assumes missing values are missing completely at random. If this assumption does not hold, bias may be introduced. In addition, it also implies that not all subjects in the exposed set will be included in the analysis, which may introduce bias if there is differential dropout between the arms.

The secondary endpoints were not included in the testing strategy, and are therefore considered supportive only. Secondary endpoints were based on the PPS.

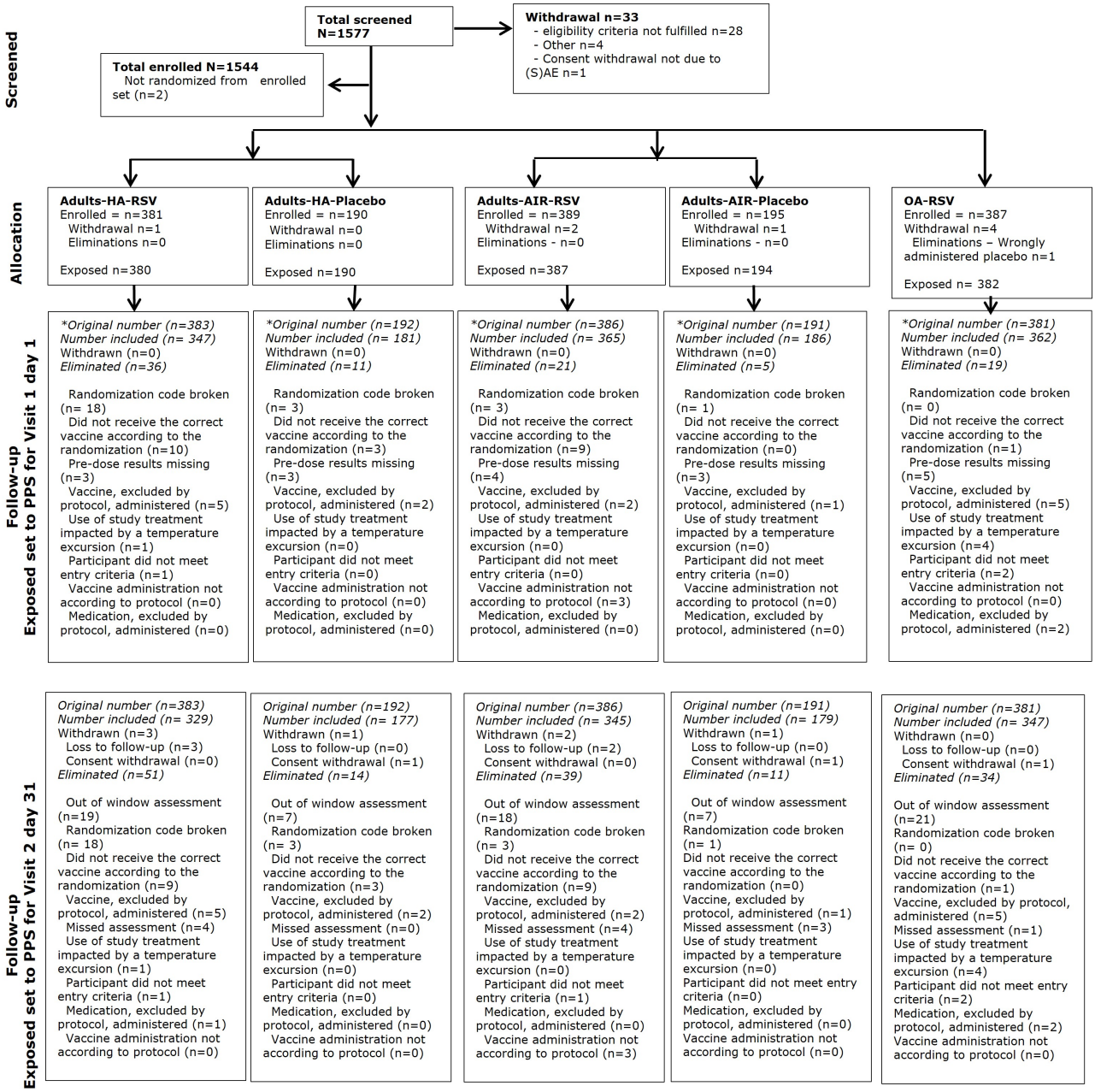
The CMI subset was thus not randomly selected but represented the first participants included from the selected sites. However, this is acceptable as the CMI analyses are not considered pivotal in the benefit-risk analyses.

Results

Participant flow

The study was conducted in 60 centres across 8 countries. The flow of participants is shown in Figure 2. In this study, 1577 participants were screened, and 1544 participants were enrolled in the study, of which 1533 (99.3%) participants were planned to be included in the exposed set (ES, according to the planned study intervention administration): 380 in the Adults-HA-RSV group, 190 in the Adults-HA-Placebo group, 387 in the Adults-AIR-RSV group, 194 in the Adults-AIR-Placebo group and 382 in the OA-RSV group. The actual number of participants who received the study intervention and were included in the ES was 383 in the Adults-HA-RSV group, 192 in the Adults-HA-Placebo group, 386 in the Adults-AIR-RSV group, 191 in the Adults-AIR-Placebo group and 381 in the OA-RSV group. The differences between the number of participants in the planned study intervention administration and the actual number of participants that received the study intervention are mainly due to randomisation errors. Additionally, 1 participant from the OA-RSV group received placebo (instead of the RSVPreF3 investigational vaccine) and was excluded from the ES.

Figure 2 Flow chart – disposition of participants



Source: Tables 14.1.1.2; 14.1.1.3; 14.1.1.4; AIR: At increased risk; HA: Healthy adults; N: number of participants; OA: Older adults; PPS: Per Protocol Set; RSV: RSVPreF3 OA investigational vaccine. Source: Table 14.1.1.1 - Table 14.1.1.6. *Original number = is the number in the group *after* the randomisation errors described by the MAH.

The MAH states that “The differences between the number of participants in the planned study intervention administration and the actual number of participants that received the study intervention are mainly due to randomisation errors.” However, as these numbers are group-specific (i.e. 381 planned versus 383 actual for Adults-HA-RSV and 190 versus 192 for Adults-HA-Placebo), it appears that the errors occurred after randomisation. The MAH clarified that all errors occurred after screening during the randomization process. The errors were as follows:

- 8 participants were incorrectly randomized in Adults-AIR-RSV, 3 into Adults-AIR-Placebo, and 8 into the Adults-HA-RSV as they did not have the correct presence or absence of comorbidities of interest.
- 1 participant being 59 YOA at time of study intervention administration was incorrectly randomized in OA-RSV group and was reassigned to Adults-HA-RSV group.
- 1 participant randomized in the Adults-HA-Placebo group incorrectly received RSV vaccine and was reassigned to the Adult-HA-RSV.
- 1 participant was incorrectly assigned in CMI strata and randomized in Adults-AIR-RSV group.
- 1 participant was incorrectly assigned in CMI strata in the OA-RSV group.

In the Adults-HA group, a high number of individuals (4.7%) had the randomisation code broken (elimination code 1060) compared to other groups 0.5-1.6%. This code was added in SAP amendment 2 (15 May 2023) to 'eliminate participant whose randomization was broken," nearly 7 months after the first participant first visit on 28 October 2022 (also see section "Conduct of the Study"). The MAH stated that due to wording included in the protocol deviation, which contained unblinding information that is not related to safety events, the central study team was unblinded to allocation of 25 participants before official unblinding. The observed discrepancy in the different study groups is primarily a consequence of differences in the number of participants in the Adults-HA compared to the Adults-AIR group at the respective sites. Sufficient details have been provided, major impact is unlikely. Major impact on the results is considered unlikely.

The number of participants excluded from the exposed set to the per protocol set for the reason "Randomisation procedures (did not receive the correct vaccine according to randomisation allocation) was 10/383 for Visit 1 and 9/383 for Visit 2. The MAH was asked to explain the reason for fewer participants given this code in Visit 2 for a vaccine which is only administered once. This might be explained by the increase in withdrawals. As this is not considered to influence the benefit-risk, the issue is not further pursued.

Reasons for withdrawal

Reasons for withdrawal and the number of participants completing the study are provided in Table 5.

Table 5 Summary of study completion with reasons for withdrawal = Exposed set

	Adults-HA-RSV N=383		Adults-HA-Placebo N=192		Adults-AIR-RSV N=386		Adults-AIR-Placebo N=191		OA-RSV N=381		Total= 1533	
	n	%	n	%	n	%	n	%	n	%	n	%
Completed up to Visit 3	369	*96.3*	187	*97.4*	380	*98.4*	190	*99.5*	373	*97.9*	1499	*97.8*
Withdrawn from the study	14	*3.7*	5	*2.6*	6	*1.6*	1	*0.5*	8	*2.1*	34	*2.2*
Primary reason for withdrawal												
Adverse event requiring expedited reporting	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*
Unsolicited non-serious adverse event	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*
Solicited adverse event	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*
Consent withdrawal, not due to a (S)AE	2	*0.5*	3	*1.6*	2	*0.5*	1	*0.5*	5	*1.3*	13	*0.8*
Migrated / moved from the study area	1	*0.3*	1	*0.5*	0	*0*	0	*0*	0	*0*	2	*0.1*
Lost to follow-up	10	*2.6*	1	*0.5*	4	*1.0*	0	*0*	3	*0.8*	18	*1.2*
Other	1	*0.3*	0	*0*	0	*0*	0	*0*	0	*0*	1	*0.1*

Data Source: Table 14.1.2.1. Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-HA-Placebo = Healthy adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-Placebo = At increased risk adult participants (50-59 YOA) receiving

a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1)
Completed up to visit 3 = number of participants who completed the last study visit/contact
Withdrawn = number of participants who did not complete their last visit/contact
N = number of participants
n/% = number/percentage of participants in a given category

There does not appear to be any substantial difference on withdrawal rates or reasons for withdrawal within the same sub-cohort groups, although a larger percentage of withdrawals and lost-to-follow up were observed in the Adults-HA group.

Recruitment

Study ADJ-018 was initiated 28 October 2022 (first participant first visit). The last subject last visit for visit 3 (month 6) was 28 August 2023. The results of the immunogenicity objectives are based on the blood samples collected up to Visit 2 (Day 31) (data lock point [DLP]: 05 September 2023). The 6-month safety analysis is also presented in the CSR and contains all safety data from study start until the safety DLP on 01 September 2023.

Conduct of the study

Amendments

The original protocol (dated 26 July 2022) was amended once, on 25 May 2023. The purpose of this amendment was to record events of atrial fibrillation (AF) as Adverse Events of Special Interest (AESIs). In the efficacy study (RSV OA=ADJ-006), at the time of safety analysis (DLP of 30 April 2022), a numerical imbalance was observed within 30 days postvaccination, with 10 events of AFs (among which 7 [0.1%] were serious) in the RSVPreF3 group versus 4 (among which 1 [<0.1%] was serious) in the placebo group. No imbalance was observed for serious events of AF reported within 6 months postvaccination. These safety data were reviewed by the project safety review team (SRT) and the independent data monitoring committee (IDMC), and no safety signals were identified. However, GSK is of the opinion that a detailed assessment of all AF cases is required. Therefore, AF will be considered was an AESI.

There were 2 amendments to the SAP.

- SAP Amendment 1 dated 09 May 2023. The original SAP date 19 October 2022 was amended to include recording of AF as an AESI. In addition, the safety reporting for participant belonging to OA stratum who received placebo was described, 65-69 YOA was changed to 60-69 YOA in all age category definitions, additional exploratory analyses were added.
- SAP Amendment 2 Is dated on 15 May 2023 and encompassed the addition of elimination code 1060 “Randomisation code was broken” to eliminate participant whose randomisation was broken from the PPS.

Protocol Deviations

The number of participants with at least 1 important protocol deviation was 331 (21.0 %) (92 [24.1%] in the Adults-HA-RSV group, 37 [19.5%] in the Adults-HA-Placebo group, 91 [23.4%] in the Adults-AIR-RSV group, 41 [21.0%] in the Adults-AIR-Placebo group and 70 [18.1%] in the OA-RSV group Table 6).

Deviations related to study procedures were reported in 201 (12.7%) participants (59 [15.5%] in the Adults-HA-RSV group, 24 [12.6%] in the Adults-HA-Placebo group, 57 [14.7%] in the Adults-AIR-RSV group, 28 [14.4%] in the Adults-AIR-Placebo group and 33 [8.5%] in the OA-RSV group). The majority of

these protocol deviations were related to central/internal/external deviations for CMI. Deviations related to assessment or timepoint completion were reported in 129 (8.2%) participants (35 [9.2%] in the Adults-HA-RSV group, 18 [9.5%] in the Adults-HA-Placebo group, 33 [8.5%] in the Adults-AIR-RSV group, 13 [6.7%] in the Adults-AIR-Placebo group and 30 [7.8%] in the OA-RSV group).

Table 6 Summary of important protocol deviations leading to elimination from any analyses – Screened Set

	Adults-HA-RSV		Adults-HA-Placebo		Adults-AIR-RSV		Adults-AIR-Placebo		OA-RSV	
	N=381		N=190		N=389		N=195		N=387	
	n	%	n	%	n	%	n	%	n	%
At least one important protocol deviation	92	24.1	37	19.5	91	23.4	41	21.0	70	18.1
Study procedures	59	15.5	24	12.6	57	14.7	28	14.4	33	8.5
Central/internal/external lab deviation - CMI	48	12.6	21	11.1	47	12.1	24	12.3	31	8.0
Randomization code broken	18	4.7	3	1.6	3	0.8	1	0.5	0	0
Randomization procedures (did not receive the correct vaccine according to the randomization allocation)	7	1.8	1	0.5	10	2.6	3	1.5	2	0.5
Assessment or time point completion	35	9.2	18	9.5	33	8.5	13	6.7	30	7.8
Out of window assessment - humoral	18	4.7	7	3.7	19	4.9	7	3.6	21	5.4
Pre-dose results are missing - CMI	9	2.4	8	4.2	4	1.0	1	0.5	2	0.5
Pre-dose results are missing - humoral	3	0.8	3	1.6	4	1.0	3	1.5	5	1.3
Missed assessment - CMI	6	1.6	5	2.6	2	0.5	1	0.5	2	0.5
Out of window assessment - CMI	4	1.0	2	1.1	4	1.0	0	0	4	1.0
Missed assessment - humoral	4	1.0	0	0	5	1.3	2	1.0	1	0.3
Administration of any medication forbidden by the protocol	6	1.6	2	1.1	2	0.5	1	0.5	7	1.8
Vaccine, excluded by the protocol, was administered	5	1.3	2	1.1	2	0.5	1	0.5	5	1.3
Medication, excluded by the protocol, was administered	1	0.3	0	0	0	0	0	0	2	0.5
Wrong study treatment/administration/dose	1	0.3	0	0	5	1.3	0	0	6	1.6
Use of study treatment impacted by a temperature excursion	1	0.3	0	0	0	0	0	0	4	1.0
Not administering any study treatment	0	0	0	0	2	0.5	0	0	1	0.3
Vaccine administration not according to protocol	0	0	0	0	3	0.8	0	0	0	0
Wrong study treatment or assignment administered	0	0	0	0	0	0	0	0	1	0.3
Eligibility criteria not met	1	0.3	0	0	1	0.3	0	0	2	0.5
Participant did not meet entry criteria	1	0.3	0	0	1	0.3	0	0	2	0.5

Source: Table 14.1.6.1 Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-HA-Placebo = Healthy adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-Placebo = At increased risk adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) N = number of participants; n/% = number/percentage of participants in a given category; occ = number of occurrences

The amendment to the study protocol occurred before the first subject first visit (FSFV) and occurred due to an imbalance of atrial fibrillation events seen in ADJ-006. The addition of atrial fibrillation as AESI is appreciated.

The protocol deviations appear balanced over groups.

The MAH states that when the trend concerning out of window visits was noticed as 1 of the reasons for high elimination from PPS, remedial actions were taken by the study team to prevent increase in out of

window visits at Visit 3 and Visit 4. Upon request, the MAH was asked to specify what remedial actions these were. These included 1) Visit schedule at each site and each country being tracked closely. 2) Reports on upcoming visits with the minimum and maximum dates to conduct these visits being provided on a regular basis to local delivery leads. 3) Out of window blood samples being closely monitored by the laboratory study manager. 4) Out of window visits were tracked by the Central Monitoring team and discussed with the study team. In case of trends at country or site level, this was escalated to the local teams so that specific actions could be taken. Follow-up and clarification with the local team and study sites on the visit schedules. These actions appeared adequate.

Baseline data

Baseline data is given per groups exposed in Table 7. There were demographic differences between the Adults-HA, Adults-AIR, and OA-RSV group in terms of medical history and age. Within randomized groups (placebo versus vaccine) demographic differences were minimal.

Adults-HA group had a median age of 55 years, and was 42.3% (RSVPre3) and 38.0% (placebo) male.

Adults-AIR group had a median age of 55 years, and 15.6% (RSVPreF3 group) versus 18% (placebo) group) and was 51.8% (RSVPRE3) and 55% (placebo) male. Regarding co-morbidities of interest, 31.0% (RSVPreF3) and 30.2% (placebo) had at least 2 pre-existing comorbidities of interest of which diabetes mellitus was the most common.

OA group had a median age of 69 years, 49 (12%) of individuals were >=80 years of age, and 50.7% was male." Regarding co-morbidities of interest, 13.2% had at least 2 pre-existing comorbidities of interest of which diabetes mellitus was the most common.

Table 7 Summary of demography and baseline characteristics – Exposed Set

	Adults-HA				Adults-AIR-				OA-		Total	
	RSV N=383		Placebo N=192		RSV N=386		Placebo N=191		RSV N=381		N=1533	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years) at vaccination												
N with data	383		192		386		191		381		1533	
Median	55.0		55.0		55.0		56.0		69.0		57.0	
Minimum	50		50		50		50		60		50	
Maximum	59		59		59		59		90		90	
Age group												
50-59 YOA	383	*100*	192	*100*	386	*100*	191	*100*	0	*0*	1152	*75.1*
60-69 YOA	0	*0*	0	*0*	0	*0*	0	*0*	202	*53.0*	202	*13.2*
70-79 YOA	0	*0*	0	*0*	0	*0*	0	*0*	130	*34.1*	130	*8.5*
>=80 YOA	0	*0*	0	*0*	0	*0*	0	*0*	49	*12.9*	49	*3.2*
Country												
Argentina	38	*9.9*	18	*9.4*	52	*13.5*	28	*14.7*	42	*11.0*	178	*11.6*
Canada	61	*15.9*	30	*15.6*	53	*13.7*	25	*13.1*	51	*13.4*	220	*14.4*
Germany	48	*12.5*	28	*14.6*	80	*20.7*	38	*19.9*	54	*14.2*	248	*16.2*
Japan	35	*9.1*	21	*10.9*	37	*9.6*	19	*9.9*	38	*10.0*	150	*9.8*
Netherlands	11	*2.9*	3	*1.6*	5	*1.3*	4	*2.1*	15	*3.9*	38	*2.5*
Poland	37	*9.7*	16	*8.3*	39	*10.1*	18	*9.4*	34	*8.9*	144	*9.4*
Spain	50	*13.1*	27	*14.1*	50	*13.0*	22	*11.5*	49	*12.9*	198	*12.9*
United States	103	*26.9*	49	*25.5*	70	*18.1*	37	*19.4*	98	*25.7*	357	*23.3*
Sex												
Male	162	*42.3*	73	*38.0*	200	*51.8*	106	*55.5*	193	*50.7*	734	*47.9*
Female	221	*57.7*	119	*62.0*	186	*48.2*	85	*44.5*	188	*49.3*	799	*52.1*
Race												
American Indian Or Alaska Native	0	0	0	0	4	1.2	3	1.7	1	0.3	8	0.6
Asian	39	11.9	20	11.3	41	11.9	22	12.3	41	11.8	163	11.8

	Adults-HA				Adults-AIR-				OA-		Total	
	RSV N=383		Placebo N=192		RSV N=386		Placebo N=191		RSV N=381		N=1533	
	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Black Or African American	13	4.0	8	4.5	15	4.3	3	1.7	11	3.2	50	3.6
Native Hawaiian Or Other Pacific Islander	0	0	0	0	0	0	2	1.1	1	0.3	3	0.2
White	271	82.4	145	81.9	284	82.3	147	82.1	293	84.4	1140	82.8
Multiple	4	1.2	3	1.7	1	0.3	1	0.6	0	0	9	0.7
Unknown	2	0.6	1	0.6	0	0	1	0.6	0	0	4	0.3
Ethnicity												
Hispanic Or Latino	48	*12.5*	23	*12.0*	63	*16.3*	35	*18.3*	50	*13.1*	219	*14.3*
Not Hispanic Or Latino	335	*87.5*	168	*87.5*	323	*83.7*	156	*81.7*	330	*86.6*	1312	*85.6*
Unknown	0	*0*	1	*0.5*	0	*0*	0	*0*	1	*0.3*	2	*0.1*
BMI (kg/m²)												
N with data	383		192		385		191		381		1532	
Median	27.1		27.0		30.1		29.9		27.0		28.1	
Minimum	15.3		17.9		14.0		18.0		17.7		14.0	
Maximum	50.2		58.2		60.7		52.4		61.1		61.1	
Smoking status for tobacco												
Current smoker	66	*17.2*	36	*18.8*	83	*21.5*	49	*25.7*	44	*11.5*	278	*18.1*
Former smoker	99	*25.8*	37	*19.3*	133	*34.5*	50	*26.2*	133	*34.9*	452	*29.5*
Never smoker	217	*56.7*	119	*62.0*	170	*44.0*	92	*48.2*	204	*53.5*	802	*52.3*
Unknown	1	*0.3*	0	*0*	0	*0*	0	*0*	0	*0*	1	*0.1*
Smoking status for e-cigarettes												
Current smoker	8	*2.1*	3	*1.6*	8	*2.1*	5	*2.6*	2	*0.5*	26	*1.7*
Former smoker	4	*1.0*	1	*0.5*	5	*1.3*	0	*0*	2	*0.5*	12	*0.8*
Never smoker	371	*96.9*	188	*97.9*	373	*96.6*	186	*97.4*	377	*99.0*	1495	*97.5*
Comorbidity of interest												
Exactly 1 pre-existing comorbidity of interest	0	*0*	0	*0*	267	*69.2*	136	*71.2*	94	*24.7*	497	*32.4*
At least 2 pre-existing comorbidities of interest	0	*0*	0	*0*	119	*30.8*	55	*28.8*	51	*13.4*	225	*14.7*
Chronic pulmonary disease	0	*0*	0	*0*	148	*38.3*	79	*41.4*	59	*15.5*	286	*18.7*
Diabetes mellitus	0	*0*	0	*0*	188	*48.7*	92	*48.2*	67	*17.6*	347	*22.6*
Chronic liver or renal disease	0	*0*	0	*0*	57	*14.8*	23	*12.0*	17	*4.5*	97	*6.3*
Charlson Comorbidity Index categories												
Low/med risk	383	100	192	100	315	81.6	161	84.3	163	42.8	1214	79.2
High risk	0	0	0	0	71	18.4	30	15.7	218	57.2	319	20.8
Charlson Comorbidity Index score												
N with data	383		192		386		191		381		1533	
Median	1.0		1.0		2.0		2.0		3.0		1.0	
Minimum	1		1		1		1		2		1	
Maximum	2		2		6		5		6		6	

Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-HA-Placebo = Healthy adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-Placebo = At increased risk adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); N = number of participants; n/% = number/percentage of participants in a given category BMI = Body mass index; YOA = Years of age; Charlson Comorbidity Index: Low/medium risk = Participants with comorbidity score at baseline less than 3; High risk = Participants with comorbidity score at baseline greater than or equal to 3;

As expected due to the differing inclusion criteria, the Adults-HA group was healthier than the Adults-AIR group and OA-RSV group. The adults-HA group also had relatively more females than males, however no difference was observed when comparing the RSV group versus the placebo group. The population of Adults-HA and adults-AIR seem representative of their respective populations.

Comparison to study ADJ-006 for immunobridging

Compared to the primary efficacy study ADJ-006, the patients in the OA-RSV group were similar; the median age was the same (69 years), and the percent of individuals >=80 years of age (ADJ-018 12.9%, ADJ-006 8.7%) and the percent of participants not Hispanic or Latino (ADJ-018 94.5%, ADJ-006 85.6%) were similar.

Numbers analysed

The participant flow, including participants randomised, vaccinated, discontinued and ongoing, is presented above. The analyses sets are presented in Table 8. Primary immunogenicity analyses were performed in the per protocol set of immunogenicity.

Table 8 Groups analysed

Analysis set	Adults-HA RSV N (%)	Adults-HA Placebo N (%)	Adults-AIR N (%)	Adults-AIR Placebo N (%)	OA-RSV N (%)	Total N (%)
Enrolled set (planned)	381	190	389	195	387	1542* (+2)
Enrolled set (actual)	383	192	386	191	381	1533
Exposed set	380 (99.7%)	190 (100%)	387 (99.5%)	194 (99.5%)	382 (98.7%)	1533 (99.3%)
Per protocol set of immunogenicity (D1)	347 (91.1%)	181 (95.3%)	365 (93.8%)	186 (95.4%)	362 (93.5%)	1441 (93.3%)
Per protocol set of immunogenicity (D31)	329 (86.4%)	177 (93.2%)	345 (88.7%)	179 (91.8%)	347 (89.7%)	1377 (89.2%)
Safety set	377 (99.0%)	191 (100.5%)	379 (97.4%)	188 (96.4%)	379 (97.9%)	1514 (98.1%)

The percentage (%) listed represents the percentage of the planned enrolled set in the respective group. *Two enrolled individuals were eliminated before randomisation. Two patients were not randomized. Numbers for the safety set are derived from table 12.1 in the CTD.

In the study protocol, a 10% attrition rate was accounted for from enrolled to evaluable participants. Based on the number or participants planned to be enrolled (i.e. prior to the randomisation errors) an attrition rate ranging from 7-17% was seen.

Outcomes and estimation

Primary endpoint:

The success criteria for the 4 co-primary objectives were met for the Adults-HA-RSV and Adults-AIR-RSV groups for RSV-A and RSV-B neutralization titers at 1 month post-RSVPreF3 OA investigational vaccine administration, showing non-inferiority compared to OA-RSV group both in terms of GMT ratio as well as SRR difference. The success criterion was defined as the following:

> The UL of the 2-sided CI on the group GMT ratio [OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group] is ≤1.5 and the UL of the 2-sided CI for the SRR difference is ≤0.10,

according to the significance level provided by a testing procedure applied to control the global type I error at 2.5% (1-sided)

The results for the Adults-HA group are shown in Table 9. The results for the Adults-AIR group is shown in table 10. Reverse cumulative distribution curves are shown in Figure 3 and Figure 4.

Table 9 Ratio of adjusted GMTs and SRRs difference for RSV-A and RSV-B neutralization titers (ED60) between the OA-RSV and Adults-HA-RSV groups, after the RSVPreF3 OA investigational vaccine dose at day 31 - Per Protocol Set for humoral

		Adults-HA-RSV				OA-RSV				OA-RSV vs Adults-HA-RSV	
Assay	Time point	n	% or Value	LL	UL	n	% or Value	LL	UL	% or Value	95%/97.5%* CI LL UL
RSV-A NEUT (ED60)	Adjusted GMT (a)	326	7893.5	7167.5	8692.9	342	7492.6	6819.1	8232.7	0.95	0.83 1.09
	SRR (b): D31/ baseline(D1)	270	82.8	78.3	86.8	275	80.4	75.8	84.5	-2.41	-8.30 3.50
RSV-B NEUT (ED60)	Adjusted GMT (a)	326	9009.5	8226.8	9866.6	341	8058.2	7373.1	8807.0	0.89	0.77 1.03
	SRR (b): D31/ baseline(D1)	255	78.2	73.3	82.6	254	74.5	69.5	79.0	-3.73	-11.09 3.68

Source: Table 2.7 and 2.8 in CTD.
*Due to the graphical testing procedure, the 97.5% CI is used for establishing non-inferiority in the comparison between Adults-HA-RSV and OA-RSV for RSV-B neutralizing titers. For all other comparisons the 95%CI was used.
Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); OA-RSV = 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 (OA-RSV/Adults-HA-RSV) (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 (OA-RSV -Adults-HA-RSV)
CI = Confidence interval; GMT = Geometric mean titer; SRR = Seroresponse rate; LL = Lower limit; UL = Upper limit

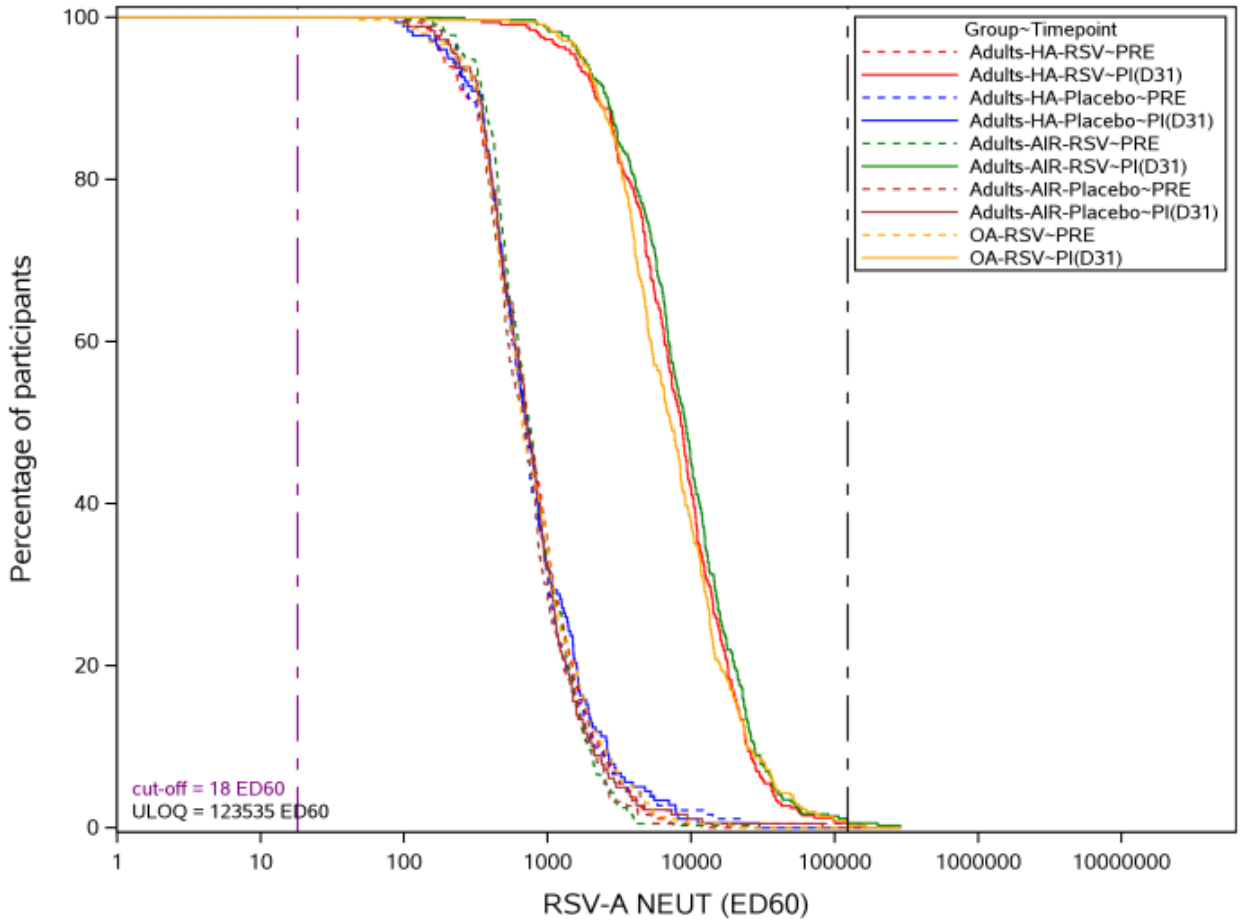
Table 10 Ratio of adjusted GMTs and SRRs difference for RSV-A and RSV-B neutralization titers (ED60) between the OA-RSV and Adults-AIR-RSV groups, after the RSVPreF3 OA investigational vaccine dose at day 31 - Per Protocol Set for humoral

		Adults-AIR-RSV				OA-RSV				OA-RSV vs Adults-AIR-RSV	
Assay	Time point	n	% or Value	LL	UL	n	% or Value	LL	UL	% or Value	95% CI LL; UL
RSV-A NEUT (ED60)	Adjusted GMT (a)	343	8922.7	8118.2	9806.9	342	7440.1	6768.4	8178.5	0.83	0.73; 0.95
	SRR (b): D31/ baseline(D1)	298	86.9	82.8	90.3	275	80.4	75.8	84.5	-6.47	-12.05; -0.94
RSV-B NEUT	Adjusted GMT (a)	343	10054.7	9225.4	10958.7	341	8062.8	7395.9	8789.9	0.80	0.71;0.91

(ED60)	SRR (b): D31/ baseline(D1)	280	81.6	77.1	85.6	254	74.5	69.5	79.0	-7.15	-13.34; -0.94

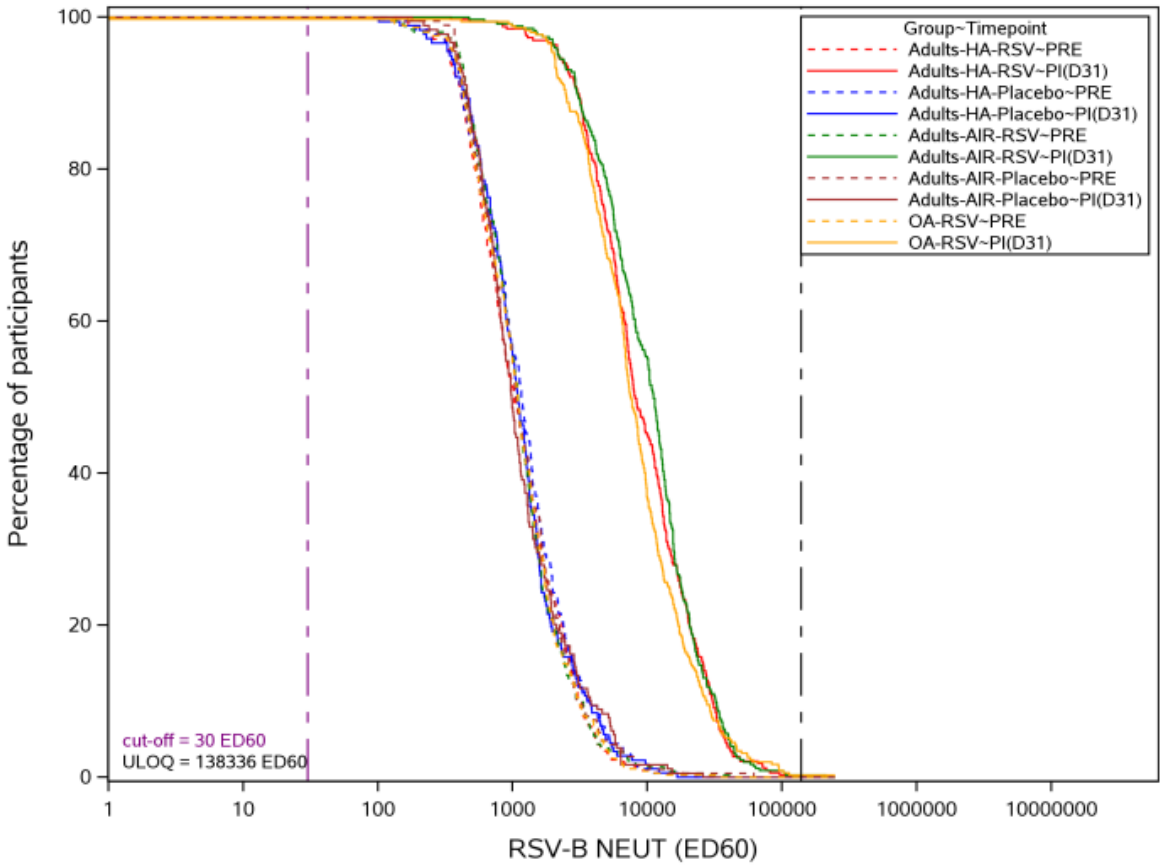
Source: Table 2.8, 2.10 in CTD. Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (≥ 60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1);
N = 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 (OA-RSV/Adults-HA-RSV) (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 (OA-RSV -Adults-HA-RSV)
CI = Confidence interval; GMT = Geometric mean titer; SRR = Seroresponse rate; LL = Lower limit; UL = Upper limit

Figure 3 Reverse cumulative distribution curve for RSV-A neutralizing titers (ED60) per group



Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-HA-Placebo = Healthy adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-Placebo = At increased risk adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1). PRE = Pre-vaccination; PI(D31) = 1 month post RSV vaccination

Figure 4 Reverse cumulative distribution curve for RSV-B neutralizing titers (ED60) per group and timepoint



Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-HA-Placebo = Healthy adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-Placebo = At increased risk adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1). PRE = Pre-vaccination; PI(D31) = 1 month post RSV vaccination

Supplementary analysis of primary endpoint based on ES

As the percentage of vaccinated participants with serological results excluded from the PPS was more than 5%, a second analysis based on the ES was performed to complement the PPS analysis. Results were comparable; for all four co-primary endpoints the immune response in the 50-59 year old population (Adults-HA and Adults-AIR) was non-inferior to the response in the OA-RSV population.

All four primary endpoints showed non-inferiority of the immunogenic response of 50-59 years olds (Adults-AIR-RSV and Adults-HA-RSV) compared to ⩾60 year olds, based on both the GMT ratio (UL <1.5) and SRR difference (UL <10%), applying the graphical testing procedure.

In the supplementary analysis performed in the ES group, due >5% elimination rate from the PPS group, for all four primary endpoints the immune response in the 50-59 year old population (Adults-HA and Adults-AIR) was non-inferior to the response in the OA-RSV population. Robustness of the results were

further supported by the reverse cumulative distribution curves which did not show different immune response profiles in groups receiving the vaccine.

Secondary (immunogenicity) analyses

The results of the secondary objectives are based on the PPS.

RSV-A and RSV-B neutralization titers expressed as GMT, at pre-study intervention administration, 1 month, are provided in Table 11 and Table 12. At baseline (Day 1, pre-vaccination), all participants had RSV-A and RSV-B neutralization titers above the pre-defined technical assay cut-off, suggesting previous exposure to RSV. Baseline GMTs were approximately the same in each group (RSVA;RSVB): Adults-HA-RSV (758.8; 1091.1); Adults-HA Placebo (796.9; 1197.7); Adults-AIR-RSV (781.7; 1141.6); Adults-AIR-Placebo (729.8; 1167.2); OA-RSV (772.2;1104.2). At day 31, the neutralization titers (ED60) were as follows (RSVA ; RSVB): Adults-HA-RSV (7925.4; 8971.9); Adults-HA-Placebo (796.9; 1145.3); Adults-Air RSV (8821.9; 9967.3); Adults-AIR-placebo (774.9; 1141.7); OA-RSV (7461.9; 8144.5).

The SRR showed a similar pattern of being minimal 0.6% - 3.9% for the placebo groups and being between 74.5% - 82.8% for the treatment groups.

Table 11 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

			Adults-HA-RSV				Adults-HA-Placebo				Adults-AIR-RSV				Adults-AIR-Placebo				OA-RSV			
					95% CI				95% CI				95% CI				95% CI				95% CI	
Assay	Time point		n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL
RSV-A NEUT (ED60)	PRE	N	347				181				365				186				362			
		>= 18 ED60	347	100	98.9	100	181	100	98.0	100	365	100	99.0	100	186	100	98.0	100	362	100	99.0	100
		GMT		768.8	704.7	838.9		772.0	677.9	879.1		781.7	727.5	840.0		729.8	648.6	821.0		772.2	706.6	843.8
	PI(D31)	N	329				177				345				179				347			
		>= 18 ED60	329	100	98.9	100	177	100	97.9	100	345	100	98.9	100	179	100	98.0	100	347	100	98.9	100
		GMT		7925.4	7125.6	8815.0		796.9	696.4	912.0		8821.9	7971.0	9763.6		774.9	683.7	878.3		7461.9	6724.9	8279.6
		MGI: D31 / baseline (D1)	326	10.08	9.07	11.20	175	1.04	0.96	1.13	343	11.63	10.52	12.86	176	1.04	0.98	1.11	342	9.58	8.63	10.64
		SRR: D31 / baseline (D1)	270	82.8	78.3	86.8	5	2.9	0.9	6.5	298	86.9	82.8	90.3	1	0.6	0.0	3.1	275	80.4	75.8	84.5

Data Source: M5.3.5.1, RSV OA=ADJ-018 (219238) Report (29-NOV-2023) Table 14.2.2.14
Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-HA-Placebo = Healthy adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-Placebo = At increased risk adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1)
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

Table 12 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

			Adults-HA-RSV				Adults-HA-Placebo				Adults-AIR-RSV				Adults-AIR-Placebo				OA-RSV			
					95% CI				95% CI				95% CI				95% CI				95% CI	
Assay	Time point		n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL	n	% or value	LL	UL
RSV-B NEUT (ED60)	PRE	N	347				181				365				186				362			
		>= 30 ED60	347	100	98.9	100	181	100	98.0	100	365	100	99.0	100	186	100	98.0	100	362	100	99.0	100
		GMT		1091.1	1000.3	1190.2		1197.7	1055.7	1358.8		1141.6	1051.0	1240.0		1167.2	1035.0	1316.1		1104.2	1016.2	1199.9
	PI(D31)	N	329				177				345				179				346			
		>= 30 ED60	329	100	98.9	100	177	100	97.9	100	345	100	98.9	100	179	100	98.0	100	346	100	98.9	100
		GMT		8971.9	8109.6	9925.8		1145.3	1012.4	1295.5		9967.3	9059.3	10966.3		1141.7	1007.9	1293.1		8144.5	7388.9	8977.4
		MGI: D31 / baseline (D1)	326	8.12	7.32	9.01	175	0.95	0.88	1.03	343	9.05	8.23	9.94	176	0.97	0.90	1.04	341	7.22	6.56	7.95
		SRR: D31 / baseline (D1)	255	78.2	73.3	82.6	3	1.7	0.4	4.9	280	81.6	77.1	85.6	1	0.6	0.0	3.1	254	74.5	69.5	79.0

Data Source: M5.3.5.1, RSV OA=ADJ-018 (219238) Report (29-NOV-2023) Table 14.2.2.18
Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-HA-Placebo = Healthy adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-Placebo = At increased risk adult participants (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1)
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

In this application only data up until 1 month is provided. This is acceptable for the purpose of this application.

The baseline GMTs appeared comparable between groups with no specific trend based on age or co-morbidity. A substantial immune response was seen in all groups receiving active immunisation that is within the same order of magnitude for both age groups. However, it is noted that for the groups receiving the active vaccination, the Adults AIR group had the highest magnitude increase of the titres (Adults-HA = 8.12 [7.32-9.01]; Adults AIR=9.05[8.23-9.94]; OA = 7.22[6.56-9.95]). This is not necessarily expected but may be due to chance as the confidence intervals do overlap, and the SRR does not show this pattern. There is not a clinical reason to assume that adults at increased risk for RSV would have higher baseline titres and a better vaccine response.

Secondary endpoint: CMI response

A RSVPreF3-specific CD4+ T-cell response was elicited post-vaccination in the treatment groups compared to their respective baselines and to the placebo. At Day 31, the median frequency of RSVPreF3-specific CD4+ T-cells was 1616.0 (Adults-HA-RSV), 1379.0 (Adults-AIR-RSV), 1033.0 (OA-RSV), 281.0 (Adults-HA-Placebo) and 258.0 (Adults-AIR-Placebo).

In line with results included in the MAA, RSVPreF3 vaccine was able to induce CD4+ T-cells in both the 50-59 YOA and the older adults. The CMI analyses are of limited value in the benefit-risk analyses.

Ancillary analyses

Analyses of GMT's were performed in subgroups by comorbidity of interest, CCI, and age category.

Medical history (Comorbidity of interest and CCI)

Comorbidity of interest

At 1 month post-vaccination (Day 31), a trend toward slightly higher RSV-A and RSV-B neutralization GMTs, MGI and SRR was observed for participants with existing comorbidities in the Adults-AIR-RSV group as compared to the OA-RSV group, except for GMTs for participants with exactly 1 pre-existing comorbidity of interest.

Among the 4 specific chronic comorbidities of interest, at 1 month postvaccination (Day 31), a trend toward higher RSV-A neutralization MGI and SRR was observed in the Adults-AIR-RSV group as compared to the OA-RSV group. No specific trend was observed for GMTs.

Among the 4 specific chronic comorbidities of interest, at 1 month post-vaccination (Day 31), a trend toward higher RSV-B neutralization MGI and SRR was observed in the Adults-AIR-RSV group as compared to OA-RSV group, except for participants with chronic pulmonary disease. No specific trend was observed for GMTs.

CCI

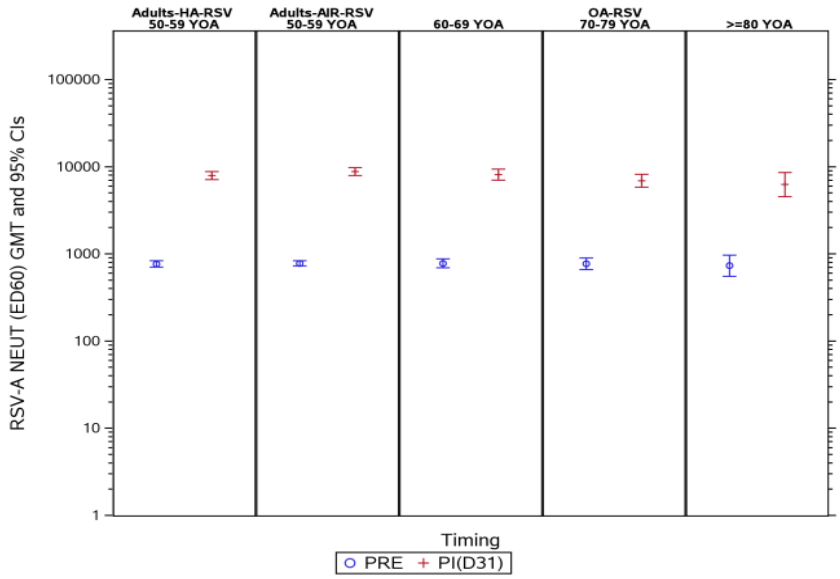
1 month post-vaccination (Day 31), participant in the CCI high-risk category had higher RSV-A neutralization GMTs as compared to participants in the CCI low risk category in the Adults-AIR-RSV group.

1 month post-vaccination (Day 31), participants in the CCI high-risk category had higher RSV-B neutralization GMTs as compared to participants in the CCI low risk category.

Age category

The seroresponse rate (RSV A and RSV B, ED60) for 50-59 years olds was between 82% and 87% for 50-59 year olds. For 60-69 year olds it was 82.7%, for 70-79 year olds it was 78.3% and for >= 80 year olds it was 76.2%. The pre- and post-vaccination titers are depicted in Figure 5 for RSV-A. RSV-B graphics are not shown as these were comparable to RSV-A.

Figure 5 GMTs and their 95% CIs for RSV-A neutralizing titers (ED60), by age group - exposed set.



Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1; OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); 95% CI = 95% confidence interval; GMT = Geometric mean titer; PRE = Pre-vaccination; PI(D31) = 1 month post RSV vaccination

Sex

GMT

- Overall, the RSV-A neutralization GMTs (at Day 31) were 7925.4 ED60 in the Adults-HA-RSV group, 8821.9 ED60 in the Adults-AIR-RSV group and 7461.9 ED60 in the OA-RSV group.
- In males, the RSV-A neutralization GMTs (at Day 31) were 7227.8 ED60 in the Adults-HA-RSV group, 8426.6 ED60 in the Adults-AIR-RSV group and 7123.4 ED60 in the OA-RSV group.
- In females, the RSV-A neutralization GMTs (at Day 31) were 8478.1 ED60 in the Adults-HA-RSV group, 9268.9 ED60 in the Adults-AIR-RSV group and 7835.8 ED60 in the OA-RSV group.

SRR

- Overall, the observed SRR (≥4-fold increase in the RSV-A neutralization titer compared to baseline) was 82.8%, 86.9% and 80.4% participants in the Adults-HA-RSV, Adults-AIR-RSV and OA-RSV groups, respectively.
- In males, the observed SRR (≥4-fold increase in the RSV-A neutralization titer compared to baseline) was 78.8%, 88.2% and 76.7% participants in the Adults-HA-RSV, Adults-AIR-RSV and OA-RSV groups, respectively.

- In females, the observed SRR (≥4-fold increase in the RSV-A neutralization titer compared to baseline) was 85.7%, 85.5% and 84.3% participants in the Adults-HA-RSV, Adults-AIR-RSV and OA-RSV groups, respectively.

RSV-B neutralization titers

GMT

- Overall, the RSV-B neutralization GMTs (at Day 31) were 8971.9 ED60 in the Adults-HA-RSV group, 9967.3 ED60 in the Adults-AIR-RSV group and 8144.5 ED60 in the OA-RSV group.
- In males, the RSV-B neutralization GMTs (at Day 31) were 7974.8 ED60 in the Adults-HA-RSV group, 9737.1 ED60 in the Adults-AIR-RSV group and 7879.2 ED60 in the OA-RSV group.
- In females, the RSV-B neutralization GMTs (at Day 31) were 9779.4 ED60 in the Adults-HA-RSV group, 10221.5 ED60 in the Adults-AIR-RSV group and 8435.4 ED60 in the OA-RSV.

SRR

- Overall, the observed SRR (≥4-fold increase in the RSV-B neutralization titer compared to baseline) was 78.2%, 81.6% and 74.5% participants in the Adults-HA-RSV, Adults-AIR-RSV and OA-RSV groups, respectively.
- In males, the observed SRR (≥4-fold increase in the RSV-B neutralization titer compared to baseline) was 74.5%, 80.3% and 71.6% participants in the Adults-HA-RSV, Adults-AIR-RSV and OA-RSV groups, respectively.
- In females, the observed SRR (≥4-fold increase in the RSV-B neutralization titer compared to baseline) was 81.0%, 83.0% and 77.6% participants in the Adults-HA-RSV, Adults-AIR-RSV and OA-RSV groups, respectively.

The subgroup analyses should be viewed as exploratory. Seroresponse rate decreased very slightly with increasing age, however differences were minimal and the immune response was still substantial in the ≥80 year old group. There did not appear to be an obvious trend based on medical history (number of co-morbidities and CCI). Upon request, the MAH submitted a subgroup analyses based on sex. The subgroup analysis of the immune response in terms of GMT, SRR and MGI presented did not suggest any meaningful differences in the immune response by sex.

The limited number of subgroups is acceptable.

Subgroups based on race would be too small to achieve meaningful results.

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 13 Summary of Efficacy (immunogenicity) for trial ADJ-018

Title: A Phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including adults at increased risk of respiratory syncytial virus lower respiratory tract disease, compared to older adults ≥ 60 years of age.		
Study identifier	Protocol number: RSV OA=ADJ-018 EudraCT number: 2022-001981-36	
Design	Phase 3, observer-blind, placebo-controlled, randomized, multicountry, multi-center, non-inferiority study with 2 cohorts.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Approximately 12 months not applicable not applicable

Hypothesis	Non-inferiority: NI for each primary objective will be claimed to be successful if the upper limit of the 2-sided CI for the GMT ratio will be **≤1.5** and the upper limit of the 2-sided CI for the seroresponse rate (SRR) difference will be ⩽0.10, according to the significance level provided by the graphical testing procedure.		
Treatments groups	Adults-HA-RSV Group		1 dose of Arexvy (120 µg RSVPreF3 recombinant antigen adjuvanted with $AS01_E$) administered intramuscularly (IM) n= 381 randomised n=383 exposed*
	Adults-HA-Placebo Group		1 dose of placebo (saline) administered IM n= 190 randomised n=192 exposed*
	Adults-AIR-RSV Group		1 dose of Arexvy n= 386 randomised n=389 exposed*
	Adults-AIR-Placebo Group		1 dose of placebo (saline) administered IM n= 195 randomised n=194 exposed*
	OA-RSV Group		1 dose of placebo (saline) administered IM n= 387 randomised n=381 exposed*
Endpoints and definitions	(Co)Primary Endpoint	RSV-A neutralization antibody titers expressed as both group GMT ratio (OA-RSV/Adults-HA-RSV) and group SRR difference (OA-RSV - Adults-HA-RSV)†	
	(Co)Primary Endpoint	RSV-B neutralization antibody titers expressed as both group GMT ratio (OA-RSV/Adults-HA-RSV) and group SRR difference (OA-RSV - Adults-HA-RSV)‡	
	(Co)Primary Endpoint	RSV-A neutralization antibody titers expressed as both group GMT ratio (OA-RSV/Adults-AIR-RSV) and group SRR difference (OA-RSV - Adults-AIR-RSV) †	
	(Co)Primary Endpoint	RSV-B neutralization antibody titers expressed as both group GMT ratio (OA-RSV/Adults-AIR-RSV) and group SRR difference (OA-RSV - Adults-AIR-RSV) †	
	Note: † 95% CI used for establishing non-inferiority based on testing procedure ‡ 97.5% CI used for establishing non-inferiority based on testing procedure		
Database lock	05 September 2023		

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. Analysis per group is based on the administered intervention. Contribution of participants to Per Protocol Set was to be defined by timepoint Time point: Day 31			
Descriptive statistics and estimate variability (unadjusted)	Treatment group	Adults-HA-RSV	Adults-AIR-RSV	OA-RSV
	Number of subject GMT (RSVA) (95%CI)	326 7925.4 (7125.6-8815.0)	343 8821.9 (7971.0-9763.6)	342 7461.9 (6724.9-8279.6)
	Number of subject GMT (RSVB) (95%CI)	326 8971.9 (8109.6-9925.8)	343 9967.3 (9059.3-10966.3)	341 8144.5 (7388.9-8977.4)
	Number of subject SRR (RSVA) (95%CI)	270 82.8 (78.3- 86.8)	298 86.9 (82.8-90.3)	275 80.4 (75.8-84.5)
	Number of subject SRR (RSVB) (95%CI)	255 78.2 (73.3- 82.6)	280 81.6 (77.1-85.6)	254 74.5 (69.5-79.0)

Effect estimate per comparison	RSV-A neutralization group GMT ratio and group SRR difference	Comparison groups	OA-RSV versus Adults-HA-RSV
		Ratio of adjusted GMTs (95%CI)	0.95(0.83; 1.09)
		SRR(95%CI)	-2.41(-8.30; 3.50)
	RSV-B neutralization group GMT ratio and group SRR difference	Comparison groups	OA-RSV versus Adults-HA-RSV
		Ratio of adjusted GMTs (97.5%CI)	0.89 (0.77; 1.03)
		SRR(97.5%CI)	-3.73 (-11.09; 3.68)
	RSV-A neutralization group GMT ratio and group SRR difference	Comparison groups	OA-RSV versus Adults-AIR-RSV
		Ratio of adjusted GMTs (95%CI)	0.83 (0.73; 0.95)
		SRR(95%CI)	-6.47 (-12.05; -0.94)
	RSV-B neutralization group GMT ratio and group SRR difference	Comparison groups	OA-RSV versus Adults-AIR-RSV
		Ratio of adjusted GMTs (95%CI)	0.80 (0.71; 0.91)
		SRR(95%CI)	-7.15 (-13.34; - 0.94)

Analysis performed across trials (pooled analyses and meta-analysis)

None

Clinical studies in special populations

None

Supportive studies

None

2.4.2. Discussion on clinical efficacy

The current indication approved by the EMA 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;

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

Design and conduct of clinical studies

To support the current variation the MAH provides the results of study RSV OA=ADJ-018, a Phase 3, placebo-controlled, observer-blind, multicentre study designed to demonstrate non-inferiority of the immune response in the 50-59 YOA group compared to older adults ≥60 YOA.

The immunobridging approach to compare the immune response in adults 50-59 YOA to that of adults ≥60 YOA, in whom VE was demonstrated, is in accordance with scientific advice by CHMP. Vaccine efficacy can be inferred by demonstrating non-inferior immune responses between the younger population and the population for which efficacy has been established.

The study-design for trial ADJ-018 was not discussed in previous scientific advice by the CHMP. However, the design of a similar trial (ADJ-014) which sought to extend the indication to adults 18-59 years was discussed, and some recommendations are relevant for the current application. The CHMP stated that 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 included as secondary analyses (i.e., in each of HA and AIR and for each of RSV-A and B).

The in- and exclusion criteria in the current study are generally similar to the in- and exclusion criteria used for study ADJ-006, aside from age, used to determine efficacy in the older adult population. The study included two Cohorts. Cohort 1 participants received either placebo or Arexvy and comprised of adults 50-59 YOA; it was divided in 2 sub-cohorts consisting of either adults with pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease (AIR sub-cohort) or healthy adults without pre-defined, stable, chronic medical conditions (HA Sub-cohort). Participants in Cohort 2 were ≥60 YOA and all received Arexvy (OA-RSV). The population for which the extension of indication is being sought (i.e. adults 50 through 59 years of age who are at increased risk for RSV disease), is represented by the Adults-AIR sub cohort. The population of the healthy-Adults cohort is not represented in the sought-after indication.

There were four primary objectives investigating the non-inferiority of the immune response based on neutralizing antibodies of the Adults-AIR-RSV and Adults-HA-RSV groups compared to the response of the Adults-OA-RSV group, for both RSV-A and B. Within each objective, both GMT ratio's and the SRR were used as co-primary endpoints. The use of the GMT ratios is appropriate in a population that is expected to have been primed by natural exposure(s) to RSV.

Cohort 1 was observer-blinded until Day 31 analysis. Beyond Day 31, only the participants remained blinded. The level of blinding is acceptable, as blinding is not expected to alter the immunogenicity results.

The MAH describes a quality error leading to 85 participants potentially receiving a higher dose of RSVPreF3 antigen and a lower volume of adjuvant. The potential administered dose (123 – 137 µg) falls within the range of Phase 3 acceptance (102-138 µg/dose). In each randomized group, approximately the same percentage of people received an incorrect dose minimizing the impact of this error: 28 (7.3%) adults-HA-RSV, 20 (5.2%) adults-AIR-RSV, and 37 (9.7%) -OA RSV. Immunogenicity analyses (GMT, SRR, GMT ratio, SRR difference) stratified by presence of reconstitution errors does not provide reason to believe the incorrect reconstitution and the normal reconstitution resulted in differing immunogenicity patterns.

Efficacy data and additional analyse

Participant flow and demographics

In this study, 1544 participants were enrolled. The actual number of participants who received the study intervention and were included in the exposed set differed from the number planned to be enrolled. The MAH stated that the differences between the planned and actual number of receiving the study intervention are mainly due to randomisation errors. However, as these numbers are group-specific (i.e. 381 planned versus 383 actual for Adults-HA-RSV and 190 versus 192 for Adults-HA-Placebo), it appears

that the errors were identified *after* randomisation. Upon request the MAH further elaborated on these errors, which took place after screening and during the randomisation process. The analysis on the per protocol set and the exposed set did not lead to different conclusions, therefore it can be agreed that any major impact of these errors is unlikely.

As expected, due to the differing inclusion criteria, the Adults-HA group was healthier than the Adults-AIR group and healthier and younger than the OA-RSV group. Compared to the population in the primary efficacy study ADJ-006, the OA-RSV group was similar: the median age was the same (69 years) and the percent of individuals >=80 years of age was also similar (8.7%).

The MAH states that when the trend concerning out of window visits was noticed as 1 of the reasons for high elimination from PPS, remedial actions were taken by the study team to prevent increase in out of window visits at Visit 3 and Visit 4, which are considered acceptable.

Immunogenicity results

In this application immunogenicity data up until 1 month is provided. This is acceptable for the purpose of this application. All four primary endpoints showed non-inferiority of the immunogenic response of 50-59 years olds (Adults-AIR-RSV and Adults-HA-RSV) compared to ≥60 year olds, based on both the GMT ratio (UL <1.5) and SRR (UL <10%). Thus, as immunogenicity is comparable between the entire 50-59 YOA population, both healthy and at increased risk of RSV, and the ≥60 year old population. The MAH had accounted for a 10% attrition rate from the enrolled to evaluable participants, which was exceeded in nearly all study groups. Results from a supplementary analyses using the exposed set were similar from the PPS group, both for the GMT ratio and the SRR, indicating a robust response. Missing values were not replaced, therefore participants with missing values were also not included in the analysis based on the exposed set.

At baseline (Day 1, pre-vaccination), all participants had RSV-A and RSV-B neutralization titers above the pre-defined technical assay cut-off, suggesting previous exposure to RSV. Baseline GMT's were approximately the same in each group for each serotype (RSVA and RSVB). At one month, the neutralization titers (ED60) were similar among groups having received the intervention. The SRR showed a similar pattern of being minimally different (0.6% - 3.9% for the placebo groups, and being between 74.5% - 86.9% for the treatment groups.

CMI analyses

The CMI response was performed in a subset of participants. The analyses are viewed with interest, but are not considered pivotal for the benefit-risk. At day 31, the vaccine elicits a CD4+ T-cell response in all groups receiving the RSVPreF3 vaccine, which is in line with the results in study ADJ-004.

Analysis by baseline age and sex

Seroresponse rate decreased very slightly with increasing age, however the immune response was still substantial in the ≥80 year old group. The limited number of subgroups is acceptable. Upon request the MAH submitted a subgroup analyses based on sex, which did not reveal any meaningful differences in immune response between the sexes.

2.4.3. Conclusions on the clinical efficacy

In conclusion, the results indicate that the RSVPreF3 vaccine elicits a similar immune response in individuals ≥60 years of age compared to individuals 50-59 years of age, whether healthy or at increased risk of RSV-LRTD.

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 and -009). 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 study ADJ-018, a phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including both healthy adults and adults at increased risk of RSV LRTD, compared to older adults (≥ 60 years of age). 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 or systemic events event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days, Table 14)
- 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).
- Percentage of participants reporting any SAEs and pIMDs after study intervention administration (Day 1) up to Month 6.
- Percentage of participants reporting SAEs and pIMDs related to study intervention administration after study intervention administration (Day 1) up to study end (Month 12).
- Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (Month 12).

The current submission provides safety data with a follow-up of at least 6 months.

Adverse events of special interest (AESIs) collected during this study include potential immune-mediated diseases (pIMDs) and Atrial Fibrillation (AF). The pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.

Table 14 Intensity of solicited events

Event	Intensity grade	Parameter
Solicited administration site events		
Pain at the injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Erythema/Swelling*	0	≤ 20 mm
	1	> 20 - ≤ 50 mm
	2	> 50 - ≤ 100 mm
	3	> 100 mm
Solicited systemic events		
Temperature**	0	< 38.0°C (100.4°F)
	1	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
	2	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
	3	> 39.0°C (102.2°F)

Event	Intensity grade	Parameter
Headache/Fatigue/ Myalgia/Arthralgia	0	Normal
	1	Event that is easily tolerated
	2	Event that interferes with normal activity
	3	Event that prevents normal activity

*Measurement of greatest surface diameter ** Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route (i.e. oral, axillary or tympanic).

The safety endpoints are appropriate to assess the reactogenicity and safety of Arexvy. The overall design of the collection of safety data is conform the other phase 3 trials for Arexvy. Reactogenicity was followed for 4 days in the Phase 3 trials which was based on the experience during the Phase 2 trial and knowledge of AS01 adjuvanted vaccines. There was no specific subset to assess safety endpoints. Rather, all enrolled patients participated in the collection of safety data.

No subgroup analyses were performed for the safety endpoints. This is acceptable, as the number of events would be too small to gain meaningful insight, even in the larger subgroups such as sex. In the initial MAA, sex was investigated as a subgroup, and no differences (even in the reactogenicity endpoints) were observed.

Patient exposure

The analysis of reactogenicity and safety was performed on the exposed set (ES), defined as all participants who received the study intervention. The analysis per group is based on the administered intervention. The DLP for the safety analysis was 01 September 2023 with a follow-up of at least 6 months.

A total of 1151 participants (Table 15) received 1 dose of the RSVPreF3 OA vaccine, and 383 participants received the placebo. All participants (100%) in the Adults-HA-RSV (N=383), Adults-AIR-RSV (N=386), and OA-RSV (N=381) groups received 1 dose of RSVPreF3 OA vaccine and all participants (100%) in Adults-HA-Placebo (N=192) and Adults-AIR-Placebo (N=191) group received 1 dose of placebo.

Table 15 Number of participants and doses evaluated for safety in studies

Study	Study intervention	Study groups	Age (years)	Number of participants	Number of doses
RSV OA= ADJ-018	OA	Adults-HA-RSV	50-59	383	383
		Adults-AIR-RSV		386	386
		Sub-total (Adults-RSV)		769	769
		OA-RSV	≥60	381	381
		Total (RSV groups)		1150	1150
	Placebo	Adults-HA-Placebo	50-59	192	192
		Adults-AIR-Placebo		191	191
		Total (Placebo groups)		383	383

Data Source: M5.3.5.1, RSV OA=ADJ-018 (219238) Report (29-NOV-2023) Table 14.1.3.1 ; AIR=At Increased Risk; HA=Healthy Adults; OA=Older Adults; RSV= Respiratory Syncytial Virus; YOA=Years Of Age. Number of patients based on enrolled set.

No separate subsets were used for the safety analyses. In the pooled groups, the median age was 55.0 years in the Adults RSV groups, 56.0 years in the Adults-Placebo groups and 69.0 years in the OA RSV group.

The 50-59 years olds at increased risk of RSV related LRTD for whom the indication in sought are represented in the reactogenicity and safety analysis. However, the healthy 50-59 year olds are included in the safety analysis, but not in the sought after indication. The numbers analysed are sufficient to

analyse the reactogenicity and safety profile in 50-59 years olds (either healthy or at risk) for the purpose of this line-extension.

Pooled results are provided in this assessment report (i.e. Adults-RSV group, Adults-Placebo group, and OA-RSV group). Unpooled results are only discussed if there appeared to be an imbalance within pooled groups.

Adverse events

A summary of local and systemic adverse events occurring withing 4 days following vaccination in shown in Table 16.

Table 16 Summary of any adverse event within 4 days following vaccination

	Adults-RSV		Adults-Placebo		OA -RSV	
N	769	%	383	%	381	0
Any adverse event	634	82.4	128	33.4	267	70.1
Grade 3 event	56	7.3	10	2.6	20	5.2
Administration-site adverse event	580	75.4	48	12.5	238	62.5
Grade 3 event	31	4.0	1	0.3	11	2.9
Systemic adverse event	439	57.1	108	28.2	162	42.5
Grade 3 event	39	5.1	9	2.3	11	2.9

Table made by assessor from unpooled data: source Table 14.3.1.2 & Table 14.3.1.3.
Adults-RSV: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-Placebo: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of placebo at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1);

Solicited adverse events

Solicited administration site events

The most frequently reported (Grade 3) solicited administration site event was pain, followed by erythema and swelling (Table 17). Across the study groups, the median duration of each solicited administration-site event was equal to or below 4.0 days for any grade. Across the study groups, the median duration of each solicited administration-site events ongoing beyond the 4-day follow-up period was equal to or below 8.0 days for any grade.

Table 17 Percentage of participants with solicited administration site events within 4 days following vaccination - Exposed Set (Pooled Analysis)

	Adults-RSV				Adults-Placebo				OA-RSV			
			95% CI				95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Erythema (mm)												
N	756				379				379			
Any	100	13.2	10.9	15.9	2	0.5	0.1	1.9	46	12.1	9.0	15.9
>100	4	0.5	0.1	1.3	0	0	0	1.0	3	0.8	0.2	2.3
Medically attended visits	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Pain												

	Adults-RSV				Adults-Placebo				OA-RSV			
			95% CI				95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
N	756				379				379			
Any	573	75.8	72.6	78.8	46	12.1	9.0	15.9	232	61.2	56.1	66.1
Grade 3	26	3.4	2.3	5.0	1	0.3	0.0	1.5	8	2.1	0.9	4.1
Medically attended visits	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Swelling (mm)												
N	756				379				379			
Any	79	10.4	8.4	12.9	3	0.8	0.2	2.3	29	7.7	5.2	10.8
>100	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Medically attended visits	0	0	0	0.5	0	0	0	1.0	0	0	0	1.0

Adults-RSV: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-Placebo: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of placebo at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); N = number of participants with diary card; n/% = number/percentage of participants presenting at least one type of symptom;

Solicited systemic adverse events

The most frequently reported (Grade 3) solicited systemic events were fatigue, myalgia headache and arthralgia (Table 18).

Table 18 Percentage of participants with solicited systemic events within 4 days following vaccination, including grade 3 events - Exposed Set (Pooled Analysis)

	Adults-RSV				Adults-Placebo				OA-RSV			
			95% CI				95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Arthralgia												
N	756				380				379			
Any	177	23.4	20.4	26.6	30	7.9	5.4	11.1	49	12.9	9.7	16.7
Grade 3	13	1.7	0.9	2.9	3	0.8	0.2	2.3	4	1.1	0.3	2.7
Medically attended visits	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Fatigue												
N	756				380				379			
Any	301	39.8	36.3	43.4	69	18.2	14.4	22.4	90	23.7	19.6	28.4
Grade 3	21	2.8	1.7	4.2	3	0.8	0.2	2.3	7	1.8	0.7	3.8
Medically attended visits	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Fever (°C)												
N	756				380				379			
>= 38.0	24	3.2	2.0	4.7	4	1.1	0.3	2.7	6	1.6	0.6	3.4
> 38.5	6	0.8	0.3	1.7	3	0.8	0.2	2.3	1	0.3	0.0	1.5
> 39.0	1	0.1	0.0	0.7	2	0.5	0.1	1.9	0	0	0	1.0
> 39.5	0	0	0	0.5	2	0.5	0.1	1.9	0	0	0	1.0
> 40.0	0	0	0	0.5	0	0	0	1.0	0	0	0	1.0

Medically attended visits	2	0.3	0.0	1.0	0	0	0	1.0	0	0	0	1.0
Headache												
N	756				380				379			
Any	240	31.7	28.4	35.2	64	16.8	13.2	21.0	80	21.1	17.1	25.6
Grade 3	20	2.6	1.6	4.1	4	1.1	0.3	2.7	3	0.8	0.2	2.3
Medically attended visits	2	0.3	0.0	1.0	0	0	0	1.0	1	0.3	0.0	1.5
Myalgia												
N	756				380				379			
Any	269	35.6	32.2	39.1	37	9.7	6.9	13.2	80	21.1	17.1	25.6
Grade 3	19	2.5	1.5	3.9	2	0.5	0.1	1.9	3	0.8	0.2	2.3
Medically attended visits	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5

Data Source: M5.3.5.1, RSV OA=ADJ-018 (219238) Report (29-NOV-2023) Appendix 16.1.14, Table 3

Adults-RSV: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-Placebo: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of placebo at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); N = number of participants with diary card; n/% = number/percentage of participants presenting at least one type of symptom; For Fever, Grade 3 corresponds to temperature > 39.0 C

The majority of participants receiving Arexvy experienced a solicited adverse event within 4 days after vaccination. The frequency was approximately 82% in the Adults-RSV group, 33% in the placebo group, and 70% in the OA-RSV group. For grade 3 events the frequency was 7.3%, 2.6%% and 5.1% respectively.

The most frequently reported solicited administration site events was pain, followed by erythema, and swelling, and the most frequently reported systemic events were fatigue, myalgiaheadache and arthralgia. Thus, the type of solicited adverse events was comparable in the current study to the known safety profile. A higher reactogenicity is seen in the younger Adults-RSV population (50-59 years old), however this is expected and within acceptable range.

Unsolicited adverse events

Within 30 minutes

One unsolicited AE, dizziness, was reported in 1 (0.3%) participant in the Adults-Placebo group.

Within 30 days

Within 30 days, unsolicited AEs were reported in 106 (13.8%) participants in the AdultsRSV group, 46 (12.0%) participants in the Adults--Placebo group and 62 (16.3%) participants in the OA---RSV group (Table 19). At the SOC level, the most frequently reported unsolicited AE SOC was infections and infestations, reported in 32 (4.2%) participants in the Adults-RSV group, 17 (4.4%) participants in the Adults-Placebo group and 25 (6.6%) participants in the OA-RSV group.

Table 19 Summary unsolicited (serious and non-serious) adverse events - Exposed Set (Pooled Analysis, modified by assessor)

	Adults-RSV N=769			Adults-Placebo N=383			OA-RSV N=381		
	occ	n	%	occ	n	%	occ	n	%
Any unsolicited adverse event within 30 days of vaccination	167	106	13.8	60	46	12.0	88	62	16.3
Any Grade 3 unsolicited AE within 30 days of vaccination	9	8	1.0	4	4	1.0	2	2	0.5
Any related unsolicited AE within 30 days of vaccination	36	26	3.4	12	8	2.1	14	12	3.1
Any Grade 3 related unsolicited AE within 30 days of vaccination	0	0	0	0	0	0	1	1	0.3
Any unsolicited MAE within 30 days of vaccination	43	36	4.7	26	23	6.0	36	27	7.1
Any non-serious unsolicited MAE within 30 days of vaccination	38	33	4.3	26	23	6.0	34	25	6.6
Any unsolicited AE with onset within 30 minutes of vaccination	0	0	0	1	1	0.3	0	0	0
Any SAE with onset within 6 months of vaccination	20	16	2.1	8	8	2.1	9	9	2.4
Any serious related adverse event up to Data Lock Point	0	0	0	0	0	0	1	1	0.3
Any pIMD with onset within 6 months of vaccination	4	4	0.5	1	1	0.3	3	3	0.8
Any pIMD related up to Data Lock Point	0	0	0	0	0	0	1	1	0.3
Any fatal serious adverse event up to Data Lock Point	0	0	0	0	0	0	0	0	0

Data Source: Appendix 16.1.14, Table 8. AE: adverse event; MAE: medically attended adverse event; SAE: serious adverse event. Adults-RSV: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-Placebo: Pooling of healthy and at increased risk participants (50-59 YOA) receiving a single dose of placebo at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); N = number of participants n/% = number/percentage of participants presenting at least one type of adverse event pIMD = potential immune mediated-disease; occ = number of occurrences = number of unsolicited adverse events reported by a participant for a given category; The analysis of unsolicited adverse event includes non-serious and serious adverse events.

The MAH appeared to only have reported hypersensitivity reactions within the first 30 minutes of vaccine administration. The MAH was requested to review all hypersensitivity related AEs occurring, not limited to within 30 minutes after vaccination, present the information in tabulated format, and determine the frequency for inclusion in section 4.8 of the SmPC. Based on the data provided, the frequency of the AEs possibly linked to hypersensitivity and anaphylactic reactions remains consistent with the current frequency for these reactions (categorised as uncommon) in Section 4.8 of the SmPC.

Unsolicited adverse events related to the vaccination

Unsolicited AEs considered by the investigator to be related to study interventions were reported in 26 (3.4%) participants in the Adults-RSV group, 8 (2.1%) participants in the Adults-Placebo group and 12 (3.1%) participants in the OA-RSV group. The 3 most frequently reported unsolicited AEs considered by the investigator to be related to the study intervention were (Table 20):

- General disorders and administration site conditions (10 [1.3%] participants in the Adults-RSV group, 1 [0.3%] participant in the Adults-Placebo group and 5 [1.3%] participants in the OA-RSV group).
- Gastrointestinal disorders (7 [0.9%] participants in the Adults-RSV group, 2 [0.5%] participants in the Adults-Placebo group and 5 [1.3%] participants in the OA-RSV group).
- Skin and subcutaneous tissue disorders (3 [0.4%] participants in the Adults-RSV group, 2 [0.5%] participants in the Adults-Placebo group and 1 [0.3%] participant in the OA-RSV group).

Table 20 Summary of participants with at least one related unsolicited (serious and non-serious) adverse event with onset within 30 days of vaccination - Exposed Set (Pooled Analysis)

	Adults-RSV N=769				Adults-Placebo N=383				OA-RSV N=381			
			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
Any related unsolicited adverse event	26	3.4	2.2	4.9	8	2.1	0.9	4.1	12	3.1	1.6	5.4
General disorders and administration site conditions (10018065)	10	1.3	0.6	2.4	1	0.3	0.0	1.4	5	1.3	0.4	3.0
Injection site reactions (10022097)	6	0.8	0.3	1.7	0	0	0	1.0	2	0.5	0.1	1.9
Injection site pruritus (10022093)	6	0.8	0.3	1.7	0	0	0	1.0	0	0	0	1.0
Injection site bruising (10022052)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Injection site induration (10022075)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Injection site pain (10022086)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Asthenic conditions (10003550)	1	0.1	0.0	0.7	1	0.3	0.0	1.4	2	0.5	0.1	1.9
Asthenia (10003549)	1	0.1	0.0	0.7	0	0	0	1.0	2	0.5	0.1	1.9
Fatigue (10016256)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Administration site reactions NEC (10057196)	2	0.3	0.0	0.9	0	0	0	1.0	0	0	0	1.0
Administration site bruise (10075094)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Administration site warmth (10075971)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Feelings and sensations NEC (10068759)	2	0.3	0.0	0.9	0	0	0	1.0	0	0	0	1.0
Chills (10008531)	2	0.3	0.0	0.9	0	0	0	1.0	0	0	0	1.0
General signs and symptoms NEC (10018072)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Influenza like illness (10022004)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Gastrointestinal disorders (10017947)	7	0.9	0.4	1.9	2	0.5	0.1	1.9	5	1.3	0.4	3.0
Diarrhoea (excl infective) (10012736)	4	0.5	0.1	1.3	2	0.5	0.1	1.9	2	0.5	0.1	1.9
Diarrhoea (10012735)	4	0.5	0.1	1.3	2	0.5	0.1	1.9	2	0.5	0.1	1.9
Nausea and vomiting symptoms (10028817)	3	0.4	0.1	1.1	0	0	0	1.0	2	0.5	0.1	1.9
Vomiting (10047700)	1	0.1	0.0	0.7	0	0	0	1.0	2	0.5	0.1	1.9
Nausea (10028813)	2	0.3	0.0	0.9	0	0	0	1.0	0	0	0	1.0
Gastrointestinal and abdominal pains (excl oral and throat) (10017926)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Abdominal pain (10000081)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Salivary gland infections and inflammations (10039415)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Noninfective sialoadenitis (10075243)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Skin and subcutaneous tissue disorders (10040785)	3	0.4	0.1	1.1	2	0.5	0.1	1.9	1	0.3	0.0	1.5
Dermatitis and eczema (10012435)	2	0.3	0.0	0.9	1	0.3	0.0	1.4	0	0	0	1.0
Dermatitis (10012431)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Dermatitis atopic (10012438)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Eczema nummular (10014201)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Dermal and epidermal conditions NEC (10012424)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Dry skin (10013786)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Erythemas (10015151)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Erythema (10015150)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Urticarias (10046736)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Urticaria (10046735)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Musculoskeletal and connective tissue disorders (10028395)	2	0.3	0.0	0.9	2	0.5	0.1	1.9	1	0.3	0.0	1.5
Muscle pains (10028323)	1	0.1	0.0	0.7	2	0.5	0.1	1.9	1	0.3	0.0	1.5
Myalgia (10028411)	1	0.1	0.0	0.7	2	0.5	0.1	1.9	1	0.3	0.0	1.5
Joint related signs and symptoms (10023226)	2	0.3	0.0	0.9	1	0.3	0.0	1.4	0	0	0	1.0
Arthralgia (10003239)	2	0.3	0.0	0.9	1	0.3	0.0	1.4	0	0	0	1.0
Joint swelling (10023232)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0

	Adults-RSV N=769				Adults-Placebo N=383				OA-RSV N=381			
			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
Blood and lymphatic system disorders (10005329)	3	0.4	0.1	1.1	1	0.3	0.0	1.4	0	0	0	1.0
Lymphatic system disorders NEC (10025198)	3	0.4	0.1	1.1	1	0.3	0.0	1.4	0	0	0	1.0
Lymphadenopathy (10025197)	3	0.4	0.1	1.1	1	0.3	0.0	1.4	0	0	0	1.0
Infections and infestations (10021881)	2	0.3	0.0	0.9	0	0	0	1.0	1	0.3	0.0	1.5
Herpes viral infections (10019972)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Herpes simplex (10019948)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Influenza viral infections (10022005)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Influenza (10022000)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Upper respiratory tract infections (10046309)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Upper respiratory tract infection (10046306)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Respiratory, thoracic and mediastinal disorders (10038738)	1	0.1	0.0	0.7	1	0.3	0.0	1.4	1	0.3	0.0	1.5
Upper respiratory tract signs and symptoms (10046313)	1	0.1	0.0	0.7	1	0.3	0.0	1.4	1	0.3	0.0	1.5
Oropharyngeal pain (10068319)	1	0.1	0.0	0.7	1	0.3	0.0	1.4	0	0	0	1.0
Rhinorrhoea (10039101)	0	0	0	0.5	0	0	0	1.0	1	0.3	0.0	1.5
Nervous system disorders (10029205)	0	0	0	0.5	2	0.5	0.1	1.9	0	0	0	1.0
Headaches NEC (10019233)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Headache (10019211)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Neurological signs and symptoms NEC (10029306)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Dizziness (10013573)	0	0	0	0.5	1	0.3	0.0	1.4	0	0	0	1.0
Cardiac disorders (10007541)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Cardiac signs and symptoms NEC (10007609)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Palpitations (10033557)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Metabolism and nutrition disorders (10027433)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Hyperglycaemic conditions NEC (10020638)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0
Hyperglycaemia (10020635)	1	0.1	0.0	0.7	0	0	0	1.0	0	0	0	1.0

Data Source: M5.3.5.1, RSV OA=ADJ-018 (219238) Report (29-NOV-2023) Appendix 16.1.14, Table 11;

Adults-RSV = Healthy adult participants or Adults AIR (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults- Placebo = Healthy adult participants or Adults AIR (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); 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; The analysis of unsolicited adverse event includes non-serious and serious adverse events.

Unsolicited AEs were reported in 106 (13.8%) participants in the Adults-RSV group, 46 (12.0%) participants in the Adults--Placebo group and 62 (16.3%) participants in the OA--RSV group. At the SOC level, the most frequently reported unsolicited AE was “infections and infestations”,- reported in 32 (4.2%) participants in the Adults-RSV group, 17 (4.4%) participants in the Adults-Placebo group and 25 (6.6%) participants in the OA-RSV group. The higher frequency seen in the OA-RSV group is probably related to the higher age in this group. Unlike the reactogenicity, which are measured over a small period of time and are more specific to the intervention, the higher age and presence of comorbidities would translate into a higher frequency of events for this age group.

Unsolicited AEs considered by the investigator to be related to study interventions were reported in 26 (3.4%) participants in the Adults-RSV group, 8 (2.1%) participants in the Adults--Placebo group and

12 (3.1%) participants in the OA--RSV group. At PT-level, cases with an apparent disbalance between placebo and intervention groups (such as lymphadenopathy) are already reported in section 4.8 of the SmPC as an adverse effect of Arexvy-. Other cases were single cases, and as these do not provide a clear safety signal, do not need to be included as new adverse reactions in section 4.8 of the SmPC.

Upon request, the MAH recalculated the AE frequencies in Table 1 of the SmPC based on a pooled population consisting of both the ADJ-018 population and the population which has been used to generate SmPC Table 1 resulting in change of the frequency for injection site erythema.

Serious adverse event/deaths/other significant events

SAEs

Within 6 months following vaccination, at least 1 SAE was reported in 16 (2.1%) participants in the Adults-RSV group, 8 (2.1%) participants in the Adults-Placebo group and 9 (2.4%) in the OA-RSV group, see Table 21. There were no (S)AEs leading to study or treatment discontinuation.

SAEs related to study intervention administration were reported in none (0%) of the participants of the Adults-RSV group, none (0%) of the participants in the Adults-Placebo group and 1 (0.3%) participant in the OA-RSV group. This event was Cold type haemolytic anaemia with onset reported to be 53 days after the study intervention administration. This event was also reported as a pIMDs. The MAH stated that the participant had a history of laboratory findings suggestive of haemolytic anaemia (raised serum bilirubin, anaemia and raised lactate dehydrogenase) prior to receiving the study intervention and that the presence of haemolytic anaemia prior study intervention cannot be ruled out.

Table 21 Summary of participants with at least one serious unsolicited adverse event with onset within 6 months of vaccination – Exposed Set

	Adults-RSV			Adults-Placebo			OA-RSV	
Primary System Organ Class (CODE) High Level Term (CODE) Preferred Term (CODE)	n	%		n	%		n	%
Any serious adverse event	16	2.1		8	2.1		9	2.4
Infections and infestations (10021881)	6	0.8		4	1.0		2	0.5
Lower respiratory tract and lung infections (10025101)	4	0.5		0	0.0		2	0.5
Pneumonia (10035664)	3	0.4		0	0.0		2	0.5
Infective exacerbation of chronic obstructive airways disease (10056971)	1	0.1		0	0.0		0	0
Bacterial infections NEC (10004047)	1	0.1		1	0.3		0	0
Cellulitis (10007882)	1	0.1		1	0.3		0	0
Bone and joint infections (10005940)	0	0.0		1	0.3		0	0
Osteomyelitis (10031252)	0	0.0		1	0.3		0	0
Coronavirus infections (10084510)	0	0.0		1	0.3		0	0
COVID-19 (10084268)	0	0.0		1	0.3		0	0
Dental and oral soft tissue infections (10012326)	0	0.0		1	0.3		0	0
Abscess oral (10000311)	0	0.0		1	0.3		0	0
Enterococcal infections (10014889)	1	0.1		0	0.0		0	0
Enterococcal bacteraemia (10014885)	1	0.1		0	0.0		0	0
Upper respiratory tract infections (10046309)	1	0.1		0	0.0		0	0
Acute sinusitis (10001076)	1	0.1		0	0.0		0	0
Injury, poisoning and procedural complications (10022117)	2	0.3		0	0.0		2	0.5
Limb fractures and dislocations (10075886)	1	0.1		0	0.0		1	0.3
Femur fracture (10016454)	1	0.1		0	0.0		0	0
Hip fracture (10020100)	0	0.0		0	0.0		1	0.3
Musculoskeletal procedural complications (10028392)	0	0.0		0	0.0		1	0.3
Kyphosis postoperative (10056490)	0	0.0		0	0.0		1	0.3
Poisoning and toxicity (10035777)	1	0.1		0	0.0		0	0

	Adults-RSV			Adults-Placebo			OA-RSV	
Primary System Organ Class (CODE) High Level Term (CODE) Preferred Term (CODE)	n	%		n	%		n	%
Alcohol poisoning (10001605)	1	0.1		0	0.0		0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	1	0.1		1	0.3		1	0.3
Colorectal neoplasms malignant (10010023)	1	0.1		0	0.0		1	0.3
Adenocarcinoma of colon (10001167)	1	0.1		0	0.0		1	0.3
Breast and nipple neoplasms malignant (10006290)	0	0.0		1	0.3		0	0
Breast cancer (10006187)	0	0.0		1	0.3		0	0
Respiratory, thoracic and mediastinal disorders (10038738)	3	0.4		0	0.0		0	0
Bronchospasm and obstruction (10006484)	2	0.3		0	0.0		0	0
Chronic obstructive pulmonary disease (10009033)	2	0.3		0	0.0		0	0
Asthma (10003553)	1	0.1		0	0.0		0	0
Respiratory failures (excl neonatal) (10052549)	1	0.1		0	0.0		0	0
Acute respiratory failure (10001053)	1	0.1		0	0.0		0	0
Cardiac disorders (10007541)	0	0.0		1	0.3		1	0.3
Noninfectious pericarditis (10034494)	0	0.0		1	0.3		0	0
Pericarditis (10034484)	0	0.0		1	0.3		0	0
Supraventricular arrhythmias (10042600)	0	0.0		0	0.0		1	0.3
Atrial fibrillation (10003658)	0	0.0		0	0.0		1	0.3
Metabolism and nutrition disorders (10027433)	1	0.1		1	0.3		0	0
General nutritional disorders NEC (10018067)	1	0.1		1	0.3		0	0
Obesity (10029883)	1	0.1		1	0.3		0	0
Musculoskeletal and connective tissue disorders (10028395)	1	0.1		0	0.0		1	0.3
Crystal arthropathic disorders (10011505)	1	0.1		0	0.0		0	0
Gouty arthritis (10018634)	1	0.1		0	0.0		0	0
Osteoarthropathies (10057178)	0	0.0		0	0.0		1	0.3
Osteoarthritis (10031161)	0	0.0		0	0.0		1	0.3
Nervous system disorders (10029205)	2	0.3		0	0.0		0	0
Central nervous system haemorrhages and cerebrovascular accidents (10007948)	2	0.3		0	0.0		0	0
Cerebellar stroke (10079062)	1	0.1		0	0.0		0	0
Cerebrovascular accident (10008190)	1	0.1		0	0.0		0	0
Psychiatric disorders (10037175)	1	0.1		1	0.3		0	0
Depressive disorders (10012401)	1	0.1		1	0.3		0	0
Depression (10012378)	1	0.1		1	0.3		0	0
Blood and lymphatic system disorders (10005329)	0	0.0		0	0.0		1	0.3
Anaemias haemolytic immune (10002052)	0	0.0		0	0.0		1	0.3
Cold type haemolytic anaemia (10009868)	0	0.0		0	0.0		1	0.3
Gastrointestinal disorders (10017947)	0	0.0		0	0.0		1	0.3
Inguinal hernias (10022017)	0	0.0		0	0.0		1	0.3
Inguinal hernia (10022016)	0	0.0		0	0.0		1	0.3
Hepatobiliary disorders (10019805)	1	0.1		0	0.0		0	0
Hepatocellular damage and hepatitis NEC (10019833)	1	0.1		0	0.0		0	0
Non-alcoholic fatty liver (10029530)	1	0.1		0	0.0		0	0

Data Source: Table 14.3.1.38 Adults-RSV = Healthy adult participants or Adults AIR (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults- Placebo = Healthy adult participants or Adults AIR (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); N = number of participants; n/% = number/percentage of participants presenting at least one type of adverse event

The frequency of serious unsolicited adverse events did not appear to be different between placebo and intervention groups (either pooled or unpooled).

The single SAE considered to be related to the study intervention occurred in the OA-RSV group (cold-type haemolytic anaemia). Unlike the investigator, the MAH considered that there was no reasonable

possibility that the cold agglutinin disease and autoimmune haemolytic anaemia may have been caused by the vaccine.

This case occurred 52 days after vaccination in RSV OA group. . Diagnostic work-up did not reveal an alternative reason for the haemolytic anaemia. The MAH stated that participant had a history of laboratory findings suggestive of haemolytic anaemia (raised serum bilirubin, anaemia and raised lactate dehydrogenase) prior to receiving the study intervention, and that the presence of haemolytic anaemia prior study intervention cannot be ruled out. In the narratives, only the laboratory findings post-vaccination are provided. Upon request the MAH provided laboratory values prior to vaccination, as well as a full, updated narrative. Patient had a pre-existing anaemia (since 2016) and hyperbiliribinemia (since 2018). A few months prior to the administration of the Arexvy vaccine, the patient developed (in addition to the chronic laboratory findings) a LDH of approximately 2x ULN. These findings were enough for the MAH to suggest that the cold-type haemolytic anemia was pre-existent.

A rise in LDH could have signaled the start of the AIHA, however as no erythrocyte morphology or Coombs test was performed at the time, and many (temporary) health issues may lead to cell damage and therefore a rise in LDH, this cannot be definitively diagnosed in retrospect. Primary cold-type auto-immune haemolytic anaemia (AIHA) is possible (without an obvious cause), and secondary cold-type AIHA can be related to an underlying infection or malignancy. There was no alternative reason for the AIHA, however, the patient did develop an immune-response from the vaccine. The MAH agrees to specifically describe all available information, including information such as diagnostic tests results, from reports of auto-immune hemolytic anaemia in future PSURs. This event is being closely monitored using all available sources.

A review of the SAE narratives did not reveal any other events considered by the assessor to be possibly related.

*AESI*s

Atrial fibrillation

There were 2 (1 non-serious and 1 serious) events of AF, each reported in 1 participant in the OA-RSV group, up to the safety DLP.

The non-serious event occurred at 12 days after study intervention administration during an episode of pneumonia for which the participant was hospitalized. The participant had a relevant medical history of arrhythmia and hypertension, and concurrent unsolicited AEs of heart failure NYHA II and acute renal failure. This event was assessed as moderate in intensity. The other report of AF was reported as a serious event and occurred at 49 days post-vaccination for a participant hospitalized due to a stroke. The participant had a relevant medical history of hypertension and hypercholesterolemia.

Both cases of AF were assessed as unrelated to vaccination by the investigator. The MAH believes these events more plausibly reflect the epidemiology of AF in the older adult population and the expected disease course of AF rather than a vaccine effect.

pIMDs

Within 6 months following vaccination, pIMDs were reported in 4 (0.5%) participants in the Adults-RSV group, 1 (0.3%) participant in Adults-Placebo group and 3 (0.8%) participants in the OA-RSV group (Table 22). Up to DLP for the safety analysis (01 September 2023), 1 (0.3%) participant in the OA-RSV group reported a pIMD considered by the investigator to be related to study intervention. This was cold type haemolytic anaemia, which is detailed in the previous section (SAE's).

Table 22 Summary of participants with at least one pIMD with onset within 6 months of vaccination – Exposed Set, Modified by assessor

	Adults-RSV N=769		Adults-Placebo N=383		OA-RSV N=381	
Primary System Organ Class (CODE) High Level Term (CODE) Preferred Term (CODE)	n	%	n	%	n	%
Any pIMD	4	0.5	1	0.3	3	0.8
Musculoskeletal and connective tissue disorders (10028395)	2	0.3	0	0.0	1	0.3
Connective tissue disorders NEC (10074472)	0	0.0	0	0.0	1	0.3
Polymyalgia rheumatica (10036099)	0	0.0	0	0.0	1	0.3
Crystal arthropathic disorders (10011505)	1	0.1	0	0.0	0	0.0
Gouty arthritis (10018634)	1	0.1	0	0.0	0	0.0
Spondyloarthropathies (10052775)	1	0.1	0	0.0	0	0.0
Spondylitis (10061371)	1	0.1	0	0.0	0	0.0
Cardiac disorders (10007541)	1	0.1	1	0.3	0	0.0
Noninfectious pericarditis (10034494)	1	0.1	1	0.3	0	0.0
Pericarditis (10034484)	1	0.1	1	0.3	0	0.0
Blood and lymphatic system disorders (10005329)	0	0	0	0	1	0.3
Anaemias haemolytic immune (10002052)	0	0	0	0	1	0.3
Cold type haemolytic anaemia (10009868)	0	0	0	0	1	0.3
Metabolism and nutrition disorders (10027433)	1	0.1	0	0	0	0
Disorders of purine metabolism (10070968)	1	0.1	0	0	0	0
Gout (10018627)	1	0.1	0	0	0	0
Skin and subcutaneous tissue disorders (10040785)	0	0	0	0	1	0.3
Psoriatic conditions (10065874)	0	0	0	0	1	0.3
Psoriasis (10037153)	0	0	0	0	1	0.3

Data Source: Table 14.3.1.41 Adults-RSV = Healthy adult participants or Adults AIR (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults- Placebo = Healthy adult participants or Adults AIR (50-59 YOA) receiving a single dose of placebo vaccine at Visit 1 (Day 1); OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); 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; pIMD = potential immune mediated disease

Regarding pIMDs

Within 6 months following vaccination, pIMDs were reported in 4 (0.5%) participants in the Adults-RSV group, 1 (0.3%) participant in Adults-Placebo group and 3 (0.8%) participants in the OA-RSV group. No pIMDs were reported in the Healthy-Adults group.

The pIMDs reported were pericarditis (1 participant each in Adults-AIR-RSV group and Adults-AIR-Placebo group), spondylitis (1 participant in the Adults-AIR-RSV group), polymyalgia rheumatica (1 participant in the OA-RSV group), gouty arthritis (1 participant in Adults-AIR-RSV group), cold type haemolytic anaemia (1 participant in OA-RSV group), gout (1 participant in Adults-AIR-RSV group) and worsening of psoriasis (1 participant in OA-RSV group)). Although slightly more pIMDs were reported in groups receiving Arexvy, these represent single cases and do not provide a clear safety signal.

Regarding atrial fibrillation

The first event of non-serious AF was reported to have occurred 12 days after the study intervention administration in a participant aged 67 years. The event was reported to have occurred during an episode of pneumonia for which the participant was hospitalised. The participant had a relevant medical history of arrhythmia and hypertension, and concurrent unsolicited AEs of heart failure NYHA II and acute renal failure. During an initial clinical presentation, the difference between atrial fibrillation with acute heart-failure, and pneumonia resulting in atrial fibrillation is not always clear-cut. Due to the relatively short 12-day interval between vaccination and the adverse event the MAH was requested to the clinical findings based on which the diagnosis “pneumonia” was based. These findings were a chest CT scan that showed,

in the right lung some nodular consolidation zones and areas of frosted glass merging with each other, creating larger peribronchial consolidation zones and spreading in the ventral region, suggesting extensive inflammatory changes in the right lung. Pleural effusion dorsally, up to 1.4 cm wide, was noted. There were no inflammatory changes in the left lung. Several lymph nodes around the head, up to 1.5 cm in diameter most likely reactive, were observed. As such, it is reasonable to assume the atrial fibrillation was induced by the infectious pathology.

Pregnancies

In the study, zero (0%) pregnancies were reported.

Deaths

Up to the safety DLP, no SAEs with fatal outcome were reported in any of the study groups

Laboratory findings

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

Discontinuation due to adverse events

There were no (S)AEs leading to study or treatment discontinuation.

Post marketing experience

Since first approval 3 May 2023 until 31 October 2023 (approximately 6 months), it is estimated that 6 246 500 doses have been distributed globally.

As of 31 October 2023, the MAH received 401 case reports of suspected adverse reactions in association with Arexvy, describing 1005 events:

- 54 events were serious (5.4%),
- 951 were non-serious (94.6%).

Most reports originate from the US and describe mostly expected events already listed in the PI and non-serious non-specific events. In terms of serious events, no significant pattern and event clusters can be observed. Overall, the reported events are consistent with the known safety profile of the product.

The review of the cumulative spontaneous post-marketing data did not identify any signals and did not result in any additional label changes or other safety actions for this product.

More details on these reports and the post-marketing safety experience will be reported and assessed in the first Periodic Benefit-Risk Evaluation Report (PBRER) with DLP of 02 November 2023 (target sign-off date January 2024).

2.5.1. Discussion on clinical safety

The safety data presented for this extension of indication is derived from study ADJ-018, a phase 3, observer-blind, randomised, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including both healthy adults and adults at increased risk of RSV LRTD, compared to older adults (≥ 60 years of age). The data adds to the known safety profile of Arexvy.

The reactogenicity in the 50–59-year-old groups was comparable to the known safety profile. The majority of participants receiving Arexvy experienced a solicited event within the first 4 days. These events were generally mild to moderate in intensity, transient, and self-limiting. The frequency was higher in younger Adults-RSV group (82%) compared to the OA-RSV group (70.1%). This is expected and the reactogenicity profile in adults aged 50-59 years remained within acceptable range. The MAH provides the frequency reactogenicity events for study participants 60 years and older in the text of section 4.8 of the SmPC and states that there was a “higher incidence” for the 50–59-year-old population. Upon request, the MAH provided the specific frequencies for the 50–59-year-olds in the text.

At PT-level, adverse events related to the intervention showed a slightly higher frequency for the intervention group than in the placebo group (such as lymphadenopathy). These related AEs were either already included in Table 1 of the SmPC as an adverse effect or were single cases and therefore not considered a strong signal for inclusion. Hence, no new safety concerns emerged. However, the frequency of the adverse reactions listed in Table 1 were recalculated using the pooled data of both the RSV OA=ADJ-006 and -018 studies populations. Therefore, the adverse reaction ‘injection site erythema’ was changed from common to very common. The frequency of AEs possibly linked to hypersensitivity and anaphylactic reactions (up until 6 months post-vaccination) remains consistent with the current frequency for these reactions (categorised as uncommon) in Section 4.8 of the SmPC. There were no deaths, pregnancies, or discontinuations due to serious or non-serious adverse events.

Atrial fibrillation (AF) and potential immune mediated disorders (pIMDs) were collected as adverse events of special interest (AESIs). Within 6 months following vaccination, pIMDs were reported in 4 (0.5%) participants in the Adults-RSV group, 1 (0.3%) participant in Adults-Placebo group and 3 (0.8%) participants in the OA-RSV group. None of the pIMDs were considered related to the vaccine by the investigator, except 1 case of cold-type haemolytic anaemia. The MAH provided data to support their claim that the AIHA was pre-existent, however there is insufficient evidence to definitively support this claim. The MAH has agreed to specifically describe all available information, including information such as diagnostic tests results, from reports of auto-immune hemolytic anaemia in future PSURs. This event is being closely monitored using all available sources.

Additionally, two cases of AF were reported in the study. Upon review of these two cases, none are considered to be related to the vaccine.

No subgroup analyses were performed for the safety endpoints. This is acceptable, as the number of events would be too limited to gain meaningful insight. Notably, during the MAA it was observed that gender did not influence the safety profile in older adults >60 years of age; therefore it is unlikely to be of major influence in the currently evaluated age group.

In general, unpooled data (Adults-HA-RSV, Adults-HA-Placebo, Adults-AIR-RSV, Adults-AIR-Placebo, OA-RSV) did not reveal any differences from the pooled data (Adults-RSV, Adults-Placebo, OA-RSV), aside from the fact that no pIMDs occurred in the Adults-HA-RSV and Adults-HA-Placebo groups. However, provided the low overall rate of pIMDs, and the fact that this population was either younger, or healthier than the other groups, this is not unexpected.

2.5.2. Conclusions on clinical safety

Overall, the safety profile in the population 50-59 year old was similar to the safety profile in the older adults (>60 years) and no new safety signals 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 1.1 with this application.

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

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

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

Pharmacovigilance plan

No routine pharmacovigilance (PhV) activities beyond adverse reaction reporting and signal detection are required. No additional PhV activities are proposed.

Risk minimisation measures

No risk minimisation measures beyond routine are required. No additional risk minimisation measures are proposed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1,4.6, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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:

The amendments for the proposed Patient leaflet as a result of the inclusion of an extension of the indication to adults 50-59 Years of Age are minimal. No change to the layout is proposed and only a minimal change to the content. The proposed changes are in section 1 and section 4 to add the data for the additional age group and section 5 and update to the current QRD.

It is agreed with the MAH that it is not necessary to perform an additional user consultation.

2.7.2. Labelling and package leaflet exemptions

None requested.

2.7.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Arexvy (Respiratory syncytial virus, glycoprotein F, recombinant, stabilised in the pre-fusion conformation, adjuvanted with $AS01_E$) is included in the additional monitoring list as it contains a new active substance, which on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed therapeutic indication 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.

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 and re-infection 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 or older adults), re-infections can also lead to more severe diseases. In adults, the highest burden of disease is in older people and those with comorbidities such as lung or heart disease and diabetes.

The 50–59-year-old population relevant for this extension of indication has more limited epidemiological data available those ≥60 years of age and are less likely to be tested for RSV leading to an underestimation of the disease burden. The available epidemiological points to increasing incidences of RSV morbidity and mortality with increasing age, and that most hospitalisations in the ≤60 year old adult population occur in patients with pre-existing comorbidities such (e.g. obesity, diabetes, or chronic cardiopulmonary, renal, or immunocompromising conditions). In literature, RSV-related disease leads to hospitalisation rates between 45-82 / 100 000 people years in 50–64-year-olds (Widmer, J Infect Dis, 2012; McLaughlin, Open Forum Infect Dis, 2022), and 178/100 000 for ≥65 year olds. In the ≤65 year old population individuals with the aforementioned comorbidities have rates of RSV-associated illness that are 1.2–28 times higher than those without underlying conditions.

3.1.2. Available therapies and unmet medical need

Treatment

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. 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

The RSV vaccines Arexvy and Abrysvo are currently approved in the EU for the active immunization of individuals 60 years and older. Abrysvo is also indicated for the passive immunization of infants through immunization of the mother during pregnancy.

Unmet medical need

RSV is the third most frequent cause of medically significant respiratory tract disease in adults (after influenza and rhinovirus, prior to the COVID-19 pandemic). [Juhn, 2023; Zhou, 2020]

There is no licensed vaccine for the prevention of RSV-associated diseases in adults 50-59 years of age, overall or for those with comorbidities that increase the risk of severe RSV infections.

3.1.3. Main clinical studies

The main evidence for this extension of indication is derived from ADJ-018, a phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including both healthy adults (Adults HA-RSV) and adults at increased risk of RSV LRTD (Adults AIR-RSV), compared to older adults (≥ 60 years of age). Efficacy was not determined in this extension of the indication. An immunobridging approach to compare the immune response in adults 50-59 YOA to that of adults ≥60 YOA, in whom VE was demonstrated, was used. This is in alignment with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

3.2. Favourable effects

The primary immunogenicity objectives were to demonstrate non inferiority of the humoral immune response (in terms of RSV-A and RSV-B neutralising titers) following the administration of Arexvy at 1-month post-vaccination in participants 50 through 59 years of age with and without pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease, compared to participants 60 years of age and older, in whom VE was demonstrated at the initial application.

The four co-primary endpoints of the pivotal study of this application (ADJ-018) were met and showed non-inferiority of the immunogenic response of 50-59 years olds (Adults-AIR-RSV and Adults-HA-RSV) compared to ≥60-year-olds as measured by neutralizing antibody titers for both RSV-A and RSV-B subtypes. The robustness of the response was further supported by the seroresponse rate (Adults-HA RSV A 82.8%; Adults-HA-RSV-B 78.2%; Adults-AIR-RSV-A 86.9%; Adults-AIR-RSV-B 81.6%; OA-RSV-A 80.4%; OA-RSV-B 74.5%) and by sensitivity analyses conducted in the enrolled subset.

3.3. Uncertainties and limitations about favourable effects

There is no correlate of protection known for RSV disease. Therefore, the benefit of Arexvy in the 50–59-year-old population is based on immunobridging to the ≥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 addition, the current submission only

presents 1-month immunogenicity data; therefore, the durability of the immunogenicity response in adults aged 50-59 years of age could not be shown. Further follow-up is expected, as the study was ongoing at the time of submission. Immunogenicity data post-1 month would be necessary to determine if the antibody kinetics for 50-59 and ≥60-year-olds are similar. This would be valuable, as the need for revaccination is currently being studied in ≥60-year-olds and not in 50-59 year old. The company should submit the final study report via type II variation.

3.4. Unfavourable effects

The safety data presented for this extension of indication is derived from study ADJ-018, and includes a follow-up of at least 6 months.

- Since a similar safety profile was observed for the population 50-59 year old with or without pre-defined, stable, chronic medical conditions leading to an increased risk for RSV disease, the results of those groups (HA and AIR) were pooled. A higher reactogenicity is seen in the younger Adults-RSV population (50-59 years old), however this is expected and within acceptable range. The most frequently reported solicited administration site events were pain, erythema, and swelling, and the most frequently reported systemic events were fatigue, myalgia, arthralgia and headache. Considering that certain adverse event frequencies are higher in the 50-59 year old population, the company was requested to revise the AE frequencies in section 4.8 of the SmPC based on a pooled population consisting of both the ADJ-018 population and the population which has been used to generate the table in the initial application (ADJ-006). As a consequence, the frequency of the adverse reaction 'injection site erythema' was amended from common to very common.
- Unsolicited AEs: Unsolicited AEs considered by the investigator to be related to study interventions were reported in 26 (3.4%) participants in the Adults-RSV group, 8 (2.1%) participants in the Adults-Placebo group and 12 (3.1%) participants in the OA-RSV group. Based on the provided information, the type of adverse events reported do not provide new safety signals.
- AESIs: Although slightly more pIMDs were reported in groups receiving Arexvy (0.5% Adults-RSV; 0.3% Adults-Placebo; 0.8% OA-RSV) these represent single cases of a certain pIMDs and do not provide a clear safety signal. Two cases of atrial fibrillation were reported, both in the OA-RSV groups, both considered by the investigator to be unrelated to the vaccine.
- SAEs: no numerical imbalance in the incidence of SAE was observed between study groups and age categories. No SAEs with fatal outcome were reported in the study. A single SAE considered to be related to the study intervention occurred in the OA-RSV group (cold-type haemolytic anaemia). The MAH provided data to support their claim that the AIHA was pre-existent, however there is insufficient evidence to definitively support this claim. The MAH has agreed to specifically describe all available information, including information such as diagnostic tests results, from reports of auto-immune hemolytic anaemia in future PSURs. This event is being closely monitored using all available sources. The MAH will follow up and discuss in PSURs future cases of auto-immune haemolytic anaemia (AIHA) from all available sources, including information such as diagnostic test results.
- There were no discontinuations due to serious or non-serious adverse events.

Overall, the safety profile of Arexvy in the population 50-59 year old (including HA and AIR) was similar to the safety profile in the older adults (>60 years) and no new safety concerns or have been identified.

3.5. Uncertainties and limitations about unfavourable effects

-

A single SAE considered to be related to the study intervention as per investigator assessment occurred in the OA-RSV group (cold-type haemolytic anaemia in a patient with pre-existing anaemia and hyperbilirribemia). The MAH considers the event not related to vaccination and pre-existent, since a few months prior to vaccination, the patient developed a LDH of approximately 2x ULN. It is acknowledged that the rise in LDH could have indicated the start of the AIHA, however, no erythrocyte morphology or Coombs tests were performed at that time. Many other temporary health issues may lead to cell damage and therefore a rise in LDH, and this cannot be excluded in retrospect. It is considered that Primary cold-type auto-immune haemolytic anaemia (AIHA) is possible (without an obvious cause), and secondary cold-type AIHA can be related to an underlying infection or malignancy. There was no alternative reason for the AIHA, however, the patient did develop an immune-response from the vaccine and therefore the causality cannot be excluded. The MAH will follow up and discuss in PSURs future cases of auto-immune haemolytic anaemia (AIHA) from all available sources, including information such as diagnostic test results, which is acceptable.

3.6. Effects Table

Table 23 Effects (immunogenicity) Table for Arexvy extension of indication to 50-59 year olds data cut-off: 05 September 2023 (day 31) for immunogenicity and 01 September 2023 (6 month) for safety

Effect	Short description	Unit	Adults-HA	Adults-AIR	OA-RSV	Uncertainties / Strength of evidence
Favourable Effects						
GMT-ratio (CI)	GMT ratio OA-RSV / Adults group for RSV-A at day 31 post-vaccination	ED60	0.95† (0.83 1.09)	0.83 † (0.73-0.95)	-	Met pre-defined criteria for non-inferiority
	GMT ratio OA-RSV / Adults group for RSV-B at day 31 post-vaccination	ED60	0.89‡ (0.77-1.03)	0.80 † (0.71-0.91)	-	
Unfavourable Effects						
Reacto-genicity	Solicited administration site effects[a]	% of individuals	75.4%		62.5%	Transient effect, majority mild to moderate in severity.
	Solicited systemic effects[b]	% of individuals	57.1%		42.5%	

Adults-HA-RSV = Healthy adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); Adults-AIR-RSV = At increased risk adult participants (50-59 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1; OA-RSV = Older adult participants (>=60 YOA) receiving a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1); GMT = Geometric mean titer; CI = confidence interval; †95% CI used for establishing non-inferiority; ‡97.5% CI used for establishing non-inferiority Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

RSV constitutes an important disease burden in the elderly population, leading to approximately 250,000 hospitalisations and 17,000 deaths per year in the EU. The burden of RSV in the 50- 59 years of age adult population is most likely underestimated due to a number of factors including undertesting, delayed testing, lower viral load in adults, and the presence of underlying conditions. However, average annual

RSV-related hospitalisation rates of 45-82 / 100 000 PY have been reported in adults ≤65 years. Those with chronic medical conditions (e.g., obesity, diabetes, or chronic cardiopulmonary, renal, or immunocompromising conditions) have rates of RSV-associated illness that are 1.2–28 times higher than those without. No prophylactic vaccine is licensed for the 50-59 age group and no treatment, other than supportive care, exists for adults younger than 60 years of age.

Overall, the immune response 1 month post-vaccination with Arexvy for 50-59 year olds is non-inferior to the response seen in ≥60 year old population for whom vaccine efficacy has previously been demonstrated. These results apply to both healthy 50–59-year-olds, and those with comorbidities leading to an increased risk of RSV-related LRTD. An acceptable safety profile was observed in all age groups.

The results are considered robust. All four co-primary endpoints showed non-inferiority, both using GMT-ratios and seroresponse rates. No differing insights were provided from either a sensitivity analysis performed due to a ≥10% attrition rate, or the reverse cumulative distribution curves.

Further follow-up is expected, as the study was ongoing at the time of the submission. Immunogenicity data post-1 month would be necessary to determine if the antibody kinetics for 50-59 and ≥60-year-olds are similar. This would be valuable, as the need for revaccination is currently being studied in ≥60-year-olds and not in 50-59 year olds. The company should submit the final study report via type II variation.

The safety population is sufficient for an adequate assessment of the safety profile of Arexvy in 50–59-year-olds. The observed safety profile is mainly characterised by reactogenicity. The most frequently reported AEs were injection-site pain, followed by fatigue, myalgia, headache and arthralgia. Reactogenicity reactions occurred with a higher frequency in 50–59-year-olds, but were still mostly mild to moderate, transient and self-limiting. Based on a pooled analysis consisting of both studies ADJ-018 and the pivotal study for the initial application ADJ-006, the frequency of the adverse reaction 'injection site erythema' was amended from common to very common.

There were no related SAEs or pIMDs considered to be related by the MAH. A single pIMD (auto-immune haemolytic anaemia) has been flagged for active follow-up in the PSUR.

The burden of disease due to RSV in adults ≥60 YOA has been well recognized, and the two currently approved vaccines target this population. In adults 50-59 YOA, RSV infection is also linked to high morbidity causing a significant number of hospitalizations. It has also been described that the presence of underlying comorbidities increases the risk of RSV associated hospitalization. Based on the non-inferiority of the immunogenic response for RSV-A and RSV-B of 50-59 years olds (Adults-AIR-RSV and Adults-HA-RSV) compared to ≥60-year-old in whom efficacy was demonstrated in the initial application, it can be estimated that the vaccine will provide favourable benefit in the younger age group. The immunobinding approach is in alignment with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1.).

3.6.2. Balance of benefits and risks

The 50–59-year-old population relevant for this extension of indication has more limited epidemiological data available those ≥60 years of age and are less likely to be tested for RSV leading to an underestimation of the disease burden. Nevertheless, the available epidemiological data shows increasing incidences of RSV morbidity and mortality with increasing age, and that most hospitalisations in the ≤60-year-old adult population occur in patients with pre-existing comorbidities such (e.g. obesity, diabetes, or chronic cardiopulmonary, renal, or immunocompromising conditions).

In this application, the available data for Arexvy indicate that a robust immune response is produced by the vaccine in both healthy adults and adults at increased risk of RSV-related LRTD. This response is non-inferior to the response in the population of ≥60 year olds from whom efficacy was previously demonstrated. Therefore as per the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1.) efficacy can be inferred for adults aged 50-59 years of age.

Overall, the safety profile of Arexvy in the population 50-59 year old (including HA and AIR) was similar to the safety profile in the older adults (>60 years) and no new safety concerns have been identified for extension of indication. The overall benefit risk of Arexvy in the applied indication is positive.

3.6.3. Additional considerations on the benefit-risk balance

None

3.7. Conclusions

The overall benefit risk 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 change:

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

Extension of indication to include treatment of adults 50-59 years of age who are at increased risk for RSV disease for AREXVY, based on results from study 219238 (RSV OA=ADJ-018); this is a phase 3, observer-blind, placebo-controlled, randomized, multi-country, multi-center, non-inferiority study with 2 cohorts to evaluate immunogenicity, reactogenicity and safety of a single dose of RSVPreF3 OA in adults 50-59 years of age. As a consequence, sections 4.1, 4.6, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 2.0 of the RMP is acceptable. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI, to bring it in line with the latest QRD template version 10.3, and to update the list of local representatives in the Package Leaflet. As part of the application, the MAH requested a 1-year extension of the market protection.

Amendments to the marketing authorisation

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see Appendix 1).