EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2023
EMA/227054/2023
Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report

Arexvy

Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation (RSVPreF3) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

Procedure No. EMEA/H/C/006054/0000

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# Administrative information

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| Name of the medicinal product: | Arexvy |
| Applicant: | GlaxoSmithkline Biologicals S.A.<br>Rue de l'Institut 89<br>1330 Rixensart<br>BELGIUM |
| Active substance: | Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation (RSVPreF3) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology |
| Common Name: | Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted) |
| Pharmaco-therapeutic group (ATC Code): | Not yet assigned |
| Therapeutic indication(s): | 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.<br><br>The use of this vaccine should be in accordance with official recommendations. |
| Pharmaceutical form(s): | Powder and suspension for suspension for injection |
| Strength(s): | 120 µg / 0.5 ml |
| Route(s) of administration: | Intramuscular use |
| Packaging: | powder: vial (glass); suspension: vial (glass) |

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| Package size(s): | 1 powder vial + 1 suspension vial and 10 powder vials + 10 suspension vials |

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# List of abbreviations

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse event |
| AESI | Adverse Events of Special Interest |
| ANCOVA | Analysis of Covariance |
| ARI | Acute Respiratory Infection |
| $AS01_B$ | Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21) |
| $AS01_E$ | Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21) |
| CAP | Community-Acquired Pneumonia |
| CBER | Center for Biologics Evaluation and Research, US |
| CCI | Charlson Comorbidity Index |
| CD | Community Dwelling |
| CD4 | Cluster of differentiation marker 4 |
| CD8 | Cluster of differentiation marker 8 |
| CD40L | Cluster of differentiation marker 40 ligand |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| CMI | Cell-Mediated Immunity |
| COPD | Chronic Obstructive Pulmonary Disease |
| CSR | Clinical Study Report |
| DLP | Data lock point |
| ED60 | Estimated Dose: serum dilution giving a 60% reduction of the signal compared to a control without serum |
| ELISA | Enzyme-linked immunosorbent assay |
| ELU/mL | ELISA unit per mL also referred to in other documents as EU/mL |
| EMA | European Medicines Agency, EU |
| ES | Exposed Set |
| EU | European Union |
| EPC | End of Production Cells |
| F | Fusion |
| FDA | Food and Drug Administration, US |
| FLU-QIV | Influenza Quadrivalent Inactivated Vaccine |
| GCP | Good Clinical Practice |
| GM | Geometric Mean |
| GMC | Geometric Mean Concentration |
| GMT | Geometric Mean Titre |
| GSK | GlaxoSmithKline Biologicals SA |
| HI | Hemagglutination Inhibition |
| hMPV | Human Metapneumovirus |
| ICS | Intracellular Cytokine Staining |
| IDMC | Independent Data Monitoring Committee |
| IFN-γ | Interferon gamma |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| LL | Lower Limit |
| LRTD | Lower Respiratory Tract Disease |
| LRTI | Lower Respiratory Tract Infection |

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| LTCF | Long-Term Care Facility |
| MCB | Master Cell Bank |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mES | modified Exposed Set |
| NAb | Neutralising Antibody |
| NH | Northern Hemisphere |
| OA | Older Adult |
| PCR | Polymerase Chain Reaction |
| pIMD | Potential Immune-Mediated Disease |
| PIP | Paediatric Investigation Plan |
| PPSi | Per-Protocol Set for immunogenicity |
| PTB | Preterm Birth |
| PPQ | Process Performance Qualification |
| qRT-PCR | Quantitative Reverse Transcription Polymerase Chain Reaction |
| RR | Relative Risk |
| RSV | Respiratory Syncytial Virus |
| RSVPreF3 OA | RSV PreFusion protein 3 Older Adult |
| RTI | Respiratory tract infection |
| RT-PCR | Reverse Transcription Polymerase Chain Reaction |
| SA | Scientific Advice |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SH | Southern Hemisphere |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| SSS | Solicited Safety Set |
| TNF-α | Tumour Necrosis Factor alpha |
| UL | Upper Limit |
| VE | Vaccine Efficacy |
| QC | Quality Control |
| YOA | Years Of Age |
| WCB | Working Cell Bank |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant GlaxoSmithkline Biologicals S.A. submitted on 29 September 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Arexvy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

"Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older.

Consideration should be given to official vaccine recommendations on the appropriate use. "

## *1.2. Legal basis, dossier content*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

## *1.3. Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0456/2021 on the agreement of a paediatric investigation plan (PIP) EMEA-002904-PIP01-20, including the granting of a waiver for infants and toddlers from birth to less than 2 years of age in accordance with Article 13 on the grounds that the product is likely to be unsafe in this paediatric population.

At the time of submission of the application, the PIP P/0456/2021 was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

### 1.4.2. Derogations from market exclusivity

Not applicable.

## *1.5. Applicant's request for consideration*

### 1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

### 1.5.2. Additional Data exclusivity / Marketing protection

Not applicable

### 1.5.3. New active Substance status

The applicant requested the active substance recombinant respiratory syncytial virus pre-fusion F protein, adjuvanted with $AS01_E$ contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## *1.6. PRIME*

Not applicable

## *1.7. Scientific advice*

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 20 September 2018 | EMEA/H/SA/3912/1/2018/III | *Mair Powell, Filip Josephson* |
| 12 December 2019 | EMEA/H/SA/3912/2/2019/III | *Walter Janssens, Mair Powell* |
| 15 October 2020 | EMEA/H/SA/3912/2/FU/1/2020/II | *Ingrid Schellens, Mair Powell* |
| 29 January 2021 | EMA/SA/0000046207 | *Mair Powell, Johannes Hendrikus Ovelgönne* |
| 24 February 2022 | EMA/SA/0000076116 | *Anders Lignell, Mair Powell* |

The scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- Product related substances

- Preclinical safety package supporting initiation of the Ph I/II study and MAA
- Ph I/II study design (population, sample size, endpoints, statistical analysis, clinical assays)
- Clinical data package to support initiation of Ph III
- Ph III studies design (population, dose selection, active and passive surveillance of ARI, primary and secondary endpoints, case definitions, statistical analysis and success criteria, demonstration of lot-to-lot consistency, clinical assays for characterisation of immune response and related endpoints, safety/reactogenicity assessment and safety database)
- Impact of COVID-19 pandemic in the Ph III conduct and mitigation measures
- Inclusion and validation of PRO instruments
- Study design and proposed non-inferiority margins of the RSV studies to evaluate the concomitant administration of the RSVPreF3 OA vaccine with Flu vaccines
- Co-administration study with SARS-CoV-2 mRNA vaccine and resulting SmPC claims
- Adequacy of the overall data package to support the MAA and inclusion of data and analyses in SmPC

## *1.8. Steps taken for the assessment of the product*

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Daniela Philadelphy

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| The application was received by the EMA on | 29 September 2022 |
| Accelerated Assessment procedure was agreed-upon by CHMP on | 15 September 2022 |
| The procedure started on | 27 October 2022 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 22 December 2022 |
| The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | N/A |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 3 January 2023 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 9-12 January 2023 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 24 January 2023 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 27 February 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 17 March 2023 |

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| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 28 March 2023 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 31 March and 19 April 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 20 April 2023 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Arexvy on | 26 April 2023 |
| Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) | 28 March 2023 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Respiratory syncytial virus (RSV) is a ribonucleic acid (RNA) virus belonging to the Pneumovirus genus in the Paramyxoviridae family of which 2 antigenically distinct subtypes exist, RSV-A and RSV-B.

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 or older adults), re-infections can also lead to more severe disease, involving the lower respiratory tract. In older adults, immunosenescence and the presence of underlying medical conditions can lead to an increased risk of severe RSV disease, which may result in severe lower respiratory tract infections, cardiac complications, and exacerbations of underlying diseases (such as COPD, asthma, and chronic heart failure). RSV can lead to severe outcomes in these populations, such as pneumonia, hospitalisation, and death [Prasad, 2021].

### 2.1.2. Epidemiology

In temperate climates throughout the world, RSV predictably causes fall-winter epidemics. In (sub) tropical regions, viral activity is more endemic, and outbreaks are less temporally focused. The RSV-A and RSV-B subtypes co-circulate, and the predominance of one over the other varies by year and geographic location.

An international prospective cohort study among 3 European countries, as part of the RESCEU research consortium, followed participants ≥60 YOA for the 2017-2018 (N=513) and 2018-2019 (N=527) RSV seasons

[Korsten et al., Eur Respir J 2021;57:2002688]. RSV was confirmed in 4.2% of participants in the first season and 7.2% in the second season. Based on a prospective cohort study conducted from October 2007 to April 2010 in 12 European countries, a 5.9% prevalence of RSV among LRTI outpatients ≥60 YOA was found [Bruyndonckx et al., Int J of infect. Dis. 2020; 95:384-390].

A meta-analysis based on a systematic literature review was conducted in 2020 to determine the burden of disease of RSV in adults ≥60 YOA in industrialised countries. 24 studies were included in the meta-analysis, leading to an estimated RSV-ARI attack rate of 1.09% (95% CI: 0.40-2.93), with an RSV-ARI hospitalisation rate of 0.13 % (95% CI:0.8-2.2) and an in-hospital case fatality rate of 6.8% (95% CI: 6.4-7.21). When applying these estimates to the European population estimate of adults aged 60 and older (estimated 2019 population aged ≥ 60 years in geographic Europe (EU, EEA and other): 188,795,000)), 2 million cases of RSV-ARI are estimated each year, accounting for 250,000 hospitalisations and 17,000 in-hospital deaths [Savic et al. Influenza Other Respi viruses. 2022;1–10]. In Finland, a retrospective study found a hospitalisation attack rate of 58.3/100 000 for adults ≥65 YOA over 4 seasons, varying from 19.3 to 117.6 [Auvinen et al., Influenza Other Respi Viruses. 2022; 16:276-288].

In adults, the highest burden of disease is in older people and those with comorbidities such as lung or heart disease and diabetes. In these patient populations, RSV can exacerbate conditions like chronic obstructive pulmonary disease (COPD), asthma, chronic heart failure, and lead to severe outcomes such as pneumonia, hospitalisation, and death.

### 2.1.3. 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.

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

*Prevention*

There is no licensed vaccine for the prevention of RSV-associated diseases.

In children 2 preventative options are available: Synagis and Beyfortus. Synagis (palivizumab) is a humanised monoclonal antibody indicated for prophylaxis of RSV in children at high risk of RSV disease, including preterm infants. Beyfortus (nirsevimab) is a human monoclonal antibody indicated for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.

## 2.2. About the product

The candidate Respiratory Syncytial Virus (RSV) vaccine (Arexvy) consists of 120 µg of the RSVPreF3 recombinant antigen and the $AS01_E$ Adjuvant System and is administered as a single dose. 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 F protein has been selected because it is a major surface antigen of RSV that is well conserved among the two antigenically distinct RSV-A and RSV-B subgroups. The F protein is necessary for the virus entry/cell fusion process and is the main target of the neutralising antibody response to RSV.

Arexvy is designed to:

- Boost the serum-neutralising antibody (NAb) response to prevent RSV infection and enhance the inhibition of viral replication. The aim of this vaccinal approach is to trigger an increase in RSV NAbs significantly above the natural infection levels observed in older adults.
- Boost or *de novo* induction of a RSV-specific circulating T cell response to promote viral clearance and reduce disease severity (driven directly or indirectly by T cells).

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 RSV-A and RSV-B subtypes in adults 60 years of age and older.*

The recommended dosing regimen for Arexvy is a single dose of 0.5ml.

## 2.3. Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on fact that it may be able to fulfil the unmet medical need for licensed vaccines that have a protective effect against RSV in the elderly population. Currently, there are no treatment or prophylaxis options available against RSV, which causes a significant burden of disease in the elderly population.

Development programme

The clinical development programme for Arexvy to support licensure in adults ≥60 years of age consists 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 halted the development of a maternal vaccination program using the investigational RSV Maternal (RSVPreF3) vaccine due to imbalances in preterm birth (PTB), observed in one study. A higher proportion of neonatal deaths (death of an infant within the first 28 days of life) was also observed, which was considered to be a consequence of PTB. The vaccine formulation used in the RSV Maternal program contained 120 µg of RSVPreF3 antigen (the same as used in the RSVPreF3 OA vaccine), unadjuvanted.

Compliance with CHMP guidance

The most relevant CHMP guidelines applied:

- "Guideline on clinical evaluation of vaccines" (CPMP/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).

## *2.4. Quality aspects*

### 2.4.1. Introduction

The finished product is presented as a preservative-free powder and suspension for suspension for injection containing 120 µg of RSVPreF3 antigen (powder) adjuvanted with $AS01_E$ (suspension).

RSVPreF3 antigen consists of an engineered version of the RSV fusion (F) surface glycoprotein, stabilised in the pre-fusion trimeric conformation of the naturally occurring protein and is produced by recombinant DNA technology in Chinese Hamster Ovary Cells (CHO cells).

Other ingredients of the antigen powder component are Trehalose Dihydrate, Polysorbate 80, Potassium Dihydrogen phosphate and Dipotassium phosphate.

The $AS01_E$ adjuvant system is composed of the immuno-enhancers: plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella Minnesota*. These are combined with liposomes, which consist of the excipients dioleoyl phosphatidylcholine (DOPC) and cholesterol. Other ingredients of the adjuvant are Sodium chloride, Disodium phosphate, Potassium dihydrogen phosphate, and Water for injections.

The pharmaceutical form of the Finish Product before reconstitution, as mentioned in the SmPC, is powder and suspension for suspension for injection. The monodose product (powder and suspension) is supplied in separate type I glass vials with butyl rubber stoppers. The liquid $AS01_E$ is used to reconstitute the RSVPreF3 lyophilised antigen immediately prior to administration. One dose of reconstituted RSVPreF3 older adults vaccine (0.5 mL) contains 120 µg RSVPreF3 and 25 ug of each of the QS-21 and MPL immune enhancers.

### 2.4.2. Active substance

#### *2.4.2.1. General Information*

The fusion (F) protein is a major surface protein of RSV that is conserved among RSV groups A and B. This protein plays a critical role in RSV infectivity as it is involved in virus entry and cell-to-cell spread of the virus. Native RSV F is initially translated as a F0 protein precursor that is then cleaved at two closely spaced sites by a furin-like enzyme. This cleavage triggers the release of a small peptide (p27) while generating a fusion-competent F molecule made of the two disulfide-linked F1 and F2 chains (F2 N-terminal to F1).

The RSV F protein is present in the form of homotrimers in a metastable pre-fusion structure anchored in the virus membrane. Binding with the target cell triggers a series of conformational changes in the F protein including the formation of a pre-hairpin intermediate, in which the hydrophobic fusion peptide at the N-terminus of the F1 chain is inserted into the target membrane. Refolding of this intermediate results in the assembly of a highly stable post-fusion structure. RSV F also mediates the fusion of cell membranes of infected cells, leading to the formation of syncytia.

The RSVPreF3 antigen is an engineered version of the RSV fusion (F) surface glycoprotein, stabilised in the trimeric pre-fusion conformation of the naturally occurring F protein and eliminate triggering and

rearrangement into the post-F conformation. This is accomplished by the introduction of Cysteine residues leading to the formation of a disulfide bond; filling the cavities by hydrophobic substitutions, resulting in the pre-fusion molecule and a C terminal “foldon” domain.

The calculated average molecular weight of the RSVPreF3 protein based on the mature protein amino acid sequence (492 amino acids) is 54.5 kDa.

#### *2.4.2.2. Manufacture, process controls and characterisation*

Manufacture and quality control of RSVPreF3 antigen is performed by GSK Biologicals, at Wavre, Belgium. This site also stores the Working Cell banks and Master cell banks. The site holds a valid GMP certificate.

Production of the Respiratory Syncytial Virus (RSV) trimetric glycoprotein F (RSVPreF3 antigen) Purified Bulk can be divided into the following stages: Cell culture, Purification, Storage.

Production of recombinant RSV glycoprotein F antigen is based on the amplification of a Chinese Hamster Ovary (CHO) cell line transfected with a DNA plasmid bearing the sequence of modified RSV glycoprotein F.

CHO transfected cells are amplified through a series of cultures to finally reach the high biomass density required for the inoculation of the production bioreactor at the appropriate scale.

At the end of the culture step, the culture harvest is clarified by depth filtration. The clarified harvest is further processed by several purification steps, including different types of chromatography, viral inactivation, nanofiltration, ultrafiltration and filtration for bioburden control before freezing and storage.

There is no reprocessing during active substance manufacturing.

One single cell culture provides one single harvest (intermediate) on which one single clarification is performed. From this, one single batch of RSVPreF3 bulk antigen is obtained by purification.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, are described for each step.

The active substance manufacturing process is considered acceptable.

##### *Control of Materials*

The CHO cell line used was derived from a parental CHO cell line. Vials of the pre-Master Cell Bank (pre-MCB) were prepared in serum-free medium.

The RSVPreF3 protein is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells using a two-tiered Cell Bank System (i.e., Master Cell Bank and Working Cell Bank).

Two working cell banks (WCBs) were manufactured from the master cell bank (MCB) by the same supplier according to the same manufacturing process. End of production cells (EPC) has been generated from both WCBs.

The quality control and characterisation tests for MCB, WCBs and EPCs are presented. The tests include tests for adventitious agents, identity and purity and are considered in line with the relevant requirements of Ph. Eur. 5.2.3 on “Cell substrates for the production of vaccines for human use” and ICH Q5A (R1) and ICHQ5D. The methods used and results are presented. The specifications are sufficiently justified.

Characterisation of the MCB, WCBs and EPC is presented in detail. Based on the provided information the cell substrate can be considered as being stable from the MCB stage up to the EPC stage within the commercial process. Overall, the Scientific Advices provided by the EMA have been sufficiently taken into account.

The composition of solutions and materials was provided. No human or animal-derived raw materials are used for the production of the RSVPreF3 Master Cell Bank, Working Cell Banks and Active Substance. Materials of human or animal-derived origin used in early steps of cell bank preparation have been adequately evaluated from a TSE and viral safety perspective (See adventitious agents section). All raw materials used in the active substance manufacturing process are obtained with certificates of analysis from their respective suppliers and confirmatory identity and/or release testing are undertaken as necessary. In-house specifications for non-compendial raw materials have been included in Module 3. Information on significant consumables is provided as requested.

### Control of critical steps and intermediates

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical quality attributes (QA), process parameters (PP) and in-process tests. The number of Critical Process Parameters (CPPs) is limited. However, the assignment of a parameter as being critical or non-critical, as well as their ranges are sufficiently justified. Filter integrity testing is performed after nanofiltration and bioburden reduction filtration. Acceptance criteria are provided. In case of filter failure, a deviation is opened and impact on product quality is assessed.

The company performs Quality Control (QC) release tests on the single harvest intermediate isolated during the manufacturing process, on the active substance and on the finished product. A batch will be discarded if it fails to conform to its specifications.

The Single Harvest step marks the end of the cell culture before purification.

Satisfactory quality control (QC) release testing results have been provided for RSVPreF3 single harvests used to prepare process performance qualification (PPQ) batches. This includes testing for bioburden, mycoplasma and extraneous agents. The indicated holding times of the eluates or filtrates are justified.

### Process Validation

The submitted validation studies comprise three full scale PPQ batches (manufactured according to the commercial process) in the commercial facility. The RSVPreF3 active substance manufacturing process has been validated adequately.

The assessment of comparability between the reference batches used in clinical studies and PPQ batches manufactured in commercial facilities was performed in accordance with the International Conference of Harmonisation (ICH) Q5E guideline (CPMP/ICH/5721/03).

Active substance batches used for manufacturing of clinical batches were selected as reference batches to establish comparability with commercial material (see next paragraph). Subsequently so called non-GMP reproducibility batches or engineering batches have been manufactured to gain process knowledge and were used to confirm consistent process performance of the PPQ batches.

The actual values for the process parameters applied for the three PPQ batches are provided and are within the indicated ranges and/or the acceptance criteria. All attributes evaluated on PPQ batches were shown to be comparable to reference batches, with some exceptions. These have been justified as being due to process changes and having no impact on the product quality attributes as well as product comparability.

RSVPreF3 quantity and recovery are consistent. Overall, the analysis supports the conclusion that the commercial process is reproducible and sufficiently controlled and able to deliver a consistent product quality.

Manufacturing process development

The active substance manufacturing process has evolved during the clinical development of RSVPreF3 vaccine. The manufacturing process of RSVPreF3 active substance used for production of the PPQ and first commercial active substance batches is described in detail.

A brief summary of the RSVPreF3 active substance manufacturing process development throughout the clinical development phases is provided.

Detailed information on the four processes and the major changes during development are presented. The rationale for the changes is provided. The main changes introduced throughout development were scale-up, changes in antigen production to increase productivity, optimization for the chromatography steps, improve viral clearance robustness and transfer of the manufacturing to different facilities. Comparability has been established between the different RSVPreF3 DS batches used during clinical product development. Major changes between process Phase 3 (clinical) and commercial (PPQ) are discussed in sufficient detail and justified. Sufficient details on the changes applied on analytical methods and control strategy per critical quality attribute (CQA) are presented, respectively for Single Harvest and active substance.

Characterisation

The RSVPreF3 antigen is a recombinant fusion (F) surface glycoprotein, stabilised in the pre-fusion conformation of the naturally occurring F protein.

The physico-chemical and immunological properties of the active substance were assessed using different complementary analytical techniques. Overall, the characterization testing panel is considered suited for its purpose and results are comprehensively presented.

The tests performed on the RSVPreF3 active substance clinical Phase 3 batches and PPQ (and technical development batches manufactured according to the commercial process), briefly describe their objectives and results. Interim reference standard (IRS) batch was used as the reference material for the characterisation tests. For each method, the result is presented in pictures of gels, chromatograms (overlays), spectra or tables, where appropriate.

Analytical data on the secondary structure, tertiary structure, isoelectric focusing, primary sequence, post-translational modifications and glycosylation patterns showed no major differences between the batches manufactured according to Phase 3 and commercial processes and the interim reference standard.

*Product-related impurities*

Product related impurities (aggregates) and process related impurities (including host cell proteins and DNA) present in the AS have been investigated throughout manufacturing development including batches used in nonclinical and clinical studies.

### *2.4.2.3. Specification*

The specifications include appropriate tests for identity and potency by ELISA, physicochemical properties (pH, Description), antigen content and product-related substances by RP-UPLC, antigen purity and high molecular weight species by SEC-UPLC, endotoxin content by chromogenic kinetic method and HCP by ELISA. There are no separate end-of-shelf life specifications for the active substance.

The proposed specifications are sufficiently justified and reflect the results found for the active substance batches listed.

The active substance specification for in-vitro relative potency has been tightened in line with the tightened finished product specification. The specification for the Product-related substance has been recalculated and tightened as requested. The quality control panel for active substance has been extended with specification for aggregates.

Furthermore, an acceptance criterion on the bioburden before freezing in-process control has been assigned.

### Analytical methods

For compendial analytical procedures, the company has made reference to Ph. Eur. monographs (pH, endotoxin). All in-house analytical procedures for the QC release of commercially purified bulks have been validated according to the relevant ICH guideline Q2 (R1).

The same non-compendial analytical procedure is used for testing of identity and in vitro relative potency and for quantification of purity and product related impurities for both the active substance and finished product. Also, for RSVPreF3 content and product related substances, the test is essentially the same. An RSV process specific analytical method for HCP quantification has been developed and is adequately validated and suited for its purpose.

The method descriptions of the assay for RSVPreF3, purity, product related impurities and HCP have been clarified upon request. The validation of these methods is considered acceptable, and the methods are suited for testing active substance batches.

Unique method identifiers have been included in the dossier for all in-house methods.

### Batch analysis

Batch analysis data from PPQ batches of the active substance were provided, along with batch analysis data for batches manufactured for use in the clinical studies throughout the clinical development phases.

The results of all QC tests comply with the acceptance criteria in force at the time of testing and confirm consistency of the manufacturing processes.

### Reference materials

Reference standard (RS) used for the in vitro potency and purity release testing of commercial material is derived from a clinical Phase 3 drug substance batch.

Information as regards potential (re)qualification of future standards has been provided.

The generation of the RSFPreF3 process-specific HCP Reference Standard from a null cell line according to Phase 3 process has been described in sufficient detail and it has been demonstrated that it is a good representative of the commercial process and is suitable to be used as the reference standard for the determination of host cell proteins.

### Container Closure System

RSVPreF3 Purified Bulks are stored in sterile bottles (1000 mL) that are closed with caps. These containers are supplied clean, non-pyrogenic and sterile. The Container Closure System is shown to be suitable for long term storage of RSVPreF3 purified bulk. No risks were identified with the safety risk assessment of the container components.

#### *2.4.2.4. Stability*

A shelf-life of the active substance when stored at the intended storage conditions is proposed by the Applicant.

The stability studies conducted in line with ICH guidance include three PPQ batches. Stability-indicating release tests are included in the stability protocol. Stability of the PPQ batches available to date show that all tested parameters met the acceptance criteria, after storage at proposed storage conditions.

The long term stability data of three reproducibility batches and three PPQ batches manufactured according to the commercial process support the proposed shelf-life for commercial batches upon storage at proposed conditions. Supportive long term stability data are available for batches used in clinical development, including those from Phase 3 clinical studies. Supportive batches are considered sufficiently representative of commercial batches, however, storage conditions differ from those proposed for the commercial product but are still considered relevant.

During product development, the impact of certain physico-chemical stressors on structure and antigen stability were evaluated.

The stability results confirm that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container and storage conditions.

### 2.4.3. Finished medicinal product

#### *2.4.3.1. Description of the product and Pharmaceutical Development*

RSVPreF3/AS01$_E$ vaccine is a preservative-free suspension for intramuscular injection intended for active immunisation in the prevention of respiratory syncytial virus (RSV)-associated lower respiratory tract disease (LRTD) in adults aged 60 years and older.

The vaccine consists of two components:

- The lyophilised RSV recombinant fusion protein RSVPreF3 (trimeric RSV Fusion protein stabilised in a pre-fusion conformation). After reconstitution, 1 dose contains 120 micrograms of RSVPreF3 antigen. The RSVPreF3 antigen is provided as a mono-dose preparation.
- The liquid suspension consists of the AS01$_E$ Adjuvant System. AS01$_E$ is provided as a mono-dose preparation.

The liquid AS01$_E$ Adjuvant System is used to reconstitute the RSVPreF3 lyophilised antigen immediately prior to administration. The pharmaceutical form of the reconstituted vaccine is a liquid suspension for injection, appearing opalescent, colourless to pale brownish.

The final containers consist of a 3 mL glass vial (uncoloured glass, Type I) closed with a butyl rubber stopper and aluminium cap.

The full list of excipients is provided in section 2.2.1 above: trehalose dihydrate (cryo-protectant), polysorbate 80 (surfactant), potassium dihydrogen phosphate and dipotassium phosphate (buffering agents).

An overage is applied to compensate for loss during reconstitution, withdrawal and injection. A proper justification indicating the amount of loss due to reconstitution, withdrawal, and injection has been included

in section 3.2.P.2.2.2. The formulation development of the finished product has been described and mainly involved the adjustment of the trehalose concentration and the target pH of the final product.

The $AS01_E$ Adjuvant System is composed of two immune-enhancers, QS-21 (a triterpene glycoside purified from the bark of the tree Quillaja saponaria Molina) and MPL (3-Odesacyl-4'-monophosphoryl lipid A), using liposomes as a vehicle. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol, in a phosphate-buffered saline solution. DOPC is a semi-synthetic phospholipid and the key component of the liposomal bilayer membranes. Cholesterol serves to improve the rigidity of the structure and quenches the haemolytic activity of QS-21.

Pharmaceutical development

Three different formulations of RSVPreF3 (30 µg, 60 µg and 120 µg/dose), each reconstituted with either $AS01_B$ (50 µg MPL and QS-21 per dose), $AS01_E$ (25 µg MPL and QS-21 per dose) or unadjuvanted diluent (i.e. NaCl), were evaluated in a Phase 1/2 clinical trial (RSV older adults=ADJ-002) to define the optimal dosage of recombinant protein. The 120 µg dosage with $AS01_E$ was selected for further development and subsequent clinical studies based on an optimal immunogenicity profile and acceptable tolerability.

The finished product manufacturing process has evolved during the clinical development of RSVPreF3 vaccine. A brief summary of the RSVPreF3 finished product manufacturing process development throughout the development phases is provided.

The changes between the processes were mainly related to use of active substance from different active substance manufacturing processes (please refer to the active substance development section), changes in equipment, adaptation of the holding time of final bulk, change of manufacturing facility and scale, increase of fill volume, change of formulation (concentration of trehalose and antigen, target pH). The lyophilisation cycle has been optimised from Phase 3 to commercial process. The processes are sufficiently described and justified. A clear overview has been provided where it is shown which batch numbers were manufactured with which process, and, at which facility. Also, an overview has been provided where it is shown which batches were used in which clinical study. Information on analytical comparability of Final Container (FC) product manufactured according to Phase 3 and commercial processes, respectively, could be found in Section 3.2.P.3.5 (discussed below).

Critical Quality Attributes have been identified by a technical risk assessment. In line with Guideline ICH Q8 a QTPP (Quality Target Product Profile) has been presented. Critical Process Parameters (CPP) have been defined as PPs that can impact one or more CQAs. The assignment of CPPs for Formulation, Filling and Lyophilisation was mainly based on prior product and process knowledge, which is considered acceptable.

The suitability of the container closure system has been sufficiently justified. Extractables studies were performed, and no extractable compounds were present at levels that would be considered a safety risk. Results for the leachables study are available for up to 12 months and the study is ongoing for up to 60 months. The Applicant has committed to submitting the Leachable study results when available (REC 1).

Compatibility between the adjuvant and RSVPreF3 have been shown by interaction studies between RSVPreF3 antigen and the adjuvant and by control of several CQAs. Additional data have been submitted that support the storage of 4 hours at 2 – 8 °C. the claimed in-use stability of 4 hours at 2 – 8 °C or 25°C is considered acceptable.

*2.4.3.2. Manufacture of the product and process controls*

The manufacturing process of the RSVPreF3 finished product consists of 1) Formulation of the Final Bulk, 2) Filling and Lyophilisation, 3) Labelling and Packaging. Formulation, filling, primary packaging and lyophilisation takes place at GSK Biologicals, Wavre, Belgium (Wavre Nord). The EU batch release site is Glaxosmithkline Biologicals, Rixensart, Belgium. Both sites hold valid GMP certificates.

Flow diagrams for the Formulation and the Filling and Lyophilisation steps and a narrative description of the manufacturing process have been provided. An overview of Critical Process Parameters has been provided. It is indicated where in the process In Process testing is carried out and holding times are indicated. No reprocessing is proposed. There are no intermediates defined in the manufacturing process of RSVPreF3 finished product.

Upon request, several parameters have been added to the description of the manufacturing process. The description of the manufacturing process is sufficiently detailed. The filter material of each filter in contact with the finished product or components of the finished product and filter area of the final sterilising finished product filter have been provided.

The conditions used for sterilisation of the vials and the stoppers have been provided. The sterilization of the stoppers is in line with the reference conditions as stated in the Ph. Eur 5.1.1. For the sterilization of the vials this is not the case. Satisfactory validation data are therefore submitted for the validation of the sterilisation process of the vials. The control of CQAs by Quality Release, Process Monitoring, Characterisation or Quality Decision testing has been clearly justified. In Process testing is performed at four steps in the manufacturing process. Before sterile filtration, a test for bioburden is performed. The limit of the test (nmt 10 CFU/100mL is in line with the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015). For the sterile filtration step, only a post-use integrity test was carried out on the filter. The applicant has agreed, upon request, to implement pre-use filter integrity testing of the sterilising filter prior to release in the EU market. The principle of the test, details on when the tests are performed, solution(s) used in the test and acceptance criteria before and after filtration have been provided in section 3.2.P.3.4.

A brief description of the shipping process of RSVPreF3 finished product has been included in the dossier. This is acceptable.

For process validation purposes, an appropriate number of consecutive lots were produced. Three consecutive final bulk PPQ runs were successfully completed for formulation process and seven consecutive DP PPQ runs were successfully and consecutively executed for filling and lyophilization processes. A bracketing matrix approach was followed in order to validate the ranges for formulation and filling volumes, holding time and pooling of different active substance batches.

All the batches used in the Phase 3 older adults clinical study were used as reference batches in the comparability study. Overall, it has been demonstrated that the PPQ batches are comparable to these Phase 3 clinical batches, with some exception due to the change in holding time. However, difference was within the acceptance limits and therefore considered acceptable. Also, data demonstrating comparability with the earlier process versions are presented. It can be concluded that the manufacturing process is in a state of control and results are consistent and meet the specifications.

Hold time validation studies were performed with two small scale and one full-scale lot to support the storage of Final Bulk. The proposed maximum hold time for the Final Bulk is considered validated. The results from the PPQ also support this.

Aseptic filling is considered appropriately validated using media simulation. The filling operation is considered validated for a maximum duration. Final sterile filtration validation was performed by a bacterial challenge test, under worst-case conditions. In line with the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015), an acceptable minimum retention capacity has been shown. Also, other information relevant for filter validation is provided (type of filters, growth promoting/inhibiting properties of product matrix, potential sorption to the filter, compatibility with the solution, as well as extractables and leachables).

Control of Excipients

Specifications of the compendial excipients purchased from commercial suppliers are complying with the current editions of European and other pharmacopoeias, as applicable, which covers the justification of the specifications.

### *2.4.3.3. Product specification*

The specifications cover Description, pH, osmolality, Identity and potency (by ELISA), content of RSVPreF3 (RP-UPLC), endotoxins (chromogenic kinetic method), water content (Karl Fischer), RSVPreF3 timer and High molecular weight species (SEC-UPLC) Polysorbate 80 (HPLC) and Trehalose (H-NM).

The appearance testing includes testing for clarity and colour by an in-house method, using Ph. Eur standards. The specification for content accounts for product related substances. Product related substances are not included as a separate attribute in finished product release specifications, but a separate specification is present at active substance level, which is acceptable. The justification for not including reconstitution time in the specifications, based on the development data, is considered acceptable. Visible particulates are not controlled at release but are controlled by a QD test on the FC which is acceptable. Sub-visible particulate contamination should be principally controlled at release in accordance with Ph. Eur. 0520. However, considering the intramuscular route of administration, the type of product, and the consistently low levels in the clinical lots and PPQ lots, control by a characterisation test is acceptable. Shelf-life acceptance criteria for stability indicating tests are the same as at release. Polysorbate 80 content is not controlled at shelf life. It has been sufficiently shown that polysorbate 80 content is stable over the proposed shelf life of RSVPreF3 finished product.

The acceptance limits for description, pH for the lyophilised vaccine and osmolality are considered acceptable. The acceptance criteria for potency and content are based on the batches that were used in the older adults clinical studies and are considered properly justified.

The limit of water content is supported by stability data. The limit is in line with *Ph. Eur 0153 Vaccines for Human use*. The acceptance limits for endotoxin, trehalose and PS-80 are acceptable.

*Analytical methods*

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. pH, endotoxin and sterility are tested according to Ph. Eur methods. Osmolality is tested according to the USP method; a justification that the procedure is equivalent to the procedure described in Ph. Eur. monograph 2.2.35 has been provided). For description, in-house methods are used using Ph. Eur standards. The same analytical procedure is used for testing of RSVPreF3 content for both active substance and finished product. Also, the in vitro relative potency test is used for both active substance and finished product. This test also serves as a test for identity.

The methods for identity and potency, content and purity were validated for finished product batches. Validation results were in line with the results for active substance. All results complied, and it was shown that the methods are suitable for their intended purpose.

The endotoxin test is not validated as it is a compendial method. However, for products that contain a combination of polysorbate and phosphate, Low Endotoxin Recovery (LER) can occur. Therefore, the applicant has performed a LER study. No LER effect has been observed for the Final Product.

For all methods in section 3.2.P.5.1. a reference to the method used is made, including a method reference number. The method reference number is also be included in section 3.2.P.5.2 and section 3.2.P.5.3 in order to maintain a clear link between specifications, methods and method validations.

The information provided on the assay for identity and in vitro relative potency and on the assay for RSVPreF3 content in section 3.2.P.5.2 has been expanded upon request with aspects that are relevant for the validity of the method. The description of the chromatography methods has been expanded to include the chromatography conditions and representative chromatograms. For all methods, the system suitability criteria are in place, which are included in the SOPs, but are not included in section 3.2.P.5.2. Considering the extensive description of the system suitability criteria in the SOPs, this is considered acceptable.

*Batch analysis*

Batch analysis data have been provided for the PPQ batches of the finished product along with batch analysis data for batches manufactured for use in the clinical studies throughout the clinical development phases as well as lots used in the toxicological studies. Results complied with acceptance criteria at the time of testing.

Impurities

Impurities are not further characterised or discussed for finished product as they are covered in process-related impurities and product-related impurities covered in the active substance section. A nitrosamines risk assessment was conducted on RSVPreF3 finished product. The risk assessment is provided in 3.2.R Nitrosamines risk assessment RSVPreF3 and concludes that the risk of nitrosamines being present in RSVPreF3 active substance and finished product is negligible.

It is noted that ICHQ3D is not applicable to vaccines, and they are excluded from the scope. However, the updated Ph.Eur. monograph on pharmaceutical preparations (2619) states that for products outside the scope of general chapter 5.20 (which makes the ICH guideline binding in Ph.Eur), manufacturers of these products remain responsible for controlling the levels of elemental impurities using the principles of risk management. Elemental impurities are monitored in the leachables study, and this was deemed sufficient. According to the results, a toxicological assessment all compounds are below the PDE (Permitted Daily Exposure) or the TTC (threshold of toxicological concern) using ICP/OES to detect elemental impurities.

*Reference materials*

The reference standard is used as quantitative reference standard in the test for content and the test for potency. Qualification of the Reference standard is described in section 3.2 S.5. A protocol for future reference Standards is provided in section 3.2.R.

Container closure

The glass vials are manufactured with Type I colourless glass and are compliant with Ph. Eur. 3.2.1. The type I butyl rubber stoppers are compliant with Ph. Eur. 3.2.9. The dimensions of the vials and stoppers are

provided. The suppliers of vial, stopper and flip-off cap have been provided and representative certificates of analysis have been submitted.

#### *2.4.3.4. Stability of the product*

A shelf-life of 24 months at +2°C to +8°C for RSVPreF3 Final Container filled in 3 mL 1-dose Type I glass vial is proposed.

The claimed shelf life is based on stability data for Phase 3 clinical lots (considered fully representative of the commercial lots). Real time stability data are available for up to 24 months for one lot, up to 18 months for three lots and up to 12 months for four lots and were conducted in line with ICH guidance. No degradation is observed for the parameters tested, except for water content, which increases. This increase in moisture is expected for a lyophilised product. It has been sufficiently justified that water content will remain below the acceptance criterion after 24 months, even for batches that are at the specification limit at release.

The accelerated stability study confirmed the increase of aggregates with the increase of the temperature, as was also seen in stressed studies. Also an increase in water content is seen. Other parameters, like in vitro relative potency, remain stable when exposed to higher temperatures.

After reconstitution with $AS01_E$ adjuvant and incubation for 16 hours at +20°C ± 5°C or +25°C ± 5°C or +5°C ± 3°C for 4 hours, no effect is seen on pH and in vitro relative potency. Once reconstituted, chemical and physical in-use stability has been demonstrated for 4 hours at 2 °C – 8 °C or at room temperature up to 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours.

The Applicant concludes that the results of the Temperature cycling study show that the finished product vaccine sustains exposure to temperature excursion for up to six months at +25°C + 2°C and 3 months at +40°C + 2°C. This conclusion is agreed. However, the product is authorised for storage at 2-8 °C for up to 24 months.

During product development, the impact of certain physico-chemical stressors on structure and antigen stability were evaluated. These stress factors included those that might be more relevant to real world manufacturing process and stability conditions. It included light exposure (photostability). RSVPreF3 finished product is sensitive to light exposure. A statement regarding protection from light is included in the SmPC, product leaflet and outer carton (i.e., “Store in the original package in order to protect from light”).

Based on the long-term stability data, the claimed shelf life of 24 months at +2°C to +8°C is acceptable for the RSVPreF3 Final Container.

### 2.4.4. Finished medicinal product - $AS01_E$ adjuvant vial

#### *2.4.4.1. Description of the product and Pharmaceutical development - $AS01_E$ adjuvant vial*

The commercial presentation of $AS01_E$ (adjuvant system) is a monodose vial. This finished product component is an opalescent, colourless to pale brownish suspension for injection containing the following excipients: QS-21, MPL, dioleoyl phosphatidylcholine; cholesterol; sodium chloride; disodium phosphate anhydrous; potassium dihydrogen phosphate; water for injections. The target fill volume includes an overfill

which ensures a nominal injection volume of 0.5 mL. The primary packaging is a type I glass vial with butyl rubber stopper.

The $AS01_E$ Adjuvant System is composed of two immuno-enhancers, QS-21 (a triterpene glycoside purified from the bark of the tree *Quillaja saponaria* Molina) and MPL (3-Odesacyl- 4'-monophosphoryl lipid A), using liposomes as a vehicle. MPL is a purified, non-toxic endotoxin derivative prepared from the lipopolysaccharide of the R595 strain of *Salmonella minnesota* and is a compendial excipient.

The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol, in phosphate-buffered saline solution. DOPC is a semi-synthetic phospholipid and the key component of the liposomal bilayer membranes. Cholesterol serves to improve the rigidity of the structure and quenches haemolytic activity of QS-21.

### *2.4.4.2. Manufacture of the product and process controls - AS01E adjuvant vial*

The $AS01_E$ adjuvant is produced at GSK Bio (Wavre Nord), Avenue Fleming 20, Wavre Belgium or GSK Vaccines (Rosia), Bellaria Rosia, 53018 Sovicille, Italy.

The manufacturing process of the $AS01_E$ Adjuvant System is composed of the following steps: Preparation of CLB, preparation of QS-21 LB; Formulation of $AS01_E$ FB; Sterile filtration and Filling to produce $AS01_E$ FC. Reprocessing is not described and thus, not allowed. The description of the manufacturing process is acceptable.

The control strategy is described and aims to ensure consistent product quality and process performance. The process parameter ranges are sufficiently justified by process development and characterisation data and/or process performance qualification data. Some CPPs differ between the Rosia and the Wavre site - adequate justifications have been provided. Action limits and alert limits have been provided and justified for the fill volume/weight. The action limits for fill volume/weight range have been included in Module 3. At GSK Rosia pre- and post-use integrity testing of the sterile filter has been implemented, whereas at GSK Wavre only a post-use integrity test was carried out. The applicant has agreed, upon request, to implement pre-use filter integrity testing of the sterilising filter prior to release in the EU market. For both sites, the principle of the integrity test, details on when the tests are performed, solution(s) used in the test and acceptance criteria before and after filtration have been included in Module 3.

Detailed information on the validation of all different process steps is provided, including the production of concentrated liposome bulk (CLB), production of QS21 Liquid Bulk (QS-21 LB), formulation, sterile filtration and filling. Homogeneity in terms of filling volume has been demonstrated. The sterile filter has been adequately validated. A brief summary of the shipping validation has been provided. Long-term stability studies of CLB batches confirm stability for up to 24 months at 2 to 8°C. Stability data support the holding of $AS01_E$ Final Bulk (FB) for up to 30 days at 2 to 8°C in a stainless steel vessel or standard universal vessels.

Control of Excipients

Specifications of the compendial excipients purchased from commercial suppliers comply with the current editions of pharmacopoeias, as applicable, which covers the justification of the specifications. The semi-synthetic, plant-derived cholesterol complies with Ph. Eur. 0993; a commitment to switch to cholesterol that fully complies with Ph. Eur. 2397 (cholesterol for parenteral use) by March 2024 has been provided (REC 3). Specifications for Quality Release testing of QS-21 and DOPC are justified.

The $AS01_E$ adjuvant system does not contain novel excipients or excipients of human or animal origin.

Development - $AS01_E$ adjuvant vial

The adjuvant $AS01_E$ as well as $AS01_B$ belong to the Applicant´s proprietary liposomal AS01 adjuvant system family. QS-21, DOPC and cholesterol were previously approved as excipients for the $AS01_B$ adjuvant (applied for Shingrix) which contains a double amount of MPL, QS-21, DOPC and cholesterol compared to $AS01_E$. The manufacturing process and specifications for the different adjuvant components of $AS01_E$ and $AS01_B$, i.e. MPL, QS-21, DOPC and cholesterol, are identical (only the amount of the components in the final adjuvant composition differs). Note that the previous development Series of $AS01_E$ are used during the development and clinical studies of Mosquirix vaccine (approved via Article 58 procedure).

The overfill (to ensure a nominal dose of 0.5 mL) is adequately justified and the justification is included in Module 3.

Important physicochemical and biological properties of the $AS01_E$ adjuvant system are adequately described in the dossier. The manufacturing process of $AS01_E$ Adjuvant System has been developed through the implementation of a “Series” of manufacturing processes, which reflect changes applied to the manufacture of the intermediates, AS01 formulation or filling, from one “Series” to the next one. RSVPreF3/$AS01_E$ Phase III studies have been performed with $AS01_E$ Series 13.

The most significant changes applied to the manufacturing of $AS01_E$ Adjuvant System between Phase 3 clinical development and commercial manufacturing are: transfer of the manufacturing process to the commercial facilities; scale-up of the $AS01_E$ formulation step; change of storage containers for intermediates. No changes to the formulation (ingredients) of $AS01_E$ have been indicated.

Establishment and evolution of the analytical control strategy for the intermediates CLB and QS-21 LB as well as for $AS01_E$ FB and FC product are adequately described.

### *2.4.4.3. Product Specifications - $AS01_E$ adjuvant vial*

The $AS01_E$ FP specification is shown below and includes appropriate tests for identity, physicochemical properties, content of adjuvant constituents, impurities and sterility that are compliant with Ph. Eur. All of the tests, with the exception of MPL content, volume and osmolality, are also performed during the ongoing stability studies. The proposed specifications are sufficiently justified. The Applicant´s proposal to a commitment to re-evaluate the specification limits when data from more than 30 lots are available is endorsed (REC 2).

Analytical methods- $AS01_E$ adjuvant vial

Descriptions of the analytical methods were provided. The method descriptions have been expanded to include relevant information (injection sequence and representative chromatogram). The analytical methods are identified by method identifiers in Sections 3.2.P.5.1, 3.2.P.5.2, and 3.2.P.5.3. All methods have been appropriately validated.

Batch analysis- $AS01_E$ adjuvant vial

The presented batch release data for the subsequent $AS01_E$ adjuvant Series 10, A, B, 13, and C are within specifications and demonstrate product consistency. Series 13 $AS01_E$ lots has been used in RSV clinical studies for older adults, while Series C lots are considered representative of future commercial batches. Four Series C lots are manufactured at the Rosia site and one at the Wavre Nord site. Overall, the batch data confirm consistent production.

Characterisation of impurities $AS01_E$ adjuvant vial

The potential impurities in $AS01_E$ adjuvant system and their control strategy have been presented. Possible impurities are controlled at release of $AS01_E$ or at release of the raw materials. The low levels of impurities that may be present in $AS01_E$ FC are clinically qualified and do not pose any safety concerns. An adequate risk assessment for potential N-nitrosamine contaminants that reveals an acceptable low risk is provided under 3.2.R. Impurities have been studied in nonclinical and clinical studies.

Reference materials-$AS01_E$ adjuvant vial

For the quantification of MPL, DOPC and cholesterol, reference standards obtained from commercial suppliers are used. There is only one in-house standard. This QS-21 reference standard is used for quality control release testing of the QS-21 Liquid bulk and the $AS01_E$ Final container (QS-21 content and QS-21-H limit test by HPLC). The comparability protocol for future QS-21 standards is presented and satisfactory.

Container closure $AS01_E$ adjuvant vial

The liquid formulation is filled in 3 mL vial containers, sealed with 13 mm butyl stoppers for liquid formulations and secured with flip-off caps. The sterilization of the stoppers is in line with the reference conditions as stated in the Ph. Eur 5.1.1. For the sterilization of the vials and for sterilization of the stoppers, this is not the case. Therefore, as requested, validation data are submitted for the validation of the sterilization conditions. Representative certificates of analysis have been submitted for vial and stopper.

#### *2.4.4.4. Stability of the product- $AS01_E$ adjuvant vial*

The Applicant proposes a shelf-life of 36 months at 2-8°C for $AS01_E$ Adjuvant System (1-dose) filled in 3 mL glass vials.

The major part of the available stability data comprises the 60 months stability data of previous Series 10, A and B (2-dose) and 18 months data of Series 13 (used for clinical studies of older adults). To date only nine months real time stability data are available for PPQ FC lots (Series C, 1-dose): one GlaxoSmithKline Biologicals SA Wavre Nord, Belgium lots and three GlaxoSmithKline Vaccines S.r.l. Sovicille, Italy FC lots.

The Applicant concludes that the results of the temperature cycling study show that the $AS01_E$ sustains exposure to temperature excursion for up to 14 days at 25°C or days at 37 °C during the 36 months shelf-life. This conclusion is agreed.

Photostability data demonstrate that $AS01_E$ is not sensitive to light.

The shelf life 36 months at 2-8°C for $AS01_E$ Adjuvant System (1-dose) is acceptable based on the stability demonstrated for previous series of $AS01_E$.

Because the shorter shelf-life of the finished product vial containing RSVPreF3, this medicinal product has an overall 2 year shelf-life when stored in a refrigerator (2 °C – 8 °C) as stated in the SmPC

### 2.4.5. Post approval change management protocols

Not applicable.

### 2.4.6. Adventitious agents

The strategy used to ensure that the RSVPreF3 active substance and finished product are free of adventitious agents is in compliance with the relevant EU viral safety and TSE requirements and includes: control of raw materials; testing of the MCB and WCB, as well as end of production cells; in-process testing of harvest for adventitious agents and bacterial contamination and viral clearance validation studies.

Raw materials of animal origin were used for the first steps of cell bank system development (up to the pre-Master cell bank). A satisfactory evaluation of adventitious agents has been provided for these. The risk of TSE contamination is considered negligible due to the origin of the raw materials and the TSE certificates. The risk of other adventitious agent contamination is considered limited due to the process steps.

With the exception of casamino acids, which are used during the production process of MPL (AS01 Adjuvant System), no materials from human or animal origin are used in the manufacturing process of active substance or finished product. This source of casamino acids is compliant with current EU TSE guidelines.

The active substance manufacturing process contains various steps that were shown to contribute to virus removal/inactivation (chromatography steps, viral inactivation, nanofiltration). Virus removal/inactivation was properly validated in scale-down models using appropriate model viruses. The results confirm that the purification process has an adequate viral clearance capacity. In combination with the testing of starting materials and intermediates this viral clearance capacity reduces the risk of viral contamination to a very low and acceptable level.

### 2.4.7. Discussion on chemical, and pharmaceutical aspects

The dossier of Arexvy is of good quality. The Active Substance and Final Product manufacturing processes have been clearly described and critical process parameters have been identified and justified. The control strategy, including in-process controls and release testing, is considered acceptable. The proposed shelf life for Active Substance and Final Product are supported by data and are considered acceptable.

Comparability has been shown between the batches used in Phase 3 clinical studies and PPQ batches manufactured according to the commercial manufacturing process. Process validation is considered adequate, and it can be concluded that the manufacturing process is in a state of control and results in the manufacture of batches that are consistent and meet the specifications.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the leachable study, specification limits for the adjuvant and full compliance with cholesterol for parenteral use. These points are put forward and agreed as recommendations for future quality development.

### 2.4.8. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.4.9. Recommendations for future quality development

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

- The applicant is recommended to submit the Leachable study results for the finished product when available (REC 1).

- The specification limits for $AS01_E$ finished product (adjuvant) should be reviewed and submitted when data from more than 30 representative lots manufactured according to the commercial process are available (REC 2).

- The applicant should demonstrate full compliance with cholesterol for parenteral use (Ph. Eur. monograph 2397) by March 2024 (REC 3).

## *2.5. Non-clinical aspects*

### 2.5.1. Introduction

The Applicant proposes a protein vaccine for active immunisation of adults ≥ 60 years (i.e., non-naïve population) to boost RSV-specific humoral and cellular immune responses and prevent RSV infection-related lower respiratory tract disease. The proposed RSV vaccine is composed of a trimeric RSV fusion protein stabilised in a pre-fusion conformation (RSVPreF3) and the AS01 adjuvant system ($AS01_E$) containing the immunoenhancers QS-21 and MPL in a liposomal vehicle with DOPC and cholesterol.

### 2.5.2. Pharmacology

#### *2.5.2.1. Primary pharmacodynamic studies*

The non-clinical PD package consists of five studies; three studies to show the immunogenicity of the vaccine and the justification of the adjuvant, two studies to support manufacturing development (characterisation). Extensive data on the adjuvant system AS01 and the specific components QS-21 and MPL are not provided. GSK refers to their dossier of Shingrix, for which the adjuvant system was assessed in detail. Considering that AS01 in the currently proposed RSV vaccine is not a new adjuvant, the absence of study reports in this MAA but reference to the Shingrix MAA is acceptable.

*Immunogenicity studies*

The Applicant has submitted three primary PD studies to characterise the immunogenicity of the PreF3-$AS01_E$ vaccine in mice and two immuno-characterization studies. For four of these studies, young adult female CB6F1 mice (6-8 weeks old), naïve to RSV, have been immunised three times with RSVPreF antigen with or without adjuvant. In contrast, the human target population is non-naïve to RSV infection and ≥ 60 years old, and the vaccine will be used as a single dose. The Applicant has thoroughly explained that the non-clinical studies are only intended to show immunogenicity and not to evaluate vaccine efficacy, because a good animal model that can mimic the intended human non-naïve elderly target population and the sensitivity to RSV-related disease upon infection is not present. Although cows can be infected with bovine RSV, which is genetically related to human RSV and can cause recurrent infections, the relevance and similarity of certain

(adjuvant-induced) immune responses and immunosenescence in these animals to humans is still unknown. Therefore, the Applicant stated that the non-clinical PD package was only aiming "to evaluate the need for an adjuvant system in the protein vaccine, and to support the choice of the AS01 adjuvant system in the vaccine formulation with the PreF antigen to elicit potent F-specific $CD4^+$ T cell responses and RSV neutralising antibodies". A further selection of the final formulation and determination of vaccine efficacy (i.e., protection against RSV infection and related disease) in both males and females was performed in the clinical studies. This approach can be endorsed. The non-clinical PD studies can thus only be regarded as proof-of-concept immunogenicity studies.

The first study (20160092-0094) was conducted to justify the need for an adjuvant. Mice received 2 µg RSVPreF3 alone or in combination with 50 µg AlOH, 10 µg $AS01_B$ or an unknown amount of $AS03_A$. Immunisation with RSV antigen alone was not very immunogenic. In combination with especially $AS01_B$, RSVPreF3 induced F-specific $CD4^+$ and $CD8^+$ T cell responses and RSV-specific neutralising antibody titres after the second and third vaccination and induced proinflammatory cytokines as measured after the first and second vaccination.

The second study (20160201) was performed to select the most appropriate antigen dose for the subsequent proof-of-concept study. Mice were immunised with 2 µg, 0.5 µg or 0.125 µg RSVPreF2 in combination with 10 µg ($AS01_B$) or 5 µg ($AS01_E$) adjuvant or immunised with 2 µg, 0.5 µg or 0.125 µg RSVPreF3 in combination with 10 µg ($AS01_B$) adjuvant. Both AS01-adjuvanted PreF antigens induced cellular and humoral responses against RSV in naïve animals after the second and third immunisation. PreF2 induced higher T cell frequencies, while higher neutralising antibody titres were elicited with PreF3. 0.5 µg antigen was selected as the dose for the subsequent proof-of-concept study, based on a good balance between non-saturating responses and sufficient intensity of the responses.

The final proof-of-concept study (20170126-0174) compared antigens PreF2 and PreF3, non-adjuvanted or when combined with different AS01 doses. Mice received 0.5 µg RSVPreF2 in combination with 10 µg ($AS01_B$) or 5 µg ($AS01_E$) adjuvant, or received 0.5 µg RSVPreF3 in combination with 10 µg ($AS01_B$), 5 µg ($AS01_E$) or 2.5 µg ($AS01_F$) adjuvant. The RSVPreF antigens alone were poorly immunogenic, while RSVPreF2 and RSVPreF3 in combination with AS01 induced both B and T cell responses after the second and third immunisation. Higher T cell frequencies in the spleen and lung were induced with PreF2, while higher neutralising antibody titres and preF conformation-restricted site Φ-specific IgGs were elicited with PreF3. In general, there was no considerable difference in the height of the immune response between the adjuvant formulations, although $AS01_B$ induced slightly higher $CD4^+$ T cell frequencies in the spleen compared to lower adjuvant doses.

In the immunogenicity studies, the Applicant also paid attention to clinical signs post-immunisation. Apart from the occurrence of abnormal gait in several animals (a consequence of injection in gastrocnemius muscle), no clinical observations were noted in these PD studies.

*Immunocharacterisation studies*

The Applicant has also conducted two characterisation studies in mice to support the manufacturing process and quality of the vaccine material.

One study (cov 0100-18) was conducted to characterise the immunogenicity of lyophilised GMP drug product material for clinical study Phase 1/2. For this study, Balb/c mice were used. These mice were immunised twice with 3 µg, 1.5 µg or 0.75 µg RSVPreF3-$AS01_B$ (i.e., $1/10^{th}$, $1/20^{th}$ and $1/40^{th}$ of the lowest human dose used in clinical study RSV OA=ADJ-002). After the second immunisation, a dose-dependent neutralising

antibody response was observed, with a ≥ 4-fold increase in individual titres in mice from the highest dose group. The GMP lot was therefore considered immunogenic and useful for Phase 1/2 clinical trial.

Another study (20180258) was performed to determine the impact of p27 present in RSVPreF3 trimers on the immunogenicity of the vaccine formulation. P27 is a 27 amino acid peptide that is removed during maturation, but some trimers still contain this peptide on one of the three F proteins. The immunogenicity of batches containing 100% p27-RSVPreF3 trimers was compared to batches with 100% fully cleaved RSVPreF3 trimers and to batches containing a mix of fully and non-fully cleaved trimers. CB6F1 mice were immunised with 0.5 µg RSVPreF3 combined with 5 µg $AS01_E$. Mean group immune responses for p27-containing trimers (100% batch) were non-inferior to responses for fully cleaved trimers (100% or mixed batches) after the second and third immunisation. It was, however, noted that a mixed batch with DS material representative for Phase 3 induced higher neutralising antibody responses (but similar T cell responses) compared to the other material tested (i.e., produced with an earlier production process). The Applicant did not further explain the differences between the tested batches with respect to the representativeness for clinical material. Considering the analytical results of the corresponding batch, this material had a lower % RSVPreF3 lacking site Φ-binding by D25 Fab compared to the other batches used in this study (Table 15 of module 3.2.S.3.1). This explains why differences in neutralising antibody titres but not in cellular frequencies were observed with this Phase 3 representative batch.

#### *2.5.2.2. Secondary pharmacodynamic studies*

The absence of secondary PD studies can be endorsed.

#### *2.5.2.3. Safety pharmacology programme*

The absence of dedicated safety PD studies can be endorsed.

#### *2.5.2.4. Pharmacodynamic drug interactions*

The absence of dedicated PD drug interaction studies can be endorsed.

### 2.5.3. Pharmacokinetics

No dedicated PK or ADME studies for RSVPreF3 OA are performed. This is endorsed.

The adjuvant system AS01 is not a novel adjuvant, since several products using the adjuvant system have already been registered (a.o., Shingrix, using $AS01_B$). Therefore, no new biodistribution studies with the total adjuvant system or with the included immunoenhancers are required.

### 2.5.4. Toxicology

#### *2.5.4.1. Single dose toxicity*

No single dose toxicity studies are performed with RSVPreF3 alone or adjuvanted with $AS01_B$. This is acceptable.

### *2.5.4.2. Repeat dose toxicity*

Two GLP-compliant repeated dose toxicity studies (and) were conducted in New Zealand White rabbits (10/sex/group), which received three intramuscular injections (Day 1, Day 15 and Day 29, followed by a 4-week recovery period.) In study COV 8363131, animals were administered saline, RSVPreF3 (120 µg, 0.5 mL) or RSVPreF3 adjuvanted with $AS01_B$ (120 µg, 0.5 mL). In study COV 8384096, saline, RSVPreF3 (240 µg, 0.5 mL) or RSVPreF3 adjuvanted with $AS01_B$ (240 µg, 0.5 mL). The antigen dose is the same as (study COV 8363131) or twice (COV 8384096) the intended clinical dose, however, the clinical formulation is adjuvanted with $AS01_E$ instead of $AS01_B$ (120 µg RSVPreF3 with 0.5 mL $AS01_E$). $AS01_B$ contains a double dose of (the same) immuno-enhancers compared to $AS01_E$; therefore, the adjuvant dose can be considered more than the clinical dose. This is acceptable.

Levels of anti-RSVPreF3 IgG antibodies were increased (measured at Day 32 and 57) in 80% of females and all males administered RSVPreF3 and in 80-90% of females and all males administered RSVPreF3 adjuvanted with $AS01_B$ in the first study. In the study with twice the human dose, all animals receiving antigen showed an increase in anti-RSVPreF3 IgG antibodies. Antibody titres were higher in the adjuvanted group compared to the non-adjuvanted group. No seroconversion was observed in the saline group.

The vaccine resulted in effects on clinical pathology parameters and histopathology that are consistent with immune stimulation following administration of a vaccine, amongst others changes in white blood cell and absolute neutrophil counts, minimally to mildly decreased albumin, increased lymph node weights (ileac and popliteal), CRP and fibrinogen. No consistent effect was observed on body temperature (measured at 6, 24 and 48h).

Local effects at the injection site included minimal to slight myofiber degeneration/necrosis and minimal to moderate mixed inflammatory cell infiltrates, and were in general, more severe in the adjuvanted RSVPreF3 group.

At the end of the recovery period, all effects were resolved or reduced in incidence and/or severity.

In both studies, the Applicant has calculated safety margins based on the antigen content and standard mean body weight. However, common allometric rules do not apply to a local immune response. Moreover, the analysis of a NOAEL is not an adequate approach, as inflammatory reactions at the site of injection will occur and will be needed for an adequate immune response (i.e., absence of toxicity is not the intention of a vaccine-related toxicity study). Nevertheless, the absolute human dose (or twice the human dose) was used for the repeated dose toxicity studies, which is sufficient. From the results of these studies, no clinical safety issues are expected.

### *2.5.4.3. Genotoxicity*

The absence of genotoxicity studies is accepted. This is not required for vaccines.

### *2.5.4.4. Carcinogenicity*

The absence of carcinogenicity studies is accepted and not required for vaccines.

#### *2.5.4.5. Reproductive and developmental toxicity*

Considering the age of the target population, in principle, the absence of reproductive and developmental toxicity studies is acceptable.

#### *2.5.4.6. Toxicokinetic data*

The absence of toxicokinetic studies for RSVPreF3/AS01 can be endorsed.

#### *2.5.4.7. Local Tolerance*

The absence of a dedicated local tolerance study for RSVPreF3/AS01 can be endorsed. Local tolerance was evaluated as part of the repeat dose GLP toxicology studies in rabbits with RSVPreF3 adjuvanted with $AS01_B$.

#### *2.5.4.8. Other toxicity studies*

The absence of additional toxicity studies is acceptable.

### 2.5.5. Ecotoxicity/environmental risk assessment

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.

### 2.5.6. Discussion on non-clinical aspects

*Clinical relevance of primary PD studies*

The non-clinical studies described here have shown the immunogenicity of adjuvanted RSVPreF3 antigen in naïve mice. Thereby, it can be concluded that 1) an adjuvant is needed in the vaccine formulation for proper T and B cell responses, 2) the AS01 adjuvant system is an appropriate adjuvant for enhancing RSVPreF-induced immune responses, with no considerable difference between $AS01_B$ and $AS01_E$, 3) RSVPreF3 induces neutralising antibodies against RSV (including the pre-fusion epitope site Ø) and F-specific $CD4^+$ and $CD8^+$ T cell responses, 4) the GMP material is immunogenic in mice, and 5) p27-containing trimers have no negative impact on the induced B and T cell responses.

However, the clinical relevance of the observed immune responses and the corresponding conclusions (including selection of the antigen type and adjuvant system) is doubtful because the used antigen doses used in the murine studies are very low (compared to the doses used in the rabbit tox study and in clinical studies), and the corresponding antigen:adjuvant ratios in these non-clinical studies are different from the ones used in clinical studies and proposed in the SmPC, without further justification. In all cases, the amount of antigen in the non-clinical immunogenicity studies was considerably lower than the adjuvant dose. Different antigen:adjuvant ratios may considerably impact the desired immune response and corresponding efficacy. As such, the non-clinical proof-of-concept studies only provide proof that the selection of RSVPreF3 and the Adjuvant System AS01 can induce an immune response which is expected to be required to provide protection in humans. The proposed vaccine (120 µg RSVPreF3 and 50 µg $AS01_E$) used in the clinic was

selected based on clinical phase 1/2 data. The Applicant explained that the antigen doses selected for these studies were not based on anticipated doses in humans but chosen to identify a dose within the dynamic range of the dose-neutralizing response curves. The intention of the non-clinical program was not to select the most immunogenic doses and ratio to be used in the clinic, but to select the most appropriate combination of antigen type and adjuvant system. Immunogenicity and efficacy of the proposed vaccine have been evaluated clinically.

In addition, the Applicant has tested non-clinically both RSVPreF2 and RSVPreF3. In naïve mice, RSVPreF2 induced higher T cell responses, while RSVPreF3 induced higher neutralising titres (including pre-fusion epitope site Ø, not detected or poorly detected with RSVPreF2). The Applicant argues that both humoral and cellular immune responses are considered needed to protect elderly from severe RSV-associated lower respiratory tract disease. As only RSVPreF3 elicited neutralizing antibodies against the RSV prefusion-specific antigenic site Ø and as both antigens induced T cell responses (although PreF2 > PreF3), the Applicant had selected RSVPreF3 as the most relevant antigen to be used in elderly.

The Applicant evaluated different AS01 adjuvant doses ($AS01_B$, $AS01_E$ and $AS01_F$) in combination with RSVPreF3 in mice. There were no considerable differences in the height of the immune responses between the three AS01 doses. $AS01_B$ and $AS01_E$ were compared in the phase 1/2 clinical study leading to the selection of $AS01_E$ for phase 3 studies. The lowest dose ($AS01_F$) was not considered in the clinical phase.

The Applicant provided public literature in CTD module 4.3 (Steff et al., 2007) showing that in bRSV pre-exposed cows immunised with a single injection of non-adjuvanted RSVPreF3, this antigen could boost RSV-specific neutralising antibodies. It is acknowledged that the specific immune responses in cattle may be non-similar to (elderly) humans, but these data indicate that in non-naïve animals an adjuvant may not be needed to boost RSV-specific immune responses, in contrast to naïve animals (as shown in the non-clinical murine studies). The need for an adjuvant was further addressed in clinical studies.

In the immunogenicity studies, RSVPreF3 pre-clinical lot (study 20160092-0094) and pre-GMP lot (study 20160201 and 20170126-0174) were used to immunise animals. Immunocharacterisation study cov 0100-18 was conducted with a GMP lot used for Phase 1/2 clinical studies. In the immunocharacterisation study 20180258, Phase 3-representative material and Phase 1/2-representative material were tested and differences in antibody titres were observed. According to the Applicant, the differences between the DS processes used for non-clinical and part of Phase 1/2, Phase 3 and commercial phase would not have impacted the critical quality attributes of RSVPreF3.

The antigen material used in the non-clinical immunogenicity studies has been produced with the same process as used to produce Phase 1/2 material. As such, the non-clinical material can be considered representative for early clinical material. One characterization study (20180258) was conducted with antigen representative for clinical Phase 3 material, although some non-clinical formulations used in this study resulted in lower neutralizing antibody titres. This might be due to a difference in purification between the non-clinical material and the actual DS lot used in the clinic.

It should further be noted that the study reports did not contain individual animal data in tabulated form. The Assessor's conclusions are therefore solely based on the graphs and corresponding Applicant's descriptions of the results provided in the reports.

*Reproduction and developmental toxicity*

Although in principle, the absence of reproductive and developmental toxicity studies is acceptable for the current indication, regarding potential off-label use in pregnant women and the inclusion of complete data in

section 4.6 of the SmPC, the Applicant was requested to submit any available preclinical data on reproductive and developmental toxicity studies performed with RSVPreF3. The Applicant has provided two DART studies with RSVPreF3 (without adjuvant): one in rabbit (doses of 120 µg antigen) and one in rat (doses of 48 µg antigen). In addition, the report from a DART study with the complete product (i.e., RSVPreF3/AS01$_E$; full human dose, 120 µg PreF3) in rabbit was provided. In neither of the studies effects were observed on female fertility, embryo-foetal, pre- and postnatal development. The conclusions of these studies are reflected in section 4.6 and 5.3 of the SmPC.

*ERA*

Due to their nature, vaccines are unlikely to result in a significant risk to the environment.

### 2.5.7. Conclusion on the non-clinical aspects

Considering the above-mentioned limitations on the non-clinical animal model and study design for the selected antigen type, antigen and adjuvant doses and antigen:adjuvant ratio used in clinical studies, and that the optimal combination could still be different in RSV-primed elderly compared to RSV-naïve young mice, the non-clinical proof-of-concept program only provides proof that the selection of RSVPreF3 and the Adjuvant System AS01 can induce an immune response which is expected to be required to provide protection in humans. The final formulation, antigen and adjuvant doses (120 µg RSVPreF3 with 50 µg AS01$_E$) was selected based on clinical data.

Overall, based on the results of the repeated dose toxicity studies, no clinical safety issues are expected.

## *2.6. Clinical aspects*

### 2.6.1. Introduction

*GCP aspects*

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

The applicant 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

Overview of clinical studies included in the Arexvy dossier

| Study ID Number of study centres / location | Design | Posology and number of subjects by group | Study Population | Primary Efficacy Objective(s) |
|---|---|---|---|---|
| Pivotal study | | | | |

| Study ID<br>Number of study centres / location | Design | Posology and number of subjects by group | Study Population | Primary Efficacy Objective(s) |
|---|---|---|---|---|
| ADJ-006<br><br>278 centers in 17 countries (14 on NH, 3 on SH)<br><br>Ongoing | A Phase 3, randomised, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a *single dose* and annual revaccination doses of RSVPreF3 in adults aged 60 years and above. | IM, single dose<br>Randomisation ratio Arexvy:Placebo =1:1<br><br>RSVPreF3: Single dose<br>Randomised: 12503<br>Exposed: 12467<br><br>Placebo: Single dose<br>Randomised: 12537<br>Exposed: 12499 | Adults ≥60 years<br><br>Gender:<br>12051 M/<br>12915 F<br><br>Median Age:<br>69.5 years | To demonstrate the efficacy of a single dose of RSVPreF3 in the prevention of RT-PCR confirmed RSV associated LRTD during the first season in adults ≥ 60 YOA.<br>Criterion: The LL of the 2-sided CI for VE is above 20%. |
| Supportive studies | | | | |
| ADJ-004<br>46 centers in 5 countries<br><br>Ongoing<br>Data up to month 6 presented | Phase 3, randomised, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 and different revaccination (annual or flexible) schedules in adults aged 60 years and above. | IM<br>Randomisation: 1:1:3<br><br>Single dose group:<br>Day 1<br>Randomised: 332<br>Exposed: 331<br><br>Annual revaccination<br>Day 1, Mo 12 and Mo 24<br>Randomised: 998<br>Exposed: 993<br><br>Flexible revaccination<br>Day 1, revaccination based on immunogenicity<br>Randomised: 330<br>Exposed: 329 | Adults ≥60 years<br><br>Gender:<br>750 M/<br>903 F<br><br>Median Age:<br>70.0 years | To evaluate the humoral immune response (Nab against RSV-A and -B) following a 1-dose primary schedule of RSVPreF3 up to 12 months post-Dose 1. |
| ADJ-007<br>14 centers in 3 countries<br><br>Completed | Phase 3, randomised, self-contained, open-label, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 when co-administered with FLU-QIV vaccine in adults aged 60 years and above | IM, single dose of RSVPreF3 and FLU-QIV<br><br>Co-administration<br>Day 1: RSVPreF3 + FLU-QIV<br>Randomised: 445<br>Exposed: 442<br>Completed: 429<br><br>Control<br>Day 1 FLU-QIV; Day 31: RSVPreF3<br>Randomised: 445<br>Exposed: 443<br>Completed: 417 | Adults ≥60 years<br><br>Gender:<br>429 M/ 456 F<br><br>Median Age:<br>68.5 years | To demonstrate the non-inferiority of RSVPreF3 and FLU vaccine when both vaccines were co-administered or administered alone. |
| ADJ-009<br>19 centers in 3 countries<br>CompletedData up to month 6 presented | Phase 3, randomised, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 administrated as a single dose in adults aged 60 years and above | IM<br>Randomisation: 1:1:1<br><br>Lot 1<br>Randomised: 252<br>Exposed: 251<br><br>Lot 2<br>Randomised: 252<br>Exposed: 253<br><br>Lot 3<br>Randomised: 254<br>Exposed: 253 | Adults ≥60 years<br><br>Gender:<br>386 M/ 371 F<br><br>Median Age:<br>69.9 years | To demonstrate the lot-to-lot consistency of 3 lots of the RSVPreF3 in terms of immunogenicity. |

| Study ID<br>Number of study centres / location | Design | Posology and number of subjects by group | Study Population | Primary Efficacy Objective(s) |
|---|---|---|---|---|
| ADJ-002<br>21 centers in 2 countries<br><br>Completed | Phase 1/2, randomised, placebo-controlled, observer-blind, multi-center, dose selection and formulation study , to evaluate the safety, reactogenicity and immunogenicity of RSVPreF3 (adjuvanted with AS01E or AS01B or unadjuvanted) when administered IM according to a 0, 2 month schedule in adults aged 18-40 or 60-80 years with 4 parallel groups in Part A (1:1:1:1) and 10 parallel groups in Part B (1:1:1:1:1:1:1:1:1:1) . | Part A:<br>IM; 0.2 months schedule<br>Randomisation ratio<br>1:1:1:1<br>30 µg RSVPreF3 unadjuvanted<br>Exposed: 12<br>Completed: 12<br><br>60 µg RSVPreF3 unadjuvanted<br>Exposed: 12<br>Completed: 10<br><br>120 µg RSVPreF3 unadjuvanted<br>Exposed: 11<br>Completed: 12<br><br>Placebo: Single dose<br>Exposed: 12<br>Completed: 12 | Part A<br>Adults 18-40 YOA<br><br>Gender:<br>17 M/ 31 F<br><br>Median Age:<br>29.8 years | Humoral immune responses (in terms of RSV-A NAb titers and RSVPreF3-specific IgG Ab concentrations) to the different RSVPreF3 formulations up to 1 month after the last dose (Day 91).<br>CMI responses to the different RSVPreF3 formulations up to 1 month after the last dose (Day 91) in terms of RSVPreF3-specific polypositive CD4+/CD8+ T cells.<br>Occurrence of RSV-associated RTI during the RSV season in nasal/throat swab samples collected during the assessment visit for potential RSV-RTI in Part B. |
| | | Part B:<br>IM; 0.2 months schedule<br>Randomisation ratio<br>1:1:1:1:1:1:1:1:1:1<br>30 µg RSVPreF3 unadjuvanted<br>Exposed: 101<br>Completed: 100<br><br>60 µg RSVPreF3 unadjuvanted<br>Exposed: 97<br>Completed: 92<br><br>120 µg RSVPreF3 unadjuvanted<br>Exposed: 100<br>Completed: 97<br><br>30 µg RSVPreF3 + AS01E<br>Exposed: 101<br>Completed: 95<br><br>60 µg RSVPreF3 + AS01E<br>Exposed: 101<br>Completed: 101<br><br>120 µg RSVPreF3 + AS01E<br>Exposed: 100<br>Completed: 95<br><br>30 µg RSVPreF3 + AS01B<br>Exposed: 103<br>Completed: 100<br><br>60 µg RSVPreF3 + AS01B<br>Exposed: 100<br>Completed: 100<br><br>120 µg RSVPreF3 + AS01B<br>Exposed: 101<br>Completed: 97<br><br>Placebo<br>Exposed: 101<br>Completed: 98 | Part B<br>Adults 60-80 YOA<br><br>Gender:<br>432 M/ 573 F<br><br>Median Age:<br>67.6 years | |

| Study ID Number of study centres / location | Design | Posology and number of subjects by group | Study Population | Primary Efficacy Objective(s) |
|---|---|---|---|---|
| ADJ-011 (extension ADJ-002) 21 centers in 2 countries<br><br>Completed | Phase 2b, open-label, multi-center extension study to evaluate the safety and immunogenicity of RSVPreF3 administered IM 18 months post-Dose 2 in adults 60 years and older who participated in study ADJ-002 | IM, single dose 18 months post dose 2<br>No randomisation<br>30 µg RSVPreF3 + AS01E<br>Exposed: 39<br>Completed: 39<br><br>60 µg RSVPreF3 + AS01E<br>Exposed: 43<br>Completed: 43<br><br>120 µg RSVPreF3 + AS01E<br>Exposed: 40<br>Completed: 39 | Adults ≥60 years who had received 2 doses of RSVPreF3 vaccine adjuvanted with AS01E in study ADJ-002<br>Gender:<br>50 M/ 72 F<br>Median Age:<br>68.0 years | To evaluate the humoral immune response following IM administration of RSVPreF3 up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 in the parent study (ADJ-002) |
| DLP = Data lock point; LRTD= Lower respiratory track disease; NH = Northern Hemisphere; RSV = Respiratory syncytial virus; RTI = respiratory tract infection; SH = Southern Hemisphere. | | | | |

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

No pharmacokinetics studies have been conducted for Arexvy. This is because pharmacokinetics studies are generally not needed for vaccines, consistent with current the Guidelines on clinical evaluation of vaccines.

### *2.6.2.2. Pharmacodynamics*

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

#### *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. Arexvy is designed to enhance antigen-specific cellular immune response and neutralizing antibodies response in individuals with pre-existing immunity against RSV. 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. The adjuvant $AS01_E$ facilitates the recruitment and activation of antigen presenting cells carrying vaccine-derived antigens in the draining lymph node, which in turn leads to the generation of RSVPreF3-specific CD4+ T cells.

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

#### *Primary and Secondary pharmacology*

The bioanalytical methods used to support the clinical development of Arexvy are depicted in Table 1.

Table 1: Laboratory assays used to assess primary and secondary immunogenicity endpoints in RSVPreF3 OA clinical studies

| Component | Assay method | Laboratory | Assay unit | Assay cut-off |
|---|---|---|---|---|
| Study RSV OA=ADJ-006, -004, -007, -002, -011 EXT:002 | | | | |
| RSV-A NAb | Neutralisation | GSK Biologicals[a] | ED60 (IU/mL) | 18 (56) |
| RSV-B NAb | Neutralisation | GSK Biologicals[a] | ED60 (IU/mL) | 30 (44) |
| Study RSV OA=ADJ-006, -004, -007, -009, -002, -011 EXT:002 | | | | |
| RSVPreF3-specific IgG Ab concentrations | Enzyme-linked immunosorbent assay (ELISA) | Nexelis lab Laval, Canada | ELU/mL | 25 |
| Study RSV OA=ADJ-004, -002, -011 EXT:002 | | | | |
| RSVPreF3-specific CD4+ and CD8+ T cells expressing CD40L, IL-2, INF-γ, TNF-α, IL-13, IL-17, 4-1BB [b] | CFC | GSK Biologicals[a] | Events/$10^6$ cells | 590[c] |

Ab = antibody; CD40L = cluster of differentiation 40 ligand; CFC = cell flow cytometry; ELISA = enzyme-linked immunosorbent assay; ELU/mL = ELISA units per milliliter; ICS = intracellular cytokine staining; IFN-γ = interferon gamma, IL (IL-2; IL-13; IL-17): Interleukin; NAb = neutralising antibody; PBMC = peripheral blood mononuclear cells; RSV = respiratory syncytial virus; TNF-α: Tumour Necrosis Factor alpha; 4-1BB (CD137)

ED60: Estimated Dose: serum dilution giving a 60% reduction of the signal compared to a control without serum

a. GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium;
b. RSVPreF3-specific CD4+/CD8+ T cells expressing CD40L, IL-2, TNF-α, IFN-γ in the Phase 1/2 studies and also including IL-13, IL-17 and 4-1BB in the Phase 3 study
c. The lower limit Of Quantification (i.e. 590) was used as assay cut-off to calculate the fold increase of the frequency of RSVPreF3-specific polypositive CD4+ T cells between 2 time points

A quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) assay based on a commercially available kit was used to confirm the presence of RSV-A or RSV-B. The RSV-A and RSV-B qRT-PCR assay was validated before the start of testing in the RSV OA=ADJ-006 study. The validation report, qualification report and Standard Operating Procedures (SOPs) for this assay are provided.

RSV-A and RSV-B RNAs extracted from the swab samples were detected in a duplex qRT-PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process involved nucleic acids extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real-time RT-PCR reaction using a calibration curve (absolute quantitation). The RSV viral load was reported as copies of RSV RNA per mL of sample (assay positivity cut-off was set at the Limit of Detection: 304 copies per mL for RSV-A and 475 copies per mL for RSV-B).

The following performance parameters were assessed during validation for the RT-PCR assay:

Table 2: Summary of performance parameters assessed during validation

| Validation parameter | Acceptance criteria | Results | Status |
|---|---|---|---|
| LOD | The upper limit of the Clopper-Pearson one-sided 95% CI for the proportion of detected measurements:<br>• is ≥95% for the sample dilutions with GMC ≥LOD; and<br>• tends towards 100% for the sample dilutions with GMC >LOD | For both RSV-A/-B subtypes the upper limit of the Clopper-Pearson one-sided 95% CI for the proportion of detected measurements:<br>• was ≥95% for the sample dilutions with GMC ≥LOD; and<br>• tended towards 100% for the sample dilutions with GMC >LOD | Confirmed |
| Precision | IP CV%:<br>• ≤70 for samples in the low concentration range;<br>• ≤40 for samples in the medium concentration range;<br>• ≤40 for samples in the high concentration range | IP CV% (RSV-A):<br>Low range = 31.1<br>Medium range = 21.4<br>High range = 16.5 | Confirmed |
| | | IP CV% (RSV-B):<br>Low range = 42.7<br>Medium range = 29.1<br>High range = 16.4 | |
| Linearity | 90% of the D-Prop are within [0.60–1.67] | 95% (188/198) of D-Prop were within [0.60–1.67] (RSV-A) | Confirmed |
| | | 94% (211/224) of D-Prop were within [0.60–1.67] (RSV-B) | |

CI, confidence interval; CV, coefficient of variation; D-Prop, deviation from proportionality; GMC, geometric mean of concentrations; IP, intermediate precision; LOD, limit of detection.

Precision and linearity were confirmed over the analytical range ([LLOQ–ULOQ]) of [62.70–794371.57] copies/PCR and [16.33–806320.32] copies/PCR for RSV-A and RSV-B, respectively. The LODs of 1.90 copies/PCR for RSV-A and 2.97 copies/PCR for RSV-B were also confirmed.

Laboratory assays used in the assessment of the primary and secondary endpoints of the RSVPreF3 OA clinical studies in the dossier included neutralisation assays for the determination of functional antibodies against RSV-A and RSV-B and Enzyme-linked immunosorbent assay (ELISA) for measurement of Immunoglobulin G (IgG) antibodies (Ab) binding to the RSVPreF3 protein. CMI was characterised by the evaluation of the RSVPreF3-specific CD4+ and CD8+ T-cell frequencies using Intracellular Cytokine Staining (ICS) assay performed on PBMC samples.

## 2.6.3. Discussion on clinical pharmacology

No human pharmacokinetic studies have been performed. This can be agreed upon as pharmacokinetic studies are not usually required for vaccines.

The Applicant utilised a RT-PCR assay to determine the viral presence and several different assays to evaluate humoral and cellular immunogenicity. For all assays, validation, and qualification reports, as well as SOPs, were submitted.

It should be remarked though that during the validation exercise conducted for the different assays, parameters most susceptible to change in clinical testing conditions were validated, meaning the main parameters that define the assay performances (linearity, precision, accuracy when there is an international reference available, and the assay lower and upper limits), with other parameters being covered by

qualification experiments. . For the RT-PCR assay, a duplex RT-PCR performed at the sponsor laboratory, this is not considered a major issue as the most relevant parameters – including the LOD - have been validated. The assay is therefore considered fit for the purpose of reliably detecting the presence or absence of RSV-A or RSV-B in the clinical samples of the studies included in the dossier. The assay can be considered fit for purpose, however, full validation cannot be claimed.

The same holds true for the RSV-A and RSV-B neutralisation assays, as several relevant assay parameters such as specificity, sample stability, and assay robustness are documented in the qualification report and not repeated during validation. It is however considered that the assays are considered fit for purpose. Further, the results of these assays are only considered supportive and are not necessary for the benefit/risk assessment. It is therefore not considered a requirement that the assay is fully validated. The lack of full validation may however have implications for (future) labelling claims that are based on comparative immunogenicity.

The outcome of the assay, serum neutralising antibody (NAb) titre, is expressed in ED60 (Estimated Dilution 60) values. The Applicant indicated that the ED60 was chosen as it was used during early development of the assay, and it was considered more conservative.

Also, the RSV PreF3 IgG binding antibody assay as well as the intracellular cytokine staining (ICS) assay are considered fit for purpose, but are not considered fully validated given that several parameters were not included in the validation experiments. Both assays however only provide supportive evidence of the humoral and cellular immunogenicity of the vaccine and are considered fit for this purpose. For the ICS assay, it should be remarked that the analytical range is small, 590 – 19197 polypositive cells per million PBMC, and the global limit of blank is set (in qualification experiments) at 310 which is rather high. This may influence the range of responses that can be reliably assessed with this assay. Based on the submitted validation data the haemagglutination inhibition assay that was used in the co-vaccination study is deemed suitable for the intended use.

### 2.6.4. Conclusions on clinical pharmacology

The assays used to confirm the presence of RSV in the clinical sampleswas a duplex RT-PCR performed at the sponsor laboratory. After the qualification experiments, the validation experiments only covered assessment of LOD, precision and linearity to confirm the performances of the assay in the clinical setting. Hence the assay can, based on the provided information, not be considered fully validated. The assay is however considered fit for the purpose of reliably detecting the presence or absence of RSV-A or RSV-B in the clinical samples of the studies included in the dossier.

As immunogenicity results are only supportive for the current application, and the provided validation and qualification reports for the different assays do not raise concerns, the lack of full validation of the immunogenicity assays should not hamper the B/R evaluation.

### 2.6.5. Clinical efficacy

The pivotal study providing information on the efficacy and safety of Arexvy and supporting the proposed indication is study ADJ-006, a Phase 3 study in healthy adults ≥60 years of age. The development program has been formally discussed with CHMP at various moments throughout development, and an agreement was reached regarding the key elements of the clinical development plan.

*2.6.5.1. Dose response studies*

Study ADJ-002

This was a Phase I/II, randomised, placebo-controlled, observer-blind, multicentre study to evaluate the safety, reactogenicity and immunogenicity of the investigational RSV vaccine (adjuvanted with $AS01_E$ or $AS01_B$ or unadjuvanted) when administered intramuscularly (IM) according to a 0, 2 months schedule in adults aged 18-40 (Part A) or 60-80 years (Part B). Part A will not be further discussed.

The primary objective of the study was to evaluate the reactogenicity and safety of 2 doses of different RSVPreF3 OA vaccine formulations administered intramuscularly according to a 0, 2-month schedule, up to 1 months post-last dose (Day 91). Secondary objectives included characterising the humoral (regarding RSV-A/-B NAb titres and RSVPreF3-specific IgG Ab concentrations) and cellular (in terms of frequencies of RSVPreF3-specific polypositive CD4+ T cells) immune response to the RSVPreF3 OA vaccine formulations up to Day 91.

Eligible participants were healthy male and female participants between 60 and 80 years of age at the time of first vaccination (inclusive) with no prior exposure to any RSV vaccine.

Participants were to receive 2 doses of vaccine formulations containing different antigen amounts (30, 60 or 120 µg), non-adjuvanted or adjuvanted with either $AS01_E$ or $AS01_B$, or Placebo. Participants were randomised to 10 study groups in a 1:1:1:1:1:1:1:1:1:1 ratio. In Part B, 1005 participants were enrolled and vaccinated with at least 1 dose of RSVPreF3 OA vaccine formulations or Placebo and 975 completed the study.

*Immunogenicity Results*

All participants were seropositive for RSV-A and RSV-B neutralising antibodies as well as RSVPreF3-specific IgG at baseline (Day 1). The highest antibody levels were obtained after Dose 1 for RSV-A neutralising antibodies, see Table 3. After a peak response at Day 31, the RSV-A neutralising antibody GMTs (ED60) slightly declined between Day 31 and Day 91 and then declined further at Month 8 and Month 14 but remained above the baseline values in all treatment groups (data not shown).

A noticeable increase in the RSV-A neutralising antibody GMTs (ED60) was observed with increase in antigen dose from 30 µg to 120 µg. No noticeable effect of adjuvant was observed.

Table 3: Geometric mean of the individual ratio of RSV A Neutralising antibody titers (ED60) post-vaccination compared to pre-vaccination - Part B Per Protocol Set (modified by Assessor)

| Group | N | Timepoint description* | GMT | Timepoint description | GMT | GMT ratio (post/pre) | LL | UL |
|---|---|---|---|---|---|---|---|---|
| 30-PLAIN_B | 93 | Day 31 | 5422.6 | Prevaccination | 976.4 | 5.6 | 4.5 | 6.8 |
| | 95 | Day 61 | 5657.9 | Prevaccination | 1033.3 | 5.5 | 4.5 | 6.7 |
| | 88 | Day 91 | 3936.2 | Prevaccination | 1024.4 | 3.8 | 3.1 | 4.7 |
| 60-PLAIN_B | 90 | Day 31 | 7371.0 | Prevaccination | 1112.2 | 6.6 | 5.3 | 8.4 |
| | 90 | Day 61 | 6490.8 | Prevaccination | 1117.6 | 5.8 | 4.6 | 7.3 |
| | 84 | Day 91 | 5632.1 | Prevaccination | 1160.7 | 4.9 | 4.0 | 5.9 |
| 120-PLAIN_ B | 90 | Day 31 | 9403.1 | Prevaccination | 950.5 | 9.9 | 8.0 | 12.3 |
| | 92 | Day 61 | 7907.4 | Prevaccination | 961.9 | 8.2 | 6.6 | 10.2 |
| | 87 | Day 91 | 5956.1 | Prevaccination | 909.1 | 6.6 | 5.5 | 7.8 |
| 30-AS01E_ B | 92 | Day 31 | 5258.5 | Prevaccination | 940.1 | 5.6 | 4.5 | 6.9 |
| | 93 | Day 61 | 5019.4 | Prevaccination | 995.1 | 5.0 | 4.1 | 6.2 |
| | 84 | Day 91 | 3924.7 | Prevaccination | 1024.1 | 3.8 | 3.2 | 4.6 |
| 60-AS01E_ B | 97 | Day 31 | 6509.4 | Prevaccination | 966.2 | 6.7 | 5.5 | 8.2 |
| | 100 | Day 61 | 6201.9 | Prevaccination | 969.0 | 6.4 | 5.3 | 7.7 |
| | 91 | Day 91 | 4770.0 | Prevaccination | 947.9 | 5.0 | 4.2 | 6.0 |
| 120-AS01E_B | 94 | Day 31 | 9350.9 | Prevaccination | 988.0 | 9.5 | 7.6 | 11.8 |
| | 95 | Day 61 | 6681.7 | Prevaccination | 949.7 | 7.0 | 5.7 | 8.7 |
| | 87 | Day 91 | 5175.5 | Prevaccination | 954.8 | 5.4 | 4.4 | 6.6 |
| 30-AS01B_ B | 95 | Day 31 | 6026.1 | Prevaccination | 978.3 | 6.2 | 5.0 | 7.6 |

| Group | N | Timepoint description* | GMT | Timepoint description | GMT | GMT ratio (post/pre) | LL | UL |
|---|---|---|---|---|---|---|---|---|
| | 94 | Day 61 | 5048.9 | Prevaccination | 967.5 | 5.2 | 4.3 | 6.4 |
| | 85 | Day 91 | 4435.9 | Prevaccination | 958.6 | 4.6 | 3.8 | 5.6 |
| 60-AS01B_ B | 95 | Day 31 | 6899.5 | Prevaccination | 1038.6 | 6.6 | 5.5 | 8.1 |
| | 97 | Day 61 | 5902.1 | Prevaccination | 1036.9 | 5.7 | 4.7 | 6.9 |
| | 93 | Day 91 | 4850.5 | Prevaccination | 1035.3 | 4.7 | 3.9 | 5.6 |
| 120-AS01B_B | 93 | Day 31 | 8527.7 | Prevaccination | 1068.9 | 8.0 | 6.6 | 9.6 |
| | 98 | Day 61 | 7201.4 | Prevaccination | 1014.5 | 7.1 | 5.9 | 8.5 |
| | 92 | Day 91 | 5980.6 | Prevaccination | 998.9 | 6.0 | 5.0 | 7.2 |
| Placebo_B | 92 | Day 31 | 751.7 | Prevaccination | 818.2 | 0.9 | 0.8 | 1.0 |
| | 96 | Day 61 | 903.4 | Prevaccination | 828.3 | 1.1 | 1.0 | 1.2 |
| | 93 | Day 91 | 772.4 | Prevaccination | 859.6 | 0.9 | 0.8 | 1.0 |

* Day 31 is 1 month after vaccination 1, Day 61 is the day of vaccination 2, Day 91 is 1 month after vaccination 2.

The kinetics of RSV-B neutralising antibodies and RSVPreF3-specific IgG were comparable to the kinetics of the RSV-A neutralising antibodies.

An increase in the frequency of RSVPreF3-specific polypositive CD4+ T-cells was observed in all RSVPreF3 groups at Day 31, see Table 4.

Table 4: Descriptive statistics of the frequency of RSVPreF3 specific-CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNFa, IFNg (per million of CD4+ T-cells, by ICS) - Part B - Per Protocol Set (Modified by Assessor)

| | Prevaccination | | | Day 31 | | | Fold increase (post/pre) | |
|---|---|---|---|---|---|---|---|---|
| Group | N | GM (SD) | Median (min-max) | N | GM (SD) | Median (min-max) | GM (SD) | Median (min – max) |
| 30-Plain | 82 | 98.5 (0.9) | 208.5 (1 - 1323) | 76 | 915.5 (0.3) | 979.5 (42 - 4052) | 1.7 (0.2) | 1.6 (1 – 7) |
| 60-Plain | 77 | 86.2 (0.9) | 166.0 (1 - 1087) | 68 | 998.6 (0.5) | 1089.5 (1 - 5901) | 2.0 (0.2) | 1.8 (1 – 9) |
| 120-Plain | 84 | 142.5 (0.7) | 225.5 (1 - 1537) | 76 | 1104.9 (0.3) | 1052.0 (215 - 5412) | 1.9 (0.2) | 1.8 (1 – 6) |
| 30-AS01E | 82 | 122.0 (0.8) | 209.5 (1 - 1375) | 76 | 1501.5 (0.3) | 1594.0 (460 - 8343) | 2.5 (0.3) | 2.7 (1 – 14) |
| 60-AS01E | 82 | 118.3 (0.8) | 188.0 (1 - 967) | 73 | 1292.6 (0.5) | 1297.0 (1 - 7086) | 2.5 (0.3) | 2.1 (1 – 12) |
| 120-AS01E | 83 | 92.4 (0.9) | 192.0 (1 - 1100) | 75 | 1185.7 (0.5) | 1466.0 (1 - 4539) | 2.2 (0.2) | 2.3 (1 – 8) |
| 30-AS01B | 80 | 104.0 (0.8) | 187.5 (1 - 782) | 77 | 1961.2 (0.3) | 1952.0 (437 - 7479) | 3.2 (0.3) | 3.3 (1 – 11) |
| 60-AS01B | 87 | 97.9 (0.8) | 185.0 (1 - 2303) | 80 | 1706.2 (0.3) | 1690.5 (157 - 5949) | 3.0 (0.3) | 2.9 (1 – 10) |
| 120-AS01B | 86 | 122.3 (0.8) | 206.0 (1 - 994) | 76 | 1594.1 (0.3) | 1742.5 (195 - 5454) | 2.7 (0.2) | 2.8 (1 – 9) |
| Placebo | 84 | 102.5 (0.8) | 178.0 (1 - 990) | 77 | 113.6 (0.7) | 176.0 (1 - 822) | 1.0 (0.0) | 1.0 (1 – 1) |

N= Number of subjects with available results
GM= Geometric mean; SD=Standard deviation computed on log10 transformed data
Prevaccination = Pre-Dose 1 at Day 1;Day 31 = Post-Dose 1 at Day 31;
Source: Table 14.2.2.346 and 14.2.2.470 (modified by Assessor)

‘

*Safety results*

The safety profile of the investigational vaccine was mainly characterised by reactogenicity events. An increase in the AE reporting pattern in the adjuvanted treatment groups compared to non-adjuvanted treatment groups and Placebo was observed. $AS01_E$ was observed to be less reactogenic compared to $AS01_B$. The vast majority of AEs reported were <Grade 3 in intensity in all treatment groups. In total, 78 subjects reported 107 SAEs (including 7 SAEs leading to death for 4 subjects) from Dose 1 until the study end (Month 14). None of the SAEs was considered to be causally related to vaccination as per the investigator’s judgment.

*Conclusion*

A clear impact of increasing the dose from 30 to 120 µg could be observed based on the humoral response, with RSV-A NAb GMT ratios D31/prevaccination ranging from 5.6 to 6.2 in the 30 µg group, 6.6 to 6.7 in the 60 µg group and 8.0 to 9.9 in the 120 µg group. No clear effect of adjuvant on the humoral response was observed. In addition, no increase in binding antibody GMCs or RSV-A and -B NAb GMTs (see Table 3) could be observed on Day 91 after the second vaccination on Day 61, indicating that a second dose had no added value. Based on the cellular immune response, a slight increase in RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNFα, IFNγ, with increasing amounts of adjuvant was observed. The safety profile of the investigational vaccine was mainly characterised by reactogenicity events. An increase in the AE reporting pattern in the adjuvanted treatment groups compared to non-adjuvanted treatment groups and Placebo was observed. However, no safety concerns were identified for any of the RSVPreF3 OA investigational vaccine formulations assessed.

The formulation with 120 ug RSVPreF3 adjuvanted with $AS01_E$ was selected for further investigation in phase 3 studies.

### *2.6.5.2. Main studies*

ADJ-006: A Phase 3, randomised, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above.

*Methods*

Study ADJ-006 is a phase 3, randomised, observer-blind, placebo-controlled multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of RSVPreF3 investigational vaccine in adults ≥ 60 years of age. The design of the study is presented in Figure 1.

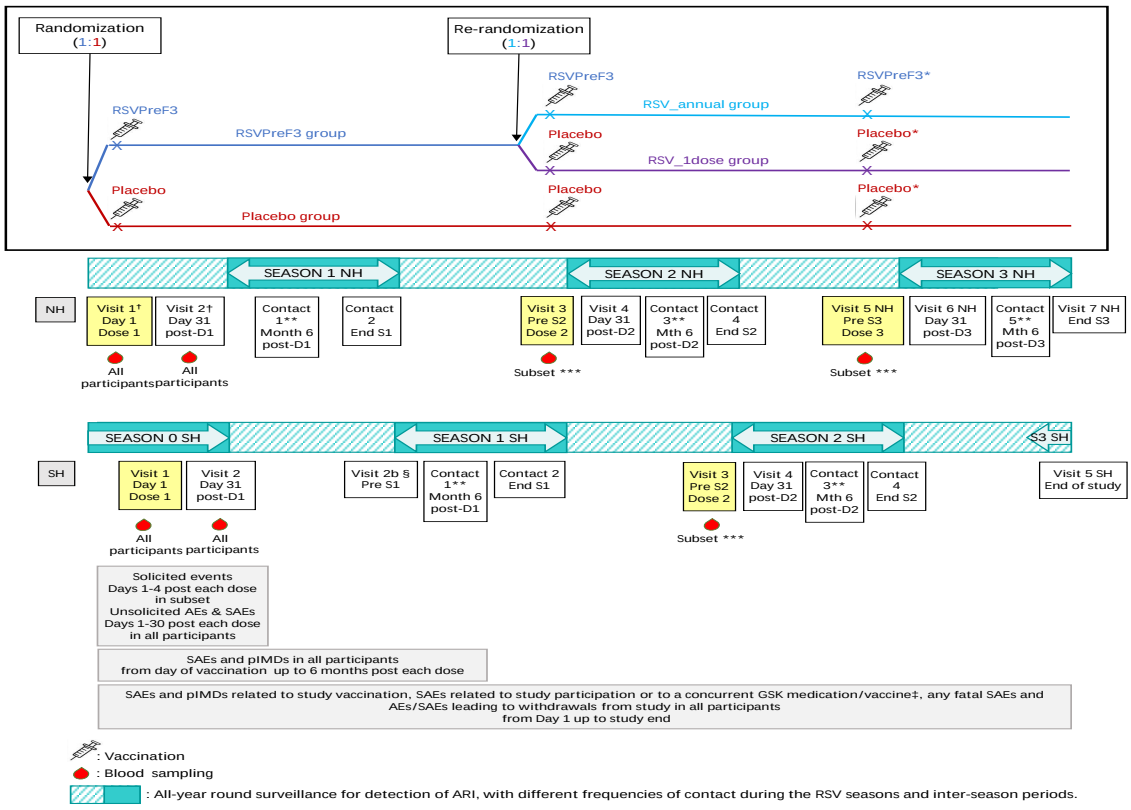



Figure 1: Study design overview.

* Dose 3 only applies to participants in the NH.

*† Depending on the time of enrollment, Visit 1 (Day 1) and Visit 2 (Day 31) in the NH can take place during Season 1.*

*** Contacts 1, 3 and 5 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.*

*§ Visit 2b in the SH (pre-Season 1 visit) should be performed at the earliest 3 months before the start of Season 1 in the SH. This Visit 2b should not be performed for participants that have their Visit 2 planned within 3 months before the start of Season 1. For all participants in the SH that have their Visit 2 more than 3 months before the start of Season 1, Visit 2b should be planned as a stand-alone visit.*

**** Blood samples should only be taken from participants in the reactogenicity and immunogenicity subset in Part 1.*

*‡ All SAEs related to study participation, or a GSK concomitant medication/vaccine are to be recorded from the time the participant consents to participate in the study. All other SAEs are to be reported after the first study intervention administration.*

The current submission includes the interim analysis of the primary objective (VE Analysis 1), as well as secondary descriptive VE, safety and immunogenicity results available at VE Analysis 1.

## Study Participants

The trial included healthy male or female participants aged 60 years and older who did not have a previous vaccination with an RSV vaccine, from whom written informed consent was obtained. Participants living in the community dwelling (CD), or long-term care facilities (LTCF) could be enrolled. Any underlying chronic condition was documented to be stable, according to the investigator's clinical judgement, with or without treatment. Exclusion criteria included participants who were immunocompromised, and administration of long-acting or chronic treatment with immune modifying drugs. In addition, normal in and exclusion criteria appropriate for a vaccine trial were in place.

### Treatments

Subjects received either a single dose of 0.5 mL Arexvy or 0.7 mL Placebo via intramuscular injection (IM) in the deltoid of the non-dominant arm.

### Objectives

Primary objective:

- To demonstrate the efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD during the first season in adults ≥ 60 YOA. (Criterion: The LL of the 2-sided CI for VE is above 20%)

Main secondary objectives:

- Efficacy - Descriptive
    - To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses, by:
        - RSV subtype (A and B) separately
        - by age category
        - baseline comorbidities
        - baseline frailty status
        - disease severity
    - To evaluate in adults ≥ 60 YOA, the efficacy of the RSVPreF3 OA investigational vaccine, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses, in the prevention of:
        - RSV-confirmed acute respiratory infection (ARI).
        - Any ARI and any LRTD
    - To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hospitalisation due to respiratory diseases during the RSV seasons in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination doses.
- Secondary – Immunogenicity
    - To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine.

For information regarding additional secondary objectives see Clinical AR.

### Outcomes/endpoints

The primary efficacy endpoint is the first occurrence of RT-PCR-confirmed by an adjudication committee of RSV-A and/or B-associated LRTD, according to the case definition (see Table 5), 15 days post-vaccination. This endpoint will also be used for several secondary objectives.

Table 5: Case definitions for evaluation of vaccine efficacy

| Endpoint | Case definition |
|---|---|
| ARI<br>(Trigger for swabbing) | Presence of:<br>● at least 2 respiratory symptoms/signs for at least 24 hours<br>OR |

<table>
<tr><td></td><td colspan="2">• at least 1 respiratory symptom/sign + 1 systemic symptom/sign for at least 24 hours</td></tr>
<tr><td></td><td>Respiratory symptoms and signs<br>- Nasal congestion/rhinorrhoea<br>- Sore throat<br>- New or increased sputum<br>- New or increased cough<br>- New or increased dyspnoea (shortness of breath)<br>- New or increased wheezing[3]<br>- New or increased crackles/ronchi[4] based on chest auscultation<br>- Respiratory rate ≥ 20 respirations/min[4]<br>- Low or decreased oxygen saturation<br>(= O2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]<br>- Need for oxygen supplementation[4]</td><td>Systemic symptoms and signs<br>- Fever[1]/feverishness[2]<br>- Fatigue<br>- Body aches<br>- Headache<br>- Decreased appetite</td></tr>
<tr><td>RT-PCR-confirmed RSV-ARI or hMPV-ARI[5]</td><td colspan="2">An event meeting the case definition of ARI with at least one RSV-positive swab or at least one hMPV-positive swab detected by RT-PCR.</td></tr>
<tr><td>LRTD</td><td colspan="2">Presence of:<br>• at least 2 lower respiratory symptoms/signs for at least 24 hours including at least 1 lower respiratory SIGN<br>OR<br>• at least 3 lower respiratory symptoms for at least 24 hours</td></tr>
<tr><td></td><td>Lower respiratory symptoms<br>- New or increased sputum<br>- New or increased cough<br>- New or increased dyspnoea (shortness of breath)</td><td>Lower respiratory signs<br>- New or increased wheezing[3]<br>- New or increased crackles/ronchi[4] based on chest auscultation<br>- Respiratory rate ≥ 20 respirations/min[4]<br>- Low or decreased oxygen saturation (= O2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]<br>- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed RSV- LRTD or hMPV-LRTD[5]</td><td colspan="2">An event meeting the case definition of LRTD with at least one RSV-positive swab or at least one hMPV-positive swab detected by RT-PCR.</td></tr>
<tr><td>RT-PCR-confirmed severe RSV LRTD or severe hMPV LRTD – Definition 1 “Clinical symptomology” [5]</td><td colspan="2">Presence of a LRTD with at least one of the following criteria:<br>• at least 2 lower respiratory SIGNS<br>• an LRTD episode assessed as ‘severe’ by the investigator[6]<br>AND<br>• with at least one RSV-positive or hMPV-positive swab detected by RT-PCR</td></tr>
<tr><td></td><td colspan="2">Lower respiratory signs<br>- New or increased wheezing[3]<br>- New or increased crackles/ronchi4i based on chest auscultation<br>- Respiratory rate ≥ 20 respirations/min[4]<br>- Low or decreased oxygen saturation (= O2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]<br>- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed severe RSV LRTD or severe hMPV LRTD – Definition 2 “Supportive therapy” [5]</td><td colspan="2">Presence of a LRTD with at least one of the following criteria[7]:<br>- Need for oxygen supplementation[4]<br>- Need for positive airway pressure therapy (e.g. CPAP)<br>- Need for other types of mechanical ventilation AND<br>- with at least one RSV-positive or hMPV-positive swab detected by RT-PCR</td></tr>
</table>

ARI: acute respiratory infection; LRTD: lower respiratory tract disease; RSV: respiratory syncytial virus; hMPV: human metapneumovirus; RT-PCR: reverse transcription polymerase chain reaction

1. Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route.
2. Feverishness is defined as the feeling of having fever without objective measurement.
3. Reported by study participant or investigator.
4. Reported by investigator.
5. Throat and/or nasal swab samples collected at ARI visits for RT-PCR testing will be collected within 6 days after ARI onset (i.e. up to Day 7). In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit within 6 days after ARI onset (i.e. within Day 3 to Day 7), then the interval for this visit and the site swab collection may be extended up to maximum 14 days after ARI onset (i.e. until Day 15).
6. The investigator will grade each ARI as mild, moderate or severe based on the grading scale.
7. In case the participant was already receiving any of these for treating/controlling any pre-existing condition, any significant change or adaptation in the used therapy should be taken into account.

In case of at least 2 concomitant ARI symptoms/signs identified by the participant (i.e., trigger for swabbing, see Table 5), the following visits and contacts will take place:

- Participant's call (Day 2): Within 24 hours of the appearance of at least 2 concomitant ARI symptoms/signs, the participant should call the site staff. During the phone call, ARI symptoms/signs reported by the participant should be recorded in the eCRF and record the onset date of each symptom mentioned. An ARI visit will be organised. The participant is reminded to take a nasal self-swab. The self-collected swab should be done preferably within 48 hours of ARI onset but not later than 5 days after ARI onset.
- ARI visit (Days 3-7): The ARI visit should take place soon after ARI onset, ideally 48 hours after ARI onset, but no later than 6 days after ARI onset (exceptions are made for suspected COVID-19 cases). Ideally, and in most cases, the ARI visit should be scheduled at least 1 day after the participant's self-swab (i.e., the nasal self-swab taken by the participant and the nasal and throat swab samples taken by the qualified site staff should not be done on the same day).

Main secondary endpoints include:

The first occurrence of RT-PCR-confirmed RSV-A and/or B-associated ARI, according to the case definition (see Table 5).
The first occurrence of ARI or LRTD, according to the case definition (see Table 5).

- Occurrence of hospitalisation due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons†.
- In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Dose 3 (pre-Season 3):
    - RSVPreF3 IgG-specific Ab concentrations.
    - NAb titers against RSV-A.
    - NAb titers against RSV-B.

For information regarding additional secondary endpoints see Clinical AR.

### Sample size

The original sample size for the study was determined assuming an attack rate of RSV-confirmed LRTD around 0.6% during the first season. Due to the potential impact of the COVID-19 pandemic measures on RSV circulation and the difficulty to estimate the attack rate for Season 1, the sample size was increased up to 23 000 in the NH.

In total 25,040 subjects have been randomised.

### Randomisation and blinding (masking)

An automated internet-based system (SBIR) was used for randomisation with randomisation ratio 1:1. The system's randomisation algorithm used a stratification by subset (subjects included in reactogenicity/immunogenicity subset or not) and a minimisation procedure accounting for centre, age and region within each subset. Minimisation factors will have equal weight in the minimisation algorithm. The minimisation procedure used an unknown fixed percentage of randomness.

The study was observer blind. Treatment administration was performed by qualified study personnel (unblinded) who will not participate in the study. Only the unblinded committee independent from the project

(firewall) reviewed the results of the unblinded analyses, which were performed by an unblinded independent external statistician.

Statistical methods

*Analysis sets*

- Exposed Set (ES): All participants who received at least the first dose of the study intervention. The allocation in a group is done in function of the administered intervention.
- Modified Exposed Set (mES) - *RSV*: the mES-*RSV* will be the primary population for efficacy analysis on RSV-confirmed cases. It will include all participants who received *at least the first dose of* the study intervention *(ES)* and who did not report an RSV-confirmed ARI prior to Day 15 after *each* vaccination. The allocation in a group is done in function of the administered intervention.
- Per Protocol set for efficacy (PPSe): the PPSe will include all participants included in the mES who:
  - received at least the first dose of the study vaccine to which they were randomised,
  - have data available for efficacy endpoint measures,
  - did not have any protocol deviations leading to exclusion.
- Solicited Safety Set (SSS): All participants who received at least the first dose of the study intervention (Exposed Set) and have solicited safety data.

*Interim analysis and multiplicity*

An optional planned interim analysis was performed as at least 35 cases were accrued (at the end of Season 1 in NH or later). The Type I error for the interim was adjusted to maintain the overall (one-sided) significance level at 2.5%. The Wang-Tsiatis approach was planned to be used [Wang, 1987]. This alpha spending method (with boundaries between O'Brien-Fleming and Pocock boundaries) depends on the quantity of information accumulated at the time of interim analysis (using gsDesign package in R).

For analysis of season 1, only the primary objective was type I error controlled, i.e., demonstration of efficacy of RSV vaccine against RSV-confirmed LRTD during the first season. All other endpoints were supportive. Therefore, no adjustment of alpha for multiplicity was applied.

Type I error was controlled over all seasons. If efficacy was demonstrated during the first season, testing of the confirmatory objectives in the next seasons will be done sequentially.

*Primary efficacy endpoint and primary efficacy analysis*

The primary efficacy endpoint is the first occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, with cases identified according to the case definition with an onset of 15 days post vaccination and confirmed by an external adjudication committee.

Missing or non-evaluable measurements were not imputed for the primary analysis and were considered missing (completely) at random.

The primary efficacy analysis was based on a Poisson regression model adjusted for age and region and using an exact conditional method and performed for the mES population. The model will estimate the mean

number of cases as a function of the different covariates (age included in categories 60-69y, 70-79y, >=80y and region included as North America, Europe, Asia, SH) and the logarithm of the follow up time. For the primary efficacy analysis, the follow up time starts on Day 15 post-vaccination and ends at the first occurrence of the event or at the last contact or database cut-off date. Vaccine efficacy (VE) is defined as 1-RR, where RR = Relative Risk calculated as the ratio of incidence rates (Arexvy / Placebo), presented with an adjusted CI and a one-sided p-value for testing $H_0$: VE ≤ 20%.

As sensitivity analysis a Cox Proportional Hazard regression model was performed adjusted for age and region and based on the mES population.

Supportive analyses are: 1. A re-randomisation test based on the method presented in [Wang, 2020]. 2. An analysis including all RSV RT-PCR confirmed LRTD cases either fulfilling case definition (as confirmed by GSK internal review) and/or confirmed by the study Investigators. 3. An analysis considering the RSV cases only confirmed by the GSK qRT-PCR. 4. An analysis excluding RSV cases with respiratory co-infections (e.g. hMPV, SARS-COV-2, FLU, etc.).

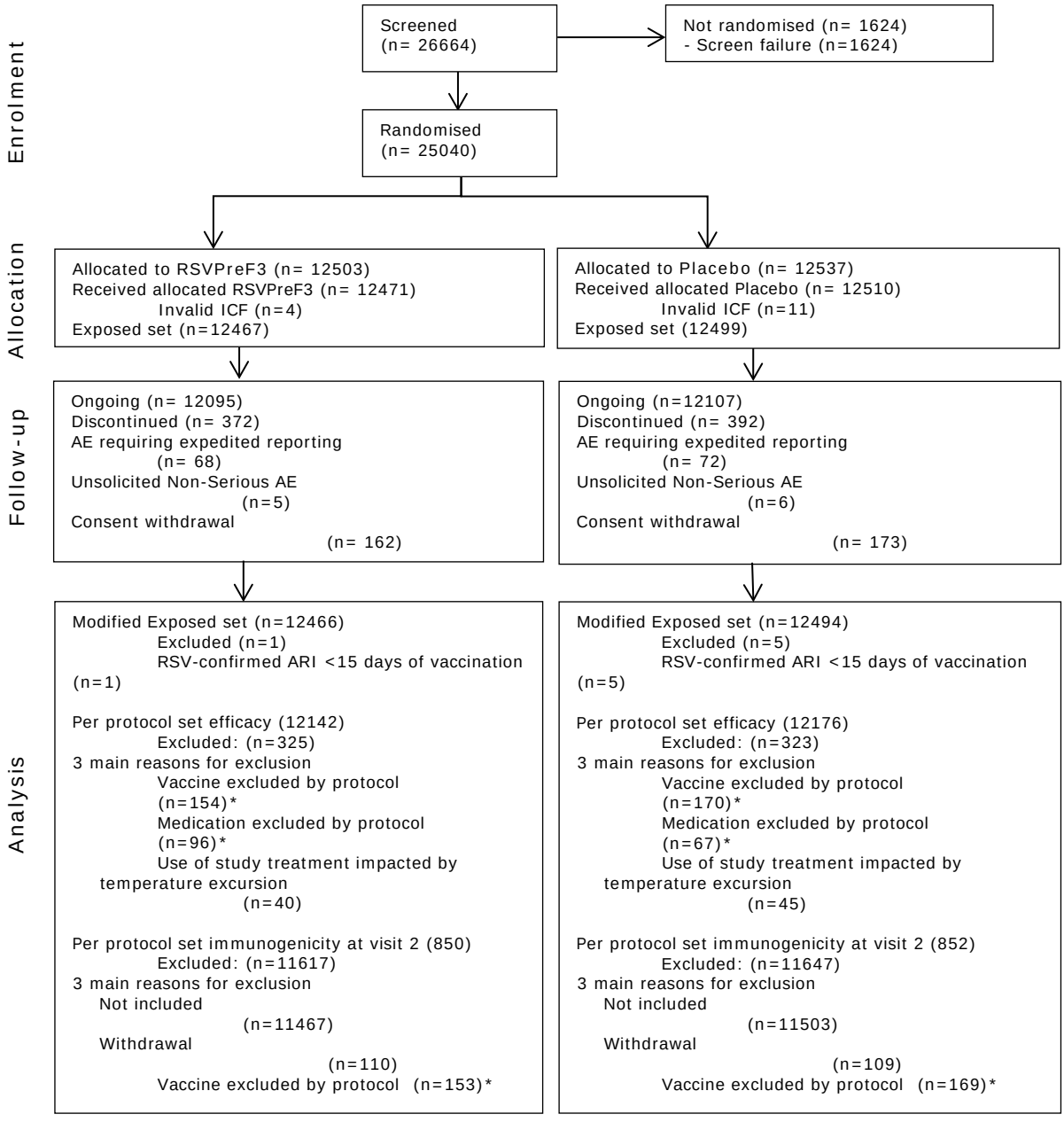
*Secondary efficacy analyses*

The same analysis method as described for the primary efficacy endpoint was used for the secondary efficacy endpoints. As the secondary endpoints were not included in the confirmatory testing strategy, the results of the secondary efficacy endpoints are not type I error controlled and considered supportive.

The analysis of secondary efficacy endpoints related to RSV-confirmed cases are performed on the mES population, while the ES population will be the primary population for secondary efficacy endpoints not related to RSV or hMPV.

*Results*

- Participant flow




* Included eliminations related to Covid-19, e.g. vaccination and medication.

- Recruitment

Study ADJ-006 was initiated on 25 May 2021 (first participant first visit). The data lock point for interim efficacy analyses at VE analysis 1 was 11 April 2022, the data lock point for safety analyses at VE analysis 1 was 30 April 2022. The study remains ongoing.

The study is being conducted in 278 active sites in 17 countries, 14 countries in the Northern hemisphere (US, Canada, Mexico, Belgium, Estonia, Finland, Italy, Germany, Poland, UK, Spain, Russia, South Korea, and Japan) and 3 in the Southern hemisphere (Australia, New Zealand and South Africa).

- Conduct of the study

*Amendments*

The original protocol (16 October 2020) was amended 3 times:

Protocol Amendment 1 (25 February 2021)

- Increase sample size based on reduced attack rate due to restrictive measures in place to control the COVID-19 pandemic.
- Implement consultation with regulatory authorities, including removal of lot-to-lot consistency evaluation and change in start of ARI surveillance.

Protocol Amendment 2 (06 October 2021)

- Adapt the trigger for the assessment of the primary objective to allow the assessment of the primary objective once the required number of cases have been accumulated.
- Inclusion of an optional interim analysis in case number of cases triggering the final analysis of the primary objective is not achieved at the end of Season 1 in Northern Hemisphere.
- Move evaluation of efficacy against any ARI and any LRTD to secondary descriptive objective.
- Assessment of immunogenicity in terms of NAb against RSV-B is added.

Protocol Amendment 3 (24 January 2022)

- Include the assessment of the efficacy of annual revaccinations
- Add evaluation of efficacy against each RSV subtype independently as secondary confirmatory objective at the end of the study, conditional to the number of cases accrued.

*Protocol deviations*

The number of participants with at least 1 important PD was consistent between both groups (5.9% [n=741] of participants in the RSVPreF3 group and 6.1% [n=771] in the Placebo group). Most of the important PDs were related to “out of window assessment for immunogenicity” (308 vs 341), followed by “administration of vaccine excluded by the protocol” (151 vs 162), ”missed assessment (immunology)” (77 vs 72), and “administration of medication excluded by the protocol” (94 vs 67).

- Baseline data

The baseline demographic data of the ES population in study ADJ-006 is shown in Table 6.

Demographics and baseline characteristics of participants in the ES were well-balanced between the 2 treatment groups. The median age of participants at first dose was 69.0 years in both groups, with a similar proportion of participants in each age category across groups (74.3% were ≥65 YOA, 44.1% were ≥70 YOA, 8.2% were ≥80 YOA in the RSVPreF3 group 74.6% were ≥65 YOA, 44.1% were ≥70 YOA, 8.2% were ≥80 YOA in the placebo group). Approximately half the participants were female (51.7%), and most were White (79.4%) and not of Hispanic or Latino origin (94.5%). Demographics and baseline characteristics of participants in the PPSe, PPSi and SSS were largely comparable to the baseline characteristics in the ES.

Table 6: Summary of demography and baseline characteristics — ES (ADJ-006) (modified by Assessor)

| | RSVPreF3 N=12467 | | Placebo N=12499 | | Total N=24966 | |
|---|---|---|---|---|---|---|
| | Value or n | % | Value or n | % | Value or n | % |
| Age (years) at vaccination at Visit 1 | | | | | | |
| N | 12467 | | 12499 | | 24966 | |
| Mean (Standard deviation) | 69.5 (6.5) | | 69.6 (6.4) | | 69.5 (6.5 | |
| Median (Minimum – Maximum) | 69.0 (59-102) | | 69.0 (59 – 98) | | 69.0 (59 – 102) | |
| Age category | | | | | | |
| >=65 YOA | 9259 | 74.3 | 9329 | 74.6 | 18588 | 74.5 |
| >=70 YOA | 5504 | 44.1 | 5519 | 44.1 | 11023 | 44.2 |
| >=80 YOA | 1017 | 8.2 | 1028 | 8.2 | 2045 | 8.2 |
| 60-69 YOA | 6963 | 55.9 | 6980 | 55.8 | 13943 | 55.8 |
| 70-79 YOA | 4487 | 36.0 | 4491 | 35.9 | 8978 | 36.0 |
| Sex | | | | | | |
| Male | 5979 | 48.0 | 6072 | 48.6 | 12051 | 48.3 |
| Female | 6488 | 52.0 | 6427 | 51.4 | 12915 | 51.7 |
| Ethnicity | | | | | | |
| Hispanic Or Latino | 682 | 5.5 | 682 | 5.5 | 1364 | 5.5 |
| Not Hispanic Or Latino | 11780 | 94.5 | 11811 | 94.5 | 23591 | 94.5 |
| Unknown | 5 | 0.0 | 6 | 0.0 | 11 | 0.0 |
| Race (sub-category) | | | | | | |
| African | 1064 | 8.5 | 1101 | 8.8 | 2165 | 8.7 |
| Asian | 953 | 7.6 | 956 | 7.7 | 1909 | 7.6 |
| White | 9887 | 79.3 | 9932 | 79.5 | 19819 | 79.4 |
| Other | 563 | 4.5 | 510 | 4.1 | 1073 | 4.3 |
| Hemisphere | | | | | | |
| Northern hemisphere | 11496 | 92.2 | 11522 | 92.2 | 23018 | 92.2 |
| Southern hemisphere | 971 | 7.8 | 977 | 7.8 | 1948 | 7.8 |
| Type Of Residence | | | | | | |
| Community Dwelling | 12306 | 98.7 | 12351 | 98.8 | 24657 | 98.8 |
| Long-Term Care Facilities | 161 | 1.3 | 148 | 1.2 | 309 | 1.2 |
| BMI (kg/m²) | | | | | | |
| N | 12457 | | 12490 | | 24947 | |
| Mean (Standard deviation) | 29.1 (6.1) | | 29.1 (6.0) | | 29.1 (6.1) | |
| Median (Minimum – Maximum) | 28.3 (12.6–116.7) | | 28.3 (13.1-69.8) | | 28.3 (12.6-116.7) | |
| Frailty Status | | | | | | |
| Frail | 189 | 1.5 | 177 | 1.4 | 366 | 1.5 |
| Pre-Frail | 4793 | 38.4 | 4781 | 38.3 | 9574 | 38.3 |
| Fit | 7464 | 59.9 | 7521 | 60.2 | 14985 | 60.0 |
| Unknown | 21 | 0.2 | 20 | 0.2 | 41 | 0.2 |
| Smoking status for tobacco | | | | | | |
| Current smoker | 1644 | 13.2 | 1665 | 13.3 | 3309 | 13.3 |
| Former smoker | 4311 | 34.6 | 4430 | 35.4 | 8741 | 35.0 |
| Never smoker | 6511 | 52.2 | 6404 | 51.2 | 12915 | 51.7 |
| Unknown | 1 | 0.0 | 0 | 0 | 1 | 0.0 |
| Smoking status for e-cigarettes | | | | | | |
| Current smoker | 121 | 1.0 | 109 | 0.9 | 230 | 0.9 |
| Former smoker | 89 | 0.7 | 78 | 0.6 | 167 | 0.7 |
| Never smoker | 12256 | 98.3 | 12312 | 98.5 | 24568 | 98.4 |
| Unknown | 1 | 0.0 | 0 | 0 | 1 | 0.0 |
| Charlson Comorbidity Index - Categories | | | | | | |
| Low/Medium risk | 8235 | 66.1 | 8368 | 66.9 | 16603 | 66.5 |
| High risk | 4232 | 33.9 | 4131 | 33.1 | 8363 | 33.5 |
| Charlson Comorbidity Index - Score | | | | | | |
| N | 12467 | | 12499 | | 24966 | |
| Mean (Standard deviation) | 3.2 (1.2) | | 3.2 (1.2) | | 3.2 (1.2) | |
| Median (Minimum – Maximum) | 3.0 (2 – 11) | | 3.0 (2 – 11) | | 3.0 (2 – 11) | |
| Comorbidity of interest | | | | | | |
| At least 1 pre-existing comorbidity of interest | 4937 | 39.6 | 4864 | 38.9 | 9801 | 39.3 |
| At least 1 pre-existing Cardio-respiratory condition | 2496 | 20.0 | 2422 | 19.4 | 4918 | 19.7 |
| At least 1 pre-existing Endocrinometabolic condition | 3200 | 25.7 | 3236 | 25.9 | 6436 | 25.8 |

| | RSVPreF3 N=12467 | | Placebo N=12499 | | Total N=24966 | |
|---|---|---|---|---|---|---|
| | Value or n | % | Value or n | % | Value or n | % |

N = number of participants: n / % = number / percentage of participants in a given category; Value = value of the considered parameter
Age computed based on incomplete date of birth (only year was available), however the minimum exact age was 60 years.
Frailty status: Frail = Participants with a walking speed <0.4m/s or who were not able to perform the test; Pre-Frail = Participants with a walking speed between 0.4-0.99 m/s; Fit = Participants with a walking speed >=1 m/s
Charlson Comorbidity Index: Low/medium Risk = Participants with comorbidity score at baseline less than or equal to 3; High Risk = Participants with comorbidity score at baseline greater than 3

- Numbers analysed

The participant flow, including participants randomised, vaccinated, discontinued and ongoing, is presented above.

Primary efficacy analysis was performed on the mES (for endpoints related to RSV-confirmed cases). Additional analyses were performed on the PPSe and on the ES to complement the primary analysis of the primary objective.

The primary analysis of immunogenicity was performed on the PPSi for participants included in the immunogenicity and reactogenicity subset. As more than 5% of participants were excluded from the PPSi, a second analysis of immunogenicity was performed on the ES.

| Analysis set | RSVPreF3 N (%) | Placebo N (%) | Total N (%) |
|---|---|---|---|
| Enrolled set | | | 26664 |
| Exposed set | 12467 | 12499 | 24966 |
| Modified exposed set | 12466 (100) | 12494 (100) | 24960 (100) |
| Per protocol set of efficacy | 12142 (97.4) | 12176 (97.4) | 24318 (97.4) |
| Per protocol set of immunogenicity at visit 2 | 850 (6.8) | 852 (6.8) | 1702 (6.8) |
| Solicited safety set | 879 (7.1) | 878 (7.0) | 1757 (7.0) |

- Outcomes and estimation

Primary objective

*Interim analysis*

The submission contains data of the interim analysis. An interim analysis was triggered when 35 cases of RSV-confirmed LRTD were accrued. In total, 47 externally adjudicated cases of RSV-confirmed LRTD cases were accrued up to the data lock point of 11 April 2022 in the primary cohort for efficacy (i.e., mES). Cases with ARI visit up to DLP for efficacy analyses (11 April 2022) were taken into consideration.

Analysis of the primary objective is presented in Table 7.

Table 7: VE against first occurrence of RT-PCR-confirmed RSV LRTD up to VE Analysis 1, using Poisson method – mES (ADJ-006)

| Endpoint | RSVPreF3 | | | | Placebo | | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | T (year) | n/T (per 1000) | N | n | T (year) | n/T (per 1000) | % | 96.95% CI | | P-value |
| | | | | | | | | | | LL | UL | |
| RT-PCR-confirmed RSV LRTD | 12466 | 7 | 6865.9 | 1.0 | 12494 | 40 | 6857.3 | 5.8 | 82.58 | 57.89 | 94.08 | <0.0001 |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants
n = number of participants with at least one RT-PCR-confirmed RSV LRTD; RSV LRTD = RSV LRTD identified by Adjudication Committee
T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years
n/T (per 1000) = Incidence rate of participants reporting at least one event
96.95% CI = 96.95% confidence interval - adjustment of alpha level at interim obtained using Wang-Tsiatis method.
LL = Lower Limit, UL = Upper Limit
VE (%) = Vaccine Efficacy (Poisson method - adjusted by age and region)
P-value = Two-sided Exact P-value conditional to number of cases comparing incidence rates; Note: Cases reported from Day 15 post-vaccination up to efficacy data lock point = 11APR2022
Source: Table 14.2.1.1 (20JUL2022 14:17 GMT)

This result was confirmed in the ES and PPSe population: VE was 83.8% (96.95% CI: 61.1, 94.5, number of events 7 vs 43) and 81.7% (96.95% CI: 55.5, 93.8, number of events 7 vs 38) respectively. Results of the sensitivity analysis estimated using a Cox proportional hazard regression model, adjusted for the covariates age and region are consistent with the primary analysis (VE: 82.5% [96.95% CI: 57.6, 92.8]).

The cumulative incidence curves present the cumulative numbers of RT-PCR-confirmed RSV LRTD reported from Day 15 post-vaccination up to VE Analysis 1 in both groups (Figure 2).

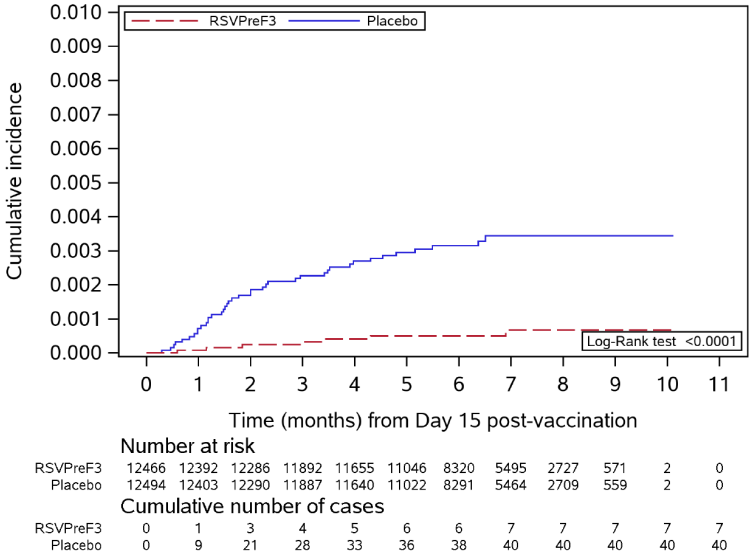



Figure 2: Cumulative incidence curves for RT-PCR-confirmed RSV LRTD reported up to VE analysis 1 modified Exposed Set. *Note, cases reported from Day 15 post-vaccination up to efficacy data lock point (11 April 2022). Cases included were identified by Adjudication committee.*

*VE Analysis 2 (End of Season 1 in SH)*

Of the 24981 vaccinated participants, 24966 (12467 in RSVPreF3 group and 12499 in Placebo group) were included in the Exposed set (ES) at VE1 (15 participants were excluded due to an invalid ICF). At the time of VE2, a valid ICF had been obtained for 7 out of these 15 participants, increasing the number of participants in the ES from 24966 (at VE1) to 24973 (at VE2) and those in the mES from 24960 (at VE1) to 24967 (at VE2).

VE analysis 2 (VE2) was based on efficacy data collected up to DLP 30 September 2022 or Dose 2 (revaccination) if administered before. In total, 57 externally adjudicated cases of RSV-confirmed LRTD have been accrued up to the efficacy DLP in the mES. This represents 10 additional cases as compared to VE1.

Analysis of the primary objective is presented in Table 8.

Table 8 Vaccine efficacy against first occurrence of RT-PCR-confirmed RSV LRTD up to end of season 1 in Southern Hemisphere, using Poisson method (VE Analysis 2) - mES (AJD-006)

| Endpoint | RSVPreF3 | | | | Placebo | | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | T (year) | n/T (per 1000) | N | n | T (year) | n/T (per 1000) | % | 96.95% CI | | P-value |
| | | | | | | | | | | LL | UL | |
| RT-PCR-confirmed RSV LRTD | 12469 | 10 | 11721.8 | 0.9 | 12495 | 47 | 11689.6 | 4.0 | 78.86 | 57.61 | 90.48 | <0.0001 |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants
n = number of participants with at least one RT-PCR-confirmed RSV LRTD; RSV LRTD = RSV LRTD identified by Adjudication Committee
T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date or up to Dose 2 administration) expressed in years
n/T (per 1000) = Incidence rate of participants reporting at least one event
95% CI = 95% confidence interval. LL = Lower Limit, UL = Upper Limit
VE (%) = Vaccine Efficacy (Poisson method - adjusted by age and region)
P P-value = Two sided Exact P-value conditional to number of cases comparing incidence rates and testing the null hypothesis VE<=0%; Note : Cases reported from Day 15 post-vaccination up to efficacy data lock point = 30SEP2022 or up to Dose 2 administration

The median follow-up time up to VE Analysis 2 in the mES was 11.5 months (11.6 months for both groups in the NH, and 9.1 months for both groups in the SH).

The cumulative incidence curves present the cumulative numbers of RT-PCR-confirmed RSV LRTD reported from Day 15 post-vaccination up to VE Analysis 2 in both groups (Figure 3).

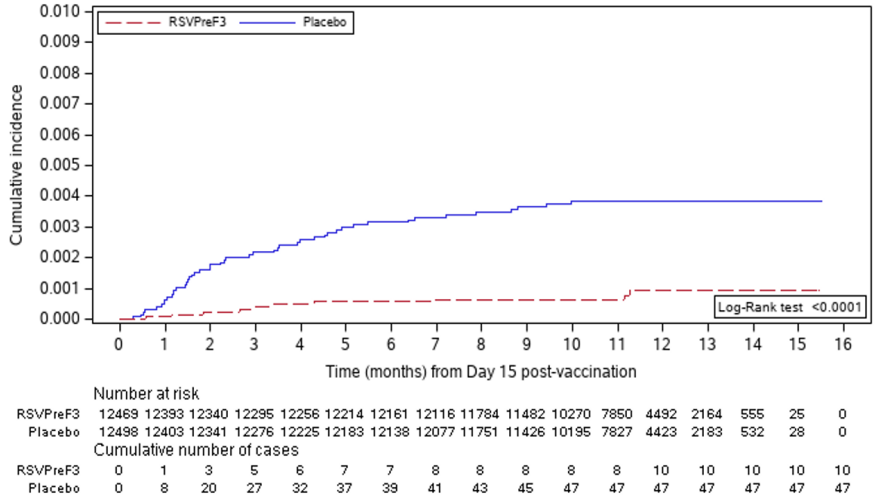



Figure 3 Cumulative incidence curves for RT-PCR-confirmed RSV LRTD reported up to end of season 1 in Southern Hemisphere (VE analysis 2) modified Exposed Set. Note, cases reported from Day 15 post-vaccination up to efficacy data lock point (30SEP2022) or up to Dose 2 administration. Cases included were identified by Adjudication committee.

Secondary objective: VE against RSV-associated LRTD in subgroups

*Interim analysis*

Results of the VE against first occurrence of RSV-confirmed LRTD in the main subgroups based on RSV subtype, age, and presence of comorbidities is presented in Table 9.

Table 9: VE against first occurrence of RT-PCR-confirmed RSV LRTD up to VE Analysis 1 by RSV subtype, age category and presence of comorbidities using Poisson method – mES (ADJ-006) (Modified by Assessor)

| | | RSVPreF3 | | | | Placebo | | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | 95% CI | | |
| Endpoint | Subgroup | N | n | T (year) | n/T (per 1000) | N | n | T(year) | n/T (per 1000) | % | LL | UL | P-value |
| RSV subtype | | | | | | | | | | | | | |
| RT-PCR-confirmed RSV LRTD | RSV-A | 12466 | 2 | 6867.4 | 0.3 | 12494 | 13 | 6868.9 | 1.9 | 84.62 | 32.08 | 98.32 | 0.0074 |
| | RSV-B | 12466 | 5 | 6866.7 | 0.7 | 12494 | 26 | 6862.3 | 3.8 | 80.88 | 49.40 | 94.27 | 0.0002 |
| Age category | | | | | | | | | | | | | |
| RT-PCR-confirmed RSV LRTD | 60-69 YOA | 6963 | 4 | 3850.8 | 1.0 | 6979 | 21 | 3836.4 | 5.5 | 80.96 | 43.56 | 95.25 | 0.0009 |
| | 70-79 YOA | 4487 | 1 | 2463.6 | 0.4 | 4487 | 16 | 2461.6 | 6.5 | 93.81 | 60.15 | 99.85 | 0.0003 |
| | >=80 YOA | 1016 | 2 | 551.4 | 3.6 | 1028 | 3 | 559.3 | 5.4 | 33.83 | -477.68 | 94.47 | 0.9931 |
| Comorbidities | | | | | | | | | | | | | |
| RT-PCR-confirmed RSV LRTD | No pre-existing comorbidity of interest | 7529 | 6 | 4094.1 | 1.5 | 7633 | 22 | 4148.1 | 5.3 | 72.46 | 29.97 | 90.87 | 0.0040 |
| | At least 1 pre-existing comorbidity of interest | 4937 | 1 | 2771.8 | 0.4 | 4861 | 18 | 2709.1 | 6.6 | 94.61 | 65.88 | 99.87 | <0.0001 |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
≥65 YOA = ≥65 years old participants; ≥70 YOA = >=70 years old participants; ≥80 YOA = ≥80 years old participants;
60-69 YOA = 60-69 years old participants; 70-79 YOA = 70-79 years old participants
N = number of participants; n = number of participants with at least one RT-PCR-confirmed RSV-A/B LRTD; RSV LRTD= RSV LRTD identified by Adjudication Committee
T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; n/T (per 1000) = Incidence rate of participants reporting at least one event
95% CI = 95% confidence interval. LL = Lower Limit, UL = Upper Limit; VE (%) = Vaccine Efficacy (Poisson method - adjusted by region); P-value = Two-sided Exact P-value conditional to number of cases comparing incidence rates; Note: Cases reported from Day 15 post-vaccination up to efficacy data lock point = 11APR2022
Source: M5.3.5.1, RSV OA=ADJ-006 (212494) Report (13-AUG-2022), Table 14.2.1.16, Table 14.2.1.17, Table 14.2.1.21

One hospitalisation due to RSV-confirmed respiratory disease or complication was reported in the Placebo group which limits conclusions that can be drawn. In total, 42.9% of participants in the RSVPreF3 group and 60.0% of participants in the Placebo group required medical visits during the RSV-confirmed LRTD episodes.

No VE was observed against any LRTD (6.8% [95% CI: -1.7, 14.6], 988 cases vs 1059).

Secondary objective: VE against RSV-associated ARI

Analysis of VE of a single dose of the RSVPreF3 vaccine against first occurrence of RT-PCR-confirmed RSV ARI is presented in Table 10.

Table 10: VE against first occurrence of RT-PCR-confirmed RSV ARI up to VE Analysis 1, using Poisson method – mES (ADJ-006)

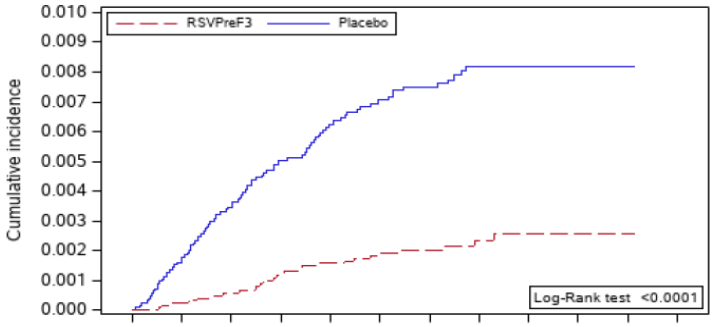
| | RSVPreF3 | | | | Placebo | | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 95% CI | | |
| Endpoint | N | n | T(year) | n/T (per 1000) | N | n | T(year) | n/T (per 1000) | % | LL | UL | P-value |
| RT-PCR-confirmed RSV ARI | 12466 | 27 | 6858.7 | 3.9 | 12494 | 95 | 6837.8 | 13.9 | 71.71 | 56.23 | 82.27 | <0.0001 |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants; n = number of participants with at least one RT-PCR-confirmed RSV ARI

| | RSVPreF3 | | | | Placebo | | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 95% CI | | |
| Endpoint | N | n | T(year) | n/T (per 1000) | N | n | T(year) | n/T (per 1000) | % | LL | UL | P-value |

T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; n/T (per 1000) = Incidence rate of participants reporting at least one event
95% CI = 95% confidence interval. LL = Lower Limit, UL = Upper Limit
VE (%) = Vaccine Efficacy (Poisson method - adjusted by age and region)
P-value = Two-sided Exact P-value conditional to number of cases comparing incidence rates; Note: Cases reported from Day 15 post-vaccination up to efficacy data lock point = 11APR2022
Source: Table 14.2.1.26 (20JUL2022 14:17 GMT)

The cumulative incidence curves for RSV ARI cases are presented in Figure 4.




Number at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RSVPreF3 | 12466 | 12390 | 12282 | 11881 | 11641 | 11029 | 8305 | 5481 | 2717 | 570 | 2 | 0 |
| Placebo | 12494 | 12390 | 12268 | 11853 | 11597 | 10973 | 8255 | 5441 | 2697 | 554 | 2 | 0 |

Cumulative number of cases

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RSVPreF3 | 0 | 3 | 7 | 15 | 19 | 23 | 24 | 26 | 27 | 27 | 27 | 27 |
| Placebo | 0 | 22 | 43 | 62 | 76 | 86 | 90 | 95 | 95 | 95 | 95 | 95 |

Log-rank test p-value is <0.0001
RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
Note: Cases reported from Day 15 post-vaccination up to efficacy data lock point = 11APR2022
Source: Figure 14.2.1.27 (20JUL2022 15:37 GMT)

Figure 4: Cumulative incidence curves for RT-PCR-confirmed-RSV ARI reported up to VE Analysis 1 — mES (ADJ-006)

Results for the subgroup analyses were in line with the results for RSV-confirmed LRTD.

The observed percentage of participants who required medical visits during the RSV-confirmed ARI episode was lower in the RSVPreF3 group (29.6%) vs. Placebo group (40.0%).

No VE was observed against any ARI (2.4% [95% CI: -3.3, 7.8]).

Secondary objective: subgroup analyses

A forest plot of relevant subgroups (including hemisphere, region, ethnicity, race, sex, comorbidities and frailty, RSV subtype, age) using all categories of the variables is presented in Figure 5.

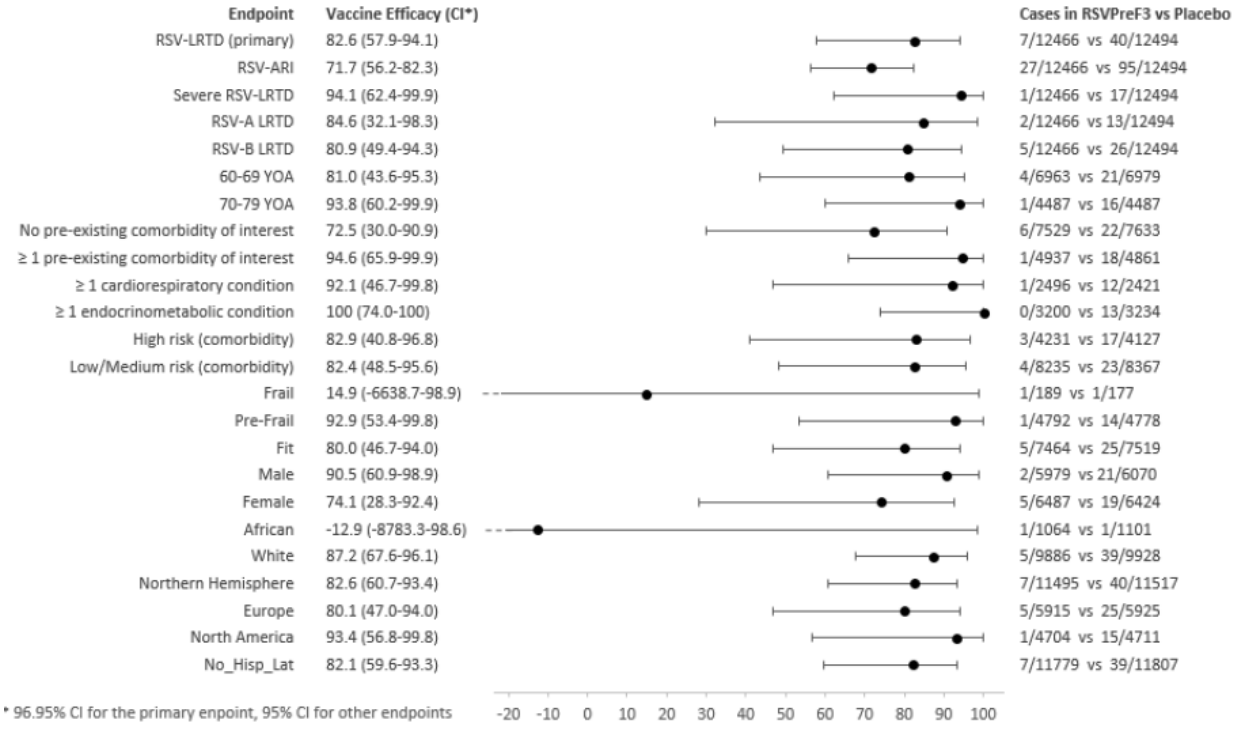



Figure 5 Forest plots of relevant subgroups. Subgroups with 0 or 1 case in total are not presented (subgroups: southern hemisphere, Hispanic/Latino, Asian; Other race, Asia); RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine ; Placebo = Participants receiving Placebo; Severe RSV-LRTD based on Definition 1: clinical symptomology; YOA= Years of age; Cardiorespiratory condition = COPD, Asthma, Any chronic respiratory/pulmonary disease, Chronic heart failure; Endocrino-metabolic conditions = Diabetes mellitus Type 1 or Type 2, Advanced liver or renal disease; High risk = Participants with co-morbidity score at baseline greater than 3 (Charlson Index); Low/Medium risk = Participants with co-morbidity score at baseline less than or equal to 3 (Charlson Index); Frail = Participants with a walking speed <0.4m/s or who were not able to perform the test Pre-Frail = participants with a walking speed between 0.4-0.99 m/s; Fit = Participants with a walking speed >=1m/s; African: Black or African American; White = White-Caucasian/European Heritage or White – Arabic/North African Heritage; Europe = Participants from Europe (Belgium, Estonia, Finland, Germany, Italy, Poland, Russia, Spain, UK); North Am = Participants from North America (US, Canada, Mexico); No_Hisp_Lat = Not Hispanic or Latino

### Secondary objective: Immunogenicity

Evaluation of the humoral immune response was performed in a subset of participants, referred to as immunogenicity subset. This subset was planned to include approximately 1800 participants (corresponding to ~7% of the total study population). Participants contributing to the immunogenicity subset were recruited from a selected number of countries and selected number of sites. In the selected sites, the investigator allocated the first participants in each age category to the immunogenicity subset until the allocated target was reached.

*Neutralising antibodies*

Immunogenicity as measured by neutralising antibody titres for RSV-A and -B are presented in Table 11 and Figure 6.

Table 11: RSV-A and RSV-B NAb titres GMT and MGI – PPSi (ADJ-006) (modified by Assessor)

| | | RSVPreF3 group | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subtype | Timepoint | N | GMT (95% CI) | n | MGI (95% CI) | N | GMT (95% CI) | n | MGI (95% CI) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| RSV-A | Day 1 | 885 | 918.0 (865.7 – 973.5 | | | 892 | 928.6 (877.5 – 982.6) | | |
| | Day 31 | 848 | 92329.7 (8699.3–10005.8) | 844 | 10.2 (9.5 – 11.0) | 846 | 873.6 (822.6 – 927.8) | 846 | 0.9 (0.9 - 1.0) |
| RSV-B | Day 1 | 885 | 1195.8 (1130.5–1264.8) | | | 892 | 1244.1 (1174.4-1317.9) | | |
| | Day 31 | 848 | 10178.9 (9564.1–10833.1) | 844 | 8.6 (8.0 – 9.2) | 846 | 1263.1 (1185.0-1346.3) | 846 | 1.0 (1.0 - 1.1) |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants with available results; n/% = number / percentage of participants with titer within the specified range
n for MGI = number of participants with available results at both time points
GMT = geometric mean titer; MGI = mean geometric increase; 95% CI = 95% confidence interval. LL = Lower Limit, UL = Upper Limit
PRE (D1) = Pre-vaccination at day 1 (Visit 1); PI (D31) = Post-vaccination at day 31 (Visit 2)
Source: Table 14.2.2.4 (20JUL2022 15:33 GMT) and Table 14.2.2.8 (20JUL2022 15:33 GMT)

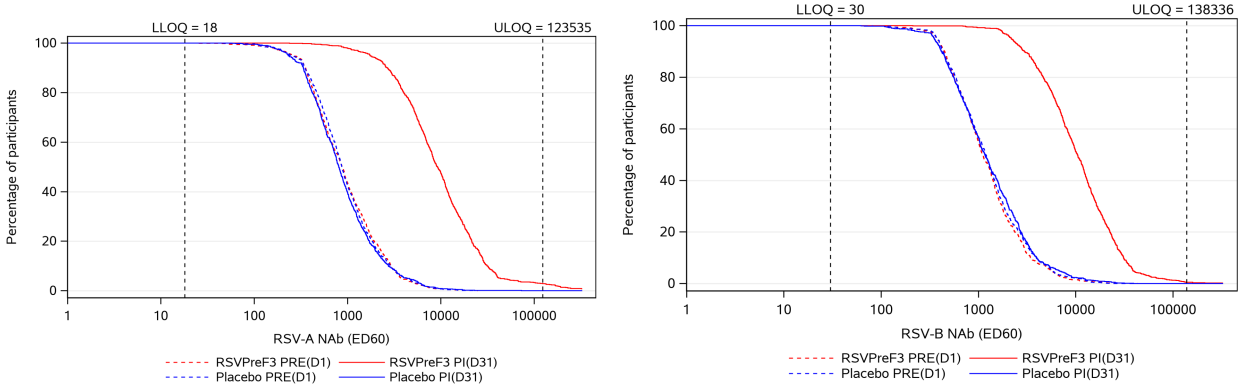



Figure 6: Reverse cumulative distribution curve for RSV-A and RSV-B neutralising antibody titre (ED60) by timepoint Per Protocol Set for immunogenicity (ADJ-006)

Immunogenicity results on RSV-A and RSV-B NAbs titres obtained in the ES were consistent with the results obtained in the PPSi.

No difference was observed for subgroup analyses by age category (only results for RSV-A NAb shown in Figure 7).

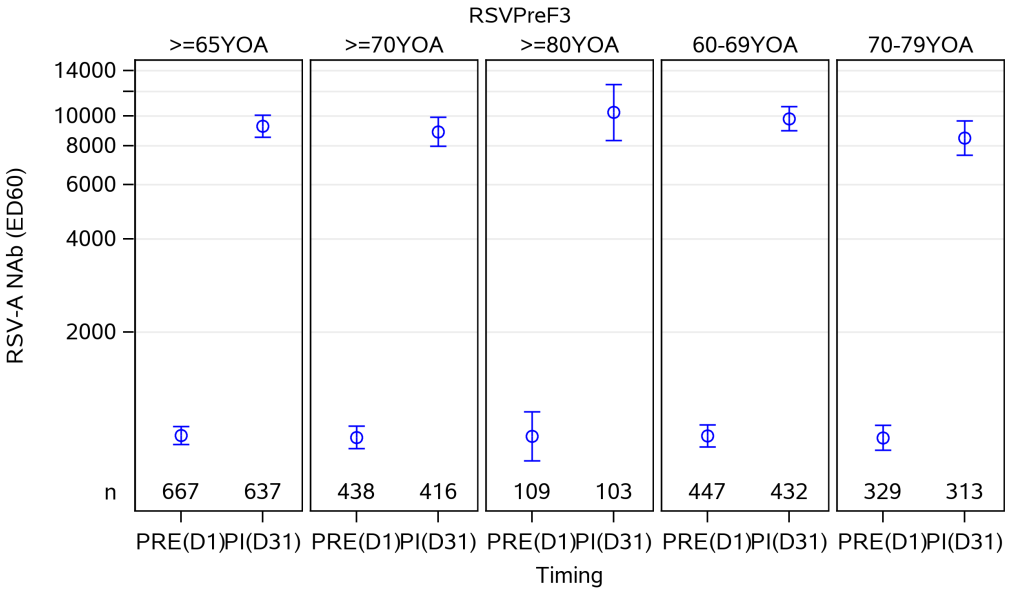



Figure 7: GMTs and their 95% CIs for RSV-A neutralising antibody titre (ED60) by age category Per Protocol Set for immunogenicity

Immunogenicity results on RSVPreF3-specific IgG antibody concentrations were consistent with the results for the neutralising antibodies.

- Ancillary analyses

*Sex*

The observed VE against RSV-confirmed LRTD was 90.5% in males (95% CI: 60.9, 98.9) and 74.1% in females (95% CI: 28.3, 92.4), see Table 12.

Table 12: Vaccine efficacy against first occurrence of RT-PCR-confirmed RSV LRTD up to VE analysis 1 by sex, using Poisson method - modified Exposed Set (ADJ-006)

| | | RSVPreF3 | | | | Placebo | | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | 95% CI | | |
| Endpoint | Subgroup | N | n | T(year) | n/T (per 1000) | N | n | T(year) | n/T (per 1000) | % | LL | UL | P-value |
| RT-PCR-confirmed RSV LRTD | Male | 5979 | 2 | 3338.9 | 0.6 | 6070 | 21 | 3374.4 | 6.2 | 90.45 | 60.92 | 98.91 | <0.0001 |
| | Female | 6487 | 5 | 3526.9 | 1.4 | 6424 | 19 | 3482.9 | 5.5 | 74.10 | 28.27 | 92.44 | 0.0059 |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants; n = number of participants with at least one RT-PCR-confirmed RSV LRTD; RSV LRTD= RSV LRTD identified by Adjudication Committee
T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; n/T (per 1000) = Incidence rate of participants reporting at least one event
95% CI = 95% confidence interval. LL = Lower Limit, UL = Upper Limit; VE (%) = Vaccine Efficacy (Poisson method - adjusted by age and region); P-value = Two-sided Exact P-value conditional to number of cases comparing incidence rates; Note: Cases reported from Day 15 post-vaccination up to efficacy data lock point = 11APR2022
Source: Table 14.2.1.15.5 (SOURCE: /GSKVX/Files/PROJECTS/CLINICAL/RSV OA=ADJ/STUDIES/212494/STAT/ANALYSIS_BLINDED /ANALYSIS_E1_02/PROGRAM_V1/ARES/TEVT1VEPOIS.SAS - 20JUL2022 17:11 GMT SAS 9.4 TEVT1VEPOISRSVLRTDV1MESSEX)

*Race, Ethnicity and Region*

The VEs of Arexvy, for which an adequate number of cases were identified, were consistent across major demographic and baseline characteristic subgroups.

- Summary of main efficacy results

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 for trial ADJ-006

| Title: A Phase 3, randomised, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above | | | |
|---|---|---|---|
| Study identifier | Protocol number: RSV OA=ADJ-006<br>EudraCT number: 2020-000753-28 | | |
| Design | Phase 3, randomised, observer-blind, placebo-controlled multi-country study conducted in both Northern (NH) and Southern hemisphere (SH) over three RSV (respiratory syncytial virus) seasons.<br>*Only data generated during the first season are available and presented in this summary.* | | |
| | Duration of main phase:<br><br><br><br><br>Duration of Run-in phase:<br>Duration of Extension phase: | | • Approximately 3 years (i.e., up to 3 consecutive RSV seasons) per participant in the NH.<br>• Approximately 2.5 to 3 years (i.e., up to at least 2 consecutive RSV seasons) per participant in the SH.<br><br>not applicable<br>not applicable |
| Hypothesis | Vaccine efficacy (superiority); the lower limit (LL) of the 2-sided confidence interval (CI) for vaccine efficacy (VE) is above 20%. | | |
| Treatments groups | RSVPreF3 | | 1 dose of Arexvy (120 µg RSVPreF3 recombinant antigen adjuvanted with AS01E) administered intramuscularly (IM)<br>n= 12 503 randomised<br>n=12467 exposed. |
| | Placebo | | 1 dose of placebo (saline) administered IM<br>n= 12537 randomised<br>n=12499 exposed. |
| Endpoints and definitions | Primary Endpoint | First occurrence of RSV-A and/or B-associated LRTD (lower respiratory tract disease) | First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, according to the case definition. |
| | Secondary Descriptive Endpoints | First occurrence of RSV-A and B-associated LRTD separately | First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition, for RSV subtype A and RSV subtype B separately. |

| | | | |
|---|---|---|---|
| | | First occurrence of RSV-A and/or B-associated LRTD by age categories | First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, according to the case definition, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA. |
| | | First occurrence of RSV-A and/or B-associated LRTD by baseline comorbidities | First occurrence of RT-PCR-confirmed RSV-A and/or B associated LRTD according to the case definitions, by baseline comorbidities. |
| Database lock | For interim report: 11 April 2022 | | |
| Results and Analysis | | | |
| Analysis description | Primary Analysis – First occurrence of RSV-A and/or B-associated LRTD. VE was estimated with a Poisson regression model adjusted for age and region. | | |
| Analysis population and time point description | Modified Exposed Set (mES): It includes all participants who received at least the first dose of the study intervention (exposed set) and who did not report an RSV -confirmed ARI prior to Day 15 after vaccination.<br><br>Timepoint: The interim VE Analysis 1 of the primary efficacy endpoint was event driven. The interim analysis included 47 RSV LRTD cases confirmed by an external adjudication committee, which was above the minimum of 35 cases pre-specified in the protocol to trigger the optional interim analysis. Since the success criterion was met, this analysis is considered final for the primary endpoint. | | |
| Descriptive statistics and estimate variability | Treatment group | RSVPreF3 | Placebo |
| | Number of subjects (mES) | 12466 | 12494 |
| | RSV-confirmed LRTD | 7 | 40 |
| Effect estimate per comparison | Primary endpoint | Comparison groups | RSVPreF3 vs Placebo |
| | | Vaccine efficacy (%) | 82.6 |
| | | 96.95% CI (%) | 57.9 – 94.1 |
| | | P-value (Poisson method) | P-value <0.0001 |
| Notes | As a sensitivity analysis, VE was estimated using a Cox proportional hazard regression model, adjusted for the covariates age and region. Results are consistent with the primary analysis (VE: 82.52% [96.95% CI: 57.58, 92.80%]). | | |
| Analysis description | Secondary analysis - First occurrence of RSV-A and B-associated LRTD separately | | |
| Analysis population and time point description | Set: mES<br>Timepoint: Same timepoint as the primary endpoint. | | |
| Descriptive statistics and estimate variability | Treatment group | RSVPreF3 | Placebo |
| | Number of subjects (mES) | 12466 | 12494 |
| | RSV A-confirmed LRTD | 2 | 13 |
| | RSV B-confirmed LRTD | 5 | 26 |
| Effect estimate per comparison | Comparison groups | RSVPreF3 vs Placebo | |
| | RSV subtype | RSV A | RSV B |
| | Vaccine efficacy (%) | 84.6 | 80.9 |
| | 95% CI (%) | 32.1 – 98.3 | 49.4 – 94.3 |
| Analysis description | Secondary analysis - First occurrence of RSV-associated LRTD by age group | | |
| Analysis population and time point description | Set: mES<br>Timepoint: Same timepoint as the primary endpoint. | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | RSVPreF3 | Placebo |
| | Number of subjects ≥65 YoA (mES) | 9258 | 9325 |
| | RSV-confirmed LRTD | 5 | 29 |
| | Number of subjects ≥70 YoA (mES) | 5503 | 5515 |
| | RSV-confirmed LRTD | 3 | 19 |
| | Number of subjects ≥80 YoA (mES) | 1016 | 1028 |
| | RSV-confirmed LRTD | 2 | 3 |
| Effect estimate per comparison | RSV-associated LRTD in **≥65** YOA | Comparison groups | RSVPreF3 vs Placebo |
| | | Vaccine efficacy (%) | 82.7 |
| | | 95% CI (%) | 54.9-94.8 |
| | RSV-associated LRTD in **≥70** YOA | Comparison groups | RSVPreF3 vs Placebo |
| | | Vaccine efficacy (%) | 84.4 |
| | | 95% CI (%) | 46.9-97.0 |
| | RSV-associated LRTD in **≥80** YOA | Comparison groups | RSVPreF3 vs Placebo |
| | | Vaccine efficacy (%) | 33.8 |
| | | 95% CI (%) | -477.7-94.5 |
| Analysis description | Secondary analysis - First occurrence of RSV-associated LRTD by baseline comorbidities | | |
| Analysis population and time point description | Set: mES<br>Timepoint: Same timepoint as the primary endpoint. | | |
| Descriptive statistics and estimate variability | Treatment group | RSVPreF3 | Placebo |
| | Number of subjects with no pre-existing comorbidities (mES) | 7529 | 7633 |
| | RSV-confirmed LRTD | 6 | 22 |
| | Number of subjects with at least 1 pre-existing comorbidity of interest (mES) | 4937 | 4861 |
| | RSV-confirmed LRTD | 1 | 18 |
| | Number of subjects at least 1 pre-existing cardiorespiratory condition (mES) | 2496 | 2421 |
| | RSV-confirmed LRTD | 1 | 12 |
| Effect estimate per comparison | RSV-associated LRTD in subjects with no pre-existing comorbidities (mES) | Comparison groups | RSVPreF3 vs Placebo |
| | | Vaccine efficacy (%) | 72.5 |
| | | 95% CI (%) | 30.0 – 90.9 |
| | RSV-associated LRTD in subjects with at least 1 pre-existing comorbidity of interest (mES) | Comparison groups | RSVPreF3 vs Placebo |
| | | Vaccine efficacy (%) | 94.6 |
| | | 95% CI (%) | 65.9 – 99.9 |
| | RSV-associated LRTD in subjects with at least 1 pre-existing cardiorespiratory condition (mES) | Comparison groups | RSVPreF3 vs Placebo |
| | | Vaccine efficacy (%) | 92.1 |
| | | 95% CI (%) | 46.7 – 99.8 |
| Notes | All subgroup analyses point to consistent VE. | | |

### *2.6.5.3. Clinical studies in special populations*

*Elderly population*

All studies included in the current submission included older adults (≥ 60 years of age).

| | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| Controlled Trials | 14220/26856 | 5062/26856 | 556/26856 |
| Non-Controlled trials | 1268/2410 | 545/2410 | 43/2410 |

### *2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)*

A side-by-side display of immunogenicity responses obtained during studies ADJ-006, ADJ-004, ADJ-007 and ADJ-009, conducted in older adults ≥60 years of age with no prior RSV vaccination, is presented below. Demographic characteristics of the participants were generally comparable across the intervention groups: median age ranging from 67.0 to 70.0 years old, and approximately half of the participants were male. In studies ADJ-006, -004 and 009, a majority of participants were White, while in study ADJ-007 50.1% were of mixed race, and 31.1% were White. In all studies, most participants were of not Hispanic or Latino ethnicity.

A substantial immune response was observed in all Phase 3 studies in RSV vaccine-naïve adults ≥60 years of age, as assessed by neutralising antibodies (see Table 14). The results in the Phase 3 were in line with the neutralizing antibody GMTs observed in Part B of study ADJ-002 for participants receiving 120 µg RSV vaccine adjuvated with $AS01_E$; with RSV-A NAb GMTs increasing from 988.0 pre-vaccination to 9350.9 Day 30 post-vaccination (mean geometric increase 9.5; 95% CI 7.6-11.8) and RSV-B GMTs increasing from 1368.0 pre-vaccination to 12544.4 Day 30 postvaccination (mean geometric increase 9.2; 95% CI 7.3-11.5). A trend toward lower immunogenicity with increasing age was seen.

Table 14: RSV-A and RSV-B NAb titres (ED60) GMTs prevaccination and 1 month after the RSVPreF3 vaccination and MGI – PPSi (ADJ-004, ADJ-006 and ADJ-007) (Modified by the Assessor)

| | | Prevaccination | | 1 month post-vaccination with RSVPreF3 | | Mean geometric increase | |
|---|---|---|---|---|---|---|---|
| Study | Group | N | GMT (95% CI) | N | GMT (95% CI) | n | Value (95% CI) |
| RSV-A | | | | | | | |
| ADJ-006 | Placebo | 892 | 928.6 (877.5-982.6) | 846 | 873.6 (822.6-927.8) | 846 | 0.9 (0.9-1.0) |
| | RSVPreF3 006 | 885 | 918.0 (865.7-973.5) | 848 | 9329.7 (8699.3-10005.8) | 844 | 10.2 (9.5-11.0) |
| ADJ-004 | Total 004 | 986 | 862.7 (819.1-908.7) | 941 | 9107.3 (8521.2-9733.7) | 940 | 10.5 (9.9-11.2) |
| ADJ-007 | Control 007 | 411 | 951.0 (873.9-1034.8) | 398 | 12255.0 (11160.4-13456.9) | 398 | 12.95 (11.75-14.28) |
| RSV-B | | | | | | | |
| ADJ-006 | Placebo | 892 | 1244.1 (1174.4-1317.9) | 846 | 1263.1 (1185.0-1346.3) | 846 | 1.0 (1.0-1.1) |
| | RSVPreF3 006 | 885 | 1195.8 (1130.5-1264.8) | 848 | 10178.9 (9564.1-10833.1) | 844 | 8.6 (8.0-9.2) |
| ADJ-004 | Total 004 | 987 | 1233.9 (1170.3-1301.0) | 941 | 9650.3 (9108.1-10224.8) | 941 | 7.8 (7.4-8.3) |
| ADJ-007 | Control 007 | 211 | 1570.9 (1396.9-1766.7) | 205 | 14207.1 (12526.5-16113.1) | 205 | 9.23 (8.01-10.63) |

Data source RSV-A: M5.3.5.2, RSV OA=ADJ-004 (212496) Report Amendment 1 (02-AUG-2022), Table 14.2.2.1, M5.3.5.1, RSV OA=ADJ-006 (212494) Report (13-AUG-2022), Table 14.2.2.4, M5.3.5.1, RSV OA=ADJ-007 (214488) Report Amendment 1 (02-AUG-2022), Table 11.4

Data source RSV-B: M5.3.5.2, RSV OA=ADJ-004 (212496) Report Amendment 1 (02-AUG-2022), Table 14.2.2.3, M5.3.5.1, RSV OA=ADJ-006 (212494) Report (13-AUG-2022), Table 14.2.2.8, M5.3.5.1, RSV OA=ADJ-007 (214488) Report Amendment 1 (02-AUG-2022), Table 14.2.2.29.1

ED60 = estimated dilution 60%; GMT = geometric mean antibody titers, MGI = mean geometric increase, NAb = neutralising antibody; PPSi = per-protocol set for immunogenicity; RSVPreF3 = RSV PreFusion protein 3; 95% CI = 95% confidence interval, LL = lower limit, UL = upper limit

Placebo = participants receiving placebo; RSVPreF3 006 = participants receiving RSVPreF3 OA vaccine (pooled lots);

Total 004: Participants receiving 1 dose of RSVPreF3 OA vaccine in all 3 groups
Control 007 = Participants receiving a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA vaccine at Visit 2 (Day 31).
N = number of participants with available results; n for MGI = number of participants with available results at both time points

Immunogenicity results on RSVPreF3-specific IgG antibody concentrations were consistent with the results for the neutralising antibodies.

### *2.6.5.5. Supportive studies*

The supportive studies, ADJ-004, -007, -009 and -011, all evaluated immunogenicity of RSVPreF3. No efficacy results were obtained.

Study ADJ-004 was a randomised, open-label, multi-centre, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above. The study is ongoing and only data on a single administration with RSVPreF3 vaccine are available. Follow-up until 6 months after vaccination is included in the submission.

The data presented indicate that RSVPreF3 is immunogenic as it induces a robust immune response at 30 days postvaccination as measured by both RSV-A and RSV-B neutralising antibodies and RSVPreF3 specific binding antibodies as well as RSVPreF3-specific CD4+ T-cells. No RSVPreF3-specific CD8+ T-cells were induced. The cellular and humoral immune response declined over time from 30 days to 6 months post-vaccination but remained above respective baseline levels.

Study ADJ-007 was a multicentre, multi-country, randomised, controlled, open label study to evaluate the humoral immune response, reactogenicity and safety of a single dose of RSVPreF3 OA when co-administered with FLU-QIV or given separately in adults ≥60 years of age. The primary objective of the study was to demonstrate the non-inferiority of RSVPreF3 OA (in terms of RSV-A NAb titres) and FLU-QIV (in terms of HI Ab titres) when co-administered (Co-Ad group) compared to when administered alone (Control group).

The co-primary objectives for immunogenicity were met:

- One month after the RSVPreF3 OA investigational vaccine dose, the RSV-A neutralising antibody titres (ED60) in the Co-Ad group were shown to be non-inferior compared to the Control group, see Table 15. (Success Criterion: The upper limit (UL) of the 2-sided 95% confidence interval (CI) on the group GMT ratio [Control group divided by Co-Ad group] for RSV investigational vaccine is ≤1.5).
- One month after the FLU vaccine dose, the HI antibody titres for each of the FLU vaccine strains in the Co-Ad group were shown to be non-inferior compared to the Control group, see Table 16. (Success Criterion: The UL of the 2-sided 95% CI on the group GMT ratio [Control group divided by Co-Ad group] for each of the FLU vaccine strains is ≤1.5).

Table 15: Ratio of RSV-A NAb titres (ED60) GMTs between the Control group and (over) the Co-Ad group, 1 month after the RSVPreF3 OA - PPSi (Final analysis) – ADJ-007

| | | Co-Ad group | | | | Control group | | | | Control group vs Co-Ad group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| Time point | | n | % or value | LL | UL | n | % or value | LL | UL | value | LL | UL |
| PRE | N | 435 | | | | 411 | | | | | | |
| | ≥18 ED60 | 435 | 100 | 99.2 | 100 | 411 | 100 | 99.1 | 100 | | | |
| | GMT | | 1053.7 | 971.8 | 1142.5 | | 951.0 | 873.9 | 1034.8 | | | |
| PI | N | 427 | | | | 398 | | | | | | |
| | ≥18 ED60 | 427 | 100 | 99.1 | 100 | 398 | 100 | 99.1 | 100 | | | |
| | GMT (a) | | 10060.5 | 9126.0 | 11090.7 | | 12255.0 | 11160.4 | 13456.9 | 1.27 | 1.12 | 1.44 |
| | Visit comparison / PRE | | | | | | | | | | | |
| | MGI | | 9.61 | 8.70 | 10.61 | | 12.95 | 11.75 | 14.28 | | | |

Data source: M5.3.5.1, RSV OA=ADJ-007 (214488) Report Amendment 1 (02-AUG-2022), Table 11.4
GMT = geometric mean titer; MGI = mean geometric increase; NAb = neutralising antibody; PPSi = per-protocol set for immunogenicity
Co Ad group = Participants receiving a single dose of RSVPreF3 OA vaccine and a single dose of FLU-QIV vaccine at Visit 1 (Day 1);
Control group = Participants receiving a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA vaccine at Visit 2 (Day 31).
N = number of participants with available results; n/% = number / percentage of participants with titer within the specified range
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
(a): comparison is done using the adjusted group ratio of GMT (Control group/Co Ad group) (ANCOVA model applied to the logarithm-transformed titers). The ANCOVA model included the treatment group, the age category (age at vaccination: 60-69, 70-79 or ≥80 years), country and sex as fixed effects and the pre-dose log-10 titer as covariate.
PRE = Pre-vaccination; PI = Post-vaccination (PI(D31) = 1 month post FLU+RSV vaccination (Co Ad group) or FLU_QIV vaccination (Control group); PI(D61) = 1 month post RSV vaccination (Control group))

In line with the results for RSV-A neutralising antibody titres, the GMT ratio of RSV-B neutralising antibody titres (Control group over Co-Ad group) at 1 month after vaccination was 1.27 (95% CI: 1.08, 1.49) (data based on a subset of participants).

Table 16: Ratio of HI GMTs for each of the FLU-QIV vaccine strains between the Control group and (over) the Co-Ad group, 1 month after the FLU-QIV vaccine dose - PPSi (Final analysis) ADJ-007

| | | | Co-Ad group | | | | Control group | | | | Control group vs Co-Ad group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| Antibody | Time point | | N | Value | LL | UL | N | Value | LL | UL | value | LL | UL |
| Flu A/Hong Kong/2671/2019 | PRE | GMT | 435 | 61.4 | 53.8 | 69.9 | 437 | 63.3 | 55.7 | 71.9 | | | |
| H3N2 HI (1/DIL) | PI(D31) | GMT (a) | 427 | 295.2 | 263.6 | 330.6 | 411 | 346.8 | 306.6 | 392.3 | 1.17 | 1.02 | 1.35 |
| | | MGI | 427 | 4.81 | 4.22 | 5.48 | 410 | 5.50 | 4.81 | 6.29 | | | |
| Flu A/Victoria/2570/2019 | PRE | GMT | 435 | 20.0 | 18.0 | 22.3 | 437 | 19.9 | 17.8 | 22.2 | | | |
| H1N1 HI (1/DIL) | PI(D31) | GMT (a) | 427 | 267.1 | 235.6 | 302.8 | 411 | 325.4 | 282.5 | 374.9 | 1.22 | 1.03 | 1.44 |
| | | MGI | 427 | 13.36 | 11.58 | 15.42 | 410 | 16.25 | 14.08 | 18.76 | | | |
| Flu B/Phuket/3073/2013 | PRE | GMT | 435 | 10.4 | 9.5 | 11.3 | 437 | 10.8 | 9.9 | 11.7 | | | |
| Yamagata HI (1/DIL) | PI(D31) | GMT (a) | 427 | 28.9 | 26.0 | 32.1 | 411 | 34.8 | 31.1 | 39.0 | 1.17 | 1.04 | 1.32 |
| | | MGI | 427 | 2.82 | 2.55 | 3.12 | 410 | 3.22 | 2.90 | 3.58 | | | |
| Flu B/Washington/02/2019 | PRE | GMT | 435 | 12.2 | 11.1 | 13.4 | 437 | 13.5 | 12.2 | 15.1 | | | |
| Victoria HI (1/DIL) | PI(D31) | GMT (a) | 427 | 41.6 | 37.1 | 46.6 | 411 | 47.9 | 41.9 | 54.8 | 1.10 | 0.95 | 1.26 |
| | | MGI | 427 | 3.43 | 3.06 | 3.85 | 410 | 3.60 | 3.18 | 4.08 | | | |

Data source: M5.3.5.1, RSV OA=ADJ-007 (214488) Report Amendment 1 (02-AUG-2022), Table 11.5
GMT = geometric mean titer; MGI = mean geometric increase; PPSi = per-protocol set for immunogenicity
Co Ad group = Participants receiving a single dose of RSVPreF3 OA vaccine and a single dose of FLU-QIV vaccine at Visit 1 (Day 1);
Control group = Participants receiving a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA vaccine at Visit 2 (Day 31).
N = number of participants with available results; 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
(a): comparison is done using the adjusted group ratio of GMT (Control group/Co Ad group) (ANCOVA model applied to the logarithm-transformed titers). The ANCOVA model included the treatment group, the age category (age at vaccination: 60-69, 70-79 or ≥80 years), country and sex as fixed effects and the pre-dose log-10 titer as covariate.
PRE = Pre-vaccination; PI(D31) = 1 month post FLU+RSV vaccination (Co Ad group) or FLU-QIV vaccination (Control group)

The secondary objective evaluating HI seroconversion rate (SCR) was met for all the FLU strains, except the FLU B/Yamagata strain (Reference criterion: The UL of the 2-sided 95% CI on the group difference [Control group minus Co-Ad group] in SCR of ≤10%). See Table 17.

Table 17: Difference between groups in the percentage of participants with SCR for each of the 4 strains of the HI Ab titers – PPSi (ADJ-007)

| | | | Co-Ad group | | | | Control group | | | | Control group vs Co-Ad group | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | | | | 95% CI | |
| Antibody | Time point | | n | % | LL | UL | n | % | LL | UL | value | LL | UL |
| Flu A/Hong Kong/2671/ 2019 H3N2 HI (1/DIL) | PI(D31) | N | 427 | | | | 410 | | | | | | |
| | | Seroconversion rate (a) | 232 | 54.3 | 49.5 | 59.1 | 233 | 56.8 | 51.9 | 61.7 | 2.50 | -4.24 | 9.20 |
| Flu A/Victoria/2570/2019 H1N1 HI (1/DIL) | PI(D31) | N | 427 | | | | 410 | | | | | | |
| | | Seroconversion rate (a) | 337 | 78.9 | 74.7 | 82.7 | 342 | 83.4 | 79.5 | 86.9 | 4.49 | -0.82 | 9.79 |
| Flu B/Phuket/3073/2013 Yamagata HI (1/DIL) | PI(D31) | N | 427 | | | | 410 | | | | | | |
| | | Seroconversion rate (a) | 123 | 28.8 | 24.6 | 33.4 | 134 | 32.7 | 28.2 | 37.5 | 3.88 | -2.38 | 10.12 |
| Flu B/Washington/02/2019 Victoria HI (1/DIL) | PI(D31) | N | 427 | | | | 410 | | | | | | |
| | | Seroconversion rate (a) | 152 | 35.6 | 31.1 | 40.3 | 147 | 35.9 | 31.2 | 40.7 | 0.26 | -6.23 | 6.75 |

Data source: M5.3.5.1, RSV OA=ADJ-007 (214488) Report Amendment 1 (02-AUG-2022), Table 14.2.2.32.1
HI = hemagglutinin inhibition; PPSi = per-protocol set for immunogenicity
Co Ad group = Participants receiving a single dose of RSVPreF3 OA vaccine and a single dose of FLU-QIV vaccine at Visit 1 (Day 1);
Control group = Participants receiving a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA vaccine at Visit 2 (Day 31).
N = number of participants with available results; n/% = number / percentage of participants with rate within the specified range
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
(a): comparison is done by the difference of % between groups (Control group minus Co Ad group)
PI(D31) = 1 month post FLU+RSV vaccination (Co Ad group) or FLU_QIV vaccination (Control group)
SCR=Seroconversion Rate: the percentage of vaccinees who have either a HI pre-dose titer <1:10 and a post-dose titer ≥1:40 or a pre-dose titer ≥1:10 and at least a four-fold increase in post-dose titer.

Study ADJ-009 was a multicentre, multi-country, randomised, double-blind study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administrated as a single dose in adults aged 60 years and above. The 3 lots of RSVPreF3 investigational vaccine elicited a consistent response in the participants as measured by RSVPreF3-specific IgG GMCs at 30 days postvaccination.

Study ADJ-011 was a phase 2b, open-label, multi-centre, extension study to evaluate the safety and immunogenicity of a revaccination dose of the RSVPreF3 older adults (OA) investigational vaccine administered intramuscularly 18 months post-Dose 2 in adults 60 years and older who participated in the ADJ-002 study.

Of the 40 participants in the ES of the 120-AS01E_B group, 38 (95.0%) and 34 (85.0%), participants were included in the PPS on Day 1 (= 18 months post dose and before receipt of dose 3) and Day 31 (=1 month

post-dose 3), respectively for immunogenicity assessments. Kinetics of the of RSV-A and RSV-B neutralizing antibody GMTs over time are shown in Figure 9.

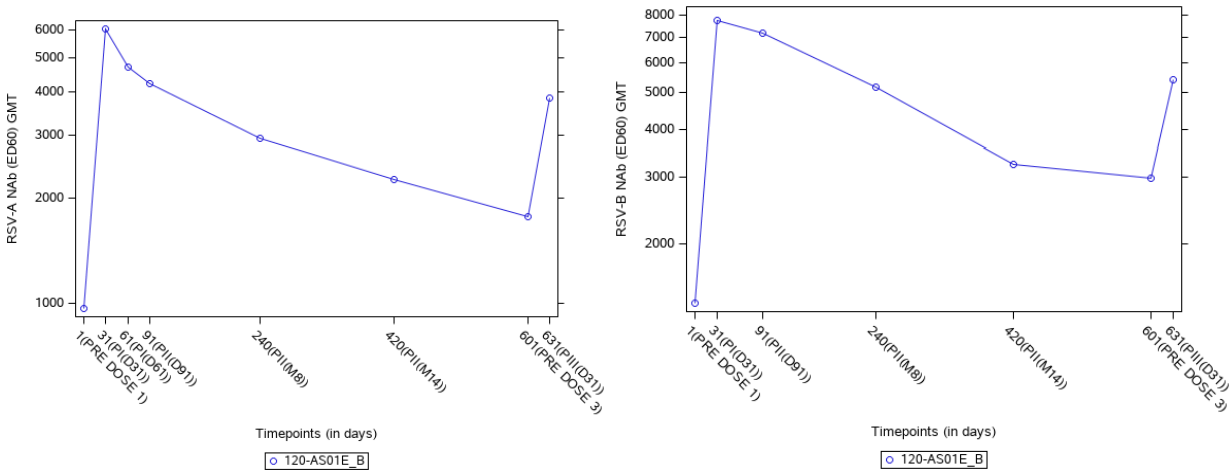



Figure 8 Kinetics of RSV-A (left) RSV-B (right) neutralizing antibody GMTs (ED60), on participants with results available at all timepoints as of Day 1 in RSV OA=ADJ-002 up to Day 31 in RSV OA=ADJ-011 - Per-Protocol Set of 002 and 011. PRE DOSE 1 = Pre-Dose 1 at Day 1 in parent study; PI(D31) = Post-Dose 1 at Day 31 in parent study; PI(D61) = Post-Dose 1 at Day 61 in parent study; PII(D91) = Post-Dose 2 at Day 91 in parent study; PII(M8) = Post-Dose 2 at Month 8 in parent study; PII(M14) = Post-Dose 2 at Month 14 in parent study; PRE DOSE 3 = Pre-Dose 3 at Day 1; PIII(D31) = Post-Dose 3 at Day 31 Source: Figure 14.2.2.26 (22MAR2022 11:38 GMT) and Figure 14.2.2.28 (22MAR2022 11:38 GMT)

## 2.6.6. Discussion on clinical efficacy

The sought indication for RSVPreF3 is active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older. Inclusion of the subtypes of the pathogen in the indication is not in line with the usual approach to the indication statement for vaccines intended to address multiple subtypes. The fact that the vaccine is efficacious in prevention of LRTD caused by both RSV-A and RSV-B is included in section 5.1 of the SmPC, where the estimated VE is presented.

Currently there is no immune correlate of protection for RSV disease that could be used to infer protective efficacy based on immune responses and there is no vaccine licensed for the prevention of RSV. Therefore, vaccine efficacy trials in which candidate vaccines are compared with control groups that do not receive vaccination against RSV are required.

This application is based on the efficacy data from a single pivotal Phase 3 trial, study ADJ-006. Three Phase 3 supportive clinical studies using the proposed vaccination regimen mainly investigated immunogenicity and safety. The development program has been formally discussed with CHMP at various moments throughout development, and an agreement was reached regarding the key elements of the clinical development plan.

Two of the Phase 3 studies (RSV OA=ADJ-006 and RSV OA=ADJ-004) including the single pivotal Phase 3 efficacy study (RSV OA=ADJ-006) are still ongoing. For adjuvanted seasonal vaccines, persistence of immune response following primary vaccination should be investigated as well as the need for annual revaccination. The Applicant has committed to submit the data for Study ADJ-004 and ADJ-006 on antibody persistence,

responses to booster doses and efficacy of booster vaccination. These studies will be followed-up as Committee Recommendation (REC).

*Dose selection*

The dose and regimen that was chosen to be tested in the pivotal clinical efficacy study was a single dose of 120 µg RSVPreF3 antigen adjuvanted with $AS01_E$. The choice for a single dose of 120µg RSVPreF3/$AS01_E$ as the formulation and posology to be tested in the Phase 3 studies was agreed by CHMP (EMEA/H/SA/3912/2/FU/1/2020/II), based on the results of study ADJ-002. Based on humoral immune response the use of the highest dose of antigen tested as a single dose was supported, as a clear impact of increasing the antigen dose from 30 to 120 µg could be observed. No added value of a second vaccination 2 months after the first dose was seen. No clear impact of adding an adjuvant was observed on the humoral immune response. In terms of the cellular immune response, a statistically significant increase (p-value < 0.025) in RSVPreF3-specific CD4+ T-cells expressing at least 2 markers among IL-2, CD40L, TNFα, IFNγ, was observed with the adjuvanted formulation as compared to unadjuvanted formulation. It is theoretically agreed that induction of CD4+ T-cell responses could be beneficial in terms of protection per se. Although, in the Phase 2 dose finding study the added value of the adjuvant is not clearly shown in terms of immunogenicity and the impact on protection was not evaluated, considering the safety profile of the adjuvanted vaccine was acceptable (see safety section) no objection is raised.

*Design and conduct of clinical studies*

The single pivotal trial used to estimate vaccine efficacy, study ADJ-006, was a randomised, observer-blind, placebo-controlled multi-country study. The design of the study has been previously discussed with CHMP in a scientific advice and is considered generally acceptable. It is not fully understood why the study was not performed double-blind by for example masking the injection. However, whilst the Applicant terms this study observer blind, due to visual appearance differences between vaccine and placebo, only those conducting the injections will be aware of the treatment assignments, which is appropriate and acceptable (EMEA/H/SA/3912/2/2019/III), if appropriately implemented. However, in case subjects become unblinded, due to differences in the appearance of the injection, the knowledge of the intervention and expectation about its protective effect may affect the behaviour of participants in the study. Therefore, the Applicant was asked to present more detailed information on the frequency of ARI contact and timing and frequency of swabs taken to ensure reporting behaviour was not affected by potential unblinding. The data provided did not give rise to concern and no major impact on behaviour was observed. The number of RSV-confirmed LRTD cases for the primary objective was claimed to be monitored in an unblinded manner by the Independent Data Monitoring Committee (IDMC) during Season 1. In preparation of the IDMC meetings, unblinded analyses are performed by an independent external statistician. The IDMC has made recommendation to GSK for continuing the study without sample size reassessment based on the review of the top line results from the interim analysis. A Firewall team received the statistical outputs of VE analysis 1 only after the IDMC had indicated that the pre-specified success criterion had been met, upon review of top line efficacy and safety results. The firewall reviews the unblinded summaries to prevent the potential risk of unblinding at participant level and only blinded data is released to the study team. In addition, during SA the ability to maintain blinded follow-up for cases in an ongoing study once success is declared after an interim analysis was questioned.

The investigational RSVPreF3 vaccine was administered as a single IM dose of 0.5 mL which is identical to the proposed posology. The study population included in the main study, participants ≥60 years of age with and without underlying respiratory and cardiopulmonary disease, is the population expected to benefit from the vaccine and is in line with the RSV guideline and the targeted indication. The randomisation procedure is based on a minimisation procedure accounting for the factors centre, age and region, with a randomness percentage of 20%. It is unclear why minimization/dynamic allocation was applied for this large trial as this procedure is mainly applied in case stratification is not possible due to many prognostic factors for small trials (Guideline on adjustment for baseline covariates in clinical trials). Dynamic allocation does not guarantee balance within combinations of prognostic factors. However, based on the data presented on the balance within the combination of prognostic factors (baseline comorbidities, baseline frailty status, centre, age and region), there is no indication that the performed randomisation/minimisation procedure led to an imbalance.

The primary objective was to demonstrate the efficacy of a single dose of the RSVPreF3 vaccine in the prevention of RSV-confirmed LRTD during the first season in adults ≥ 60 YOA, with a success criterion of the LL of the 2-sided CI for VE being above 20%. The primary endpoint, the case definition for RSV-confirmed LRTD and the case definition for ARI to trigger swabbing have been agreed upon by CHMP. The evaluation of vaccine efficacy in different subgroups defined by age, baseline comorbidities and frailty status is considered relevant to determine robustness across the overall target population to ensure generalisability. In addition, the objective to determine vaccine efficacy against both RSV-A and RSV-B confirmed LRTD separately is considered relevant, as these subtypes usually co-circulate.

*Interim analysis*

The current clinical study report presents results of the interim analysis of the primary objective. The VE Analysis 1 was case-driven and was performed with 47 cases of RSV-confirmed LRTD accrued in the primary cohort for efficacy up to efficacy data lock point (DLP) on 11 April 2022. According to the final SAP, the primary analysis was planned to be performed when at least 56 cases of RSV-confirmed and externally adjudicated LRTDs have been accrued in the primary cohort for efficacy (i.e., mES). If the number of events triggering VE Analysis 1 (at least 56 cases) is not achieved at the end of Season 1 in NH, an optional interim analysis might be performed when at least 35 cases have been accrued (at the end of Season 1 in NH or later). The interim analysis was triggered at the end of NH season 1 (30 April 2022). At end of NH season 1, 30 April 2022, the DLP for the vaccine efficacy analysis 1 (VE Analysis 1) was retrospectively defined as the date of the ARI visit for the last swab considered for the analysis, 11 April 2022, in order to have all relevant information (swab samples being shipped/tested, follow-up information on ARI collected and entered in the eCRF screen, ARI data fully cleaned) to support adequate external adjudication for the cleaned data of the end of season 1. Between 11 April 2022 and 30 April 2022, there was only one additional RT-PCR-confirmed RSV LRTD which took place in the SH in the placebo group, therefore, a DLP on 30 April 2022 would have provided slightly more favourable results.

There is a design switch between a fixed sample design (after at least 56 cases) and a group sequential design (interim analysis at the end of Season 1 if at least 35 cases have been accrued and final analysis after 60 cases or when all data associated to the primary objective are available), which also could affect the type I error. Simulation results confirm that the adaptive design controls type-I-error but rely on strong distributional assumptions. Nevertheless, the adaptation is based on the total number of events in a blinded way. The asymptotic distribution of the usual chi-square test statistic is not affected by this interim examination.

*Multiplicity*

As multiplicity is not controlled for the secondary endpoints at this interim analysis, all secondary analyses are exploratory only and use 95% CIs.

*Efficacy data and additional analyses*

*Main results*

There was a total of 50 externally adjudicated cases of RSV-confirmed LRTD occurring after the first dose of either RSVPreF3 or placebo. Of these, 47 cases occurred 15 or more days after administration of RSVPreF3 or placebo, 7 in the RSVPreF3 group and 40 in the placebo group. The primary VE as estimated in the primary efficacy population based on the Poisson model adjusted for age and region was 82.6% (96.95% CI: 57.9, 94.1). Cox regression analysis provided a similar estimated VE as estimated through Poisson regression (82.5% vs 82.6%). Since a minimisation procedure was used, additional sensitivity analyses were requested. The outcomes of these analyses supported the primary outcome and did not give rise to any concerns. No more than a single episode of RSV-confirmed ARI and RSV-confirmed LRTD was reported by any participant in the mES and ES. It was clarified that the primary analysis (VE Analysis 1) was performed on all cases that occurred during the study up to DLP. In total, there were 8 cases in the placebo group occurring outside the season. For hospitalization due to RT-PCR confirmed RSV respiratory diseases or for complication related to respiratory diseases only data during RSV Season 1 was used in the VE analysis 1.

*Secondary outcomes*

The cumulative incidence curve suggests that vaccine efficacy remains high up to at least 6 months. As the median follow-up was 6.7 months, VE after 6 months could not be accurately determined. The Applicant is asked to present results for VE over the full first season (including NH and SH) and multiple seasons as soon as the information becomes available. The Applicant confirmed that all data will be presented once available. In addition, the Applicant provided the results for VE analysis 2, which was based on data collected for the first full season, up to DLP of 30 September 2022 or revaccination (dose 2) if administered before 30 September. In total, 10 additional externally adjudicated cases of RSV-confirmed LRTD were observed compared to the interim analysis. Overall, the results of VE2 are in line with the interim analysis. At VE2, the estimated level of protection demonstrated against RSV-confirmed LRTD was 78.9% (95% CI: 57.6, 90.5; $p < 0.0001$). The cumulative incidence curve suggests that vaccine efficacy remains high up to the end of a full season and for at least 11 months.

Estimated VE against LRTD caused by RSV-A and RSV-B was substantial and comparable, with estimated VE against each subtype being >80% and LL being well above 20%. For 1 case in the placebo group information on serotype was missing, as the external test used to confirm RSV infection did not distinguish between RSV-A and RSV-B subtype.

The estimated VE against RSV-confirmed LRTD was >80% in all age groups tested (with LL >20%), except the group ≥80 years of age. In the group aged ≥80 years, there were not enough cases to draw a conclusion on efficacy, with in total 5 cases (2 in the RSVPreF3 group vs 3 in the placebo group). However, no trend in declining VE was observed when comparing estimated VE in the age groups 60-69 years of age and 70-79 years of age, being 81.0% (95% CI: 43.6-95.3) and 93.8% (95% CI: 60.2-99.9) respectively. This is reassuring.

Approximately 39% of participants in the primary efficacy population, and the overall study population had at least one comorbidity at baseline such as cardiovascular disease, respiratory disease, or diabetes. The estimated VE against RSV-confirmed LRTD more than 15 days post-vaccination was high in subjects with at least 1 pre-existing comorbidity of interest, 94.6% (1 vs. 18 cases), and 72.5% (6 vs. 22 cases) in those who did not have any comorbidity at baseline. As pre-existing comorbidities can lead to an increased risk of severe RSV disease, high vaccine efficacy in participants with comorbidities is assuring.

The number of severe RSV-confirmed LRTD cases based on requirement of supportive therapy was too low to draw meaningful conclusions, as only 4 cases were observed, all in the placebo group. Severe RSV-confirmed LRTD based on investigator assessment of severity and/or having at least 2 lower respiratory signs, were observed in 18 cases, of which 1 occurred in the RSVPreF3 group and 17 in the placebo group. Of these 18 participants, 9 (all in the placebo group) experienced severe LRTD according to the investigator. The Applicant provided narratives for all participants who experienced severe LRTD according to definition 1, to be able to ascertain the level of severity of disease. Based on the narratives presented it is not agreed that all 18 cases, or even the 9 cases that were identified by the investigators, can be considered severe. Having at least 2 lower respiratory signs is not enough to determine disease severity. Definition 2 based on supportive therapy required is still considered the most objective measure to indicate disease severity. There were not enough cases to draw a conclusion on efficacy, with in total 4 participants, all in the placebo group, requiring supplemental oxygen.

The estimated VE for both males and females was high, with the estimated lower limit of the 95% CI being above 20% for both subgroups. However, a difference was observed with estimated VE being 90.5% in males and 74.1% in females. As this difference in point estimate of VE is driven by a difference of only 3 cases in the RSVPreF3 group between males and females, this might be due to chance. At the end of season 1 in the SH, the observed VE against RSV-confirmed LRTD was 86.9% (95% CI: 56.7, 97.5) in males and 71.3% (95% CI: 31.4, 89.6) in females. The RSVPreF3 vaccine induced a substantial and comparable increase in titres for both neutralising and binding antibodies at 30 days postvaccination in both males and females. Given the wide and overlapping confidence intervals of VE against RSV-confirmed LRTD for males and females, no firm conclusions on any difference in VE can be drawn, while the fact that the LL of the 2-sided CI for VE is above 20% for both males and females does indicate that the vaccine is effective. Finally, the fact that the immune response in females is comparable to males indicates that there is no clear biological mechanism leading to reduced vaccine efficacy in females compared to males.

Finally, analyses of relevant subgroups show consistency in the direction of the treatment effect. Where substantial differences are observed between relevant subgroups, e.g., age ≥80 years, frail subgroup or region, these differences are most likely attributable to either chance or low number of events. In addition, the Applicant provided a forest plot for all relevant subgroups (including hemisphere, region, ethnicity, race, sex, comorbidities and frailty in addition to RSV subtype, and age) using all categories of the variables, which also shows consistency in the direction and magnitude of the treatment effect, except when there were very low number of cases.

*Secondary outcomes: RSV-confirmed ARI*

When participants experienced at least 2 respiratory symptoms/signs or 1 respiratory symptoms/sign plus 1 systemic symptom/sign for at least 24 hours, the participants experienced acute respiratory infection (ARI). ARI was the trigger to swab, after which the disease course could potentially include involvement of the lower respiratory tract to lead to LRTD. The results for RSV-confirmed ARI are in line with the results for RSV-confirmed LRTD. The estimated VE against RSV-confirmed ARI was 71.7% (95% CI: 56.2, 82.3). This high protection against RSV-confirmed ARI was observed up to at least 6 months. The subgroup analyses in

different age categories and by baseline comorbidities indicate that vaccine efficacy is not impacted by either age or presence of comorbidities. As increased age and the presence of comorbidities can lead to an increased risk of severe RSV disease, these results are encouraging.

*Immunogenicity*

Results for both neutralising antibodies (RSV-A and RSV-B) and binding antibodies have been provided in a subgroup of ~1800 participants from selected sites. Overall, these results were in general agreement with similar trends being observed between neutralising and binding antibodies.

Across studies, a consistent immune response was observed, with at 1-month postvaccination a ~10 fold increase in RSV-A neutralising antibody titres, an ~8 fold increase in RSV-B neutralising antibody titres, and a ~12 fold increase in binding antibody titres being observed. This indicates that vaccination induces a substantial increase in titres for both neutralising and binding antibodies at 30 days postvaccination, in line with a boost response in a population that has been previously exposed to RSV. Consistency across studies, shows the repeatability of the response induced.

Analysis by age category reveals, as expected, differences in GMTs based on age, with the highest response in the youngest age category. Unfortunately, it is currently unknown what the clinical relevance is of any specific GMT value, and hence differences in antibody titres between groups cannot be fully interpreted.

Currently, no information on the persistence of antibody titres over 6 months is available in the currently proposed posology of a single dose. In study ADJ-004 it was observed that antibody titres declined over time, as titres for both neutralising and binding antibodies decreased. However, the titres remained well above baseline levels. The Applicant was requested to submit any data on longer-term persistence of antibody titres over time and on the effect of revaccination on immunogenicity once it is available. Antibody titres declined further up till month 12 post vaccination, however, did remain well above baseline. Revaccination at Month 12 post dose 1 induced a substantial increase in RSV-A NAb, RSV-B NAb and IgG antibody titres but did not restore the titres to the levels observed 30 days after the first dose. This indicates that the booster potential of the vaccine is limited. However, as there is no CoP, any specific titre reached cannot be directly translated to efficacy. The impact of the limited booster ability will be shown in the ongoing efficacy study ADJ-006 which will determine VE over multiple seasons and after revaccination.

In study RSV OA=ADJ-011 (extension study of Phase 1/2 dose-finding study), neutralizing (and binding) anti-RSV GMTs gradually declined after a two-dose vaccination schedule (1 month apart) over time until M18 post-dose 2 and increased again 1 month after dose 3. However, GMTs as induced by the first vaccination could not be reached. Month 12 RSV-A serum neutralisation titres were positively correlated with titres measured 1 month post revaccination (Month 13) and a tendency towards higher fold increase in participants with lower pre-vaccination titres was observed. In the absence of an immune correlate of protection, efficacy data from RSV OA=ADJ-006 will be instrumental to complement the immunogenicity results observed post-revaccination from RSV OA=ADJ-004. This will provide evidence to assess the need of the revaccination doses.

During the pivotal study (ADJ-006) an exploratory analysis was planned to correlate the humoral immune response to the RSVPreF3 OA investigational vaccine with protection against RSV-confirmed disease. For that purpose, blood samples for humoral immune response were collected from all participants at pre-Dose 1 (Day 1) and 1-month post-Dose 1 (Day 31). These samples may be tested for a correlate of protection analysis. In addition, information on the humoral immune response pre-dose 2 and pre-dose 3 could also be used to investigate the CoP as efficacy in a second or even third season could potentially be linked to the humoral

response. The Applicant confirmed that analysis of CoP will be performed once more data are available from both multiple seasons for Study ADJ-006 and revaccination in study ADJ-004.

Induction of cellular immunity in terms of RSVPreF3-responsive CD4+ T-cells was demonstrated in studies ADJ-002 and ADJ-004 after RSVPreF3 OA vaccination. No RSVPreF3-responsive CD8+ T-cells were induced. In study ADJ-004 frequencies of RSVPreF3-responsive CD4+ T-cells declined over time (30 days to 6 months post-vaccination) but remained above baseline levels.

Overall, it can be concluded from the submitted immunogenicity analyses that the RSVPreF3 vaccine is able to induce a robust humoral immune response in the intended target population. As expected, trends toward lower humoral immune response can be seen with increasing age. However, the population ≥80 years of age still mounted a substantial immune response that was well above baseline levels, with a mean geometric increase in titres for neutralising antibodies being ≥8 for RSV-A and ≥6 for RSV-B. However, the immune response observed cannot be directly translated to efficacy as there is no correlate of protection.

*Concomitant administration of Flu vaccine*

A generally reduced immune response to RSVPreF3 can be observed when the vaccine is concomitantly given with QIV. In addition, similar results were obtained for the FLU-QIV vaccination; an immune response was elicited that was slightly reduced when comparing co-administration to non-concomitantly administered vaccines. The clinical impact of this (slightly) reduced response is unknown, given that for both RSV and influenza a correlate of protection does not exist. However, given that a clear immune response to both vaccines is observed, it can be agreed that the vaccines can be co-administered.

### 2.6.7. Conclusions on the clinical efficacy

In conclusion, the results indicate that the RSVPreF3 vaccine is efficacious, with an estimated VE of around 80% against RSV-confirmed LRTD. Protection remains high up to at least 6 months. No trend in decreasing vaccine efficacy is seen with increasing age or the presence of comorbidities, which are known risk factors for severe RSV disease. The results for RSV-confirmed ARI align with those RSV-confirmed LRTD.

The median follow-up for the interim analysis in study ADJ-006 was 6.7 months. Currently, the median follow-up time up to VE2 was 11.5 months in the mES. The information on longer-term protection is lacking as is the need for revaccination. Study ADJ-006 is designed to provide information on both efficacy of the single dose for a second RSV season and the impact of revaccination after 1 year. In addition, the immunogenicity of the second dose of RSVPreF3 will be tested. These data are considered highly relevant, and the Applicant is asked to present the data as soon as they are available (REC).

The CHMP considers the following measures necessary to address issues related to efficacy:

The Applicant should submit the results for Study ADJ-004 and ADJ-006 on antibody persistence, responses to booster doses and efficacy of booster vaccination, once available

### 2.6.8. Clinical safety

The main source of safety data to support the benefit/risk profile of the RSVPreF3 OA vaccine in the target population of older adults ≥60 years was the placebo-controlled Phase 3 efficacy study ADJ-006 study. This study represents a major part of the overall exposure to the RSVPreF3 vaccine. The safety and reactogenicity

data is further supported by data from three Phase 3 studies (ADJ-004, -007 and -009) and one Phase 1/2 dose-selection study RSV OA=ADJ-002, where applicable.

Safety assessments include monitoring and recording of solicited (administration site and systemic reactogenicity events), unsolicited adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), and deaths.

Solicited administration site events assessed in the Phase 3 studies included pain, erythema and swelling at the injection site and solicited systemic events included fever, headache, fatigue, myalgia and arthralgia. Recording of these AEs was solicited during the 4- day follow-up period after vaccination. Unsolicited AEs were assessed during the 30- day follow-up period after vaccination. Both solicited and unsolicited AEs were recorded on diary cards.

In all Phase 3 studies, SAEs and AESI were collected up to 6 months after vaccination. All SAEs and AESI considered vaccination-related, any fatal SAEs and AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of receipt of the first study vaccine until the participant is discharged from the study.

In general, the safety data was not pooled across the studies. However, aggregated analyses were performed overall and by subgroups by pooling data on medically attended unsolicited AEs, SAEs, and non-serious/serious AESI from the Phase 3 studies (RSV OA=ADJ-006, -004, -007 and -009) considering all data post-vaccination with RSVPreF3 OA, except in case of co-administration with FLU-QIV. This analysis included a total of 15 303 participants.

The investigator was to assess causality for all AEs and SAEs. AEs will be considered related if there is a reasonable possibility of a relationship to study vaccine.

#### *2.6.8.1. Patient exposure*

Across all Phase 3 studies, a total of 15,745 participants in the ES and 100 participants in the Phase 1/2 dose-finding study received at least 1 dose of the RSVPreF3 OA (120µg/AS01$_E$) vaccine (Table 18).

Table 18: Number of participants exposed to and doses administered of RSVPreF3 OA

| Study | Age | Number of participants (ES) (RSVPreF3 OA) | Number of doses (RSVPreF3 OA) |
|---|---|---|---|
| Phase 3 studies | | | |
| RSV OA=ADJ-006 | 60 years and above | 12 467 | 12 467 |
| RSV OA=ADJ-004 | | 1653 | 1653 |
| RSV OA=ADJ-007 | | 868 | 868 |
| RSV OA=ADJ-009 | | 757 | 757 |
| Total (Phase 3) | | 15 745 | 15 745 |
| Phase 1/2 study | | | |
| RSV OA=ADJ-002 (Part B) | 60 to 80 years | 100 | 197 |
| Total (Phase 1/2 and Phase 3) | | 15 845 | 15 942 |
| Data source: M5.3.5.1 and M5.3.5.2, RSV OA=ADJ-006 (212494) Report (13-AUG-2022), RSV OA=ADJ-004 (212496) Report Amendment 1 (02-AUG-2022), RSV OA=ADJ-007 (214488) Report Amendment 1 (02-AUG-2022), RSV OA=ADJ-009 (217131) Report (17-MAY-2022), RSV OA=ADJ-002 (208851) Report (12-MAY-2021). | | | |

Table 19 Number of participants by age in the clinical studies in the developmental programme

| | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| Controlled Trials | 14220/26856 | 5062/26856 | 556/26856 |
| Non-Controlled trials | 1268/2410 | 545/2410 | 43/2410 |

In all studies the demographic and baseline characteristics were well balanced between the study groups and no differences were observed between groups.

*2.6.8.2. Adverse events*

Reactogenicity

For study ADJ-006, the solicited safety set (SSS), used to determine reactogenicity, included 1,757 participants (879 in the RSVPreF3 group and 878 in the Placebo group).

In study ADJ-006, solicited AEs reported within 4 days following vaccination were observed in 71.9% participants in the RSVPreF3 group and in 27.9% participants in the Placebo group (Table 20).

Table 20: Summary of AEs, grade 3 AEs and medically attended AEs (solicited only) within 4 days following vaccination - Solicited Safety Set (ADJ-006) (modified by the Assessor)

| | RSVPreF3 | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| N | 879 | | | | 878 | | | |
| Any adverse event | 632 | 71.9 | 68.8 | 74.9 | 245 | 27.9 | 25.0 | 31.0 |
| Administration site AE | 547 | 62.2 | 58.9 | 65.4 | 88 | 10.0 | 8.1 | 12.2 |
| Systemic AE | 434 | 49.4 | 46.0 | 52.7 | 204 | 23.2 | 20.5 | 26.2 |
| Any grade 3 adverse event | 36 | 4.1 | 2.9 | 5.6 | 8 | 0.9 | 0.4 | 1.8 |
| Administration site AE | 13 | 1.5 | 0.8 | 2.5 | 0 | 0 | 0 | 0.4 |
| Systemic AE | 29 | 3.3 | 2.2 | 4.7 | 8 | 0.9 | 0.4 | 1.8 |
| Any medically attended adverse events | 2 | 0.2 | 0.0 | 0.8 | 0 | 0 | 0 | 0.4 |
| Administration site AE | 0 | 0 | 0 | 0.4 | 0 | 0 | 0 | 0.4 |
| Systemic AE | 2 | 0.2 | 0.0 | 0.8 | 0 | 0 | 0 | 0.4 |

Data Source: Table 14.3.1.4, Table 14.3.1.5, and Table 14.3.1.8
RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants with diary card
n/%= number/percentage of participants presenting at least one type of symptom
95% CI = exact 95% confidence interval, AE = adverse event; LL = Lower Limit, UL = Upper Limit

The reactogenicity profile observed during study ADJ-006 is presented in Table 21.

Table 21: Percentage of participants with solicited administration site and systemic events within 4 days following vaccination — SSS (ADJ-006) (modified by the Assessor)

| | RSVPreF3 | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| N | 879 | | | | 874 | | | |
| Solicited administration site events | | | | | | | | |
| Erythema | 66 | 7.5 | 5.9 | 9.5 | 7 | 0.8 | 0.3 | 1.6 |
| Pain | 535 | 60.9 | 57.5 | 64.1 | 81 | 9.3 | 7.4 | 11.4 |
| Swelling | 48 | 5.5 | 4.1 | 7.2 | 5 | 0.6 | 0.2 | 1.3 |
| Solicited systemic events | | | | | | | | |
| Arthralgia | 159 | 18.1 | 15.6 | 20.8 | 56 | 6.4 | 4.9 | 8.2 |
| Fatigue | 295 | 33.6 | 30.4 | 36.8 | 141 | 16.1 | 13.7 | 18.7 |
| Fever (°C) | 12 | 1.4 | 0.7 | 2.4 | 0 | 0 | 0 | 0.4 |
| Headache | 239 | 27.2 | 24.3 | 30.3 | 111 | 12.6 | 10.5 | 15.0 |
| Myalgia | 254 | 28.9 | 25.9 | 32.0 | 72 | 8.2 | 6.5 | 10.2 |

| | RSVPreF3 | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |

Data Source: M5.3.5.1, RSV OA=ADJ-006 (212494) Report 13-AUG-2022), Table 14.3.1.13, Table 14.3.1.19
RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants with diary card
n/%= number/percentage of participants presenting at least one type of event when the intensity is maximum
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

During study ADJ-006, grade 3 solicited administration site events were reported in 1.5% of participants in the RSVPreF3 group and in no participants in the Placebo group (Table 20). In the RSVPreF3 group, Grade 3 pain was reported in 1.0% of the participants; Grade 3 erythema and Grade 3 swelling were each reported in 0.2% of the participants. Grade 3 solicited systemic events were reported in 3.3% of participants in the RSVPreF3 group and 0.9% in the Placebo group (Table 20). The most frequently reported Grade 3 systemic event was fatigue (1.7% of participants in the RSVPreF3 group and 0.5% of participants in the Placebo group), followed by myalgia (1.4% of participants in the RSVPreF3 group and 0.3% of participants in the Placebo group), arthralgia (1.3% of participants in the RSVPreF3 group and 0.6% of participants in the Placebo group) and headache (1.3% of participants in the RSVPreF3 group and 0% of participants in the Placebo group).

The reactogenicity profile observed in the studies ADJ-004, ADJ-007 and ADJ-009 were overall comparable to the reactogenicity profile observed in the solicited safety set in study ADJ-006. The majority of participants in all Phase 3 studies experienced a solicited adverse event within 4 days. The most frequently reported solicited AEs were injection-site pain, myalgia, fatigue and headache.

### Unsolicited adverse events

ADJ-006

Within 30 days post-vaccination, at least 1 unsolicited AE was reported in 4,117 (33.0%) participants in the RSVPreF3 group (8,411 events) and in 2,229 (17.8%) participants in the Placebo group (3,732 events). Of note, for all participants who were not included in the SSS, all reactions following vaccination were recorded as unsolicited events, including also those reactions which were solicited in the SSS (i.e. solicited administration site events: injection site erythema, swelling and pain; and solicited systemic events: fatigue, headache, fever, myalgia and arthralgia). The more frequent occurrence of unsolicited AE in the RSVPreF3 group in the ES is mainly driven by those PTs corresponding to the reactogenicity of the vaccine.

Within 30 days post-vaccination, at least 1 Grade 3 unsolicited AE was reported in 246 (2.0%) participants in the RSVPreF3 group (336 events) and in 158 (1.3%) participants in the Placebo group (207 events). The most frequent types of Grade 3 AEs reported by SOC were consistent with those reported for any AEs with “General disorders and administration site conditions” (76 [0.6%] participants in the RSVPreF3 group and 16 [0.1%] participants in the Placebo group), “Nervous system disorders” (41 [0.3%] participants in the RSVPreF3 group and 27 [0.2%] participants in the Placebo group) and “Infections and Infestations” (28 [0.2%] participants in the RSVPreF3 group and 36 [0.3%] participants in the Placebo group).

In the solicited safety set, at least 1 unsolicited AE was reported within 30 days post-vaccination in 131 (14.9%) participants in the RSVPreF3 group and in 128 (14.6%) participants in the Placebo group. The most frequently reported unsolicited AEs (by PT) were headache (reported in 16 [1.8%] participants), followed by arthralgia (reported in 7 [0.8%] participants) and oropharyngeal pain (reported in 6 [0.7%] participants) in the RSVPreF3 group. In the Placebo group, the most frequently reported unsolicited AEs (by PT) were

arthralgia (reported in 8 [0.9%] participants), followed by upper respiratory tract infection (reported in 7 [0.8%] participants) and headache, injection site pruritis, oropharyngeal pain and nasopharyngitis (each reported in 5 [0.6%] participants). At least 1 Grade 3 unsolicited AEs was reported within 30 days post-vaccination in 1.4% of participants in both groups.

*ADJ-004, -007 and -009*

In studies ADJ-004, -007 and -009 at least 1 unsolicited AE was reported in 12.8% - 14.8% of participants within 30 days following vaccination. In study ADJ-004 the most frequently reported unsolicited AE was headache (reported in 18 [1.1%] participants), followed by arthralgia (reported in 11 [0.7%] participants) and injection site pruritus (reported in 10 [0.6%] participants). In study ADJ-007, the most frequently reported unsolicited AE was hypertension (reported in 7 [1.6%] participants), followed by upper respiratory tract infection (reported in 5 [1.2%] participants) and headache and COVID-19 infection (reported in 4 [0.9%] participants). In study ADJ-009 the most frequently reported unsolicited AE in the RSVPreF3_Grp1 and RSVPreF3_Grp2 groups was headache (reported in 4 [1.6%] participants in both groups), while COPD, headache and pruritus were the most frequently reported unsolicited AEs in the RSVPreF3_Grp3 group (each event was reported in 3 [1.2%] participants).

At least 1 Grade 3 unsolicited AE was reported in 1.2% to 2.4% of participants.

Related unsolicited adverse events

*ADJ-006*

At least 1 unsolicited AE assessed as related to the study intervention by the investigator was reported in 24.9% of participants in the RSVPreF3 group (5,584 events) and 5.8% of participants in the Placebo group (1,146 events), see Table 22.

The observed incidence of related injection site reactions, fatigue, malaise, asthenia, pyrexia, pain, discomfort, axillary pain, chills, feeling hot, feeling cold, headache, somnolence, myalgia, pain in extremity, arthralgia, nausea, rash, body temperature increased and lymphadenopathy were higher in the RSVPreF3 group compared to the placebo.

Table 22: Investigational product related unsolicited AE with onset within 30 days following vaccination by System Organ Class and Preferred Term occurring in **≥5** participants in each treatment group – ES (ADJ-006) (modified by the Assessor)

| | RSVPreF3 N=12467 | | | | Placebo N=12499 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE)<br>High Level Term (CODE)<br>Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| Any related unsolicited adverse event | 3105 | 24.9 | 24.1 | 25.7 | 731 | 5.8 | 5.4 | 6.3 |
| General disorders and administration site conditions (10018065) | 2786 | 22.3 | 21.6 | 23.1 | 409 | 3.3 | 3.0 | 3.6 |
| Injection site reactions (10022097) | 2362 | 18.9 | 18.3 | 19.6 | 267 | 2.1 | 1.9 | 2.4 |
| Injection site pain (10022086) | 1936 | 15.5 | 14.9 | 16.2 | 172 | 1.4 | 1.2 | 1.6 |
| Injection site erythema (10022061) | 449 | 3.6 | 3.3 | 3.9 | 27 | 0.2 | 0.1 | 0.3 |
| Injection site swelling (10053425) | 316 | 2.5 | 2.3 | 2.8 | 19 | 0.2 | 0.1 | 0.2 |
| Injection site pruritus (10022093) | 80 | 0.6 | 0.5 | 0.8 | 16 | 0.1 | 0.1 | 0.2 |
| Injection site warmth (10022112) | 78 | 0.6 | 0.5 | 0.8 | 5 | 0.0 | 0.0 | 0.1 |
| Injection site joint pain (10049261) | 62 | 0.5 | 0.4 | 0.6 | 4 | 0.0 | 0.0 | 0.1 |
| Injection site reaction (10022095) | 51 | 0.4 | 0.3 | 0.5 | 11 | 0.1 | 0.0 | 0.2 |
| Injection site bruising (10022052) | 31 | 0.2 | 0.2 | 0.4 | 18 | 0.1 | 0.1 | 0.2 |
| Injection site discomfort (10054266) | 26 | 0.2 | 0.1 | 0.3 | 4 | 0.0 | 0.0 | 0.1 |
| Injection site induration (10022075) | 18 | 0.1 | 0.1 | 0.2 | 2 | 0.0 | 0.0 | 0.1 |
| Injection site rash (10022094) | 11 | 0.1 | 0.0 | 0.2 | 4 | 0.0 | 0.0 | 0.1 |

| | RSVPreF3 N=12467 | | | | Placebo N=12499 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE)<br>High Level Term (CODE)<br>Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| Injection site oedema (10022085) | 14 | 0.1 | 0.1 | 0.2 | 0 | 0 | 0 | 0.0 |
| Injection site movement impairment (10056250) | 12 | 0.1 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.0 |
| Injection site haematoma (10022066) | 6 | 0.0 | 0.0 | 0.1 | 5 | 0.0 | 0.0 | 0.1 |
| Injection site mass (10022081) | 8 | 0.1 | 0.0 | 0.1 | 3 | 0.0 | 0.0 | 0.1 |
| Injection site inflammation (10022078) | 9 | 0.1 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Asthenic conditions (10003550) | 330 | 2.6 | 2.4 | 2.9 | 98 | 0.8 | 0.6 | 1.0 |
| Fatigue (10016256) | 256 | 2.1 | 1.8 | 2.3 | 77 | 0.6 | 0.5 | 0.8 |
| Malaise (10025482) | 45 | 0.4 | 0.3 | 0.5 | 10 | 0.1 | 0.0 | 0.1 |
| Asthenia (10003549) | 38 | 0.3 | 0.2 | 0.4 | 12 | 0.1 | 0.0 | 0.2 |
| Febrile disorders (10016286) | 189 | 1.5 | 1.3 | 1.7 | 21 | 0.2 | 0.1 | 0.3 |
| Pyrexia (10037660) | 189 | 1.5 | 1.3 | 1.7 | 21 | 0.2 | 0.1 | 0.3 |
| Vaccination site reactions (10068754) | 137 | 1.1 | 0.9 | 1.3 | 9 | 0.1 | 0.0 | 0.1 |
| Vaccination site pain (10068879) | 106 | 0.9 | 0.7 | 1.0 | 4 | 0.0 | 0.0 | 0.1 |
| Vaccination site erythema (10059079) | 18 | 0.1 | 0.1 | 0.2 | 0 | 0 | 0 | 0.0 |
| Vaccination site swelling (10069620) | 18 | 0.1 | 0.1 | 0.2 | 0 | 0 | 0 | 0.0 |
| Vaccination site reaction (10059080) | 8 | 0.1 | 0.0 | 0.1 | 0 | 0 | 0 | 0.0 |
| Vaccination site pruritus (10068881) | 5 | 0.0 | 0.0 | 0.1 | 0 | 0 | 0 | 0.0 |
| Pain and discomfort NEC (10033372) | 121 | 1.0 | 0.8 | 1.2 | 20 | 0.2 | 0.1 | 0.2 |
| Pain (10033371) | 93 | 0.7 | 0.6 | 0.9 | 15 | 0.1 | 0.1 | 0.2 |
| Discomfort (10013082) | 13 | 0.1 | 0.1 | 0.2 | 1 | 0.0 | 0.0 | 0.0 |
| Axillary pain (10048750) | 9 | 0.1 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Feelings and sensations NEC (10068759) | 114 | 0.9 | 0.8 | 1.1 | 25 | 0.2 | 0.1 | 0.3 |
| Chills (10008531) | 73 | 0.6 | 0.5 | 0.7 | 19 | 0.2 | 0.1 | 0.2 |
| Feeling hot (10016334) | 32 | 0.3 | 0.2 | 0.4 | 3 | 0.0 | 0.0 | 0.1 |
| Feeling cold (10016326) | 11 | 0.1 | 0.0 | 0.2 | 2 | 0.0 | 0.0 | 0.1 |
| Administration site reactions NEC (10057196) | 60 | 0.5 | 0.4 | 0.6 | 6 | 0.0 | 0.0 | 0.1 |
| Administration site pain (10058049) | 49 | 0.4 | 0.3 | 0.5 | 4 | 0.0 | 0.0 | 0.1 |
| Administration site erythema (10074796) | 15 | 0.1 | 0.1 | 0.2 | 0 | 0 | 0 | 0.0 |
| General signs and symptoms NEC (10018072) | 16 | 0.1 | 0.1 | 0.2 | 8 | 0.1 | 0.0 | 0.1 |
| Influenza like illness (10022004) | 8 | 0.1 | 0.0 | 0.1 | 4 | 0.0 | 0.0 | 0.1 |
| Swelling (10042674) | 5 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Nervous system disorders (10029205) | 519 | 4.2 | 3.8 | 4.5 | 222 | 1.8 | 1.6 | 2.0 |
| Headaches NEC (10019233) | 464 | 3.7 | 3.4 | 4.1 | 188 | 1.5 | 1.3 | 1.7 |
| Headache (10019211) | 464 | 3.7 | 3.4 | 4.1 | 183 | 1.5 | 1.3 | 1.7 |
| Neurological signs and symptoms NEC (10029306) | 34 | 0.3 | 0.2 | 0.4 | 25 | 0.2 | 0.1 | 0.3 |
| Dizziness (10013573) | 31 | 0.2 | 0.2 | 0.4 | 24 | 0.2 | 0.1 | 0.3 |
| Disturbances in consciousness NEC (10013509) | 24 | 0.2 | 0.1 | 0.3 | 7 | 0.1 | 0.0 | 0.1 |
| Lethargy (10024264) | 12 | 0.1 | 0.0 | 0.2 | 4 | 0.0 | 0.0 | 0.1 |
| Somnolence (10041349) | 11 | 0.1 | 0.0 | 0.2 | 2 | 0.0 | 0.0 | 0.1 |
| Paraesthesias and dysaesthesias (10033788) | 15 | 0.1 | 0.1 | 0.2 | 3 | 0.0 | 0.0 | 0.1 |
| Paraesthesia (10033775) | 7 | 0.1 | 0.0 | 0.1 | 2 | 0.0 | 0.0 | 0.1 |
| Hypoaesthesia (10020937) | 7 | 0.1 | 0.0 | 0.1 | 0 | 0 | 0 | 0.0 |
| Musculoskeletal and connective tissue disorders (10028395) | 269 | 2.2 | 1.9 | 2.4 | 72 | 0.6 | 0.5 | 0.7 |
| Muscle pains (10028323) | 126 | 1.0 | 0.8 | 1.2 | 26 | 0.2 | 0.1 | 0.3 |
| Myalgia (10028411) | 126 | 1.0 | 0.8 | 1.2 | 26 | 0.2 | 0.1 | 0.3 |
| Musculoskeletal and connective tissue pain and discomfort (10068757) | 71 | 0.6 | 0.4 | 0.7 | 28 | 0.2 | 0.1 | 0.3 |
| Pain in extremity (10033425) | 34 | 0.3 | 0.2 | 0.4 | 8 | 0.1 | 0.0 | 0.1 |
| Neck pain (10028836) | 16 | 0.1 | 0.1 | 0.2 | 9 | 0.1 | 0.0 | 0.1 |
| Back pain (10003988) | 11 | 0.1 | 0.0 | 0.2 | 7 | 0.1 | 0.0 | 0.1 |
| Joint related signs and symptoms (10023226) | 62 | 0.5 | 0.4 | 0.6 | 21 | 0.2 | 0.1 | 0.3 |
| Arthralgia (10003239) | 62 | 0.5 | 0.4 | 0.6 | 21 | 0.2 | 0.1 | 0.3 |
| Musculoskeletal and connective tissue conditions NEC (10080711) | 12 | 0.1 | 0.0 | 0.2 | 6 | 0.0 | 0.0 | 0.1 |
| Musculoskeletal stiffness (10052904) | 11 | 0.1 | 0.0 | 0.2 | 5 | 0.0 | 0.0 | 0.1 |
| Bone related signs and symptoms (10006006) | 5 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Bone pain (10006002) | 5 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Muscle related signs and symptoms NEC (10028326) | 5 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Respiratory, thoracic and mediastinal disorders (10038738) | 127 | 1.0 | 0.8 | 1.2 | 98 | 0.8 | 0.6 | 1.0 |
| Upper respiratory tract signs and symptoms (10046313) | 84 | 0.7 | 0.5 | 0.8 | 69 | 0.6 | 0.4 | 0.7 |
| Rhinorrhoea (10039101) | 43 | 0.3 | 0.2 | 0.5 | 38 | 0.3 | 0.2 | 0.4 |
| Oropharyngeal pain (10068319) | 32 | 0.3 | 0.2 | 0.4 | 26 | 0.2 | 0.1 | 0.3 |
| Sneezing (10041232) | 5 | 0.0 | 0.0 | 0.1 | 10 | 0.1 | 0.0 | 0.1 |
| Throat irritation (10043521) | 4 | 0.0 | 0.0 | 0.1 | 5 | 0.0 | 0.0 | 0.1 |
| Coughing and associated symptoms (10011233) | 30 | 0.2 | 0.2 | 0.3 | 21 | 0.2 | 0.1 | 0.3 |
| Cough (10011224) | 27 | 0.2 | 0.1 | 0.3 | 16 | 0.1 | 0.1 | 0.2 |

| Primary System Organ Class (CODE)<br>High Level Term (CODE)<br>Preferred Term (CODE) | RSVPreF3 N=12467 | | | | Placebo N=12499 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| Productive cough (10036790) | 3 | 0.0 | 0.0 | 0.1 | 6 | 0.0 | 0.0 | 0.1 |
| Nasal congestion and inflammations (10028736) | 19 | 0.2 | 0.1 | 0.2 | 13 | 0.1 | 0.1 | 0.2 |
| Nasal congestion (10028735) | 19 | 0.2 | 0.1 | 0.2 | 13 | 0.1 | 0.1 | 0.2 |
| Breathing abnormalities (10006334) | 8 | 0.1 | 0.0 | 0.1 | 5 | 0.0 | 0.0 | 0.1 |
| Dyspnoea (10013968) | 8 | 0.1 | 0.0 | 0.1 | 4 | 0.0 | 0.0 | 0.1 |
| Gastrointestinal disorders (10017947) | 115 | 0.9 | 0.8 | 1.1 | 55 | 0.4 | 0.3 | 0.6 |
| Nausea and vomiting symptoms (10028817) | 61 | 0.5 | 0.4 | 0.6 | 16 | 0.1 | 0.1 | 0.2 |
| Nausea (10028813) | 55 | 0.4 | 0.3 | 0.6 | 15 | 0.1 | 0.1 | 0.2 |
| Vomiting (10047700) | 7 | 0.1 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Diarrhoea (excl. infective) (10012736) | 35 | 0.3 | 0.2 | 0.4 | 23 | 0.2 | 0.1 | 0.3 |
| Diarrhoea (10012735) | 35 | 0.3 | 0.2 | 0.4 | 23 | 0.2 | 0.1 | 0.3 |
| Gastrointestinal and abdominal pains (excl. oral and throat) (10017926) | 17 | 0.1 | 0.1 | 0.2 | 13 | 0.1 | 0.1 | 0.2 |
| Abdominal pain upper (10000087) | 8 | 0.1 | 0.0 | 0.1 | 11 | 0.1 | 0.0 | 0.2 |
| Abdominal pain (10000081) | 9 | 0.1 | 0.0 | 0.1 | 3 | 0.0 | 0.0 | 0.1 |
| Infections and infestations (10021881) | 52 | 0.4 | 0.3 | 0.5 | 40 | 0.3 | 0.2 | 0.4 |
| Upper respiratory tract infections (10046309) | 28 | 0.2 | 0.1 | 0.3 | 23 | 0.2 | 0.1 | 0.3 |
| Nasopharyngitis (10028810) | 12 | 0.1 | 0.0 | 0.2 | 8 | 0.1 | 0.0 | 0.1 |
| Upper respiratory tract infection (10046306) | 5 | 0.0 | 0.0 | 0.1 | 8 | 0.1 | 0.0 | 0.1 |
| Rhinitis (10039083) | 7 | 0.1 | 0.0 | 0.1 | 5 | 0.0 | 0.0 | 0.1 |
| Herpes viral infections (10019972) | 5 | 0.0 | 0.0 | 0.1 | 7 | 0.1 | 0.0 | 0.1 |
| Viral infections NEC (10047465) | 6 | 0.0 | 0.0 | 0.1 | 3 | 0.0 | 0.0 | 0.1 |
| Skin and subcutaneous tissue disorders (10040785) | 41 | 0.3 | 0.2 | 0.4 | 24 | 0.2 | 0.1 | 0.3 |
| Apocrine and eccrine gland disorders (10002982) | 9 | 0.1 | 0.0 | 0.1 | 9 | 0.1 | 0.0 | 0.1 |
| Hyperhidrosis (10020642) | 7 | 0.1 | 0.0 | 0.1 | 7 | 0.1 | 0.0 | 0.1 |
| Pruritus NEC (10049293) | 8 | 0.1 | 0.0 | 0.1 | 9 | 0.1 | 0.0 | 0.1 |
| Pruritus (10037087) | 8 | 0.1 | 0.0 | 0.1 | 9 | 0.1 | 0.0 | 0.1 |
| Rashes, eruptions and exanthems NEC (10052566) | 16 | 0.1 | 0.1 | 0.2 | 1 | 0.0 | 0.0 | 0.0 |
| Rash (10037844) | 14 | 0.1 | 0.1 | 0.2 | 1 | 0.0 | 0.0 | 0.0 |
| Investigations (10022891) | 32 | 0.3 | 0.2 | 0.4 | 4 | 0.0 | 0.0 | 0.1 |
| Physical examination procedures and organ system status (10071941) | 31 | 0.2 | 0.2 | 0.4 | 2 | 0.0 | 0.0 | 0.1 |
| Body temperature increased (10005911) | 30 | 0.2 | 0.2 | 0.3 | 2 | 0.0 | 0.0 | 0.1 |
| Ear and labyrinth disorders (10013993) | 11 | 0.1 | 0.0 | 0.2 | 12 | 0.1 | 0.0 | 0.2 |
| Inner ear signs and symptoms (10022398) | 8 | 0.1 | 0.0 | 0.1 | 8 | 0.1 | 0.0 | 0.1 |
| Vertigo (10047340) | 6 | 0.0 | 0.0 | 0.1 | 5 | 0.0 | 0.0 | 0.1 |
| Blood and lymphatic system disorders (10005329) | 15 | 0.1 | 0.1 | 0.2 | 7 | 0.1 | 0.0 | 0.1 |
| Lymphatic system disorders NEC (10025198) | 15 | 0.1 | 0.1 | 0.2 | 3 | 0.0 | 0.0 | 0.1 |
| Lymphadenopathy (10025197) | 13 | 0.1 | 0.1 | 0.2 | 2 | 0.0 | 0.0 | 0.1 |
| Psychiatric disorders (10037175) | 18 | 0.1 | 0.1 | 0.2 | 3 | 0.0 | 0.0 | 0.1 |
| Disturbances in initiating and maintaining sleep (10013510) | 6 | 0.0 | 0.0 | 0.1 | 2 | 0.0 | 0.0 | 0.1 |
| Insomnia (10022437) | 6 | 0.0 | 0.0 | 0.1 | 2 | 0.0 | 0.0 | 0.1 |
| Eye disorders (10015919) | 14 | 0.1 | 0.1 | 0.2 | 6 | 0.0 | 0.0 | 0.1 |
| Ocular disorders NEC (10030032) | 7 | 0.1 | 0.0 | 0.1 | 2 | 0.0 | 0.0 | 0.1 |
| Eye pain (10015958) | 6 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Metabolism and nutrition disorders (10027433) | 13 | 0.1 | 0.1 | 0.2 | 6 | 0.0 | 0.0 | 0.1 |
| Appetite disorders (10003022) | 11 | 0.1 | 0.0 | 0.2 | 5 | 0.0 | 0.0 | 0.1 |
| Decreased appetite (10061428) | 11 | 0.1 | 0.0 | 0.2 | 5 | 0.0 | 0.0 | 0.1 |
| Cardiac disorders (10007541) | 9 | 0.1 | 0.0 | 0.1 | 3 | 0.0 | 0.0 | 0.1 |
| Vascular disorders (10047065) | 8 | 0.1 | 0.0 | 0.1 | 3 | 0.0 | 0.0 | 0.1 |

Data Source: M5.3.5.1, RSV OA=ADJ-006 (212494) Report (13-AUG-2022), Table 14.3.1.33
RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo

Within 30 days post-vaccination, at least 1 Grade 3 related AE was reported in 112 (0.9%) participants in the RSVPreF3 group (165 events) and 25 (0.2%) participants in the Placebo group (41 events). The observed incidence of Grade 3 related injection site pain, injection site erythema, injection site swelling, pyrexia and headache were higher in the RSVPreF3 group compared to the placebo based on relative risk.

*ADJ-004, -007 and -009*

In study ADJ-004, at least 1 unsolicited AE considered by the investigator to be related to the study vaccination was reported in 59 (3.6%) participants. The most frequently reported related unsolicited AE was injection site pruritus (10 participants [1.1%]), followed by chills (8 participants [0.5%]) and asthenia, nausea and pruritus (all 3 participants [0.2%]). At least 1 Grade 3 unsolicited AE considered by the investigator to be related to the study vaccination was reported in 6 (0.4%) participants.

In study ADJ-007, after RSVPreF3 OA dose in the Control group, at least 1 unsolicited AE considered by the investigator to be related to the study vaccination was reported in 10 (2.3%) participants. The most frequently reported related unsolicited AE was injection site pruritus (2 participants [0.5%]). All other related unsolicited AEs were reported by 1 participant. At least 1 Grade 3 unsolicited AE considered by the investigator to be related to the study vaccination was reported in 1 (0.2%) participant.

In study ADJ-009, At least 1 unsolicited AE considered by the investigator to be related to the study vaccination was reported in 11 (4.4%), 15 (5.9%) and 12 (4.7%) participants in the RSVPreF3_Grp1, RSVPreF3_Grp2 and RSVPreF3_Grp3 groups, respectively. The most frequently reported related unsolicited AEs were headache (5 participants), pruritus and oropharyngeal pain (4 participants each). At least 1 Grade 3 unsolicited AE considered by the investigator to be related to the study vaccination was reported in 1 (0.4%) participant in the RSVPreF3_Grp1 group and 3 (1.2%) participants in the RSVPreF3_Grp2 group.

Adverse events of special interest: pIMDs

Potential immune-mediated diseases (pIMDs) were considered adverse events of special interest (AESIs).

Overall, up to the data lock point (DLP), at least 1 pIMD was reported in 55 (0.4%) participants in the aggregated analysis. The most frequently reported pIMDs (by SOC) were “Metabolism and nutrition disorders” (reported in 13 [0.1%] participants) and “Musculoskeletal and connective tissue disorders” (reported in 13 [0.1%] participants), followed by “Nervous system disorders” (reported in 8 [0.1%] participants).

Overall, a total of 9 (0.1%) participants reported pIMDs considered by the investigator as related to the study vaccination (Table 23).

Table 23: Summary of participants with at least one pIMD considered possibly related with onset between vaccination and DLP – ES (ADJ-006, -004, -007, -009) (modified by the Assessor)

| | RSVPreF3 N=15303 | | | |
|---|---|---|---|---|
| | | | 95% CI | |
| Primary System Organ Class (CODE)<br>Preferred Term (CODE) | n | % | LL | UL |
| Any related pIMD | 9 | 0.1 | 0.0 | 0.1 |
| Nervous system disorders (10029205) | 3 | 0.0 | 0.0 | 0.1 |
| Bell's palsy (10004223) | 2 | 0.0 | 0.0 | 0.0 |
| Guillain-Barre syndrome (10018767) | 1 | 0.0 | 0.0 | 0.0 |
| Musculoskeletal and connective tissue disorders (10028395) | 2 | 0.0 | 0.0 | 0.0 |
| Polyarthritis (10036030) | 1 | 0.0 | 0.0 | 0.0 |
| Rheumatoid arthritis (10039073) | 1 | 0.0 | 0.0 | 0.0 |
| Blood and lymphatic system disorders (10005329) | 1 | 0.0 | 0.0 | 0.0 |
| Pancytopenia (10033661) | 1 | 0.0 | 0.0 | 0.0 |
| Endocrine disorders (10014698) | 1 | 0.0 | 0.0 | 0.0 |
| Basedow's disease (10004161) | 1 | 0.0 | 0.0 | 0.0 |
| Metabolism and nutrition disorders (10027433) | 1 | 0.0 | 0.0 | 0.0 |
| Gout (10018627) | 1 | 0.0 | 0.0 | 0.0 |
| Skin and subcutaneous tissue disorders (10040785) | 1 | 0.0 | 0.0 | 0.0 |
| Psoriasis (10037153) | 1 | 0.0 | 0.0 | 0.0 |

Data Source: M5.3.5.3, Statistical report for the aggregated safety analysis, Table number 14.3.1.37

| | RSVPreF3 N=15303 | | | |
|---|---|---|---|---|
| | | | 95% CI | |
| Primary System Organ Class (CODE)<br>Preferred Term (CODE) | n | % | LL | UL |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine.
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.
Safety Data Lock Point = For RSV OA=ADJ-004: 11FEB2022, For RSV OA=ADJ-006: 30APR2022, For RSV OA=ADJ-007: no DLP (DBF date: 18MAR2022), For RSV OA=ADJ-009: 09MAR2022

### *2.6.8.3. Serious adverse event/deaths/other significant events*

Serious Adverse Events

*Study ADJ-006*

Within 6 months following vaccination, SAEs were reported in 522 participants (4.2%) in the RSVPreF3 group (643 events) and 506 participants (4.0%) in the Placebo group (656 events), see Table 24.

Table 24: Summary of participants with at least one SAE with onset within 6 months following vaccination – ES (ADJ-006) (modified by the Assessor)

| | RSVPreF3 N=12467 | | | | Placebo N=12499 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | n | % | LL | UL | n | % | LL | UL |
| Any serious adverse event | 522 | 4.2 | 3.8 | 4.6 | 506 | 4.0 | 3.7 | 4.4 |
| Infections and infestations (10021881) | 107 | 0.9 | 0.7 | 1.0 | 115 | 0.9 | 0.8 | 1.1 |
| Cardiac disorders (10007541) | 91 | 0.7 | 0.6 | 0.9 | 86 | 0.7 | 0.6 | 0.8 |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (10029104) | 65 | 0.5 | 0.4 | 0.7 | 58 | 0.5 | 0.4 | 0.6 |
| Nervous system disorders (10029205) | 60 | 0.5 | 0.4 | 0.6 | 65 | 0.5 | 0.4 | 0.7 |
| Injury, poisoning and procedural complications (10022117) | 60 | 0.5 | 0.4 | 0.6 | 61 | 0.5 | 0.4 | 0.6 |
| Gastrointestinal disorders (10017947) | 38 | 0.3 | 0.2 | 0.4 | 40 | 0.3 | 0.2 | 0.4 |
| Respiratory, thoracic and mediastinal disorders (10038738) | 32 | 0.3 | 0.2 | 0.4 | 39 | 0.3 | 0.2 | 0.4 |
| Musculoskeletal and connective tissue disorders (10028395) | 38 | 0.3 | 0.2 | 0.4 | 23 | 0.2 | 0.1 | 0.3 |
| General disorders and administration site conditions (10018065) | 19 | 0.2 | 0.1 | 0.2 | 24 | 0.2 | 0.1 | 0.3 |
| Vascular disorders (10047065) | 19 | 0.2 | 0.1 | 0.2 | 17 | 0.1 | 0.1 | 0.2 |
| Renal and urinary disorders (10038359) | 12 | 0.1 | 0.0 | 0.2 | 13 | 0.1 | 0.1 | 0.2 |
| Hepatobiliary disorders (10019805) | 10 | 0.1 | 0.0 | 0.1 | 14 | 0.1 | 0.1 | 0.2 |
| Metabolism and nutrition disorders (10027433) | 12 | 0.1 | 0.0 | 0.2 | 6 | 0.0 | 0.0 | 0.1 |
| Reproductive system and breast disorders (10038604) | 6 | 0.0 | 0.0 | 0.1 | 8 | 0.1 | 0.0 | 0.1 |
| Eye disorders (10015919) | 8 | 0.1 | 0.0 | 0.1 | 3 | 0.0 | 0.0 | 0.1 |
| Psychiatric disorders (10037175) | 4 | 0.0 | 0.0 | 0.1 | 6 | 0.0 | 0.0 | 0.1 |
| Blood and lymphatic system disorders (10005329) | 2 | 0.0 | 0.0 | 0.1 | 4 | 0.0 | 0.0 | 0.1 |
| Immune system disorders (10021428) | 3 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 |
| Skin and subcutaneous tissue disorders (10040785) | 0 | 0 | 0 | 0.0 | 4 | 0.0 | 0.0 | 0.1 |
| Endocrine disorders (10014698) | 1 | 0.0 | 0.0 | 0.0 | 2 | 0.0 | 0.0 | 0.1 |
| Investigations (10022891) | 1 | 0.0 | 0.0 | 0.0 | 2 | 0.0 | 0.0 | 0.1 |
| Ear and labyrinth disorders (10013993) | 1 | 0.0 | 0.0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Surgical and medical procedures (10042613) | 1 | 0.0 | 0.0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Product issues (10077536) | 0 | 0 | 0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Social circumstances (10041244) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |

Data Source: M5.3.5.1, RSV OA=ADJ-006 (212494) Report (13-AUG-2022), Table 14.3.1.48
RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
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

80% CI* = 80% confidence interval for relative risk (Exact Conditional to total number of cases)
Safety Data lock point = 30APR2022

Related SAEs reported within 6 months following vaccination were reported in 9 (0.1%) participants in the RSVPreF3 group and in 6 (0.0%) participants in the Placebo group, see Table 25.

Table 25: Summary of participants with at least one related SAE with onset within 6 months following vaccination – ES (ADJ-006) (modified by the Assessor)

| | RSVPreF3 N=12467 | | | | Placebo N=12499 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| Any related serious adverse event | 9 | 0.1 | 0.0 | 0.1 | 6 | 0.0 | 0.0 | 0.1 |
| Nervous system disorders (10029205) | 4 | 0.0 | 0.0 | 0.1 | 2 | 0.0 | 0.0 | 0.1 |
| Seizure (10039906) | 1 | 0.0 | 0.0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Transient ischaemic attack (10044390) | 1 | 0.0 | 0.0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Syncope (10042772) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Bell's palsy (10004223) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Cardiac disorders (10007541) | 2 | 0.0 | 0.0 | 0.1 | 0 | 0 | 0 | 0.0 |
| Cardiopulmonary failure (10051093) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Acute myocardial infarction (10000891) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (10029104) | 2 | 0.0 | 0.0 | 0.1 | 0 | 0 | 0 | 0.0 |
| Acute myeloid leukaemia (10000880) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Non-small cell lung cancer (10061873) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Respiratory, thoracic and mediastinal disorders (10038738) | 0 | 0 | 0 | 0.0 | 2 | 0.0 | 0.0 | 0.1 |
| Pulmonary embolism (10037377) | 0 | 0 | 0 | 0.0 | 2 | 0.0 | 0.0 | 0.1 |
| Blood and lymphatic system disorders (10005329) | 0 | 0 | 0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Immune thrombocytopenia (10083842) | 0 | 0 | 0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Eye disorders (10015919) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Retinal vein occlusion (10038907) | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 |
| Vascular disorders (10047065) | 0 | 0 | 0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |
| Giant cell arteritis (10018250) | 0 | 0 | 0 | 0.0 | 1 | 0.0 | 0.0 | 0.0 |

Data Source: M5.3.5.1, RSV OA=ADJ-006 (212494) Report (13-AUG-2022), Table 14.3.1.51
RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
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
Safety Data lock point = 30APR2022

*ADJ-004, -007 and -009*

In study ADJ-004, at least 1 SAE was reported in 65 (3.9%) participants. One SAE of Guillain-Barré syndrome considered by the investigator as causally related to the RSVPreF3 OA investigational vaccine was reported in 1 (0.1%) participant.

In study ADJ-007, at least 1 SAE up to study end was reported in in 15 (3.4%) participants in the Co Ad group and 20 (4.5%) participants in the Control group. Two SAEs of acute disseminated encephalomyelitis (ADEM) considered by the investigator as causally related to the FLU-QIV were reported. No related SAEs were reported in the Control group.

In study ADJ-009, up to the safety data lock point for the final analysis, at least 1 SAE was reported in 3 (1.2%) participants in the RSVPreF3_Grp1 group (fall, sepsis, and cholecystitis), 2 (0.8%) participants in the RSVPreF3_Grp2 group (myocardial infarction and sudden cardiac death) and 2 (0.8%) participants in the RSVPreF3_Grp3 group (COPD, pleural effusion, and pulmonary oedema in 1 participant and acute myocardial infarction in the other participant). None were assessed as possibly related to the study vaccine.

*ADJ-002*

In study ADJ-002, at least 1 SAE was reported in 11 (11.0%) participants in the 120µg RSVPreF3 + $AS01_E$ group, versus 9 (8.9%) of participants in the placebo group. None of the SAEs was reported by more than 1 participant and none were considered by the investigator as causally related.

Deaths

*Study ADJ-006*

Up to DLP, at least 1 fatal SAE was reported in 49 (0.4%) participants in the RSVPreF3 group and in 58 (0.5%) participants in the Placebo group across several SOCs. Three cases of fatal SAEs were reported by the investigator as related to the study vaccination: 1 case of cardiopulmonary failure in the RSVPreF3 group and 1 case of pulmonary embolism and 1 death of unknown cause in the placebo group.

- Cardiopulmonary failure: A 60-69-year-old male who, 30 days after receiving RSVPreF3 OA, had a cardiorespiratory arrest with a fatal outcome (no autopsy was performed). The events triggering the cardiorespiratory arrest were not provided. Due to the time to onset, and predisposing medical conditions (diabetes Type II, hypertension, COPD, and obesity), the causal relationship to the vaccine product is considered unlikely.
- Pulmonary embolism: A 70-79-year-old male with past medical history of asthma who, 147 days after receiving placebo, died due to pulmonary embolism. This type of event has been described in the framework of adenovirus-based COVID vaccines (vaccine-induced immune thrombotic thrombocytopenia) which is not applicable for the study intervention received. Considering the long time to onset and the presence of other risk factors such as asthma, the event is considered unlikely related to the vaccine product.
- Death of unknown cause: A 60-69-year-old male with medical history of diabetes Type II, hyperlipidaemia, hypertension, benign prostatic hyperplasia and fatty liver disease, who, 223 days after receiving placebo died of an unknown cause. The reported death is considered unlikely related to the vaccine product in view of the long time to onset after vaccination.

*ADJ-004, -007 and -009*

In study ADJ-004, up to the DLP, SAEs with a fatal outcome were reported in 6 (0.4%) participants: 2 myocardial infarctions; 1 cardiac arrest, 1 COVID-19 pneumonia, and 2 deaths. None of the reported fatal SAEs were assessed by the investigator as causally related to vaccination.

In study ADJ-007, up to DLP, at least 1 fatal SAE was reported in 4 (0.9%) participants in the Co Ad group and in 8 (1.8%) participants in the control group across several SOCs. Of these, 1 event of acute disseminated encephalomyelitis in the Co-Ad group was considered by the investigator to be related to the study intervention FLU-QIV vaccine.

In study ADJ-009, up to the safety data lock point for the final analysis, SAEs with fatal outcomes were reported in 3 participants (2 [0.8%] in the RSVPreF3_Grp2 group and 1 [0.4%] in the RSVPreF3_Grp3 group). The events included myocardial infarction in 1 participant and sudden cardiac death in 1 participant in the RSVPreF3_Grp2 group and COPD, pleural effusion, and pulmonary oedema in 1 participant in the RSVPreF3_Grp3 group. None of the fatal SAEs were considered by the investigator to be causally related to the study intervention.

*ADJ-002*

No deaths were reported in either the 120µg RSVPreF3 + $AS01_E$ group or placebo group.

#### *2.6.8.4. Laboratory findings*

The clinical laboratory evaluations were only analysed in the Phase 1/2 study RSV OA=ADJ-002. No significant alteration of hematologic or biochemical laboratory parameters were observed. No laboratory evaluations were performed in the Phase 3 trials, which is acceptable.

#### *2.6.8.5. Safety in special populations*

Age

In the RSV OA=ADJ-006 study, the following observations were made in the RSVPreF3 group,

- Solicited administration site events: The observed percentage of participants reporting injection site pain was higher in the 60-69 YOA (67.5%) category compared to the ≥80 YOA (42.1%) category. No difference was observed between the other age categories (≥ 65 YOA, ≥ 70 YOA and 70-79 YOA). No difference was observed for erythema and swelling.
- Solicited systemic events: The observed percentage of participants with headache was higher in the 60-69 YOA (30.9%) category compared to the ≥ 80 YOA (15.9%) category. No difference was observed between the other age categories (≥ 65 YOA, ≥ 70 YOA and 70-79 YOA). For myalgia, arthralgia and fatigue, no difference was observed by age category.
- Unsolicited AEs: As unsolicited AEs within 30 days post-vaccination are driven by events linked to the vaccine reactogenicity primarily reported by participants who were not included in the SSS, observations made on unsolicited AEs are aligned with conclusions made for solicited events.

Table 26 presents the number and percentage of AEs by age category (<65, 65-74, 75-84 and ≥85 years) for study RSV OA=ADJ-006, up to the data lock point (30 April 2022).

Table 26 Overview of adverse events up to data lock point by age category – Exposed Set (ADJ-006)

| | RSVPreF3 | | | | | | | | Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <65 YOA N=3208 | | 65-74 YOA N=6587 | | 75-84 YOA N=2385 | | >=85 YOA N=287 | | <65 YOA N=3170 | | 65-74 YOA N=6681 | | 75-84 YOA N=2395 | | >=85 YOA N=253 | |
| **MedDRA Terms** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Total AEs | 1441 | 44.9 | 2852 | 43.3 | 928 | 38.9 | 92 | 32.1 | 971 | 30.6 | 1923 | 28.8 | 728 | 30.4 | 67 | 26.5 |
| Total SAEs | 128 | 4.0 | 308 | 4.7 | 148 | 6.2 | 24 | 8.4 | 128 | 4.0 | 281 | 4.2 | 167 | 7.0 | 31 | 12.3 |
| Fatal | 7 | 0.2 | 23 | 0.3 | 16 | 0.7 | 3 | 1.0 | 13 | 0.4 | 24 | 0.4 | 16 | 0.7 | 5 | 2.0 |
| Hospitalization/prolong existing hospitalization | 118 | 3.7 | 262 | 4.0 | 125 | 5.2 | 19 | 6.6 | 113 | 3.6 | 240 | 3.6 | 148 | 6.2 | 27 | 10.7 |
| Life-threatening | 10 | 0.3 | 16 | 0.2 | 6 | 0.3 | 1 | 0.3 | 5 | 0.2 | 14 | 0.2 | 5 | 0.2 | 2 | 0.8 |
| Disability/incapacity | 2 | 0.1 | 2 | 0.0 | 4 | 0.2 | 0 | 0 | 1 | 0.0 | 3 | 0.0 | 1 | 0.0 | 2 | 0.8 |
| Other (medically significant) | 11 | 0.3 | 44 | 0.7 | 16 | 0.7 | 4 | 1.4 | 7 | 0.2 | 35 | 0.5 | 10 | 0.4 | 2 | 0.8 |
| AE leading to drop-out | 11 | 0.3 | 31 | 0.5 | 23 | 1.0 | 6 | 2.1 | 16 | 0.5 | 37 | 0.6 | 20 | 0.8 | 7 | 2.8 |
| Psychiatric disorders | 28 | 0.9 | 48 | 0.7 | 14 | 0.6 | 0 | 0 | 25 | 0.8 | 26 | 0.4 | 9 | 0.4 | 1 | 0.4 |
| Nervous system disorders | 290 | 9.0 | 526 | 8.0 | 135 | 5.7 | 14 | 4.9 | 202 | 6.4 | 323 | 4.8 | 113 | 4.7 | 8 | 3.2 |
| Accidents and injuries | 50 | 1.6 | 123 | 1.9 | 52 | 2.2 | 9 | 3.1 | 56 | 1.8 | 119 | 1.8 | 50 | 2.1 | 9 | 3.6 |
| Cardiac disorders | 29 | 0.9 | 85 | 1.3 | 47 | 2.0 | 6 | 2.1 | 35 | 1.1 | 84 | 1.3 | 44 | 1.8 | 10 | 4.0 |
| Vascular disorders | 32 | 1.0 | 71 | 1.1 | 14 | 0.6 | 4 | 1.4 | 31 | 1.0 | 66 | 1.0 | 33 | 1.4 | 3 | 1.2 |
| Cerebrovascular disorders | 0 | 0 | 1 | 0.0 | 0 | 0 | 1 | 0.3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections and Infestations | 385 | 12.0 | 734 | 11.1 | 235 | 9.9 | 15 | 5.2 | 385 | 12.1 | 734 | 11.0 | 240 | 10.0 | 19 | 7.5 |
| Anticholinergic syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Quality of life decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 33 | 1.0 | 69 | 1.0 | 34 | 1.4 | 5 | 1.7 | 27 | 0.9 | 53 | 0.8 | 27 | 1.1 | 1 | 0.4 |

RSVPreF3 = Participants receiving RSVPreF3 OA investigational vaccine (pooled lots); Placebo = Participants receiving Placebo
N = number of participants
n/% = number/percentage of participants reporting the symptom at least once
Data lock point = 30APR2022

In study ADJ-004, there is a trend toward lower reactogenicity when age is increasing. No meaningful differences were observed in the analyses of unsolicited AEs by age categories.

*Aggregated analysis*

- Medically attended unsolicited AEs: The observed percentage for the SOC 'Nervous system disorders' is higher in the ≥80 YOA category (1% [95% CI: 0.6, 1.7]) compared to the 60-69 YOA (0.3% [95% CI: 0.2, 0.4]) and 70-79 YOA (0.3% [95% CI: 0.2, 0.5] categories. The reported events are expected based on the comorbidities of the participants. By PT, no differences in percentage are observed.
- SAEs: The observed percentages of participants with at least 1 SAE is higher in the ≥80 YOA category (6.6% [95% CI: 5.3, 8.0]) compared to 60-69 YOA category (3.9% [95% CI: 3.5, 4.3]), driven by the SOC "Nervous system disorders". No imbalance by PTs is observed.
- pIMDs: No difference was observed for subgroup analysis by age category

Sex

In the RSV OA=ADJ-006 study, the following observations were made in the RSVPreF3 group,

- Solicited administration site events: The observed percentage of participants with solicited administration site events was lower in males vs. females for pain (50.3% vs. 69.7%) and erythema (4.5% vs. 10.0%). No differences were observed for swelling.
- Solicited systemic events: The observed percentages of participants with solicited systemic events were lower in males vs. females for arthralgia (14.0% vs. 21.5%) and headache (20.0% vs. 33.2%). No differences were observed for fatigue and myalgia. Fever (≥ 38°C) was reported in 2.7% of female participants and 1.3% of male participants.

*Aggregated analysis*

An imbalance was seen only for the PT 'Urinary tract infection' that was more frequently reported in females (0.4 [95% CI: 0.3, 0.6]) than males (0.1 [95% CI: 0.0, 0.2]). Incidence of this event is expected to be higher in women. No differences in SAEs or pIMDs were observed.

### *2.6.8.6. Immunological events*

The goal of vaccination is to induce antibodies. Please refer to Adverse Events of Special Interest for an overview of pIMDs.

### *2.6.8.7. Safety related to drug-drug interactions and other interactions*

Concomitant influenza vaccine

The proportions of participants with AEs, injection-site AEs, systemic AEs, and vaccine-related systemic AEs were generally comparable across concomitant and non-concomitant intervention groups, see Table 27. The proportion of participants who experienced SAEs was low, with 2 cases of disseminated encephalomyelitis being considered related to the FLU-QIV vaccine. Over the duration of the study, 4 (0.9%) participants in the Co-Ad group and 8 (1.8%) participants in the Control group died. Except for 1 case of disseminated encephalomyelitis, none were considered related to the study vaccines.

The most common type of related unsolicited AEs was injection site reactions in the Co-Ad group (1.6%) and in the Control group (1.1%).

Table 27: Summary of participants by unsolicited adverse event category - Exposed Set (ADJ-007)

| | Co-Ad group N = 442 | | | | Control group N = 443 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| At least one unsolicited AE within 30 days | 83 | 18.8 | 15.2 | 22.7 | 105 | 23.7 | 19.8 | 27.9 |
| At least one related unsolicited AE within 30 days | 26 | 5.9 | 3.9 | 8.5 | 15 | 3.4 | 1.9 | 5.5 |
| At least one grade 3 unsolicited AE within 30 days | 13 | 2.9 | 1.6 | 5.0 | 15 | 3.4 | 1.9 | 5.5 |
| At least one related grade 3 unsolicited AE within 30 days | 1 | 0.2 | 0.0 | 1.3 | 2 | 0.5 | 0.1 | 1.6 |
| At least one medically attended unsolicited AE within 30 days | 35 | 7.9 | 5.6 | 10.8 | 49 | 11.1 | 8.3 | 14.4 |
| At least one serious unsolicited AE during the entire study period | 15 | 3.4 | 1.9 | 5.5 | 20 | 4.5 | 2.8 | 6.9 |
| At least one related serious unsolicited AE during the entire study period | 2 | 0.5 | 0.1 | 1.6 | 0 | 0 | 0 | 0.8 |
| At least one fatal unsolicited AE during the entire study period | 4 | 0.9 | 0.2 | 2.3 | 8 | 1.8 | 0.8 | 3.5 |
| At least one pIMD during the entire study period | 5 | 1.1 | 0.4 | 2.6 | 1 | 0.2 | 0.0 | 1.3 |
| At least one related pIMD during the entire study period | 3 | 0.7 | 0.1 | 2.0 | 1 | 0.2 | 0.0 | 1.3 |

Co-Ad group = Participants receiving a single dose of RSVPreF3 OA investigational vaccine and a single dose of FLU vaccine at Visit 1 (Day 1); Control group = Participants receiving a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).
N = number of participants
n/% = number/percentage of participants presenting at least one type of adverse event whatever the dose administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit Source: Table 14.3.1.27 *(25JUL2022 6:22 GMT)*

Overall, the safety profile in participants who were vaccinated concomitantly with FLU-QIV was similar to the safety profile in the non-concomitantly vaccinated participants, and no new safety signals are observed.

#### *2.6.8.8. Discontinuation due to adverse events*

Participants in study ADJ-006, ADJ-004 and ADJ-009 received a single dose of RSVPreF3 vaccine and, therefore, could not discontinue study intervention.

The number of discontinuations due to AEs is in all studies low, <2%. In study ADJ-006, discontinuations due to AEs were comparable between intervention groups: 0.6% in both the RSVPreF3 and placebo group. The number of discontinuations due to AEs is not expected to influence any of the conclusions drawn from the different studies.

AEs leading to discontinuation were reported across multiple SOCs.

#### *2.6.8.9. Post marketing experience*

None

### 2.6.9. Discussion on clinical safety

The clinical safety profile of RSVPreF3 was mainly derived from data obtained in study ADJ-006, which represents a major part of the overall exposure to the RSVPreF3 vaccine and is a placebo-controlled study conducted in the target population of older adults aged ≥60 years. The safety data is further supported by data from the other 3 Phase 3 studies (ADJ-004, ADJ-007 and ADJ-009) and a Phase 1/2 study ADJ-002 (where appropriate). An aggregated analysis based on data pooled across all Phase 3 studies was performed for unsolicited adverse events (AEs) with a medically attended visit, serious adverse events (SAEs) and non-serious/serious potential immune-mediated diseases (pIMDs).

Methods of collection of safety data were consistent across all Phase 3 studies. Reactogenicity as determined by solicited administration-site and systemic AEs was followed for 4 days, while non-serious, unsolicited AEs were followed for 30 days. In study ADJ-006, reactogenicity was determined in a subset of participants, which was agreed by CHMP. Therefore, in all other participants, not included in the solicited safety set (SSS), events considered solicited in the SSS were collected as unsolicited AEs. In all other Phase 3 studies, solicited AEs were collected in the exposed set (ES). In all studies, SAEs and pIMDs were collected up to 6 months or up to the data lock point. The strategy for collecting safety information was agreed by CHMP and led to a sufficient period to collect information on the outcome of the adverse events.

No pooling of the safety data was performed, which was discussed and agreed upon with CHMP.

Exposure

In total, >15000 participants were exposed to a vaccine containing 120µg RSVPreF3 adjuvanted with $AS01_E$ (Arexvy), of which 2411 were ≥80 years across all Phase 3 studies. In total 442 participants received the investigational RSVPreF3 vaccine concomitantly with FLU-QIV vaccine. The safety database, with over 15000 subjects exposed to the investigational RSVPreF3 vaccine, is considered of sufficient size to describe common and uncommon adverse events.

As stated above, reactogenicity was only measured in a subset of participants in study ADJ-006. However, as the SSS contains 1757 participants, this ensures that the reactogenicity profile can be established accurately in comparison to placebo. The demographics of the SSS are similar between the RSVPreF3 and placebo group and largely comparable to the entire population.

A vast majority of participants contributing to the safety database have been followed for at least 6 months, the safety database can be considered sufficient to support the evaluation of benefit-risk in the target population.

### Solicited Adverse Events

In study ADJ-006, reactogenicity was evaluated in 1757 participants, of which 879 received RSVPreF3 and 878 received placebo. Reactogenicity of the vaccine was higher compared to placebo, as all solicited AEs were experienced more frequently by participants in the RSVPreF3 group compared to participants in the placebo group. Within 4 days after vaccination, the percentage of participants experiencing at least 1 or more solicited AEs was 71.9% in the RSVPreF3 group versus 27.9% in the placebo group.

Injection-site pain was the most frequently reported solicited AE (reported by 60.9% of participants in the RSVPreF3 group vs 9.3% in the placebo group), followed by fatigue (33.6% of participants in the RSVPreF3 group vs 16.1% in the placebo group), myalgia (28.9% of participants in the RSVPreF3 group vs 8.2% in the placebo group) and headache (27.2% of participants in the RSVPreF3 group vs 12.6% in the placebo group). Fever (temperature ≥38 °C) was reported in few participants, although the percentage is higher in the RSVPreF3 group versus the placebo group (2.0% compared to 0.3%, respectively). The vast majority of solicited AEs were mild to moderate in intensity, with a low incidence of Grade 3 AEs (4.1% of participants in the RSVPreF3 group vs. 0.9% of participants in the placebo group experiencing any Grade 3 solicited AEs).

Across studies observations about solicited AEs were consistent, with a majority of participants experiencing 1 or more solicited AEs, and injection-site pain being the most frequently reported solicited AE, followed by fatigue, myalgia and headache. In addition, across all studies most reactogenicity reactions were mild to moderate in intensity.

Limited information could be found on the duration of solicited administration site and systemic reactions, which was requested. The Applicant calculated both mean and median duration of solicited adverse events based on the duration of all solicited events including those that are ongoing beyond 4 days post-vaccination and provide an overview table with all solicited events on PT level lasting longer than 4 days, including duration. The median duration of solicited administration site and systemic AEs was short and comparable between the 2 treatment groups, between 1-2 days. The median duration of Grade 3 solicited AEs ranged from 1 – 4 days in the RSVPreF3 group and 2 – 4 days in the placebo group.

### Unsolicited Adverse Events

In study ADJ-006 the solicited administration site and systemic AEs were collected as unsolicited AEs in participants not included in the solicited safety set (SSS). The percentage of participants experiencing an unsolicited AE was higher in the RSVPreF3 group (33.0%) compared to the placebo group (17.8%) in the ES, mainly driven by reactogenicity AEs collected as solicited AEs in the SSS. In the SSS, the percentage of participants experiencing unsolicited AEs was 14.9% in the RSVPreF3 group compared to 14.6% in the placebo group. In SOCs not linked to solicited AEs, no clear disbalance in percentage of participants experiencing PTs could be observed, except for investigations (63 [0.5%] participants in the RSVPreF3 group vs 17 [0.1%] in the placebo group).

Similar results were observed for the other Phase 3 studies, with unsolicited AEs being reported by 12.8% to 14.8% of participants. The most frequently reported AEs were linked to reactogenicity of the vaccine.

Overall, a vast majority of unsolicited AEs were mild to moderate in intensity, with the incidence of Grade 3 unsolicited AEs being <2.5%.

Related unsolicited adverse events were experienced by substantially more participants in the RSVPreF3 group, 24.9%, compared to the placebo group, 5.8%.

The following AEs considered possibly related to study vaccine are listed in 4.8: lymphadenopathy (including axillary pain), hypersensitivity reactions (such as rash), headache, nausea, abdominal pain, vomiting, myalgia, arthralgia, injection site pain, fatigue (including asthenia, lethargy and somnolence), injection site erythema, injection site swelling, fever, chills (including feeling cold), injection site pruritus, pain (pain in extremity) and malaise (including discomfort). Some PTs are clustered in a single ADR. For the clustered PTs, the frequency reported in the ADR table is based on the occurrence of all PTs that are clustered in a single term.

The Applicant reviewed all hypersensitivity related AEs in all clinical studies and presented the information in tabulated format. Rash was the most frequently reported PT for hypersensitivity reactions.

Adverse events of special interest

Potential immune-mediated diseases (pIMDs) were collected as adverse events of special interest. The percentage of participants reporting pIMDs in the aggregated dataset was low, 0.4%. In study ADJ-006 there was no disbalance in reporting of pIMDs between treatment groups, with 0.4% participants in both the RSVPreF3 and placebo group reporting a pIMD.

Of interest is 1 case of Guillain-Barré syndrome occurring 9 days after vaccination which was assessed as related to the vaccine by the investigator. Based on the narrative, the diagnosis of Guillain-Barre seems probable, and timing makes relatedness possible. However, as this is a single case, no strong conclusions can be drawn. It is deemed important to follow the occurrences of Guillain-Barré syndrome post marketing closely. Bell's palsy assessed as possibly related to the study vaccine by the investigator occurred in 2 participants in the RSVPreF3 group versus none in the placebo group. Due to concurrent illness in 1 participant and time to onset of 196 days after vaccination in the other, relatedness to RSVPreF3 administration is questioned in these cases. Finally, events of worsening of psoriasis and gout in studies ADJ-006 and ADJ-009 were reported after vaccination. Currently there is insufficient information available to draw a clear conclusion on the causal relationship between vaccination with Arexvy and exacerbation of pre-existing pIMDs based on these scant cases. Post-licensure, follow-up of pIMDs will occur in PSURs. Additionally, exacerbations of pIMDs will be determined in clinical trials.

Serious Adverse Events and Death

The proportion of participants with SAEs in the Phase 3 studies was <4.5% in all studies, which is in line with expectations in this elderly population.

In study ADJ-006, the proportion of participants experiencing a SAE was similar in both treatment groups. The SAEs occurred in similar SOCs in both treatment groups, with the most commonly reported SAEs being experienced in the SOCs of infections and infestations (107 subjects (0.7%) in the RSVPreF3 group and 115 (0.9%) in the placebo group), cardiac disorders (91 subjects (0.9%) in the RSVPreF3 group and 86 (0.7%) in the placebo group) and neoplasms benign, malignant and unspecified (65 subjects (0.5%) in the RSVPreF3 group and 58 (0.5%) in the placebo group). For the PT "Atrial fibrillation" a statistically significant difference with a RR of 7.02 (80% CI: 1.47, 75.62) was observed within 30 days post vaccination. Of the 14 events of atrial fibrillation reported, 10 in the RSVPreF3 group vs 4 in the placebo group, 6 events corresponded to new onset and 8 to recurrence of pre-existing atrial fibrillation. Although a statistically significant difference was observed between the groups, all events except one were observed in participants with pre-existing events of arrhythmias or with other risk factors/medical conditions.

The incidence of vaccination related SAEs was low; around 0.1% of participants experienced a SAE assessed as related to RSVPreF3. Considering none of the SAEs assessed as related to RSVPreF3 vaccine was reported by more than 1 participant, no strong conclusions can be drawn.

Over the course of the Phase 3 studies and the Phase 2 study, 80 participants administered RSVPreF3 died, which is not unexpected in a population ≥60 years of age. In study ADJ-006 no notable imbalance in the incidence of fatal SAEs was observed between the RSVPreF3 and placebo group. It is agreed with the Applicant that none of the deaths that occurred within the studies is related to RSVPreF3 or placebo. However, in a subset of participants reporting COVID-19 related AEs the Applicant reported a disbalance in fatalities, with 8 out of 66 participants in the RSVPreF3 group vs 2 out of 65 participants in the placebo group died. Although the overall incidence of COVID-19 AE was similar between the groups, the number of participants with Covid-19 AE with fatal outcome was fourfold as high in the RSV group as in the placebo group. The Applicant was asked to discuss this increased risk. A definitive explanation for the observed differences in occurrence of fatal cases of COVID-19 between the treatment arms was not identified by the MAH. However, currently there is not enough evidence to suggest that vaccination with RSVPreF3 would expose recipients to a higher risk of fatal COVID-19 infection. Time to onset of ≥90 days after vaccination excludes an acute reaction. In addition, there is no indication of an increase in disease severity of COVID-19 which is expected in case vaccine enhanced disease would play a role. Finally, bias due to lack of structurally collecting COVID-19 cases and reported cause of death cannot be excluded.

Safety in special populations

*Age*

Solicited reactions were reported less frequently in older adults (≥ 80 years) compared to younger adults (60 to 69 years), indicating a decrease in reactogenicity with increasing age. Even though reactogenicity decreased, the profile of AEs remained similar, with most commonly reported solicited administration site AE being injection-site pain and the most commonly reported systemic AE being fatigue, followed by myalgia. In addition, as expected an increase in medically attended unsolicited AEs and SAEs was observed with increasing age. Similar differences between younger (60 to 69 years) and older (≥ 80 years) adults were also seen in the placebo group.

*Sex*

Overall, the safety profile in the subgroups of sex was similar to the safety profile in the entire population, and no new safety signals were observed. However, reactogenicity was found to be higher in females compared to males. Higher rates of reactogenicity in females have been reported for different vaccines and do not impact the use of the vaccines. For SAEs and pIMD no difference was observed between males and females. For medically attended unsolicited AEs, the difference was driven mainly by urinary tract infections, which are known to occur more frequently in females compared to males.

*Use in Pregnancy*

Although the current application is for adults 60 years of age and older, the Applicant has also investigated an unadjuvanted investigational RSV Maternal (RSVPreF3) vaccine. This development programme has however been stopped due to observed imbalances in preterm birth. A higher proportion of neonatal deaths (death of an infant within the first 28 days of life) was also observed, which was considered to be a consequence of PTB. The vaccine formulation used in the RSV Maternal program contained 120 µg of RSVPreF3 antigen (the same as used in the RSVPreF3 OA vaccine), unadjuvanted. It can be agreed that neonatal death is not a separate signal, but most likely a result of PTB. The root cause analysis into the cause of the PTB is still ongoing.

Currently no conclusion on a causal relationship between administration of unadjuvanted RSVPreF3 and preterm birth can be drawn. Considering the composition of Arexvy is essentially the vaccine used in ADJ-009 plus an adjuvant, the information is considered relevant and is included in the SmPC, in light of the potential off-label use.

Safety related to drug-drug interactions

Concomitant injection with Flu QIV does not significantly affect the safety profile of RSVPreF3. The concomitant administration of Flu QIV with the investigation RSVPreF3 vaccine increases the reactogenicity profile. However, as a majority of AEs was mild in intensity and of short duration, the observation that the proportion of subjects experiencing a solicited AE was somewhat higher compared to the sequential vaccination is not considered clinically relevant. The occurrence of SAEs and pIMDs is balanced between the 2 groups and no new safety signals were detected. However, the applicant supplied more details of the two cases with respect to the plausibility of ADEM diagnosis. Neither of the reported ADEM cases included MRI and/or CSF analysis, therefore both cases contain insufficient information to definitively confirm an ADEM diagnosis.

Discontinuation due to AE

68 participants in RSVPreF3 group and 72 participants in placebo group experienced an AE requiring expedited reporting. Only a listing was provided for the individual studies including all unrelated and related AE leading to discontinuation. The Applicant provided a summary for all related AE leading to study discontinuation for all studies. No questions arose from the data presented.

From the safety database, any adverse event reported in clinical trials that were considered as ADRs following qualitative and quantitative assessment have been included in the Summary of Product Characteristics.

### 2.6.10. Conclusions on the clinical safety

Arexvy is a moderately reactogenic vaccine, with a majority of participants reporting 1 or more AEs; however, these were mostly mild or moderate in intensity and of short duration. The most frequently reported AEs by PT were solicited AEs: injection-site pain, fatigue, myalgia and headache. As expected, reactogenicity decreased with age. The proportions of participants with unsolicited AEs requiring a medically attended visit, pIMDs, SAEs and deaths in the RSVPreF3 group were low and comparable to the placebo group.

In conclusion, Arexvy is well tolerated in adults ≥60 years. Table 1 in section 4.8 of the SmPC reflects the frequency of ADRs.

## *2.7. Risk Management Plan*

### 2.7.1. Safety concerns

The Applicant proposed the following summary of safety concerns in the RMP version 0.3:

*Table SVIII.1. Summary of safety concerns*

| Summary of safety concerns | |
|---|---|
| Important identified risks | None |

| | |
|---|---|
| Important potential risks | None |
| Missing information | None |

The Applicant has not included any important identified risks. Based on the evaluation of safety data, it can be agreed that there are no important identified risks.

There are no important potential risks identified.

The Applicant indicated that the clinical trials excluded immunocompromised adults. Currently there is no indication that safety is of concern in this population. Follow-up as Committee Recommendation is considered appropriate: “the Applicant needs to submit the final study report for study RSV OA=ADJ-023 in immunocompromised participants, once available.” [REC]

For pregnancy and breastfeeding, the Applicant only states that the target indication of ≥60 should prevent use of the vaccine in that population. The Applicant has reported that enrolment and vaccination in RSV Maternal vaccine studies (using the same antigen as used in Arexvy) has been suspended because of an observed imbalance in the proportions of preterm births in the treatment group versus the Placebo group in one study. A higher proportion of neonatal deaths (death of an infant within the first 28 days of life) was also observed, which was considered to be a consequence of PTB. No further action is required for the RMP for the current indication in adults ≥60 years of age.

### 2.7.2. Pharmacovigilance plan

Table Part III.3. Ongoing and planned additional pharmacovigilance activities

| Study (Status) | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| *None* | | | | |
| Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances | | | | |
| *None* | | | | |
| Category 3 – Required additional pharmacovigilance activities | | | | |
| *None* | | | | |

### 2.7.3. Risk minimisation measures

None

### 2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

In addition, a minor revision is recommended to be taken into account with the next RMP update. It relates to section V.1. where it should read “No risk minimisation measures beyond standard routine measures are needed”.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

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

### 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Labelling exemptions

None requested.

### 2.9.3. Quick Response (QR) code

Not applicable.

### 2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Arexvy [Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted)] 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

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 or older adults), re-infections can also lead to more severe diseases, involving the lower respiratory tract and lower respiratory tract disease (LTRD).

It is estimated that each year RSV infections cause ~250 000 hospitalisations and ~17 000 deaths among older adults aged 65 years and older in Europe [Savic, 2020].

In adults, the highest burden of disease is in older people and those with comorbidities such as lung or heart disease and diabetes. In these patient populations, RSV can exacerbate conditions like chronic obstructive pulmonary disease (COPD), asthma, chronic heart failure leading to severe outcomes such as pneumonia, hospitalisation, and death.

### 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 guidelines. Therefore, there is currently no specific treatment for RSV infections in older adults. Treatment for RSV in older 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*

There is no licensed vaccine for the prevention of RSV-associated diseases.

In children, 2 preventative options are available: Synagis and Beyfortus. Synagis (palivizumab) is a humanised monoclonal antibody indicated RSV for prophylaxis in children with a high risk of RSV disease, including preterm infants. Beyfortus (nirsevimab) is a human monoclonal antibody indicated for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.

*Unmet medical 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. The impaired immune response in this population due to the ageing of the immune system (immunosenescence) and other risk factors, such as the presence of comorbidities and/or frailty, increase the risk of RSV disease and its complications. Older adults hospitalised with RSV infection can develop severe respiratory complications, particularly pneumonia, resulting in respiratory failure, the

requirement for supplemental oxygen and mechanical ventilation, prolonged hospitalisation, and high mortality similar to seasonal influenza. Currently there is no specific treatment and no prophylactic vaccine available.

### 3.1.3. Main clinical studies

The main evidence for efficacy for Arexvy is based on a single pivotal observer blinded, randomised, placebo-controlled trial (Study ADJ-006) conducted in 17 countries, 14 countries in the Northern hemisphere (US, Canada, Mexico, Belgium, Estonia, Finland, Italy, Germany, Poland, UK, Spain, Russia, South Korea, and Japan) and 3 in the Southern hemisphere (Australia, New Zealand and South Africa). The trial was designed to demonstrate efficacy against RSV-confirmed LRTD occurring ≥ 15 days after administration of RSVPreF3 or placebo in adult participants ≥60 years of age until the occurrence of a prespecified number of blinded endpoints triggered the endpoint-driven efficacy analysis.

Study ADJ-006 enrolled healthy adults ≥60 years of age who were randomised 1:1 to receive a single dose of RSVPreF3 (n=12,471 participants) or placebo (saline, n=12,510 participants), intramuscularly.

The efficacy analysis was event-driven, with 47 cases accrued to be included in the interim analysis.

## *3.2. Favourable effects*

- Vaccine efficacy (VE) against RSV-confirmed LRTD: The confirmatory analysis in the modified exposed set (mES) at the interim analysis based on 47 accrued cases in study ADJ-006 indicated a VE point estimate of 82.6% with an adjusted 96.95% CI of 57.9% to 94.1%, meeting the prespecified study success criterion of an alpha-adjusted LL > 20%. A sensitivity analysis using a Cox regression model based on the mES population also showed that VE was >82% with LL >20%. In addition, this result was consistent with the VE observed in the exposed set (ES) and per protocol set for efficacy (PPSe) population, with VE in both populations being >81%.
- VE against RSV subtypes: The estimated VE against LRTD caused by RSV-A and RSV-B separately was >80%, with the LL of the 2-sided CI well above the pre-defined threshold of 20%.
- VE by age category: There was no trend of declining VE when comparing VE in the age groups 60-69 years of age (estimated VE of 81.0 [95% CI 43.6-95.3] based on 4 vs 21 cases) and 70-79 years of age (estimated VE of 93.8 [95% CI 60.2-99.9] based on 1 vs 16 cases).
- VE over time: Protection against RSV-confirmed LRTD was observed up to at least 6 months.
- VE against ARI: The results for RSV-confirmed acute respiratory infection (ARI) are in line with the results for RSV-confirmed LRTD. The estimated VE against RSV-confirmed ARI was 71.7% (95% CI: 56.2, 82.3). Protection against RSV-confirmed ARI was observed up to at least 6 months. No trend in declining VE was seen with increasing age.
- Immune response: Across studies, a consistent humoral immune response was observed, with at 1 month postvaccination a ~10-fold increase in RSV-A neutralising antibody titres, an ~8-fold increase in RSV-B neutralising antibody titres, and a ~12-fold increase in binding antibody titres. In addition, across studies it was observed that RSVPreF3-specific CD4+ but not CD8+ T-cells were induced.

## 3.3. Uncertainties and limitations about favourable effects

- Durability of VE response and need for revaccination. Data on vaccine efficacy is currently limited to approximately 6 months post-vaccination; therefore, there is no information on long-term protection by Arexvy. Descriptive evaluation of efficacy after the second and third RSV seasons in the NH are planned but are still outstanding. Data on this issue would be provided post-authorization.
- VE in participants **≥80** years of age. Available data are insufficient to establish efficacy in participants ≥80 years of age. In the group aged ≥80 years in total 5 cases of RSV-confirmed LRTD (2/1,016 cases in the RSVPreF3 group vs 3/1,028 cases in the placebo group) were experienced.
- Efficacy against severe LRTD and hospitalisation. Reliable efficacy estimates against severe LRTD and hospitalisation caused by RSV could not be established due to the lack of a sufficient number of cases within the clinical studies.
- Immunocompromised populations. Data in high-risk immunocompromised populations is currently lacking.
- Persistence of immune responses in adults **≥** 60 YOA. Data from the immunogenicity study RSV OA=ADJ-004 showed that humoral and cellular immune responses increased from baseline to D31, but declined from D31 to month 6 (albeit to levels that were above baseline). The clinical relevance of this decline is unclear as there is no correlate of protection.
- Correlate of protection. There is no correlate of protection known for RSV disease. Therefore, the immune response observed cannot be directly translated to efficacy or clinical benefit in adults. This hampers the interpretation of the observed vaccine-induced immunogenicity and the clinical relevance of meeting the non-inferiority margin for concomitant vaccination.

## 3.4. Unfavourable effects

The clinical safety profile of RSVPreF3 was mainly derived from data obtained in study ADJ-006, which represents a major part of the overall exposure to the RSVPreF3 vaccine (12,467 participants vs 15,862 overall). The median safety follow-up in study ADJ-006 was 7.8 months.

- Reactogenicity. In study ADJ-006, reactogenicity was evaluated in 1,757 participants, of which 879 received RSVPreF3 and 878 received placebo. Injection-site pain was the most frequently reported solicited AE (reported by 60.9% of participants in the RSVPreF3 group vs 9.3% in the placebo group), followed by fatigue (33.6% of participants in the RSVPreF3 group vs 16.1% in the placebo group), myalgia (28.9% of participants in the RSVPreF3 group vs 8.2% in the placebo group) and headache (27.2% of participants in the RSVPreF3 group vs 12.6% in the placebo group). Solicited AEs were mostly mild to moderate in intensity, with 4.9% of participants in the RSVPreF3 group experiencing any Grade 3 solicited AE vs 0.9% in the placebo group. A consistent reactogenicity profile was observed in the different studies.
- Unsolicited AEs. Within 30 days after vaccination unsolicited AEs were reported more frequently in the RSVPreF3 group vs the placebo group (23.8% vs 18.7% in study -302 and 16.3% vs 14.8% in -301). This was driven mainly by the SOC of general disorders and administration site conditions, nervous system disorders and musculoskeletal and connective tissue disorders, which mostly reflect the reactogenicity of RSVPreF3. A vast majority of all unsolicited AEs was mild to moderate in

intensity. A similar profile was observed in the different studies. In all studies (including study ADJ-002), the incidence of Grade 3 unsolicited AEs was <2.5% of participants.

- Potential immune-mediated diseases. In study ADJ-006, pIMDs were reported by 0.4% of participants in both the RSVPreF3 and placebo group.
- SAEs. The proportion of participants with SAEs in the Phase 3 studies was <4.5% in all studies. In study ADJ-006, the proportion of participants experiencing a SAE was similar in both RSVPreF3 and placebo groups. None of the SAE considered related to investigational treatment was reported by more than 1 participants.

## *3.5. Uncertainties and limitations about unfavourable effects*

- Guillain-Barré syndrome. A single case of Guillain-Barré syndrome possibly related to RSVPreF3 vaccine was observed in study ADJ-004. As this is a single case, there is insufficient information available to determine the clinical impact. Follow-up post-licensure is warranted to investigate the incidence of GBS after vaccination with Arexvy further.
- Worsening of pre-existing immune-mediated disorders. Two cases of pIMDs assessed as possibly related to the administration of RSVPreF3 considered worsening of a pre-existing immune-mediated disorder, psoriasis and gout. Currently, no clear conclusion on the causal relationship between vaccination with Arexvy and exacerbation of pre-existing pIMDs cannot be drawn from these scant cases. Therefore, this will be followed-up in PSURs and clinical trials.

## *3.6. Effects Table*

Table 28: Effects Table for Arexvy in the prevention of RSV-confirmed LRTD in adults **≥60** years of age (data cut-off: 11 April 2022 for efficacy 30 April 2022 for safety).

| Effect | Short Description | Unit | Treatment | Placebo | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Favourable Effects | | | | | | |
| Vaccine efficacy | Prevention of RT-PCR confirmed LRTD with onset from at least 14 days after vaccination | n cases/n subjects at risk for the endpoint | 7/12466 | 40/12494 | SOE: Confirmed using Cox proportional hazard regression model as sensitivity analysis. In addition, same results in exposed set (7/12467 cases in RSVPreF3 group vs 43/12499 cases in placebo group) and per protocol set (7/12142 cases in RSVPreF3 group vs 38/12176 cases in placebo group). Not impacted by age or comorbidity.<br><br>Uncertainties: Persistence of efficacy after 6 months is unknown. The data are | ADJ-006 |
| | | VE% (96.95% CI) | 82.6 (57.9, 94.1) | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | currently based on an interim analysis | |
| Unfavourable Effects | | | | | | |
| Reactogenicity | Solicited administration site effects[a] | % of individuals | 62.2 | 10.0 | Transient effect, majority mild to moderate in severity | ADJ-006 |
| | Solicited systemic effects[b] | % of individuals | 49.4 | 23.2 | | ADJ-006 |
| SAEs | Related SAEs | % of individuals | 0.1 | 0.1 | | ADJ-006 |

Abbreviations: LRTD = lower respiratory tract disease; RT-PCR=reverse transcriptase polymerase chain reaction; SAE = serious adverse event; VE = vaccine efficacy.

[a] Solicited administration-site effects include injection-site pain, erythema and swelling

[b] Solicited systemic effects include arthralgia, fatigue, fever, headache and myalgia

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. 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. To date no prophylactic vaccine is licensed and no treatment, other than supportive care, exists for the older adult population. Arexvy is intended for active immunisation for the prevention of RSV-associated LRTD in adults ≥60 YOA, which could potentially address (part of) the unmet medical need in the elderly population.

Overall, vaccine efficacy of a single dose of Arexvy administered IM has been demonstrated for the prevention of RSV-confirmed LRTD with the onset of at least 15 days after vaccination in adults ≥60 years of age based on the interim analysis of a single large pivotal phase 3 trial. In addition, an acceptable safety profile was observed.

The results are considered robust as comparable VE is observed in the different analysis sets and in a sensitivity analysis using Cox regression analysis. In addition, the results of VE analysis 2, based on data collected for the first full season (up to data lock point of 30 September 2022 or revaccination), are in line with the results of the interim analysis. The cumulative incidence curve suggests that vaccine efficacy remains high up to the end of a full season and for at least 11 months Further follow-up is expected as study ADJ-006 is currently ongoing and will be used to evaluate the efficacy of a single dose of Arexvy over multiple seasons and the need for re-vaccination.

Subgroup analyses of the primary efficacy endpoint showed consistent results. Estimated VE was >80% in both the 60–69 year old and 70-79 year old subgroups, with no clear trend in declining VE with increasing age. In addition, in subjects with at least 1 pre-existing comorbidity of interest estimated VE was 94.6% (95% CI 65.9-99.9). These results are reassuring as age and comorbidities are known to increase the risk of severe RSV disease. Furthermore, the estimated VE against LRTD caused by either RSV-A or -B was >80% with a LL well above 20%, which is appreciated as the subtypes usually co-circulate. Finally, the results for efficacy against RSV-confirmed ARI are in line with the results of RSV-confirmed LRTD, though slightly lower, with an estimated VE against RSV-confirmed ARI of 71.7%. Similarly, analyses of other relevant subgroups (including hemisphere, region, ethnicity, race, sex, frailty) using all categories of the variables, showed

consistency in the direction and magnitude of the treatment effect, except when there were very low number of cases, which is overall reassuring.

No reliable efficacy estimate can currently be established against severe RSV-confirmed LRTD or hospitalisation; however, it is likely that severe disease will be prevented as a consequence of preventing RSV-confirmed LRTD. RSV-confirmed LRTD in the population of adults ≥80 years of age can also not be reliably established based on the current information, as too few cases were accrued.

After vaccination a substantial and consistent immune response was observed, with at 1-month postvaccination a ~10-fold increase in RSV-A neutralising antibody titres, an ~8-fold increase in RSV-B neutralising antibody titres, and a ~12-fold increase in binding antibody titres being observed across studies. However, considering there is no correlate of protection known for RSV disease, this immune response cannot be directly translated to efficacy or clinical benefit in adults. Information on the persistence of the immune response is limited. At 6 months after vaccination, the levels of neutralising and binding antibody titres were lower compared to 1 month after vaccination, however levels remained well above baseline. Similar tendencies were observed for kinetics of RSVPreF3-specific CD4+ T-cell responses. No CD8+ T-cells were induced.

The documented safety exposure is sufficient for an adequate assessment of the safety profile of Arexvy. The observed safety profile is considered acceptable and is mainly characterised by reactogenicity reactions. The most frequently reported AEs were injection-site pain, followed by fatigue, myalgia and headache. Reactogenicity reactions were mostly mild to moderate, transient and self-limited. SAEs and pIMDs were infrequent in both the Arexvy and placebo groups. However, a single case of Guillain-Barré syndrome possibly related to RSVPreF3 vaccine was observed in study ADJ-004. As this is a single case, there is insufficient information available to determine the clinical impact of this observation. Further follow-up post-licensure is warranted to gain more insight in the potential relation between RSVPre3F and Guillain-Barré syndrome.

No participants with severe immunodeficiency were included in the studies. As with other vaccines, such patients may not be protected as well as immunocompetent individuals by vaccination. In addition, safety information in these participants is lacking. Further data should be collected post-authorisation.

### 3.7.2. Balance of benefits and risks

The available clinical data for Arexvy, including the demonstrated vaccine efficacy against RSV-confirmed LRTD and ARI and induction of a robust immune response, establish the benefits of Arexvy in individuals 60 years of age and older. There are no serious safety concerns. From a clinical perspective, a positive benefit/risk balance in the proposed indication of prevention of LRTD caused by RSV can therefore be established.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

### *3.8. Conclusions*

The overall benefit/risk balance of Arexvy is positive, subject to the conditions stated in section 'Recommendations'.

## 4. Recommendations

*Outcome*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Arexvy is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

*Conditions or restrictions regarding supply and use*

Medicinal product subject to medical prescription.

*Official batch release*

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

*Other conditions and requirements of the marketing authorisation*

- Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information

being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

*Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States*

Not applicable.

*New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation (RSVPreF3) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology, contained in the medicinal product Arexvy, is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).