swissmedic

Date: 20 June 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Arexvy

International non-proprietary name: respiratory syncytial virus (RSV) pre-fusion F protein

Pharmaceutical form: Powder and suspension for suspension for injection

Dosage strength(s): 120 micrograms / 0.5 mL

Route(s) of administration: intramuscular

Marketing authorisation holder: GlaxoSmithKline AG

Marketing authorisation no.: 69310

Decision and decision date: approved on 2 May 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARI	Acute respiratory illness
AS	Adjuvant system
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
F	Fusion protein
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IM	Intramuscular
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
LRTD	Lower respiratory tract disease
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MPL	3-Odesacyl-4'-monophosphoryl lipid A
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
OA	Older adult
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
pIMD	Potential immune-mediated disease
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QS	*Quillaja saponaria*
RMP	Risk management plan
RSV	Respiratory syncytial virus
RSVPreF3	RSV pre-fusion protein 3
RT-PCR	Reverse transcriptase – polymerase chain reaction
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report

TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VE	Vaccine efficacy
YOA	Years of age

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for respiratory syncytial virus (RSV) pre-fusion F protein in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Arexvy is indicated for the active immunisation of adults 60 years of age and older for prevention of lower respiratory tract disease caused by sub-types RSV-A and RSV-B of the RSV.
Official vaccination recommendations for appropriate use should be followed.

2.2.2 Approved 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 official vaccination recommendations on the appropriate use should be observed.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Arexvy is administered IM as a single dose of 0.5 mL. The need for revaccination has not been established.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	6 February 2023
Formal control completed	27 February 2023
List of Questions (LoQ)	27 June 2023
Response to LoQ	24 September 2023
Preliminary decision	21 December 2023
Response to preliminary decision	4 February 2024
Final decision	2 May 2024
Decision	approval

3 Medical context

Respiratory syncytial virus (RSV), is a single-stranded, negative-sense ribonucleic acid virus and a member of the *Pneumoviridae* family. RSV causes acute respiratory tract illness in persons of all ages. Two subtypes, A and B, are simultaneously present in most outbreaks, with A subtypes typically causing more severe disease. The clinical manifestations vary with age and health status. RSV typically causes seasonal outbreaks throughout the world. In the northern hemisphere, these usually occur from October or November to April or May, with a peak in January or February.

Healthy adults are infected with RSV repeatedly throughout their lives and typically have symptoms restricted to the upper respiratory tract. RSV is an important and often unrecognised cause of lower respiratory tract infection (LRTI) in older adults and immunocompromised adults and an important cause of death in adults older than 50 years. Hospitalisation for RSV infection in adults may be complicated by cardiovascular events (e.g. worsening heart failure, acute coronary syndrome, arrhythmia).
Although virtually all individuals have been infected with RSV by the age of 2 years, previous infection with RSV does not appear to protect against reinfection, even in patients with high titres of specific antibodies. Several observations suggest that humoral immunity is more important in ameliorating the severity of RSV infection than in preventing disease. Although individuals can be infected with RSV more than once, subsequent infections are usually milder whether they occur in the same season or in different years.

Therapy for RSV infection of the lower respiratory tract is primarily supportive. At the time of the assessment, the only approved prophylaxis for RSV was pavilizumab, licensed only for infants who are at high risk for serious RSV disease. At the time of the assessment, there were no vaccines for the prophylaxis of RSV or drugs for the treatment of RSV approved in Switzerland. Therefore, an unmet medical need can be attested.

4 Quality aspects

4.1 Drug substance

Respiratory syncytial virus (RSV) is an RNA virus containing 3 transmembrane proteins (fusion protein (F), attachment glycoprotein (G), and small hydrophobic (SH) protein). There are 2 major antigenic strains of RSV (RSV-A and RSV-B). The F protein is highly conserved between the 2 strains. When the virion comes into contact with the host cell, the F protein undergoes a conformation shift.

The drug substance, recombinant RSV pre-fusion F antigen (RSVPreF3), is an engineered version of the F protein, stabilised in the pre-fusion conformation. RSVPreF3 is produced from a transfected mammalian cell line (Chinese hamster ovary) using several amplification steps in shake flasks, followed by amplification steps in bioreactors. The steps up to single harvest represent the upstream process, whichis followed by a downstream process represented by clarification and purification steps that lead to the purified bulk.
The purification steps aim to recover the produced RSVPreF3 while eliminating contaminants. Purifications consists of different steps including different types of chromatography and different filtration steps before freezing and storage.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release include relevant tests and acceptance criteria, e.g. for description, pH, identity, relative potency, product-related substances, structural integrity, and protein, endotoxin, and host-cell protein content. Specifications are based on clinical experience and batch analysis data (release and stability data), and are in conformance with current compendial or regulatory guidelines. All analytical methods are described and non-compendial methods have been validated in accordance with ICH guidelines.

Batch analysis data for non-clinical batches, clinical batches, and Process Performance Qualification (PPQ) batches were provided. Comparable quality was shown throughout the clinical development. Comparability between 3 RSVPreF3 PPQ batches, Phase 3 clinical batches, and technical development RSVPreF3 was demonstrated.

No significant changes were observed under the proposed storage conditions. A shelf-life of 24 months has been accepted.

4.2 Drug product

The finished product consists of a lyophilised powder vial (drug product) and an adjuvant vial ($AS01_E$ adjuvant) used to reconstitute the vaccine in order to obtain a liquid mono-dose preparation for intramuscular injection. The volume per nominal dose is 0.5 mL.

The drug product vial contains a lyophilised powder of 120 µg RSVPreF3 antigen with the following excipients: trehalose dehydrate, polysorbate 80, potassium dihydrogen phosphate, and dipotassium phosphate. All these excipients are compliant with Ph. Eur. standards.

The $AS01_E$ adjuvant vial contains a suspension for injection with the following excipients: QS-21 (a triterpene glycoside purified from the bark of the *Quillaja saponaria* Molina tree), MPL (3-Odesacyl-4'-monophosphoryl lipid A), dioleoyl phosphatidylcholine (DOPC), cholesterol, sodium chloride, anhydrous disodium phosphate, potassium dihydrogen phosphate, and water for injection. With the exception of QS-21 and DOPC, the excipients are compliant with Ph. Eur. standards. The target fill volume includes an overfill that ensures a nominal injection volume of 0.5 mL.

The manufacturing process for the drug product consists of formulation, sterile filtration, aseptic filling, lyophilisation, and visual inspection steps. Process validation studies were executed at commercial scale using 8 validation batches.

The specifications for the drug product were set based on compendial requirements, experience from clinical trials, and commercial process capability. They include relevant tests and limits, e.g. for description, pH, osmolality, identity, relative potency, protein content, bacterial endotoxin content, water content, structural integrity, polysorbate 80 content, trehalose content, and sterility. All non-compendial methods are validated in accordance with ICH guidelines.

Batch analysis data for 8 commercial consistency lots have been provided. All batch release data comply with the commercial drug product specifications.

The manufacturing process for the $AS01_E$ adjuvant consists of formulation, sterile filtration, filling, and visual inspection steps. Process validation studies were executed at commercial scale.

The specifications for the $AS01_E$ adjuvant were set based on compendial requirements, experience from clinical trials, and commercial process capability. They include relevant tests and limits, e.g. for description, pH, osmolality, sterility, volume, MPL content, QS-21 content, DOPC content, cholesterol content, limit tests for impurities, and MPL congener distribution. All non-compendial methods are validated in accordance with ICH guidelines.

Batch analysis data for commercial consistency lots have been provided. All batch release data comply with the commercial drug product specifications.

The primary container closure system for the drug product and the $AS01_E$ adjuvant consists of an uncoloured 3 mL type I glass vial. The drug product vial is sealed with a type I rubber stopper for the lyophilized formulation, and the $AS01_E$ adjuvant is sealed with a type I rubber stopper. Both, the drug product and the $AS01_E$ adjuvant vials, are covered with an aluminium flip-off cap. All components coming into contact with the finished product comply with Ph. Eur. requirements.

The drug product and the $AS01_E$ adjuvant are stored at 2-8°C (no freezing and protected from light). No significant changes were observed under the proposed storage conditions. A shelf-life of 24 months for the drug product and 36 months for the $AS01_E$ adjuvant has been accepted. As the finished product consists of 2 independent vials (drug product and $AS01_E$ adjuvant), the expiry date of the dual presentation will be determined by whichever component expires earliest. The $AS01_E$ adjuvant system may tolerate exposure to temperatures of 25ºC for up to 14 days during the 36 months shelf-life.
To avoid potential contamination and to preserve the sterility of the final reconstituted vaccine, the vaccine must be used promptly after reconstitution. If this is not possible, the reconstituted vaccine should be stored in a refrigerator (2-8°C) or at room temperature (up to +25°C) and used within a maximum of 4 hours.

4.3 Quality conclusions

The manufacturing processes (drug substance, drug product, and $AS01_E$ adjuvant) are well described and demonstrate a consistent quality. The shelf-lives of the drug substance, drug product, and $AS01_E$ adjuvant are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

5 Nonclinical aspects

5.1 Pharmacology

The immunogenicity of RSVPreF3/AS01$_E$ vaccine was tested in naïve mice following 3 intramuscular administrations. RSVPreF3 elicited a favourable humoral immune response against RSV (including the pre-fusion epitope site Ø) and fusion protein-specific $CD4^+$ and $CD8^+$ T cell responses. The AS01$_E$ adjuvant was needed for the enhancement of B and T cell responses. The studies were conducted with a lower dose of antigen and a different antigen/adjuvant ratio compared to the clinical formulation. Thus, the studies are considered to provide a proof of concept only. The lack of the full phenotypisation of the immune response is accepted, as immunogenicity and efficacy were evaluated in clinical studies. Challenge studies were not conducted, which is in line with the WHO guideline.
The lack of enhanced respiratory disease (ERD) studies is accepted considering the type of vaccine and target population (not seronegative). Based on nonclinical and clinical data, the risk for ERD in the target population is considered low.

5.2 Pharmacokinetics

No dedicated pharmacokinetic studies were conducted, which is acceptable according to the WHO guideline.

5.3 Toxicology

Vaccine safety has been evaluated in repeated-dose toxicity studies in New Zealand white rabbits.
Animals were administrated the clinical dose or double dose of antigen (120 µg and 240 µg) with 3 intramuscular injections 2 weeks apart, which exceeds the number of injections intended for humans. The adjuvant used in the formulation was AS01$_B$, which contains double amount of the same components as AS01$_E$, representing a worst-case-scenario. The vaccine was well tolerated. A transient minimal to mild acute inflammatory response, characterised by mildly to moderately increased C-reactive protein and fibrinogen, and minimally to mildly increased white blood cell count (due to increased absolute neutrophil count) 1 day after the first injection was noted, which resolved after 1 week. These findings were associated with partially or completely reversible microscopic and/or organ weight changes in the lymph nodes. Findings were similar after the second and third vaccination.
Reproductive and developmental toxicity studies with the clinical formulation of Arexvy were conducted in rabbits and with a RSVPreF3 vaccine without an adjuvant in rabbits and in rats. The results of the studies did not indicate a risk for a pregnant woman and their embryos/fetuses.
As expected from an intramuscularly administered adjuvanted vaccine, partially or completely reversible local injection site reactions, characterised by minimal to slight myofiber degeneration/necrosis and minimal to slight mixed cell infiltrate, were observed in rabbits.

5.4 Nonclinical conclusions

The nonclinical immunogenicity characterisation of Arexvy provides a proof of concept and supports the selection of antigen and adjuvant. The safety profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. From the nonclinical point of view, Arexvy is considered approvable for the proposed indication.

6 Clinical aspects

6.1 Clinical pharmacology

No clinical pharmacology studies of RSVPreF3 (RSV PreFusion protein 3) vaccine were conducted in support of this application. This is acceptable as clinical pharmacology studies are not routinely conducted as part of the evaluation of vaccines and in line with the CHMP “Guideline on Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005).

6.2 Dose finding and dose recommendation

Dose-finding study RSV OA=ADJ-002:
In this Phase 1/2, randomised, placebo-controlled, observer-blind, multi-centre study, the immune response to 3 different concentrations of pre-fusion conformation antigen RSVPreF3 (30 µg, 60 µg, or 120 µg), as well as 2 different adjuvants $AS01_B$ (adjuvant system containing MPL, QS-21, and liposome (50 µg MPL and 50 µg QS-21)), and $AS01_E$ (adjuvant system containing MPL, QS-21, and liposome (25 µg MPL and 25 µg QS-21),) in a 2-dose schedule at 0 and 2 months in adults of 18-40 or 60-80 years of age was evaluated.
The highest selected dose of 120 µg showed the highest increases in immune response and there was no further increase in antibodies after the second dose of the vaccine.
The adjuvants demonstrated an immunologic benefit of any $AS01_E$ or $AS01_B$ formulation over non-adjuvanted formulations in terms of RSVPreF3-specific CD4+ T cells. The difference in immunological response observed between $AS01_E$-based formulations and the $AS01_B$-based formulations after 1 vaccine dose was restricted to cellular response and shown to be rather limited, thus the lower dose was selected.
Therefore, the chosen formulation of 1 dose of 120 µg RSVPreF3/$AS01_E$ for the Phase 3 clinical efficacy and safety studies is in line with the study results of this dose-finding study.

6.3 Efficacy

Pivotal study RSV OA=ADJ-006:
This ongoing Phase 3, randomised, placebo-controlled, observer-blind, multi-country study aimed to demonstrate the efficacy of a single dose of RSVPreF3 OA (RSV PreFusion protein 3 Older Adult) vaccine in the prevention of RSV-confirmed lower respiratory tract disease (LRTD) in adults aged 60 years and older. This study is ongoing over 3 seasons; the current submitted data are the results of the interim analysis after the first season.
Participants were randomised in a 1:1 ratio to placebo or vaccine. There were 4 groups: 3 vaccine lot groups and 1 placebo group.
The primary objective was to demonstrate the efficacy of a single dose of the RSVPreF3 OA vaccine in the prevention of RSV-A and/or B-confirmed LRTD during the first season in adults ≥60 years of age (YOA). The primary endpoint was met if the lower limit of the 2-sided confidence interval for vaccine efficacy (VE) was above 20%.
The key secondary objectives supporting the efficacy data evaluated:

- The efficacy of a single dose of RSVPreF3 OA in the prevention of RSV-confirmed LRTD:
  - by age category (≥65 YOA, ≥70 YOA, and ≥80 YOA)
  - for each RSV subtype (A and B) separately
  - by baseline comorbidities
  - by baseline frailty status.
- To evaluate the efficacy of a single dose of RSVPreF3 OA in the prevention of severe RSV-confirmed LRTD in adults ≥60 YOA.
- To evaluate the efficacy of a single dose of RSVPreF3 OA in the prevention of complications related to RSV-confirmed acute respiratory illness (ARI) and any ARI during the RSV seasons in adults ≥60 YOA.
- To evaluate the efficacy of a single dose of RSVPreF3 OA in the prevention of hospitalisation due to respiratory diseases during the RSV seasons in adults ≥60 YOA.

- To evaluate the efficacy of a single dose of RSVPreF3 OA in the prevention of RSV-confirmed ARI in adults ≥60 YOA.

Surveillance for ARI and LRTD was performed all year round via spontaneous reporting by the study participant and by scheduled site staff contacts. ARI episodes were identified through the collection of predefined signs and symptoms belonging to the upper and lower respiratory tracts, and systemic signs and symptoms, allowing subsequent scheduling of an ARI visit, nasopharyngeal swab sampling by the site staff, and further follow-up.
For the primary efficacy endpoint, the RSV-related LRTD case definition involved both the presence of predefined lower respiratory tract symptoms and/or signs and a sample positive for RSV by qRT-PCR testing of swab samples.
For severe RSV-confirmed LRTD, 2 case definitions were used, i.e. based on clinical symptomology (i.e. requiring the presence of at least 2 lower respiratory signs or assessed as “severe” by the investigator) or based on supportive therapy (i.e. requiring the need for oxygen supplementation, positive airway pressure therapy, or other types of mechanical ventilation).

The study population included males and females ≥60 YOA at the time of vaccination, including individuals living in the community as well as long-term care facility residents with medically stable conditions (such as diabetes, hypertension, or cardiac disease). All participants were to be without severe immunocompromising conditions and with no prior exposure to any RSV vaccine.

The intended population was adequately reflected in the study and baseline characteristics were well balanced. Approximately 39% of participants in the primary efficacy population and the overall study population had at least 1 comorbidity at baseline such as cardiovascular disease, respiratory disease, or diabetes.

The primary endpoint was met with a VE of 82.6% (96.95% CI 57.9, 94.1) against the first occurrence of RSV-confirmed LRTD in adults ≥60 YOA. This result was consistent in the different sensitivity analyses. Furthermore, it was also consistent in the subgroup analyses. The VE was also high in participants with at least 1 pre-existing comorbidity of interest at 94.6% (95% CI 65.9, 99.9). However, the absolute incidence of 47 RSV-confirmed cases in approx. 24,000 patients overall appeared to be rather low. This was most likely due to the impact on the transmission of RSV of non-pharmaceutical interventions employed to address the COVID-19 pandemic.
The key secondary endpoints were also met except for VE in adults ≥80 YOA and frail patients, as the numbers of accrued RSV LRTD cases in these populations were too low to draw a conclusion. Furthermore, the number of hospitalisations due to RT-PCR-confirmed RSV respiratory disease and the number of cases with RSV-confirmed severe LRTD cases were too low to draw a conclusion about VE. For more information regarding RSV-confirmed severe LRTD cases, see the information for healthcare professionals.

Supportive studies

Study RSV OA=ADJ-004: This Phase 3, randomised, open-label, multi-centre, multi-country study aimed 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. The data presented indicate that RSVPreF3 is immunogenic, as it induces a robust immune response at 30 days post-vaccination 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 RSV OA=ADJ-007: This Phase 3, open-label, randomised, controlled, multi-country study aimed to evaluate the immune response, safety, and reactogenicity of RSVPreF3 OA investigational

vaccine when co-administered with FLU-QIV vaccine (Influenza Quadrivalent Inactivated Vaccine) in adults aged 60 years and above. The results indicated that there was no evidence of immunological interference between concomitantly administered RSVPreF3-AS01$_E$ and seasonal influenza quadrivalent vaccine regarding the immune-response**.**

Study RSV OA=ADJ-009: This Phase 3, multi-centre, multi-country, randomised, double-blind study aimed 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 geometric mean concentrations at 30 days post-vaccination.

Study RSV OA=ADJ-011: In this Phase 2b, open-label, multi-centre, extension study, the persistence of immunogenicity and immunogenicity of revaccination were evaluated. The immune response induced by the RSVPreF3 vaccine gradually declined up to 18 months post-Dose 2 (Month 20) but remained above the initial baseline levels. Following revaccination (Dose 3) at Month 20, an increase in humoral immune response was observed, but it did not reach the levels observed at Day 31 post-Dose 1 in the initial study RSV OA=ADJ-002.

6.4 Safety

Across all Phase 3 studies, a total of 15,745 participants received at least 1 dose of the RSVPreF3 OA vaccine.
In the pivotal study RSV OA=ADJ-006, 4,704 participants from North America, 5,916 participants from the EU, 876 participants from Asia, and 971 participants from the southern hemisphere (SH) received at least 1 dose of RSVPreF3 OA vaccine. The median follow up was 7.8 months.

Overall, RSVPreF3 had a markedly increased reactogenicity compared to placebo. Solicited administration site events with onset within 4 days following vaccination were reported in 62.2% of participants in the RSVPreF3 group and 10.0% of participants in the placebo group. Median duration of these events was 1-4 days.
Solicited systemic events with onset within 4 days following vaccination were reported in 49.4% of participants in the RSVPreF3 group and 23.2% of participants in the placebo group. Median duration of these events ranged from 1-2 days.
However, the rates of solicited Grade 3 reactions after RSVPreF3 were low, but still higher compared to the placebo group (1.5% for administration site events and 3.3% for systemic events, compared to 0% for administration site events and 0.9% for systemic events in the placebo group).

The frequency of SAEs reported up to 6 months post-vaccination was 4.2% in the vaccine group and 4.0% in the placebo group, without any observed clusters.

In the aggregated safety dataset, at least 1 potential immune-mediated disease (pIMD, collected as adverse events of special interest) was reported by 0.4% of participants. In study RSV OA=ADJ-006 there was no imbalance in reporting of pIMDs between treatment groups, with 0.4% participants in both the RSVPreF3 and placebo group reporting a pIMD.
There was 1 case of Guillain-Barré syndrome, occurring 9 days after vaccination, which was assessed as related to the vaccine by the investigator. However, no strong conclusion can be drawn from this single case.
There was also a numerical imbalance regarding atrial fibrillation (AF) within 30 days after vaccination (10 participants who received AREXVY (0.1%) vs. 4 participants who received placebo (< 0.1%)). However, this numerical imbalance for AF after 1 month vanishes after 6 months, and a causal relationship to the vaccine cannot be proven; therefore, this is not considered prohibitive.

6.5 Final clinical benefit-risk assessment

Respiratory syncytial virus (RSV) causes acute respiratory tract illness in persons of all ages. RSV is an important and often unrecognised cause of lower respiratory tract infection (LRTI) in older adults and immunocompromised adults and an important cause of death in adults older than 50 years.

Therapy for RSV infection of the lower respiratory tract is primarily supportive. At the time of the assessment, the only approved prophylaxis for RSV was pavilizumab, licensed only for infants who are at high risk for serious RSV disease. At the time of the assessment, there were no vaccines for the prophylaxis of RSV or drugs for the treatment of RSV approved in Switzerland. Therefore, an unmet medical need can be attested.

The pivotal study RSV OA=ADJ-006 aimed to demonstrate the efficacy of a single dose of RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults aged 60 years and older.
The intended population was adequately reflected in the study and baseline characteristics were well balanced. The primary endpoint was met and VE against the first occurrence of RT-PCR-confirmed RSV LRTD of 82.6% (96.95% CI 57.9, 94.1) in adults ≥60 YOA was demonstrated. This result was also consistent in the different sensitivity analyses. Furthermore, it was also consistent in most of the subgroup analyses. Only in adults ≥80 YOA and frail patients were the numbers of accrued RSV LRTD cases too low to draw a conclusion about VE. Furthermore, the number of hospitalisations due to RT-PCR-confirmed RSV respiratory disease and the number of cases with RSV-confirmed severe LRTD cases were too low to draw a conclusion about VE.

The majority of participants reported 1 or more AEs; however, these were mostly mild or moderate in intensity and of short duration. The most frequently reported AEs by patients 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

Taking into consideration the unmet medical need as well as the demonstrated clinical benefits and good safety profile, the benefit-risk assessment for the requested indication is considered positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Arexvy was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Arexvy

Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted)

Composition

Active substances

Respiratory syncytial virus (RSV) pre-fusion protein F (RSVPreF3 antigen), produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

Excipients

*Powder (*RSVPreF3 antigen*):* Trehalose dihydrate, polysorbate 80, potassium dihydrogen phosphate, dipotassium phosphate.
Suspension (*AS01$_E$ adjuvant):* Purified *Quillaja* saponin (QS-21), 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), dioleoyl phosphatidylcholine, cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, water for injections.
After reconstitution, one vaccine dose contains 1.78 mg sodium and 0.35 mg potassium.

Pharmaceutical form and active substance quantity per unit

Powder and suspension for suspension for injection (i.m.).
After reconstitution, 1 dose (0.5 mL) contains 120 micrograms of RSVPreF3[1] antigen adjuvanted with AS01$_E$[2].
[1] Respiratory syncytial virus (RSV) glycoprotein F stabilized in the pre-fusion conformation (RSVPreF3) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.
[2] The AS01$_E$ Adjuvant System is composed of the plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) (25 micrograms) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* (25 micrograms).
The powder is white.
The suspension is an opalescent, colourless to pale brownish liquid.

Indications/Uses

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 official vaccination recommendations on the appropriate use should be observed.

Dosage/Administration

Consideration should be given to official vaccine recommendations for immunisation schedules.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

Arexvy is administered as a single dose of 0.5 mL.
The need for revaccination has not been established.
Children and adolescents
The safety and efficacy of Arexvy in children and adolescents younger than 18 years of age have not been established. No data are available. Arexvy is currently not authorised for use in the paediatric population.

Mode of administration

Arexvy is for intramuscular injection only, preferably in the deltoid muscle.
For instructions on reconstitution of the medicinal product before administration, see “Instructions for handling”.

Contraindications

Hypersensitivity to the active substances or to any component of the vaccine (see “Composition” and “Pharmaceutical form and active substance quantity per unit”).

Warnings and precautions

Prior to immunisation
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.
As with other vaccines, vaccination with Arexvy should be postponed in individuals suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.
As with any vaccine, a protective immune response may not be elicited in all vaccinees.
Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.
Precautions for use

Do not administer the vaccine intravascularly or intradermally. No data are available on subcutaneous administration of Arexvy.

As with other vaccines administered intramuscularly, Arexvy should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these individuals.

Systemic immunosuppressive medications and immunodeficiency

Safety and immunogenicity data on Arexvy are not available for immunocompromised individuals. Patients receiving immunosuppressive treatment or patients with immunodeficiency may have a reduced immune response to Arexvy.

Excipients

This medicinal product contains less than 1 mmol of sodium (23 mg) per vaccine dose, i.e. it is almost “sodium-free”.

This medicinal product contains potassium, but less than 1 mmol (39 mg) per vaccine dose, i.e. it is almost “potassium-free”.

Interactions

Use with other vaccines

The concomitant use of Arexvy with inactivated seasonal influenza vaccine was evaluated in a study in adults from the age of 60 years . In an open-label Phase III clinical study, participants 60 years of age and older received 1 dose of Arexvy and 1 dose of inactivated seasonal influenza vaccine (Flu Quadrivalent containing a combined total of 60 micrograms Hemagglutinin (HA) per dose) at month 0 (N = 442), or 1 dose of Flu Quadrivalent at month 0 followed by a dose of Arexvy at month 1 (N = 443). The criteria for non-inferiority of the immune responses in the control versus co-administration group were met. However, numerically lower RSV-A and RSV-B neutralising antibody titres and numerically lower influenza A and B haemagglutination inhibition antibody titres were observed with co-administration of Arexvy and an inactivated seasonal influenza vaccine than when they were administered separately. The clinical relevance of these observations is not known.

If Arexvy is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Currently, there are no available data for concomitant administration of Arexvy with any other vaccine.

Pregnancy, lactation

Pregnancy

There are no data from the use of Arexvy in pregnant women. The administration of Arexvy is not recommended during pregnancy.

After administration of an investigational unadjuvanted RSVPreF3 vaccine to 3,557 pregnant women in a single clinical trial, an increase in preterm births was observed compared to placebo.
Results from animal studies with an investigational unadjuvanted RSVPreF3 vaccine and results with Arexvy do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see "Preclinical data").

Lactation

There are no data on the excretion of Arexvy in human or animal milk. Arexvy is not recommended in breast-feeding/lactating women.

Fertility

There are no data on the effects of Arexvy on human fertility. Effects on male or female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

No studies on the effects of Arexvy on the ability to drive and use machines have been performed.

Undesirable effects

The safety profile presented below is based on a placebo-controlled Phase III clinical study (conducted in Europe, North America, Asia and Southern hemisphere) in adults ≥ 60 years of age in which 12,467 adults received one dose of Arexvy and 12,499 received placebo.
Adverse drug reactions are listed below by MedDRA system organ class and by frequency according to the following convention: "very common" (≥1/10), "common" (≥1/100, <1/10), "uncommon" (≥1/1,000, <1/100), "rare" (≥1/10,000, <1/1,000), "very rare" (<1/10,000).

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	lymphadenopathy
Immune system disorders	Uncommon	hypersensitivity reactions (such as rash)
Nervous system disorders	Very common	headache (27.2%)
Respiratory, thoracic, and mediastinal disorders	Common	rhinorrhea
Gastrointestinal disorders	Uncommon	nausea, abdominal pain
Musculoskeletal and connective tissue disorders	Very common	myalgia (28.9%), arthralgia (18.1%)
	Very common	injection site pain (60.9%), fatigue (33.6%)

General disorders and administration site conditions	Common	injection site erythema, injection site swelling, fever, chills
	Uncommon	injection site pruritus
		pain, malaise

In Study RSV OA=ADJ-006 (NCT04886596), within 30 days after vaccination, atrial fibrillation was reported in 10 participants who received Arexvy and 4 participants who received placebo (of which 7 events in Arexvy arm and 1 event in placebo arm were serious); the onset of symptoms ranged from 1 to 30 days post vaccination. The currently available information on the atrial fibrillation is insufficient to determine a causal relationship to the vaccine. Within 6 months after vaccination, serious events of atrial fibrillation were reported in 13 participants who received Arexvy and 15 participants who received placebo.

Serious Adverse Events Reported from Other Studies
Study RSV OA=ADJ-004 (NCT04732871): One case of Guillain-Barré syndrome beginning 9 days after Arexvy vaccination was reported in a participant enrolled in a study site in Japan.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Insufficient data are available.

Properties/Effects

ATC code

J07BX05

Mechanism of action

Arexvy induces the functional humoral immune responses against the RSV-A and RSV-B subtypes and the antigen-specific cellular immune responses which contribute to protect against RSV-associated LRTD.
Non-clinical data show that $AS01_E$ induces a local and transient activation of the innate immune system through specific molecular pathways. The adjuvant effect of $AS01_E$ is the result of interactions between MPL and QS-21 formulated in liposomes. This 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 and induction of RSV-A and RSV-B neutralizing antibody responses. In addition, RSVPreF3 formulated with $AS01_E$ can elicit specific binding antibodies directed to site Ø, a highly neutralizing sensitive epitope, exposed only on the pre-fusion conformation of the F protein.

Pharmacodynamics

1. Efficacy of Arexvy

Efficacy of Arexvy against RSV-associated LRTD in adults 60 years and older was evaluated in an ongoing, Phase III, randomised, placebo-controlled, observer-blind clinical study (RSV OA=ADJ-006) conducted in 17 countries from Northern and Southern Hemispheres. Participants are planned to be followed for up to 36 months.

The primary population for efficacy analysis (referred to as the modified Exposed Set, included adults 60 years of age and older receiving 1 dose of Arexvy or placebo and who did not report an RSV-confirmed acute respiratory illness (ARI) prior to Day 15 after vaccination) included 24,960 participants randomised equally to receive 1 dose of Arexvy (N = 12,466) or placebo (N = 12,494). At the time of the primary efficacy analysis, participants had been followed for the development of RSV-associated LRTD for up to 10 months (median of 6.7 months).

At baseline, 39.3% of participants had at least one comorbidity of interest; 19.7% of participants had an underlying cardiorespiratory condition (COPD, asthma, any chronic respiratory/pulmonary disease, or chronic heart failure) and 25.8% of participants had endocrinometabolic conditions (diabetes, advanced liver or renal disease).

Using the Gait speed test, 38.3% of participants were ranked as pre-frail (0.4-0.99m/s walking speed) and 1.5% as frail (<0.4 m/s walking speed or who were not able to perform the test).

Efficacy against RSV-associated LRTD

The primary objective was to demonstrate the efficacy of Arexvy in the prevention of a first episode of confirmed RSV-A and/or RSV-B associated LRTD during the first season. Confirmed RSV cases were determined by quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) on nasopharyngeal swab. LRTD was defined based on the following criteria: the participant must have experienced at least 2 lower respiratory symptoms/signs including at least 1 lower respiratory sign for at least 24 hours, or experienced at least 3 lower respiratory symptoms for at least 24 hours. Lower respiratory symptoms included: new or increased sputum, new or increased cough, new or increased dyspnea (shortness of breath). Lower respiratory signs included: new or increased wheezing, crackles/ronchi, respiratory rate ≥ 20 respirations/min, low or decreased oxygen saturation (O_2 saturation <95% or ≤90 % if baseline is <95%) or need for oxygen supplementation.

Compared with placebo, Arexvy significantly reduced the risk of developing RSV-associated LRTD by 82.58% (96.95% CI: [57.89, 94.08]) in participants 60 years of age and older, which met the pre-

specified success criterion for the primary study objective (Table 1). Vaccine efficacy against RSV-LRTD is observed through the median follow-up period of 6.7 months.
The vaccine efficacy against RSV A-associated LRTD cases and RSV B-associated LRTD cases was 84.62% (95% CI [32.08, 98.32]) and 80.88% (95% CI [49.40, 94.27]), respectively.

Table 1. Efficacy Analysis: First RSV-associated LRTD Overall, by Age and co-morbidity subgroups in RSV OA=ADJ-006 (modified Exposed Set)

Subgroup	Arexvy			Placebo			
	N	n	Incidence Rate per 1,000 Person-Years	N	n	Incidence Rate per 1,000 Person-Years	% Efficacy (CI)[a]
Overall (≥ 60 years)[b]	12466	7	1.0	12494	40	5.8	82.58 (57.89, 94.08)
60-69 years	6963	4	1.0	6979	21	5.5	80.96 (43.56, 95.25)
70-79 years	4487	1	0.4	4487	16	6.5	93.81 (60.15, 99.85)
Participants with at least 1 comorbidity of interest	4937	1	0.4	4861	18	6.6	94.61 (65.88, 99.87)

[a]CI = Confidence Interval (96.95% for the overall (≥ 60 years) and 95% for all subgroup analyses). Two-sided exact CI for vaccine efficacy is derived based on Poisson model adjusted by age categories and regions.
[b]Primary confirmatory objective with pre-specified success criterion of lower limit of the 2-sided CI for vaccine efficacy above 20%
N = Number of participants included in each group
n = Number of participants having first occurrence of RSV-confirmed LRTD occurring from Day 15 post vaccination

Compared with placebo, Arexvy significantly reduced the risk of developing RSV-associated LRTD by 84.37% (95% CI: [46.91, 97.04]) in participants 70 years of age and older. The vaccine efficacy in the subgroup of participants 80 years of age and older (1016 participants in Arexvy vs 1028 participants in placebo) cannot be concluded due to the low number of total cases accrued (5 cases).
Compared with placebo, Arexvy significantly reduced the risk of developing RSV-associated LRTD in pre-frail participants by 92.92% (95% CI [53.44, 99.83]). The vaccine efficacy in the frail subgroup (189 participants in Arexvy vs 177 participants in placebo) cannot be concluded due to the low number of total cases accrued (2 cases).
Amongst 18 RSV-LRTD cases with at least 2 lower respiratory signs or preventing everyday activities, 4 cases of severe RSV-LRTD requiring oxygen supplementation occurred in the placebo group, while there were none in the RSVPreF3 group.

2. Immunogenicity of Arexvy

An immunological correlate of protection has not been established; therefore, the level of immune response that provides protection against RSV-associated LRTD is unknown.

The immune responses to Arexvy were evaluated in a Phase III immunogenicity and safety study RSV OA=ADJ-004 in adults 60 years and older. Functional humoral immune responses post-vaccination compared to pre-vaccination were evaluated with results from 940 participants for RSV-A and 941 participants for RSV-B for month 1 vs. pre-vaccination, and 928 participants for RSV-A and 929 participants for RSV-B at month 6 vs. pre-vaccination. The cell-mediated immune responses were evaluated with results from 471 participants at pre-vaccination, 410 at month 1 and 440 at month 6.

Arexvy elicited RSV-specific humoral and cellular immune responses. The geometric mean increase of the RSV-A and RSV-B neutralizing titers compared to pre-vaccination were 10.5-fold (95% CI [9.9, 11.2]) and 7.8-fold (95% CI [7.4, 8.3]) at 1-month post-vaccination, respectively, and 4.4-fold (95% CI [4.2, 4.6]) and 3.5-fold (95% CI [3.4, 3.7]) at 6-months post-vaccination, respectively. The median frequency (percentile [25^{th}, 75^{th}]) of the RSVPreF3-specific CD4+ T-cells (per million of CD4+ T cells) was 1339.0 (829.0, 2136.0) 1-month post-vaccination and 666.0 (428.0, 1049.5) 6-months post-vaccination as compared to 191.0 (71.0, 365.0) pre-vaccination.

Clinical efficacy

See under “Pharmacodynamics”.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Non-clinical data reveal no special hazards for humans based on general safety studies.

Reproductive and developmental studies with an unadjuvanted RSVPreF3 vaccine as well as results from a study with Arexvy in rabbits did not reveal vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.
For shelf life after reconstitution of the medicinal product, see “Instructions for handling”.

Special precautions for storage

Store in a refrigerator (2-8°C) in the original package to protect from light and keep out of the reach of children. Do not freeze. Discard if the vial has been frozen.
For storage conditions after reconstitution of the medicinal product, see “Instructions for handling”.

Instructions for handling

The powder and suspension should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not reconstitute the vaccine.

<u>How to prepare Arexvy:</u>

Arexvy must be reconstituted prior to administration.

1. Withdraw the entire contents of the vial containing the suspension into a syringe.
2. Add the entire contents of the syringe into the vial containing the powder.
3. Gently swirl until the powder is completely dissolved.

The reconstituted vaccine is an opalescent, colourless to pale brownish liquid.
The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not administer the vaccine.
After reconstitution, the vaccine should be used promptly; if not possible, the vaccine should be stored in the refrigerator (2-8°C) or at room temperature up to 25°C. If not used within 4 hours it should be discarded.

<u>Before administration:</u>

1. Withdraw 0.5 mL of the reconstituted vaccine into the syringe.
2. Change the needle so that you are using a new needle.

Administer the vaccine intramuscularly.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

69310 (Swissmedic)

Packs

1 vial with powder and 1 vial with suspension (B)

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

Date of revision of the text

December 2023