Unit: Technical Assessment Unit

Public assessment report for biological products

Arexvy

Administrative information:

Trade name of the medicinal product:	Arexvy
INN (or common name) of the active substance(s):	Respiratory Syncytial Virus recombinant glycoprotein F stabilized in the pre-fusion conformation Ant 120 mcg/0.5m
Manufacturer of the finished product	**for Powder**: GlaxoSmithKline Biologicals SA, Avenue Fleming 20, 1300 Wavre -Belgium **for adjuvant**: GlaxoSmithKline Biologicals SA, Avenue Fleming 20, 1300 Wavre - Belgium GlaxoSmithKline Vaccines S.r.l., Bellaria-Rosia, 53018 Sovicille, - ITALY
Marketing Authorization holder	GlaxoSmithKline Biologicals s.a., Rue de l' institute 89, B-1330 Rixensart-Belgium
Applied 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; - adults 50 through 59 years of age who are at increased risk for RSV disease. The use of this vaccine should be in accordance with official recommendations.
Pharmaceutical form(s) and strength(s):	preservative-free suspension for intramuscular injection 120 mcg/0.5ml
Route of administration	IM
Type of registration (EMA/FDA – Local)	**EMA**

List of abbreviations:

ADME: absorption, distribution, metabolism and excretion
AS01E: liposome-based Adjuvant System (25 µg MPL and 25 µg QS-21)
AIR: Adults at Increased Risk
ARI: Acute Respiratory Infection
CD8+: Cluster of Differentiation 8+
CHO: Chinese Hamster Ovary disease
CD4+ T-cells: Cluster of Differentiation 4+ T helper cells
CI: Confidence Interval
Co-Ad: Co-administration
DOPC: Dioleoyl phosphatidylcholine
EMA: European Medicines Agency
ED60: Estimated Dilution 60
FLU HD: Seasonal High Dose Quadrivalent Influenza Vaccine
FLU aQIV: adjuvanted Seasonal Quadrivalent Influenza Vaccine
FLU-QIV: Seasonal Quadrivalent Influenza Vaccine
GSK: GlaxoSmithKline
GMC: Geometric Mean Concentration
GMT: Geometric Mean Titer
HA: Healthy Adults
IgG: Immunoglobulin G
IM: Intramuscular
LRTD: Lower Respiratory Tract Disease
LL: Lower Limit
MPL: 3-O-desacyl-4′- mono-phosphoryl lipid A
NH: Northern Hemisphere
Nab: Neutralizing antibody
OA: Older Adults
PD: Pharmacodynamics
PK: Pharmacokinetics
pIMD: Potential Immune-Mediated Disease
QS-21: QS-21 Quillaja saponaria Molina, fraction 21
RSV: Respiratory Syncytial Virus
RSV-A: Respiratory Syncytial Virus A common respiratory virus that infects the nose, throat, and lungs.
RSV-B: RSV subtype B (RSVB), with higher viral loads and faster transmission time
RSVPreF3: RSV PreFusion protein F3 antigen
SAE: Serious Adverse Event
UL: Upper Limit
VE: Vaccine Efficacy
WHO: World Health Organization
YOA: Years of Age

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Dossier initial submission and evaluation process:

- The product was submitted for registration via reliance level I.
- The dossier evaluation by the registration administration units was started on 8.9.2024 after providing all the required documents (EMA detailed unredacted assessment report along with Full CTD for the product).

1. Introduction

-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).
-The finished product is presented as a preservative-free powder and suspension for injection containing 120 µg of RSVPreF3 antigen (powder) adjuvanted with AS01E (suspension).
The applicant applied for the following indications:
-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 0.5 ml.

- **Quality aspects:**

- **Drug substance:**

Manufacturer:

GlaxoSmithKline Biologicals SA, Parc de la Noire Epine, Avenue Fleming 20, 1300 Wavre -Belgium

Stability

Approved shelf life for the active substance: 36 months
Approved Storage Conditions of the active substance: -45℃ (≤-35℃)

- **Drug product:**

Manufacturer:

for Powder: GlaxoSmithKline Biologicals SA, Avenue Fleming 20, 1300 Wavre -Belgium
for adjuvant:
GlaxoSmithKline Biologicals SA, Avenue Fleming 20, 1300 Wavre -Belgium
GlaxoSmithKline Vaccines S.r.l., Bellaria-Rosia, 53018 Sovicille, - ITALY

Stability

Approved shelf life for the finished product and adjuvant: 36 months
Approved Storage Conditions of the finished product:
- Store in a refrigerator (2 °C – 8 °C). Do not freeze.
- Store in the original package in order to protect from light.

Adjuvant: Store in a refrigerator (2-8°C)
After reconstitution: Chemical and physical in-use stability has been demonstrated for 4 hours at 2 – 8 °C or at room temperature up to 25 °C.

- **Non –Clinical aspect & Clinical aspect:**

Adventitious agents

1. **Non –clinical aspect:**

➢ Arexvy (RSVPreF3 antigen) is a purified recombinant protein expressed in Chinese Hamster Ovary (CHO) cells, which has been engineered to maintain the trimeric native pre-fusion conformation preferentially. The F protein has been selected because it is a major surface antigen of the RSV virus, necessary for the virus entry/cell fusion process that is well conserved among RSV-A and
RSV-B subtypes, and it is the main target of RSV-neutralizing antibodies in human sera. The pre-fusion-specific antibodies have been shown to be more potent in their neutralization potential and are therefore considered critical for vaccine efficacy.
The antigen is adjuvanted with AS01, a liposome-based adjuvant System, contains the immuno-enhancers, the saponin Quillaja saponaria Molina, fraction 21 (QS-21) and 3-O-desacyl-4′- monophosphoryl lipid A (MPL) in a

liposomal system consists of dioleoyl phosphatidylcholine (DOPC) and cholesterol.
Arexvy is designed to boost the serum-neutralizing antibody (nAb) response to prevent RSV infection and enhance the inhibition of viral replication. The aim of this vaccine approach is to trigger an increase in RSV Nabs significantly above the natural infection levels observed in older adults. In addition, boosting 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).

- **Pharmacology:**

The non-clinical studies described here have shown the immunogenicity of adjuvanted RSVPreF3 antigen in naïve mice. Thereby, it can be concluded that an adjuvant is needed in the vaccine formulation for proper T and B cell responses and that the AS01 adjuvant system is an appropriate adjuvant for enhancing RSVPreF-induced immune responses. In addition, RSVPreF3 induces neutralizing antibodies against RSV (including the pre-fusion epitope site Ø) and F-specific CD4+ and CD8+ T cell responses. Moreover, p27-containing trimers have no negative impact on the induced B and T cell responses.
In the immunogenicity studies, young adult female CB6F1 mice (6-8 weeks old), naïve to RSV, have been immunized three times with RSVPreF3 with or without adjuvant. However, the human target population is non-naïve to RSV infection and ≥ 50 years old, and the vaccine will be used as a single dose. Moreover, the clinical relevance of the
observed immune responses is doubtful because the used antigen doses used in the murine studies are very low (compared to the doses used in the rabbit toxicology 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. Different antigen:adjuvant ratios may considerably impact the desired immune response and corresponding efficacy. Thus, the

General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.
non-clinical PD studies can only be regarded as proof-of-concept immunogenicity studies and 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. It worth noting that there is no animal model that can mimic the intended human non-naïve elderly target population and the sensitivity to RSV-related disease. 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 in these animals to humans is still unknown.
The immunogenicity, bio-distribution and toxicological studies for the adjuvant system AS01 were previously assessed in the preclinical report of an earlier approved product. Thus, it is

not considered a new adjuvant and studies for the total adjuvant system or its components are not required.

- **Pharmacokinetics:** No dedicated PK or ADME studies for RSVPreF3 are performed. This is acceptable according to the relevant EMA and WHO Guidelines they are not required for vaccines.

- **Toxicology:** In the repeated dose toxicity studies in rabbits, administration of RSVPreF3/AS01B was well tolerated for 3 administrations once every 2 weeks as an IM injection of 120 µg or 240 µg RSVPreF3/dose. It was associated with local injection site inflammation, a transient mild systemic inflammatory response and changes in draining lymph nodes that were fully or partially reversed after the 4-week recovery period. All findings are consistent with the expected effect of a vaccine. No adverse findings were identified as any changes were of limited severity, did not impact the animal's health and well-being, and demonstrated complete or partial recovery. The intramuscular administration of RSVPreF3/AS01E at 120 µg PreF3/dose was well tolerated and demonstrated no effects on female fertility, embryo-fetal, pre- and postnatal development.

- **Overall conclusion:** considering the reviewed nonclinical data, Arexvy is acceptable from the non-clinical point of view.

2. Clinical aspect:

- **Clinical Efficacy (Immunogenicity):**

All RSVPreF3 OA investigational vaccine formulations elicited robust humoral and cellular immune responses compared to Placebo during Phase 1/2 and 2b studies. The humoral immune response increased at Day 31 (1-month post-Dose 1) without further increase at Day 91 (1-month post-Dose 2), then declined at Month 8 and Month 14 but remained above pre-vaccination values in all treatment groups.

During the RSV OA=ADJ-006 (Pivotal Phase-III Study), the primary confirmatory efficacy objective was demonstrated in VE Analysis 1. Over a median follow-up of 6.7 months, VE of a single dose of RSVPreF3 OA vaccine against RSV-confirmed LRTD in participants ≥60 YOA was 82.58% (96.95% CI: 57.89, 94.08), with the LL of the CI well above the pre-defined threshold of 20%. Robustness of the primary objective result was confirmed by the planned sensitivity analyses.

- A single dose of the RSVPreF3 OA vaccine was efficacious over 2 seasons against RSV-confirmed LRTD and severe LRTD (median follow-up of 17.8 months from Day 15 post-Dose 1 up to end of Season 2 in NH).
- The study also evaluated efficacy following an annual revaccination schedule as confirmatory secondary objective. Over 2 seasons, revaccination after 12 months does not appear to confer additional efficacy benefit for the overall population. Since the LL of the

97.5% CI was above the pre-defined threshold of 20%, this secondary confirmatory objective was also met.

- VE against RSV-confirmed LRTD by RSV subtype, by age category, time of vaccination, by baseline comorbidities, and frailty status over 2 seasons was consistent with the overall confirmatory VE against RSV-confirmed LRTD, following a single dose and following annual revaccination. For participants ≥80 YOA and those in the frail subgroup, there were not enough cases and/or participants to conclude on the VE.
- No VE was observed against any ARI, any LRTD, prevention of hospitalization due to any respiratory disease, or complications related to any ARI.
- The RSVPreF3 OA vaccine was immunogenic 1-month post-vaccination with robust increases of RSV-A and RSV-B neutralizing GMTs, and RSVPreF3-binding IgG Ab GMCs compared to pre-vaccination and Placebo. These data were consistent with the data observed in other RSV OA studies.
  These data over 2 seasons of RSV OA=ADJ-006 (Pivotal Phase-III Study) support the proposed indication of the RSVPreF3 OA vaccine for the prevention of LRTD caused by RSV-A and RSV-B subtypes in adults aged 60 years and older.

  During the RSV OA=ADJ-004 (Immunogenicity study); the RSVPreF3 OA vaccine was found to be immunogenic in terms of RSV-A and RSV-B neutralizing titers, RSVPreF3-binding IgG Ab concentrations and frequency of RSVPreF3-specific CD4+ T cells for at least 12 months after administration of a single dose in adults aged ≥60 YOA.
- the RSVPreF3 OA vaccine was well tolerated with solicited adverse events mostly mild to moderate of short duration, and an acceptable safety profile when administered as single dose in adults aged ≥60 YOA. The reactogenicity and safety profiles of the RSVPreF3 OA vaccine were similar between post-Dose 1 and post-revaccination. Overall, the reported events (unsolicited AEs/SAEs/fatal SAEs) were in line with what would be expected in a population of adults ≥60 YOA.

  During RSV OA=ADJ-018 (Adults 50-59 YOA); One month after the RSVPreF3 OA vaccine dose, the RSV-A and RSV-B neutralizing titers (ED60) expressed as GMT ratio in the Adults-HA-RSV and Adults-AIR-RSV groups were shown to be non-inferior compared to the OA-RSV group. Success criterion: The UL of the 2-sided 95% CI or 97.5% CI on the group GMT ratio (OA-RSV over Adults-HA-RSV group and OA-RSV over Adults-AIR-RSV group) was ≤1.5.
- One month after the RSVPreF3 OA vaccine dose, the RSV-A and RSV-B neutralizing titers (ED60) expressed as SRR differences were shown to be non- inferior between the Adults-HA-RSV versus OA-RSV and Adults-AIR-RSV versus OA-RSV.
  These data of RSV OA=ADJ-018; support the proposed indication of the RSVPreF3 OA vaccine for the prevention of lower respiratory tract disease (LRTD) caused by

respiratory syncytial virus in adults 50 through 59 years of age who are at increased risk for RSV disease.

RSVPreF3 OA vaccine was well tolerated and showed a clinically acceptable reactogenicity and safety profile when co-administered with FLU-QIV. The observed percentages of events (unsolicited/SAEs/pIMDs) were balanced between the Co-Ad and Control groups. The observed reactogenicity profile of the Co-Ad group was driven by the RSVPreF3 OA vaccine.

➢ **Clinical Safety conclusion**

❖ During Phase 1/2 and 2b studies; RSVPreF3 OA vaccine was well tolerated and showed a clinically acceptable reactogenicity and safety profile, irrespective of the age cohort. Based on safety, reactogenicity and immunogenicity results (humoral and cellular immune response) up to 1-month post-Dose 2, the 120 µg RSVPreF3/AS01E formulation as a single dose was selected for the Phase 3 clinical development.

- ❖ The observed reactogenicity profile of the RSVPreF3 OA vaccine **during RSV OA=ADJ-006** was acceptable;

- with mostly mild to moderate solicited administration site and/or systemic events of short duration. No imbalances were observed between groups for the reported SAEs and pIMDs during the 6-month follow-up period.
- The reactogenicity and safety data post revaccination (approximately 12 months post-Dose 1) was similar to the data obtained between Dose 1 and Dose 2 either in the RSVPreF3 or in the Placebo groups. The incidences of unsolicited AEs (any, Grade 3, related), SAEs (any, related, fatal) and pIMDs (any, related) post-Dose 2 were similar to those reported post-Dose 1.
  - ❖ Reactogenicity and safety RSVPreF3 OA vaccine was well tolerated with a clinically acceptable reactogenicity and safety profile when co-administered with FLU HD vaccine in older adults. No clinically meaningful differences between the Co-Ad group and the Control group have been identified up to study end.
  - ❖ RSVPreF3 OA vaccine was well tolerated and showed a clinically acceptable reactogenicity and safety profile when co-administered with FLU-QIV. The observed percentages of events (unsolicited/SAEs/pIMDs) were balanced between the Co-Ad and Control groups. The observed reactogenicity profile of the Co-Ad group was driven by the RSVPreF3 OA vaccine.
  - ❖ RSVPreF3 OA vaccine was well tolerated and showed a clinically acceptable reactogenicity and safety profile when co-administered with FLU aQIV in older adults. No clinically meaningful differences between the Co-Ad group and the Control group have been identified up end-of-study.
  - ❖ RSVPreF3 OA vaccine was well tolerated and showed a clinically acceptable reactogenicity and safety profile. The observed percentages of solicited events,

unsolicited AEs, SAEs, and pIMDs were balanced between the 3 lots of RSVPreF3 OA vaccine.

- ❖ RSVPreF3 OA vaccine had an acceptable reactogenicity and safety profile in adults 50-59 YOA as well as in adults 60-69 YOA.

- ➢ **Benefit/ Risk discussion:**

The available safety, immunogenicity and efficacy data confirm the favorable benefit/risk profile of the RSVPreF3 OA vaccine when administered as a single dose for up to approximately 18 months after vaccination covering 2 RSV seasons. The safety profile of the vaccine is adequately reflected in the PI. Altogether, the RSVPreF3 OA vaccine is expected to address a significant medical need in the population of adults ≥ 60 YOA who are most at risk of developing RSV-LRTD.
The immunogenicity, safety and reactogenicity data from study RSV OA=ADJ-018 presented in this Application support the administration of the RSVPreF3 OA vaccine to adults 50-59 YOA who are at increased risk for RSV disease.
The benefit/risk profile of the RSVPreF3 OA vaccine for the protection against LRTD caused by RSV in adults 50- 59 YOA who are at increased risk for RSV disease is considered positive and expected to address an unmet medical need.

In conclusion the overall benefit/risk of Arexvy is favorable intended for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in:

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

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/arexvy-epar-public-assessment-report_en.pdf