NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY
FOR FACILITATED REGISTRATION PATHWAY (FRP)

Reference drug regulatory agency: European Medicines Agency (EMA)

PRODUCT NAME:
Arexvy powder and suspension for suspension for injection (MAL24086007ARZ)

ACTIVE INGREDIENT:
Respiratory syncytial virus PreFusion protein 3 (RSVPreF3) antigen 120 mcg

PRODUCT REGISTRATION HOLDER:
Glaxosmithkline Pharmaceutical Sdn. Bhd.

PRODUCT MANUFACTURER:
Glaxosmithkline Biologicals S.A, Belgium

APPROVAL DATE:
1 Aug 2024 (DCA 399)

1.0 BACKGROUND INFORMATION

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

1.2 Approved Posology:

Arexvy is administered as a single dose of 0.5ml.

The need for revaccination with a subsequent dose has not been established.

Paediatric population

The safety and efficacy of Arexvy in children have not been established. No data are available.

Method of administration

For intramuscular injection only, preferably in the deltoid muscle.

1.3 Route of Administration:

Intramuscular (IM)

1.4 Pharmacological Aspects:

Pharmacodynamic Properties

Mechanism of action

By combining the RSV-specific antigen, F-protein in prefusion conformation, with an adjuvant system ($AS01_E$), Arexvy is designed to enhance antigen-specific cellular immune response and neutralizing antibodies response in individuals with pre-existing immunity against RSV. 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.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- Arexvy vaccine is presented as 2 components:

a) RSVPreF3 (120µg): lyophilised powder of Respiratory Syncytial Virus (RSV) recombinant fusion protein RSVPreF3 (trimeric RSV Fusion protein stabilised in a pre-fusion conformation) produced in a Chinese Hamster Ovary (CHO) cell line.

b) $AS01_E$ Adjuvant System (0.5 mL liquid suspension), liposomal formulation containing immunoenhancers MPL and QS-21. DOPC (dioleoyl phosphatidylcholine) and cholesterol

are the liposome membrane constituents and liposomes are suspended in a phosphate buffered saline solution, used for the reconstitution of RSVPreF3.

- RSVPreF3 antigen consists of an engineered version of the RSV fusion (F) surface glycoprotein produced by recombinant DNA technology in Chinese Hamster Ovary Cells (CHO-K1 cells). The antigen is stabilised in the pre-fusion trimeric conformation of the naturally occurring protein by the introduction of Cysteine residues leading to the formation of a disulfide bond (DS), cavity filling hydrophobic substitutions (Cav1) and a "foldon" domain (T4-phage fibritin trimerization domain to the C-terminus) to stabilize the trimeric conformation of RSVPreF3 and eliminate triggering and rearrangement into the post-F conformation.
- The calculated average molecular weight of the RSVPreF3 protein based on the mature protein amino acid sequence (492 amino acids) is 54.5 kDa.
- 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.
- 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 1000L scale. The culture temperature in the bioreactor is then lowered to induce the expression of RSVPreF3 protein which is finally secreted into the culture medium.
- Purification consists of clarification, affinity-like chromatography, a dilution step with specific buffer (containing 2%(w/w) Polysorbate 80 at controlled temperature) for viral inactivation, anion exchange chromatography, mixed mode chromatography, nanofiltration, an ultrafiltration/diafiltration step for protein concentration and buffer exchange and a low bioburden filtration step with a polyethersulofone membrane for bioburden control before storage. The manufacturing process has been described accordingly and considered to be satisfactory.
- Process validation has been carried out following a three-stage approach (i.e. process design, process performance qualification and continued process verification). Process validation (PV) performed on 3 consecutive commercial scale drug substance batches concluded that the Product Control Strategy is considered suitable to efficiently control the product quality and that the process performance qualification was conform and ensures the reproducibility and confidence in the quality and consistency of future RSVPreF3 Drug Substance commercial production. The data from stability studies support the proposed shelf life in the proposed HDPE container.
- GMP Compliance of the drug substance manufacturer was verified by the Federal Agency for Medicines and Health Products, Belgium.

2.1.2 Finished Product

Adjuvant System $AS01_E$

- The manufacturing process consists in the preparation of the two intermediates [Concentrated Liposomes Bulk (CLB, containing MPL, DOPC and cholesterol) and QS-21 liquid bulk (LB)], followed by the formulation step (blending of water for injections, phosphate saline buffer and intermediates) and the filling step.
- The manufacturing process is identical to adjuvant system $AS01_B$ that has been previously reviewed for Shingrix vaccine. The only difference is that the two variants ($AS01_E$ & $AS01_B$) differ in their quantitative composition, $AS01_B$ has double the amount of each component compared to $AS01_E$.
- Process validation (PV) (Wavre and Rosia sites) of at least 3 consecutive commercial lots fulfilled the pre-defined acceptable criteria for critical quality attributes and showed consistent results.

- Long term stability studies results showed that $AS01_E$ is stable for 36 months when stored at 2°C to 8°C.
- GMP Compliance was verified by the Federal Agency for Medicines and Health Products (FAMHP), Belgium and AIFA Italian Medicines Agency.
- Excipients: QS-21, MPL, DOPC, cholesterol, disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, water for injection.
- The adjuvant system has passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 (R1) guidelines.

Respiratory Syncytial Virus (RSV) recombinant fusion protein (RSVPreF3)

- The manufacturing process of the lyophilized RSVPreF3 (RSVPreF3 Lyo) Final Container (FC) is composed of the following steps: 1) Formulation of the Final Bulk, 2) Filling and Lyophilisation, 3) Labelling and Packaging.
- The drug product i.e. RSVPreF3 lyophilized product at the Final Container level undergoes the routine release testing including description, pH, osmolality identity and in vitro relative potency, , RSVPreF3 content, endotoxin content, water content, RSVPreF3 trimer, high molecular weight species relative to total proteins, polysorbate 80 content, trehalose content, and sterility.
- Process validation (PV) performed on 4 consecutive commercial formulation lots and 8 filling lots concluded that the Product Control Strategy is considered suitable to efficiently control the product quality and that the process performance qualification was successfully completed. It ensures the reproducibility and confidence in the quality and consistency of future RSVPreF3 Drug Product commercial production.
- Long term stability studies results showed that RSVPreF3 is stable for 36 months at 2°C to 8°C.
- Based on the in-use stability studies, the Company proposes to use the reconstituted vaccine within a maximum of 4-hour of storage at +2°C to +8°C or up to +25°C. Beyond this incubation period, the reconstituted vaccine should be discarded.
- GMP Compliance was verified by the Federal Agency for Medicines and Health Products (FAMHP), Belgium.
- Excipients: trehalose dihydrate, polysorbate 80, potassium dihydrogen phosphate, dipotassium phosphate.
- The product has passed the evaluation following pharmacopoeial and in-house analytical test methods. In-house analytical methods were validated in accordance with the ICH Q2 (R1) guidelines.

2.2 Non-Clinical Studies

- Primary pharmacodynamic non-clinical immunogenicity data generated in naïve mice demonstrated that Arexvy adjuvanted with $AS01_E$ was able to induce higher Respiratory Syncytial Virus (RSV) neutralizing antibody responses, not only against RSV-A and -B laboratory-adapted strains but also against contemporary A and B strains, and higher F-specific CD4+ and CD8+ T cell responses in spleen and lung compared to the non-adjuvanted formulation. In accordance with international vaccine guidelines, no secondary pharmacodynamic studies or safety pharmacology studies were performed with Arexvy.
- Pharmacokinetic studies are not required for vaccines. However, the CHMP Guideline on Adjuvants in Vaccines for Human Use [EMA, 2004] mentions that “In some cases, distribution studies may be of value in understanding the mode of action of the adjuvant” while the WHO Guidelines on the Nonclinical Evaluation of Adjuvanted Vaccines [WHO, 2013] indicates that

"In certain cases biodistribution and pharmacokinetics studies can be helpful in determining the fate of the adjuvant. The feasibility and relevance of such studies should be evaluated on a case to case basis". Hence, biodistribution studies were conducted with adjuvant systems as well as its immuno-enhancer components (MPL; QS-21). The data showed that these compounds were widely distributed throughout the organism. When formulated in the liposome-based AS01, radioactive QS-21 related material is mainly eliminated via renal excretion, DOPC related material is eliminated via the expired air or faecal excretion and the synthetic analogue RC-529 is slowly eliminated from the site of injection.

- Non-clinical toxicity studies (single-dose, repeat-dose, genotoxicity, reproductive, male fertility, developmental and local tolerance) were conducted in an Organization for Economic Cooperation and Development (OECD) member country in accordance with the OECD Test Guidelines and the Principles of GLP. In summary, in the repeated dose toxicity studies in rabbits, administration of the RSVPreF3/AS01$_B$ was well tolerated for 3 administrations once every 2 weeks as an intramuscular injection of 120 mg or 240 mg 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 animal's health and well-being, and demonstrated complete or partial recovery. A safety margin to the selected clinical dose (120 µg) up to a factor 33 was calculated on a bodyweight basis. The results from the GLP toxicity studies with AS01 Adjuvant System indicate that AS01, QS-21 and MPL were generally well tolerated by the animals at the levels tested and showed mainly effects expected from the stimulation of the immune system. Indeed, these effects are consistent with a rapid but transient activation of the innate immune response observed after AS01 intramuscular administration, as evidenced by an increased production of cytokines and the rapid recruitment of monocytes and neutrophils at the injection site and draining lymph node that are no longer detected in the injection site seven days after injection.
- In conclusion, the pharmacology and toxicity studies performed in mice, rats or rabbits showed that the Arexvy induces a strong and antigen-specific immune response and is well-tolerated in these animal models. Altogether, non-clinical studies of Arexvy submitted to the NPRA are consistent with the dossier approved by the EMA, and support the selection of the final formulation, RSVPreF3/AS01$_E$, as well as safe for the use in human subjects.

2.3 Clinical Study

- The clinical development program for Arexvy to support the proposed indication consists of 6 clinical studies as listed below:
  - ➔ 1 phase 1/2 dose-finding study (ADJ-002)
  - ➔ 1 phase 2b study (ADJ-011 EXT:002)
  - ➔ 4 phase 3 studies (ADJ-006, ADJ-004, ADJ-007 and ADJ-009)
- The clinical program was initiated with the Phase I/II study ADJ-002 which evaluated the safety, reactogenicity and immunogenicity of the investigational RSV vaccine (adjuvanted with AS01E or AS01B or unadjuvanted) when administered intramuscularly (IM) according to a 0, 2 month schedule in adults aged 18-40 (Part A) or 60-80 years (Part B). As it was a first time in human study, the safety of the RSVPreF3 OA vaccine antigen was first evaluated in healthy adults 18-40 YOA (Part A) before subsequent evaluation in the older adult population 60-80 YOA (Part B). Based on safety and immunogenicity data up to 1 month

post-Dose 2, the Company selected 120 µg RSVPreF3 antigen adjuvanted with $AS01_E$ as the final vaccine formulation to be given according to a 1-dose regimen for further evaluation in Phase 3 studies.

- 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 adults ≥60 years of age.
- The supportive studies, ADJ-004, -007, -009 and -011, all evaluated immunogenicity of Arexvy. No efficacy results were obtained. Data from the immunogenicity study RSV OA=ADJ-004 up to 6 months post-Dose 1, supportive data on antibody persistence were generated up to 12 and 18 months after the second dose, respectively, in studies RSV OA=ADJ-002 and its extension -011. The results showed an increase in the humoral and cellular immune responses after revaccination with no safety concerns.
- The Applicant has stopped the development of a maternal vaccination program using the investigational RSV Maternal (RSVPreF3) vaccine due to imbalances for both preterm birth and neonatal deaths observed in one study. 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.
- All the studies included in this application were conducted in accordance with Good Clinical Practice (GCP) guidelines.

2.3.1 Efficacy

Table 1: Summary of Phase 3 Clinical Studies Conducted

Study Type & Design [N=number of participants in modified exposed set (mES) or exposed set (ES)]	**Primary/ Co-primary Objective(s) of the Study**	**Results**
Pivotal study		

<table>
<tr>
<td>ADJ-006

Phase 3, randomised, observer-blind, placebo-controlled multi- country study

Ratio: 1:1

N= 12466 (Arexvy)
N= 12494 (placebo)</td>
<td>To evaluate vaccine efficacy (VE) of a single dose of Arexvy against first occurrence of Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)-confirmed RSV-associated LRTD compared to placebo in adults ≥ 60 years of age

Success criteria: The LL of the 2-sided CI for VE is above 20%.</td>
<td><u>Primary Endpoint</u>
First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD by an adjudication committee, according to the case definition from Day 15 post-vaccination.
<table>
<tr><th rowspan="3">Endpoint</th><th colspan="2">Arexvy</th><th colspan="2">Placebo</th><th colspan="3">Vaccine Efficacy (VE)</th></tr>
<tr><th>N</th><th>n</th><th>N</th><th>n</th><th>%</th><th colspan="2">96.95% CI</th><th rowspan="2">P-value</th></tr>
<tr><th>LL</th><th>UL</th></tr>
<tr><td>RT-PCR-confirmed RSV LRTD</td><td>12466</td><td>7</td><td>12494</td><td>40</td><td>82.58</td><td>57.89</td><td>94.08</td><td><0.0001</td></tr>
</table>
</td>
</tr>
</table>

Study Type & Design (N=number of participants in mES or ES)	Primary/ Co-primary Objective(s) of the Study	Results
Pivotal study		
		The VE of a single dose of the Arexvy against first occurrence of RT-PCR-confirmed RSV-associated LRTD was **82.58%** (96.95% CI: 57.89, 94.08) with 7 RSV LRTD cases observed in the Arexvy group compared to 40 cases in the Placebo group with median follow-up time from Day 15 post-vaccination up to the efficacy data lock point of VE Analysis 1 was 6.7 months for both groups. **Conclusion:** The primary objective of study was demonstrated as the LL of the 96.95% CI of the VE against first occurrence of RT-PCR-confirmed RSV-associated LRTD was 57.89% (above 20%) and VE was 82.58%.
Supportive studies		
Study ADJ-004 Phase 3, randomised, open-label, multi-center, multi-country ongoing study with 3 parallel groups Ratio: 3:1:1 N= 993 annual group N= 329 flexible revaccination group N= 331 1 dose group	To evaluate the humoral immune response following a 1-dose primary schedule of Arexvy up to 12 months post-Dose 1 in adults ≥60 years of age	**Primary endpoint:** Humoral immune response at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), and at 6 and 12 months post-Dose 1 (Months 6 and 12), in a subset of participants: • Neutralizing antibody (NAb) titers against RSV-A. • Neutralizing antibody titers against RSV-B. At baseline (Day 1 – pre-vaccination) all participants had RSV-A NAb titers equal to or above the technical assay cut-off value (≥ 18 ED60) with the RSV-A NAb geometric mean titer (GMT) **862.7** ED60, due to previous exposure to RSV. At 1 month post-vaccination (Day 31), the RSV-A NAb GMT increased to reach a value of **9107.3** ED60, with a mean geometric increase (MGI) over baseline (Day 1) of **10.5**. After the increase observed at Day 31, RSV-A NAb GMTs declined by Month 6 (**3760.0** ED60) but remained well above baseline and the mean geometric increase (MGI) over baseline was 4.4.

Study Type & Design (N=number of participants in mES or ES)	Primary/ Co-primary Objective(s) of the Study	Results
Pivotal study		
		At baseline, all participants had RSV-B NAb titers equal to or above the technical assay cut-off value (≥ 30 ED60) with the RSV-B NAb GMT **1233.9** ED60, due to previous exposure to RSV. At 1 month post-vaccination (Day 31), the RSV-B NAb GMT increased to reach a value of **9650.3** ED60, with a MGI over baseline (Day 1) of **7.8**. After the increase observed at Day 31, RSV-B NAb GMTs declined by Month 6 (**4299.5** ED60) but remained well above baseline and the MGI over baseline was 3.5. **<u>Conclusion:</u>** Arexvy was immunogenic [preventing RSV-associated (subtypes A and B) LRTD] up to at least 6 months after administration as a single dose in participants ≥60 years of age.
Study ADJ-007 Phase 3, open-label, randomised, controlled, multi-country study with 2 parallel groups Ratio: 1:1 N= 442 (Co-Ad group) received a single dose of Arexvy and a single dose of FLU-QIV vaccine at Visit 1 (Day 1) N= 443 (Control group)	To demonstrate the non-inferiority of Arexvy when co-administered with the FLU-QIV vaccine compared to Arexvy administered alone. *Success criteria for non-inferiority: The upper limit (UL) of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for Arexvy vaccine is* ***≤1.5****.* To demonstrate the non-inferiority of FLU-QIV vaccine when co-administered with the Arexvy compared to FLU-QIV vaccine administered alone. *Success criteria for non-inferiority: The*	**<u>Co-Primary endpoints</u>** One month after the Arexvy dose (Day 31 for Co-Ad group and Day 61 for Control group), the UL of the 2-sided 95% CI for the GMT ratio [Control group divided by Co-Ad group] of RSV-A neutralizing antibodies (ED60) between the Control group and the Co-Ad group was 1.44 (≤1.5) whereas RSV-B neutralizing antibodies (ED60) between the Control group and the Co-Ad group was 1.43 (≤1.5). One month after the FLU-QIV vaccine dose, the UL of the 2-sided 95% CI on the HI (hemagglutination inhibition) antibody titer for each of the FLU-QIV vaccine strains expressed as group GMT ratio [Control group divided by Co-Ad group] for each of the FLU vaccine strains is ≤1.5. **Conclusion:** The co-primary objectives for immunogenicity were met. The co-administration of the Arexvy with the FLU-QIV vaccine was found to be statistically non-inferior to the administration of the Arexvy alone in terms of RSV-A and RSV-B neutralizing antibody titers expressed as group GMT ratio. The co-administration of the FLU-QIV vaccine with the Arexvy was found to be statistically

Study Type & Design (N=number of participants in mES or ES)	Primary/ Co-primary Objective(s) of the Study	Results
Pivotal study		
received a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the Arexvy at Visit 2 (Day 31).	*UL of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for each of the FLU-QIV vaccine strains is* ***≤1.5****.*	non-inferior to the administration of the FLU-QIV vaccine alone.
Study ADJ-009 Phase 3, randomised, double-blind, multi-country study with 3 parallel group Ratio: 1:1:1 N= 251 to Arexvy_Grp1 N= 253 to Arexvy_Grp2 N= 253 to Arexvy_Grp3	To demonstrate the lot-to-lot consistency in terms of RSVPreF3-specific immunoglobulin (Ig)G antibody concentrations expressed as group geometric mean concentration (GMC) ratio between 3 lots of the Arexvy vaccine at 30 days post-vaccination (Day 31) *Success criteria: the 2-sided 95% CI of the group GMC ratios between each pair of the 3 lots (Arexvy lot divided by another Arexvy lot) is within the pre-defined limit of* ***[0.67, 1.5].***	**<u>Primary endpoint</u>** The RSVPreF3-specific IgG group GMC ratios between group 1 and group 2 were 1.06 with 2 sided 95% CI **(LL 0.94, UL1.21).** The RSVPreF3-specific IgG group GMC ratios between group 1 and group 3 were 0.92 with 2 sided 95% CI **(LL 0.81, UL1.04).** The RSVPreF3-specific IgG group GMC ratios between group 2 and group 3 were 0.87 with 2 sided 95% CI **(LL 0.77, UL0.99).** **Conclusion:** Lot-to-lot consistency was demonstrated between the 3 Arexvy vaccine lots in terms of RSVPreF3-specific IgG antibody concentration at 1 month post-vaccination. The 2-sided 95% CI on the RSVPreF3-specific IgG group GMC ratios between each pair of the 3 lots (RSVPreF3 OA lot divided by another RSVPreF3 OA lot) were within the pre-defined limit of [0.67, 1.5].

2.3.2 Safety

- The majority of participants reported 1 or more adverse events (AE)s; however, these were mostly mild or moderate in intensity and of short duration (transient) and self-limited (ultimately resolving itself without treatment).
- The most frequently reported AEs were solicited AEs: injection-site pain, fatigue, myalgia, headache and arthralgia.
- The proportions of participants with unsolicited AEs requiring a medically attended visit, potential-immune-mediated disease (pIMD)s, SAEs and deaths in the Arexvy group were low and comparable to the placebo group.

- A single case of Guillain-Barré syndrome (GBS) was observed in study ADJ-004 and was assessed as possibly related to Arexvy vaccine by the investigator. As this is a single case, no strong conclusions can be drawn. This case caused hospitalization for 179 days and was considered as recovered/resolved.
- Overall, Arexvy is well tolerated in adults ≥60 years old.

3.0 CONCLUSION:

In conclusion, the results of clinical studies indicate that a single dose of the Arexvy vaccine is immunogenic and efficacious, with an estimated VE 82.58% against RSV-confirmed LRTD in the first RSV season. Arexvy is well tolerated in adults ≥60 years old.

Hence, Drug Control Authority (DCA) on the 399th meeting on 1st Aug 2024 has decided to approve the registration of this product with 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.