Taiwan Food and Drug Administration

Assessment Report

Trade Name：
欣剋融呼吸道融合病毒疫苗 /
Arexvy Respiratory Syncytial Virus Vaccine

Active Ingredient：
Recombinant respiratory syncytial virus (RSV) pre-fusion F protein (RSVPreF3)

License Number：MOHW-BI 001251

Applicant：荷商葛蘭素史克藥廠股份有限公司台灣分公司

Approval Date：113.1.30

Indication：

適用於 60 歲以上成人之主動免疫接種，以預防呼吸道融合病毒所引起的下呼吸道疾病(lower respiratory tract disease, LRTD)。

Arexvy is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in individuals 60 years of age and older.

Background Information

Trade Name	欣剋融呼吸道融合病毒疫苗 / Arexvy Respiratory Syncytial Virus Vaccine
Active Ingredient(s)	Recombinant respiratory syncytial virus (RSV) pre-fusion F protein (RSVPreF3)
Applicant	荷商葛蘭素史克藥廠股份有限公司台灣分公司
Dosage Form & Strengths	注射用凍晶粉末與注射用懸浮液劑 泡製後每劑 0.5 毫升，含有 120 微克抗原
Indication	適用於 60 歲以上成人之主動免疫接種，以預防呼吸道融合病毒所引起的下呼吸道疾病(lower respiratory tract disease, LRTD)。 Arexvy is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in individuals 60 years of age and older.
Posology	Arexvy 僅供肌肉注射使用，最合適的注射部位是三角肌，投予劑量為單劑 0.5 毫升。再次接種疫苗的必要性尚未確立。
Pharmacological Category **ATC Code**	J07BX05

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Respiratory syncytial virus (RSV) glycoprotein F (RSVPreF3 antigen) is an engineered version of the RSV fusion (F) surface glycoprotein stabilized in the pre-fusion conformation produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. Detailed description of the origin, history, and preparations of cell banking system are provided. Raw materials of biological origin are also justified. Characterization activity, including physico-chemical properties and immunological properties, is carried out for RSVPreF3 antigen. Characterization studies are presented including antigen profile, purity, structure, and potency. Impurities have been measured and evaluated to demonstrate consistency.

Manufacturing process with in-process controls, process development histories for process versions, process validation, specification, analytical methods and validation, batch analyses, and reference materials are provided to demonstrate the quality of drug substance using commercial process. The shelf life is based on the long term stability studies derived from drug substance batches produced with the commercial process. The applicant commits that the annual post-approval on-going stability will be tested on one batch of commercial RSVPreF3 drug substance .

2.1.2 Drug product

Arexvy RSVPreF3/AS01$_E$ vaccine consists of two components. The white cake or powder (or lyophilized preparation) containing the RSV recombinant fusion protein RSVPreF3 (120 μg of RSVPreF3 antigen/dose after reconstitution); the liquid suspension consisting of the AS01$_E$ Adjuvant System (0.5 mL/dose). The liquid AS01$_E$ Adjuvant System is used to reconstitute the RSVPreF3 lyophilized antigen immediately prior to administration. The pharmaceutical form of the reconstituted vaccine is a suspension for injection appearing opalescent, colorless to pale brownish liquid. Neither novel excipient nor excipients of human or animal origin are used in the formulation.

Drug product manufacturing process and formulation development are described appropriately. Manufacturing process within process controls, process validation, specification, and batch analyses are provided and show that the manufactures of drug product are controlled properly and consistently. The stability studies support the shelf life of RSVPreF3 for 24 months under the storage condition of 2-8°C. The applicant commits that the annual post-approval on-going stability will be tested on one batch for commercial product.

Information on the drug substance and drug product is regarded as appropriate to support the quality of Arexvy RSVPreF3/AS01$_E$ vaccine.

2.2 Preclinical Pharmacology/Toxicology Evaluation

RSVPreF3 OA is a recombinant RSV fusion (F) protein vaccine consisting of RSVPreF3 antigen and the AS01$_E$ adjuvant system.

In mice, the RSVPreF3 antigen adjuvanted with fractions of AS01$_B$ or AS01$_E$ elicited higher levels of neutralizing Ab titers against both RSV-A and RSV-B laboratory-adapted strains as well as contemporary A and B strains, and F-specific systemic and local (e.g., lung) CD4+ and CD8+ T cell responses, when compared with the unadjuvanted formulations. The results support the introduction of the AS01 Adjuvant System into the vaccine and the potential of the vaccine-induced antibodies to neutralize the contemporary RSV strains. When adjuvanted with AS01, the RSVPreF3 antigen elicited higher binding Ab titers targeting the antigenic site Ø than the PreF2 (a previous investigational antigen) did, indicating that the RSVPreF3 antigen has a "pre-fusion" conformation, and can induce Abs toward the neutralization-sensitive epitope.

In the GLP repeated-dose toxicity studies in rabbits, IM administration of RSVPreF3/AS01$_B$ for 3 doses up to 240 mcg RSVPreF3 per dose once every 2 weeks was well tolerated. Only the expected, fully or partially reversed, non-adverse findings including local injection site inflammation, mild systemic inflammatory response, and changes in draining lymph nodes were observed. The doses of RSVPreF3 in the repeated-dose toxicity study provided safety margins for up to 2-fold or 33.3-fold full human dose of 120 mcg, calculated using the absolute dose or on a BW basis, respectively.

In accordance with current vaccine guidelines on the non-clinical evaluation of vaccines, no conventional safety pharmacology, genotoxicity, or carcinogenicity studies were warranted. DART studies were also not required considering the targeted population, adults 60 years of age and older.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, the immunogenicity and efficacy of Arexvy vaccine was mainly supported by Phase III clinical studies [RSV OA=ADJ-009], [RSV OA=ADJ-006], [RSV OA=ADJ-007] and **[**RSV OA=ADJ-004**]**. The key findings from these studies are summarized below.

Firstly, the **[RSV OA=ADJ-009]** study demonstrated lot-to-lot consistency among three lots of Arexvy. That is, at 1-month after vaccination, the GMC ratios of Arexvy binding IgG antibodies between Lots 1 and 2, 1 and 3, and 2 and 3 were 1.06 with 95% CI (0.94, 1.21),

0.92 with 95% CI (0.81, 1.04), and 0.87 with 95% CI (0.77, 0.99), respectively. As all the 95% CIs were within the pre-defined equivalence margins of [0.67, 1.5], the lot-to-lot consistency objective was met.

Secondly, Study **[RSV OA=ADJ-006]** demonstrated the vaccine efficacy of Arexvy in the interim analysis (up to the end of Season 1 in Northern Hemisphere). Seven and 40 cases were reported in the Arexvy and placebo groups, respectively, resulting in an estimated VE of 82.58% with a 2-sided 96.95% CI (57.89%, 94.08%). Because the lower limit of the CI exceeded the pre-defined threshold of 20%, the success criterion for the vaccine efficacy objective was met.

Thirdly, in Study **[RSV OA=ADJ-007]**, the immune response induced by the Arexvy vaccine co-administered with FLU-QIV (Co-Ad group) was non-inferior to that induced by the two vaccines given sequentially (Control group). Specifically, 1 month after Arexvy vaccination, the GMT ratio of RSV-A neutralizing antibodies was 1.27 (95% CI: 1.12, 1.44) between the Control and the Co-Ad groups. In addition, 1 month after FLU-QIV vaccination, the GMT ratio of FLU-QIV A/H3N2, FLU-QIV A/H1N1, FLU-QIV B/Yamagata, FLU-QIV B/Victoria hemagglutination inhibition antibodies in the Control and the Co-Ad groups was 1.17 (95% CI: 1.02, 1.35), 1.22 (95% CI: 1.03, 1.44), 1.17 (95% CI: 1.04, 1.32), and 1.10 (95% CI: 0.95, 1.26), respectively. Because the upper limits of all 95% CIs were below the pre-defined non-inferiority margin of 1.5, the co-primary immunogenicity objectives were met.

Finally, the Study **[RSV OA=ADJ-004]** showed that 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.

In summary, results from the four Phase III clinical studies collectively provide sufficient evidence to support the immunogenicity and efficacy of Arexvy vaccine for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 60 years of age and older.

2.4.2 Safety Results

The most frequently reported solicited AEs were injection site pain, fatigue, myalgia, and headache. Solicited AEs were mostly mild to moderate in severity. In VE study RSV OA=ADJ-006, potential immune-mediated diseases (pIMDs) were reported by 0.3% of

subjects who received Arexvy and 0.3% of subjects who received placebo. There were no notable imbalances regarding incidence between treatment groups. A single case of Guillain-Barré syndrome was reported across clinical studies.

2.5 Bridging Study Evaluation

The subgroup analyses of studies RSV OA=ADJ 006 and RSV OA=ADJ 004 demonstrated that the immune response induced by Arexvy and the safety profile of Arexvy in Asian population were generally consistent with that of non-Asian population. The ethnic difference of vaccine efficacy and safety was expected to be minimal, thus the bridging study could be waived.

2.6 Conclusion

Efficacy and immunogenicity results from the clinical studies are sufficient to support the proposed indication, posology, and co-administration with influenza vaccines. The need for revaccination with a subsequent dose has not yet been established. The safety profile in the target population is acceptable. In conclusion, Arexvy given as active immunization for the prevention of lower respiratory tract disease (LRTD) caused by RSV in adults 60 years of age and older demonstrates a favorable risk benefit profile to recommend regular approval.

3. Post-Marketing Requirements

No post-marketing study was required.