AREXVY

Respiratory Syncytial Virus (RSV) Vaccine (recombinant, AS01$_E$ adjuvanted)

Powder and suspension for suspension for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

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 GlaxoSmithKline proprietary 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.

CLINICAL INFORMATION

Indications

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.

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

Dosage and Administration

Consideration should be given to official vaccine recommendations for immunisation schedules.

Posology

Arexvy is administered as a single dose of 0.5 mL.

The need for revaccination has not been established.

Paediatric population

The safety and efficacy of Arexvy in children have not been established.

Method of Administration

Arexvy is for intramuscular injection only, preferably in the deltoid muscle.

For instructions on reconstitution of the medicinal product before administration, see *Use and Handling*.

Contraindications

Hypersensitivity to the active substances or to any component of the vaccine (see *Qualitative and quantitative composition* and *List of Excipients*).

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.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with the vaccination process itself. It is important that procedures are in place to avoid injury from faints.

In order to improve the traceability of vaccines, the name and the batch number of the administered product should be clearly recorded.

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 immunosuppresive treatment or patients with immunodeficiency may have a reduced immune response to Arexvy.

Interactions

Use with other vaccines

Arexvy can be given concomitantly with inactivated seasonal influenza vaccine *(*see *Pharmacodynamic Effects)*.

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

No data are available for concomitant administration with other vaccines.

Pregnancy and Lactation

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.

Pregnancy

There are no data from the use of Arexvy in pregnant women from clinical trials.

After administration of an investigational unadjuvanted RSV vaccine that contained the same RSVPreF3 antigen as Arexvy to 3,557 pregnant women in a randomized controlled clinical trial, an increase in preterm births was observed compared to placebo (6.8% versus 4.9%, respectively). Currently no conclusion on a causal relationship between administration of unadjuvanted RSVPreF3 and preterm birth can be drawn.

Arexvy is not recommended during pregnancy.

Lactation

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

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. Some of the effects mentioned under *Adverse reactions* (e.g. fatigue) may temporarily affect the ability to drive or use machines.

Adverse Reactions

The safety profile presented below is based on a placebo-controlled Phase III clinical study, RSV-OA=ADJ-006 (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 (ADRs) are listed below by MedDRA system organ class and by frequency.

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <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
Respiratory, thoracic, and mediastinal disorders	Common	rhinorrhea
Gastrointestinal disorders	Uncommon	Nausea, abdominal pain, vomiting
Musculoskeletal and connective tissue disorders	Very common	myalgia, arthralgia
General disorders and administration site conditions	Very common	injection site pain, fatigue
	Common	injection site erythema, injection site swelling, fever, chills
	Uncommon	injection site pruritus
		pain, malaise

Solicited Adverse Reactions

In RSV-OA=ADJ-006 study, a subset of study participants (solicited safety set) was monitored for solicited adverse reactions using standardized paper diary cards during the 4 days (i.e., day of vaccination and the next 3 days) following a dose of Arexvy or placebo; 879 participants received Arexvy and 874 participants received placebo. The other study participants did not prospectively record solicited reactions on a diary card but may have reported them as unsolicited adverse reactions.

The reported frequences of specific solicited local (administration site) and systemic adverse reactions (per participant) are presented in Table 1.

Table 1: Percentage of Participants with Solicited Local Adverse Reactions and Systemic Adverse Reactions within 4 Days of Vaccination in Adults 60 Years of Age and Older (Solicited Safety Set with 4-Day Diary Card)

Local Adverse Reactions	**Arexvy % N = 879**	**Placebo[a] % N = 874**
Pain, Any[b]	60.9	9.3
Pain, Grade 3[b]	1	0
Erythema, >20 mm	7.5	0.8
Erythema, >100 mm	0.2	0
Swelling, >20 mm	5.5	0.6
Swelling, >100 mm	0.2	0
Systemic Adverse Reactions	**N = 879**	**N = 878**
Fatigue, Any[c]	33.6	16.1
Fatigue, Grade 3[c]	1.7	0.5
Myalgia, Any[c]	28.9	8.2

Myalgia, Grade 3[c]	1.4	0.3
Headache, Any[c]	27.2	12.6
Headache, Grade 3[c]	1.3	0
Arthralgia, Any[c]	18.1	6.4
Arthralgia, Grade 3[c]	1.3	0.6
Fever, ≥38.0°C/100.4°F[d]	2.0	0.3
Fever, >39.0°C/102.2°F[d]	0.1	0.1

N = Exposed set for solicited safety set included all participants with at least 1 documented dose.
[a] Placebo was a saline solution.
[b] Any grade pain: Defined as any pain neither interfering with nor preventing normal everyday activities (Grade 1), painful when limb is moved and interferes with everyday activities (Grade 2), or significant pain at rest and prevents normal everyday activities (Grade 3).
[c] Any grade fatigue, myalgia, headache, arthralgia: Defined as event easily tolerated (Grade 1), interfering with normal activity (Grade 2), or preventing normal activity (Grade 3).
[d] Temperature taken by any route (oral, axillary, or tympanic).

In the solicited safety set, the local administration site adverse reactions reported with Arexvy had a median duration of 2 days, and the systemic adverse reactions reported with Arexvy had a median duration ranging between 1 and 2 days.

Unsolicited Adverse Events

In all participants from RSV-OA=ADJ-006 study, unsolicited adverse events were monitored using paper diary cards during the 30-day period following vaccination (day of vaccination and the next 29 days).

Among participants in the solicited safety set, (Arexvy, n = 879 or placebo, n = 878), unsolicited adverse events occurring within 30 days after vaccination were reported in 14.9% and 14.6% of participants who received Arexvy and placebo, respectively.

In the exposed set, 24,966 participants 60 years of age and older, received at least 1 dose of Arexvy (n = 12,467) or placebo (n = 12,499). Unsolicited adverse events occurring within 30 days of vaccination were reported in 33.0% and 17.8% of participants, respectively. The higher frequency of reported unsolicited adverse events among participants who received Arexvy, compared to participants who received placebo, was primarily attributed to events that are consistent with adverse reactions solicited among participants in the reactogenicity subset.

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. There were no other notable patterns or numerical imbalances between groups for specific categories of unsolicited adverse events.

Serious Adverse Events

In RSV-OA=ADJ-006 study, participants were monitored for all serious adverse events (SAEs) that occured during the 6-month period following administration of Arexvy (n = 12,467) or placebo (n = 12,499). SAEs with onset within 6 months following vaccination

were reported at similar rates in participants who received Arexvy (4.2%) or placebo (4.0%). Serious events of atrial fibrillation were reported in 13 participants who received Arexvy and 15 participants who received placebo within 6 months after vaccination.

Deaths

From vaccination through the first analysis of the ongoing RSV-OA=ADJ-006 study, adverse events leading to death were reported for 49 participants (0.4%) who received Arexvy (n = 12,467) and 58 participants (0.5%) who received placebo (n = 12,499). Based on available information, there is no evidence of causal relationship to Arexvy. Causes of death among participants were consistent with those generally reported in adult and elderly populations.

Potential Immune-Mediated Diseases

In RSV-OA=ADJ-006 study, participants were monitored for all potential immune-mediated diseases (pIMDs) that occurred during the 6-month period following administration of Arexvy (n = 12,467) or placebo (n = 12,499). New onset pIMDs or exacerbation of existing pIMDs within 6 months following vaccination were reported for 0.3% of participants who received Arexvy and 0.3% of participants who received placebo. There were no notable imbalances between study groups in individual pIMDs reported.

Serious Adverse Events Reported From Other Studies

RSV-OA=ADJ-004: Guillain-Barré syndrome beginning 9 days after Arexvy vaccination was reported in a participant enrolled in a study site in Japan.

Overdosage

Insufficient data are available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code - J07BX05, respiratory syncytial virus vaccines

Mechanism of action

The risk of developing RSV-associated LRTD increases with age and with presence of underlying comorbidities. 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 (see *Immunogenicity of Arexvy*).

In a Phase I/II clinical trial, formulation adjuvanted with AS01$_E$ showed the ability to restore RSVPreF3-specific CD4+ T cells in adults 60 to 80 years of age to levels similar to those observed in young adults, despite lower baseline levels in the older adults.

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.

Pharmacodynamic effects

Efficacy of Arexvy

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

The study excluded participants who were immunocompromised. Participants with pre-existing, chronic, stable disease such as diabetes, hypertension, or cardiac disease were allowed to participate in the study if considered by the investigator as medically stable at the time of vaccination.

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 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 2). High 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 2. Efficacy Analysis: First RSV-associated LRTD Overall, by Age and co-morbidity subgroups in RSV-OA=ADJ-006 (modified Exposed Set)

Subgroup	Arexvy			Placebo			% Efficacy (CI)[a]
	N	n	Incidence Rate per 1,000 Person-Years	N	n	Incidence Rate per 1,000 Person-Years	
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).

Efficacy Against Severe RSV-associated LRTD and RSV-associated ARI

In study RSV-OA=ADJ-006, severe RSV-associated LRTD was defined as RT-PCR confirmed RSV-associated LRTD with at least 2 lower respiratory signs, or as an RT-PCR confirmed RSV-associated LRTD episode assessed as 'severe' by the investigator. One case of severe RSV-associated LRTD in the Arexvy group and 17 cases in the placebo group were reported, amongst which 2 cases required supportive therapy. Compared with placebo, Arexvy significantly reduced the risk of developing severe RSV-associated LRTD by 94.10 % (95% CI [62.37, 99.86]) in participants 60 years of age and older.

Acute respiratory illness (ARI) was defined by the presence of at least 2 respiratory symptoms/signs for at least 24 hours, or at least 1 respiratory symptom/sign + 1 systemic symptom/sign (fever or feverishness, fatigue, body aches, headache, decreased appetite) for at least 24 hours. Arexvy significantly reduced the risk of developing confirmed RSV-associated ARI in adults ≥ 60 years of age by 71.71% (95% CI [56.23, 82.27]).

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 RSV-A and RSV-B neutralizing titers 1 month post-immunisation were 10.5-fold (95% CI [9.9, 11.2]) and 7.8-fold (95% CI [7.4, 8.3]), 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.

Immunogenicity following concomitant vaccination

In an open-label Phase III clinical study, participants 60 years of age and older received 1 dose of Arexvy and inactivated unadjuvanted 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 as the 2-sided 95% confidence interval upper limits on the group geometric mean titer ratios were below 1.50 for the RSV-A neutralizing antibodies and haemagglutinin inhibition antibodies against the strains Flu A/Hong Kong/H3N2, Flu A/Victoria/H1N1, Flu B/Phuket/Yamagata, and Flu B/Washington/Victoria. However, numerically lower RSV A and B neutralizing titres and numerically lower influenza A and B haemagglutination inhibition titres were observed when Arexvy and inactivated seasonal influenza vaccine were co-administered than when they were administered separately. The clinical relevance of this finding is unknown.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical studies

See *Pharmacodynamic Effects*.

Non-Clinical Information

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

PHARMACEUTICAL INFORMATION

List of Excipients

Powder (RSVPreF3 antigen):

Trehalose dihydrate
Polysorbate 80
Potassium dihydrogen phosphate
Dipotassium phosphate

Suspension (AS01$_E$ Adjuvant System):

Dioleoyl phosphatidylcholine
Cholesterol
Sodium chloride
Disodium phosphate, anhydrous
Potassium dihydrogen phosphate
Water for injections

Shelf Life

The expiry date is indicated on the packaging.

Storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze. Discard if the vial has been frozen.

Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see *Use and Handling*.

The storage conditions are detailed on the packaging.

Nature and Contents of Container

- Powder for 1 dose in a vial (type I glass) with stopper (butyl rubber).
- Suspension for 1 dose in a vial (type I glass) with a stopper (butyl rubber).

Arexvy is available in a pack size of 1 vial of powder plus 1 vial of suspension or in a pack size of 10 vials of powder plus 10 vials of suspension.

Incompatibilities

Arexvy must not be mixed with other medicinal products.

Use and 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.

How to prepare Arexvy:

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°C – 8°C) or at room temperature up to 25°C. If not used within 4 hours it should be discarded.

Before administration:

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.

Not all presentations are available in every country.

Version number: GDS02/IPI01(SI)

Date of issue: 09 June 2023

Manufacturer responsible for batch release:

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