



**Pharmacovigilance Plan Review Memorandum
AREXVY™ (BLA 125775/0)**

To: Santosh Nanda, DVM PhD MBA
Chair, BLA Review Committee,
Regulatory Review Branch 3 (RRB 3) / Division of Vaccines
and Related Products Applications (DVRPA) / Office of
Vaccines Research and Review (OVRR)

From: Firoozeh Alvandi, MD
Medical Officer, Pharmacovigilance Branch 1 (PB1) /
Division of Pharmacovigilance (DPV) / Office of Biostatistics
and Pharmacovigilance (OBPV)

Through: Adamma Mba-Jonas, MD, MPH
Branch Chief, PB1/DPV/OBPV

Narayan Nair, MD
Division Director, DPV/OBPV

STN: Original BLA 125775/0

Product: Proposed brand name: AREXVY
(Respiratory Syncytial Virus Vaccine Recombinant, A
djuvanted suspension for intramuscular injection)

Proposed indication: Active immunization for the prevention of lower respiratory
tract disease (LRTD) caused by respiratory syncytial virus
(RSV) in adults 60 years of age and older

BLA Submission Date: September 02, 2022

Sponsor: GlaxoSmithKline Biological

Action Due Date: May 03, 2023

1. OBJECTIVE

This memo reviews the adequacy of the pharmacovigilance plan submitted by GlaxoSmithKline (GSK) Biologicals for original BLA 125775/0 for AREXVY™ Respiratory Syncytial Virus, Recombinant (pre-fusion F protein; CHO cells) Vaccine with AS01E Adjuvant, for the indication of active immunization for the prevention of respiratory syncytial virus (RSV) disease caused by subtypes A and B in adults 60 years of age and older.

2. INTRODUCTION

2.1 Background

RSV is considered the third most frequent cause) of medically significant respiratory tract disease in adults, after influenza and rhinovirus, and is estimated to cause 60,000-160,000 hospitalizations and 6,000-10,000 annual deaths in US adults older than 65 years of age.^{1,2} RSV annual attack rate in adults older than 60 years of age is estimated as between 2% to 10% in the community and as between 5% to 10% in older adults in settings such as care facilities³; rates increase with increasing age and in patients with comorbidities such as chronic obstructive pulmonary disease, asthma, chronic heart failure.^{2,4,5}

RSV infection does not confer long-term immunity and thus re-infection with RSV can occur throughout life and in all age groups^{6,7}. Currently there is no vaccine and no specific treatment for RSV. Based on this the sponsor considers that there is unmet medical need and received priority review.

2.2 Product information

The product AREXVY [RSV PreFusion protein 3 older adult vaccine (RSVPreF3 OA)] is a recombinant RSV fusion protein vaccine consisting of RSVPreF3 antigen and the AS01E adjuvant system. The F protein is a major surface antigen of the virus and is necessary for viral entry and cell fusion process.

RSVPreF3 OA (older age) vaccine consists of a freeze-dried preparation containing RSVPreF3 antigen drug substance and excipients, filled into a 3 mL glass vial for Reconstitution prior to administration, with AS01E. The reconstituted suspension for

¹ Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005;352:1749–59.

² Centers for Disease Control and Prevention (CDC): <https://www.cdc.gov/rsv/high-risk/older-adults.html> (accessed March 10, 2023)

³ Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized problem. *Drugs Aging*. 2015 Apr;32(4):261-9.

⁴ Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory Syncytial Virus Infection among Hospitalized Adults, 2017-2020. *Clin Infect Dis*. 2022; 23;74(6):1004-11.

⁵ Prasad N, Walker TA, Waite B, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Adults With Chronic Medical Conditions. *Clin Infect Dis*. 2021;73(1):e158-e163.

⁶ Simoes EA. Respiratory syncytial virus infection. *Lancet*. 1999;354:847-52.

⁷ Krilov LR. Respiratory syncytial virus disease: update on treatment and prevention. *Expert Rev Anti Infect Ther*. 2011;9:27-32.

injection is to be administered intramuscularly in patients age 60 and older. The vaccine is expected to boost or induce *de novo* induction of RSV-specific circulating T cell response to enhance viral clearance and to reduce disease severity, by boosting neutralizing antibody (NAb) response to prevent RSV infection and enhance the inhibition of viral replication in this patient population. Given the degree of amino acid sequence homology for the F protein between the 2 subtypes of RSV (RSV-A and RSV-B), the vaccine is expected to induce cross neutralizing antibody.

2.3 Regulatory History

On September 02, 2022, the sponsor submitted BLA STN 125775 in support of AREXVY™ Respiratory Syncytial Virus, Recombinant (pre-fusion F protein; CHO cells) Vaccine with AS01E Adjuvant, for immunization of adults age 60 and older.

3. MATERIALS REVIEWED

Materials reviewed for this pharmacovigilance plan assessment are listed below:

Original BLA submission STN 125775/0

- Module 1.16.1: Pharmacovigilance Plan/Risk Management Plans (version 1 dated August 11, 2023)
- Module 1.14.1.2: Draft Labeling (annotated draft labeling)
- Module 2.5: Clinical Overview.
- Module 2.7.4: Summary of Clinical Safety
- Module 5 Clinical Study Reports:
 - Module 5.3.5.1: Study Reports of Controlled Clinical Studies
 - Clinical trial RSV OA=ADJ-006 study report body
 - Clinical trial RSV OA=ADJ-007 study report body
 - Module 5.3.5.2: Study Reports of Uncontrolled Clinical Studies
 - Clinical trial RSV OA=ADJ-004 study report body
 - Module 16.1.1: Study 006 Protocol
- Module 1.11.3 Response (dated November 11, 2022) to IR (dated November 09, 2022) STN 125775/0/06
- Module 1.11.3 Response (dated February 17, 2023) to IR (dated February 09, 2023) STN 125775/0/20
- Module 1.11.3 Response (dated February 23, 2023) to IR (dated February 16, 2023) STN 125775/0/21
- Module 5.3.5.3: Safety Update (dated December 19, 2022) STN 125775/0/10
- IND 18540/209: Response (proposed postmarketing study) dated March 17, 2023, to FDA's February 09, 2023 request for postmarketing study to evaluate risk of pIMDs
- Module 1.11.3: Response dated March 31, 2023 to PMR notification/PMC request dated March 22, 2023 (including atrial fibrillation questionnaire) STN 125775/0/33
- Module 1.11.3 Response (dated April 17, 2023) to IR (dated February 16, 2023) STN 125775/0/39
- Module 1.11.3 Response (dated April 20, 2023) to IR (dated April 19, 2023) STN 125775/0/41
- Literature review as listed in foot notes

4. CLINICAL SAFETY DATABASE

The safety data submitted in support of this BLA by the sponsor is based primarily on the pivotal placebo-controlled efficacy study RSV OA=ADJ-006 (Study 006), with supporting data from immunogenicity study RSV OA=ADJ-004 (Study 004), and inactivated seasonal quadrivalent influenza vaccine (FLU-QIV (Fluarix Quadrivalent or Fluarix Tetra) coadministration study RSV OA=ADJ-007 (Study 007).

4.1 RSV OA=ADJ-006 (Study 006)

RSV OA=ADJ-006 (Study 006) is an ongoing pivotal phase 3, randomized, placebo (saline) controlled, observer-blind, multi-country efficacy clinical trial. Available data consists of interim data evaluating the efficacy and safety of investigational RSVPreF3 OA vaccine (AREXVY) administered as a single dose in adults ≥ 60 years of age.

Study title: *“A Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of GSK’s RSVPreF3 OA investigational vaccine in adults aged 60 years and above”* (referred to henceforth as study 006).

Study duration: The study was initiated on May 25, 2021, and was ongoing at the time of submission of the BLA. Study duration is anticipated to be 2.5-3 years. Data lock for safety analysis was April 30, 2022.

Key inclusion criteria:

- Males and females age ≥ 60 years of age at the time of consent, including those with stable chronic medical conditions, and those taking inhaled and topical steroids.

Key exclusion criteria:

- Confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy
- Recurrent or uncontrolled neurological disorders or seizures
- Known hypersensitivity to any component of the vaccine
- Chronic administration (more than total of 14 consecutive days) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the first study vaccine administration or planned administration during the study period, including prednisone ≥ 20 mg/day, or equivalent (inhaled and topical steroids are allowed).
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g. infliximab).

Safety endpoints:

Safety is a secondary objective in this efficacy study, and endpoints are listed below:

- Occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after each vaccination (day of vaccination (day 1) and an additional 3 days afterwards)

- Occurrence of unsolicited adverse events (AEs) assessed for 30 days post vaccination (day 1 and for an additional 29 days afterwards)
- Occurrence of all serious adverse events (SAEs) and potential immune mediated diseases (pIMDs) for up to 6 months after vaccination (*see appendix for list of pIMDs)
- Occurrence of SAEs and potential immune-mediated diseases (pIMDs) related to vaccination from day 1 up to end of study
- Occurrence of any fatal SAEs from day 1 up to end of study,
- Occurrence, intensity, and duration of AEs/SAEs leading to discontinuation of study.

Relative risks and confidence intervals for occurrence of AEs were calculated. Safety data analyses were otherwise descriptive.

Safety Review Study 006

The safety population associated with this study consists of 24,966 participants, including 12,467 participants who received at least 1 dose of RSVPreF3 OA (henceforth referred to as RSVPreF3 or AREXVY group), and 12,499 participants in the placebo (saline solution) group.

The solicited safety set was described in the submission as consisting of a subset of 879 participants in the RSVPreF3 group and 878 participants in the placebo group) who recorded adverse events for the first 4 days (day of vaccination and 3 days thereafter) on a diary card. Primary analyses of solicited adverse events were performed on this set. The remainder of study participants reported AEs as unsolicited adverse events. An IR was submitted to the sponsor on November 09, 2022, requesting clarification regarding the method used for the selection of the solicited subset. In their response, the sponsor indicated that the solicited safety set was developed by randomly allocating the first participants at each site to the either the solicited placebo group or the solicited RSVPreF3 group, until a predefined target number of patients within each age group (60-69, 70-79, and ages 80 and older) was reached. Further, per the sponsor, “*The countries (sites) that participated in the subset were selected to allow a meaningful representation for each region, proportionally to the total sample size expected to be enrolled in that region (actual subset distribution in study RSV OA=ADJ-006),*” which was approximately 44% for North America (including US, Canada and Mexico), 36% for European Union, 10% for Asia/Pacific, and 10% for and Southern Hemisphere.

Median safety followup time from vaccination administration (day 1) to the DLP was 7.8 months in the vaccine and the placebo groups.

Treatment Emergent Adverse Events (TEAEs)

Adverse events were reported in 71.9% (n= 632) participants of the safety solicited set within 4 days post RSVPreF3 administration, and in 27.9% (n=245) participants within 4 days of placebo administration; confidence intervals for these values did not overlap. Among the solicited AEs, administration site events were reported in 62.2% (n=547) of solicited safety set participants in the RSVPreF3 group and in 10.0% (n=88) of participants in the placebo group, The most commonly reported administration site

event in the solicited safety set within 4 days post vaccination was injection site pain, reported in 60.9% (n=535) participants in the RSVPreF3 group and in 9.3% (n=81) participants in the placebo group. Additional commonly reported AEs (>5%) were erythema which was reported in 7.1% (n=66) participants in the RSVPreF3 group and in 0.8% (n=7) of the placebo group, and swelling which was reported in 5.5% (n=48) participants in the RSVPreF3 group and in 0.6% (n=5) participants in the placebo group. Confidence interval values did not overlap for any of these AEs.

Among solicited AEs, systemic adverse events within 4 days post vaccination were reported in 49.4% (n=434) of the solicited safety set participants in the RSVPreF3 group and in 23.2% (n=204) of participants in the placebo group. The most commonly (>5%) reported systemic solicited AEs were fatigue, which was reported in 33.6% (n=295) of RSVPreF3 group and in 16.1% (n=141) of placebo group participants, myalgia, which was reported in 28.9% (n=254) of RSVPreF3 group and in 8.2% (n=72) of placebo group participants, headache, which was reported in 27.2% (n=239) of RSVPreF3 group and 12.6% (n=111) of placebo group participants, and arthralgia, which was reported in 18.1% (n=159) of RSVPreF3 group and in 6.4% (n=56) of placebo group participants. Confidence intervals did not overlap for any of these AEs when comparing the two groups.

Unsolicited adverse events occurring in the exposed set within 30 days of vaccination were reported in 33.0% (n=4117) of participants in the RSVPreF3 group and in 17.8% (n=2229) of participants in the placebo group; confidence interval values did not overlap. The most commonly reported unsolicited AE was injection site pain, reported in 15.8% (n=1967) participants in the RSVPreF3 group and in 1.4% (n=174) participants in the placebo group. The other most frequently reported AEs (>2%) were headache, reported in 5.2% (n=651) participants in the RSVPreF3 group and in 2.9% (n=362) participants in the placebo group and fatigue, which was reported in 2.6% (n=318) participants in the RSVPreF3 group and in 1.1% (n=133) participants in the placebo group; confidence interval values did not overlap for these events.

Of note, a numerical imbalance was noted in the number of atrial fibrillation events reported within 30 days of vaccination. Ten participants in the RSVPreF3 group reported this AE, compared to 4 participants in the placebo group. The relative risk of 2.51 was not statistically significant. Seven cases in the RSVPreF3 group were SAEs, compared to 1 case in the placebo group. Two cases in RSVPreF3 group were new onset, compared to 1 in placebo group. All atrial fibrillation occurred in subjects with predisposing/concomitant medical conditions and risk factors.

Reviewer comment: Although administration site and other solicited adverse events occurred more commonly in the RSVPreF3 group, this is expected given the immunologically active components in the vaccine. No concerning safety issues were identified in the safety data for the solicited safety set. Although the number of cases of atrial fibrillation observed during the trial within the first 30 days was small, the numerical imbalance of cases of atrial fibrillation observed

between recipients of RSVPreF3 and recipients of placebo is somewhat concerning.

Serious Adverse events (SAEs):

522 participants (4.2%) in the RSVPreF3 group and 506 participants (4.0%) in the placebo group reported at least 1 SAE with onset within 6 months following vaccination; confidence intervals for these values overlapped. The most common SOC associated with SAEs seen during the study were:

- a) infections and infestations, reported in 0.9% (n=107) of RSVPreF3 and in 0.9% (n=115) of the placebo group. The most commonly experienced SAEs within this SOC were COVID 19 infections reported in 0.2% (n=31) participants in each group;
- b) cardiac disorders, reported in 0.7% (n=91) RSVPreF3 and in 0.7% (n=86) of the placebo group. The most commonly experienced SAEs within this SOC were ischemic coronary artery disorders reported in 0.2% (n=30) participants in the RSVPreF3 group and in 0.3% (n=36) in the placebo group;
- c) nervous system disorders, reported in 0.5% (n=60) RSVPreF3 and 0.5% (n=65) of the placebo group. The most commonly reported SAEs within this SOC, experienced by 0.2% of participants in each group, were central nervous system hemorrhages and cerebrovascular accidents, reported by 24 participants in the RSVPreF3 group and 29 participants in the placebo group.

pIMDs:

A pIMD event was the new onset of a pIMD, or exacerbation of preexisting potential immune-mediated disease. As of 6 months post-vaccination, a least 1 pIMD was experienced by 40 participants (0.3%) in the RSVPreF3 group and 34 participants (0.3%) in the placebo group during the study; the relative risk of 1.18 was not statistically significant. The most commonly reported pIMD was gout, experienced by 11 individuals in the vaccine group and 10 individuals in the control group. No individual pIMD was found to occur statistically significantly more frequently in the vaccine group.

Reviewer comment: In the 6 months following vaccination, a numerical imbalance is observed in the number of pIMDs occurring between the study arms; this finding is potentially concerning given the adjuvant that makes up part of the study vaccine.

Deaths:

Death occurring within 6 months of vaccination was reported in 39 participants (0.3%) in the RSVPreF3 group and in 46 placebo recipients (0.4%). The most common SOC for causes of death ($\geq 0.1\%$) were cardiac disorders reported in 0.1% of participants (n=11) in the RSVPreF3 group and in 0.1% (n=16) of participants in the placebo group), and infections and infestations reported in 0.1% of participants (n=11) in the RSVPreF3 group and in 0.1% of participants (n=10) in the placebo group. The most common cause of death in both groups was Coronavirus infection, reported in 0.1% (n=8) in the RSVPreF3 group and in "0.0%" (n=2) in the placebo group). Confidence interval values overlapped for these AEs.

Reviewer comment: Evaluation of cases of death do not suggest safety issues related to the vaccine.

Safety Update:

The sponsor submitted a safety update on December 19, 2022 for pivotal study 006 which provided additional safety information as of DLP of September 30, 2022. This submission provided data for study subjects over a median safety followup time of 12 months after 1 dose of the product RSVPreF3. Key safety data from that update is summarized below:

- 1) As of the DLP of September 30, 2022, there were a total of 14 atrial fibrillation events in the RSVPreF3 group and 16 in the placebo group; the data no longer demonstrates the numerical imbalance that was observed within 30 days of vaccination.

As of the September 30, 2022 DLP, additional pIMDs reported since the April 30, 2022 DLP included gout (1 event each in the RSVPreF3 group and the placebo group), polymyalgia rheumatica (3 events in the RSVPreF3 group and 1 in the placebo group), palindromic rheumatism (1 event in the placebo group), psoriasis (1 event in the RSVPreF3 group), pericarditis (1 event in the RSVPreF3 group), ulcerative colitis (1 event each in the RSVPreF3 group and the placebo group), myasthenia gravis (1 event in the RSVPreF3 group), thrombocytopenia (1 event in the RSVPreF3 group in a 72 year old male later diagnosed with lymphoma) and immune thrombocytopenia (1 event in the placebo group).

As of the DLP of September 30, 2022, or up to the second dose administration, 88 (0.7%) participants died in the RSVPreF3 group, and 95 (0.8%) participants died in the placebo group. This represents an additional 39 deaths in the RSVPreF3 and an additional 37 deaths in the placebo group since the initial DLP of April 30, 2022. Causes of death were consistent with and similar to the findings as of the initial (April 30, 2022) DLP and raise no new safety concerns.

Reviewer comment: Review of the safety update for this trial demonstrates similar rates of atrial fibrillation between control and vaccine groups when followup was extended to approximately 1 year. There were no new/additional case(s) of GBS or ADEM. The review of the followup/safety update information did not demonstrate new safety concerns.

4.2 RSV OA=ADJ-007 (Study 007)

RSV OA=ADJ-007 (Study 007) was a phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above. The Co-Ad group consisted of participants who received a single dose of RSVPreF3 OA investigational vaccine and a single dose of

Fluarix Quadrivalent vaccine ("FLU vaccine") at visit 1 (Day 1). The control group received FLU vaccine at visit 1 and RSVPreF3 at visit 2 (Day 31).

Study duration: The study was initiated on April 27, 2021 and was completed on February 08, 2022. Data lock point was November 03, 2021. Final report was dated August 02, 2022.

Key inclusion criteria:

- Males and females age ≥ 60 years of age at the time of consent, including those with stable chronic medical conditions

Key exclusion criteria:

- Confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy
- Recurrent or uncontrolled neurological disorders or seizures
- Known hypersensitivity to any component of the vaccine
- History of GBS, anaphylaxis, febrile seizures, Bell's palsy and narcolepsy
- Administration of immunoglobulins and/or any blood components or plasma derivatives during the period starting 90 days before the first study vaccine administration or planned administration during the study period
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g. infliximab)
- Chronic administration (more than total of 14 consecutive days) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the first study vaccine administration or planned administration during the study period, including prednisone ≥ 20 mg/day, or equivalent (inhaled and topical steroids are allowed)
- Administration of an influenza vaccine during the 6 months preceding the study FLU vaccine administration

Safety endpoints:

Safety is a secondary objective in this efficacy study. The safety endpoints were safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and FLU vaccine, co-administered or administered alone, including:

- Percentage of participants reporting each solicited event with onset within 4 days after vaccine administration (the day of vaccination and 3 subsequent days)
- Percentage of participants reporting unsolicited adverse events (pIMD, non-serious AE or serious AE) within 30 days after vaccine administration (the day of vaccination and 29 subsequent days)
- Percentage of participants reporting SAEs after vaccine administration (Day 1) up to study end (6 months after last vaccination)
- Percentage of participants reporting pIMDs after vaccine administration (Day 1) up to study end (6 months after last vaccination)

Safety Review Study 007

The safety population consists of 885 participants, with 442 participants in the Co-Ad group and 443 participants in the control group.

Treatment Emergent Adverse Events (TEAEs)

Solicited AEs in the four days following vaccination were reported in 279 (63.7%) of Co-Ad group participants and in 248 (56.6%) of control group participants; confidence intervals for those estimates overlap.

Solicited systemic administration site events within 4 days post vaccination were reported in 234 (53.4%) participants in the Co-Ad group and in 195 (44.5%) participants in the control group. Confidence intervals for these values overlapped.

Solicited systemic adverse events were reported within 4 days post vaccination in 176 (40.2%) of Co-Ad group participants and 183 (41.8%) participants in the control group; confidence intervals for these values overlap. The most commonly (>10%) reported solicited systemic events were fatigue (98 participants, 22.4% of the Co-Ad group and 105 participants, 24.0% in the control group), myalgia (97 participants, 22.1% in the Co-Ad group and 100 participants, 22.8% in the control group), headache (95 participants, 21.7% in the Co-Ad group and 98 participants, 22.4% in the control group), and arthralgia (17 participants, 16.2% in the Co-Ad group and 58 participants, 13.2% in the control group). Confidence interval for these values overlapped.

At least 1 unsolicited AE was reported within 30 days of vaccination by 18.8% of participants (n=83) in the Co-Ad group and 23.7% of participants (n=105) in the control group; confidence intervals for these values overlap. The most common ($\geq 2\%$) unsolicited AEs in the Co-Ad group were headache (2.3% of participants, n=10, compared to 2.0% in the control group, n=9), and cough (2.0% of participants, n=9, compared to 0.7% of participants in the control group, n=3); confidence intervals for these values overlapped.

SAEs:

At least 1 SAE was reported in 15 (3.4%) participants in the Co-Ad group and 20 (4.5%) participants in the control group. The most common SAE in both the Co-Ad group and the control group was COVID-19 infection, experienced by 4 participants (0.9%) and 6 participants (1.4%) in the control group. Confidence intervals between the two groups overlapped for all SAEs reported.

pIMDs:

At least 1 pIMD was reported in 5 (1.1%) participants in the Co-Ad group and in 1 (0.2%) participant in the control group. The single pIMD in the control group was a case of gout. Three (0.7%) cases of gout were reported in the Co-Ad group; one participant had preexisting gout, the case narrative for the second participant did not clearly specify whether there was preexisting disease, and no narrative was provided for the third participant. There were 2 cases of acute disseminated encephalomyelitis reported in the Co-Ad group (0.5%). Of note, there were no cases of ADEM in the control group.

These cases were reported by the same investigator at the same investigational site and are described below:

- 1) 71 year old male who exhibited signs/symptoms of ADEM 7 days post vaccine coadministration. CT scan was performed which demonstrated “2 previous strokes associated with Wallerian Demyelination.” No MRI was performed. Brighton Collaboration Level 3 ADEM was diagnosed. The participant died 22 days post vaccine administration. The sponsor considered the possibility that white matter atrophy may be associated with CT findings of chronic stage (months to years) of Wallerian Demyelination. Per the sponsor, differential diagnoses such as HIV, tuberculosis, vasculitis, ischemic stroke, lymphoma, sarcoidosis, disruption of the blood brain barrier, or venous thrombosis were not investigated. The sponsor considered the case as not having sufficient information to meet ADEM case definition.
- 2) 71 year old female with history of hypertension and hyperlipidemia who presented with double vision, headache, confusion, shaking hands and gait ataxia 22 days post vaccine coadministration. Participant was diagnosed with Brighton Collaboration Level 3 ADEM based on symptomology. No MRI was performed. Per the sponsor, differential diagnoses such as HIV, tuberculosis, vasculitis, ischemic stroke, lymphoma, sarcoidosis, disruption of the blood brain barrier, or venous thrombosis were not investigated. The sponsor considered the case as not having sufficient information to meet ADEM case definition.

Reviewer comment: 2 cases of ADEM occurred among 890 vaccinees in the vaccine coadministration group, while there were no cases of ADEM in the control group. This numerical imbalance is potentially concerning given the adjuvant that makes up part of the study vaccine. The imbalance may suggest that, administered concomitantly with another vaccine, the vaccine could increase the risk of immune-mediated disease.

Death: There were 4 (0.9%) deaths reported in participants in the Co-Ad group and 8 (1.8%) in participants in the control group. The most frequent cause of death was COVID 19 virus infection (2 participants in the Co-Ad group and 3 participants in the control group). Other causes of death in the Co-Ad group included acute disseminated encephalomyelitis (case described above), and 1 case of congestive heart failure (a 67 year old male with diabetes who developed congestive heart failure and died 116 days post Co-Ad vaccination; cause of death was reported as “natural causes”).

4.3 RSV OA=ADJ-004 (Study 004)

RSV OA=ADJ-004 is a phase 3, randomized, open-label, multi-country study 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 was conducted in 3 parallel groups in a 3:1:1 ratio as follows: 1) RSV annual group, in which participants received the first dose (Dose 1) at Day 1, followed by revaccination doses at 12 months post-Dose 1 and at 24 months post-Dose 1; 2) RSV flexible revaccination group, in which participants received the first dose (Dose 1) at Day 1, with a revaccination dose scheduled for whenever a

revaccination would be needed, based on immunogenicity data from this study and efficacy results from study RSV OA=ADJ-006 study (discussed above); and 3) RSV 1 dose group, in which participants received a single dose (Dose 1) at Day 1.

Study duration: The study was initiated on February 15, 2021, and 6 month analysis was completed on December 12, 2021. Data lock point was February 11, 2022. Final report was dated August 02, 2022. Duration of follow-up for each participant will be 36 months.

Key inclusion criteria:

- Males and females age ≥ 60 years of age at the time of consent, including those with stable chronic medical conditions

Key exclusion criteria:

- Confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy
- Recurrent or uncontrolled neurological disorders or seizures
- Known hypersensitivity to any component of the vaccine
- Hypersensitivity to latex
- Administration of immunoglobulins and/or any blood components or plasma derivatives during the period starting 90 days before the first study vaccine administration or planned administration during the study period
- Receipt or planned receipt of drug, vaccine or medical device for the period beginning 30 days before study participation
- Chronic administration (more than total of 14 consecutive days) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the first study vaccine administration or planned administration during the study period, including prednisone ≥ 20 mg/day, or equivalent (inhaled and topical steroids are allowed)
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g. infliximab)

Safety endpoints:

Safety is a secondary objective of the study. Endpoints of the study are listed below:

- 1) Occurrence, intensity and duration of each solicited administration site and systemic event during a 4-day follow-up period (on the day of vaccination and 3 subsequent days) after each vaccination
- 2) Occurrence of any unsolicited AE during a 30-day follow-up period (on the day of vaccination and 29 subsequent days) after each vaccination
- 3) Occurrence of all SAEs and pIMDs up to 6 months after each vaccination
- 4) Occurrence of fatal SAEs, related SAEs and related pIMDs from first vaccination (Day 1) up to study end (Month 36)

The safety data analyses were descriptive.

Safety Review Study 004

The safety population consisted of 1,653 participants who received at least 1 dose of study product, with 993 participants in RSV annual group, 329 participants in the RSV flexible revaccination group, and 331 participants in the RSV 1 dose group.

Treatment Emergent Adverse Events (TEAEs):

Solicited AEs were reported in 73.9% (n=1217) of participants within 4 day post vaccination. Solicited administration site adverse events within 4 days posts vaccination were reported in 62.2% (n=1024) of participants. The most commonly (>5%) solicited administration site adverse events reported within 4 days following vaccination were administration site pain, reported by 60.5% of participants (n=996), erythema, which was reported in 9.7% (n=159), and swelling which was reported in 7.5% (n=124).

Solicited systemic adverse events within 4 days posts vaccination were reported in 49.5% (n=815) of participants. The most commonly (>10%) solicited systemic adverse event reported within 4 days following vaccination were myalgia, which was reported by 33.5% of participants (n=551), fatigue, which was reported by 31.4% (n=517), headache which was reported by 20.4% (n=336), and arthralgia which was reported by 15.5% (n=255) of participants.

At least 1 unsolicited AE was reported in 212 (12.8%) of participants within 30 days following vaccination, with the most common (>1%) being headache (1.1%, n=18).

SAEs:

Within the 6 months following vaccination, there were 65 participants (3.9%) who reported at least 1 SAE, with the most common SAE reported being atrial fibrillation reported in 5 (0.3%) participants. Other SAEs reported in more than 1 participant were coronary artery disease reported in 4 participants (0.2%), myocardial infarction reported in 4 participants (0.2%), and COVID-19 reported in 4 participants (0.2%). Of note, there was also a single case of GBS, discussed further below.

pIMDs:

There were 7 participants (0.4%) who reported at least 1 pIMD including rheumatoid arthritis (0.2%, n=2), polyneuropathy in malignancy (0.1%, n=1), microscopic colitis (0.1%, n=1), gout (0.1%, n=1), lichen planus (0.1%, n=1), and Guillain-Barre Syndrome (GBS) (0.1%, n=1). The single case of GBS occurred in a 78 year old female who experienced lower limb weakness 9 days post vaccination with RSVPreF3, and developed difficulty walking, upper limb weakness, and respiratory difficulty due to respiratory muscle weakness. The patient was hospitalized and found to have a normal MRI but positive laboratory test for ganglioside (GM1-IgG) immunoglobulins. The patient was diagnosed with Brighton Collaboration Level 3 GBS. She was treated with IVIG and recovered 6 months post vaccination.

Reviewer comment: GBS is of particular concern given the use of an adjuvant (AS01_E) similar to one that has been previously associated with this condition (AS01_B). AS01_B is used in Shingrix vaccine. Data from a postmarket observational study suggested an increased risk of GBS within 42 days post

vaccination with Shingrix, and it is suspected that the association between GBS and the vaccine may be due to the immunostimulating capabilities of the AS01_B adjuvant. GBS was added to the Warnings and Precautions section of the Shingrix label in March of 2021,^{8,9}.

The single case of GBS occurred among 1653 vaccinees in the RVSPref3 vaccine recipients in study 004, while there was no case of GBS in any of the placebo/control groups in other studies submitted in support of this BLA, representing a numerical imbalance for this AE.

Deaths: There were a total of 4 deaths (0.2%) within 6 months of vaccination. Deaths were due to COVID 19 pneumonia (35 days post vaccination in a 71 year old male), “natural causes” (79 days post vaccination in a 68 year old male with hypertension, obesity, hyperlipidemia, and diabetes), myocardial infarction, prostate cancer, and cardiac arrest (302 days post vaccination in a 90 year old male with preexisting coronary disease), and ‘cause not specified’ (150 days post vaccination in a 61 year old male for whom no additional medical history/information/autopsy information was available).

Reviewer comment: Review of available information in case narratives did not identify evidence suggestive of a causal relationship between vaccination and death.

5. POSTMARKET DATA

There are no postmarket data available as AREXVY has not been licensed/marketed in any country.

6. PHARMCOVIGILANCE PLAN

6.1 Summary of Sponsor-proposed Pharmacovigilance Plan

The sponsor proposed routine pharmacovigilance, including review and reporting of adverse events in the postmarket setting, periodic aggregate safety reports, literature review, custom MedDRA query for pIMD signal detection, and use of targeted followup questionnaires (TFUQs) specifically developed for AREXVY “to ensure the collection of consistent detailed information on... [selected] pIMDs.” The information captured by the TFUQs will include description of the adverse event (e.g. signs and/or symptoms, start and end date), diagnostic tests performed, outcome of the event, and medical history.

The following is a summary of the sponsor’s product safety specifications:

Important Identified Risks:

None

Important Potential Risks:

⁸ <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-requires-warning-about-guillain-barre-syndrome-gbs-be-included-prescribing-information-shingrix>

⁹ <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0280849d-5c78-4a9d-8941-4eab429f6bd8> (accessed April 24, 2023)

Risk of potential Immune-Mediated Disorders (pIMDs) following AREXVY vaccination in adults ≥ 60 years of age – Potential direct action of adjuvant as immunostimulant that may potentially induce abnormal immune response or trigger onset of immune mediated disease.

Safety Related Missing Information

- Persistence of immunogenicity in adults ≥ 60 years of age
- Use in immunocompromised adults ≥ 60 years of age
- Children and adolescents
- Pregnancy and lactation

6.2 Assessment of Sponsor-proposed Pharmacovigilance Plan

6.2.1 Important Identified Risks

None

6.2.2 Important Potential Risks

pIMDs:

The single important potential risk identified by the sponsor is the risk of Immune-Mediated Disorders (pIMDs) following AREXVY vaccination due to potential direct action of adjuvant. Based on the clinical trial data, the sponsor considered the risk of pIMD “*equally distributed between the AREXVY and placebo groups...[and]... consistent with events anticipated to be reported by the population under study.*” However, given the ability of the adjuvant to act as an immunostimulant, there exists a potential risk that it could induce an abnormal immune response triggering onset of immune-mediated disease. The sponsor has identified a predefined list of pIMDs, including ADEM, autoimmune thrombocytopenia, Bells palsy, giant cell arteritis, Guillain-Barre syndrome, multiple sclerosis, polymyalgia rheumatica, psoriasis and psoriatic arthritis, rheumatoid arthritis, and single organ cutaneous vasculitis. The sponsor initially proposed routine pharmacovigilance with TFUQs for spontaneously reported pIMD cases as adequate to further characterize this risk in the postmarket period.

DPV determined that the sponsor’s proposed pharmacovigilance activities would not be adequate to address the safety concerns of GBS and ADEM. According to published VAERS analyses, the reporting rate of ADEM in association with seasonal influenza vaccination is 0.05 per million, and in association with H1N1 vaccination is 0.15 per million doses distributed¹⁰. Additionally, the Vaccine Safety Datalink study has reported no confirmed cases of ADEM in association with influenza vaccines among 20 million influenza vaccines and 1.7 million monovalent H1N1 vaccine administrations¹¹.

¹⁰ Gubernot D, et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021;39:3666-3677 VAERS study; Pelegriano (2015) at https://journals.lww.com/epidem/Fulltext/2015/01000/Acute_Disseminated_Encephalomyelitis_Following.31.aspx

¹¹ Baxter R, Lewis E, Goddard K, Fireman B, Bakshi N, DeStefano F, Gee J, Tseng HF, Naleway AL, Klein NP. Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis. Clin Infect Dis. 2016 Dec 1;63(11):1456-1462.

Compared to the published overall background rate of GBS (0.3-0.6 per 100,000 per year)¹² and the reported risk of ADEM in association with influenza vaccination, the observation of 2 cases from among 15,745 vaccinees in the safety database is suggestive of a possible serious risk of ADEM in association with AREXVY vaccination.

With respect to GBS, a single case of GBS in the safety database occurred among the 15,745 RVSPref3 vaccine recipients, and there were no cases of GBS in any of the placebo or control groups in the other studies submitted in support of this BLA. GBS has a reported background rate of 1.5 to 3 cases per 100,000 per year in the US among adults >60 years of age¹³. Compared to published background rates of GBS, the observation of 1 case from among 15,745 vaccinees is suggestive of a possible serious risk of GBS in association with AREXVY vaccination.

Based on concerns regarding pIMDs, a study to further characterize the serious potential risk of development of pIMDs was presented as a potential safety postmarketing requirement (PMR) under Section 505(o) of Federal Food, Drug, and Cosmetic Act (FDCA) at the Safety Working Group meeting on March 09, 2023. The CBER Biologics Effectiveness and Safety (BEST) Program is not sufficient to assess the serious risks of Guillain-Barré (GBS) and acute disseminated encephalomyelitis (ADEM) following vaccination with AREXVY in lieu of a postmarketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). As per the 2019 draft guidance, Postmarketing Studies and Clinical Trials - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, this determination “takes into consideration multiple factors, some of which may be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly approved drug, subsequent exposure of patients to a drug).” At this time, the data sources in the CBER BEST Program are not sufficient to identify the safety outcomes due to uncertainties in vaccine uptake in the post-approval period. Of note, the BEST Program does not include foreign data sources. Should there be future use of the product outside U.S., then the sponsor may access foreign data sources in addition to U.S. data sources, for assessment of such rare serious risks. A finding of insufficiency based on uncertainty at the time of approval is consistent with current Guidance. Accordingly, the Safety Working Group concurred with need for a safety-related PMR study conducted by the sponsor.

As of April 20, 2023, the sponsor has confirmed that it will conduct a PMR to evaluate the risk of ADEM and GBS following receipt of Arexvy. The sponsor has proposed a self-controlled risk interval study to be conducted in FDA’s Sentinel program that will tentatively be titled “A postmarketing active surveillance study to evaluate the potential risk of immune-mediated demyelinating events in adults 60 years and older vaccinated

¹² Daniela Pohl, Gulay Alper, Keith Van Haren, Andrew J. Kornberg, Claudia F. Lucchinetti, Silvia Tenembaum, Anita L. Belman. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. *Neurology* Aug 2016, 87 (9 Supplement 2) S38-S45; DOI: 10.1212/WNL.0000000000002825. https://n.neurology.org/content/87/9_Supplement_2/S38.long#sec-3

¹³ Yen C, Wei K, Wang W, Huang Y, Chang Y. Risk of Guillain-Barré Syndrome Among Older Adults Receiving Influenza Vaccine in Taiwan. *JAMA Netw Open*. 2022;5(9):e2232571.

with GSK's RSVPreF3 OA vaccine in the United States." Primary endpoints would be GBS and ADEM of new onset within 42 days of receipt of Arexvy. The sponsor has proposed a sample size of 1.9 million for detection of 11 cases based on background rate for ADEM of 0.45/100,000 person-years, to provide 80% power given a relative risk of 7. This sample size would also accommodate a calculated needed sample size of 1.7 million based on the background rate of 2/100,000 for GBS. The sponsor agreed to continuation of PMR study until event accrual target. The sponsor has provided the following milestone dates for study:

Final protocol submission	June 30, 2024 (no change to original proposed date)
Start of data accrual	July 30, 2024 (revised from June 30, 2024)
End of data accrual	June 30, 2030, or accrual of required number of cases
Date of final report submission	December 31, 2031

The sponsor has also agreed to expedited 15-day reporting of GBS and ADEM as well as assessments (based on interval and cumulative data) in periodic safety reports.

DPV's assessment is that the proposed study will be adequate to fulfill the PMR, and the proposed pharmacovigilance actions are adequate to mitigate the risks of GBS and ADEM.

Atrial Fibrillation:

Atrial fibrillation was not included in the sponsor's PVP as a safety specification. When queried about this omission by CBER in Information Requests, the sponsor argued that there was no evidence of plausible vaccine-related increased risk for atrial fibrillation demonstrated by data from the placebo controlled pivotal phase 3 clinical trial study 006. Additionally, the sponsor pointed out that the imbalance was observed within the 30 days postvaccination period only, and not subsequently observed by 6 months post-vaccination, and that occurrence of atrial fibrillation during the study did not occur at rates greater than published background rates. However, the numerical imbalance observed in trial 006 and the temporal association with receipt of the vaccine raises concerns about a risk of atrial fibrillation related to vaccination. After discussing this issue and receiving concurrence at the Safety Working Group meeting on March 09, 2023, CBER communicated to the sponsor that risk of atrial fibrillation should be explored and characterized in a postmarket commitment (PMC) study.

As of April 20, 2023, the sponsor has agreed to include atrial fibrillation as a secondary endpoint in the above described study (current proposed title "A postmarketing active surveillance study to evaluate the potential risk of immune-mediated demyelinating events in adults 60 years and older vaccinated with GSK's RSVPreF3 OA vaccine in the United States"). Evaluation of atrial fibrillation within this study will be conducted as a PMC; milestones will be the same as those for the PMR. The sponsor also indicated that it will undertake active collection of safety data to evaluate atrial fibrillation by incorporating focused detailed questionnaires into ongoing study 006. The sponsor has

also agreed to expedited 15-day reporting of supraventricular arrhythmias as well as assessments (based on interval and cumulative data) in periodic safety reports.

DPV's assessment is that the proposed study will be adequate to fulfill the PMC, and the proposed pharmacovigilance actions are adequate to mitigate the risk of atrial fibrillation.

6.2.3 Missing Information

Persistence of immunogenicity in adults ≥ 60 years of age is being evaluated in ongoing study 004, including safety, reactogenicity, the immunogenicity profile of AREXVY vaccine for up to 3 years following a single dose vaccination regimen and at different revaccination schedules after the initial vaccine dose in adults aged 60 years and above. DPV defers to OVRP for evaluation for the need for additional studies to assess immunogenicity.

Immunocompromised individuals were excluded from clinical trials as, per the sponsor, immunocompromised individuals are at risk of mounting poor immune response to the vaccine which may in that case not provide sufficient protection from RSV. The product insert (Section 5.3) indicates that response to the vaccine may be diminished in this population. In the PVP, the sponsor indicates that a future clinical trial to evaluate AREXVY in immunocompromised individuals and characterize this efficacy issue is under consideration.

Children and adolescents were not included in clinical trials, and the target population for the indication excludes the pediatric population. Section 8.4 of the product insert states that safety and effectiveness in individuals younger than 18 has not been established and that Arexvy is not approved for use in persons <60 years of age.

Pregnant and lactating individuals were not included in clinical trials and the target population for the indication is for one that would generally be expected to exclude women of childbearing/lactating age. OVRP is communicating with sponsor about appropriate labeling in Section 8.1. Please refer to the final product insert for agreed-upon labeling.

7. DPV ASSESSMENT AND RECOMMENDATIONS

- Should AREXVY be approved, OBPV/DPV, agrees with the sponsor's proposed pharmacovigilance plan (dated August 11, 2022) to include routine pharmacovigilance in accordance with 21 CFR 600.80.
- DPV agrees with the plan to conduct a safety PMR under Section 505(o) of FDCA, titled "A post-marketing active surveillance study to evaluate the potential risk of immune-mediated demyelinating events in adults 60 years and older vaccinated with GSK's RSVPreF3 OA vaccine in the United States"), to assess the potential serious risk of GBS and ADEM following receipt of Arexvy.

- DPV agrees with the plan to conduct a PMC to assess risk of atrial fibrillation as a secondary endpoint within the above-mentioned study. Please see the approval letter for the PMR/PMC study milestone dates.
- An updated PVP reflecting the above studies as well as inclusion of fibrillation as a safety specification will be requested after approval, should the product be approved.
- The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS) at this time.

Please see the final version of the package insert submitted by the sponsor for the final agreed upon language for the label.

APPENDIX

*List of potential immune mediated diseases (pIMDs):

- Antiphospholipid syndrome
- Autoimmune aplastic anemia
- Autoimmune hemolytic anemia
- Autoimmune lymphoproliferative syndrome (ALPS)
- Autoimmune neutropenia
- Autoimmune pancytopenia
- Autoimmune thrombocytopenia
- Evans syndrome
- Pernicious anemia
- Thrombosis with thrombocytopenia syndrome (TTS)
- Thrombotic thrombocytopenic purpura
- Idiopathic myocarditis/pericarditis
- Idiopathic pulmonary fibrosis
- Pulmonary alveolar proteinosis (PAP)
- Pluroparenchymal fibroelastosis (PPFE)
- Addison's disease
- Autoimmune/immune mediated thyroiditis
- Autoimmune diseases of testis and ovary
- Autoimmune hyperlipidemia
- Autoimmune hypophysitis
- Diabetes mellitus type I
- Grave's or Basedow's disease
- Insulin autoimmune syndrome
- Polyglandular autoimmune syndrome
- Ocular autoimmune /immune mediated disorders
- Autoimmune / Immune-mediated pancreatitis
- Celiac disease
- Inflammatory bowel disease (including Crohn's disease, ulcerative colitis, ileitis, proctitis, microscopic colitis)
- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Idiopathic inflammatory myopathies
- Gout
- Mixed connective tissue disorder
- Polymyalgia rheumatica (PMR)
- Psoriatic arthritis (PsA)
- Relapsing polychondritis
- Rheumatoid arthritis
- Sjögren's syndrome
- Spondyloarthritis

Systemic lupus erythematosus
 Systemic sclerosis
 Acute disseminated encephalomyelitis (ADEM) (including other inflammatory-demyelinating variants)
 Guillain-Barre syndrome (GBS)
 Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)
 Multiple sclerosis (MS)
 Myasthenia gravis
 Narcolepsy
 Peripheral inflammatory demyelinating neuropathies and plexopathies
 Transverse myelitis (TM)
 Autoimmune/immune mediated glomerulonephritis
 Alopecia areata
 Autoimmune/immune mediated blistering dermatoses
 Erythema multiforme
 Erythema nodosum
 Interstitial granulomatous dermatitis
 Lichen planus
 Localized scleroderma
 Palisaded neutrophilic granulomatous dermatitis
 Psoriasis
 Pyoderma gangrenosum
 Stevens-Johnson syndrome (SJS)
 Sweet's syndrome
 Vitiligo
 Large or medium or small sized vasculitis
 Anti-synthetase syndrome
 Capillary leak syndrome
 Goodpasture syndrome
 Immune mediated enhancement of disease:
 Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)
 Immunoglobulin G4 related disease
 Langerhans' cell histiocytosis
 Multisystem inflammatory syndromes
 Overlap syndrome
 Pulmonary renal syndrome
 Raynaud's phenomenon
 Sarcoidosis
 Susac's syndrome