Summary Basis for Regulatory Action

Date:	May 3, 2023
From:	Santosh Nanda, DVM, PhD Review Committee Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA STN:	125775/0
Applicant:	GlaxoSmithKline Biologicals SA
Submission Receipt Date:	September 2, 2022
Action Due Date:	May 3, 2023
Proper Name:	Respiratory Syncytial Virus Vaccine, Adjuvanted
Proprietary Name:	AREXVY
Indication:	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR/DVP) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	 Judy Beeler, OVRR/DVP Roberta Lynne Crim, OVRR/DVP Ewan Plant, OVRR/DVP Marina Zaitseva, OVRR/DVP Erin Hill, OCBQ/DMPQ Erin Hill, OCBQ/DMPQ Hsiaoling (Charlene) Wang, OCBQ/DBSQC Ritu Agarwal, OCBQ/DBSQC Varsha Garnepudi, OCBQ/DBSQC Jing Lin, OCBQ/DBSQC Simleen Kaur, OCBQ/DBSQC
Clinical • Clinical (OVRR/DVRPA) Postmarketing safety • Pharmacovigilance review (OBPV/DE) • Benefit / Risk Analyst • Real World Evidence • BIMO	 Nicholas Geagan, OVRR/DVRPA Firoozeh Alvandi, OBPV/DPV Osman Yogurtcu, OBPV/DABRA Yun Lu, OBPV/DABRA Malcolm Nasirah, OCBQ/DIS/BMB
Statistical • Clinical data (OBPV/DB) • Nonclinical data	 Ross Peterson, OBPV/DB Ho-Hsiang Wu, OBPV/DB
Nonclinical/Pharmacology/Toxicology • Toxicology (OVRR/DVRPA) • Pharmacology (OVRR/DVP)	 Nabil Al-Humadi, OVRR/DVRPA Judy Beeler, OVRR/DVP Marina Zaitseva, OVRR/DVP
Labeling • Promotional (OCBQ/APLB) • PNR (OCBQ/APLB) • Carton & Container	 Oluchi Elekwachi, OCBQ/DCM/APLB Oluchi Elekwachi, OCBQ/DCM/APLB Daphne Stewart, OVRR/DVRPA Ching Yim-Banzuelo, OVRR/DVRPA
Other Review: • Consults	 Brenda Baldwin, OVRR/DVRPA
Advisory Committee Summary	A Vaccines and Related Biological Products Committee (VRBPAC) meeting was convened on March 1, 2023. A majority of the Committee (10 out of 12 votes) agreed that the data support the safety of AREXVY, and the Committee unanimously agreed (11 out of 11 votes) that the data support the effectiveness of AREXVY for prevention of LRTD caused by RSV in individuals 60 years of age and older.

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1. Introduction

GlaxoSmithKline Biologicals (GSK) submitted Biologics License Application (BLA) 125775/0 for licensure of their respiratory syncytial virus (RSV) vaccine. The proper name of the vaccine is Respiratory Syncytial Virus Vaccine, Adjuvanted and the proprietary name is AREXVY. AREXVY is indicated for active immunization for the prevention of LRTD caused by RSV in individuals 60 years of age and older.

AREXVY consists of an RSVPreF3 antigen component, i.e., 120 µg of recombinant RSV surface glycoprotein F from an RSV-A strain that is stabilized in the pre-fusion trimeric conformation, and an $AS01_E$ adjuvant component. AREXVY is administered intramuscularly (IM) as a single (0.5 mL) dose.

The $AS01_E$ adjuvant component is GSK's proprietary adjuvant suspension component that contains Monophosphoryl Lipid A (b) (4) (MPL, a chemically detoxified form of the lipopolysaccharide derived from the Gram-negative bacterium *Salmonella minnesota* (b) (4)) and QS-21 [a saponin (triterpene glycoside) purified from the bark of the South American tree *Quillaja saponaria* Molina]. To form $AS01_E$ adjuvant, MPL and QS-21 are combined in a liposomal formulation that contains the same ingredients as in $AS01_B$ adjuvant, the adjuvant in SHINGRIX, and consists of dioleoyl phosphatidylcholine (DOPC) and cholesterol in phosphate-buffered saline solution. However, $AS01_E$ adjuvant contains half the amount of MPL and QS-21 in $AS01_B$ adjuvant.

AREXVY will be supplied in a ten-dose configuration that contains ten single-dose vials of lyophilized antigen component and ten single-dose vials of adjuvant suspension component. The antigen component must be reconstituted with the adjuvant component to form AREXVY before use. After reconstitution, each 0.5 mL dose contains:

- 120 micrograms (µg) of the recombinant RSVPreF3 antigen
- 25 µg of MPL
- 25 µg of QS-21

Each dose of AREXVY also contains 14.7 mg of Trehalose, 4.4 mg of sodium chloride, 0.83 mg of potassium dihydrogen phosphate, 0.26 mg of dipotassium phosphate, 0.18 mg of polysorbate 80, 0.15 mg of disodium phosphate anhydrous, 0.5 mg of DOPC, and 0.125 mg of cholesterol. After reconstitution, AREXVY is a sterile, opalescent, colorless to pale brownish liquid.

The dating period for the RSVPreF3 antigen component of Respiratory Syncytial Virus Vaccine, Adjuvanted shall be 24 months from the date of manufacture when stored at 2ºC to 8ºC. The dating period for the $AS01_E$ adjuvant suspension component of Respiratory Syncytial Virus Vaccine, Adjuvanted shall be 36 months from the date of manufacture when stored at 2ºC to 8ºC. The dates of manufacture of the RSVPreF3 antigen and $AS01_E$ adjuvant components are defined as the dates of filling into final containers. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The expiration date for the packaged product, lyophilized antigen component and adjuvant suspension component, is dependent on the shortest expiration date of any component.

2. Background

RSV is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. Symptoms consistent with an upper respiratory tract infection can include rhinorrhea, pharyngitis, cough, headache, fatigue, and fever. Symptomatic RSV re-infections are common and continue throughout adulthood, manifested as acute upper respiratory tract infections. In older adults, RSV is a common cause of lower respiratory tract disease and re-infections can lead to severe disease. Those who are hospitalized may require oxygen, intubation, and/or mechanical ventilation.

RSV disease among adults 65 years of age and older results in an average of 177,000 hospitalizations in the United States (US) each year; during 1999-2018, the highest mortality was seen in this age group with a mortality rate of 14.7 per 100,000 (CDC, 2022; Hansen et al, 2022). The severity of RSV disease increases with age and comorbidities (e.g., chronic obstructive pulmonary disease, congestive heart failure, asthma) (Falsey et al, 2005; Walsh et al, 2004; Korsten et al, 2021; McClure et al, 2014; Branche et al, 2022).

RSV disease represents a serious condition in individuals 65 years of age and older with an unmet medical need; there are no specific treatment options for RSV disease among adults.

Table 1. Regulatory History

Regulatory Event / Milestone	Date
1. Pre-IND meeting	April 18, 2018
2. IND submission	October 19, 2018
3. Fast Track designation granted	December14, 2018
4. Pre-BLA meeting	CMC – July 20, 2022 Clinical - August 23, 2022
5. BLA submission received	September 2, 2022
6. BLA filed	November 1, 2022
7. Mid-Cycle communication	December 20, 2022 (Cancelled by GSK)
8. Late-Cycle meeting	February 17, 2023 (Cancelled by GSK)
9. Action Due Date	May 3, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Manufacturing Overview

AREXVY consists of the RSVPreF3 antigen component and the $AS01_E$ adjuvant suspension component. The liquid $AS01_E$ adjuvant component is used to reconstitute the lyophilized RSVPreF3 antigen component extemporaneously prior to administration.

RSVPreF3 Antigen Component of AREXVY

Composition

The composition of the RSVPreF3 antigen component final container (FC) and the function of the ingredients are provided in Table 1.

Table 1. Composition of RSVPreF3 Antigen Component FC (Single dose)

Ingredients	Quantity per 0.5mL dose [1]	Function
RSVPreF3 antigen	120 µg	Immunogen
(b) (4)		

(b) (4) .

Specifications and Methods

The tests and specifications applied for routine release of the RSVPreF3 antigen component FC are shown in Table 2.

Table 2. Control of RSVPreF3 Antigen Component FC: Tests and Specifications

Test	Acceptance criteria
Description	White cake or powder, clear colorless liquid after reconstitution with WFI (b) (4)
(b) (4)	
(b) (4)	
Identity (b) (4)	
IVRP (b) (4)	
RSVPreF3 content (b) (4)	
Endotoxin (b) (4)	
(b) (4)	
RSVPreF3 (b) (4)	
PS80 (b) (4)	
Trehalose content (b) (4)	
Sterility test (b) (4)	Absence of growth
Sterility test (b) (4)	Absence of growth

(b) (4)

The potency of the DP is (b) (4)

(b) (4)

Stability

The (b) (4) test and (b) (4) are stability indicating tests. Other parameters included in the stability evaluation of the RSVPreF3 antigen FC are description, sterility test (b) (4) sterility test (b) (4) and container closure integrity test. The dating period for the RSVPreF3 antigen (b) (4) shall be 24 months when stored at (b) (4). The stability data provided in the submission support a dating period of 24 months from the date of manufacture (i.e., date for the start of filling) when stored at +2°C to +8°C for the RSVPreF3 antigen FC lots filled in 3 mL glass vials.

The AS01$_E$ Adjuvant Component of AREXVY

Mechanism of Action of AS01$_E$ Adjuvant

The AS01$_E$ adjuvant induces a transient activation of the innate immune system by two immune enhancers: MPL, (b) (4) Nonclinical studies conducted by GSK indicate that both MPL and QS-21 are required to (b) (4)

Composition

The AS01$_E$ adjuvant component is formulated with 25 µg of each of the two immune enhancers: QS-21 and MPL, using liposomes as a vehicle. The bilayers of the liposomal membrane are composed of DOPC and cholesterol. DOPC is a (b) (4) Cholesterol (b) (4) Cholesterol (b) (4). These lipids are not considered as novel. The composition of the AS01$_E$ adjuvant component and the function of the ingredients are provided in Table 3.

Table 3. Composition of AS01$_E$ Adjuvant Component FC (Single dose)

Ingredients	Quantity (per 0.5 mL dose)[1]	Function
Monophosphoryl Lipid A (b) (4) (MPL)	25 µg	(b) (4)
Purified *Quillaja* Saponin[2] (QS-21)	25 µg	
Dioleoyl phosphatidylcholine (DOPC)	500 µg	
Cholesterol	125 µg	
Disodium phosphate anhydrous (Na_2HPO_4)	150 µg	
Potassium dihydrogen phosphate (KH_2PO_4)	(b) (4)	
Sodium chloride (NaCl)	(b) (4)	
Water for injection	(b) (4)	

(b) (4) effective dose of 0.5 mL.
[2]Purified fraction 21 of *Quillaja saponaria* Molina

Manufacturing
Manufacturing of the AS01$_E$ adjuvant component involves (b) (4) Formulation and filling of AS01$_E$, labeling, packaging, quality control and stability testing, and quality control testing of the final product are performed by GSK at (b) (4) facility and at the GSK's facility (b) (4). Labeling and packaging are also performed at (b) (4) GSK Vaccines (b) (4).

An evaluation of extractables and leachables was performed on the container/closure systems used for the (b) (4) intermediates and for AS01$_E$ adjuvant. After careful evaluation, the applicant concluded that the levels of extractables and leachables are not expected to present significant toxicological concerns.

Specifications and Methods
The tests and specifications applied for routine release of the AS01$_E$ adjuvant component FC are presented in Table 4.

Table 4. AS01$_E$ Adjuvant Component FC Release Specifications

Tests	Acceptance criteria	
Description	Opalescent, colorless to pale brownish liquid (b) (4)	
Volume	(b) (4)	
MPL content (b) (4)		
QS-21 content (b) (4)	QS-21 content	(b) (4)
	(b) (4)	(b) (4)
Cholesterol content and DOPC content (b) (4)	Cholesterol content	(b) (4)
	DOPC content	(b) (4)
(b) (4)		
	(b) (4)	
Sterility test (b) (4)		Absence of growth
	(b) (4)	Absence of growth
(b) (4)		

Stability

The stability data generated support a dating period of 36 months from the date of manufacture (i.e., the date of filling into final containers) when stored at +2°C to +8°C for the AS01$_E$ adjuvant filled in 3 mL glass vials.

The AREXVY Vaccine

Product Composition

As previously described, AREXVY consists of lyophilized RSVPreF3 antigen component that is reconstituted at the time of use with AS01$_E$ adjuvant component. A single dose of AREXVY is 0.5 mL and it does not contain preservatives. The composition of the reconstituted vaccine and the function of the ingredients are provided in Table 5.

Table 5. Composition of AREXVY

Ingredients	Quantity per 0.5mL dose [1,2]	Function
Active substance		
RSVPreF3 antigen	120 µg	Immunogen
Excipients		
Trehalose dihydrate	14.7 mg	Stabilizer: • Cryoprotectant • Lyoprotectant
Polysorbate 80	0.18 mg	Surfactant: (b) (4)
Potassium dihydrogen phosphate (KH_2PO_4)	(b) (4)	Buffer (b) (4)
Dipotassium phosphate K_2HPO_4	0.26 mg	Buffer (b) (4)
$AS01_E$ components		
3-O-deacyl-4'-monophosphory; lipid A (MPL)	25 µg	Immune enhancer
Purified Quillaja Saponin (QS-21)	25 µg	Immune enhancer
Dioleoyl phosphocholine (DOPC)	500 µg	Liposome membrane constituent
Cholesterol	125 µg	Liposome membrane constituent (b) (4)
Sodium chloride	4.4 mg	Tonicity agent
Disodium phosphate anhydrous (Na_2HPO_4)	0.15 mg	Buffer
Potassium dihydrogen phosphate (KH_2PO_4)	(b) (4)	Buffer
Water for injection	0.5 mL	Solvent

(b) (4) effective dose of 0.5mL is administered.
(b) (4) .

Presentation and Packaging System
AREXVY is supplied in a ten-dose configuration that contains ten single-dose vials of lyophilized antigen component and ten single-dose vials of adjuvant suspension component.

Stability
GSK conducted in-use stability studies to determine the maximum temperature and time period that the reconstituted vaccine can retain its physicochemical properties. The critical quality attributes (CQAs) used to monitor the stability of the reconstituted vaccine are appearance, (b) (4) . The characterization studies not only demonstrated compatibility between RSVPreF3 antigen and $AS01_E$ adjuvant suspension, but also showed that the (b) (4) of the RSVPreF3 antigen when the two are mixed and stored at 2°C to 8°C. Based on the data generated, GSK concluded that the time of use of AREXVY, the reconstituted vaccine, is limited to 4 hours at 2°C to 8°C, or at room temperature, while protected from light.

The carton label and the Prescribing Information (PI) state that after reconstitution, AREXVY should be administered immediately or protected from light while stored refrigerated between 2°C and 8°C (36°F and 46°F) or at room temperature and used within 4 hours. The reconstituted vaccine should be discarded if not used within 4 hours.

Comparability Protocols (CPs)

GSK submitted CPs in the BLA for the replacement of reference standards, internal controls, and key reagents:

For the RSVPreF3 antigen:

(b) (4)

For the AS01$_E$ adjuvant:

(b) (4)

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. CBER reviewed these CPs and agreed with the reporting category of annual report for the changes listed above, with the exception that GSK may submit qualifying information on an internal control or reference standard batch as a CBE-30 following agreement with CBER and in limited situations when a batch does not fully meet the acceptance criteria in the comparability protocol and there is a limited supply of the approved batch.

b. Testing Specifications

Analytical Chemistry

The analytical methods and their validations and/or qualifications reviewed for the antigen and adjuvant components of AREXVY were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of AREXVY are listed in the table below. The activities performed and inspectional histories are noted in Table 6.

Table 6. Manufacturing Facilities Table for AREXVY

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
GSK Biologicals S.A. (b) (4) *DP formulation, filling, lyophilization, labeling, testing*	(b) (4)		Waiver	CBER/DMPQ (b) (4) NAI ORA/OBPO (b) (4) VAI
GSK Vaccines (b) (4) (b) (4) *DP labeling, packaging, testing* *DP (adjuvant) formulation, filling, labeling, testing*	(b) (4)		Waiver	(b) (3) (A) Compliant ORA/OBPO (b) (4) VAI
(b) (4) *DP labeling, testing*	(b) (4)		Waiver	CBER/DMPQ (b) (4) VAI

Acronym key: GSK - GlaxoSmithKline; DS – drug substance; DP – drug product; OBPO – Office of Biological Products Operations; DMPQ – Division of Manufacturing and Product Quality; ORA – Office of Regulatory Affairs; NAI – No Action Indicated; VAI – Voluntary Action Indicated

CBER/DMPQ conducted a pre-approval inspection (PAI) of GSK Biologicals S.A. in (b) (4) . A Form FDA 483 list of observations was not issued, and the inspection was classified NAI. ORA/OBPO conducted a surveillance inspection in (b) (4) and a Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

(b) (3) (A)

CBER/DMPQ conducted a pre-license inspection (PLI) at (b) (4) , and a Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

AREXVY is supplied in a ten-dose configuration that contains ten single-dose vials of lyophilized antigen component and ten single-dose vials of adjuvant suspension component. The container closure system for both the lyophilized antigen and adjuvant suspension components are presented in 3 mL Type (b) (4) uncolored glass vial (b) (4) The 13 mm bulk stopper (b) (4) for the lyophilized antigen component is constructed of Bromobutyl type (b) (4) rubber, and the stopper (b) (4) for the adjuvant suspension component is constructed of Chlorobutyl type (b) (4) rubber. Stoppers (b) (4) . Vial flip-off caps (b) (4)) are used to secure the stopper to the vial and are constructed of a colored polypropylene top fixed on a natural aluminum varnished cap. GSK performed the container closure integrity testing at the (b) (4), Belgium facility, employing the (b) (4) container closure integrity test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacture of this product does not significantly alter the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

AREXVY has not been evaluated in repeat-dose toxicity studies or in reproductive-developmental toxicity study in animals. However, RSVPreF3 antigen alone or in combination with $AS01_B$ adjuvant (used in SHINGRIX and contains two times the amount of MPL and QS 21 as in $AS01_E$) has been evaluated in two repeat-dose toxicity studies in rabbits. Based on nonclinical toxicity assessments, there were no significant safety issues reported in the rabbits. In addition, the $AS01_E$ adjuvant components (i.e., MPL, QS21) were evaluated in three safety pharmacology studies, ten general toxicology studies, ten genotoxicology studies, five reproductive toxicology studies, and three local tolerance studies.

AREXVY has not been evaluated for its carcinogenic or mutagenic potential or for impairment of fertility.

Overall, based on the nonclinical toxicity assessments provided in the submission, CBER concluded that there are no significant safety issues.

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral and cellular immune responses to AREXVY, were obtained in the clinical studies. The data demonstrate that AREXVY

induces an immune response against RSVpreF3 that protects against LRTD caused by RSV.

6. Clinical/Statistical

a. Clinical Program

The applicant included data from 5 clinical studies in the BLA to support the safety and effectiveness of AREXVY. The pivotal clinical studies which will be discussed in this SBRA are shown in Table 7.

Table 7. Overview of Pivotal Clinical Studies

Phase Study # - Status	**Description**	**Study Groups**	**# of Participants 120 µg RSVPreF3 / 25 µg AS01$_E$**	**# of Participants Placebo (Saline)**
Phase 3 Study Study 006[b] – ongoing Location: Northern and Southern Hemisphere	Randomized, placebo-controlled, observer-blind, safety, immunogenicity, and VE study Primary objective: · VE of RSVPreF3-AS01$_E$ to prevent RSV-confirmed LRTD Key secondary objectives: · VE of RSVPreF3-AS01$_E$ to prevent RSV-confirmed LRTD by subtype (RSV-A, RSV-B), by age, baseline comorbidities	RSVPreF3-AS01$_E$ Placebo	VE analysis 1[a] 12467	12499
Phase 3 Study Study 004[b] – ongoing	Randomized, open-label study to evaluate the immunogenicity, safety, and immune persistence of RSVPreF3-AS01$_E$ following different revaccination schedules · [only safety data from this study are presented in this briefing document]	RSV_annual RSV_flexible revaccination RSV_1 dose	Month 6: RSV_annual: 993 RSV_flexible revaccination: 329 RSV_1 dose: 331	--- --- ---
Phase 3 Study Study 007[b] – completed	Randomized, co-administration study seasonal quadrivalent influenza vaccine (FLU)	Co-Ad Separate	Co-Ad: 442 (co-ad) Separate:426 of 443 received RSVPreF3-AS01$_E$)	---

Phase Study # - Status	Description	Study Groups	# of Participants 120 µg RSVPreF3 / 25 µg AS01$_E$	# of Participants Placebo (Saline)
Phase 3 Study Study 009[b] – completed	Randomized, double-blind, lot consistency study	vaccine_Grp1 (Lot 1) vaccine_Grp2 (Lot 2) vaccine_Grp3 (Lot 3)	251 253 253	--- --- ---
Phase 1/2 Study Study 002 – completed	Randomized, dose and formulation selection study Part B: 60-80 years of age	Relevant study groups (Part B): 120 µg RSVPreF3 / AS01$_E$ Placebo: saline	100 ---	--- 101
Phase 2 Study Study 011 – completed USA, Belgium	Extension study to evaluate the safety and immunogenicity of RSVPreF3-AS01$_E$ (3rd dose) administered ~18 mo after Dose 2 in certain RSV OA=ADJ-002 groups (including 120 µg RSVPreF3-AS01$_E$ study group)	120ug RSVPreF3 / AS01$_E$	---	---
		Total:	15845	12600

Source: adapted from 125775.0 tabular-listing.pdf.
Ab=Antibody, FLU=Seasonal Quadrivalent Influenza Vaccine [Fluarix Quadrivalent; GSK], LRTD=Lower Respiratory Tract Disease, NAb=Neutralizing antibody, RSV=Respiratory Syncytial Virus, RSVPreF3 =RSV PreFusion protein 3, VE=Vaccine Efficacy.
[a] VE analysis #1: Season 1 was defined as 1 October to 30 April in Northern hemisphere and from 1 March to 30 September in Southern hemisphere. Northern hemisphere (US, Canada, Mexico, Europe, Russia, South Korea, Japan), Southern hemisphere (Australia, New Zealand, S Africa).
[b] Main Studies to Support Safety and Effectiveness
[c] Subjects from Study 011 did not contribute to the overall safety data as they either previously received the final formulation in Study 002 or had received a different formulation than the final one (120µg AS01$_E$).

RSV OA=ADJ-006 is an ongoing Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of AREXVY in adults ages 60 years and older through three RSV seasons. The study is being conducted in a total of 278 active centers in 17 countries (Australia, Belgium, Canada, Estonia, Finland, Germany, Italy, Japan, South Korea, Mexico, New Zealand, Poland, Russian Federation, South Africa, Spain, United Kingdom, and United States). A total of 25,040 participants were randomized 1:1:1:3 to either one of three vaccine lots or placebo (saline).

A total of 25,040 were randomized and 24,981 received the study intervention. At VE Analysis 1, fifteen participants were excluded due to invalid informed consent. The exposed set (ES) included 24,966 participants (12,467 vaccine, 12,499 placebo).

Safety evaluation included the following parameters: solicited local and systemic AEs for 4 days postvaccination; unsolicited, non-serious local and systemic AEs through 30 days postvaccination; all SAEs/pIMDs up to 6 months following each dose; all

related SAEs/pIMDs/deaths from beginning until end of study. Solicited events and the humoral immune response were evaluated in subsets of participants, referred to as reactogenicity subset (N=1757; RSVPreF3 = 879, Placebo = 878) and immunogenicity subset (N=1777; RSVPreF3 = 885, Placebo = 892).

An external LRTD Adjudication Committee was set up with blinded qualified external experts in the respiratory medicine and/or infectious diseases. This committee reviewed all RSV qRT-PCR-confirmed cases fulfilling either the LRTD case definition or reported as LRTD by the investigator. Only adjudicated cases were considered for the efficacy endpoint analysis. For all statistical analyses, the 3 AREXVY lots were pooled, and results presented for vaccine group vs. placebo group. The final analysis of the primary objective was case driven. It was planned to be performed when at least 56 cases of RSV-confirmed and externally adjudicated LRTDs were accrued in the primary cohort for efficacy (mES). The primary efficacy objective was met in an interim analysis, if the LL of the 96.95% CI for VE was >20%. The VE analysis was performed when 47 cases of RSV-confirmed LRTD accrued in the primary cohort for efficacy up to efficacy data lock point (DLP) on April 11, 2022 (all available efficacy data of acute respiratory illness (ARI) cases with ARI visit up to efficacy DLP included and adjudicated by LRTD Adjudication Committee). The analysis included data from participants enrolled in the Northern Hemisphere (NH) and in the Southern Hemisphere (SH). The case split was 7 cases in the RSVPreF3-AS01$_E$ group compared to 40 cases in the placebo group with a VE of 82.6% (96.95% CI 57.9, 94.1). The median follow-up time in the Modified Exposed Set (mES) from Day 15 post-vaccination up to the efficacy data lock point (DLP) of vaccine efficacy (VE) Analysis 1 was 6.7 months for both groups (range: 0, 10.1 months). All the RT-PCR-confirmed RSV LRTD cases occurred in the Northern Hemisphere (NH); for both study groups, the median follow-up time in the NH was 6.9 months.

Table 8. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD, mES, Study 006

Endpoint	RSVPreF3-AS01$_E$ N=12466 n	RSVPreF3-AS01$_E$ N=12466 n/T (per 1000)	Placebo N=12494 n	Placebo N=12494 n/T (per 1000)	VE % 96.95% CI (LL, UL)
RT-PCR-confirmed RSV LRTD	7	1.0	40	5.8	82.6 (57.9, 94.1)

Source: Adapted from STN 125775, RSV OA=ADJ-006 Clinical Study Report, Table 11.4.
Placebo: saline
mES (modified exposed set): defined as participants who received at least the first dose of the study intervention and are included in the ES and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination.
Abbreviations: N=number of participants, n=number of participants with at least one RT-PCR-confirmed RSV LRTD identified by adjudication committee, n/T (per 1000)=incidence rate of participants reporting at least one event, T (year)=sum of follow-up time (from Day 15 post-vaccination until first occurrence of the event or till the efficacy data lock point or until drop-out date) expressed in years; CI=confidence interval, LL=Lower Limit; UL=Upper Limit; VE=vaccine efficacy

In addition to the primary efficacy analysis, vaccine efficacy against RSV subgroups A and B were also individually calculated (Table 9). The observed VE against first

occurrence of LRTD caused by RSV-A was 84.6% (95% CI 32.1, 98.3) and against RSV-B was 80.9% (95% CI 49.4, 94.3).

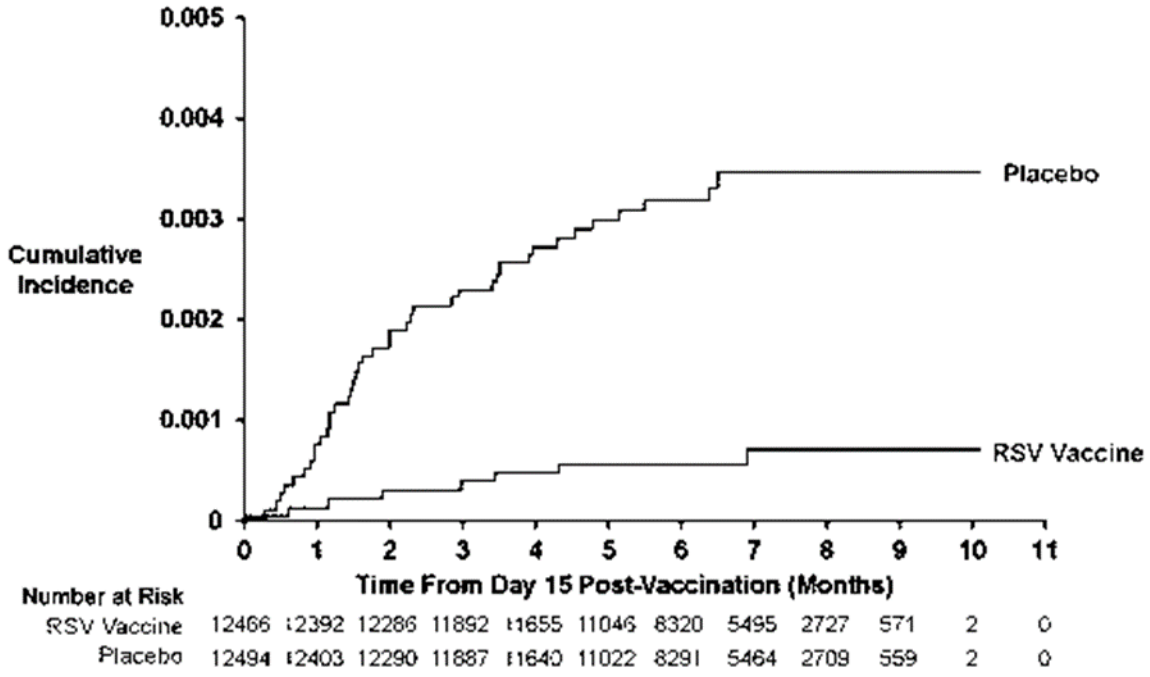
Table 9. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD Up to VE Analysis 1 by RSV Subtype, mES, Study 006

Endpoint	RSVPreF3-AS01$_E$ N=12466 n	RSVPreF3-AS01$_E$ N=12466 n/T (per 1000)	Placebo N=12494 n	Placebo N=12494 n/T (per 1000)	VE % 95% CI (LL, UL)
RT-PCR-confirmed RSV-A LRTD	2	0.3	13	1.9	84.6 (32.1, 98.3)
RT-PCR-confirmed RSV-B LRTD	5	0.7	26	3.8	80.9 (49.4, 94.3)

Source: Adapted from STN 125775, RSV OA=ADJ-006 Clinical Study Report, Table 11.5.
Placebo: saline
mES (modified exposed set): defined as participants who received at least the first dose of the study intervention and are included in the ES and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination.
Abbreviations: N=number of participants, n=number of participants with at least one RT-PCR-confirmed RSV LRTD identified by adjudication committee, n/T (per 1000) =incidence rate of participants reporting at least one event, T (year)=sum of follow-up time (from Day 15 post-vaccination until first occurrence of the event or till the efficacy data lock point or until drop-out date) expressed in years; CI=confidence interval; LL=Lower Limit; UL=Upper Limit, VE=vaccine efficacy

The cumulative incidence curves present the cumulative numbers of RT-PCR-confirmed RSV LRTD reported from Day 15 post-vaccination up to VE Analysis 1 in both groups (Figure 1). Starting at approximately 1 month after vaccination, the curves diverge, with more cases accumulating in the placebo group than the AREXVY group. Cases continued to accrue at a faster rate in the placebo group compared to the AREXVY group through approximately 7 months following vaccination, which was near the median duration of follow-up for participants in the study at the time of data cutoff (6.7 months).

Figure 1. Cumulative Incidence Curves for qRT-PCR-Confirmed RSV LRTD Reported up to VE Analysis 1, mES



Source: Adapted from STN 125775, RSV OA=ADJ-006 Clinical Study Report, Table 11.1
Abbreviations: LRTD=lower respiratory tract disease; mES=modified Exposed Set; qRT-PCR=quantitative reverse transcription polymerase chain reaction; VE=vaccine efficacy

Vaccine efficacy was also analyzed by age subgroup and was comparable to the overall efficacy results in the 60-69 YOA subgroup and 70-79 YOA subgroup [81.0% (95% CI 43.6, 95.3) and 93.8% (95% CI 60.2, 99.9), respectively] (Table 10). The number of cases (2 AREXVY, 3 placebo) among participants >80 YOA was too small to make conclusions about VE from the results of VE analysis 1.

Table 10. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD up to VE Analysis 1 by Age Group, mES, Study 006

Subgroup	N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ n/T (per 1000)	N	Placebo n	Placebo n/T (per 1000)	VE % 95% CI (LL, UL)
≥65 YOA	9258	5	1.0	9325	29	5.7	82.7 (54.9, 94.8)
60-69 YOA	6963	4	1.0	6979	21	5.5	81.0 (43.6, 95.3)
70-79 YOA	4487	1	0.4	4487	16	6.5	93.8 (60.2, 99.9)

Source: Adapted from STN 125775, RSV OA=ADJ-006 Clinical Study Report, Table 11.6.
Placebo: saline
mES (modified exposed set): defined as participants who received at least the first dose of the study intervention and are included in the ES and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination.
Abbreviations: N=number of participants in the specified age group, n=number of participants with at least one RT-PCR-confirmed RSV LRTD identified by adjudication committee, n/T (per 1000)=incidence rate of participants reporting at least one event, T (year)=sum of follow-up time (from Day 15 post-vaccination until first occurrence of the event or till the efficacy data lock point or until

drop-out date) expressed in years; CI=confidence interval; LL=Lower Limit; UL=Upper Limit; VE=vaccine efficacy; YOA=years of age

When VE analysis was performed by baseline comorbidities, the VE efficacy was higher in participants with at least 1 pre-existing comorbidity of interest compared to those with no pre-existing comorbidity [94.6% (95% CI 65.9, 99.9) and 72.5% (95% CI 30.0, 90.9), respectively].

Table 11. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD up to VE Analysis 1 by Baseline Comorbidity[a], mES, Study 006

Subgroup	RSVPreF3-AS01$_E$ N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ n/T (per 1000)	Placebo N	Placebo n	Placebo n/T (per 1000)	VE % 95% CI (LL, UL)
No pre-existing comorbidity	7529	6	1.5	7633	22	5.3	72.5 (30.0, 90.9)
At least 1 pre-existing comorbidity	4937	1	0.4	4861	18	6.6	94.6 (65.9, 99.9)
At least 1 cardiorespiratory condition	2496	1	0.7	2421	12	8.9	92.1 (46.7, 99.8)
At least 1 metabolic condition	3200	0	0.0	3234	13	7.2	100.0 (74.0, 100.0)

Source: Adapted from RSV OA=ADJ-006 report, Table 14.2.1.21.
Placebo: saline
mES=modified exposed set, defined as participants who received at least the first dose of the study intervention and are included in the ES and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination.
a. Co-morbidities associated with increased risk for severe RSV disease: cardiorespiratory conditions=COPD, asthma, any chronic respiratory/pulmonary disease, chronic heart failure; metabolic conditions=Diabetes mellitus Type 1 or Type 2, advanced liver, or renal disease
Abbreviations: N=number of participants; n=number of participants with at least one RT-PCR-confirmed RSV LRTD; T (year)=sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; n/T (per 1000)=Incidence rate of participants reporting at least one event; CI=confidence interval, LRTD=lower respiratory tract disease; RT-PCR= reverse transcriptase-polymerase chain reaction, LL=Lower Limit, UL=Upper Limit, VE=vaccine efficacy

The number of cases among frail participants was too small to make definitive conclusions about VE in frail participants in Season 1. A total of 2 RSV-confirmed LRTD cases (1 AREXVY, 1 placebo) occurred in 366 frail participants. The number of cases among frail participants was too small to make conclusions about VE in frail participants in Season 1.

Severe RSV-confirmed LRTD was defined based on clinical symptomology (Definition 1) or based on use of supportive therapy (Definition 2). Table 12 shows that the observed VE against RT-PCR-confirmed RSV severe LRTD based on case definition 1 was 94.1% (95% CI 62.4, 99.9).

The number of RT-PCR-confirmed RSV severe LRTD cases (based on supportive therapy [definition 2]; see Table 12) was too small to make conclusions about VE

against RT-PCR-confirmed RSV severe LRTD. A total of 2 RT-PCR-confirmed RSV severe LRTD cases (severe LRTD definition 2), both in the placebo group, were reported. The 2 cases of RT-PCR-confirmed RSV severe LRTD that met definition 2 also met the criteria for definition 1.

Table 13. VE Against First Occurrence of RT-PCR-Confirmed RSV Severe LRTD up to VE Analysis 1 by, mES, Study 006

Definition	RSVPreF3-AS01$_E$ N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ n/T (per 1000)	Placebo N	Placebo n	Placebo n/T (per 1000)	VE % 95% CI (LL, UL)
Definition 1: Clinical symptomology	12466	1	0.1	12494	17	2.5	94.1 (62.4, 99.9)
Definition 2: Supportive therapy	12466	0	0.0	12494	2	0.3	100.0 (-252.1, 100.0)

Source: Adapted from RSV OA=ADJ-006 report, Table 11.10.
Placebo: saline
mES=modified exposed set, defined as participants who received at least the first dose of the study intervention and are included in the ES and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination.
Abbreviations: N=number of participants; n=number of participants with at least one RT-PCR-confirmed RSV LRTD; T (year)=sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years; n/T (per 1000)=Incidence rate of participants reporting at least one event; CI=confidence interval, LRTD=lower respiratory tract disease; RT-PCR= reverse transcriptase-polymerase chain reaction, LL=Lower Limit, UL=Upper Limit, VE=vaccine efficacy

The number of RT-PCR-confirmed RSV severe LRTD cases was too small to make definitive conclusions about VE against RT-PCR-confirmed RSV severe LRTD in Season 1 based on definition 2.

Although the RSVPreF3 investigational vaccine was more reactogenic than Placebo, the majority of ARs were mild-moderate and of short duration. A numerical imbalance was noted in atrial fibrillation within 30 days post vaccination. No imbalances were observed between groups for deaths and pIMDs. The data generated from Study RSV OA=ADJ-006 support the safety and effectiveness of AREXVY.

RSV OA=ADJ-004 is an ongoing Phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of AREXVY and different revaccination schedules up to 3 years following a single dose [annual (3 doses), flexible revaccination (2 doses) and single dose] in adults ≥60 YOA. A total of 1720 subjects were enrolled, of which 1653 received one dose of AREXVY at Day 1 (993 subjects in the RSV Annual group, 329 in the RSV Flexible Revaccination group, and 331 in the RSV 1-Dose group). The study is ongoing, and an interim report including data collected up to Month 6 is submitted to this BLA. At the time of this submission, both the RSV Annual and RSV Flexible Revaccination groups had not received any revaccination but only the first dose. Therefore, all three groups received the same intervention of one dose of AREXVY. The study was conducted at 46 centers in 5 countries: 10 in Finland, 8 in Germany, 3

in Japan, 7 in Taiwan, and 18 in the United States. There was one participant in the RSV Flexible Revaccination group who reported a case of Guillain-Barré Syndrome (GBS), which was recorded as both a related SAE and pIMD. The VRBPAC meeting held on March 1, 2023, expressed concern about this one case of GBS regarding the safety of AREXVY.

RSV OA=ADJ-007 is being conducted to evaluate the immunogenicity, safety and reactogenicity of AREXVY in adults ≥60 YOA when concomitantly administered with FLU-QIV (Fluarix Quadrivalent; GSK). A total of 880 healthy adults ≥60 YOA were randomized 1:1 to one of the two groups. This study was conducted in 14 centers in 3 countries: 7 in New Zealand, 5 in Panama, and 2 in South Africa. The primary objectives to demonstrate non-inferiority of concomitant administration of AREXVY and FLU-QIV were met based on the predefined success criteria of the UL of the 2-sided 95% CI of the group GMT ratio being <1.5 compared to AREXVY or FLU-QIV vaccine administration alone. The ratio of RSV-A neutralizing antibody titers GMTs between the control group and the Co-Ad group 1 month after AREXVY administration had an UL of 1.28 and the ratio of HI antibody titers GMTs for each of the FLU-QIV vaccine strains between the control group and the Co-Ad group 1 month after AREXVY administration was a range of UL of 1.10 – 1.22. The solicited and unsolicited safety results were similar to that of RSV OA=ADJ-006. Two cases of acute disseminated encephalomyelitis (ADEM) were reported in the concomitant use group that were considered as possibly related to either AREXVY or FLU-QIV vaccination. There was no evidence for interference in immune responses to the vaccine antigens contained in AREXVY and FLU-QIV when the vaccines were administered concomitantly compared to separately (FLU-QIV followed 1 month later by AREXVY). Solicited and unsolicited, non-serious adverse events in both study groups were similar in frequency and type of event.

Dose Selection

RSV OA=ADJ-002 was a supportive Phase 1/2 dose and formulation study evaluating three dosages (30 µg, 60 µg, and 120 µg RSVPreF3) with or without AS01 adjuvant. Compared to unadjuvanted formulations, vaccine formulations containing $AS01_E$ or $AS01_B$ induced humoral immune responses and higher frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 markers in vitro among IL-2, CD40L, TNF-alpha, IFN-gamma. Both adjuvanted formulations had acceptable reactogenicity profile. The safety and immunogenicity data provided in this study supported selection of 120 µg RSVPreF3 with $AS01_E$ administered as a single dose for further evaluation in the Phase 3 studies.

Lot Consistency

RSV OA=ADJ-009 was a Phase 3, randomized, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of AREXVY administrated as a single dose in adults ≥ 60 YOA. This study met the predefined study success criteria for demonstration of similar immune responses across 3 lots of AREXVY; the 2-sided 95% CI for pair-wise comparisons of RSVPreF3-specific IgG GMC ratios for 3 vaccine lots were within the pre-defined limit of [0.67, 1.5]. The safety database included 757 adults ≥60 YOA. A total of 4 participants reported at least 1 non-fatal

SAE (fall, sepsis, cholecystitis, and acute myocardial infarction), none of which were considered by the study investigator or FDA to be related to study vaccination. A total of 3 deaths occurred in the study (myocardial infarction, sudden cardiac death, and pleural effusion), none of which were considered by the study investigator or FDA to be related to study vaccination.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) Clinical Investigator (CI) inspections were issued for two foreign and two domestic clinical study sites that participated in the conduct of study protocol 212494. The inspections did not reveal substantive issues that impact the data submitted in this BLA.

c. Pediatrics

A presentation of GSK's Pediatric Plan was made to the FDA Pediatric Review Committee (PeRC) on January 24, 2023. The committee agreed with the applicant's request for a partial waiver in pediatric subjects from birth to 2 years of age because the product would be ineffective and/or unsafe in the pediatric group [Section 505B(a)(5)B)(ii)] and a deferral in pediatric subjects 2 years to less than 18 years of age because the drug or biological product is ready for approval for use in adults before pediatric studies are complete [505B(a)(4)(i)(I)].

7. Safety and Pharmacovigilance

At the time of the data lock points (DLPs), a total of 15,745 AREXVY recipients and 12,499 placebo recipients from four Phase 3 studies were included in the Exposed Set. The median of the durations of follow-up from Day 1 to safety DLP across all Phase 3 studies was 7.2 months (Study 004: 306 days, Study 006: 236 days, Study 007: 211 days, Study 009: 120 days).

Safety evaluation methods were consistent across all seven studies in the clinical development program. Safety evaluation included the following parameters: solicited local and systemic AEs for 4 days postvaccination; unsolicited, non-serious local and systemic AEs through 30 days postvaccination; SAEs/pIMDs/deaths through study end. All participants recorded unsolicited AEs (Days 1-30) on a paper diary card. Participants in the reactogenicity subset also recorded solicited local and systemic reactions (Days 1-4) on the diary card.

AREXVY is noted to have increased reactogenicity when compared to placebo; the rates of Grade 3 reactions after AREXVY vaccination were low (≤1.7%). The frequency of SAEs reported up to 6 months postvaccination was 4.0% and 4.5% in the vaccine and placebo groups, respectively. In both study groups, many of the SAEs were events common to the older adult population and/or associated with underlying medical conditions (e.g., respiratory infections and cardiac disorders).

One (1) SAE (Guillain-Barre syndrome that occurred 9 days after AREXVY vaccination; also categorized as a pIMD) was considered by the study investigator and FDA to be related to vaccination.

Although the solicited and unsolicited safety results were similar to that of Study 006, one (1) death due to acute disseminated encephalomyelitis occurred in a participant 22 days after receiving concomitant AREXVY and seasonal influenza vaccine (Fluarix Quadrivalent; GSK) in Study 007 and it was considered by the study investigator to be possibly related to Fluarix Quadrivalent vaccination and by FDA as possibly related to Fluarix Quadrivalent vaccination or AREXVY vaccination. A numerical imbalance was noted in atrial fibrillation within 30 days postvaccination. No imbalances were observed between groups for deaths and pIMDs.

The data generated from Study RSV OA=ADJ-006 support the safety and effectiveness of AREXVY.

Pharmacovigilance Plan

The applicant must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). In addition to the reporting requirements in 21 CFR 600.80, the applicant must submit adverse experience reports for Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and supraventricular arrhythmia as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS). GBS, ADEM, and supraventricular arrhythmia reports must be submitted as 15-day expedited reports for 3 years following the date of product licensure.

In addition, the Applicant is required to conduct a postmarketing active surveillance study in individuals 60 years and older vaccinated with AREXVY to evaluate the serious risks of GBS and ADEM. The sponsor also commits to evaluating the potential risk of atrial fibrillation as a secondary endpoint in that study.

8. Labeling

The proposed proprietary name, AREXVY, was reviewed and found acceptable by the Advertising and Promotional Labeling Branch (APLB) on November 18, 2022, and their recommendation was accepted by OVRR. CBER communicated the acceptability of the proprietary name to the applicant on December 1, 2022.

The review team negotiated revisions to the PI. All labeling issues regarding the PI and the carton and container labels were resolved following communications with the Applicant. The review team reviewed the proposed Prescribing Information (PI) submitted on May 2, 2023, the carton label submitted on April 24, 2023, and container labels submitted on April 19, 2023, and found them to be acceptable.

9. Advisory Committee Meeting

A Vaccines and Related Biological Products Committee (VRBPAC) meeting was convened on March 1, 2023. A majority of the Committee (10 out of 12 votes) agreed that the data support the safety of AREXVY, and the Committee (11 out of 11 votes) unanimously agreed that the data support the effectiveness of AREXVY for prevention of LRTD caused by RSV in individuals 60 years of age and older.

The committee members emphasized the need for postmarketing surveillance to continue to assess GBS, potential immune-mediated diseases (pIMDs) in general, and atrial fibrillation. Also, the Committee highlighted the incomplete information on safety and effectiveness with repeat vaccination and concomitant use with other vaccines. Several committee members noted the lack of second season efficacy data that are forthcoming, the need for additional studies on prevention of severe outcomes in at-risk populations and the need for repeat vaccination and expressed their opinion that these should be addressed in near future.

10. Other Relevant Regulatory Issues

The submission was granted priority review on November 1, 2022, based on the quality of safety and efficacy data from the pivotal Phase 3 study.

The pre-license inspection (PLI) for the DS and DP manufacturing facilities and the final release testing facility are waived based on their inspection histories and compliance status. The basis for waiving the inspection of these facilities is documented in a separate inspection waiver memo dated March 8, 2023.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in this original BLA submission, the Review Committee recommends approval of AREXVY for the labeled indication and usage.

b. Benefit/Risk Assessment

The Review Committee is in agreement that there are more benefits than risks associated with administering a single dose of AREXVY to individuals 60 years of age and older. However, there are still some uncertainties regarding the long-term immunogenicity and efficacy of AREXVY, its use in immunocompromised populations, concomitant use with relevant vaccines (except the flu vaccine), and the potential for immune-mediated diseases such as GBS and ADEM. Postmarketing safety studies to evaluate GBS, ADEM, and other immune-mediated demyelinating conditions associated with AREXVY have been required. Also, the sponsor has been advised to include cardiac disorders as an important potential risk in the pharmacovigilance plan.

c. Requirements and Recommendation for Postmarketing Activities

The Applicant has committed to conduct the following postmarketing activities, which are specified in the approval letter.

PEDIATRIC REQUIREMENTS

The required studies are listed below.

1. Deferred pediatric study under PREA (Study RSV OA=ADJ-015), to evaluate safety and effectiveness in children and adolescents 2 to 18 years of age.

   Final Protocol Submission: January 31, 2024
   Study Completion Date: April 14, 2026
   Final Report Submission: May 30, 2026

2. Deferred pediatric study under PREA (Study RSV OA=ADJ-016) to evaluate the safety and effectiveness in children and adolescents 2 to 18 years of age.

   Final Protocol Submission: January 31, 2026
   Study Completion Date: April 18, 2028
   Final Report Submission: May 30, 2028

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of GBS and ADEM.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that GSK is required to conduct the following study:

3. EPI-RSV-041 VS US DB (220149), a postmarketing active surveillance study, to evaluate Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) in adults 60 years and older vaccinated with AREXVY in the United States. Using a self-controlled risk interval (SCRI) design, the study will be conducted in the Sentinel System, and evaluate 1.9 million individuals vaccinated with AREXVY.

GSK submitted a timetable on April 17, 2023, which states that they will conduct this study according to the following schedule:

   Final Protocol Submission: June 30, 2024
   Study Completion Date: June 30, 2030
   Final Report Submission: December 31, 2031

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge GSK's written commitment as described in their letter of April 20, 2023, as outlined below:

4. EPI-RSV-041 VS US DB (220149), a postmarketing active surveillance study, to evaluate atrial fibrillation in adults 60 years and older vaccinated with AREXVY in

the United States. Using a self-controlled risk interval (SCRI) design, the study will be conducted in the Sentinel System.

Final Protocol Submission: June 30, 2024
Study Completion Date: June 30, 2030
Final Report Submission: December 31, 2031

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