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U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting March 1, 2023

FDA Review of Efficacy and Safety of AREXVY (RSVpreF3-AS01$_E$) Biologics Licensing Application

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Division of Vaccines and Related Products Applications

Outline

- Introduction
- Overview of Clinical Studies
- Efficacy Data
- Safety Data
- Pharmacovigilance Plan
- Summary and Voting Questions for VRBPAC

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AREXVY– RSVPreF3-AS01$_E$

Vaccine composition	RSV recombinant stabilized prefusion trimeric F (preF3) protein subunit vaccine Each 0.5 mL contains: • 120 µg RSV RSVPreF3 recombinant antigen derived from the RSV fusion surface glycoprotein of an RSV-A strain • AS01$_E$ adjuvant[a]: liposome-based[b] adjuvant system containing 25µg QS-21 and 25µg 3-O-desacyl-4′-monophosphoryl lipid A (MPL).
Dosing regimen	A single 0.5 mL (120µg) dose administered intramuscularly
Applicant's proposed indication	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older

[a]Shingrix (GSK) is adjuvanted with AS01$_B$ (50µg QS-21, 50µg MPL)

[b]Liposomes composed of Dioleoyl phosphatidylcholine (DOPC) and cholesterol in a phosphate-buffered saline solution containing disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water.

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Clinical Studies

Study Number	Country	Description	Population	Study Groups: # Randomized	
				RSVPreF3	Placebo/ Control
RSV OA=ADJ-006 (*Ongoing*) Safety and Efficacy	US, Germany, United Kingdom, Poland, Canada, South Africa, Spain, Japan, Belgium, Finland, Republic of South Korea, Russian Federation, Mexico, Estonia, Australia, Italy, New Zealand	Phase 3, randomized, controlled, Observer-blind	**Adults ≥ 60 years**	RSVPreF3: 12,467	Placebo: 12,499
RSV OA=ADJ-007 Concomitant Influenza QIV	New Zealand, Panama, South Africa	Phase 3, randomized, controlled, Open-label	**Adults ≥ 60 years**	Co-Ad: 442	Control: 443
RSV OA=ADJ-009 Lot consistency	Canada, Sweden, US	Phase 3, randomized, Double-blind	**Adults ≥ 60 years**	RSVPreF3 Lot1, 2, 3: 757	
RSV OA=ADJ-004 (*Ongoing*) Re-vaccination	US, Finland, Germany, Taiwan, Japan	Phase 3, randomized, Open-label **(safety and immunogenicity)**	**Adults ≥ 60 years**	RSV_annual: 993 RSV_flexible revaccination: 329 RSV_1dose: 331	

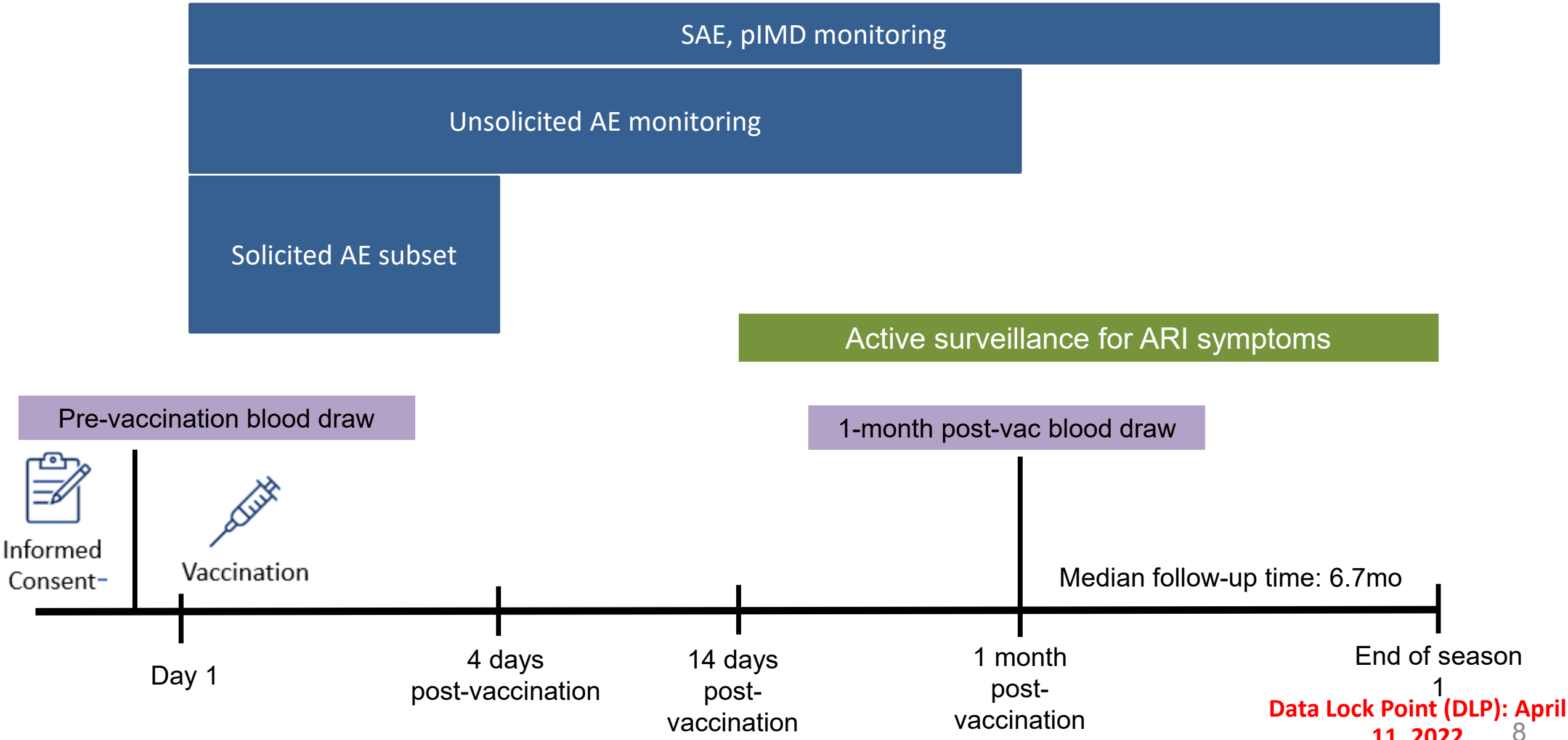
Study 006 Design

Ongoing Phase 3 Efficacy and Safety Study

- Total of 24,966 participants ≥60 years of age
- Study groups: RSVpreF3 or placebo (randomized 1:1), IM injection
- Primary efficacy assessed during first RSV season
- Study to be conducted over 2-3 RSV seasons

- Randomization stratified by age: 60-69 years, 70-79 years, ≥80 years
- Enrolled healthy adults and adults with stable chronic diseases
- Participants were actively monitored for acute respiratory illness (ARI) and lower respiratory tract disease (LRTD) symptoms 14 days after study vaccination
- RT-qPCR testing performed in all participants meeting criteria for acute respiratory illness case definitions.
- Safety monitoring:
  - Subset of participants: solicited local and systemic adverse reactions (4 days)
  - All participants: unsolicited adverse events (1 month); potential immune mediated diseases (pIMDs), and serious adverse events (SAEs) (entire study)

Study 006: Timeline – Season 1



Data Lock Point (DLP): April 11, 2022

This study design figure covers Season 1. The study is planned to cover 3 consecutive RSV seasons in the Northern hemisphere and at least 2 consecutive RSV seasons in the Southern hemisphere.

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Study 006: Case Definitions

Acute respiratory illness (ARI) (Trigger for swabbing)	Presence of at least 2 respiratory symptoms/signs for at least 24 hours OR at least 1 respiratory symptom/sign + 1 systemic symptom/sign for at least 24 hours	
	Respiratory symptoms and signs (e.g.) • Nasal congestion/rhinorrhea • Sore throat • New or increased sputum • New or increased cough	**Systemic symptoms and signs (e.g.)** • Fever/feverishness • Fatigue • Body aches • Headache

Endpoint	Case Definition	
Lower respiratory tract disease (LRTD)	Presence of: at least **2 lower** respiratory symptoms/signs for at least 24 hours including at least **1 lower respiratory SIGN** **OR** at least **3 lower** respiratory symptoms for at least 24 hours	
	Lower respiratory symptoms • New or increased sputum • New or increased cough • New or increased dyspnea (shortness of breath)	**Lower respiratory signs** • New or increased wheezing • New or increased crackles/rhonchi based on chest auscultation • Respiratory rate ≥ 20 respirations/min • Low or decreased oxygen saturation (= O2 saturation <95% or ≤90% if pre-season baseline is <95%) • Need for oxygen supplementation

RT-PCR-confirmed RSV ARI, RSV LRTD, and severe RSV LRTD meet the conditions of their respective case definitions with at least 1 RSV-positive swab detected by RT-PCR

Study 006: Primary Efficacy Endpoint and Objectives

Primary endpoint

Efficacy objective: To demonstrate the vaccine efficacy (VE) of RSVPreF3 in preventing RSV-LRTD, starting on Day 15 after vaccination, in the 1st RSV season.
Primary Endpoint: VE against first occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD

Vaccine efficacy (VE) defined as 1 – Risk Ratio (1-RR)

The primary objective would be met if the lower limit of the CI for VE for RSV-LRTD is >20%

Study 006: Secondary Objectives and Safety Evaluations

Secondary Objectives; Descriptive

- VE by age category, baseline comorbidities, frailty status, and subtype
- VE against severe RSV-confirmed LRTD
- VE against RSV-ARI

Secondary Objective; Immunogenicity

- Humoral immune response based on RSVPreF3 IgG-specific Ab concentrations and NAb titers against RSV-A and/or RSV-B

Safety Evaluations

- Solicited local and systemic adverse events (AE) (Day 1-4)
- Unsolicited adverse reactions (AR) at 30-day
- Serious adverse events (SAE) up to data-lock point (DLP)
- Potential immune mediated diseases (pIMD) up to DLP

Study 006: Analysis Populations

Population	RSVPreF3-AS01$_E$ N=12,467 n (%)	Placebo N=12,499 n (%)	Description
Exposed set (ES)	12,467 (100)	12,499 (100)	Participants who received at least the first dose of the study intervention.
Modified Exposed set (mES)	12,466 (100)	12,494 (100)	Participants in the ES who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination.
Per protocol set (PPS)	12,142 (97.4)	12,176 (97.4)	Participants in the mES who have data available for efficacy endpoint measures and did not have any protocol deviations leading to exclusion.
Solicited Safety set (SSS)	879 (7.1)	878 (7.0)	Participants in the ES who have solicited safety data.

Study 006: Demographics

Characteristic	RSVpreF3-AS01$_E$ N=12467	Placebo N=12499
Sex, n (%)	--	--
Male	5979 (48.0)	6072 (48.6)
Female	6488 (52.0)	6427 (51.4)
Age, years	--	--
Mean age (SD)	69.0 (6.5)	69.6 (6.4)
Median age (min, max)	69.0 (59, 102)	69.0 (59, 98)
60-69 YOA	6963 (55.9)	6980 (55.8)
70-79 YOA	4487 (36.0)	4491 (35.9)
≥80 YOA	1017 (8.2)	1028 (8.2)
Hemisphere, n (%)	--	--
Northern hemisphere	11496 (92.2)	11522 (92.2)
Southern hemisphere	971 (7.8)	977 (7.8)
Frailty Status, n (%)		
Frail	189 (1.5)	177 (1.4)
Pre-Frail	4793 (38.4)	4781 (38.3)
Fit	7464 (59.9)	7521 (60.2)
Unknown	21 (0.2)	20 (0.2)
Comorbidity of interest, n (%)	--	--
At least 1 pre-existing comorbidity of interest	4937 (39.6)	4864 (38.9)
At least 1 pre-existing Cardiorespiratory condition	2496 (20.0)	2422 (19.4)
At least 1 pre-existing Metabolic condition	3200 (25.7)	3236 (25.9)

Study 006: Demographics (cont.)

Characteristic	RSVpreF3-AS01$_E$ N=12467	Placebo N=12499
Race, n (%)	--	--
African American/Black	1064 (8.5)	1101 (8.8)
American Indian or Alaska Native	44 (0.4)	35 (0.3)
Asian	953 (7.6)	956 (7.6)
Native Hawaiian or other Pacific Islander	11 (0.1)	6 (0.0)
White	9887 (79.3)	9932 (79.5)
Other	508 (4.1)	469 (3.8)
Ethnicity, n (%)	--	--
Hispanic/Latino	682 (5.5)	682 (5.5)
Not Hispanic/Latino	11780 (94.5)	11811 (94.5)
Unknown	5 (0.0)	6 (0.0)

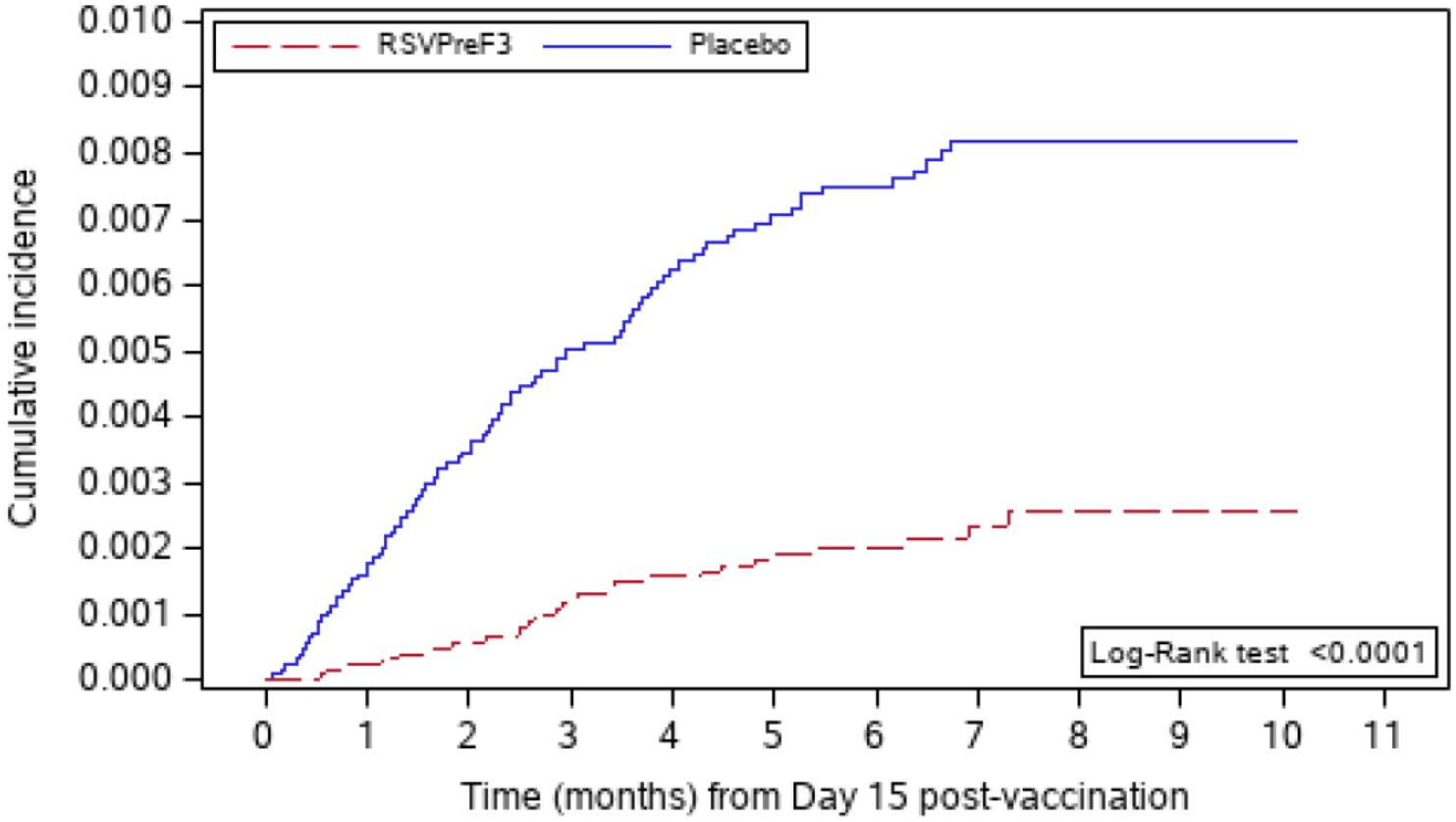
Study 006: LRTD Efficacy, Primary Analysis

VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD Up to VE Analysis 1, mES

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

Study 006: Cumulative Incidence Curves

Cumulative Incidence Curves for RT-qPCR-Confirmed RSV LRTD Reported up to VE Analysis 1, mES



Number at risk

RSVPreF3	12466	12390	12282	11881	11641	11029	8305	5481	2717	570	2	0
Placebo	12494	12390	12268	11853	11597	10973	8255	5441	2697	554	2	0

Cumulative number of cases

RSVPreF3	0	3	7	15	19	23	24	26	27	27	27	27
Placebo	0	22	43	62	76	86	90	95	95	95	95	95

Study 006: LRTD Efficacy – RSV Subtype

VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD Up to VE Analysis 1 by RSV Subtype, mES

Subtype	RSVPreF3-AS01$_E$ N=12466 n	RSVPreF3-AS01$_E$ N=12466 Incidence Rate per 1000 Person-Years	Placebo N=12494 n	Placebo N=12494 Incidence Rate per 1000 Person-Years	VE % 95% CI (LL, UL)
RSV-A	2	0.3	13	1.9	84.6 (32.1, 98.3)
RSV-B	5	0.7	26	3.8	80.9 (49.4, 94.3)

Study 006: LRTD Efficacy – Age Subgroups

VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD up to VE Analysis 1, mES

Subgroup	N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ Incidence Rate per 1000 Person-Years	N	Placebo n	Placebo Incidence Rate per 1000 Person-Years	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)
≥80 YOA	1016	2	3.6	1028	3	5.4	--

For participants ≥ 80 YOA, there were not enough cases to make conclusions regarding VE

Study 006: LRTD Efficacy - Comorbidities

VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD up to VE Analysis 1 by Baseline Comorbidity, mES

Subgroup	RSVPreF3-AS01$_E$ N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ Incidence Rate per 1000 Person-Years	Placebo N	Placebo n	Placebo Incidence Rate per 1000 Person-Years	VE 95% CI (LL, UL)
No pre-existing Comorbidity	7529	6	1.5	7633	22	5.3	72.5 (30.0, 90.9)
A least 1 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)

Study 006: Efficacy- Frailty Status

VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD up to VE Analysis 1 by Frailty Status, mES

Subgroup	RSVPreF3-AS01$_E$ N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ Incidence Rate per 1000 Person-Years	Placebo N	Placebo n	Placebo Incidence Rate per 1000 Person-Years	VE % 95% CI (LL, UL)
Fit	7464	5	1.2	7519	25	5.9	80.0 (46.7, 94.0)
Pre-frail	4792	1	0.4	4778	14	5.5	92.9 (53.4, 99.8)
Frail	189	1	10.4	177	1	10.8	--

The physical frailty status of the participants was assessed at baseline by a Gait Speed test.

- Based on the time required to walk the selected length of walk (3 or 4 meters), participants were categorized into frail, pre-frail, or fit subgroups.

Study 006: Efficacy- RSV Severe-LRTD

VE Against First Occurrence of RT-PCR-Confirmed RSV severe LRTD up to VE Analysis 1 by, mES

Definition	RSVPreF3-AS01$_E$ N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ Incidence Rate per 1000 Person-Years	Placebo N	Placebo n	Placebo Incidence Rate per 1000 Person-Years	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	--

RT-PCR-confirmed severe RSV LRTD Definition 1 "Clinical symptomology"	Presence of a LRTD with at least one of the following criteria: • At least 2 lower respiratory signs • An LRTD episode assessed as 'severe' by the investigator AND With at least one RSV-positive swab detected by RT-PCR
RT-PCR-confirmed severe RSV LRTD Definition 2 "Supportive therapy"	Presence of a LRTD with at least one of the following criteria: • Need for oxygen supplementation • Need for positive airway pressure therapy (e.g., CPAP) • Need for other types of mechanical ventilation AND With at least 1 RSV-positive swab detected by RT-PCR

Study 006: Efficacy-ARI

VE Against First Occurrence of RT-PCR-Confirmed RSV ARI up to VE Analysis 1, mES

RSVPreF3-AS01$_E$ N	RSVPreF3-AS01$_E$ n	RSVPreF3-AS01$_E$ Incidence Rate per 1000 Person-Years	Placebo N	Placebo n	Placebo Incidence Rate per 1000 Person-Years	VE % 95% CI (LL, UL)
12466	27	3.9	12494	95	13.9	71.7 (56.2, 82.3)

Acute respiratory illness (ARI) (Trigger for swabbing)	Presence of at least 2 respiratory symptoms/signs for at least 24 hours OR at least 1 respiratory symptom/sign + 1 systemic symptom/sign for at least 24 hours	
	Respiratory symptoms and signs (e.g.) • Nasal congestion/rhinorrhea • Sore throat • New or increased sputum • New or increased cough	**Systemic symptoms and signs (e.g.)** • Fever/feverishness • Fatigue • Body aches • Headache

Study 007: Concomitant use with Influenza Vaccine (QIV) Study Design

- Phase 3 immunogenicity and safety FLU-QIV (Fluarix Quadrivalent) **concomitant administration study**
- Total of 885 participants were randomized 1:1 to one of two study groups:
  - Co-Ad group (N=442) – Single dose of RSVPreF3 and a single dose of FLU vaccine (Fluarix Quadrivalent; GSK) at Day 1
  - Control group (N=443) – Single dose of FLU vaccine at Day 1 followed by a single dose of RSVPreF3 at Day 31
- Enrolled healthy adults ≥60 YOA including adults with chronic stable medical conditions (e.g., diabetes, hypertension, or cardiac disease)

Study 007: Concomitant use with Influenza Vaccine (QIV)

<u>Primary Immunogenicity Objectives:</u>

- Non-Inferiority (NI) of the immune responses to vaccine antigens contained in RSVPreF3 when co-administered with FLU-QIV (So. Hemisphere) 1-month post-vaccination
  - Criteria for NI were met
- Non-Inferiority (NI) of the immune responses to vaccine antigens contained in FLU-QIV when co-administered with RSVPreF3-AS01$_E$ (So. Hemisphere) 1-month post-vaccination
  - Criteria for NI were met

<u>Safety:</u>

- Rates of solicited ARs and Unsolicited AEs consistent with those seen in Study 006
- Safety profile when RSVPreF3 administered concomitantly with FLU-QIV was acceptable compared to when administered separately.
  - Higher percentage of participants reported solicited administration site events in the Co-Ad group compared to the Control group (Co-Ad 53%, Control 39.9%)
- Two cases of ADEM were reported in the Co-Ad group, one reported as a fatal event

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Study 006: Subject Disposition

Population	RSVPreF3-AS01$_E$ N=12,467 n (%)	Placebo N=12,499 n (%)
Participants withdrawn after vaccination	372 (3.0)	392 (3.1)
Reason for withdrawal	--	--
Adverse Event Requiring Expedited Reporting	68 (0.5)	72 (0.6)
Unsolicited Non-Serious Adverse Event	5 (0.0)	6 (0.0)
Consent Withdrawal, Not Due to an AE	162 (1.3)	173 (1.4)
Migrated/Moved From the Study Area	17 (0.1)	14 (0.1)
Lost To Follow-Up	104 (0.8)	104 (0.8)
Other	16 (0.1)	23 (0.2)
Solicited Safety subset	879 (7.1)	878 (7.0)

DLP: April 30, 2022

Study 006: Safety Overview

Event	RSVPreF3-AS01$_E$ N=12467 n (%)	Placebo N=12499 n (%)
Immediate unsolicited AE within 30 minutes after vaccination[a]	98 (0.8)	18 (0.1)
General disorders and administration site conditions	90 (0.7)	9 (0.1)
Nervous system disorders	10 (0.1)	5 (0.0)
Unsolicited non-serious AE within 30 days	4117 (33.0)	2229 (17.8)
SAEs		
within 30 days	91 (0.7)	91 (0.7)
up to 6 months	522 (4.2)	506 (4.0)
from Day 1 to data lock point	608 (4.9)	607 (4.9)
Deaths to data lock point	49 (0.4)	58 (0.5)
Withdrawal due to AE	23 (0.2)	23 (0.2)
pIMDs up to 6 months post-vaccination	40 (0.3)	34 (0.3)

[a]No episodes of anaphylaxis occurred within 30 minutes after vaccination

Study 006: Solicited Local ARs Within 4 Days

Local Adverse Reactions	RSVPreF3-AS01$_E$ N = 879 (%)	Placebo N = 874 (%)
Pain[a]	--	--
≥ Grade 1	60.9	9.3
Grade 3	1.0	<0.1
Erythema[b]	--	--
≥Grade 1	7.5	0.8
Grade 3	0.2	<0.1
Swelling[b]	--	--
≥ Grade 1	5.5	0.6
Grade 3	0.2	<0.1

[a]Grade 1: does not interfere with activity; Grade 2: interferes with activity; Grade 3: significant pain at rest and prevents normal everyday activities.
[b]Grade 1: 25 mm to 50 mm; Grade 2: >50 mm to 100 mm; Grade 3: >100mm

Study 006: Solicited Systemic ARs Within 4 Days

Systemic Adverse Reactions	RSVPreF3-AS01$_E$ N = 879 (%)	Placebo N = 874 (%)
Fatigue[a]	--	--
≥ Grade 1	33.6	16.1
Grade 3	1.7	0.5
Myalgia[a]	--	--
≥ Grade 1	28.9	8.2
Grade 3	1.4	0.3
Headache[a]	--	--
≥ Grade 1	27.2	12.6
Grade 3	1.3	<0.1
Arthralgia[a]	--	--
≥ Grade 1	18.1	6.4
Grade 3	1.3	0.6
Fever[b]	--	--
≥ Grade 1	2.0	0.3
Grade 3	0.1	0.1

[a]Grade 1: does not interfere with activity; Grade 2: some interference with activity; Grade 3: prevents daily routine activity.

[b]Grade 1 temperature ≥38.0°C by any route (oral, axillary, or tympanic); Grade 3 fever defined as >39.0°C.

Study 006: Unsolicited AEs Within 30 Days

- Rates of non-serious unsolicited AEs were higher in the RSVPreF3, group compared with placebo (RSVPreF3 33.0%, placebo 17.8%). Most common by MedDRA System Organ Class:
  - *General disorders and administration site conditions; Nervous system disorders; Infections and infestations;* and *Respiratory, thoracic and mediastinal disorders*

- Significant imbalance noted in events characterized as *General disorders and administration site conditions* (RSVPreF3 23.5%, placebo 4.6%)
  - *Injection site pain* (15.8% RSVPreF3; placebo 1.4%) and *Asthenic conditions* (RSVPreF3 3.3%; placebo 1.3)

- Numerical imbalance noted in events of **atrial fibrillation**: RSVPreF3: 10 events [0.1%] versus placebo: 4 events [<0.1%] within 30 days post-vaccination
  - All occurred in participants with relevant predisposing/concurrent medical conditions and risk factors
  - Onset: 1 to 30 days post-vaccination (RSVPreF3 median: 18.5; placebo median: 10.5)
  - None of these AEs were fatal
  - None assessed as related by investigator
  - **FDA review of these cases is ongoing**

- Hypersensitivity Reactions (Rash/Injection site rash) occurred in <0.1 to 0.2% of participants

Aggregated Safety Data

Non-fatal SAEs

- SAEs occurring within 6 months after study intervention: 4.0% of vaccine recipients and 4.5% of placebo recipients. Most common by MedDRA System Organ Class:
  - *Nervous system disorders; Infections and infestations;* and *Cardiac disorders*
- One SAE considered related to vaccination by the FDA (Guillain-Barré syndrome 9 days post-vaccination with RSVPreF3)

Overall deaths up to DLP

- Deaths reported in 0.4% of vaccine recipients and 0.5% placebo recipients.
  - Most frequently in the SOCs of *Cardiac Disorders* (0.1% in both groups) and *Infections and Infestations* (0.1% in both groups).
- In Study 007, 1 case of acute disseminated encephalomyelitis (ADEM) in Co-Ad group considered as possibly related to intervention

Aggregated Potential Immune Mediated Diseases (pIMDs)

pIMDs within 6 months after study intervention:

- Overall: 0.4% of RSVPreF3 recipients vs. 0.3% of placebo recipients.
- The most frequently reported by SOC were:
  - *Metabolism and nutrition disorders*
  - *Musculoskeletal and connective tissue disorders*
  - *Nervous system disorders*
- In Study 006 there were 6 pIMDs considered possibly related to RSVPreF3 vaccinations by study investigators:
  - *Bell's palsy (n=2), pancytopenia, Graves' disease (hyperthyroidism), gout, and psoriasis*
- In Study 007, 2 cases of ADEM were considered as possibly related to either RSVPreF3 or FLU-QIV in the Co-Ad group (including one fatal case previously described.)
- In Study 004, 1 case of GBS was considered as related to RSVPreF3

Acute Disseminated Encephalomyelitis

71-year-old male (Co-Ad group):

- Found lying on the floor shaking and shivering requiring hospitalization with a blood glucose reading of 1.4mmol/L seven days post co-administration of the study vaccines.
- Reported as ADEM based on CT scan, Brighton Collaboration Level 3
- The participant died 22 days after co-administration of the study vaccines.

71-year-old female (Co-Ad group):

Medical history of hyperlipidemia and hypertension

- Tiredness and headaches with intermittent double vision, forgetfulness, confusion, hand shaking, gait ataxia and clumsiness 22 days after the co-administration of the study vaccines
- Reported as ADEM based on symptomatology, Brighton Collaboration Level 3
- The participant demonstrated improvement, but the outcome was reported as not resolved by the time of receipt of the study report.

FDA review of these cases is ongoing, additional information has been requested

2 cases of ADEM in Study 007 (N= 890 vaccinees)

No cases of ADEM observed in Study 006 (N=24,966; n=12,467 vaccine) or other studies (N=2,370 vaccinees)

Total: 2 cases/~15,000 vaccinees

Guillain-Barré syndrome

78-year-old female:

Lower limb weakness starting 9 days post-vaccination

- Difficulty walking, developed upper limb and respiratory muscle weakness
- Hospitalized
  - Elevated CSF protein (146 mg/dL), ganglioside immunoglobulins (GM1-IgG) were positive,
  - MRI normal
  - Treated with IVIG for GBS
- Diagnosed with GBS, Brighton Collaboration Level 3
- Discharged from hospital 6 months post-vaccination

1 case of GBS in Study 004
(N= 1633 vaccinees)

- Symptom onset: 9 days post-vaccination

No cases of GBS observed in Study 006 (N=24,966; n=12,467 vaccine) or other studies (n=~1200 vaccinees)

Total: 1 case/~15,000 vaccinees

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Pharmacovigilance Plan

Missing information	Immunocompromised older adults
Surveillance Activities	• A post-authorization clinical trial evaluating AREXVY in immunocompromised individuals is being designed

Important potential risks	Potential Immune-Mediated Disorders (pIMDs)

Surveillance activities	Applicant will conduct passive surveillance activities for continued vaccine safety monitoring, including routine pharmacovigilance and:
	• Expedited reporting for all cases of:
	  • GBS, ADEM, and other immune-mediated demyelinating conditions and neurologic conditions
	  • Supraventricular arrhythmias
	• Aggregate analysis, in periodic safety reports, for:
	  • GBS, ADEM, and other immune-mediated demyelinating conditions
	  • Supraventricular arrhythmias

Note that the following are currently under discussion between FDA and the Applicant:

- Plans for a postmarketing safety study to assess the risk of GBS, ADEM, and other immune-mediated demyelinating conditions among individuals vaccinated with AREXVY.
- Determination of the inclusion of Cardiac Disorders as an *important potential risk* in the PVP.

Outline

- Introduction
- Overview of Clinical Studies
- Pivotal Study Data
- Concomitant Administration Data
- Aggregated Safety Data
- Pharmacovigilance Plan
- Summary and Voting Questions for VRBPAC

Summary: Efficacy

- VE against first occurrence of RT-PCR-confirmed RSV LRTD was 82.6% (96.95% CI 57.9, 94.1) in adults ≥60 YOA
- Subgroup analysis showed that VE was demonstrated for: RSV-A and RSV-B virus subtypes; age groups 60-69 YOA and 70-79 YOA; participants with at least 1 pre-existing comorbidity of interest, and RSV-ARI.
  - VE in participants ≥80 YOA inconclusive due to low number of cases
- VE demonstrated for Severe LRTD based on clinical symptomatology definition but the numbers of accrued cases meeting the definition based on supportive therapy were too small to estimate efficacy precisely.
- Data are not currently available on:
  - Duration of vaccine effectiveness
  - VE in immunocompromised individuals

Summary: Safety

- A total of 15,745 RSVPreF3 recipients from four phase 3 studies were included in the Exposed Set. The median durations of follow-up was 7.2 months.
- RSVPreF3 is noted to have increased reactogenicity when compared to placebo, but the rates of Grade 3 reactions after vaccination in both groups were low (≤1.7%).
- Within 30 days post-vaccination a numerical imbalance was observed for events of atrial fibrillation in Study 006. FDA review of these events is ongoing.
- The frequency of SAEs reported up to 6 months post-vaccination was 4.0% and 4.5% in the RSVPreF3 and placebo groups.
- One (1) SAE (GBS) was considered by the study investigator and FDA to be related to vaccination.
- One (1) death due to ADEM considered by FDA as possibly related to FLU or RSVPreF3 vaccination.
- Up to the time of the DLPs at least one pIMD was reported by 0.4% and 0.3% of vaccine and placebo recipients, including 2 cases of ADEM in the Co-Ad group in Study 007
- A safety update was submitted for an extended safety follow-up at Month 6-12, containing SAE and pIMD data, and FDA review of these data are ongoing at this time.

Voting Questions for VRBPAC

1. Are the available data adequate to support the safety of AREXVY (RSVPreF3+AS01$_E$) when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV?

   Please vote "Yes" or "No"

2. Are the available data adequate to support the effectiveness of AREXVY (RSVPreF3+AS01$_E$) for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older?

   Please vote "Yes" or "No"