Vaccines and Related Biological Products Advisory Committee Meeting
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FDA Briefing Document

Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted
(Proposed Trade Name: Arexvy)

Applicant:
GlaxoSmithKline Biologicals

Table of Contents

Glossary 4
1. Executive Summary 5
2. Background 7
2.1 General Product Information 7
2.3 Clinical Manifestations, Diagnosis, and Treatment 8
2.4 Vaccine-Associated Enhanced Respiratory Disease 8
3. Overview of Clinical Studies 9
3.1 Study 006 12
3.1.1 Objectives 12
3.1.2 Design Overview 15
3.1.3 Population 16
3.1.4 Efficacy Analyses 19
3.1.5 Safety Analyses 24
3.2 Study 007 29
3.2.1 Objectives 29
3.2.2 Design Overview 30
3.2.3 Population 30
3.2.4 Immunogenicity Analyses 32
3.2.5 Safety Analyses 33
4. Integrated Overview of Safety 37
4.1 Safety Assessment Methods 37
4.2 Safety Database 37
4.2.1 Studies/Clinical Trials Used to Evaluate Safety 37
4.2.2 Demographic and Baseline Characteristics of Safety Populations 38
4.3 Safety Results 39
4.3.1 Serious Adverse Events 39
4.3.2 pIMDs 40
4.4 Product-Product Interactions 40
5. Pharmacovigilance Plan 41
6. Overall Summary 41
7. Topics for VRBPAC Discussion 42
8. References 43

List of Tables

Table 1. Clinical Studies 10
Table 2. Case Definitions 12
Table 3. Analysis Populations 17
Table 4. Demographic and Baseline Characteristics 17
Table 5. Subject Disposition, Study 006 18

Table 6. Disposition, Safety Population, Study 006 19
Table 7. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD, mES, Study 006..... 19
Table 8. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD Up to VE Analysis 1 by RSV Subtype, mES, Study 006 20
Table 9.VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD up to VE Analysis 1 by Age Group, mES, Study 006..... 22
Table 10. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD up to VE Analysis 1 by Baseline Comorbidity[a], mES, Study 006 22
Table 11. VE Against First Occurrence of RT-PCR-Confirmed RSV ARI up to VE Analysis 1, mES, Study 006 23
Table 12. VE Against First Occurrence of RT-PCR-Confirmed RSV Severe LRTD up to VE Analysis 1 by, mES, Study 006 24
Table 13. Overview of Adverse Events, Study 006..... 24
Table 14. Percentage of Participants With Solicited Local Adverse Reactions and Systemic Adverse Reactions Within 4 Days of Vaccination in Adults 60 Years of Age and Older, Solicited Safety Set, Study 006 25
Table 15. Demographics. Study 007..... 31
Table 16. Subject Disposition, All Randomized Subjects, Study 007 32
Table 17. Ratio of RSV-A Neutralizing Antibody Titers (IU/mL) GMTs Between the Control Group and the Co-Ad Group, 1 Month After RSVPreF3 Vaccine Dose, PPS, Study 007..... 32
Table 18. Ratio of HI GMTs for Each of the FLU Vaccine Strains Between the Control Group and the Co-Ad Group, 1 Month After RSVPreF3 Vaccine Dose, PPS, Study 007..... 33
Table 19. Overview of Adverse Events, ES, Study 007 34
Table 20. Percentage of Participants With Solicited Local Adverse Reactions Within 4 Days of RSVPreF3-AS01$_E$ Vaccination in Adults 60 Years of Age and Older, Exposed Set, Study 007 .34
Table 21. Percentage of Participants With Solicited Systemic Adverse Reactions Within 4 Days of RSVPreF3-AS01$_E$ Vaccination in Adults ≥60 Years of Age, Exposed Set, Study 007..... 35
Table 22. Data Lock Points for Safety Analyses 37
Table 23. Number of Participants in Integrated Safety Summary, ES 38
Table 24. Number of Vaccine Participants at Safety Analysis Time Points, ES 38
Table 25. Safety Overview..... 39

List of Figures

Figure 1. Cumulative Incidence Curves for qRT-PCR-Confirmed RSV LRTD Reported up to VE Analysis 1, mES..... 21

Glossary

ADEM	acute disseminated encephalomyelitis
AE	adverse event
ARI	acute respiratory illness
$AS01_E$	adjuvant system containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
BMI	body mass index
CD	community dwelling
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DLP	data lock point
eCRF	electronic Case Report Form
ELISA	enzyme-linked immunosorbent assay
EOC	Executive Oversight Committee
EQ-5D	EuroQol 5-dimension health questionnaire
ES	Exposed Set
F protein	fusion protein
FI-RSV	formalin-inactivated RSV
FLU	Fluarix Quadrivalent; GSK
FLU-PRO	Influenza Patient-Reported Outcome
GMT	geometric mean titer
GSK	GlaxoSmithKline Biologicals SA
hMPV	human metapneumovirus
HR-QoL	Health-Related Quality of Life
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
LL	lower limit
LRTD	lower respiratory tract diseases
LTCF	long-term care facility
MedDRA	Medical Dictionary for Regulatory Activities
mES	modified Exposed Set
MPL	3-O-desacyl-4'- monophosphoryl lipid A
NAb	neutralizing antibody
NH	northern hemisphere
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
pIMD	potential immune-mediated disease
PPS	Per Protocol Set
QS-21	*Quillaja saponaria* Molina, fraction 21
RSVPreF3 OA	RSV PreFusion protein 3 Older Adult
RT-PCR	reverse transcriptase polymerase chain reaction
RSV	respiratory syncytial virus
S1	season 1
SAC	Scientific Advisory Committee
SAE	serious adverse event
SH	southern hemisphere
SOC	System Organ Class
SRT	Safety Review Team
US	United States
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
YOA	years of age

1. Executive Summary

GlaxoSmithKline Biologicals submitted a Biologics Licensing Application (BLA) for a recombinant respiratory syncytial virus (RSV) adjuvanted vaccine, Arexvy [RSVPreF3-AS01$_E$], for active immunization to prevent RSV-associated lower respiratory tract disease (LRTD) in adults ≥60 years of age (YOA). Arexvy consists of 120 µg of RSVPreF3 recombinant antigen with AS01$_E$ adjuvant, administered as a single dose.

The BLA contains data from 5 clinical studies to support the safety and effectiveness of RSVPreF3-AS01$_E$. Efficacy was demonstrated based on RSV-confirmed LRTD.

Efficacy of RSVPreF3-AS01$_E$ to prevent RSV-associated LRTD (primary endpoint) in adults ≥60 YOA was evaluated in study RSV OA=ADJ-006 (study 006), an ongoing, phase 3, randomized, placebo controlled, observer-blind, international study. Enrolled participants included adults with underlying cardiorespiratory (e.g., chronic obstructive pulmonary disease, asthma, chronic heart failure) and metabolic conditions (e.g., diabetes, advanced liver, or renal disease). The primary vaccine efficacy (VE) analysis was case-driven, and a planned interim analysis was performed when 47 cases of RSV-confirmed LRTD accrued in the modified exposed analysis set (mES). A total of 24,966 participants (12,467 vaccine,12,499 saline placebo) enrolled in the study, of which 12,466 vaccine and 12,494 placebo recipients were included in mES. The primary endpoint, VE against first occurrence of RT-PCR-confirmed RSV LRTD was 82.6% (96.95% CI 57.9, 94.1). The median follow-up time from Day 15 post-vaccination up to April 11, 2022 (efficacy data lock point) [DLP] was 6.7 months for both study groups. The planned duration of VE and safety follow-up is up to 36 months.

Analyses of secondary outcomes included: VE against first occurrence of RSV-A associated LRTD and RSV-B associated LRTD was 84.6% (95% CI 32.1, 98.3) and 80.9% (95% CI 49.4, 94.3), respectively. VE against first occurrence of RSV LRTD by age subgroup was 82.7% (95% CI 54.9, 94.8) for ⩾65 YOA and 84.4% (95% CI 46.9, 97.0) for participants ⩾70 YOA. VE against first occurrence of RT-PCR-confirmed RSV acute respiratory illness (ARI) was 71.7% (95% CI 56.2, 82.3). VE against RT-PCR-confirmed RSV severe LRTD based on clinical symptomatology (case definition 1) was 94.1% (95% CI 62.4, 99.9). The number of RSV severe LRTD cases based on supportive therapy (definition 2) was too small to make conclusions about VE against RT-PCR-confirmed RSV severe LRTD. The numbers of accrued RSV LRTD cases at the time of the interim analysis were too small to make conclusions about VE in adults ⩾ 80 YOA and by physical frailty (based on the time to walk 3 or 4 meters).

The safety of RSVPreF3-AS01$_E$ after a single dose was evaluated in 5 studies (15,862 final vaccine formulation [120 µg RSVPreF3 + AS01$_E$], 12,600 placebo), which included sites in North America, South America, Europe, Asia, Australia, New Zealand, and South Africa. In the four phase 3 studies, the median duration of safety follow-up for 15,762 vaccinees and 12,600 placebo recipients up to the safety DLP was 7.8 months. Solicited adverse reactions (study 006 reactogenicity subset) were more frequently reported in the vaccine than the placebo group, which commonly included injection site pain (60.9% vs. 9.3%), fatigue (33.6% vs. 16.1%), myalgia (28.9% vs. 8.2%), and were also the most common grade 3 reactions (grade 3 injection site pain [1.0% vs. 0%], grade 3 fatigue [1.7% vs. 0.5%)], grade 3 myalgia [1.4% vs. 0.3%]. Grade 3 injection site pain was defined as significant pain at rest and prevents normal activities and grade 3 fatigue and

myalgia were both defined as preventing normal activity. Fever (defined as oral, axillary, or tympanic T≥38.0°C) occurred in 2.0% and 0.3% of vaccine and placebo recipients, respectively. The percentage of participants in the pooled analysis set reporting at least 1 unsolicited, non-serious AEs through 1-month post-vaccination was 28.7% and 17.8% among vaccine and placebo recipients, respectively; the higher frequency of reported unsolicited adverse events among RSVPreF3-AS01$_E$ recipients than placebo recipients was primarily attributed to events that were consistent with adverse reactions solicited among participants in the study 006 reactogenicity subset.

Up to the time of the DLP, the percentage of participants reporting at least 1 serious adverse event (SAE) in the four phase 3 studies (006, 004, 007, and 009) was 4.0% among vaccine recipients and 4.1% in the placebo group for first occurrence, including 70 (0.4%) and 58 (0.4%) fatal outcomes, respectively. One (1) death due to acute disseminated encephalomyelitis (also reported as a potential immune mediated disease) occurred in a participant 22 days after receiving concomitant RSVPreF3-AS01$_E$ and seasonal influenza (Fluarix Quadrivalent; GSK) [study 007], which was considered by the study investigator and FDA as possibly related to study vaccination. There were no meaningful imbalances in the overall rates of SAEs within 1 month following vaccination between vaccine and placebo recipients in the Safety Population, however a numerical imbalance was noted in events of atrial fibrillation with seven events (0.1%) in the RSVpreF3-AS01$_E$ group and one event (<0.1%) in the placebo group.

Up to the time of the DLP, at least 1 potential immune mediated disease (pIMD) was reported in 0.4% and 0.3% of vaccine and placebo recipients in the four phase 3 studies (006, 004, 007, and 009), respectively. Among vaccine recipients, 1 pIMD (Guillain-Barre syndrome that occurred 9 days after RSVPreF3-AS01$_E$ vaccination) was considered by the study investigator and FDA to be related to vaccination. Six pIMDs (Bell's palsy [n=2], pancytopenia, Graves' disease [hyperthyroidism], gout, and psoriasis) were considered as possibly related to RSVPreF3-AS01$_E$ vaccination by the study investigators and by FDA. Three pIMDs (ADEM [n=2], gout [n=1]) in concomitant vaccine study 007 were considered by the study investigator to be possibly related to influenza vaccine (FLU), and by FDA to be possibly related to FLU or RSVPreF3-AS01$_E$ vaccination. One pIMD (rheumatoid arthritis; medical history of joint pain, onset of symptoms 99 days after vaccination) was consider by the study investigator but not FDA to be possibly related to RSVPreF3-AS01$_E$ vaccination.

In Study 007, there was no evidence for interference in immune responses to the vaccine antigens contained in RSVPreF3-AS01$_E$ and FLU (Fluarix Quadrivalent; GSK) when the vaccines were administered concomitantly compared to separately (FLU followed 1 month later by RSVPreF3-AS01$_E$). There were two cases of acute disseminated encephalomyelitis, described above in the safety section, reported in the concomitant vaccine group considered possibly related to study vaccinations. Solicited and unsolicited, non-serious adverse events in both study groups were similar in frequency and type of event.

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) will convene on March 1, 2023, to discuss and vote on whether the available safety and effectiveness data support licensure of GSK's recombinant respiratory syncytial virus (RSV) adjuvanted vaccine, Arexvy, for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

2. Background

2.1 General Product Information

Procut name: Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted

Proposed trade name: Arexvy

Product description: Arexvy consists of recombinant RSVPreF3 antigen with $AS01_E$ adjuvant, administered as a single dose. The RSV fusion protein was derived from the RSV fusion (F) surface glycoprotein of an RSV-A strain and stabilized in the pre-fusion trimeric conformation (abbreviated RSVPreF3) of the naturally occurring F protein.

Arexvy is a suspension for injection supplied as a single dose vial of lyophilized RSVPreF3 antigen component to be reconstituted with the accompanying vial of $AS01_E$ adjuvant suspension component. The $AS01_E$ adjuvant suspension component is composed of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* and QS-21, a saponin purified from plant extract *Quillaja saponaria* Molina, combined in a liposomal formulation. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in a phosphate-buffered saline solution containing disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride, and water for injection. After reconstitution, a single 0.5mL dose of Arexvy is formulated to contain 120 µg of RSVPreF3 antigen, 25 µg of MPL, and 25 µg of QS-21.

Proposed indication (GSK proposal): RSVPreF3-$AS01_E$ is a recombinant vaccine indicated for active immunization for the prevention of LRTD caused by respiratory syncytial virus (RSV)-A and RSV-B subtypes in adults ≥60 YOA.

Proposed dosage and administration: Arexvy is administrated as a single 0.5 mL dose injected intramuscularly.

2.2 Epidemiology

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 fusion (F) protein is a major surface glycoprotein of the virus, facilitates entry into the host cell. RSV strains are grouped within a single serotype but are separated into 2 major phylogenetic lineages (subtypes RSV-A and RSV-B) originally determined by cross neutralization studies and confirmed to be due mainly to antigenic differences in the RSV glycoprotein G (Cane, 2001; Johnson et al, 1987; Sullender, 2000). Currently, RSV-A and RSV-B strains are differentiated by sequences within the N-terminal 270 nucleotides of the RSV glycoprotein G gene. Both subtypes tend to co-circulate during each season, however, the prevalence of the RSV subtype dominating local annual outbreaks is variable and unpredictable.

2.3 Clinical Manifestations, Diagnosis, and Treatment

RSV is transmitted by large droplets, replicates exclusively in the respiratory epithelium, and causes a wide spectrum of clinical disease, from mild upper respiratory illness to life threatening bronchiolitis and pneumonia. Symptomatic RSV infections and re-infections can manifest as acute upper and/or lower respiratory tract infections. Symptoms consistent with an upper respiratory tract infection include rhinorrhea, pharyngitis, cough, headache, fatigue, and fever.

High risk populations include infants and young children, elderly, immunocompromised individuals (hematologic malignancies, hematopoietic stem cell transplant recipients, lung transplant recipients), and those with underlying cardiopulmonary conditions. In older adults, RSV infections can lead to severe disease, requiring hospitalization for respiratory support, including supplemental oxygen, intubation, and/or mechanical ventilation (Falsey et al, 2019; Prasad et al, 2021). For older adults, treatment for RSV infection is limited to supportive care.

Palivizumab (Synagis; MedImmune), is a monoclonal antibody approved by the FDA for prevention of severe RSV disease in high-risk infants. Currently, there is no vaccine available for prevention of RSV disease.

2.4 Vaccine-Associated Enhanced Respiratory Disease

In the late 1960's, evaluation of a formalin-inactivated RSV vaccine (FI-RSV) in RSV-naïve infants was associated with enhanced respiratory disease (ERD) following subsequent natural RSV infection (Kim et al, 1969). The mechanisms responsible for FI-RSV vaccine associated ERD are still not fully understood, however, studies suggest that inadequate production of neutralizing antibody despite an increase in overall antibody titer and an exaggerated Th2 response after subsequent infection may be implicated (Chin et al, 1969; Kapikian et al, 1969; Fulginiti et al, 1969). The risk of ERD in older children and adults is low, due to priming by prior natural RSV infection (Acosta et al. 2016).

On May 17, 2017, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened to discuss the data needed to support clinical trials of candidate RSV vaccines in RSV-naïve infants, with a particular focus on mitigating the risk of ERD. The consensus among committee members was that although studies in adults and RSV-experienced infants would not necessarily predict subsequent risk of ERD for an RSV-naïve infant population, immunogenicity and safety data from these populations could be supportive of evaluation of RSV vaccine candidates in RSV-naïve infants.

3. Overview of Clinical Studies

Data from 5 clinical studies with RSVPreF3-AS01$_E$ were submitted to support the current Biologics License Application (BLA), summarized in Table 1 below.

RSV OA=ADJ-006 (referred to as Study 006 throughout this document) 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 RSVPreF3-AS01$_E$ in adults ages 60 years and older and is the focus of the BLA review. RSV OA=ADJ-007 (referred to as Study 007 throughout this document) is a Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3-AS01$_E$ vaccine when co-administered with FLU vaccine in adults aged 60 years and above. Results from Study 006 and 007 are discussed in detail in Section 3.1 and 3.2. SAEs and pIMDs from studies 004 and 009 are described in the integrated safety assessment (Section 4).

RSV OA=ADJ-004 (referred to as Study 004 throughout this document) is an ongoing Phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3-AS01$_E$ investigational vaccine 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. Safety data up to the Month 6 timepoint [February 11, 2022] were provided in the BLA and is included in the integrated safety assessment. Immunogenicity data from study 004 are not described in this document since none of the participants were re-vaccinated.

RSV OA=ADJ-009 (referred to as Study 009 throughout this document) is a Phase 3, randomized, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3-AS01$_E$ vaccine administrated as a single dose in adults aged 60 years and above. This study met the predefined study success criteria for demonstration of similar immune response across 3 lots of RSVPreF3-AS01$_E$. 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.

RSV OA=ADJ-002 is 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. The safety and immunogenicity data provided in this study supported selection of 120 µg RSVPreF3-AS01$_E$ administered as a single dose for further evaluation in the phase 3 studies.

Table 1. 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 – 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 – ongoing	Randomized, open-label to evaluate the immunogenicity, safety, and immune persistence of RSVPreF3-AS01$_E$ following different revaccination schedules · [only safety data from this study is 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 – 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 – completed	Randomized, double-blind, lot consistency study	vaccine_Grp1 (Lot 1) vaccine_Grp2 (Lot 2) vaccine_Grp3 (Lot 3)	251 253 253	--- --- ---
Supportive 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
		Total:	15862	12600

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).
4. Main Studies to Support Safety and Effectiveness

This briefing document presents clinical data from four Phase 3 studies (RSV OA=ADJ-006, -004, -007, and -009; abbreviated hereafter as studies 006, 004, 007, and 009.). No additional safety concerns were noted in the analysis of study 002 and the AEs were consistent with the safety data described in the phase 3 studies.

3.1 Study 006

NCT0488696

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-AS01$_E$ investigational vaccine in adults aged 60 years and above."

Vaccine efficacy (VE) data from 15 days post-vaccination up to the VE data lock point (DLP) (median 6.7 months) were provided with the BLA. The planned duration of VE and safety follow-up is up to 36 months. The median safety follow-up time from the day of vaccination (Day 1) to the safety DLP was 7.8 months in the vaccine and the placebo (saline) groups. 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 the time this briefing document was prepared.

Certain secondary objectives including immunogenicity and patient reported outcomes are not presented in this document. Only the study design elements pertaining to the primary clinical endpoint VE and safety endpoints are described in Section 4.

3.1.1 Objectives

Primary Objectives and Endpoints

1. To demonstrate the efficacy of a single dose of the RSVPreF3-AS01$_E$ vaccine to prevent RSV-confirmed LRTD during the first season in adults ≥60 YOA.

   Endpoint: First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, according to the case definition which includes signs and symptoms of lower respiratory tract disease (see Table 2 below).

Table 2. Case Definitions

Endpoint	Case Definition
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

Arexvy (Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted)

Endpoint	Case Definition
Respiratory symptoms and signs	• Nasal congestion/rhinorrhea • Sore throat • New or increased sputum • New or increased cough • New or increased dyspnea (shortness of breath) • New or increased wheezing[c] • New or increased crackles/ronchi[d] based on chest auscultation • Respiratory rate ≥20 respirations/min[d] • Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90% if pre-season baseline is <95%)[d] • Need for oxygen supplementation[d]
Systemic symptoms and signs	• Fever[a]/feverishness[b] • Fatigue • Body aches • Headache • Decreased appetite
RT-PCR-confirmed RSV ARI[e]	An event meeting the case definition of ARI with at least 1 RSV-positive swab detected by RT-PCR.
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[c] • New or increased crackles/ronchi[d] based on chest auscultation • Respiratory rate ≥20 respirations/min[d] • Low or decreased oxygen saturation (=O_2 saturation <95% or ≤90% if pre-season baseline is <95%)[d] • Need for oxygen supplementation[d]
RT-PCR-confirmed RSV LRTD[e]	An event meeting the case definition of LRTD with at least 1 RSV-positive swab detected by RT-PCR.
RT-PCR-confirmed severe RSV LRTD Definition 1 “Clinical symptomology”[e]	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[g] AND With at least one RSV-positive swab detected by RT-PCR

Endpoint	Case Definition
RT-PCR-confirmed severe RSV LRTD Definition 2 "Supportive therapy"[e]	Presence of a LRTD with at least one of the following criteria[h]: • Need for oxygen supplementation[d] • 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

Source: Adapted from RSV OA=ADJ-006 CSR, Appendix 16.1.1.
Abbreviations: ARI=acute respiratory infection; LRTD=lower respiratory tract disease; RSV: respiratory syncytial virus; RT-PCR=reverse transcription polymerase chain reaction
a. Fever is defined as a temperature ≥ 38.0°C by any route.
b. Feverishness is defined as the feeling of having fever without objective measurement.
c. Reported by study participant or investigator.
d. Reported by investigator. Peripheral arterial oxygen saturation (SpO2%) was assessed using pulse oximetry at each protocol defined visit and each ARI visit. For the purpose of the study, the same validated oxygen saturation device has been provided to each study site.
e. Throat and/or nasal swab samples collected at ARI visits for RT-PCR testing were collected within 6 days after ARI onset (i.e., up to Day 7). In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it was not possible to perform the ARI visit within 6 days after ARI onset (i.e., within Day 3 to Day 7), then the interval for this visit and the site swab collection could be extended up to maximum 14 days after ARI onset (i.e., until Day 15).
f. Severe LRTD: defined as an ARI/LRTD episode which prevents normal, everyday activities. Such an event would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.
g. The investigator graded each ARI as severe based on a predefined criteria of: an ARI/LRTD episode which prevents normal, everyday activities. Such an event would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.
h. In case the participant was already receiving any of these for treating/controlling any pre-existing condition, any significant change or adaptation in the used therapy was to be taken into account.

Key Secondary Objectives and Endpoints

1. To evaluate the efficacy of RSVPreF3-AS01$_E$ vaccine to prevent RSV-confirmed LRTD for each RSV subtype (A and B)
2. To evaluate vaccine efficacy in the prevention of RSV-confirmed LRTD by age category, following a single dose of the RSVPreF3-AS01$_E$ vaccine.
3. To evaluate the efficacy of RSVPreF3-AS01$_E$ vaccine RSV-confirmed LRTD in adults ≥60 YOA by baseline comorbidities.
4. To evaluate the efficacy of RSVPreF3-AS01$_E$ vaccine to prevent RSV-confirmed LRTD by baseline frailty status in adults ≥60 YOA.
5. To evaluate the efficacy of RSVPreF3-AS01$_E$ vaccine to prevent severe RSV-confirmed LRTD in adults ≥60 YOA.
6. To evaluate the efficacy of RSVPreF3-AS01$_E$ vaccine to prevent RSV-confirmed ARI in adults ≥60 YOA.

Secondary Endpoints

- First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition, for RSV subtype A and RSV subtype B separately.
- First occurrence of RT-PCR-confirmed RSV-A and/or B-associated severe LRTD
  - For the following age categories: ≥65 YOA, ≥70 YOA, and ≥80 YOA.
  - By baseline comorbidity
  - By baseline frailty status
  - Against severe RSV-confirmed LRTD in adults ≥60 YOA.

Safety Objective and Endpoints

- To evaluate the safety of the RSVPreF3-AS01$_E$ vaccine.
  Endpoints
  - Subset: solicited local and systemic events during the 4-day follow-up period after each vaccination
  - In all participants: Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination, SAEs and pIMDs from the day of vaccination up to 6 months after each vaccination

3.1.2 Design Overview

Study 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 RSVPreF3-AS01$_E$ 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 25040 participants were randomized 1:1:1:3 to either one of three vaccine lots or placebo (saline).

Recruitment into the study began end of May 2021 in the northern hemisphere (NH) and in June 2021 in the southern hemisphere (SH). Surveillance for acute respiratory illness (ARI) is performed during the entire study via spontaneous reporting by the study participant (from Day 1 onwards) and via scheduled site staff contacts (from Day 31 onwards) with different frequencies of contact during the RSV seasons and the inter-season periods. Swab samples were collected for qRT-PCR testing in all participants meeting criteria for ARI case definitions. Only swab samples that were collected within 14 days after ARI onset were considered for case counting and analysis. In the case of multiple RSV events reported for the same participant, only the first event was considered for the primary analysis of all primary/secondary VE endpoints.

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).

This study used a Data Monitoring Committee (DMC) to review unblinded cumulative safety data throughout the study and the interim analysis for efficacy. The DMC was independent of the study team and included only external members.

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 RSVPreF3-AS01$_E$ vaccine lots were pooled, and results presented for RSVPreF3-AS01$_E$ group vs. Placebo group. The primary efficacy objective was met if the LL of the 96.95% CI for VE was >20%.

3.1.3 Population

Participants were included in the study if they were ≥60 YOA at the time of first vaccination, and who live in the community or in a long-term care facility (LTCF). Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension, or cardiac disease, are allowed to participate in this study if the medical condition is considered by the investigator to be stable.

Participants were excluded from the study if they had previous vaccination with an RSV vaccine, any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy (based on medical history and physical examination), any history of dementia or any medical condition that moderately or severely impairs cognition, or recurrent or uncontrolled neurologic disorders or seizures.

3.1.3.1 Populations Enrolled/Analyzed

A total of 26,664 participants were enrolled in the study, of which 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).

Analysis Populations

Populations used for the study analyses are displayed in Table 3 below. The Exposed set was the primary population for efficacy analysis on the following endpoints (without laboratory confirmation of RSV infection): hospitalization, complications, any ARI/LRTD, all-cause mortality. The Modified Exposed set was the primary population for VE analysis for endpoints related to RSV-confirmed cases.

Table 3. Analysis Populations

Population	Description
Enrolled set	Participants who agreed to participate in a clinical study after completion of the informed consent process.
Exposed set (ES)	Participants who received at least the first dose of the study intervention. Analyses were performed according to the study product administered.
Modified Exposed set (mES)	Participants who received at least the first dose of the study intervention, are included in the ES, and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination. The primary and secondary VE analyses were based on the mES.
Per protocol set (PPS)	Participants in the mES who received at least the first dose of the study intervention to which they were randomized, have data available for efficacy endpoint measures, and did not have any protocol deviations leading to exclusion.
Solicited Safety set (SSS)	Participants who received at least the first dose of the study intervention (Exposed Set) and have solicited safety data.

Source: Adapted from STN 125775.0, RSV OA=ADJ-006 Clinical Study Report: Table 9.5

3.1.3.1.1 Demographics

The demographics of participants in the Exposed set are shown in Table 4.

The median age at the time of vaccination was 69.0 years; 13,943 (55.8%) participants were 60 to 69 years of age, 8,978 (36.0%) participants were 70 to 79 years of age, and 2,045 (8.2%) participants were 80 years of age and older. Overall, 79.4% were White, 8.7% were Black, 7.6% were Asian, and 4.3% were characterized as 'other' racial group; 5.5% were of Hispanic or Latino ethnicity; 51.7% were female. The demographic characterizes were similar between the vaccine and placebo groups. The demographics of the Solicited Safety set also generally reflected what was observed in the Exposed set.

Table 4. Demographic and Baseline Characteristics

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	69.0	69.0
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)
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)

Characteristic	RSVpreF3-AS01$_E$ N=12467	Placebo N=12499
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)
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)

Source: Adapted from STN 125775.0, RSV OA=ADJ-006 Clinical Study Report: Table 11.1
Abbreviations: RSVPreF3 = PreFusion protein 3; N = number of participants; n/% = number / percentage of participants in a given category; YOA = Years Of Age
Frailty status: Frail = Participants with a walking speed <0.4m/s or who were not able to perform the test; Pre-Frail = Participants with a walking speed between 0.4-0.99 m/s; Fit = Participants with a walking speed >=1 m/s

3.1.3.1.2 Subject Disposition

Of the 26664 enrolled, 24966 were randomized to receive RSVPreF3-AS01$_E$ (n=12,467) or placebo (n=12,499). Disposition of 24966 participants who contributed to the analyses of safety and efficacy are presented in Table 5 below. The most common reason for exclusion from the per protocol set was due to a vaccine excluded by the protocol having been administered (0.8% of all randomized participants). Up to VE analysis 1, a total of 764 participants (RSVPreF3-AS01E 372 and placebo 392) were withdrawn from the study. The primary reasons for withdrawal up to VE Analysis 1 were: Consent withdrawal not due to an AE or SAE (335 participants overall), Loss to follow-up (208 participants overall), and AE requiring expedited reporting (140 participants overall).

Table 5. Subject Disposition, Study 006

Population	RSVPreF3-AS01$_E$ N=12467 n (%)	Placebo N=12499 n (%)
Exposed Set (ES)	12467 (100)	12499 (100)
Modified Exposed Set (mES)	12466 (100)	12494 (100)
Per Protocol Set	12142 (97.4)	12176 (97.4)
Solicited Safety Set (SSS)	879 (7.1)	878 (7.0)

Source: Adapted from STN 125775.0, RSV OA=ADJ-006 Clinical Study Report: Figure 10.1.
Abbreviations: RSVPreF3-RSV=PreFusion protein 3; N=total number of subjects; n/%=number/percentage of subjects in a given category.

Disposition of 24966 participants who contributed to the safety population are presented in Table 6.

Table 6. Disposition, Safety Population, Study 006

Population	RSVpreF-AS01$_E$ N=12467 n (%)	Placebo N=12499 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.)

Source: Adapted from STN 125775.0, RSV OA=ADJ-006 Clinical Study Report: Table 14.1.2.1
Abbreviations: RSVPreF3-RSV=PreFusion protein 3; N=total number of subjects; n/%=number/percentage of subjects in a given category

3.1.4 Efficacy Analyses

3.1.4.1 Analyses of Primary Endpoint(s)

The VE analysis was case-driven and 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). As of the DLP, there were 47 cases of first-episode RSV LRTD occurring after Day 15 (14 days after vaccination). 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 primary objective was demonstrated, as the lower limit [LL] of the 95% CI for the VE was >20% (Table 7).

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 7. 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 8). The observed VE against first occurrence of LRTD caused by RSV-A was 84.62% (95%CI 32.1, 98.3) and against RSV-B was 80.9% (95% CI 49.4, 94.3).

Table 8. VE Against First Occurrence of RT-PCR-Confirmed RSV LRTD Up to VE Analysis 1 by RSV Subtype, mES, Study 006

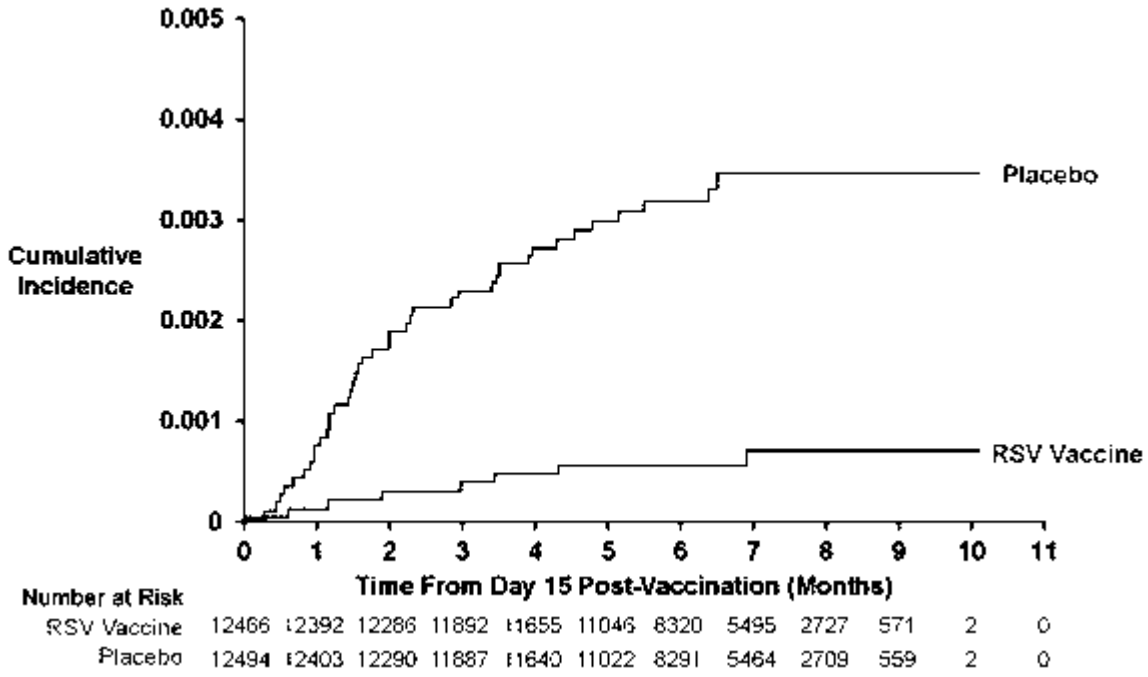
Endpoint	RSVPreF3-AS01$_E$ N=12466 n	RSVPreF3-AS01$_E$ N=12466 n/T (per 1000)	Placebo N=12494 n	Placebo N=12494 n/T (per 1000)	VE % 95% CI (LL, UL)
RT-PCR-confirmed RSV-A LRTD	2	0.3	13	1.9	84.6 (32.1, 98.3)
RT-PCR-confirmed RSV-B LRTD	5	0.7	26	3.8	80.9 (49.4, 94.3)

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

Cumulative Incidence Curve

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 RSVpreF3-AS01$_E$ group. Cases continued to accrue at a faster rate in the placebo group compared to the RSVpreF3-AS01$_E$ 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

3.1.4.2 Subpopulation Analyses

Age

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 9). The number of cases (2 RSVPreF3-AS01$_E$, 3 placebo) among participants ≥80 YOA was too small to make conclusions about VE from the results of VE analysis 1.

Table 9.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

Baseline Co-Morbidities

Table 10 shows the VE analysis 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 10. 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

Baseline Frailty Status

The physical frailty status of all 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. The VE point estimates for RSV-confirmed LRTD were 80.0% (95% CI 46.7, 94.0) in fit, and 92.9% (95% CI 53.4, 99.8) in pre-frail participants, respectively.

A total of 2 RSV-confirmed LRTD cases (1 RSVPreF3-AS01$_E$, 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.

3.1.4.3 Other Secondary Endpoints

RSV-Confirmed ARI

Table 11 shows that the observed VE of a single dose of the RSVPreF3-AS01$_E$ vaccine against first occurrence of RT-PCR-confirmed RSV ARI based on the case definitions described in section 4.1.1 was 71.7% (95%CI 56.2, 82.3). No participants in either group reported more than 1 episode of RSV-confirmed ARI.

Table 11. VE Against First Occurrence of RT-PCR-Confirmed RSV ARI up to VE Analysis 1, mES, Study 006

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)
12466	27	3.9	12494	95	13.9	71.7 (56.2, 82.3)

Source: Adapted from STN 125775, RSV OA=ADJ-006 Clinical Study Report, Table 11.11.
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 ARI 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

Severe RSV-Confirmed LRTD

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 2) 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 12. 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

3.1.5 Safety Analyses

Reactogenicity analysis was performed on the Solicited Safety Set, for participants included in the reactogenicity and immunogenicity subsets. All other safety analyses were performed on all participants included in the ES.

3.1.5.1 Overview of Adverse Events

As of April 30, 2022 (safety DLP), a total of 24,966 participants received at least 1 dose of RSVPreF3-AS01$_E$, (n=12,467) or placebo (n=12,499). Table 13 provides an overview of the rates of adverse events in the RSVPreF3-AS01$_E$ group compared to the placebo group during the study period. The rates of solicited and unsolicited reactions were higher among RSVPreF3-AS01$_E$ compared to placebo recipients. AEs leading to withdrawal from the study occurred in 0.2% of participants in each group. SAEs were reported by 4.2% and 4.0% of participants in the RSVPreF3-AS01$_E$ group and placebo group respectively with none of the SAEs being considered related to study intervention. At the time of data cutoff, AEs that led to death occurred in 49 (0.4%) RSVPreF3-AS01$_E$ recipients and 58 (0.5%) of placebo recipients. None of these deaths were considered related to study intervention.

Table 13. Overview of Adverse Events, Study 006

Event	RSVPreF3-AS01$_E$ n/N (%)[a]	Placebo n/N (%)[a]
Immediate unsolicited AE within 30 minutes after vaccination	98/12467 (0.8)	18/12499 (0.1)
Solicited injection site reaction within 4 days	547/879 (62.2)	88/874 (10.0)
Solicited systemic adverse reaction within 4 days	434/879 (49.4)	204/878 (23.2)
Unsolicited non-serious AE within 30 days	4117/12467 (33.0)	2229/12499 (17.8)

Event	RSVPreF3-AS01$_E$ n/N (%)[a]	Placebo n/N (%)[a]
SAEs	--	--
within 30 days	91/12467 (0.7)	91/12499 (0.7)
up to 6 months	522/12467 (4.2)	506/12499 (4.0)
from Day 1 to data lock point[b]	608/12467 (4.9)	607/12499 (4.9)
Deaths to data lock point[b]	49/12467 (0.4)	58/12499 (0.5)
Withdrawal due to AE[c]	23/12467 (0.2)	23/12499 (0.2)
pIMDs up to 6 months post-vaccination	40/12467 (0.3)	34/12499 (0.3)

Source: Study 006 report.pdf, Table 2.12, page 33; Table 2.14, page 34; Table 14.3.2.4, pages 4803-4816; Table 14.3.1.44, page 3408. Study 006 annex.pdf, Table 7, page 166.
Placebo: saline
a. N=number of participants. n/%=number/percentage of participants presenting at least one type of adverse event
For solicited adverse reactions: N=number of participants with diary card. n/%=number/percentage of participants presenting at least one type of symptom
b. Safety Data lock point=30APR2022.
c. Withdrawn=number of participants who did not complete the last study visit/contact

Solicited Adverse Reactions

A subset of participants (solicited safety set, total N: 1,757 (879 RSVPreF3-AS01$_E$, 874 placebo) was monitored for solicited adverse reactions (Table 14). Within 4 days post-vaccination, the proportion of participants reporting any local reaction was higher in the RSVPreF3-AS01$_E$ group (62.2%) compared to the placebo group (10.0%). The most frequently reported local reaction in both groups was pain at the injection site. Severe (Grade 3) solicited local reactions were rare, reported by 1.5% of RSVPreF3-AS01$_E$ recipients and none of the placebo recipients.

Within 4 days post-vaccination, the proportion of participants reporting any systemic adverse reaction was higher in the RSVPreF3-AS01$_E$ group (49.4%) compared to the placebo group (23.2%). Fatigue was the most frequently reported systemic AR (RSVPreF3-AS01$_E$ 33.6%: placebo 16.1%), followed by myalgia (RSVPreF3-AS01$_E$ 28.9%; placebo 8.2%) and headache (RSVPreF3-AS01$_E$ 27.2%; placebo 12.6%). Fever was reported in 2.0% of participants in the RSVPreF3-AS01$_E$ group and 0.3% in the placebo group. Fever with a maximum temperature ≥39.0°C was reported in 0.1% of participants in each group. Overall, severe (Grade 3) systemic ARs were reported in 3.3% of RSVPreF3-AS01$_E$ recipients and 0.9% of placebo recipients.

Table 14. Percentage of Participants With Solicited Local Adverse Reactions and Systemic Adverse Reactions Within 4 Days of Vaccination in Adults 60 Years of Age and Older, Solicited Safety Set, Study 006

Adverse Reaction	RSVPreF3-AS01$_E$ (%)	Placebo[a] (%)
Local Adverse Reactions	N=879	N=874
Pain	60.9	9.3
Grade 3[b]	1.0	0
Erythema	7.5	0.8
>100 mm	0.2	0
Swelling	5.5	0.6
>100 mm	0.2	0

Arexvy (Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted)

Adverse Reaction	RSVPreF3-AS01$_E$ (%)	Placebo[a] (%)
Systemic Adverse Reactions	N=879	N=878
Fatigue	33.6	16.1
Grade 3[c]	1.7	0.5
Myalgia	28.9	8.2
Grade 3[c]	1.4	0.3
Headache	27.2	12.6
Grade 3[c]	1.3	0
Arthralgia	18.1	6.4
Grade 3[c]	1.3	0.6
Fever[d]	2.0	0.3
Grade 3[d]	0.1	0.1

Source: Adapted from Study 006 report.pdf, Tables 12.2 and 12.3, pages 146-147 and 151-153.
Abbreviations: %=n/N; N=Exposed set for solicited safety set included all participants with at least 1 documented dose; n=Number of participants presenting with solicited adverse reaction described.
Solicited Safety Set: defined as all participants who received at least the first dose of the study intervention (ES) and have solicited safety data.
a. Placebo: saline
b. Grade 3 pain: Defined as significant pain at rest and prevents normal everyday activities.
c. Grade 3 fatigue, myalgia, headache, arthralgia: Defined as preventing normal activity.
d. Fever defined as a temperature ≥38.0°C by any route (oral, axillary, or tympanic); Grade 3 fever defined as >39.0°C.

The median duration of injection site adverse reactions reported after RSVPreF3-AS01$_E$ vaccination within 4 days post-vaccination was 2.0 days for all reactions in the RSVPreF3-AS01$_E$ group and 1.0 to 4.0 days in the placebo group depending on the reaction reported. The median duration of systemic adverse reactions reported after RSVPreF3-AS01$_E$ vaccination and placebo injection ranged from 1.0 day to 2.0 days in both groups.

Unsolicited AEs (Non-Serious): Within 30 Days Postvaccination

Rates of non-serious unsolicited AEs within 30 days postvaccination were higher in the RSVPreF3-AS01$_E$, group compared with placebo (vaccine 33.0% vs placebo 17.8%). The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) included *General disorders and administration site conditions* (vaccine 23.5% vs placebo 4.6%), *Nervous system disorders* (vaccine 6.4% vs placebo 3.9%), *Infections and infestations* (vaccine 3.9% vs placebo 4.0%), *Respiratory, thoracic, and mediastinal disorders* (vaccine 4.0% vs placebo 3.5%), and *Musculoskeletal and connective tissue disorders* (vaccine 4.4% vs placebo 2.6%).

The discordant percentages of *General disorders and administration site conditions* in RSVPreF3 group were primarily due to *Injection site pain* with 15.8% of RSVPreF3-AS01$_E$ recipients reporting this unsolicited AE compared to 1.4% in the placebo group and *Asthenic conditions* (vaccine 3.3% vs placebo 1.3%). The discordant percentages of *Nervous system disorders* in the RSVPreF3-AS01$_E$ group were primarily due to *Headaches* with 6.4% of vaccine recipients reporting this AE compared to 3.9% in the Placebo group. The discordant percentages of *Musculoskeletal and connective tissue disorders* in the RSVPreF3-AS01$_E$ group were primarily due to *Muscle pains* with 1.2% of vaccine recipients reporting this AE compared to 0.4% in the placebo group.

At least 1 Grade 3 unsolicited AE was reported in 2.0% of participants in the RSVPreF3-AS01$_E$ group and in 1.3% in the placebo group. The most frequent types reported by SOC were similar to those reported as any grade AEs being *General disorders and administration site conditions* (vaccine 0.6% vs placebo 0.1%), *Nervous system disorders* (vaccine 0.3% vs placebo 0.2%), and *Infections and infestations* (vaccine 0.2% vs placebo 0.3%). Grade 3 unsolicited AEs assessed as related to study intervention by the study investigator were consistent with reactogenicity symptoms among participants in the reactogenicity subset; FDA agrees with the study investigator's assessment.

3.1.5.2 Deaths

Deaths (Day 1 to data lock point) were reported in 0.4% and 0.5% in the RSVPreF3-AS01$_E$ group and the placebo group, respectively. The most frequently reported fatal SAE (by SOC) were *Cardiac Disorders* and *Infections and Infestations*. In general, the causes of death among study participants were representative of the most common causes of death among the elderly adult population.

Two deaths occurring within 6 months of study intervention were considered by the study investigator to be related to study intervention [RSVPreF3-AS01$_E$ (n=1): cardiopulmonary failure, Placebo (n=1): Pulmonary embolism]. Based on independent review of event narratives, FDA considered the deaths to be more likely attributable to the participant's underlying medical conditions and risk factors (e.g., hypertension, diabetes mellitus Type II, smoking habit) and/or concurrent medical conditions (e.g., COPD, asthma) and does not consider the events as related to study intervention.

3.1.5.3 Nonfatal Serious Adverse Events

The frequency of non-fatal SAEs reported within 30 days after vaccination was 0.7% in both the RSVPreF3-AS01$_E$ and placebo groups. A higher number of participants in the RSVPreF3-AS01$_E$ group compared to the placebo group reported atrial fibrillation as an unsolicited event (vaccine: 10 events [0.1%], placebo: 4 events [<0.1%]), of which 8 were SAEs (vaccine: 7, placebo: 1). Three SAEs corresponded to new onset atrial fibrillation (2 in RSVPreF3-AS01$_E$ group; 1 in placebo group) with a time to onset from 12 to 24 days after vaccination. All atrial fibrillation SAEs occurred in participants age 64 to 77 years old with relevant predisposing/concurrent medical conditions and risk factors. None of these SAEs were fatal. FDA review of these cases is ongoing.

The frequency of non-fatal SAEs reported up to 6 months post-vaccination was 4.2% in the RSVPreF3-AS01$_E$ group and 4.0% in the placebo group. SAEs were most commonly reported in the following SOCs*: Infections and Infestations* [0.9% RSVPreF3-AS01$_E$, 0.9% placebo, frequently due to COVID-19 (0.2% participants in each study group)]*, Cardiac Disorders* [0.7% RSVPreF3-AS01$_E$, 0.7% placebo, frequently due to ischemic coronary artery disorders (0.2% RSVPreF3-AS01$_E$, 0.3% placebo)]*,* and *Nervous system disorders* [0.5% RSVPreF3-AS01$_E$, 0.5% placebo group, mostly due to central nervous system (CNS) hemorrhages and cerebrovascular accidents (0.2% in each study group)]. Atrial fibrillation was reported in 0.1% of RSVPreF3-AS01$_E$ and 0.1% of placebo participants.

Also, please see section 4.3.1.

None of the non-fatal SAEs in the study were considered by the study investigators or by FDA to be related to RSVPreF3-AS01$_E$ vaccination.

3.1.5.4 Potential Immune Mediated Disease

Potential Immune-Mediated Disease (pIMDs)

From Day 1 to the 6-month data lock point, the frequency of pIMDs was 0.3% in both RSVPreF3-AS01$_E$ and placebo groups (n=40 RSVPreF3-AS01$_E$, n=34 placebo). Three subjects reported 2 pIMD events with 2 of the subjects reporting separate episodes of gout and the third having a significant medical history of autoimmune disease. The most frequently reported pIMDs were in the SOCs: *Metabolism and nutrition* (vaccine n=11 vs placebo n=10; all events being gout), *Musculoskeletal and connective tissue disorders* (vaccine n=10 vs placebo n=5), and *Nervous system disorders* (vaccine n=5 vs placebo n=3).

Four SAEs in the RSVPreF3-AS01$_E$ group were also considered to be pIMDs compared to 10 in the placebo group.

Eleven pIMDs were considered by the study investigator to be possibly related to study intervention (6 RSVPreF3-AS01$_E$, 5 placebo group). Of the 11 pIMDs, six (gout, pancytopenia, Bell's palsy [n=2], psoriasis, Graves' Disease) that were reported by RSVPreF3-AS01$_E$ recipients and considered as possibly related to study intervention by FDA.

Narratives for the 11 events considered as possibly related by the study investigator are presented below:

RSVPreF3-AS01$_E$

- *Gout*: A 61-year-old male with a past medical history of gout developed an exacerbation (inflammation in the left foot) 1 day following study intervention. 148 days after RSVPreF3-AS01$_E$ vaccination, the participant developed articular gout.
- *Pancytopenia*: A 75-year-old male developed weakness, fatigue, bruising, shortness of breath, hot sweats, dizziness, and chills with the development of pancytopenia 183 days after RSVPreF3-AS01$_E$ vaccination.
- *Bell's palsy*: A previously healthy 72-year-old male developed new onset Bell's palsy 196 days following RSVPreF3-AS01$_E$ vaccination.
- *Bell's palsy:* A 78-year-old male developed right-sided muscle weakness of face, dysrhythmia, visual issues, and stroke 41 days after RSVPreF3-AS01$_E$ vaccination, and was diagnosed with Bell's palsy (Grade 3, SAE). The event was considered as possible beginning of Herpes zoster opticus/ophthalmicus.
- *Psoriasis (aggravated):* A 74-year-old male with a history of psoriasis presented with aggravation of his underlying psoriasis 4 days following study intervention.
- *Graves' Disease:* A 62-year-old female with no relevant medical conditions was diagnosed with Graves' Disease 272 days from study intervention.

Placebo

- *Immune thrombocytopenia, atrial fibrillation, gout*: A 78-year-old male with a history of ankylosing spondylitis developed symptoms of intermittent headaches, chills, dizziness, fatigue developed immune thrombocytopenia (Grade 3, SAE) 6 days following study intervention. Atrial fibrillation and gout occurred >70 days after vaccination.
- *Trigeminal neuralgia*: A 76-year-old male developed trigeminal neuralgia 14 days after receiving placebo.
- *Polyarthritis*: A 75-year-old female with a history of joint pain developed polyarthritis 2 days following study administration. At Visit 2 the subject reported to have history of joint pain, right knee joint pain, and ankle joint pain with moderate muscle pain on day 3 and arthralgia on day 4.
- *Giant cell arteritis*: A 90-year-old male with a history of macular degeneration developed acute visual changes and was reported with giant cell arteritis (Grade 3, SAE) 32 days from study intervention. He underwent biopsy which confirmed the diagnosis of giant cell arteritis. The subject's symptoms progressed (bilateral blindness) despite treatment with steroids.
- *Psoriasis*: A 74-year-old male with a history of psoriasis reported psoriasis aggravated during a monthly surveillance phone call 4 days following study intervention.

3.1.5.5 Dropouts and/or Discontinuations

One hundred and twenty-one SAEs were reported in participants who withdrew from the study. One event in the RSVPreF3-AS01E group was considered as possibly related by the study investigator (acute myeloid leukemia with onset of symptoms 17 days post-vaccination). FDA did not consider this event to be related to vaccination.

3.2 Study 007

NCT 04841577

Title: "A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3-AS01$_E$ vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above."

This study was conducted to evaluate the immunogenicity, safety and reactogenicity of RSVPreF3-AS01$_E$ vaccine in adults ≥60 YOA when co-administered with Fluarix Quadrivalent (FLU; GSK). Clinical data up to the Month 6 timepoint for immunogenicity and up to the DLP for safety at Month 6 were provided in the BLA. Only the study design elements pertaining to these data are presented in this briefing document.

3.2.1 Objectives

Primary Objectives and Endpoints

1. To demonstrate the non-inferiority of RSVPreF3-AS01$_E$ vaccine when co-administered with the FLU vaccine compared to RSVPreF3-AS01$_E$ vaccine administration alone

Endpoint: RSV-A neutralization GMT, measured at 1 month after the RSVPreF3-AS01$_E$ vaccine.

2. To demonstrate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3-AS01$_E$ vaccine compared to FLU vaccine administration alone

   Endpoint: HI GMT for each influenza vaccine strain, measured at 1 month after the FLU vaccine dose

Pertinent Secondary Objectives and Endpoints

1. To evaluate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3-AS01$_E$ vaccine compared to FLU vaccine administered alone.

   Endpoint: HI seroconversion rate (SCR) for each of the FLU vaccine strains, measured at 1 month after the FLU vaccine dose

2. To evaluate the safety and reactogenicity following administration of the RSVPreF3-AS01$_E$ vaccine and FLU vaccine, co-administered or administered alone.

   Endpoints:

   Percentage of participants reporting

   - Solicited events with onset within 4 days after vaccine administration
   - Unsolicited AEs within 30 days after vaccine administration
   - SAEs and pIMDs after vaccine administration up to study end

3.2.2 Design Overview

Study 007 is a phase 3, randomized, self-contained, open-label, multi-country study with objectives to evaluate immunogenicity, reactogenicity, and safety of a single dose of RSVPreF3-AS01$_E$ vaccine when concomitantly administered with a single dose of FLU vaccine (Fluarix Quadrivalent; GSK) compared to sequential administration of FLU vaccine and RSVPreF3-AS01$_E$ 1-month post-vaccination. 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.

This study has 2 parallel arms: A Co-Ad group in which participants received a single dose of RSVPreF3-AS01$_E$ and a single dose of FLU vaccine at Visit 1 (Day 1); and a Control group in which participants will receive a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of RSVPreF3-AS01$_E$ at Visit 2 (Day 31).

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.

3.2.3 Population

Except for 1 exclusion criterion (administration of an influenza vaccine during the 6 months preceding the study FLU vaccine administration), the eligibility criteria in this study were the same as Study 006 (see Section 3.1.3).

3.2.3.1 Demographics

The demographics for participants in the Exposed set are shown in Table 15.

Among subjects in the ES, there were more females (52%) than males and the median age was 67 YOA. Overall, the majority of subjects were Mixed Race (49%), followed by White (31%), Black/African American (16.3%), and Māori (1.6%). The majority of subjects reported Not Hispanic or Latino ethnicity (66%).

Table 15. Demographics. Study 007

Characteristic	Co-Ad group N=442	Control group N=443
Sex, n (%)	--	--
Male	214 (48.4)	215 (48.5)
Female	228 (51.6)	228 (51.5)
Age, years	--	--
Mean age (SD)	68.4 (6.9)	68.6 (6.9)
Median age (min, max)	67.0 (59, 106)	68.0 (59, 101)
60-69 YOA	260 (58.8)	259 (58.5)
70-79 YOA	144 (32.6)	144 (32.5)
≥80 YOA	38 (8.6)	40 (9.0)
Race, n (%)	--	--
African American/Black	72 (16.3)	70 (15.8)
Asian	4 (0.9)	5 (1.1)
Native Hawaiian or other Pacific Islander	2 (0.5)	1 (0.2)
White	137 (31.0)	135 (30.5)
Maori	7 (1.6)	5 (1.1)
Mixed Race	218 (49.3)	227 (51.2)
Other	2 (0.5)	0 (0.0)
Ethnicity, n (%)	--	--
Hispanic/Latino	152 (34.4)	155 (35.0)
Not Hispanic/Latino	290 (65.6)	287 (64.8)
Unknown	0 (0.0)	1 (0.2)
Country, n (%)	--	--
New Zealand	145 (32.8)	145 (32.7)
Panama	153 (34.6)	157 (35.4)
South Africa	144 (32.6)	141 (31.8)

Source: Adapted from STN 125775.0, RSV OA=ADJ-007 Clinical Study Report: Table 11.1

3.2.3.2 Subject Disposition

Of the 890 enrolled participants, 885 were included in the Exposed set (n=442 Co-Ad group; n=443 Control group). The per protocol sets for immunogenicity for Visit 2 and Visit 3 included 837 and 397 participants, respectively (Table 16).

Table 16. Subject Disposition, All Randomized Subjects, Study 007

Population	Co-Ad Group N=445 n (%)	Control N=445 n (%)
Enrolled	445 (100)	445 (100)
Exposed Set	442 (99.3)	443 (99.6)
Per Protocol Set (for immunogenicity) (Visit 2)	427 (96.0)	410 (92.1)
Per Protocol Set (for immunogenicity) (Visit 3)	--	397 (89.2)

Source: Adapted from study 007 report.pdf, Figure 10.1.
Abbreviations: Co-Ad=co-administration; RSVPreF3-RSV=PreFusion protein 3; Control group=participants receiving a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3-AS01$_E$ vaccine at Visit 2 (Day 31); GMT=geometric mean titer, 95% CI=95% confidence interval; LL=Lower Limit; UL=Upper Limit; N=total number of subjects; n/%=number/percentage of subjects in a given category.

Of the 885 subjects in the ES, 63 subjects (7.0%) had one or more protocol deviations that resulted in exclusion from the PPS analysis; 13 (2.9%) in the Co-Ad group and 50 (11.2%) in the Placebo group. The most common reason for protocol deviation was related to missed/out of window assessment or out of window treatment administration (4 participants in the Co-Ad group and 37 participants in the Control group) followed by study treatment not administered per protocol (17 participants in the Control group)

3.2.4 Immunogenicity Analyses

3.2.4.1 Analyses of Primary Endpoint(s)

The primary analyses of immunogenicity were performed on the PPS. As the percentage of participants with serological results excluded (eliminations) from the PPS for analysis of immunogenicity at the end-of-study was 2.7% in the Co-Ad group and 5.6% in the Control group at Visit 2, and 6.1% in the Control group at Visit 3, a second analysis based on the ES was performed to complement the PPS analysis.

Table 17 shows the ratio of RSV-A neutralizing antibody titers (IU/mL) GMTs between the control group and the Co-Ad group 1 month after RSVPreF3-AS01$_E$ administration. Non-inferiority of the Co-Ad group compared to the Control group was met with an UL of 1.28 based on the pre-specified success criterion of the UL of the 2-sided 95% CI of the group GMT ratio being <1.5.

Table 17. Ratio of RSV-A Neutralizing Antibody Titers (IU/mL) GMTs Between the Control Group and the Co-Ad Group, 1 Month After RSVPreF3 Vaccine Dose, PPS, Study 007

Time Point	Co-Ad group N=427	Control Group N=398	GMT Ratio: Control Group vs Co-Ad[a]	95% CI (LL, UL)
GMT[a]	21178.1	24665.0	1.13	(1.00, 1.28)

Source: Adapted from study 007 report.pdf, Table 14.2.2.2.1.
Abbreviations: Co-Ad group=Participants receiving a single dose of RSVPreF3-AS01$_E$ vaccine and a single dose of FLU vaccine at Visit 1 (Day 1); Control group=participants receiving a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3-AS01$_E$ vaccine at Visit 2 (Day 31); N=number of participants with available results; %=percentage of participants with titer within the specified range
GMT=geometric mean titer, 95% CI=95% confidence interval; LL=Lower Limit; UL=Upper Limit
Per-protocol set (PPS): defined as defined as subjects who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination data, minus participants with protocol deviations that lead to exclusion.
a. comparison is done using the adjusted group ratio of GMT (Control group/Co-Ad group) (ANCOVA model applied to the logarithm-transformed titers).

Table 18 shows the ratio of HI antibody titers GMTs for each of the FLU vaccine strains between the control group and the Co-Ad group 1 month after RSVPreF3-AS01$_E$ administration. Non-inferiority of the Co-Ad group compared to the Control group was met with a range of UL of 1.10 – 1.22 based on the pre-specified success criterion of the UL of the 2-sided 95% CI of the group GMT ratio being <1.5.

Table 18. Ratio of HI GMTs for Each of the FLU Vaccine Strains Between the Control Group and the Co-Ad Group, 1 Month After RSVPreF3 Vaccine Dose, PPS, Study 007

Strain Time Point	Co-Ad Group N=427 95% CI (LL, UL)	Control Group N=411 95% CI (LL, UL)	GMT Ratio: Control Group vs Co-Ad Group 95% CI (LL, UL)
FLU A/Hong Kong	--	--	--
GMT[a]	295.2 (263.6, 330.6)	346.8 (306.6, 392.3)	1.17 (1.02, 1.35)
FLU A/Victoria	--	--	--
GMT[a]	267.1 (235.6, 302.8)	325 (282.5, 374.9)	1.22 (1.03, 1.44)
FLU B/Phuket	--	--	--
GMT[a]	28.9 (26.0, 32.1)	34.8 (31.1, 39.0)	1.17 (1.04, 1.32)
FLU A/Washington		--	--
GMT[a]	41.6 (37.1, 46.6)	47.9 (41.9, 54.8)	1.10 (0.95, 1.26)

Source: Adapted from study 007 report, page 65, Table 11.5.
Abbreviations: Co-Ad group=Participants receiving a single dose of RSVPreF3-AS01$_E$ vaccine and a single dose of FLU vaccine at Visit 1 (Day 1); Control group=participants receiving a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3-AS01$_E$ vaccine at Visit 2 (Day 31); N=number of participants with available results.
Per-protocol set (PPS): defined as defined as subjects who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination data, minus participants with protocol deviations that lead to exclusion.
GMT=geometric mean titer, 95% CI=95% confidence interval; LL=Lower Limit; UL=Upper Limit
a. comparison is done using the adjusted group ratio of GMT (Control group/Co-Ad group) (ANCOVA model applied to the logarithm-transformed titers).

3.2.4.2 Analyses of Secondary Endpoints

At 1-month post-vaccination (Day 31, Visit 2), the percentage of participants with HI antibody titers equal to or above the seroconversion rate (SCR) was: 54.3%, 78.9%, 28.8%, and 35.6% of participants in the Co-Ad group and 56.8%, 83.4%, 32.7%, and 35.9% of participants in the Control group for FLU A/H3N2, FLU A/H1N1, FLU B/Yamagata, and FLU B/Victoria strain, respectively.

At 1-month post-vaccination (Day 31, Visit 2), the group difference (Control group minus Co-Ad group) in the percentage of participants with HI SCR for FLU A/H3N2, FLU A/H1N1, FLU B/Yamagata, and FLU B/Victoria strains was 2.50 (95% CI: -4.24, 9.20), 4.49 (95% CI: -0.82, 9.79), 3.88 (95% CI: -2.38, 10.12), and 0.26 (95% CI: -6.23, 6.75), respectively. The UL of the 2-sided 95% CI on the group difference in SCR was below 10% for all strains except for FLU B/Yamagata (10.12).

3.2.5 Safety Analyses

3.2.5.1 Overview of Adverse Events

A total of 885 participants were included in the ES (442 participants in the Co-Ad group and 443 participants in the Control group). Table 19 provides an overview of the rates of adverse events in the Co-Ad group compared to the Control group during the study period. The rates of solicited adverse reactions and unsolicited adverse events were comparable between the two groups. No participants withdrew from the study due to an AE. Non-fatal SAEs were reported by 3.4% and 4.5% of participants in the Co-Ad group

and Control group respectively with none of the SAEs being considered related to study intervention. AEs that led to death occurred in 4 (0.9%) in the Co-Ad group and 8 (1.8%) of those in the Control group.

Table 19. Overview of Adverse Events, ES, Study 007

Event	Co-Ad n/N (%)	Control n/N (%)
Solicited RSVPreF3-AS01$_E$ injection site reaction within 4 days	242/438 (55.3)	167/419 (39.9)
Solicited systemic adverse reaction within 4 days[a]	176/438 (40.2)	143/419 (34.1)
Unsolicited non-serious AE within 30 days[b]	83/442 (18.8)	105/443 (23.7)
SAEs	--	--
Up to 6 months[b]	15/442 (3.4)	20/443 (4.5)
Deaths[b]	4/442 (0.9)	8/443 (1.8)
Withdrawal due to AE[b]	--	--
pIMDs up to 6 months post-vaccination[b]	5/442 (1.1)	1/443 (0.2)

Source: Study 007 report.pdf, Table 14.3.1.2, Table 14.3.1.6., Table 12.3.
Co-Ad group=Participants receiving a single dose of RSVPreF3-AS01$_E$ vaccine and a single dose of FLU vaccine at Visit 1 (Day 1); Control group=participants receiving a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3-AS01$_E$ vaccine at Visit 2 (Day 31);
Exposed Set (ES): defined as all subjects with at least one documented study vaccine administered. N=number of participants with safety data available for the specified adverse event. n/%=number/percentage of participants presenting the specified adverse event.
[a] Co-Ad group: Visit 1 (FLU and RSVPreF3-AS01$_E$); Control: Visit 2 (RSVPreF3-AS01$_E$ alone).
For solicited adverse reactions: N=number of participants with diary card. n/%= number/percentage of participants presenting at least one type of symptom.
[b] Events described in Control group after any dose (i.e., after FLU or RSVPreF3-AS01$_E$ vaccination)
Withdrawn=number of participants who did not complete the last study visit/contact.

Solicited Adverse Reactions

Solicited AEs within 4 days of vaccination were reported in 63.7% of participants in the Co-Ad group and 56.6% of participants in the control group.

Solicited Administration-Site Events

Table 20 presents the percentages of solicited local adverse reactions following RSVPreF3-AS01$_E$ vaccination. Within 4 days post-vaccination, the proportion of participants reporting any local reaction was similar between the two groups (Co-Ad 53.6%; Control 44.5%). The most frequently reported local reaction in both groups within 4 days of RSVPreF3-AS01$_E$ vaccination was pain at the injection site (Co-Ad 47.9%, Control 39.1%). Severe (Grade 3) solicited local reactions were reported as 3.0% in the Co-Ad group and 1.4% in the Control group within 4 days of any dose.

Table 20. Percentage of Participants With Solicited Local Adverse Reactions Within 4 Days of RSVPreF3-AS01$_E$ Vaccination in Adults 60 Years of Age and Older, Exposed Set, Study 007

Adverse Reaction	Co-Ad (Visit 1) N=438 n (%)	Control (Visit 2) N=419 n (%)
Pain	210 (47.9)	164 (39.1)
Grade 3	12 (2.7)	6 (1.4)
Erythema	18 (4.1)	9 (2.1)
>100 mm	0 (0)	0 (0)

Adverse Reaction	Co-Ad (Visit 1) N=438 n (%)	Control (Visit 2) N=419 n (%)
Swelling	14 (3.2)	4 (1.0)
>100 mm	0 (0)	0 (0)

Source: Adapted from Study 007 report.pdf, Table 12.1.
Abbreviations: %=n/N; N=Exposed set for solicited safety set included all participants with at least 1 documented dose; n=Number of participants presenting with solicited adverse reaction described
Exposed Set (ES): defined as all subjects with at least one documented study vaccine administered.
Grade 3 pain: Defined as significant pain at rest and prevents normal everyday activities.

Solicited Systemic Events

Table 21 presents the percentages of solicited systemic adverse reactions following RSVPreF3-AS01$_E$ vaccination. Within 4 days of any dose, solicited systemic events were reported in 40.2% of participants in the Co-Ad group and 41.8% of participants in the control group. The most frequently reported systemic events following RSVPreF3-AS01$_E$ vaccination were fatigue (Co-Ad group 22.4%; Control group 17.9%) followed by Myalgia (Co-Ad group 22.1%; Control group 19.6%) and Headache (Co-Ad group 21.7%; Control group 16.2%). Fever with a maximum temperature ⩾39.0°C was reported in 0.7% of participants in the Co-Ad group and 0.2% of participants in the Control group following RSVPreF3-AS01$_E$ vaccination. Within 4 days of any dose, solicited grade 3 events were reported in 2.5% of participants in the Co-Ad group and 3.2% of participants in the Control group.

Table 21. Percentage of Participants With Solicited Systemic Adverse Reactions Within 4 Days of RSVPreF3-AS01$_E$ Vaccination in Adults ≥60 Years of Age, Exposed Set, Study 007

Adverse Reaction	Co-Ad group (Visit 1) N=438	Control (Visit 2) N=438
Fatigue	98 (22.4)	75 (17.9)
Grade 3	4 (0.9)	4 (1.0)
Myalgia	97 (22.1)	82 (19.6)
Grade 3	3 (0.7)	5 (1.2)
Headache	95 (21.7)	68 (16.2)
Grade 3	2 (0.5)	4 (1.0)
Arthralgia	71 (16.2)	47 (11.2)
Grade 3	3 (0.7)	3 (0.7)
Fever	--	--
≥38.0 °C	11 (2.5)	4 (1.0)
>38.5 °C	7 (1.6)	2 (0.5)
>39.0 °C	3 (0.7)	1 (0.2)
>39.5 °C	2 (0.5)	1 (0.2)
>40.0 °C	0 (0)	0 (0.0)

Source: Adapted from Study 007 report.pdf, Table 12.2.
Abbreviations: %=n/N; N=Exposed set for solicited safety set included all participants with at least 1 documented dose; n=Number of participants presenting with solicited adverse reaction described
Exposed Set (ES): defined as all subjects with at least one documented study vaccine administered.
Grade 3 fatigue, myalgia, headache, arthralgia: Defined as preventing normal activity. Fever defined as a temperature ≥38.0°C by any route (oral, axillary, or tympanic); Grade 3 fever defined as >39.0°C.

The median duration of injection site adverse reactions reported after each dose across both groups was ≤2.5 days for any grade and ≤1.5 days for Grade 3 events. The median

duration of systemic adverse reactions reported after each dose across both groups was ≤2 days for any grade and ≤2.5 days for Grade 3 AEs.

Unsolicited AEs (Non-Serious): 30 Days Postvaccination

Rates of unsolicited AEs within 30 days postvaccination were similar between study groups (Co-Ad 18.8% vs Control 23.7%). The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) included *Infections and infestations* (Co-Ad 5.4% vs Control 9.0%), *General disorders and administration site conditions* (Co-Ad 4.3% vs Control 3.8%), and *Nervous system disorders* (Co-Ad 4.1% vs Control 3.2%).

3.2.5.2 Deaths

Overall, SAEs with a fatal outcome were reported in 4 (0.9%) participants in the Co-Ad group and 8 (1.8%) participants in the Control group. The most frequent SAE with fatal outcome was COVID-19.

One event was considered by the study investigator to be possibly related to FLU vaccination. FDA considered the event to be possibly related to FLU or RSVPreF3-$AS01_E$ vaccination.

- *Acute disseminated encephalomyelitis*: A 71-year-old male in the Co-Ad group who developed shaking and shivering was hospitalized and diagnosed with acute disseminated encephalomyelitis (Grade 3, SAE; also characterized as a pIMD) 7 days from the co-administration of the study vaccines. The participant died 22 days from the co-administration of the study vaccines.

3.2.5.3 Nonfatal Serious Adverse Events

A total of 15 (3.4%) of participants reported at least 1 non-fatal SAE within 6 months after vaccination in the Co-Ad group and 20 (4.5%) in the Control group. A total of two ADEM cases were reported in the Co-Ad group; 1 case (fatal) was described in section 4.2.5.2 and the other ADEM case was non-fatal. Both cases of ADEM cases were also reported as pIMDs.

3.2.5.4 Potential Immune-Mediated Disease

Adverse events defined as pIMDs were reported in 5 (1.1%) of participants in the Co-Ad group and 1 (0.2%) of participants in the control group. There were 3 pIMDs reported in the Co-Ad group (2 cases of acute disseminated encephalomyelitis [ADEM], and 1 case of gout) and 1 participant in the Control group (gout after FLU vaccination). The study investigator considered the 3 pIMDs in the Co-Ad group to be possibly related to FLU vaccine and the FDA considered the events to be possibly related to FLU or RSVPreF3-$AS01_E$ vaccination. The narrative of one of the cases of ADEM resulting in death was described above. The narrative for the other participant with ADEM is described below. Additional narrative information regarding the two cases of ADEM has been requested from the Sponsor.

- *Acute disseminated encephalomyelitis*: A 71-year-old female in the Co-Ad group with a medical history of hyperlipidemia and hypertension developed worsening of tiredness and headaches with intermittent double vision, forgetfulness, and confusion 22 days after the co-administration of the study vaccines and was diagnosed with

ADEM. The participant demonstrated improvement, but the outcome was reported as not resolved by the time of receipt of the study report.

3.2.5.5 Dropouts and/or Discontinuations

Thirteen SAEs were reported in a total of 13 participants who withdrew from the study. None of the events were considered by the study investigator or FDA to be related to study intervention.

4. Integrated Overview of Safety

This section presents SAEs and pIMDs reported in four phase 3 studies (006, 004, 007, and 009).

4.1 Safety Assessment Methods

The occurrence of SAEs and pIMDs from the day of vaccination to the following timepoints: 6 months post-vaccination (Studies 006, 004, 007) and to the safety DLP (four phase 3 studies) is presented in this aggregated safety analysis. See Table 22 for DLPs for each study included in this analysis. For Study 006, safety data are presented up to the safety DLP of April 30, 2022. A safety update was submitted for an extended safety follow-up at Month 6-12 (DLP September 30, 2022), and FDA review of these data are ongoing at the time this briefing document was prepared. For Study 009, the median duration of safety follow-up (up to the DLP) was 4 months.

Table 22. Data Lock Points for Safety Analyses

Study RSV OA=ADJ-xxx	DLP for Safety Follow-Up Post-RSVPreF3-AS01$_E$ Vaccination (Months)
006	April 30, 2022 (7.8 months*)
004	February 11, 2022 (at least 6 months)
007	February 8, 2022 (6 months)
009	March 9, 2022 (at least 1 month for all participants)

Source: Adapted from iss.pdf, page 23, Table 2.
Abbreviation: DLP=data lock point
For studies 007 and -009, the entire study period equals 6 months post RSVPreF3 AS01E vaccination *7.8 months refers to the median safety follow-up time in study 006.

4.2 Safety Database

4.2.1 Studies/Clinical Trials Used to Evaluate Safety

At the time of the DLPs, a total of 15745 RSVPreF3-AS01$_E$ recipients and 12,499 placebo recipients from four phase 3 studies were included in the Exposed Set (Table 23 and Table 24). The median 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).

Table 23. Number of Participants in Integrated Safety Summary, ES

Study RSV OA=ADJ-xxx	RSVPreF3-AS01$_E$ N	Placebo (saline) N
Phase 3 studies	--	--
006	12467	12499
004	1653	--
007	868[a]	--
009	757	--
Total	15745	12499

Source: Adapted from iss.pdf, page 37, Table 6.
Abbreviations: N=Number of participants in the Exposed set at the time of data lock point.
Exposed Set: defined as all participants who received at least the first dose of the study intervention.
a. Study 007: 868 received RSVPreF3-AS01$_E$ concomitantly or 1 month after receiving a seasonal influenza quadrivalent vaccine (Fluarix Quadrivalent; GSK).

Table 24. Number of Vaccine Participants at Safety Analysis Time Points, ES

Study	ES at 1 Month n/N (%)	ES at 6 Months n/N (%)	ES at DLP n/N (%)
006[a]	24898/24966 (99.7%)	22405/24966 (89.7%)	24267/24966 (97.2%)
004	1652/1653 (99.9%)	1631/1653 (98.7%)	1614/1653 (97.6%)
007	865/868 (99.7%)	692/868 (80.1%)	10/868 (1.1%)[b]
009	754/757 (99.6%)	-	752/757 (99.3%)

Source: FDA-generated table.
Abbreviations: n=number of participants in the ES at the specified timepoint; N=Number of participants in the ES at the time of data lock point (DLP).
Exposed Set (ES) is defined as all participants who received at least the first dose of the study intervention.
a. Study 006: Number of participants at safety analysis timepoints 1-month post-vaccination, 6 months post-vaccination, at DLP, by study group: Vaccine, N: 12444, 11199, 12128. Placebo, N: 12445 at 1 month, 11206 at 6 months, 12139 at DLP.
b. Ten participants (2 Co-Ad, 8 control group) had safety data longer than 6 months after RSVPreF3-AS01$_E$ vaccination.

4.2.2 Demographic and Baseline Characteristics of Safety Populations

In Study 006, overall (both study groups combined), the median age at the time of enrollment was 69.0 years; 55% of participants were 60-69 YOA, 36% were 70-79 YOA, and 8% were ≥80 YOA; the age distribution in the vaccine and placebo groups was similar, as well as for gender (female: 52.0% vaccine, 51.4% placebo). Overall (both study groups combined), 94% of participants were not Hispanic or Latino, 79% were White, 8% were Black or African, and 7% were Asian. 39.6% and 38.9% of participants in the vaccine group and placebo groups, respectively, had at least 1 pre-existing comorbidity of interest defined in the protocol (i.e., chronic obstructive pulmonary disorder [COPD], asthma, any chronic respiratory/pulmonary disease, diabetes mellitus Type 1 or Type 2, chronic heart failure, advanced liver, or renal disease). Participants classified as ‘never smoker’ for tobacco was similar between study groups: (52.2% vaccine group, 51.2% Placebo group).

Demographics relating to median age, gender, and ethnicity were similar in Studies 004, 007, and 009 and consistent with that observed in Study 006. In Studies 004 and 009, Participants were mainly White (67.8% and 91.8%, respectively), and Asian (30.0% and 3.4%, respectively). In Study 007, most of the participants were of mixed race (50.3%), followed by White (30.7%) and Black or African American (16.0%).

4.3 Safety Results

Table 25. Safety Overview

Event	RSVPreF3-AS01$_E$ n/N (%)	Placebo (Saline) n/N (%)
SAEs	--	--
Within 6 months post-vaccination[a-c]	587/14520 (4.0)	506/11206 (4.5)
Up to DLP [a-d]	630/14504 (4.3)	507/12139 (4.2)
Deaths up to DLP [a-d]	63/14504 (0.4)	58/12139 (0.5)
pIMDs	--	--
Up to 6 months post-vaccination[a-c]	53/12852 (0.4)	34/11206 (0.3)
Up to DLP [a-d]	60/14504 (0.4)	44/12139 (0.4)

Source: FDA-generated table.
Abbreviations: AE=adverse event; DLP=data lock point; %=n/N; n=number of participants reporting at least one specified event at the designated timepoint; N=Exposed set, defined as participants with at least 1 documented dose at the designated timepoint; n=number of participants reporting the AE described; pIMD=potential immune-mediated disease; SAE=serious adverse event
a. Study 006
b. Study 004
c. Study 007
d. Study 009

4.3.1 Serious Adverse Events

SAEs occurring within 6 months after study intervention (Studies 006, 004, and 007) were reported in 4.0% of vaccine recipients and 4.5% of placebo recipients.
SAEs were most commonly reported in the following SOCs:

- *Infections and Infestations*, frequently due to COVID-19
- *Cardiac Disorders*, most commonly due to ischemic coronary artery disorders, atrial fibrillation.
- *Nervous system disorders*, commonly due to CNS hemorrhages and cerebrovascular accidents

Please see Section 3.1.5.3 (Study 006) and Section 3.2.5.3 (Study 007) for additional details.

Up to the DLP (April 30, 2022; February 11, 2022; February 8, 2022; and March 9, 2022 for Studies 006, 004, 007, and 009, respectively), at least 1 SAE was reported in 4.3% of vaccine recipients and 4.2% of placebo recipients. The most frequently reported SAEs by SOC were *Infections and infestation*s, *Cardiac disorders*, and *Neoplasm benign, malignant, and unspecified*. At least 1 SAE considered by the investigator and the FDA to be related to the study vaccination was reported in 1 participant.

- 1 SAE (Guillain-Barré syndrome occurring 9 days after RSVPreF3-AS01$_E$ vaccination; study 004) was considered by the study investigator and by FDA to be related to RSVPreF3-AS01$_E$ vaccination. See Section 4.3.2 for case narrative.

Deaths

Up to the DLP, deaths were reported for 0.4% of vaccine recipients and 0.5% placebo recipients. Fatal outcomes were categorized most frequently in the SOCs of *Cardiac Disorders* (0.1% vaccine, 0.1% placebo) and *Infections and Infestations* (0.1% vaccine,

0.1% placebo). Two deaths occurring within 6 months of study intervention (Study 006) were considered by the study investigator to be related to study invention (RSVPreF3-AS01$_E$ (n=1): cardiopulmonary failure, Placebo (n=1): Pulmonary embolism). Based on independent review of event narratives, FDA considered the deaths to be more likely attributable to the participant's underlying medical conditions and risk factors (e.g., hypertension, diabetes mellitus Type II, smoking habit) and/or concurrent medical conditions (e.g., COPD, asthma) and does not consider the events as related to study intervention. One participant in Study 007 had a SAE with a fatal outcome (acute disseminated encephalomyelitis) that was considered by the study investigator to be possibly related to FLU vaccine and by FDA to be possibly related to the FLU or RSVPreF3-AS01$_E$ vaccination; see Section 3.2.5.2 for the case narrative.

4.3.2 pIMDs

pIMDs occurring within 6 months after study intervention (Studies 006, 004, and 007) were reported in 0.4% of vaccine recipients and 0.3% of placebo recipients.

Overall, up to the DLP, at least 1 pIMD was reported in 55 (0.4%) participants. The most frequently reported pIMDs (by SOC) were *Metabolism and nutrition disorders* (reported in 13 [0.1%] participants) and *Musculoskeletal and connective tissue disorders* (reported in 13 [0.1%] participants), followed by *Nervous system disorders* (reported in 8 [0.1%] participants).

Among vaccine recipients across all studies, 1 pIMD (Guillain-Barre syndrome that occurred 9 days after RSVPreF3-AS01$_E$ vaccination in Study 004) was considered by the study investigator and FDA to be related to vaccination (see narrative below).

- Guillain-Barre syndrome: A 78-year-old female developed lower limb weakness, which started 9 days after RSVPreF3-AS01$_E$ vaccination Dose 1. She had difficulty walking the next day, developed upper limb and respiratory muscle weakness over the subsequent 3 days, and was hospitalized for further examination. Cerebrospinal fluid (CSF) protein was elevated (146 mg/dL). Ganglioside immunoglobulins (GM1-IgG) was positive. She started immunoglobulin treatment for Guillain-Barre syndrome. The pIMD was considered by the study investigator and FDA to be related to study intervention.

Six pIMDs (all in Study 006; Bell's palsy [n=2], pancytopenia, Graves' disease [hyperthyroidism], gout, and psoriasis) were considered as possibly related to RSVPreF3-AS01$_E$ vaccination by the study investigators and by FDA; see Section 3.1.5.4 for case narratives. Three pIMDs (ADEM [n=2], gout n=1]) in concomitant vaccine Study 007 were considered by the study investigator to be possibly related to influenza vaccine (FLU), and by FDA to be possibly related to FLU or RSVPreF3-AS01$_E$ vaccination; see Section 3.2.5.2 and 3.2.5.4 narratives for the ADEM cases.

4.4 Product-Product Interactions

The safety of RSVPreF3-AS01$_E$ when co-administered with FLU vaccine was evaluated compared to the safety of RSVPreF3-AS01$_E$ and FLU vaccine administered one month apart (Study 007). The frequency and severity of reported solicited and unsolicited, non-serious AEs were similar between the two study groups. See Section 3.2.5 for details.

5. Pharmacovigilance Plan

The Applicant's proposed pharmacovigilance plan includes routine pharmacovigilance activities with adverse event reporting and assessment of aggregate postmarketing safety data. Additionally, the applicant lists pIMDs following Arexvy vaccination as important potential risks and proposes targeted follow-up questionnaires to further characterize spontaneously reported pIMDs (including acute disseminated encephalomyelitis, autoimmune thrombocytopenia, Bell's palsy, giant cell arteritis, Guillain-Barré syndrome, multiple sclerosis, polymyalgia rheumatica, psoriasis and psoriatic arthritis, rheumatoid arthritis, and single organ cutaneous vasculitis). Review of the proposed pharmacovigilance plan is ongoing, and FDA will provide further recommendations regarding safety specifications and pharmacovigilance actions as needed.

6. Overall Summary

The BLA contains clinical data from 4 main studies (006, 004, 007, and 009) to support the efficacy and safety of vaccine candidate, RSVPreF3-AS01$_E$.

Efficacy

Vaccine efficacy against first occurrence of RT-PCR-confirmed RSV LRTD [82.6% (96.95% CI 57.9, 94.1) in adults ≥60 YOA was demonstrated, based on the results from planned interim analysis 1 (median duration of efficacy follow-up was 6.9 months). Planned duration of VE follow-up in Study 006 is up to 36 months.

Analyses of secondary outcomes included: VE against first occurrence of RSV-A associated LRTD and RSV-B associated LRTD was 84.6% (95% CI 32.1, 98.3) and 80.9% (95% CI 49.4, 94.3), respectively. VE against first occurrence of RSV LRTD by age subgroup was 82.7% (95% CI 54.9, 94.8) for ⩾65 YOA and 84.4% (95% CI 46.9, 97.0) for participants ⩾70 YOA. VE against first occurrence of RT-PCR-confirmed RSV ARI was 71.7% (95%CI 56.2, 82.3). VE against RT-PCR-confirmed RSV severe LRTD based on clinical symptomatology (case definition 1) was 94.1% (95% CI 62.4, 99.9). The number of RSV severe LRTD cases based on supportive therapy (definition 2) was too small to make conclusions about VE against RT-PCR-confirmed RSV severe LRTD. The numbers of accrued RSV LRTD cases at the time of the interim analysis were too small to make conclusions about VE in adults ⩾80 YOA and by physical frailty (based on the time to walk 3 or 4 meters).

Safety

At the time of the DLPs, a total of 15745 RSVPreF3-AS01$_E$ recipients from four phase 3 studies were included in the Exposed Set. The median durations of follow-up from Day 1 to safety DLP across all Phase 3 studies was 7.2 months.

RSVPreF3-AS01$_E$ is noted to have increased reactogenicity when compared to placebo, and the rates of Grade 3 reactions after RSVPreF3-AS01$_E$ vaccination were low (≤1.7%).

The frequency of SAEs reported up to 6 months post-vaccination was 4.0% and 4.5% in the vaccine and placebo groups. 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 RSVPreF3-AS01$_E$ vaccination; also categorized as a pIMD) was considered by the study investigator and FDA to be related to vaccination.

One (1) death due to acute disseminated encephalomyelitis occurred in a participant 22 days after receiving concomitant RSVPreF3-AS01$_E$ and seasonal influenza vaccine (Fluarix Quadrivalent; GSK) [study 007]) was considered by the study investigator to be possibly related to FLU vaccine and FDA as possibly related to FLU or RSVPreF3-AS01$_E$ vaccination.

Up to the time of the DLPs (Studies 006, 007,004 and 009), at least one pIMD was reported by 0.4% and 0.3% of vaccine and placebo recipients, respectively. Among vaccine recipients, 1 pIMD (Guillain-Barre syndrome that occurred 9 days after RSVPreF3-AS01$_E$ vaccination) was considered by the study investigator and FDA to be related to vaccination. Six pIMDs (Bell's palsy [n=2], pancytopenia, Graves' disease [hyperthyroidism], gout, and psoriasis) were considered as possibly related to RSVPreF3-AS01$_E$ vaccination by the study investigators and by FDA. Three pIMDs (ADEM [n=2], gout n=1]) in concomitant vaccine Study 007 were considered by the study investigator to be possibly related to influenza vaccine (FLU), and by FDA to be possibly related to FLU or RSVPreF3-AS01$_E$ vaccination.

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 the time this briefing document was prepared.

Manufacturing lot consistency

The statistical criteria for lot consistency were met based on the results of Study 009.

Concomitant Vaccination

There was no evidence of immunological interference when RSVPreF3-AS01$_E$ was concomitantly administered with a seasonal influenza quadrivalent vaccine, and vice versa.

No studies have been conducted to assess the safety of RSVPreF3-AS01$_E$ when concomitantly administered with other commonly administered vaccines in the adults ≥60 YOA, e.g., Shingrix, pneumococcal vaccine, Tdap and COVID-19 vaccines.

The duration of vaccine effectiveness and timing or need for revaccination cannot be determined at this time based on the currently available data.

7. Topics for VRBPAC Discussion

VRBPAC will convene on March 1, 2023, to discuss and vote on whether the available safety and effectiveness data support licensure of GSK's recombinant respiratory syncytial virus (RSV) adjuvanted vaccine, Arexvy, for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

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