

BLA Clinical Review Memorandum

Application Type	BLA
STN	125775.0
CBER Received Date	September 2, 2022
PDUFA Goal Date	May 3, 2023
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes
Reviewer Name	Nicholas Geagan, D.O.
Review Completion Date / Stamped Date	05/03/2023
Supervisory Concurrence	<p>Lucia Lee, MD Medical Officer-Team Leader CRB1, DVRPA, OVRR, CBER</p> <p>Douglas Pratt, MD, MPH Associate Director, Medical Affairs DVRPA, OVRR, CBER</p>
Applicant	GlaxoSmithKline Biologicals
Established Name	Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted
(Proposed) Trade Name	Arexvy
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	<p>After reconstitution, a single dose of 0.5 mL contains 120 µg of RSVPreF3 antigen adjuvanted with AS01_E</p> <p>AS01_E contains 25 µg of QS-21 and 25 µg of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) in liposomes composed of 0.5 mg dioleoyl phosphatidylcholine and 0.125 mg cholesterol.</p>
Dosage Form(s) and Route(s) of Administration	Suspension, intramuscular
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	<p>Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV)</p> <p>Population: adults 60 years of age and older</p>
Orphan Designated (Yes/No)	No

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GLOSSARY

ADEM	acute disseminated encephalomyelitis
AE	adverse event
ARI	acute respiratory infection
AS01 _E	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
BLA	Biologics Licensing Application
CBER	Center for Biologics Evaluation and Research
CD	cluster of differentiation
CI	confidence interval
CMI	cell-mediated immunity
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DLP	data lock point
eCRF	electronic Case Report Form
ERD	enhanced respiratory disease
ES	Exposed Set
FI-RSV	formalin-inactivated RSV vaccine
FLU	Fluarix Quadrivalent influenza vaccine
GBS	Guillain-Barré syndrome
GMC	geometric mean concentration
GMT	geometric mean titer
GSK	GlaxoSmithKline Biologicals
ICS-10P	10-parameters intracellular cytokine staining assay
IDMC	Independent Data Monitoring Committee
IFN	interferon
IL	interleukin
IU	international units
LL	lower limit
LLOQ	lower limit of quantification
LRTD	lower respiratory tract disease
MedDRA	Medical Dictionary for Regulatory Activities
MGI	mean geometric increase
mES	modified Exposed Set
MPL	3-O-desacyl-4'-monophosphoryl lipid A
NAb	neutralizing antibody
NH	northern hemisphere
pIMD	potential immune-mediated disease
PPS	Per Protocol Set
PPSi	Per Protocol Set for immunogenicity
QS-21	<i>Quillaja saponaria</i> Molina, fraction 21
RSVPreF3-AS01 _E	RSV PreFusion protein 3 Older Adult
RT-PCR	reverse transcriptase-polymerase chain reaction
RSV	respiratory syncytial virus
SAE	serious adverse event
SCR	seroconversion rate
SH	southern hemisphere
SOC	system organ class

TNF	tumor necrosis factor
UL	upper limit
ULOQ	upper limit of quantification
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 of RSVPreF3-AS01_E to prevent RSV-associated LRTD in adults ≥60 YOA was evaluated in Study RSV OA=ADJ-006 (Study 006), an ongoing, phase 3, randomized, placebo-controlled, observer-blind, international clinical trial. 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 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 reverse transcriptase-polymerase chain reaction (RT-PCR) - confirmed RSV LRTD was 82.6% (96.95% confidence interval [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 by serological subtype: VE against first occurrence of RSV-A associated LRTD and RSV-B associated LRTD were 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. 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. VE against first occurrence of RT-PCR-confirmed RSV acute respiratory infection (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 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 (15,845 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 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, including injection site pain (60.9% vs. 9.3%), fatigue (33.6% vs. 16.1%), myalgia (28.9% vs. 8.2%); more severe reactions were uncommon but were also reported more frequently in the vaccine group (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%]). The percentage of participants in the pooled analysis set reporting at least 1 unsolicited, non-serious adverse

events (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 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 of September 30, 2022, 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 ten events (0.08%) in the RSVpreF3-AS01_E group and 4 events (0.03%) in the placebo group.

Up to the time of the DLP in the four phase 3 studies (006, 004, 007, and 009), at least 1 potential immune-mediated disease (pIMD) was reported in 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 (acute disseminated encephalomyelitis [ADEM] [n=2], gout [n=1]) in concomitant vaccine Study 007 were considered by the study investigator to be possibly related to Fluarix Quadrivalent 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 considered 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.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed individually.

1.2 Patient Experience Data

Please see CDER reviewer consult memo (Dr. Ji Li).

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input checked="" type="checkbox"/>	Patient-reported outcome	Module 5.3.5.4
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting summary report	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

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 most often 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.

Among adults 65 years of age and older RSV disease results in an average of 177,000 hospitalizations in the United States (US) per year during 1999-2018. During the same time period 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, a major surface glycoprotein of the virus, facilitates entry into the host cell. The PreF conformation of the F protein is the main target of RSV NAb in humans following natural exposure to RSV ([Magro, 2012](#); [Ngwuta, 2015](#); [Smith 2012](#); [McLellan, 2013](#)). 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.

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 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.

RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans. There is currently no immune marker and threshold widely accepted as predictive of protection against RSV. The durability of naturally acquired immunity after RSV infection is also not well understood. Studies of immune response after RSV infection indicate an initial rise in serum antibody levels, with a return to baseline by 16-20 months post-infection ([Falsey et al, 2006](#)). Although high rates of re-infection and short durability of protection after infection were observed in an RSV human challenge study in young adults ([Hall et al, 1991](#)), another study among elderly individuals suggest that natural re-infection with RSV was rarely observed over two consecutive years ([Johnson et al, 1962](#)).

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, and/or mechanical ventilation ([Falsey et al, 2019](#); [Prasad et al, 2021](#)).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

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.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, there is no vaccine available for prevention of RSV disease.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Currently, RSVPreF3-AS01_E vaccine is not licensed in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Major Regulatory Activity

The following timeline includes a list of major regulatory activity associated with the submission of the BLA:

- December 17, 2019: Type C Meeting re: discussion of proposed submission package
- September 15, 2020: Type C Meeting re: feedback on adequacy of the Phase 2 RSV OA=ADJ-004 and Phase 3 RSV OA-ADJ-006 study design
- March 08, 2021: Type B End-of-Phase 2 Meeting re: discussion on phase 3 program.
- February 18, 2022: Type C Meeting re: acceptability of the proposed BLA clinical package
- August 23, 2022: Pre-BLA Meeting
 - The Applicant sought to obtain CBER concurrence on the clinical data supporting review of the BLA.

2.6 Other Relevant Background Information

In the late 1960s, 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 immune response after subsequent infection may be implicated ([Chin et al, 1969](#); [Kapikian et al, 1969](#); [Fulginiti et al, 1969](#)). Pre-fusion F appears to be absent on the surface of formalin-inactivated respiratory syncytial virus which may have major implications for discriminating current pre-F-based immunogens from FI-RSV used in historical vaccine trials ([Killikelly et al, 2016](#)). The risk of ERD in older children and adults is low, probably due to priming of the immune system 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. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized and integrated to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Safety, efficacy, and immunogenicity data from four main studies were provided in this application to support licensure of an adjuvanted, recombinant Respiratory Syncytial Virus vaccine, and were conducted in accordance with Good Clinical Practice and International Committee on Harmonization guidelines. The informed consent form for each study contained all the essential elements as stated in 21 CFR 50.25. In accordance with 21 CFR 312.120, the Applicant provided the required elements to ensure that each study conformed with Good Clinical Practice.

3.3 Financial Disclosures

Covered clinical study (name and/or number): RSV OA=ADJ-006, RSV OA=ADJ-007, RSV OA=ADJ-004, RSV OA=ADJ-009, RSV OA=ADJ-002, RSV OA=ADJ-011
Was a list of clinical investigators provided? X Yes
Total number of investigators identified: <u>1532</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p> <p>Is an attachment provided with details of the disclosable financial interests/arrangements? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant)</p> <p>Is a description of the steps taken to minimize potential bias provided? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)</p>
<p>Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u></p> <p>Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)</p>

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The RSVPreF3 antigen is an engineered recombinant protein, derived from the RSV fusion (F) surface glycoprotein of an RSV-A strain (RSV-A A2 strain) that has been stabilized in its trimeric and PreF conformation. Manufacturing process development, in-process testing, release and

stability testing were reviewed and support licensure. The data supports the proposed expiry dating for Drug Product. Facility information and data provided in the BLA were reviewed by CBER reviewers and found to be sufficient and acceptable.

4.2 Assay Validation

RT-PCR assay was validated for its intended use to confirm RSV cases in study 006. Please see Drs. Judy Beeler and Ross Peterson's memo for additional details.

4.3 Nonclinical Pharmacology/Toxicology

Arexvy has not been evaluated in repeat-dose toxicity studies or in reproductive-developmental toxicity study in animals. However, RSVPreF3 antigen alone or in combination with AS01B adjuvant (used in Shingrix and contains double the amount of 3-O-desacyl-4'-monophosphoryl lipid A [MPL] and *Quillaja saponaria* Molina, fraction 21 [QS-21] than AS01E) has been evaluated in two repeat-dose toxicity studies in rabbits. Based on nonclinical toxicity assessments, there are no significant safety issues reported in the rabbits. Please see Dr. Nabil Al-Humadi's memo for additional details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Arexvy induces an immune response against RSVpreF that protects against lower respiratory tract disease caused by RSV.

4.5 Statistical

No major statistical issues were identified that would impact the clinical reviewer's interpretation of the data and conclusions. Please see statistical review memo (Dr. Ross Peterson) for additional details.

4.6 Pharmacovigilance

The assessment for Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) will be conducted in an active surveillance study, EPI-RSV-041 VS US DB, as a postmarketing requirement. In the same study, the Applicant agreed to assess atrial fibrillation as a postmarketing commitment. Please see Dr. Firoozeh Alvandi's memo for additional details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This BLA contains 5 clinical studies. The data to support vaccine efficacy are based on results from Study 006. Descriptive immunogenicity data were summarized in section 7. The main studies contributing the safety database are studies 006, 009, 007 and 004.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- Amendment 0: module 1 (financial certification and disclosure, Applicant meeting and other correspondence, package insert), module 2 (clinical overview and summaries), module 5 (clinical study reports)
- Amendment 2: module 1 (agreed iPSP)
- Amendment 5: module 1 (response to information request pertaining to Study RSV OA=ADJ-006 to explain the criteria by which subjects were selected to be in the solicited safety set)
- Amendment 9: module 5 (12-month safety data accrued from Study RSV OA=ADJ-006)

- Amendment 20, 33: module 1 (response to information request pertaining to pharmacovigilance plan for ADEM, Guillain-Barre syndrome, and cardiac disorders).
- Amendment 21: module 1 (response to information request re: details on ADEM cases)
- Amendment 23: module 1 (response to information request re: vaccine efficacy against ARI excluding LRTD)
- Amendments 37, 40, 43, 45, 46: module 1 (draft package insert and revisions)

5.3 Table of Clinical 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 ^b – ongoing Location: Northern and Southern Hemisphere	Randomized, placebo-controlled, observer-blind, safety, immunogenicity, and VE study Primary objective: · VE of RSVPreF3-AS01 _E to prevent RSV-confirmed LRTD Key secondary objectives: · VE of RSVPreF3-AS01 _E to prevent RSV-confirmed LRTD by subtype (RSV-A, RSV-B), by age, baseline comorbidities	RSVPreF3-AS01 _E Placebo	VE analysis 1 ^a 12467	12499
Phase 3 Study Study 004 ^b – ongoing	Randomized, open-label study to evaluate the immunogenicity, safety, and immune persistence of RSVPreF3-AS01 _E following different revaccination schedules · [only safety data from this study are presented in this briefing document]	RSV_annual RSV_flexible revaccination RSV_1 dose	Month 6: RSV_annual: 993 RSV_flexible revaccination: 329 RSV_1 dose: 331	--- --- ---
Phase 3 Study Study 007 ^b – completed	Randomized, co-administration study seasonal quadrivalent influenza vaccine (FLU)	Co-Ad Separate	Co-Ad: 442 (co-ad) Separate: 426 of 443 received RSVPreF3- AS01 _E)	--
Phase 3 Study Study 009 ^b – completed	Randomized, double-blind, lot consistency study	vaccine_Grp1 (Lot 1) vaccine_Grp2 (Lot 2) vaccine_Grp3 (Lot 3)	251 253 253	--- --- ---
Phase 1/2 Study Study 002 – completed	Randomized, dose and formulation selection study Part B: 60-80 years of age	Relevant study groups (Part B): 120 µg RSVPreF3 / AS01 _E Placebo: saline	100 ---	--- 101
Phase 2 Study Study 011 ^c – completed USA, Belgium	Extension study to evaluate the safety and immunogenicity of RSVPreF3-AS01 _E (3 rd dose) administered ~18 mo after Dose 2 in certain RSV OA=ADJ-002 groups (including 120 µg RSVPreF3- AS01 _E study group)	---	---	---
Total:			15845	12600

Source: adapted from 125775.0 tabular-listing.pdf.

Ab=Antibody, FLU=Seasonal Quadrivalent Influenza Vaccine [Fluarix Quadrivalent; GSK], LRTD=Lower Respiratory Tract Disease, NAb=Neutralizing antibody, RSV=Respiratory Syncytial Virus, RSVPreF3 =RSV PreFusion protein 3, VE=Vaccine Efficacy.

a. VE analysis #1: Season 1 was defined as 1 October to 30 April in Northern hemisphere and from 1 March to 30 September in Southern hemisphere. Northern hemisphere (US, Canada, Mexico, Europe, Russia, South Korea, Japan), Southern hemisphere (Australia, New Zealand, S Africa).

b. Main Studies to Support Safety and Effectiveness

c. Subjects from Study 011 did not contribute to the overall safety data as they either previously received the final formulation in Study 002 or had received a different formulation than the final one (120µg AS01_E).

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting

On March 1, 2023, a VRBPAC meeting was held to discuss the safety and effectiveness of RSVPreF3-AS01_E for active immunization to prevent LRTD caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults ≥60 years of age.

- The committee members generally agreed that the available evidence supported the safety of RSVPreF3-AS01_E. They emphasized the need for postmarketing surveillance to continue to assess Guillain Barre Syndrome, potential immune-mediated diseases (pIMDs) in general, and atrial fibrillation. Also, the committee highlighted the incomplete information on safety and effectiveness with repeat vaccination and concomitant use with other vaccines.
- Committee members agreed that the effectiveness of RSVPreF3-AS01_E to prevent lower respiratory tract disease caused by RSV was demonstrated; however, several committee members noted the lack of second season efficacy data, the need for additional studies on prevention of severe outcomes in at-risk populations and repeat vaccination.

There was broad committee consensus that if RSVPreF3-AS01_E were approved, a postmarketing evaluation, as described above, would be critical to further define the benefits and risks of RSVPreF3-AS01_E.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 RSV OA=ADJ-006

NCT04886596

Title: "A Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose of GSK's RSVPreF3-AS01_E investigational vaccine in adults aged 60 years and above."

6.1.1 Objectives

Primary Objectives, Endpoints, and Statistical Criteria

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 ([Appendix 1](#)).
 - *Statistical Criterion:* The lower limit (LL) of the 2-sided 95% CI for VE is above 20%

Secondary Objectives and Endpoints

1. To evaluate the humoral immune response to the RSVPreF3-AS01_E vaccine.
 - *Endpoint:* In a subset of participants, at pre-Dose 1 (Day 1) and 30 days post-Dose 1 (Day 31)
 - RSVPreF3 IgG-specific Ab concentrations
 - Neutralizing antibody (NAb) titers against RSV-A
 - NAb titers against RSV-B
2. To evaluate the efficacy of RSVPreF3-AS01_E vaccine to prevent RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥60 YOA.
 - *Endpoint:* First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition, for RSV subtype A and RSV subtype B separately.
3. To evaluate vaccine efficacy in the prevention of RSV-confirmed LRTD by age category, following a single dose of the RSVPreF3-AS01_E vaccine.
 - *Endpoint:* First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, according to the case definition, in the following age categories: ≥65 YOA, ≥70 YOA, and ≥80 YOA.
4. To evaluate the efficacy of RSVPreF3-AS01_E vaccine RSV-confirmed LRTD in adults ≥60 YOA by baseline comorbidities.
 - *Endpoint:* First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, according to the case definition, by baseline comorbidities.
5. To evaluate the efficacy of RSVPreF3-AS01_E vaccine to prevent RSV-confirmed LRTD by baseline frailty status in adults ≥60 YOA.
 - *Endpoint:* First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, according to the case definition, by baseline frailty status.

6. To evaluate the efficacy of RSVPreF3-AS01_E vaccine to prevent severe RSV-confirmed LRTD in adults ≥60 YOA.
 - *Endpoint:* First occurrence of RT-PCR-confirmed RSV-A and/or B-associated severe LRTD, according to the case definitions ([Appendix 1](#)).
7. To evaluate the efficacy of RSVPreF3-AS01_E vaccine to prevent RSV-confirmed ARI in adults ≥60 YOA.
 - *Endpoint:* First occurrence of RT-PCR-confirmed RSV-A and/or B-associated ARI, according to the case definition.
8. To evaluate the efficacy of RSVPreF3-AS01_E vaccine to prevent any ARI and any LRTD in adults ≥60 YOA.
 - *Endpoint:* First occurrence of ARI or LRTD, according to the case definition ([Appendix 1](#)).

Secondary Objectives and Endpoints (Safety)

9. To evaluate the reactogenicity of the RSVPreF3-AS01_E investigational vaccine.
 - *Endpoint:* In a subset of participants, occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after each vaccination.
10. To evaluate the safety of the RSVPreF3-AS01_E investigational vaccine.
 - *Endpoints:*
 - In all participants:
 - Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination
 - Occurrence of all SAEs from the day of vaccination up to 6 months after each vaccination
 - Occurrence of all pIMDs from the day of vaccination up to 6 months after each vaccination
 - Occurrence of SAEs related to study vaccination from Day 1 up to study end
 - Occurrence of pIMDs related to study vaccination from Day 1 up to study end.
 - Occurrence of any fatal SAEs from Day 1 up to study end.

6.1.2 Design Overview

Study RSV OA=ADJ-006 is an ongoing Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of RSVPreF3-AS01_E in adults ages 60 years and older through three RSV seasons. The study is being conducted in a total of 278 centers in 17 countries (Australia, Belgium, Canada, Estonia, Finland, Germany, Italy, Japan, South Korea, Mexico, New Zealand, Poland, Russian Federation, South Africa, Spain, United Kingdom, and United States). A total of 25,040 participants were randomized 1:1:1:3 to either one of three vaccine lots or placebo (saline).

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 from 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 were evaluated in subsets of participants, referred to as reactogenicity subset (N=1,757; RSVPreF3=879, Placebo=878). 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 members external to the Applicant.

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.

6.1.3 Population

Individuals were eligible to be included if they met all of the following inclusion criteria:

- ≥60 YOA at the time of first vaccination, who live in the community or in a long-term care facility.
- Participants who can and will comply with the requirements of the protocol.
- Written or witnessed informed consent obtained from the participant prior to performance of any study specific procedure.
- Participants who are medically stable in the opinion of the investigator at the time of first vaccination. 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 considered by the investigator as medically stable.

Individuals were not eligible to be included if they met any of the following exclusion criteria:

- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy, based on medical history and physical examination.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Hypersensitivity to latex.
- Serious or unstable chronic illness.
- Any history of dementia or any medical condition that moderately or severely impairs cognition.
- Recurrent or un-controlled neurologic disorders or seizures. Participants with medically controlled active or chronic neurological diseases can be enrolled in the study as per investigator assessment, provided that their condition will allow them to comply with the requirements of the protocol.
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study.

- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Use of any investigational or non-registered product other than the study interventions during the period beginning 30 days before the first dose of study vaccines and ending 30 days after the last vaccine administration, or planned use during the study period
- Planned or actual administration of vaccine not foreseen by the study protocol in the period starting 30 days before each dose and ending 30 days after each dose of study vaccine administration.
- Previous vaccination with an RSV vaccine
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the first study vaccine administration
- Chronic administration of immunosuppressants or other immune-modifying drugs.
- Concurrently participating in another clinical study, at any time during the study period
- History of chronic alcohol consumption and/or drug abuse
- Bedridden individuals
- Planned move during the study period
- Participation of any study personnel or their immediate dependents, family, or household members.
- Planned leave or holiday of 4 consecutive weeks or more during the RSV seasons covered by the study

6.1.4 Study Treatments or Agents Mandated by the Protocol

All study interventions were administered intramuscularly as a single dose. The vaccine was prepared and administered by study personnel (unblinded) who did not participate in data collection, evaluation or review of any study endpoint (i.e., reactogenicity, safety, efficacy).

Table 2. Study Interventions, Study RSV OA=ADJ-006

Treatment Type	Formulation^a	Dose Volume
RSVPreF3-AS01 _E Lot 1	RSVPreF3 (120 µg) + AS01E	0.5mL
RSVPreF3-AS01 _E Lot 2	RSVPreF3 (120 µg) + AS01E	0.5mL
RSVPreF3-AS01 _E Lot 3	RSVPreF3 (120 µg) + AS01E	0.5mL
Placebo	NaCl	0.6-0.8mL

Source: Adapted from STN 125775, RSV OA=ADJ-006 Clinical Study Report, Table 10

a. The vaccine was prepared and administered by study personnel (unblinded) who did not participate in data collection.

RSVPreF3-AS01_E (Lot 1; Lot 2; Lot 3)

- Composition: 120 µg of RSVPreF3, AS01_E (25 µg QS-21, 25 µg MPL, liposomes)
- Presentation: RSVPreF3: lyophilized (vial); AS01_E: suspension (vial)

Placebo (comparator)

- Composition: NaCl
- Presentation: Pre-filled syringe

6.1.5 Directions for Use

RSVPreF3-AS01_E:

- Preparation: Using an intermediate device, the AS01_E adjuvant suspension was transferred into the vial containing lyophilized RSVPreF3 antigen. The vial was swirled and the volume was withdrawn into the same intermediate device.
- After reconstitution, a 0.5 mL dose was administered intramuscularly into the subject's deltoid muscle.

Placebo: Each the full volume of the pre-filled syringe (0.6 – 0.8 mL) was administered intramuscularly into the subject's deltoid muscle.

6.1.6 Sites and Centers

A total of 278 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)

6.1.7 Surveillance/Monitoring

Safety Monitoring

- *Clinical Assessments*: physical exam before vaccination (Day 1)
- Adverse Event Monitoring:
 - Solicited local reactions: Days 1-4 postvaccination
 - Erythema, swelling, pain
 - Grading scale:
 - Erythema/swelling: 0: ≤20 mm, grade 1: 20- ≤50 mm, grade 2: >50-≤100 mm, grade 3: >100 mm
 - Pain: 0: none; mild (grade 1): any pain neither interfering with nor preventing everyday activities; moderate (grade 2): painful when limb is moved and interferes with everyday activities; severe (grade 3): significant pain at rest, prevents everyday activities.
 - Solicited systemic AEs: Days 1-4 postvaccination
 - Headache, fatigue, myalgia, arthralgia, fever (defined as T ≥38.0°C regardless of route; measured by oral, axillary or tympanic temperature)
 - Grading scale
 - Headache, fatigue, myalgia, arthralgia: 0: none; mild (grade 1): easily tolerated; moderate (grade 2): interferes with normal activity; severe (grade 3): prevents normal activity.
 - Fever: grade 1: ≥38.0°C- ≤38.5°C, grade 2: ≥38.5°C- ≤39.0°C, grade 3: >39.0°C
- COVID-19 cases: Days 1 through Month 6 postvaccination
- Any other unsolicited injection site or systemic AEs: Days 1-30 postvaccination
- SAEs, pIMDs, AEs leading to withdrawal from the study: Day1 through Month 6 postvaccination

All participants recorded and unsolicited AEs (Days 1-30) on a paper diary card. Participants in the reactogenicity subset also recorded solicited local and systemic reactions (Days 1-4) on the diary card.

Withdrawals/Discontinuation

'Discontinuation' of study intervention means any participant who has not received all

planned doses of vaccine. A participant who discontinued study intervention may, if deemed appropriate by the investigator, continue other study procedures (e.g. subsequent dose, efficacy, safety or immunogenicity) if planned in the study protocol.

Participants who do not consent for the annual revaccinations was considered withdrawals from the study.

Independent Data Monitoring Committee (IDMC): Unblinded evaluation of safety data was performed by an IDMC on a regular basis. In preparation of the IDMC meetings, unblinded analyses was performed by an IES to maintain the study blind. Only the outcomes and recommendations of the IDMC was communicated to the study team. Operational details were provided in the IDMC Charter.

6.1.8 Endpoints and Criteria for Study Success

See Section [6.1.1](#) above.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The final analysis of the primary objective was case-driven. It was planned to be performed when at least 56 cases of RSV-confirmed and externally adjudicated LRTDs were accrued in the primary cohort for efficacy (mES). The efficacy of RSV vaccine against RSV confirmed LRTD was demonstrated if the LL of the two-sided 95% CI of VE is above 20%. The same success criterion was applied to the interim analyses (LL > 20%). Using the adjusted alpha for interim, 96.95% CIs were computed for the primary endpoint and for sensitivity analysis related to the primary; 95% CIs were used for other secondary and descriptive analyses.

As the number of events triggering VE Analysis 1 (at least 56 cases) was not achieved at the end of Season 1 in the NH, an optional pre-defined interim analysis was performed when at least 35 cases were accrued (at the end of Season 1 in the NH or later). An adjustment of the Type I error was done in order to maintain the overall significance level at 2.5%.

For all statistical analyses described below, data obtained with the 3 RSVPreF3-AS01_E vaccine lots were pooled, and results are presented for RSVPreF3 group vs. Placebo group. Only analyses pertaining to the endpoints evaluable at VE Analysis 1 are described in this memo.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

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

Analysis Populations

Populations used for the study analyses are displayed in [Table 3](#). 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	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

Per-Protocol set for immunogenicity (PPSi): please see Section [7.1.1](#).

6.1.10.1.1 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 characteristics 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-AS01E 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, n (%)	6963 (55.9)	6980 (55.8)
70-79 YOA, n (%)	4487 (36.0)	4491 (35.9)
≥80 YOA, n (%)	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; SD=standard deviation; 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

6.1.10.1.2 Subject Disposition

Disposition of 24,966 participants who contributed to the analyses of safety and efficacy are presented in [Table 5](#). 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-AS01_E 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	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 24,966 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

6.1.11 Efficacy Analyses

Please see [Appendix 1](#) for case definitions.

An external LRTD Adjudication Committee reviewed all RSV RT-PCR-confirmed cases fulfilling LRTD case definition (as confirmed by GSK internal review) as well as investigator reported LRTD cases. Only adjudicated cases were considered for the primary VE Analysis.

6.1.11.1 Analyses of Primary Endpoint(s)

The final analysis of the primary objective was planned to be performed when 56 cases of RSV-confirmed and externally adjudicated LRTDs had been accrued with the option of an interim analysis with appropriate statistical adjustments after accrual of 35 cases in the primary cohort for efficacy (mES). At the time the planned interim analysis, an additional 12 cases of LRTD had accrued after the initial 35 cases needed for the interim analysis.

The VE analysis was performed when 47 cases of RSV-confirmed LRTD accrued in the primary cohort for efficacy up to efficacy data lock point (DLP) on April 11, 2022 (all available efficacy data of acute respiratory illness (ARI) cases with ARI visit up to efficacy DLP included and adjudicated by LRTD Adjudication Committee). The analysis included data from participants enrolled in the NH and in the 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 of the interim analysis was demonstrated, as the lower limit [LL] of the 96.95% CI for the VE was >20% ([Table 7](#)).

The median follow-up time in the mES from Day 15 post-vaccination up to the efficacy 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 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 84.6% (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

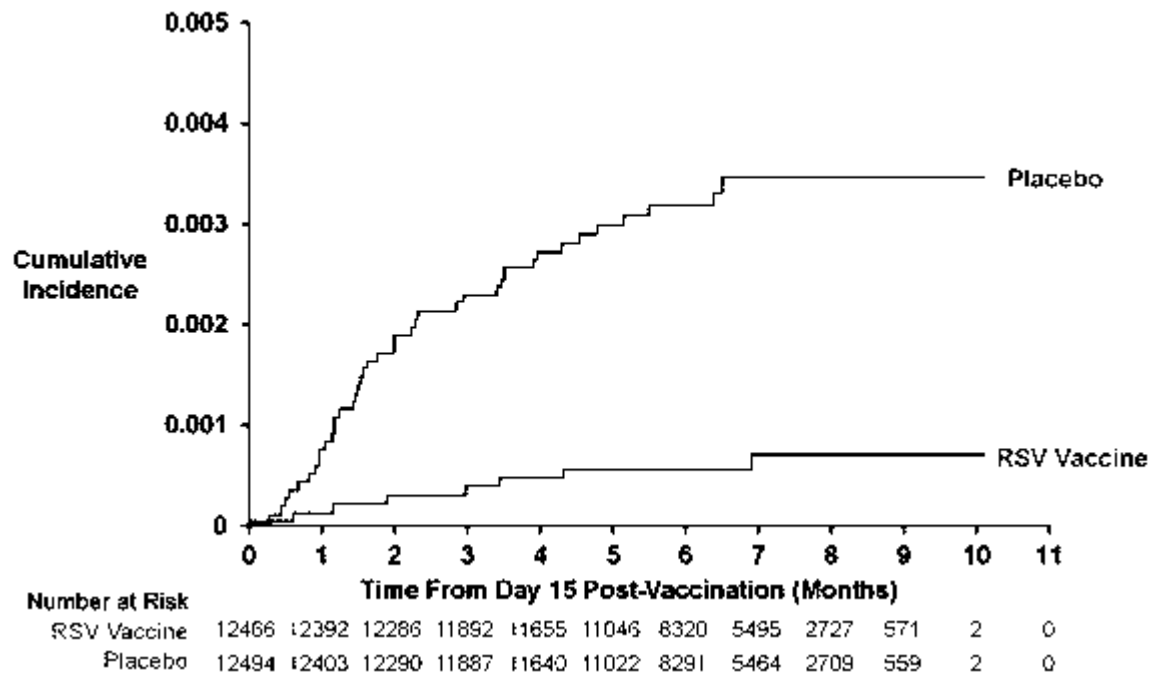
mES (modified exposed set): defined as participants who received at least the first dose of the study intervention and are included in the ES and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination.

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

6.1.11.2 Analyses of Secondary Endpoints

Immunogenicity (RSV-A and RSV-B neutralizing antibody): please see Section [7.1.5](#).

6.1.11.3 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-AS01E, 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.

Reviewer Comment

The number of cases among frail participants was too small to make definitive conclusions about VE in frail participants in Season 1.

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 [Appendix 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 12](#)) was too small to make conclusions about VE against RT-PCR-confirmed RSV severe LRTD. A total of 2 RT-PCR-confirmed RSV severe LRTD cases (severe LRTD definition 2), both in the placebo group, were reported. The 2 cases of RT-PCR-confirmed RSV severe LRTD that met definition 2 also met the criteria for definition 1.

Table 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

Reviewer Comment

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

6.1.11.4 Dropouts and/or Discontinuations

One hundred and twenty-one SAEs were reported in participants who withdrew from the study. One event in the RSVPreF3-AS01_E 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.

6.1.12 Safety Analyses

6.1.12.1 Methods

See Section [6.1.2](#) above.

6.1.12.2 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). 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. [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.

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)	88/878 (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)
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, 878 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=878
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

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 $\geq 38.0^{\circ}\text{C}$ by any route (oral, axillary, or tympanic); Grade 3 fever defined as $>39.0^{\circ}\text{C}$.

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): 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.

6.1.12.3 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].

Up to the second DLP of September 30, 2022, 39 additional participants died in the RSVPreF3 group and 37 additional participants died in the Placebo group. Similar to the data presented to the first DLP the most frequently reported fatal SAEs by SOC were *Cardiac Disorders*, *General disorders and administration site conditions*, and *Infections and Infestations*. One new fatal SAE (unknown cause) occurring 326 days following vaccination was considered as related by the investigator in the Placebo group.

Reviewer Comment

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., chronic obstructive pulmonary disease [COPD], asthma) and does not consider the events as related to study intervention.

6.1.12.4 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 [0.08%], placebo: 4 events [0.03%]), 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 aged 64 to 77 years old with relevant predisposing/concurrent medical conditions and cardiac risk factors. None of these SAEs were fatal. The study investigator considered none of these events related to vaccination.

Reviewer Comment

Atrial fibrillation is a common condition in the population studied and all participants with new onset atrial fibrillation had predisposing/concurrent medical conditions or cardiac risk factors. Also, the onset of symptoms for the serious new onset atrial fibrillation was variable (12 to 24 days post vaccination). The currently available information on the atrial fibrillation is insufficient to determine a causal relationship to the vaccine.

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 0.08% of RSVPreF3-AS01_E and 0.03% of placebo participants.

Non-fatal SAEs assessed as related to the study intervention by the investigator within 6 months following vaccination were reported in 8 participants (<0.1%) in the RSVPreF3 group (seizure, transient ischemic attack, syncope, Bell's palsy, acute myocardial infarction, acute myeloid leukemia, non-small cell lung cancer, retinal vein occlusion) and 5 participants (<0.1%) in the Placebo group (seizure, transient ischemic attack, pulmonary embolism, immune thrombocytopenia).

Up to the second DLP, 2 new non-fatal SAEs, both in the RSVPreF3 group, were considered by the investigator to be related to study intervention (chronic lymphocytic leukemia and thrombocytopenia).

Reviewer Comment

Considering the presence of pre-existing medical conditions, risk factors (hypertension, diabetes mellitus Type II, smoking habit), and/or concurrent medical conditions (COPD, asthma), as alternative explanations for the onset of these events, none were considered as related by FDA.

6.1.12.5 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=41 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 SOC: *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.

In total up to the second DLP, pIMDs assessed as related to the study intervention by the investigator were reported in 5 participants in the RSVPreF3 group and 4 participants in the Placebo group.

Narratives for the 9 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.
- *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.
- *Myasthenia gravis*: A 62-year-old male was diagnosed with myasthenia gravis (Grade 2) 291 days from RSVPreF3-AS01_E. He was started on pyridostigmine for treatment and his condition was reported as improving.
- *Thrombocytopenia*: A 72-year-old male with a history of lymphoma presented with mild-grade 1 thrombocytopenia requiring hospitalization 273 days following vaccination with RSVPreF3-AS01_E. The outcome was not recovered/not resolved at the time of receipt of study report.

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.
- *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.

Reviewer Comment

Nine pIMDs were considered by the study investigator to be possibly related to study intervention (5 RSVPreF3-AS01_E, 4 placebo group). Of the 9 pIMDs, five (gout, pancytopenia, Bell's palsy [n=2], Myasthenia gravis) that were reported by RSVPreF3-AS01_E recipients and considered as possibly related to study intervention by FDA.

6.1.12.7 Dropouts and/or Discontinuations

See Section [6.1.10.1.2](#).

6.1.13 Study Summary and Conclusions

Study RSV OA=ADJ-006 was designed as an efficacy and safety study conducted in 17 countries. Adults aged ≥60 YOA received either RSVPreF3-AS01_E or Placebo.

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).

Although the RSVPreF3 investigational vaccine was more reactogenic than Placebo, severe (Grade 3) ARs were uncommon. A numerical imbalance was noted in atrial fibrillation (vaccine: 10 events, placebo: 4 events) within 30 days post vaccination. No notable imbalances were observed between treatment groups for deaths and pIMDs. The data generated from Study RSV OA=ADJ-006 support the safety and effectiveness of RSVPreF3-AS01_E.

6.2 RSV OA=ADJ-004

NCT04732871

Title: "A 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 in adults aged 60 years and above"

This study is being conducted to evaluate the immunogenicity, safety, and persistence of the immune response up to 3 years following a single dose of RSVPreF3-AS01_E investigational vaccine in adults ≥ 60 YOA. Clinical data up to the Month 6 timepoint for immunogenicity and up to the DLP for safety at Month 6 [February 11, 2022] were provided in this BLA. Study design elements pertaining to revaccination are not presented in this memo.

6.2.1 Objectives

Primary Objective and Endpoints

To evaluate the humoral immune response following a 1-dose primary schedule of RSVPreF3-AS01_E vaccine.

Endpoints: RSV-A neutralizing geometric mean titer (GMT), RSV-B neutralizing GMT

Timepoints: pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), 6 month post-Dose 1 (Month 6)

Secondary Objectives and Endpoints

1. To further evaluate the humoral immune (HI) response following a 1-dose primary schedule of RSVPreF3-AS01_E vaccine
 - *Endpoint:* RSVPreF3-specific IgG GMT
 - *Timepoints:* pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), 6 month post-Dose 1 (Month 6)
2. To evaluate the cell-mediated immunity (CMI) response following 1 dose of the RSVPreF3-AS01_E vaccine
 - *Endpoints:* Frequency of RSVPreF3-specific cluster of differentiation (CD) 4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, interleukin (IL) -2, tumor necrosis factor (TNF) - α , interferon (IFN) - γ , IL-13, IL-17.
 - *Timepoints:* pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), 6 month post-Dose 1 (Month 6)

3. To evaluate the safety and reactogenicity of each vaccination schedule of the RSVPreF3-AS01_E vaccine.
 - Endpoints:
 - Occurrence of solicited local and systemic reactions with an onset during the 4-day follow-up period after vaccination
 - Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination
 - Occurrence of SAEs from the day of vaccination up to 6 months after vaccination
 - Occurrence of pIMDs from the day of vaccination up to 6 months after vaccination

6.2.2 Design Overview

Study-004 is a randomized, open-label, multi-country study with objectives to evaluate the immunogenicity, reactogenicity, safety, and persistence of a single dose of the RSVPreF3-AS01_E investigational vaccine and different revaccination schedules in adults aged 60 years and above. A total of 1,653 participants ≥60 YOA were randomized 3:1:1 to one of the 3 groups listed in [Table 15](#).

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 (i.e., 6 months after Dose 2 or 3, depending on the study group).

Table 15. Study Design, Study 004

Study Group	Primary Vaccination (Day 1)	Revaccination Year 1 (Month 12)	Revaccination Year 2 (Month 24)	Exposed Set N	Immuno-genicity Humoral N	Immuno-genicity CMI N
RSV_annual: 3 doses	RSVPreF3-AS01 _E	RSVPreF3-AS01 _E	RSVPreF3-AS01 _E	993	342	342
RSV_flexible revaccination: 2 doses	RSVPreF3-AS01 _E	*	*	329	321	111
RSV_1dose	RSVPreF3-AS01 _E	(none)	(none)	331	324	113

Source: Adapted from Study 004 protocol.pdf, page 37, Table 7.

*Based on immunogenicity data from this study (RSV OA=ADJ-004) and efficacy results from the Phase 3 Study RSV OA=ADJ-006, revaccination might be decided for this group.

Exposed Set (ES): participants who received at least 1 dose.

Per-Protocol Set (PPS): participants who received at least 1 dose as randomized, and have post-vaccination data and no protocol deviations that led to exclusion.

CMI=Cell-mediated immunity

N: number of participants in ES and PPS, as applicable.

6.2.3 Population

Except for 1 exclusion criterion, the inclusion and exclusion criteria are the same as Study RSV OA=ADJ-006 (see Section [6.1.3](#)).

Planned leave for 4 consecutive weeks during the RSV seasons covered by the study, that would prohibit the reporting of ARI cases and attendance to ARI visit was not an exclusion criterion in Study RSV OA=ADJ-004.

6.2.4 Study Treatments or Agents Mandated by the Protocol

RSVPreF3-AS01_E

- Composition: 120 µg of RSVPreF3, AS01_E (25 µg QS-21, 25 µg MPL, liposomes)
- Presentation: RSVPreF3: lyophilized powder (vial); AS01_E: suspension for injection (vial)
- Lot #s (administered to all groups at Day 1): RSVPreF3: lot DRSVA029A, AS01_E: lot DA01A085A

6.2.5 Directions for Use

RSVPreF3-AS01_E: same as for Study RSV OA=ADJ-006 (see Section [6.1.5](#)).

6.2.6 Sites and Centers

The study was conducted at 46 sites in 5 countries: Finland (10 sites), Germany (8 sites), Japan (3 sites), Taiwan (7 sites), and the US (18 sites).

6.2.7 Surveillance/Monitoring

Safety Monitoring

- Solicited local reactions: same as Study 006
- Unsolicited AEs: same as Study 006
- SAEs, pIMDs: Day 1 through 6 months after the last vaccination

Solicited AEs and unsolicited AEs were recorded on a paper diary card.

Immunogenicity

Blood samples were collected at Day 1, 31 and Month 6.

- Humoral immunity (HI): subset from RSV_annual study group (n=342), and all participants from the RSV_flexible revaccination (n=321) and RSV_1dose (n= 324) study groups.
- Cell-mediated immunity (CMI): subsets from RSV_annual group (n=342, RSV_flexible revaccination (n=111) and RSV_1dose (n=113) study groups.

For the RSV_annual study group, HI and CMI were assessed in the same subset of 342 participants.

Table 16. Laboratory Assays

Assessment	Parameter	Method	Laboratory
Humoral Immunity	RSV- A neutralizing antibody	Neutralization	GSK ((b) (4) Belgium)
Humoral Immunity	RSV- B neutralizing antibody	Neutralization	GSK ((b) (4) Belgium)
Humoral Immunity	RSVPreF3-specific IgG	ELISA	(b) (4)
Cell-mediated Immunity	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	ICS-10P	GSK (Rixensart, Belgium)

Source: adapted from Study 004 protocol.pdf, page 53, Table 12.

Abbreviations: ELISA=enzyme-linked immunosorbent assay, ICS-10P=10-parameters intracellular cytokine staining assay.

6.2.8 Endpoints and Criteria for Study Success

Endpoints: see Section [6.2.1](#). There were no hypotheses tested.

6.2.9 Statistical Considerations & Statistical Analysis Plan

All immunogenicity analyses were descriptive. Analyses of the primary vaccination time points up to Month 12 (timepoint for re-vaccination #1) were performed for the 3 study groups combined.

- GMT, geometric mean concentration (GMC): For antibody titers/concentrations below the assay cut-off, $\frac{1}{2}$ lower limit of quantification (LLOQ) was used for GMT/GMC calculations. Antibody titers/concentrations above the upper limit of quantification (ULOQ), the ULOQ was used for GMT/GMC calculations. Neutralizing antibody responses reported in international units (IU) /mL were presented in this memo, unless otherwise specified.
- The mean geometric increase (MGI) was calculated by the geometric mean of ratios of antibody titers/concentrations of each post-primary vaccination time point over pre-Dose 1 (Day 1).
- The frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers, including at least one cytokine among CD40L, 41BB, IL-2, TNF- α , IFN- γ , IL-13, IL-17 were reported as cells per million CD4+ and/or CD8+ T cells.

Safety Analyses

The number and percentage of participants reporting

- Each solicited injection site reaction (any grade, Grade 3) and solicited systemic event (any grade, Grade 3) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) were tabulated after Dose 1. For fever, the number and percentage of participants reporting fever by half degree ($^{\circ}$ C) cumulative increments during the 4-day follow-up period were tabulated after Dose 1.
- Any unsolicited AE during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) with its exact 95% CI were tabulated for Dose 1 by MedDRA Primary System Organ Class (SOC) and preferred term.
- At least one SAE reported from Dose 1 up to 6 months post-Dose 1 were classified by MedDRA terms and tabulated.
- At least one pIMD reported from Dose 1 up to 6 months post-Dose 1 were classified by MedDRA terms and tabulated.

Missing or non-evaluable measurements were not replaced. The analysis of solicited events included only vaccinated participants with documented solicited safety data (i.e., paper diary completed).

6.2.10 Study Population and Disposition

A total of 1,720 participants were enrolled in the study. The study started February 15, 2021 (first participant, first visit) and is ongoing. The last visit date for the Month 6 analysis was December 20, 2021. The DLP for the safety analysis at Month 6 was February 11, 2022.

6.2.10.1 Populations Enrolled/Analyzed

Exposed set (ES): All participants who received at least 1 dose of the study intervention. Safety analyses were based on the ES.

Per Protocol set (PPS): All participants 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. The primary analysis for immunogenicity was performed on the PPS.

6.2.10.1.1 Demographics

See Section [7.1.2](#).

6.2.10.1.2 Subject Disposition

Of 1,720 enrolled participants, 1,653 received 1 dose of RSVPreF3-AS01_E at Day 1 and were included in the ES (993 RSV_annual group, 329 RSV_flexible revaccination group, 331 in the RSV_1dose group).

The PPS for humoral immunity analyses ranged from 929 to 987 participants, depending on the time point assessed. The PPS for cell-mediated immunity ranged from 530 to 566 participants, depending on the time point assessed. Up to Month 6, a total of 32/1,653 (1.9%) participants withdrew from the study (17 from the RSV_annual group, 9 from the RSV_flexible revaccination group, and 6 from the RSV_1dose group); main reason for discontinuation was voluntary withdrawal of consent.

6.2.11 Immunogenicity Analyses

RSV-A and RSV-B NAb and cell-mediated immune responses are presented in Section 7 of this memo.

6.2.11.1 Analyses of Primary Endpoint(s)

Please see Section [7.1.5](#).

6.2.11.2 Analyses of Secondary Endpoints

RSV IgG responses at 1 month post-vaccination were consistent with the primary analyses presented in Study 009 (see Section [6.4.11.1](#)).

6.2.11.3 Subpopulation Analyses

No systematic trend was observed between males and females. The humoral immune response at Day 31 decreased as age increases but at Month 6, this tendency was no longer observed between age categories. At Day 31 and Month 6, a trend toward lower humoral immune response was observed for the Asian participants compared to participants from North America and Europe.

6.2.11.4 Dropouts and/or Discontinuations

The number of participants with at least one important protocol deviation was 118 (6.9%). Most of the protocol deviations were related to missed/out of window assessment or timepoint completion (61 participants) followed by excluded medication, vaccine, or device (45 participants).

6.2.12 Safety Analyses

6.2.12.1 Methods

Please see Section [6.2.7](#).

6.2.12.2 Overview of Adverse Events

Overall (3 groups combined),

- Solicited local and systemic adverse reactions (Day 1-4)
 - Solicited local adverse reactions were reported by 62.2% of participants. The most frequently reported event was injection site pain (60.5%). Injection site pain was the most frequently reported local reaction (60.5%) Grade 3 solicited local reactions were reported by 1.5% of participants.
 - Solicited systemic adverse reactions were reported by 49.5% of participants. Myalgia and fatigue were the most commonly reported events (33.5% and 31.4% of participants, respectively). Grade 3 solicited systemic events were reported by 2.9% of participants.
- Unsolicited AEs (Day 1-30)
 - 12.8% of participants reported at least 1 unsolicited AE. The most commonly reported unsolicited AEs were headache (1.1%), arthralgia (0.7%) and injection-site pruritus (0.6%).

6.2.12.3 Deaths

A total of six (0.4%) deaths were reported during the study up to the DLP (COVID-19 pneumonia, natural causes [79 days post-vaccination], myocardial infarction [130 days post-vaccination], unspecified [150 days post-vaccination], prostate cancer [179 days post-vaccination], cardiac arrest [302 days post-vaccination]). None of the deaths were considered by the study investigator or the FDA clinical reviewer to be related to study vaccination.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 65 (3.9%) of participants reported at least 1 SAE within 6 months after RSVPreF3-AS01_E vaccination. One (1) SAE was considered by the study investigator and this FDA clinical reviewer to be related to study intervention (Guillain-Barré syndrome), which was also reported as a pIMD [see Section [6.2.12.5](#) for further information].

6.2.12.5 Potential Immune-Mediated Diseases

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 protein was elevated (146 mg/dL). Magnetic resonance imaging showed no significant findings. Ganglioside immunoglobulins (GM1-IgG) was positive. She started immunoglobulin treatment for Guillain-Barre syndrome. During her hospitalization, she was treated for ventilator-associated pneumonia, underwent tracheotomy for type 2 chronic respiratory failure, and started anticoagulation therapy for bilateral deep venous thromboses. She was transferred to the rehabilitation unit, eventually able to perform daily life activities, and discharged from the hospital approximately 6 months after Dose 1. The pIMD was considered by the study investigator and this FDA clinical reviewer to be related to RSVPre3-AS01_E vaccination.

6.2.12.7 Dropouts and/or Discontinuations

See Section [6.2.11.4](#).

6.2.13 Study Summary and Conclusions

Immunogenicity: please see Section [7.1.11](#).

The frequencies of solicited local and systemic adverse reactions, and unsolicited AEs reported within 30 days post-vaccination were consistent with the results from Study 006. 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 the clinical reviewer to be related to vaccination.

6.3 RSV OA=ADJ-007 **NCT04841577**

Title: "A Phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3-AS01_E investigational vaccine when co-administered with FLU vaccine in adults aged 60 years and above."

This study is being conducted to evaluate the immunogenicity, safety and reactogenicity of RSVPreF3-AS01_E investigational vaccine in adults ≥60 YOA when co-administered with Fluarix Quadrivalent influenza vaccine (FLU). Clinical data up to the Month 6 timepoint for immunogenicity and up to the DLP for safety at Month 6 were provided in this BLA. Only the study design elements pertaining to these data are presented in this memo.

6.3.1 Objectives

Primary Objectives and Endpoints

1. To demonstrate the non-inferiority of RSVPreF3-AS01_E investigational vaccine when co-administered with the FLU vaccine compared to RSVPreF3-AS01_E investigational vaccine administration alone
 - a. RSV-A neutralization antibody titers expressed as group GMT ratio, 1 month after the RSVPreF3-AS01_E investigational vaccine dose.
 - i. Success Criteria: The upper limit (UL) of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for RSVPreF3-AS01_E investigational vaccine is ≤1.5.
2. To demonstrate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3-AS01_E investigational vaccine compared to FLU vaccine administration alone
 - a. HI antibody titers for each of the FLU vaccine strains expressed as group GMT ratio, 1 month after the FLU vaccine dose
 - i. Success Criteria: The UL of the 2-sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) for each of the FLU vaccine strains is ≤1.5.

Secondary Objectives and Endpoints

1. To evaluate the non-inferiority of FLU vaccine when co-administered with the RSVPreF3-AS01_E investigational vaccine compared to FLU vaccine administered alone.
 - a. HI seroconversion status for each of the FLU vaccine strains expressed as seroconversion rate (SCR), 1 month after the FLU vaccine dose
 - i. Success Criteria: The UL of the 2-sided 95% CI on the group difference (Control group minus Co-Ad group) in SCR is ≤10% for anti-HI antibodies.
2. To evaluate the humoral immune response to RSVPreF3-AS01_E investigational vaccine when co-administered with the FLU vaccine or administered alone.
 - a. RSV-A neutralization antibody titers expressed as MGI at 1 month after the RSVPreF3-AS01_E investigational vaccine dose
 - b. RSV-B neutralizing antibody titers expressed as group GMT ratio and MGI at 1 month after the RSVPreF3-AS01_E investigational vaccine dose in a subset

3. To evaluate the humoral immune response to the FLU vaccine when co-administered with the RSVPreF3-AS01_E investigational vaccine or administered alone.
 - a. HI antibody titers for each of the FLU vaccine strains expressed as GMT, at Day 1 and Day 31
 - b. HI seroconversion and seroprotection status for each of the FLU vaccine strains expressed as SCR, from Day 1 to Day 31
 - c. HI antibody titers for each of the FLU vaccine strains expressed as MGI, 1 month after the FLU vaccine dose.
4. To evaluate the safety and reactogenicity following administration of the RSVPreF3OA investigational vaccine and FLU vaccine, co-administered or administered alone.
 - a. Percentage of participants reporting each solicited event with onset within 4 days after vaccine administration
 - b. Percentage of participants reporting unsolicited AEs within 30 days after vaccine administration
 - c. Percentage of participants reporting SAEs after vaccine administration up to study end
 - d. Percentage of participants reporting pIMDs after vaccine administration up to study end.

Tertiary objective and Endpoint

1. To further evaluate the humoral immune response to RSVPreF3-AS01_E investigational vaccine when co-administered with the FLU vaccine or administered alone
 - a. RSVPreF3-specific IgG concentrations expressed as group GMC ratio and MGI at 1 month after the RSVPreF3-AS01_E investigational vaccine dose in a subset.

6.3.2 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 received 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.

6.3.3 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 [6.1.3](#)).

6.3.4 Study Treatments or Agents Mandated by the Protocol

RSVPreF3-AS01_E

- Composition: 120 µg of RSVPreF3, AS01_E (25 µg QS-21, 25 µg MPL, liposomes)
- Presentation: RSVPreF3: lyophilized powder (vial); AS01_E: suspension for injection (vial)
- Lot #s (administered to all groups at Day 1): RSVPreF3: lot DRSVA029A, DA01A086A

FLU

- Composition: 0.5 mL of FLU containing 15 µg hemagglutinin per strain/dose
 - Strains: A/Victoria/2570/2019 (H1N1), IVR-215; A/Hong Kong/2671/2019 (H3N2), NIB-121; B/Washington/02/2019, wild type; B/Phuket/3073/2013, wild type
- Presentation: Syringe, suspension for injection
- Lot #s: AFLBA534A

6.3.5 Directions for Use

See Section [6.3.4](#).

6.3.6 Sites and Centers

14 centers in 3 countries: 7 in New Zealand, 5 in Panama, and 2 in South Africa

6.3.7 Surveillance/Monitoring

Safety monitoring were the same as those in Study 006 (see Section [6.1.7](#)).

Blood samples were collected at Day 1, 31, and 61.

Co-Ad Group:

- Pre-dose 1 (Day 1): RSV-A neutralizing antibody, H1N1 strain HA, H3N2 strain HA, B/Yamagata stain HA, B/Victoria strain HA
 - Immunogenicity subset: RSV-B neutralizing antibody, RSVPreF32-specific IgG antibody
- Day 31: RSV-A neutralizing antibody, H1N1 strain HA, H3N2 strain HA, B/Yamagata stain HA, B/Victoria strain HA
 - Immunogenicity subset: RSV-B neutralizing antibody, RSVPreF32-specific IgG antibody

Control Group:

- Pre-FLU dose (Day 1): H1N1 strain HA, H3N2 strain HA, B/Yamagata stain HA, B/Victoria strain HA
- Post-FLU dose (Day 31); H1N1 strain HA, H3N2 strain HA, B/Yamagata stain HA, B/Victoria strain HA
- Pre-RSV dose (Day 31): RSV-A neutralizing antibody
 - Immunogenicity subset: RSV-B neutralizing antibody, RSVPreF32-specific IgG antibody
- Post-RSV dose (Day 61): RSV-A neutralizing antibody
 - Immunogenicity subset: RSV-B neutralizing antibody, RSVPreF32-specific IgG antibody

6.3.8 Endpoints and Criteria for Study Success

See Section [6.3.1](#).

6.3.9 Statistical Considerations & Statistical Analysis Plan

Overall, the sample size provided $\geq 90\%$ power to achieve the primary objectives using a 1-sided 2.5% alpha-level. A hierarchical procedure was planned to be used for the multiple study objectives.

6.3.10 Study Population and 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 17](#)).

Table 17. 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).

6.3.10.1 Populations Enrolled/Analyzed

- ES: defined as all subjects with at least one documented study vaccine administered.
- PPS: 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. The primary analysis for immunogenicity was performed on the PPS.

6.3.10.1.1 Demographics

The demographics for participants in the Exposed set are shown in [Table 18](#).

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 18. 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 (minimum, maximum)	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
Abbreviations: SD=standard deviation; YOA=years of age

6.3.10.1.2 Subject Disposition

A total of 976 participants were enrolled into the study, of which 890 were randomized and 885 received at least 1 dose of the study interventions and were included in the ES. Of these 885 participants at end-of-study analysis, 837 (94.6%) were included in the PPS for Visit 2 and 397 were included in the PPS for Visit 3.

During the entire study period, a total of 39 participants had withdrawn from the study. The main reasons for withdrawal were lost to follow-up (15) and AE requiring reporting (14).

6.3.11 Immunogenicity Analyses

6.3.11.1 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 19](#) 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 19. 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 20](#) 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 20. 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	Co-Ad Group GMT ^a N=427 95% CI (LL, UL)	Control Group GMT ^a N=411 95% CI (LL, UL)	GMT Ratio: Control Group vs Co-Ad Group 95% CI (LL, UL)
FLU A/Hong Kong	295.2 (263.6, 330.6)	346.8 (306.6, 392.3)	1.17 (1.02, 1.35)
FLU A/Victoria	267.1 (235.6, 302.8)	325 (282.5, 374.9)	1.22 (1.03, 1.44)
FLU B/Phuket	28.9 (26.0, 32.1)	34.8 (31.1, 39.0)	1.17 (1.04, 1.32)
FLU A/Washington	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).

6.3.11.2 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).

6.3.11.3 Subpopulation Analyses

No significant differences in immunogenicity were noted with regards to age.

6.3.11.4 Dropouts and/or Discontinuations

The number of participants with at least 1 important protocol deviation was 13 (2.9%) in the Co-Ad group and 50 (11.2%) in the Control group. Most of the protocol deviations were 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).

6.3.12 Safety Analyses

6.3.12.1 Methods

See Section [6.3.7](#).

6.3.12.2 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 21](#) 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 21. 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 22](#) 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 22. 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)
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 23](#) 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 $\geq 39.0^{\circ}\text{C}$ 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 23. 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 n (%)	Control Visit 2 N=438 n (%)
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)

Adverse Reaction	Co-Ad Group Visit 1 N=438 n (%)	Control Visit 2 N=438 n (%)
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%).

6.3.12.3 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.

- *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.

Reviewer Comment

FDA considered the event to be possibly related to FLU or RSVPreF3-AS01_E vaccination.

6.3.12.4 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 [6.3.12.3](#) and the other ADEM case was non-fatal. Both cases of ADEM were also reported as pIMDs.

6.3.12.5 Potential Immune-Mediated Diseases (pIMDs)

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.

- 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.

Reviewer Comment

FDA considered the event to be possibly related to FLU or RSVPreF3-AS01_E vaccination.

6.3.12.6 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.

6.3.13 Study Summary and Conclusions

The primary objectives to demonstrate non-inferiority of co-administration of RSVPreF3-AS01_E investigational vaccine and Fluarix Quadrivalent (FLU) vaccine was met based on the predefined success criterion of the UL of the 2-sided 95% CI of the group GMT ratio being <1.5. The ratio of RSV-A neutralizing antibody titers GMTs between the control group and the Co-Ad group 1 month after RSVPreF3-AS01_E administration had an UL of 1.28 and 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 was a range of UL of 1.10 – 1.22. The solicited and unsolicited safety results were similar to that of Study 006. Two cases of ADEM were reported in the co-administration group that were considered as possibly related to either RSVPreF3-AS01_E or FLU vaccination.

6.4 RSV OA=ADJ-009

NCT05059301

Title: “A Phase 3, randomized, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3-AS01_E investigational vaccine administered as a single dose in adults aged 60 years and above.”

In this BLA, the Applicant provided the final analysis for immunogenicity from all participants up Day 31 and safety data up to the DLP of March 9, 2022. An analysis including the remaining safety data up to 6 months after vaccination will be performed at study end and will be submitted at a later date.

This review will focus primarily on the primary objective to demonstrate lot-to-lot consistency based on IgG GMCs at 1-month post-vaccination. In regard to safety, the frequencies of solicited reactions and unsolicited, non-serious AEs were similar to the results in Study 006; see Section [6.1.12](#) for further details. Since the population in this study was similar to that of Study 006, Section [6.4.12](#) will focus primarily on reported SAEs and pIMDs.

6.4.1 Objectives

Primary Objective, Endpoint, and Statistical Criteria

To demonstrate the lot-to-lot consistency of 3 lots of RSVPreF3-AS01_E vaccine.

Endpoint: RSVPreF3-specific IgG GMC at 1 month post-vaccination

Statistical criteria for equivalence: The 2-sided 95% CI of the group GMC ratios between each pair of the 3 lots (RSVPreF3-AS01_E vaccine lot divided by another RSVPreF3-AS01_E vaccine lot) is within the pre-defined limit of [0.67, 1.5].

Secondary Objectives and Endpoints

To evaluate the safety and reactogenicity of 3 lots of RSVPreF3-AS01_E vaccine.

Endpoints:

- Occurrence of solicited local and systemic reactions with an onset during the 4-day follow-up period after vaccination
- Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after vaccination
- Occurrence of SAEs from the day of vaccination up to 6 months after vaccination
- Occurrence of pIMDs from the day of vaccination up to 6 months after vaccination

6.4.2 Design Overview

Study 009 is a randomized, double-blind, study with 3 parallel groups: (Lot 1, Lot 2, Lot 3).

Participants were randomly assigned (1:1:1) to the 3 study groups to receive 1 of the 3 lots RSVPreF3-AS01_E vaccine, each composed of randomized combinations of antigen and adjuvant lots.

The study was conducted in a double-blind manner (blinded to the vaccine lots) from study start up to final immunogenicity analysis. Study participants will remain blinded to study end; however, study investigators received a copy of the Clinical Study Report containing results of the final analyses on immunogenicity and safety data up to Day 31; consequently, study investigators could become unblinded the vaccine assignment for certain participants through review of the summary results.

6.4.3 Population

The eligibility criteria in this study were the same as Study 006 (see Section [6.1.3](#)).

6.4.4 Study Treatments or Agents Mandated by the Protocol

Table 24. Study Design, Study 009

Study Group	Lot Numbers
Lot 1	RSVPreF3: DRSVA033A AS01 _E : DA01A086A
Lot 2	RSVPreF3: DRSVA039A AS01 _E : DA01A085A
Lot 3	RSVPreF3: DRSVA040A AS01 _E : DA01A088A

Source: Adapted from Study 009 synopsis.pdf, Table 2.2.

6.4.5 Directions for Use

Please see Section [6.1.5](#).

6.4.6 Sites and Centers

The study was conducted at 19 sites in 3 countries: Canada (7 sites), Sweden (3 sites), and the US (9 sites).

6.4.7 Surveillance/Monitoring

See Section [6.1.7](#) for details of safety monitoring

Immunogenicity

Blood samples were collected from all participants at pre-vaccination (Day 1) and 1-month post-vaccination (Day 31).

6.4.8 Endpoints and Criteria for Study Success

Please see Section [6.4.1](#).

6.4.9 Statistical Considerations & Statistical Analysis Plan

Primary Immunogenicity Analysis

Between group comparisons

The RSVPreF3 IgG GMC ratios at 30 days post-vaccination (Day 31) were computed for each pair of RSVPreF3-AS01_E vaccine lots (Lot 1 over Lot 2, Lot 1 over Lot 3, Lot 2 over Lot 3).

The 2-sided 95% CI for the GMC ratio was derived from an analysis of covariance model on log₁₀ transformed titer. The model included the treatment group and the age category (age at vaccination: 60-69, 70-79, or ≥80 years) as fixed effects, and the pre-dose log₁₀-transformed titer as covariate. Missing data was not replaced. For purposes of GMC calculations, IgG concentrations below the assay LLOQ were replaced by 1/2 assay LLOQ.

Safety Analyses for SAEs and pIMDs

The number and percentage of participants reporting

- At least one SAE reported from Dose 1 up to 6 months post-Dose 1 were classified by MedDRA terms and tabulated.
- At least one pIMD reported from Dose 1 up to 6 months post-Dose 1 were classified by MedDRA terms and tabulated.

6.4.10 Study Population and Disposition

A total of 770 participants were enrolled in the study. The study started October 1, 2021 (first participant, first visit) and is ongoing. The last visit date for the final immunogenicity analysis was January 24, 2022. The DLP for the safety analysis was March 9, 2022.

6.4.10.1 Populations Enrolled/Analyzed

Exposed set (ES): participants who received the study intervention.

Per Protocol Set (PPS): participants who received the study intervention as per-protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without

intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

Analyses of the primary and secondary immunogenicity endpoints are based on the PPS.

6.4.10.1.1 Demographics

See Section [7.1.2](#).

6.4.10.1.2 Subject Disposition

Of the 770 enrolled participants, 757 (98.3%) participants (n=251, 253, and 253 in the Lot 1, Lot 2, and Lot 3, respectively) were included in ES.

A total of 708 (93.5%) (n=234, 237, and 237 in the Lot 1, Lot 2, and Lot 3 study groups, respectively) were included in the immunogenicity PPS at Day 31.

6.4.11 Immunogenicity Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

Lot-to-lot consistency was demonstrated between the 3 RSVPreF3-AS01_E vaccine lots, as measured by RSVPreF3-specific IgG GMC at 1 month post-vaccination. The 2-sided 95% CI for pair-wise comparisons of RSVPreF3-specific IgG GMC ratios for 3 vaccine lots were within the pre-defined limit of [0.67, 1.5].

Table 25. RSVPreF3 IgG GMCs at 1 Month Post-vaccination, Study 009

RSVPreF3-AS01 _E Lot #	RSVPreF3 IgG GMC (EU/mL)
Lot 1 (N=234)	86041
Lot 2 (N=234)	80518
Lot 3 (N=237)	94290

Source: adapted from Study 009 report.pdf, Tables11.3-11.5.

N=number of participants with available results

Per-Protocol Set: participants who received the study intervention as per-protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

Table 26. Pair-wise Comparisons of the Ratio of RSVPreF3 IgG GMCs, Study 009

RSVPreF3-AS01 _E Lot Comparison	GMC Ratio (95% CI)
Lot 1/Lot 2	1.06 (0.94, 1.21)
Lot 1/Lot 3	0.92 (0.81, 1.04)
Lot 2/Lot 3	0.87 (0.77, 0.99)

Source: adapted from Study 009 report.pdf, Tables11.3-11.5.

Comparisons used the adjusted group ratio of GMC (Lot 1/Lot 2) (ANCOVA model applied to the log₁₀ transformed titers). The ANCOVA model includes the treatment group and the age category (age at vaccination: 60-69, 70-79 or ≥80 years) as fixed effects and the pre-dose log₁₀ titer as covariate.

N=number of participants with available results

Per-Protocol Set: participants who received the study intervention as per-protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

The ratios of RSVPreF3-specific IgG antibody GMC between groups at 1 month post-vaccination were as follows:

- Lot 1 over Lot 2: 1.06 (95% CI: 0.94, 1.21)
- Lot 1 over Lot 3: 0.92 (95% CI: 0.81, 1.04)
- Lot 2 over Lot 3: 0.87 (95% CI: 0.77, 0.99)

6.4.11.2 Dropouts and/or Discontinuations

The number of participants with at least 1 important protocol deviation leading to elimination from any analyses was 18 (7.1%), 15 (6.0%), and 17 (6.7%) in Lot 1 group, Lot 2 group, and Lot 3 group, respectively. Most of the protocol deviations were related to missed/out of window assessment or time point completion (10, 8, and 8 participants in the Lot 1, Lot 2, and Lot 3 study groups, respectively).

6.4.12 Safety Analyses

6.4.12.1 Methods

See Section [6.4.1](#).

6.4.12.2 Overview of Adverse Events

6.4.12.3 Deaths

A total 3 deaths were reported during the study: 2 [0.8%] in the Lot 2 group [myocardial infarction and sudden cardiac death] and 1 [0.4%] in the Lot 3 group [COPD, pleural effusion, and pulmonary edema]. None of the deaths were considered by the study investigator or the FDA reviewer to be related to study vaccination.

6.4.12.4 Nonfatal Serious Adverse Events

At the time of the DLP, at least 1 SAE was reported in 3 (1.2%) Lot 1 participants (fall, sepsis, and cholecystitis), 2 (0.8%) Lot 2 participants (myocardial infarction and sudden cardiac death) and 2 (0.8%) Lot 3 participants (chronic obstructive pulmonary disease [COPD], pleural effusion, and pulmonary edema in 1 participant and acute myocardial infarction in the other participant). None of the SAEs were considered by the study investigator or the FDA clinical reviewer to be causally related to study vaccination.

6.4.12.5 Potential Immune-Mediated Diseases

Two (0.8%) Lot 3 participants reported a pIMD exacerbation of psoriasis. One of the events was considered by the study investigator to be related to vaccination which occurred 15 days after vaccination.

Reviewer Comment

Psoriasis was a pre-existing condition in both participants. The FDA reviewer considered both events to be temporally following but unrelated to vaccination.

6.4.12.7 Dropouts and/or Discontinuations

See Section [6.4.11.2](#).

6.4.13 Study Summary and Conclusions

The primary objective to demonstrate lot consistency was demonstrated for 3 vaccine lots; the 2-sided 95% CI for pair-wise comparisons of RSVPreF3-specific IgG GMC ratios for 3 vaccine lots were within the pre-defined limit of [0.67, 1.5]. No new safety signals were identified from review of the safety data from Study 009. Up to the DLP, the reported SAEs and piMDs were consistent with events reported in Study 006.

6.5 RSV OA=ADJ-002 and RSV OA=ADJ-011 Ext 002

RSV OA=ADJ-002

NCT03814590

Title: "Phase I/II, observer-blind, safety, reactogenicity and immunogenicity study of GSK Biologicals' respiratory syncytial virus (RSV) vaccine GSK3844766A in subjects aged 18-40 or 60-80 years"

Study RSV OA=ADJ-002 was designed to assess the safety (primary objective) and immunogenicity (secondary objective) of three dosages (30 µg, 60 µg, 120 µg RSVPreF3) with or without AS01-adjuvant. Nine vaccine formulations were administered according to a 0, 2-month schedule. In part A, a total of 48 adults 18-40 years of age (12 per study group) received an unadjuvanted formulation or saline placebo. In part B, each dose level was administered without adjuvant, with AS01_B adjuvant, or with AS01_E adjuvant (total of 1,005 adults 60-80 years of age [~100 per study group and 1 saline placebo group]). The study was conducted in the US and Belgium.

Analyses pertaining to selection of the dose and adjuvant for later phase studies is described in this section.

Results

The exposed set was comprised of 48 and 1,005 participants in Part A and Part B, respectively.

The immunogenicity per-protocol set was comprised of 46 and 1,000 participants in Part A and Part B, respectively.

Safety (Part A and B)

The frequencies of solicited adverse reactions were lower after administration of AS01_E-based formulations than AS01_B-based formulations.

SAEs: Deaths were reported for 0 participants in Part A and 4 (0.4%) participants in Part B (unknown reason [n=1], aortic aneurysm with consequent cardio-respiratory arrest/hemorrhagic shock [n=1]), cardiac arrest and respiratory distress [n=1], lung carcinoma [n=1]). In Part A, no non-fatal SAEs were reported from Dose 1 up to 30 days post-Dose 2. In Part B, the frequency of SAEs in the 120ug RSVPreF3-AS01E group (n=7) was similar to the saline placebo group (n=5). None of the SAEs (fatal, non-fatal) were considered by the study investigator or the FDA clinical reviewer to be related to study vaccination.

Two pIMDs (0.2%) were reported between Day 91 (i.e., 1 month post-Dose 2) and 6 months post-Dose 2 (1 in the 30 µg RSVPreF3 group [autoimmune encephalitis] and 1 in the saline placebo group [gout]). None of the pIMDs were considered by the study investigators or the FDA clinical reviewer to be related to vaccination.

Immunogenicity (Part A and B)

For all vaccine formulations, RSV-A neutralizing GMTs peaked 1 month after the first dose, with no notable change after the second dose. RSV-A neutralizing titers were higher after the 120 µg dosage than 30 µg and 60 µg dosages with the same adjuvant content and 30 µg and 60 µg dosages unadjuvanted. Compared to unadjuvanted formulations, vaccine formulations containing AS01_E or AS01_B induced higher frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 markers *in vitro* among IL-2, CD40L, TNF-α, IFN-γ.

Conclusions

The safety and immunogenicity data support selection of 120 µg RSVPreF3-AS01_E, administered as a single dose, for further evaluation in phase 3 studies.

Study RSV OA=ADJ-011 Ext 002

NCT04657198

Title: “A phase 2b, open-label, multi-center, extension study to evaluate the safety and immunogenicity of a revaccination dose of the RSVPreF3 older adults (OA) investigational vaccine administered intramuscularly 18 months post-Dose 2 in adults 60 years and older who participated in the RSV OA=ADJ-002 study”

Adults who received 30 µg, 60 µg, and 120 µg RSVPreF3 + AS01E formulations in Study RSV OA=ADJ-002 (parent study) and enrolled in Study RSV OA=ADJ-011 (~40 participants/ per dosage cohort) then received RSVPreF3-AS01_E (120 µg RSVPreF3 + AS01E) as a third RSV dose approximately 18 months after completing a 2-dose series with RSVPreF3-AS01_E in the parent study.

Since the proposed primary series consists of a single dose of RSVPreF3-AS01_E, immunogenicity results from Study RSV OA=ADJ-011 were not presented in this memo. In the RSV OA=ADJ-011 study group who received 2 prior doses of RSVPreF3-AS01_E (120 µg RSVPreF3 + AS01_E) in the parent study, 1 SAE (prostate cancer) was reported in a 74-year participant within 6 months after the third RSVPreF3-AS01_E (120 µg RSVPreF3 + AS01_E), which was considered by the study investigator and the FDA clinical reviewer as unrelated to vaccination. No deaths were reported during the study period. No participant reported AEs defined as pIMDs.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication

The Applicant proposed indication is for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) A and B subtypes.

An integrated summary of efficacy is not presented in this section, since results from a single phase 3 clinical endpoint efficacy study (Study 006) were submitted to support the proposed indication. Clinical review of Study 006 efficacy results is presented in Section [6.1](#) of this memo.

This section summarizes descriptive analyses of humoral (RSV NAb) and cellular responses following Dose 1 in studies 006, -004, and -002, and integrated subpopulation analyses from studies 006, -004, -002 and -007.

Study Design

Study 006 started February 11, 2021, and designed as a randomized, placebo controlled study conducted in 17 countries (Northern Hemisphere [US, Canada, Mexico, Europe, Russia, South Korea, Japan] and Southern Hemisphere [Australia, New Zealand, S Africa]). The planned duration is approximately 3 years for participants from the Northern hemisphere and 2.5 to 3 years for participants from the Southern hemisphere. The DLP for immunogenicity analyses was April 11, 2022.

Study 004 is being conducted during a similar timeframe as efficacy Study 006. Study 004 started May 25, 2021, and designed as a randomized study conducted in 5 countries (US, Finland, Germany, Japan, and Taiwan). Immunogenicity and immune persistence following several RSVPreF3-AS01_E revaccination schedules. The planned duration of the study is 3 years. At the time the BLA was submitted, all participants had received RSVPreF3-AS01_E vaccine on Day 1; since no revaccinations had been administered up to the Month 6 timepoint, results up to Month 6 are presented for the 3 study groups combined (i.e., RSV_annual, RSV_flexible revaccination and RSV_1dose).

In phase 1/2 Study RSV OA=ADJ-002, a dose-ranging study, RSVPreF3-AS01_E (120 µg RSVPreF3 + AS01_E) was evaluated in part B; 2 doses were administered at 0 and 2 months to adults 60-80 years of age, and immune persistence was assessed up to 12 months after Dose 2 (Month 14). The study was conducted in the US and Belgium. Since the proposed primary series consisted of a single dose, immune responses presented in this section represent data up to Dose 2 (i.e., Day 1, Day 31, Day 61).

Study 007 was a concomitant use study in which RSV NAb responses were evaluated 1 month after RSVPreF3-AS01_E was concomitantly administered with FLU or administered separately.

Population: In studies 006, -004, and -007, enrollment was stratified by age (60-69, 70-79, ≥80 years of age) to ensure adequate representation of each age group (40%, 30% and 10% respectively, with the remaining 20% distributed freely across the 3 age categories).

7.1.1 Methods of Integration

RSV-A and RSV-B NAb

In this BLA, RSV-A and RSV-B NAb responses were provided at timepoints pre-vaccination and 1-month post-vaccination for studies described in Section 7.1, and also pre-dose 2 (Day 61) [Study 002] and 6 months post-dose 1 [Study 004]. Unit of Measure: when neutralizing antibody titers reported in International Units (IU)/mL was not provided in the BLA, the results presented in section 7 of this memo were reported in ED60.

In Study 006, the PPSi was defined as participants who received at least the first dose of the study intervention to which they were randomized and had post-vaccination immunogenicity data available and did not meet protocol deviations that led to exclusion. A total of 1,777 (n=885 RSVPreF3-AS01_E, n=892 placebo) participants were included in the PPSi, which comprised 7% of the study population.

In Study 004, the PPS was defined as participants who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination data and did not meet protocol deviations that led to exclusion. A total of 995 participants (3 study groups combined) comprised the PPS.

In Study 002, the PPS was defined as participants who met all eligibility criteria, received study vaccines per protocol, complied with protocol-specified post-vaccination blood sampling visits, post-vaccination immunogenicity results were available for at least one assay component at the corresponding time points, and did not meet protocol deviations that led to exclusion. The PPS for the RSVPreF3-AS01_E group ranged from 93 to 101, depending on the timepoint.

Cellular Immune Responses

The Applicant's 10-parameters intracellular cytokine staining assay (ICS-10P) was used to assess the frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least 1 cytokine among CD40L, IL-2, TNF- α , IFN- γ , IL-13, IL-17 and 4-1BB. Results were reported as cells per million CD4+ and/or CD8+ T cells.

The results presented in section 7 were measured using a validated ICS-10P. In this BLA, cellular immune responses from Study 004 were provided at timepoints pre-dose 1, 1 month and 6 months post-Dose 1.

7.1.2 Demographics and Baseline Characteristics

Immunogenicity

Study 006 [Day 13 PPSi]: Overall (RSVPreF3 and placebo groups): the mean age was 70.3 years (standard deviation \pm 6.8) (77.3% were 60-69 years of age, 49.4% were 70-79 year of age, and 12.5 were \geq 80 year of age), 51.9% were female, 93.9% were not Hispanic or Latino; 72.9% were White, 9.4% were Black or African, and 12.5% were Asian. A total of 89.8% of participants were recruited in the NH. 99.1% of participants lived in the general community, and 0.9% lived in a long-term care facility. 1.6% and 41.7% were characterized as frail and pre-frail respectively. 36.0% of participants had at least 1 pre-existing comorbidity of interest defined in the protocol (i.e., COPD, asthma, any chronic respiratory/pulmonary disease, diabetes mellitus Type I or Type II, chronic heart failure, advanced liver or renal disease). Overall, 53.5% of participants were classified as 'never smoker' for tobacco. The proportion of participants in each demographic characteristic was similar between RSVPreF3-AS01_E and placebo groups.

Study 004: Except for the geographic and racial group distributions, the demographic and baseline characteristics for the Study 004 PPS for humoral immunogenicity was similar to the Study 006 PPS for immunogenicity. In the Study 004 PPS for humoral immunogenicity, the most common racial groups were White (55.3%) and Asian (43.8%); the geographic distribution of the study population was: 41.2% Europe, 34.8% Asia, and 24.0% North America. The characteristics of Study 004 PPS for cell-mediated immunogenicity were similar to the Study 004 PPS for humoral immunogenicity

Study 007: see Section [6.3.10](#).

Study 002: the demographic and baseline characteristics for Study 002 were similar to Study 006 PPSi.

7.1.3 Subject Disposition

For Study 006, the PPSi included a total of 1,777 (n=885 RSVPreF3-AS01_E, n=892 placebo), which comprised 7% of the study population. For Study RSV OA=ADJ-004, the PPS for humoral immunity analyses ranged from 929 to 987 participants, depending on the time point assessed; the PPS for cell-mediated immunity ranged from 530 to 566 participants, depending on the time point assessed. For Study 002, the PPS for the RSVPreF3-AS01_E group ranged from 93 to 101, depending on the timepoint.

7.1.4 Analysis of Primary Endpoint(s)

Descriptive evaluation of RSV neutralizing GMTs was a primary endpoint in Study 004 and a secondary endpoint in Study 006.

Antibody persistence up to 6 months post-vaccination

Study 004 was conducted in the Northern Hemisphere and approximately the same timeframe as efficacy Study 006.

Prior to vaccination, all participants assessed for RSV NAb responses had RSV-A and RSV-B NAb titers at or above the assay LLOQ (RSV-A ≥ 56 IU/mL, RSV-B ≥ 44 IU/mL), which is expected for adults who have had previous natural exposure to RSV.

RSV-A NAb: the mean geometric ratio (from Day 1 to Day 31) was similar in both studies (10.7-fold increase in Study 004 [all study groups] and 10.2-fold increase in the RSVPreF3 group of Study 006). At Month 6 in Study 004, the GMT ratio (from Day 1 Month 6) was 4.4.

Table 27. RSV OA=ADJ-004 and -006: RSV Neutralizing GMTs and GMT Ratios at Day 31 and at Month 6 Compared to Baseline (Day 1), PPSi

Timepoint	Parameter	Study 006 RSVPreF3- AS01E N=885 (n); Value	Study 006 RSVPreF3-AS01E N=885 95% CI (LL, UL)	Study 006 Placebo N=892 (n); value	Study 006 Placebo N=892 95% CI (LL, UL)	Study 004 RSVPreF3- AS01E (All Groups) N=986 (n); value	Study 004 RSVPreF3-AS01E (All Groups) N=986 95% CI (LL, UL)
RSV-A NAb	--	--	--	--	--	--	--
D1	GMT	(885); 1941	(1833, 2056)	(892); 1953	(1849, 2064)	(986); 1799	(1707, 1895)
D31	GMT	(848); 21161	(19769, 22652)	(846); 1984	(1867, 2107)	(941); 19259	(18052, 20546)
(D31 / D1)	GMT ratio	(844); 10.9	(10.2, 11.7)	(846); 1	(1, 1.1)	(940); 10.7	(10, 11.4)
M6	GMT	--	--	--	--	(929); 7957	(7495, 8447)
(M6 / D1)	GMT ratio	--	--	--	--	(928); 4.5	(4.2, 4.7)
RSV-B NAb	--	--	--	--	--	--	--
D1	GMT	(885); 1336	(1262, 1414)	(892); 1374	(1296, 1456)	(987); 1408	(1334, 1486)
D31	GMT	(848); 11234	(10525, 11991)	(846); 1350	(1268, 1438)	(941); 10948	(10330, 11603)
(D31 / D1)	GMT ratio	(844); 8.5	(7.9, 9.1)	(846); 1	1, 1	(941); 7.8	(7.3, 8.3)
M6	GMT	--	--	--	--	(929); 5012	(4746, 5292)
(M6 / D1)	GMT ratio	--	--	--	--	(929); 3.6	(3.4, 3.8)

Source: Adapted from RSV OA=ADJ-006 report, Table 14.2.2.4 and RSV OA=ADJ-004 report Table 14.2.2.2.

PPSi=per-protocol set for immunogenicity: defined as participants who received at least the first dose of the study intervention to which they were randomized and had post-vaccination immunogenicity data available, and did not meet protocol deviations that led to exclusion.

N=number of participants with available results; n%=number / percentage of participants with titer equal to or above specified value

D=day; NAb=neutralizing antibody; D1=pre-vaccination at Day 1; D31=30 days post-Dose 1; M6=6 months post-Dose 1

Placebo=saline

7.1.5 Analysis of Secondary Endpoint(s)

Humoral antibody responses

RSV neutralizing antibody responses for Study 006 are described in Section [7.1.4](#).

RSVPreF3 IgG responses: please see Section [6.4](#) of this memo.

Cellular-mediated immune responses

In Study 004 (all study groups combined), the median frequency of RSVPreF3-specific CD4+ T cells (per million of CD4+ T cells, by ICS) expressing at least 2 activation markers, including at least 1 cytokine among CD40L, 41BB, IL-2, TNF- α , IFN- γ , IL-13, IL-17, was 191 at pre-Dose #1 (Day 1), 1,339 at 1 month post—Dose #1 (Day 31), and 666 at 6 months post-Dose #1 (Month 6).

7.1.6 Other Endpoints

Not applicable.

7.1.7 Subpopulations

Immunogenicity

Integrated subpopulation analyses summarized in this paragraph are based on RSV-A and RSV-B neutralizing GMTs pre-vaccination and 1 month post-vaccination from studies 004, -006, -007 and -002.

- Overall (all studies combined), there were no notable differences observed for subgroup analyses by age or sex. The number of frail participants was too small to make definitive conclusions about differences in RSV NAb responses.
- The baseline levels of RSV-A NAb (636.1 ED60), and RSV-B NAb (975.2 ED60) in Asia were lower compared to North America (> 916.4 ED60 for RSV-A and >1,153.0 ED60 for RSV-B) and Europe, which could account for lower titers for Asian participants compared to participants from North America and Europe.

7.1.8 Efficacy Persistence

Not applicable.

7.1.9 Product-Product Interactions

Results from a single concomitant vaccine study, Study 007, was provided in the BLA. The immunogenicity objectives were to evaluate antibody responses when RSV PreF3 OA vaccine was concomitantly administered with FLU, and vice versa. The non-inferiority criteria for RSV and influenza endpoints were met, as measured by RSV-A and RSV-B neutralizing GMTs and HAI GMTs to each influenza vaccine strain. Clinical review of Study 007 is presented in Section [6.3](#).

7.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7.1.11 Efficacy Conclusions

The primary objective of Study 006 was demonstrated as VE of a single dose of RSVPreF3-AS01_E against RSV-confirmed LRTD in participants ≥60 YOA was 82.58% (96.95% CI: 57.89, 94.08), with the LL of the CI above the pre-defined threshold of 20%.

RSVPreF3-AS01_E showed increases of RSV-A and RSV-B NAb GMTs, and RSVPreF3-specific IgG Ab GMCs 1-month post-vaccination with compared to pre-vaccination and Placebo. Additionally, RSVPreF3-AS01_E RSV-A and RSV-B NAb titers, and RSVPreF3-specific IgG Ab concentrations remained above pre-vaccination levels up to at least 6 months after administration as a single dose. The specific level of neutralizing antibody that is associated with protection against LRTD has not been identified.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 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 28](#) 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 28. 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.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

At the time of the DLPs, a total of 15,745 RSVPreF3-AS01_E recipients and 12,499 placebo recipients from four phase 3 studies were included in the Exposed Set ([Table 29](#) and [Table 30](#)). 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 29. 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 30. 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.

8.2.2 Overall Exposure, Demographics of Pooled 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%).

8.2.3 Categorization of Adverse Events

See Section [8.1](#).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Not applicable.

8.4 Safety Results

Table 31. 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

8.4.1 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 SOC 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 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. 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 [6.3.12.3](#) for the case narrative.

8.4.2 Nonfatal 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 [6.1](#) (Study 006) and Section [6.3](#) (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 infestations*, *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 [6.2.12.5](#) for case narrative.

8.4.3 Potential Immune Mediated Diseases

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 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 [6.1.12.5](#) 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 [6.3.12.3](#) and [6.3.12.5](#) narratives for the ADEM cases.

8.5 Product-Product Interactions

The safety of RSVPreF3-AS01_E when concomitantly administered with Fluarix Quadrivalent (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 [6.3.12](#) for details.

8.6 Safety Conclusions

At the time of the DLPs, a total of 15,745 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 ($\leq 1.7\%$).

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.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

AREXVY is not approved for use in persons <60 years of age.

In a clinical study that enrolled pregnant individuals who received an investigational unadjuvanted RSV vaccine that contained the same RSVPreF3 antigen as AREXVY, an increase in preterm births was observed compared to pregnant individuals who received placebo (sucrose reconstituted with saline).

9.1.2 Use During Lactation

Arexvy is not intended to be used in breastfeeding/lactating women

9.1.3 Pediatric Use and PREA (Pediatric Research Equity Act) Considerations

Evidence from an animal model strongly suggests that AREXVY would be unsafe in individuals younger than 2 years of age because of an increased risk of enhanced respiratory disease. Safety and effectiveness in individuals 2 years through 17 years of age have not been established.

9.1.4 Immunocompromised Patients

Safety and immunogenicity data on Arexvy are not available for immunocompromised individuals.

9.1.5 Geriatric Use

Arexvy is approved for use in individuals 60 years of age and older. See Section 6 for study details.

10. CONCLUSIONS

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). 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. 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 by physical frailty (based on the time to walk 3 or 4 meters).

Safety

At the time of the DLPs, a total of 15,745 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.

Although RSVPreF3-AS01_E is noted to have increased reactogenicity when compared to placebo, 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). There was a numerical imbalance in atrial fibrillation in Study 006 (10 in RSVPreF3-AS01_E and 4 in Placebo recipients). Currently available information on atrial fibrillation is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between groups for specific categories of serious adverse events.

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.

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 US-licensed seasonal influenza quadrivalent vaccine (Fluarix Quadrivalent; GSK).

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.

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

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See [Table 32](#).

Table 32. Risk-Benefit Analysis

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> RSV is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. Among adults 65 years of age and older, RSV disease results in an average of 177,000 hospitalizations in the US per year with a mortality rate of 14.7 per 100,000. RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans. 	<ul style="list-style-type: none"> LRTD due to RSV infection in older adults is a serious and life-threatening condition and can be associated with significant morbidity and mortality.
Unmet Medical Need	<ul style="list-style-type: none"> For older adults, treatment for RSV infection is limited to supportive care. There is currently no vaccine available for prevention of RSV disease. 	<ul style="list-style-type: none"> Prevention of lower respiratory tract disease by an effective vaccine would address an unmet medical need.
Clinical Benefit	<ul style="list-style-type: none"> After a single season, RSVPreF3-AS01_E was shown to have efficacy against RSV LRTD in adults ≥60 YOA with a VE of 82.6% (96.95% CI 57.9, 94.1) in a randomized, double-blind clinical study in which 12,467 received RSVPreF3-AS01_E compared to 12,499 placebo recipients. In subgroup analyses, VE was demonstrated against RSV-A and RSV-B associated LRTD, RSV severe LRTD based on clinical symptomatology, RSV ARI, and in the ≥65YOA and ≥70YOA age subgroups. The number of accrued RSV LRTD cases was too small to make conclusions about VE in adults ≥80YOA. 	<ul style="list-style-type: none"> The efficacy data from RSV OA=ADJ-006 support the effectiveness of RSVPreF3-AS01_E for the prevention of lower respiratory tract disease caused by respiratory syncytial virus in adults ≥60 years of age. The Applicant committed to further study the protection provided by the vaccine in 2 subsequent seasons.
Risk	<ul style="list-style-type: none"> The rates of solicited adverse reactions after vaccination in Study 006 were as follows: pain (60.9%), erythema (7.5%), swelling (5.5%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), arthralgia (18.1%), fever (2.0%). Solicited ARs reported as severe/Grade3 were uncommon and accounted for ≤1.7% of cases. Two cases of clinically diagnosed Acute Disseminated Encephalomyelitis (ADEM) were reported in Study 007 within 1 month of vaccination in the coadministration group when RSVPreF3-AS01_E was administered concomitantly with an influenza vaccine. One case of Guillain-Barre syndrome was reported in Study 004 with onset 9 days following administration of RSVPreF3-AS01_E. 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, placebo: 4 events) 	<ul style="list-style-type: none"> The data from the submitted clinical studies adequately characterizes the reactogenicity of RSVPreF3-AS01_E. The single case of Guillain-Barre syndrome and two cases of ADEM reported in clinical studies do not establish a causal relationship to vaccination. Further evaluations in post-marking studies are needed to assess Guillain-Barre syndrome and ADEM following vaccination. The safety of RSVPreF3-AS01_E is acceptable for its intended use.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	See "Clinical Benefit" and "Risk" sections above.	<ul style="list-style-type: none">• The safety data provided in the prescribing information adequately mitigate the risks.• Applicant's proposed pharmacovigilance plan will evaluate the risk of GBS, ADEM, atrial fibrillation and other uncommon adverse events that may be associated with RSVPreF3-AS01_E vaccination.

11.2 Risk-Benefit Summary and Assessment

A single dose of RSVPreF3-AS01_E was effective to prevent lower respiratory tract disease. The known and potential risks of RSVPreF3-AS01_E include common local and systemic adverse reactions.

In conclusion, the overall clinical benefits of RSVPreF3-AS01_E in adults ≥60YOA to prevent RSV LRTD outweigh the potential risks. The safety of RSVPreF3-AS01_E is adequately described in the prescribing information.

11.3 Recommendations on Regulatory Actions

Based on the clinical data presented in this application, this clinical reviewer recommends approval of Arexvy for the active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in adults 60 years of age and older.

11.4 Labeling Review and Recommendations

The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

11.5 Recommendations on Postmarketing Actions

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).

In addition to routine pharmacovigilance surveillance, the Applicant commits to a post-marketing active surveillance study, EPI-RSV-041 VS US DB, to evaluate the potential risk of immune-mediated demyelinating events, including GBS and ADEM, in adults 60 years and older vaccinated with RSVPreF3-AS01_E. The Applicant agreed to, in the same study (EPI-RSV-041 VS US DB), assess atrial fibrillation in as a post-marketing commitment.

The Applicant has committed to continue to conduct Study 006 and Study 004 until their completion in the end of Q3 2024 to assess the durability of protection of a single dose over 3 RSV seasons and to evaluate the immunogenicity and efficacy of annual revaccination and flexible revaccination schedules with the RSVPreF3-AS01_E vaccine.

APPENDIX 1 RSV OA=ADJ-006 CASE DEFINITIONS

Table 33. Case Definitions, Study 006

Endpoint	Case Definition
ARI (Trigger for swabbing)	Presence of at least 2 respiratory symptoms/signs for at least 24 hours OR at least 1 respiratory symptom/sign + 1 systemic symptom/sign for at least 24 hours
Respiratory symptoms and signs (ARI)	<ul style="list-style-type: none"> • 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 (= O₂ saturation <95% or $\leq 90\%$ if pre-season baseline is <95%)^d • Need for oxygen supplementation^d
Systemic symptoms and signs (ARI)	<ul style="list-style-type: none"> • 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 (LRTD)	<ul style="list-style-type: none"> • New or increased sputum • New or increased cough • New or increased dyspnea (shortness of breath)
Lower respiratory signs (LRTD)	<ul style="list-style-type: none"> • 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 (=O₂ saturation <95% or $\leq 90\%$ if pre-season baseline is <95%)^d • Need for oxygen supplementation^d

Endpoint	Case Definition
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 Supportive therapy ^e	Presence of a LRTD with at least one of the following criteria ^g : <ul style="list-style-type: none"> • 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; CPAP=continuous positive airway pressure; LRTD=lower respiratory tract disease; RSV: respiratory syncytial virus; RT-PCR=reverse transcription polymerase chain reaction

a. Fever is defined as a temperature $\geq 38.0^{\circ}\text{C}$ 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, as assessed by the study investigator, was 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. 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.