

Application Type	BLA, Original Application
STN	125775/0
CBER Received Date	September 2, 2022
PDUFA Goal Date	May 2, 2023
Division / Office	DVP/OVRR
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Applicant	GlaxoSmithKline Biologicals
Established Name	RSV Vaccine Recombinant, Adjuvanted
(Proposed) Trade Name	AREXVY
Pharmacologic Class	RSV Vaccine
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, containing 120 mcg of RSVPreF3 OA antigen adjuvanted with AS01 _E per 0.5 mL dose, Intramuscular
Dosing Regimen	Single dose of 0.5 mL
Indication(s) and Intended Population(s)	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus RSV-A and RSV-B subtypes in adults 60 years of age and older.

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Glossary

Ab	Antibody
AE	Adverse Event
ANCOVA	Analysis of Covariance
ARI	Acute Respiratory Infection
AS01 _E	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DLP	Data Lock Point
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HA	Hemagglutinin
HI	Hemagglutinin Inhibition
hMPV	Human Metapneumovirus
(Ig)G	Immunoglobulin G
ISS	Integrated Summary of Safety
ISE	Integrated Summary of Efficacy
LRTD	Lower Respiratory Tract Disease
LL	Lower Limit
MAAE	Medically Attended Adverse Events
mES	Modified Exposed Set
nAb	Neutralizing Antibody
NH	Northern Hemisphere
OA	Older Adult
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
PPSI	Per Protocol Set for Immunogenicity
RSV	Respiratory Syncytial Virus
RSVPreF3 OA	RSV PreFusion protein 3 Older Adult
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAE	Serious Adverse Event
SCR	Seroconversion Rate

SD	Standard Deviation
SH	Southern Hemisphere
SPR	Seroprotection Rate
SSS	Solicited Safety Set
TTO	Time To Onset
UL	Upper Limit
ULOQ	Upper Limit of Quantitation
VE	Vaccine Efficacy
YOA	Years Of Age

1. Executive Summary

GlaxoSmithKline (GSK) submitted a Biologics License Application (BLA) to seek approval of a Respiratory Syncytial Virus PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine for the prevention of lower respiratory tract disease (LRTD) caused by RSV-A and RSV-B subtypes in adults 60 years of age and older. The vaccine formulation includes 120 mcg of RSVPreF3 OA antigen adjuvanted with 25 µg MPL, 25 µg QS-21, and liposome. Efficacy, immunogenicity, and safety data were primarily obtained from four Phase 3 clinical studies to support licensure of this vaccine:

- RSV OA=ADJ-004: A phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above. Subjects were randomized in a 3:1:1 ratio to one of the following groups: 1) three RSV shots administered annually over two years (RSV Annual); 2) one RSV shot with the potential for a second if necessary (RSV Flexible Revaccination); and 3) a single RSV shot (RSV 1-Dose). At the time of this submission, both RSV Annual and RSV Flexible Revaccination groups had not received any revaccination but only the first dose. In the interim report, all immunogenicity and safety endpoints were analyzed descriptively and there was no success criterion specified for the trial.
- RSV OA=ADJ-006: A phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose of RSVPreF3 OA investigational vaccine in adults aged 60 years and above. Subjects were randomized to either a single dose of RSVPreF3 OA or placebo. The primary efficacy endpoint was the first occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, assessed during the first RSV season. The success criterion was that the lower limit (LL) of the 2-sided CI for VE was above 20%. One interim analysis was pre-specified using Wang-Tsiatis boundaries with $\Delta = 0.3$ and information fraction = 0.80, corresponding to an alpha value of 3.05%. At the interim analysis, 7 and 40 cases were reported in the RSVPreF3 and Placebo groups, respectively, where the estimated VE was 82.58% with 2-sided 96.95% CI (57.89%, 94.08%). Because the LL of the 2-sided CI was above 20%, the interim analysis met the success criterion.
- RSV OA=ADJ-007: A phase 3, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with Quadrivalent Inactivated Influenza Vaccine (FLU-QIV) in adults aged 60 years and above. Subjects were randomized in a 1:1 ratio to either co-administration of the RSV and FLU-QIVs or staggered administration of FLU-QIV and RSV vaccine 30 days apart. The co-primary immunogenicity objectives were demonstrating non-inferiority of 1) RSV-A neutralization antibody titers expressed as GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose; and 2) HI antibody titers for each of the four FLU-QIV strains expressed as GMT ratio, 1 month after the FLU-QIV dose. For each comparison, the non-inferiority success criterion was that the upper limit of the 95%

CI for GMT ratio ≤ 1.5 (Control group divided by the Co-Ad group). All group GMT ratios met the success criterion.

- RSV OA=ADJ-009: A phase 3, randomized, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administered as a single dose in adults aged 60 years and above. Subjects were randomized in a 1:1:1 ratio to one of 3 RSV vaccine lots. The primary immunogenicity objective was demonstrating lot-to-lot consistency in terms of RSVPreF3-specific immunoglobulin (Ig)G antibody concentrations expressed as GMC ratio at 30 days post-vaccination. For each comparison, the lot-to-lot consistency success criterion was that the 95% CI of GMC ratio was between 0.67 and 1.5. All group GMC ratios met the success criterion.

Overall, the RSVPreF3 OA investigational vaccine met the pre-specified efficacy, non-inferiority, and lot-to-lot consistency objectives evaluated in the respective Phase 3 studies. No major statistical issues have been identified.

Based on safety data collected from Study RSV OA=ADJ-006, compared to placebo, the RSVPreF3 OA investigational vaccine elicited higher rates of solicited local and systemic reactions within 4 days after the study dose as well as higher rates of unsolicited AEs. No substantial differences in the rates of related SAEs and pIMDs were observed between the RSVPreF3 OA investigational vaccine and placebo groups.

Based on safety data collected from Study RSV OA=ADJ-007, when administered with FLU-QIV, the RSVPreF3 OA investigational vaccine elicited higher rates of solicited local and systemic reactions within 4 days after the study dose but generally similar rates of unsolicited AEs than when administered alone. No substantial differences in the rates of related SAEs and pIMDs were observed between the RSVPreF3 OA investigational vaccine when administered with FLU-QIV than when administered alone. No deaths occurred that were considered related to the RSVPreF3 OA investigational vaccine when administered with FLU-QIV.

The safety data collected from Studies RSV OA=ADJ-004 and RSV OA=ADJ-009 were generally consistent with the safety data collected from the RSVPreF3 group in Study RSV OA=ADJ-006 and the Control group from Study RSV OA=ADJ-007 in terms of both solicited local and systemic reactions and unsolicited AEs.

In Study RSV OA=ADJ-004, there was one participant in the RSV Flexible Revaccination group who reported a case of Guillain-Barré Syndrome (GBS), which was recorded as both a related SAE and pIMD. The Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held on March 1, 2023 identified the one case of GBS as a cause for concern regarding the safety of the RSVPreF3 OA investigational vaccine.

Across the four Phase 3 studies, one death was considered related to the RSVPreF3 OA investigational vaccine by the investigator.

In summary, the efficacy, immunogenicity, and safety data thus in general support licensure of the RSVPreF3 OA investigational vaccine.

2. Clinical and Regulatory Background

This BLA was submitted to seek licensure of a RSVPreF3 OA vaccine intended to prevent LRTD caused by RSV-A and RSV-B subtypes in adults 60 years of age and older. The Priority Review designation was granted in September 2022. The BLA is supported primarily by efficacy, immunogenicity, and safety data from four Phase 3 clinical studies, i.e., RSV OA=ADJ-004, RSV OA=ADJ-006, RSV OA=ADJ-007 and RSV OA=ADJ-009.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

No data integrity issues were identified during the review.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to reviews of other review disciplines.

5. Sources of Clinical Data and Other Information Considered

5.1 Review Strategy

This review memo focuses on the four Phase 3 clinical studies supporting the RSVPreF3 OA vaccine and the integrated summary of safety (ISS). The Phase 1/2 and Phase 2b studies are not included in this memo.

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

The following documents submitted to the BLA are reviewed:

125775/0.0 (submitted on 9/2/2022)

1. Module 5. Clinical Study Reports
 - RSV OA=ADJ-004 Clinical Study Protocol
 - RSV OA=ADJ-004 Clinical Study Analysis Plan
 - RSV OA=ADJ-004 Clinical Study Report
 - RSV OA=ADJ-006 Clinical Study Protocol

- RSV OA=ADJ-006 Clinical Study Analysis Plan
- RSV OA=ADJ-006 Clinical Study Report
- RSV OA=ADJ-007 Clinical Study Protocol
- RSV OA=ADJ-007 Clinical Study Analysis Plan
- RSV OA=ADJ-007 Clinical Study Report
- RSV OA=ADJ-009 Clinical Study Protocol
- RSV OA=ADJ-009 Clinical Study Analysis Plan
- RSV OA=ADJ-009 Clinical Study Report
- Integrated Summary of Safety

125775/0.4 (submitted on 11/4/2022)

1. Module 1. Information Amendments
 - Response to 21 October 2022 information request.

125775/0.10 (submitted on 12/19/2022)

1. Module 5. Clinical Study Reports
 - Addendum to Integrated Summary of Safety

5.3 Table of Studies/Clinical Trials

One Phase 1/2, one Phase 2b, and four Phase 3 clinical studies were conducted to support licensure of RSVPreF3 OA vaccine and are summarized in Table 1.

Table 1: Clinical Studies Supporting Licensure of RSVPreF3 OA

Study	N	Age	Description
RSV OA=ADJ- 002	1,053	Adults 18 – 40 and 60 – 80 YOA	Phase 1/2, randomized, placebo-controlled, observer-blind, multi-center, descriptive study with 14 parallel groups using different vaccine formulations.
RSV OA=ADJ- 011	126	Older Adults ≥ 60 YOA	Phase 2b, open-label, multi-center, extension, descriptive study with 3 parallel groups using different revaccination formulations among a subset of subjects who participated in the RSV OA=ADJ-002 study.
RSV OA=ADJ- 004	1,720	Older Adults ≥ 60 YOA	Phase 3, randomized, open-label, multi-center, descriptive study with 3 parallel groups using different revaccination schedules.
RSV OA=ADJ- 006	26,664	Older Adults ≥ 60 YOA	Phase 3, randomized, placebo-controlled, observer-blind, multi-center, efficacy study with 4 parallel groups (RSVPreF3 OA Lot 1/Lot 2/Lot 3:Placebo = 1:1:1:3) before Season 1
RSV OA=ADJ- 007	976	Older Adults ≥ 60 YOA	Phase 3, randomized (1:1), controlled, open-label, multi-center, co-administration study with FLU-QIV.
RSV OA=ADJ- 009	770	Older Adults ≥ 60 YOA	Phase 3, randomized (1:1:1), double-blind, multi-center, lot-to-lot consistency study with 3 parallel groups.

N = number of enrolled subjects.

Source: Adapted from RSV OA=ADJ-004, RSV OA=ADJ-006, RSV OA=ADJ-007, and RSV OA=ADJ-009 Clinical Study Reports.

5.4 Consultations

5.4.1 Advisory Committee Meeting

A VRBPAC meeting was held on March 1, 2023.

With respect to the safety of the RSVPreF3 OA investigational vaccine, 10/12 committee members voted Yes to the voting question “Are the available data adequate to support the safety of AREXVY (RSVPreF3+AS01E) when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV?”

With respect to the effectiveness of the RSVPreF3 OA investigational vaccine, all 12 committee members unanimously voted Yes to the voting question: “Are the available data adequate to support the effectiveness of AREXVY (RSVPreF3+AS01E) for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older?”

6. Discussion of Individual Studies/Clinical Trials

6.1 Clinical Study RSV OA=ADJ-004

Title of Study: A phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above.

Dates:

1. Study initiation date (First Subject First Visit): 15 February 2021
2. Data Lock Point (DLP) for safety analysis at Month 6: 11 February 2022

6.1.1 Objectives

Primary Immunogenicity Objective:

1. To evaluate the humoral immune response following a 1-dose primary schedule of RSVPreF3 OA investigational vaccine up to 12 months post-Dose 1.

Secondary Immunogenicity Objectives:

1. To further evaluate the humoral immune response following a 1-dose primary schedule of RSVPreF3 OA investigational vaccine up to 12 months post-Dose 1.
2. To evaluate the humoral immune response following 1 dose of the RSVPreF3 OA investigational vaccine and following revaccination doses, up to study end.

Safety Objective:

1. To evaluate the safety and reactogenicity of each vaccination schedule of the RSVPreF3 OA investigational vaccine in all subjects.

6.1.2 Design Overview

Subjects were randomized with a ratio of 3:1:1 to one of the following groups:

1. The RSV Annual group, in which subjects received a single dose of the RSVPreF3 OA investigational vaccine on Day 1 followed by revaccination doses at 12 months post-Dose 1 and at 24 months post-Dose 1.
2. The RSV Flexible Revaccination group, in which subjects received a single dose of the RSVPreF3 OA investigational vaccine where a revaccination dose will be given whenever a revaccination would be needed based on immunogenicity data.
3. The RSV 1-Dose group, in which subjects received a single dose of the RSVPreF3 OA investigational vaccine on Day 1.

The randomization algorithm used a minimization procedure, where age category (60-69, 70-79 or ≥ 80 years), center, sex, and setting were included as minimization factors.

For immunogenicity, blood sample collection was scheduled by group:

1. For the RSV Annual group, blood samples for humoral and CMI responses were collected from a subset of subjects at Day 1, Day 31 and Month 6, and will be further collected at Months 12, 13, 18, 24, 25, 30 and 36.
2. For the RSV Flexible Revaccination group: Blood samples for humoral (applicable for all subjects) and CMI (a subset of subjects) responses were collected at Day 1, Day 31 and Month 6, and will be further collected at Months 12, 18, 24, 30 and 36. An additional blood sample will be taken after a revaccination dose is given for this group.
3. The RSV 1-Dose group: blood samples for humoral (applicable for all subjects) and CMI (a subset of subjects) responses were collected at Day 1, Day 31 and Month 6, and will be further collected at Months 12, 18, 24, 30 and 36.

For safety, solicited AEs and unsolicited AEs were collected for four and 30 days after vaccination, respectively, while both SAEs and pIMDs were collected for six months after vaccination.

Reviewer's Comment:

- *The study is ongoing, and an interim report including data collected up to Month 6 is submitted to this BLA. At the time of this submission, both the RSV Annual and RSV Flexible Revaccination groups had not received any revaccination but only the first dose. Therefore, all three groups received the same intervention of one dose of RSVPreF3 OA investigational vaccine.*

6.1.3 Population

Subjects ≥ 60 YOA were enrolled.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The vaccine formulation evaluated in this study was 120 mcg of RSVPreF3 OA antigen adjuvanted with AS01E per 0.5 mL dose.

6.1.6 Sites and Centers

The study was conducted at 46 centers in 5 countries: 10 in Finland, 8 in Germany, 3 in Japan, 7 in Taiwan, and 18 in the United States.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Study Success Criteria

All endpoints were descriptive; thus, there was no success criterion for the trial.

Primary Immunogenicity Endpoints:

1. Humoral immune response at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), and at 6 and 12 months post-Dose 1 (Months 6 and 12), in a subset of subjects:
 - Neutralizing antibody titers against RSV-A.
 - Neutralizing antibody titers against RSV-B.

Secondary Immunogenicity Endpoints:

1. Humoral immune response at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), and at 6 and 12 months post-Dose 1 (Months 6 and 12), in a subset of subjects:
 - RSVPreF3-specific IgG antibody concentrations.
2. Humoral immune response at Months 18, 24, 30 and 36 post-Dose 1, and at 1 month after each revaccination dose (Months 13 and 25), in a subset of subjects:
 - Neutralizing antibody titers against RSV-A and RSV-B.
 - RSVPreF3-specific IgG antibody concentrations.

Safety Endpoints:

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

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

For the immunogenicity analyses, missing data were not replaced. Titers below the technical assay cut-off were replaced by half the technical assay cut-off; titers above the

ULOQ were replaced by the LLOQ. The immunogenicity analyses were performed on the Per Protocol Set (PPS), defined as:

- PPS: All participants who received at least 1 dose of the study intervention to which they were randomized and have post-vaccination data, minus participants with protocol deviations that lead to exclusion.

For the primary immunogenicity analysis, at each time point that blood samples were collected the following analyses were provided:

- Percentages of subjects with antibody (Ab) titers/concentrations above the LLOQ and their 95% CIs
- Geometric mean titers (GMTs)/geometric mean concentrations (GMCs) and their 95% CIs
- Distribution of Ab titers/concentrations using reverse cumulative curves
- Mean geometric increases (MGIs) and their 95% CIs

Analysis of Safety

All safety data were summarized descriptively. Safety analyses were performed on the Exposed Set (ES) which is a subset of the Enrolled Set. Both are defined as follows:

- Enrolled Set: Participants who agreed to participate in a clinical study after completion of the informed consent process. This definition applies to all Phase 3 studies reviewed in this memo.
- ES: All subjects who received at least the first dose of the study intervention. This definition applies to all Phase 3 studies reviewed in this memo.

Sample Size Determination

The sample size was not determined based on statistical considerations.

6.1.10 Study Population and Disposition

A total of 1720 subjects were included in the Enrolled Set, of which 1660 were randomized and 1653 received 1 dose of the RSVPreF3 OA investigational vaccine at Day 1 and were included in the ES (993 subjects in the RSV Annual group, 329 in the RSV Flexible Revaccination group, and 331 in the RSV 1-Dose group). Table 2 displays the demographics of the ES. Overall, no major imbalances were observed between the vaccine groups. Additionally, the demographics of the PPS were balanced and similar to that of the ES.

Table 2: Summary of demography and baseline characteristics – ES

-	RSV Annual N=993	RSV Annual N=993	RSV Flexible Revaccination N=329	RSV Flexible Revaccination N=329	RSV 1- Dose N=331	RSV 1- Dose N=331	Total N=1653	Total N=1653
-	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years) at vaccine administration	-	-	-	-	-	-	-	-
N	993	-	329	-	331	-	1653	-
Mean	70.1	-	69.9	-	69.9	-	70.0	-
Standard deviation	6.6	-	6.7	-	6.7	-	6.6	-
Median	69.0	-	69.0	-	69.0	-	69.0	-
Minimum	59	-	59	-	59	-	59	-
Maximum	92	-	89	-	88	-	92	-
Age category	-	-	-	-	-	-	-	-
60-69 YOA	491	49.4	164	49.8	165	49.8	820	49.6
70-79 YOA	374	37.7	123	37.4	124	37.5	621	37.6
>=65 YOA	779	78.4	247	75.1	250	75.5	1276	77.2
>=70 YOA	502	50.6	165	50.2	166	50.2	833	50.4
>=80 YOA	128	12.9	42	12.8	42	12.7	212	12.8
Sex	-	-	-	-	-	-	-	-
Male	451	45.4	147	44.7	152	45.9	750	45.4
Female	542	54.6	182	55.3	179	54.1	903	54.6
Ethnicity	-	-	-	-	-	-	-	-
Hispanic Or Latino	24	2.4	5	1.5	3	0.9	32	1.9
Not Hispanic Or Latino	969	97.6	324	98.5	328	99.1	1621	98.1
Race	-	-	-	-	-	-	-	-
American Indian Or Alaska Native	2	0.2	0	0	0	0	2	0.1
Asian	296	29.8	102	31.0	98	29.6	496	30.0
Black Or African American	19	1.9	8	2.4	6	1.8	33	2.0
Native Hawaiian Or Other Pacific Islander	0	0	0	0	0	0	0	0
White	676	68.1	219	66.6	226	68.3	1121	67.8
Other	0	0	0	0	1	0.3	1	0.1

Table 2: Summary of demography and baseline characteristics – ES (continued)

-	RSV Annual N=993	RSV Annual N=993	RSV Flexible Revaccination N=329	RSV Flexible Revaccination N=329	RSV 1-Dose N=331	RSV 1- Dose N=331	Total N=1653	Total N=1653
-	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Region	-	-	-	-	-	-	-	-
North America	262	26.4	83	25.2	88	26.6	433	26.2
Europe	436	43.9	145	44.1	146	44.1	727	44.0
Asia	295	29.7	101	30.7	97	29.3	493	29.8
Type of residence	-	-	-	-	-	-	-	-
Community Dwelling	992	99.9	329	100	331	100	1652	99.9
Long-term care facility	1	0.1	0	0	0	0	1	0.1
Smoking Status	-	-	-	-	-	-	-	-
Never smoked	599	60.3	190	57.8	193	58.3	982	59.4
Current smoker	106	10.7	31	9.4	39	11.8	176	10.6
Former smoker	288	29.0	108	32.8	99	29.9	495	29.9

N = number of subjects.

n/% = number / percentage of subjects in a given category.

Age computed based on incomplete date of birth (only year was available).

Source: Table 11.1 from RSV OA=ADJ-004 Clinical Study Report.

Of the 1653 subjects included in the ES, a total of 987 subjects were included in the PPS on Day 1 (342 subjects in the RSV Annual group, 321 in the RSV Flexible Revaccination group, and 324 in the RSV 1-Dose group). Participant dispositions from the ES to the PPS on Day 31 are presented in Table 3. A total of 941 subjects were included in the PPS on Day 31 (331 subjects in the RSV Annual group, 300 in the RSV Flexible Revaccination group, and 310 in the RSV 1-Dose group). A total of 929 subjects were included in the PPS on Month 6 (323 subjects in the RSV Annual group, 294 in the RSV Flexible Revaccination group, and 312 in the RSV 1-Dose group).

Table 3: Summary of participant disposition from Exposed Set to Per Protocol Set for Humoral Immunogenicity at Day 31

-	RSV Annual N=993	RSV Annual N=993	RSV Flexible Revaccination N=329	RSV Flexible Revaccination N=329	RSV 1- Dose N=331	RSV 1- Dose N=331	Total N=1653	Total N=1653
-	n	%	n	%	n	%	n	%
Withdrawals	5	0.5	3	0.9	1	0.3	9	0.5
Adverse event requiring expedited reporting	0	0	0	0	1	0.3	1	0.1
Consent withdrawal, not due to an adverse event and/or a serious adverse event	2	0.2	2	0.6	0	0	4	0.2
Lost to follow-up	3	0.3	1	0.3	0	0	4	0.2
Eliminations	657	66.2	26	7.9	20	6.0	703	42.5
Participant not in humoral subset (2600)	642	64.7	0	0	0	0	642	38.8
Vaccine, excluded by the protocol, was administered (1040)	7	0.7	4	1.2	0	0	11	0.7
Vaccine, excluded by the protocol, was administered (C1040)	13	1.3	6	1.8	7	2.1	26	1.6
Randomization procedures (1050)	1	0.1	0	0	0	0	1	0.1
Study treatment not administered per protocol (1070)	1	0.1	0	0	0	0	1	0.1
Eligibility criteria not met (2010)	0	0	1	0.3	0	0	1	0.1
Medication, excluded by the protocol, was administered (2040)	0	0	1	0.3	0	0	1	0.1
Intercurrent medical condition (2050)	0	0	2	0.6	0	0	2	0.1
Out of window assessment for immunogenicity (2090)	2	0.2	5	1.5	8	2.4	15	0.9
Missed assessment (2100)	2	0.2	3	0.9	0	0	5	0.3
Missed assessment (C2100)	0	0	3	0.9	0	0	3	0.2
Central/internal/external lab deviations (2120)	0	0	4	1.2	6	1.8	10	0.6
Number of participants included in Per Protocol Set for humoral immunogenicity at Day 31	331	33.3	300	91.2	310	93.7	941	56.9

N = number of participants.

n/% = number / percentage of participants in a given category.

Elimination codes starting with 'c' indicate that the elimination is related to COVID-19.

Source: Table 14.1.1.3 from RSV OA=ADJ-004 Clinical Study Report.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

Tables 4 and 5 display RSV-A/B neutralizing antibodies (NAb) GMTs and MGIs for each group and across groups. At Day 1 (pre-vaccination), all participants had detectable RSV-A/B NAbs due to previous exposure to RSV.

Across groups, the RSV-A NAb titers MGI at Day 31 over baseline was 10.5 with 95% CI (9.9, 11.2) and at Month 6 over baseline was 4.4 with 95% CI (4.2, 4.6). The RSV-B NAb titers MGI at Day 31 over baseline was 7.8 with 95% CI (7.4, 8.3) and at Month 6 over baseline was 3.5 with 95% CI (3.4, 3.7).

Reviewer's Comment:

- *All efficacy, immunogenicity, and safety analyses presented in this review memo were verified using the Study Data Tabulation Model datasets.*

Table 4: RSV-A NAb and RSV-B NAb GMTs and MGIs for RSV Annual, RSV Flexible Revaccination, and RSV 1-Dose Groups – Per-Protocol Set for Humoral Immunogenicity

-	-	-	RSV AN	RSV AN	RSV AN	RSV AN	RSV FR	RSV FR	RSV FR	RSV FR	RSV 1D	RSV 1D	RSV 1D	RSV 1D
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI
RSV-A NAb	D1	GMT	342	832.4	763.4	907.7	321	865.7	791.4	947.0	323	892.9	812.6	981.1
RSV-A NAb	D31	GMT	331	8856.3	7937.3	9881.8	300	8906.6	7972.3	9950.3	310	9587.6	8454.0	10873.3
RSV-A NAb	D31 / D1	MGI	331	10.5	9.4	11.8	300	10.4	9.3	11.6	309	10.7	9.5	12.0
RSV-A NAb	M6	GMT	323	3475.8	3150.2	3835.2	294	3600.1	3242.2	3997.5	312	4249.1	3821.5	4724.4
RSV-A NAb	M6 / D1	MGI	323	4.2	3.9	4.6	294	4.2	3.9	4.6	311	4.8	4.3	5.2
RSV-B NAb	D1	GMT	342	1138.7	1046.2	1239.3	321	1331.0	1211.4	1462.4	324	1246.0	1131.2	1372.5
RSV-B NAb	D31	GMT	331	9293.5	8439.1	10234.4	300	9955.2	9002.1	11009.3	310	9748.4	8781.4	10821.9
RSV-B NAb	D31 / D1	MGI	331	8.2	7.4	9.0	300	7.4	6.7	8.3	310	7.8	7.0	8.7
RSV-B NAb	M6	GMT	323	3890.0	3570.0	4238.8	294	4484.6	4063.8	4949.0	312	4583.2	4165.3	5043.0
RSV-B NAb	M6 / D1	MGI	323	3.5	3.2	3.8	294	3.4	3.1	3.7	312	3.7	3.4	4.0

RSV AN = RSV Annual; RSV FR = RSV Flexible Revaccination; RSV 1D = RSV 1-Dose.

N = number of participants.

CI = 95% CI.

D1 = Pre-vaccination at Day 1; D31 = 30 days post-Dose 1; M6 = 6 months post-Dose 1.

Source: Adapted from Tables 2.2 and 2.3 from RSV OA=ADJ-004 Clinical Study Report.

Table 5: RSV-A NAb and RSV-B NAb GMTs and MGIs for Total – Per-Protocol Set for Humoral Immunogenicity

-	-	-	Total	Total	Total	Total
Antibody	Time point	-	N	Value	LL CI	UL CI
RSV-A NAb	D1	GMT	986	862.7	819.1	908.7
RSV-A NAb	D31	GMT	941	9107.3	8521.2	9733.7
RSV-A NAb	D31 / D1	MGI	940	10.5	9.9	11.2
RSV-A NAb	M6	GMT	929	3760.0	3542.7	3990.6
RSV-A NAb	M6 / D1	MGI	928	4.4	4.2	4.6
RSV-B NAb	D1	GMT	987	1233.9	1170.3	1301.0
RSV-B NAb	D31	GMT	941	9650.3	9108.1	10224.8
RSV-B NAb	D31 / D1	MGI	941	7.8	7.4	8.3
RSV-B NAb	M6	GMT	929	4299.5	4074.2	4537.2
RSV-B NAb	M6 / D1	MGI	929	3.5	3.4	3.7

N = number of participants.

CI = 95% CI.

D1 = Pre-vaccination at Day 1; D31 = 30 days post-Dose 1; M6 = 6 months post-Dose 1.

Source: Adapted from Tables 2.2 and 2.3 from RSV OA=ADJ-004 Clinical Study Report.

6.1.11.2 Analyses of Secondary Endpoints

Tables 6 and 7 display RSVPreF3 Specific IgG GMCs and MGIs for each group and across groups. At Day 1 (pre-vaccination), all participants had detectable RSVPreF3-specific IgG Abs due to previous exposure to RSV.

Across groups, the RSVPreF3 Specific IgG MGI at Day 31 over baseline was 12.2 with 95% CI (11.6, 12.8) and at Month 6 over baseline was 4.7 with 95% CI (4.5, 4.9).

Table 6: RSVPreF3-Specific IgG GMCs and MGIs for RSV Annual, RSV Flexible Revaccination, and RSV 1-Dose Groups – Per-Protocol Set for Humoral Immunogenicity

-	-	-	RSV AN	RSV AN	RSV AN	RSV AN	RSV FR	RSV FR	RSV FR	RSV FR	RSV 1D	RSV 1D	RSV 1D	RSV 1D
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI
RSVPreF3 Specific IgG	D1	GMC	342	7334.7	6868.3	7832.8	320	7449.2	6960.4	7972.4	324	7696.2	7150.5	8283.6
RSVPreF3 Specific IgG	D31	GMC	331	87117.9	80878.4	93838.8	300	92664.7	86050.1	99787.8	310	94222.2	87655.8	101280.4
RSVPreF3 Specific IgG	D31 / D1	MGI	331	11.8	10.8	12.9	299	12.6	11.6	13.7	310	12.2	11.2	13.4
RSVPreF3 Specific IgG	M6	GMC	323	33773.1	31348.1	36385.7	294	35193.5	32623.6	37965.9	312	36584.9	34006.5	39358.8
RSVPreF3 Specific IgG	M6 / D1	MGI	323	4.6	4.3	5.0	293	4.8	4.5	5.2	312	4.8	4.4	5.1

RSV AN = RSV Annual; RSV FR = RSV Flexible Revaccination; RSV 1D = RSV 1-Dose.

N = number of participants.

CI = 95% CI.

D1 = Pre-vaccination at Day 1; D31 = 30 days post-Dose 1; M6 = 6 months post-Dose 1.

Source: Adapted from Table 2.4 from RSV OA=ADJ-004 Clinical Study Report.

Table 7: RSVPreF3-Specific IgG GMCs and MGIs for Total – Per-Protocol Set for Humoral Immunogenicity

-	-	-	Total	Total	Total	Total
Antibody	Time point	-	N	Value	LL CI	UL CI
RSVPreF3 Specific IgG	D1	GMC	986	7489.2	7197.4	7792.8
RSVPreF3 Specific IgG	D31	GMC	941	91173.7	87387.7	95123.8
RSVPreF3 Specific IgG	D31 / D1	MGI	940	12.2	11.6	12.8
RSVPreF3 Specific IgG	M6	GMC	929	35147.8	33671.8	36688.4
RSVPreF3 Specific IgG	M6 / D1	MGI	928	4.7	4.5	4.9

N = number of participants.

CI = 95% CI.

D1 = Pre-vaccination at Day 1; D31 = 30 days post-Dose 1; M6 = 6 months post-Dose 1.

Source: Adapted from Table 2.4 from RSV OA=ADJ-004 Clinical Study Report.

6.1.12 Analyses of Safety Endpoints

Percentages of subjects reporting solicited local and systemic reactions within 4 days after the study dose for all three groups and the total are displayed in Table 8. The most frequently reported solicited local reaction was pain (60.2%, 61.3%, and 61.0% in the RSV Annual, RSV Flexible Revaccination, and RSV 1-Dose groups, respectively), while the most frequently reported solicited systemic reaction was myalgia (33.9%, 32.6%, and 33.1% in the RSV Annual, RSV Flexible Revaccination, and RSV 1-Dose groups, respectively).

Table 8: Percentage of subjects with solicited local and systemic events within 4 days following the study dose – ES

Local Adverse Reactions	RSV Annual % (n) N = 989	RSV Flexible Revaccination % (n) N = 328	RSV 1-Dose % (n) N = 328	Total % (n) N = 1645
Pain	60.2% (595)	61.3% (201)	61.0% (200)	60.5% (996)
Pain, Grade 3	1.8% (18)	0.9% (3)	0.3% (1)	1.3% (22)
Erythema	10.0% (99)	11.6% (38)	6.7% (22)	9.7% (159)
Erythema, > 100 mm	0.1% (1)	0	0	0.1% (1)
Swelling	7.6% (75)	10.1% (33)	4.9% (16)	7.5% (124)
Swelling > 100 mm	0.2% (2)	0	0	0.1% (2)
Systemic Adverse Reactions	N = 989	N = 328	N = 329	N = 1646
Fatigue	31.0% (307)	30.5% (100)	33.4% (110)	31.4% (517)
Fatigue, Grade 3	1.7% (17)	0.9% (3)	1.5% (5)	1.5% (25)
Myalgia	33.9% (335)	32.6% (107)	33.1% (109)	33.5% (551)
Myalgia, Grade 3	2.3% (23)	1.2% (4)	0.9% (3)	1.8% (30)
Headache	18.9% (187)	21.3% (70)	24.0% (79)	20.4% (336)
Headache, Grade 3	0.7% (7)	0.3% (1)	1.5% (5)	0.8% (13)
Arthralgia	15.9% (157)	14.9% (49)	14.9% (49)	15.5% (255)
Arthralgia, Grade 3	0.8% (8)	0.6% (2)	0	0.6% (10)
Fever	1.3% (13)	1.5% (5)	2.1% (7)	1.5% (25)
Fever, Grade 3	0	0	0	0

n/% = number/percentage of participants presenting at least one type of event.

N = number of participants who completed the diary card.

Grade 3 pain: defined as significant pain at rest and prevents normal everyday activities.

Grade 3 fatigue, myalgia, headache, arthralgia: Defined as preventing normal activity.

Fever defined as a temperature $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ by any route (oral, axillary, or tympanic); Grade 3 fever defined as $> 39.0^{\circ}\text{C}/102.2^{\circ}\text{F}$.

Source: Adapted from Tables 12.3 and 12.4 from RSV OA=ADJ-004 Clinical Study Report.

Percentages of subjects reporting unsolicited AEs after the study dose for all three groups and the total are displayed in Tables 9 and 10. There was one participant in the RSV Flexible Revaccination group who reported a case of GBS, which was recorded as both a related SAE and pIMD up to the DLP of 11 February 2022. The VRBPAC meeting held on March 1, 2023 identified the one case of GBS as a cause for concern regarding the safety of the RSVPreF3 OA investigational vaccine. A total of 6 deaths (3, 1, and 2 in the RSV Annual, RSV Flexible Revaccination, and RSV 1-Dose groups, respectively) were reported up to the DLP, but none were considered to be related to the study treatment.

Table 9: Summary of Subjects by Unsolicited AE Category for RSV Annual, RSV Flexible Revaccination, and RSV 1-Dose Groups – ES

-	RSV AN N=993	RSV AN N=993	RSV AN N=993	RSV AN N=993	RSV FR N=329	RSV FR N=329	RSV FR N=329	RSV FR N=329	RSV 1D N=331	RSV 1D N=331	RSV 1D N=331	RSV 1D N=331
-	n	%	LL CI	UL CI	n	%	LL CI	UL CI	n	%	LL CI	UL CI
At least one unsolicited AE within 30 days post-vaccination	119	12.0	10.0	14.2	40	12.2	8.8	16.2	53	16.0	12.2	20.4
At least one grade 3 unsolicited AE within 30 days post-vaccination	9	0.9	0.4	1.7	6	1.8	0.7	3.9	5	1.5	0.5	3.5
At least one related unsolicited AE within 30 days post-vaccination	33	3.3	2.3	4.6	13	4.0	2.1	6.7	13	3.9	2.1	6.6
At least one grade 3 related unsolicited AE within 30 days post-vaccination	2	0.2	0.0	0.7	3	0.9	0.2	2.6	1	0.3	0.0	1.7
At least one medically attended unsolicited AE within 30 days post-vaccination	45	4.5	3.3	6.0	13	4.0	2.1	6.7	27	8.2	5.4	11.6
At least one SAE up to 6 months post-vaccination	36	3.6	2.6	5.0	15	4.6	2.6	7.4	14	4.2	2.3	7.0
At least one related SAE up to DLP	0	0	0	0.4	1	0.3	0.0	1.7	0	0	0	1.1
At least one pIMD up to 6 months post-vaccination	4	0.4	0.1	1.0	3	0.9	0.2	2.6	0	0	0	1.1
At least one related pIMD up to DLP	0	0	0	0.4	1	0.3	0.0	1.7	0	0	0	1.1
At least one fatal SAE up to DLP	3	0.3	0.1	0.9	1	0.3	0.0	1.7	2	0.6	0.1	2.2

RSV AN = RSV Annual; RSV FR = RSV Flexible Revaccination; RSV 1D = RSV 1-Dose.

N = number of subjects.

n/% = number/percentage of subjects presenting at least one type of adverse event.

CI = 95% CI.

Safety DLP = 11FEB2022.

Source: Table 12.5 from RSV OA=ADJ-004 Clinical Study Report.

Table 10: Summary of Subjects by Unsolicited AE Category for Total – ES

-	Total N=1653	Total N=1653	Total N=1653	Total N=1653
-	n	%	LL CI	UL CI
At least one unsolicited AE within 30 days post-vaccination	212	12.8	11.3	14.5
At least one grade 3 unsolicited AE within 30 days post-vaccination	20	1.2	0.7	1.9
At least one related unsolicited AE within 30 days post-vaccination	59	3.6	2.7	4.6
At least one grade 3 related unsolicited AE within 30 days post-vaccination	6	0.4	0.1	0.8
At least one medically attended unsolicited AE within 30 days post-vaccination	85	5.1	4.1	6.3
At least one SAE up to 6 months post-vaccination	65	3.9	3.0	5.0
At least one related SAE up to DLP	1	0.1	0.0	0.3
At least one pIMD up to 6 months post-vaccination	7	0.4	0.2	0.9
At least one related pIMD up to DLP	1	0.1	0.0	0.3
At least one fatal SAE up to DLP	6	0.4	0.1	0.8

N = number of subjects.

n/% = number/percentage of subjects presenting at least one type of adverse event.

CI = 95% CI.

Safety DLP = 11FEB2022.

Source: Table 12.5 from RSV OA=ADJ-004 Clinical Study Report.

6.2 Clinical Study RSV OA=ADJ-006

Title of Study: A phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination doses of RSVPreF3 OA investigational vaccine in adults aged 60 years and above.

Dates:

1. Study initiation date (First Subject First Visit): 25 May 2021
2. DLP for efficacy analyses: 11 April 2022
3. DLP for safety analyses: 30 April 2022

6.2.1 Objectives

Since the study is still ongoing, not all objectives were evaluated in the efficacy interim analysis. Only those objectives that were evaluated in the interim analysis are summarized below.

Primary Efficacy Objective:

1. To demonstrate the efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD during the first season in adults ≥ 60 YOA.

Secondary Efficacy Objectives:

1. To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe RSV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine.
2. To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed acute respiratory infection (ARI) in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine.

Secondary Immunogenicity Objective:

1. To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine.

Safety Objectives:

1. To evaluate the reactogenicity of the RSVPreF3 OA investigational vaccine.
2. To evaluate the safety of the RSVPreF3 OA investigational vaccine.

6.2.2 Design Overview

The study consisted of two parts. For Part 1, ~25000 subjects were randomized with a ratio of 1:1:1:3 to 1 of 4 study groups (i.e., RSVPreF3 OA Lot 1/RSVPreF3 OA Lot 2/RSVPreF3 OA Lot 3 and Placebo). The randomization algorithm used a minimization procedure, where both age category (60-69, 70-79 or ≥ 80 years) and region were included as minimization factors. Approximately 1800 participants were planned to be included in the reactogenicity and immunogenicity subset.

Note that the original version of the trial protocol included a sequential analysis of efficacy and lot-consistency. Per CBER's recommendation, lot-consistency was removed in a trial protocol amendment and was instead evaluated in Study RSV OA=ADJ-009. Hence, the 3 RSV lots are an artifact of the original version of the trial protocol which additionally included lot-consistency.

Subjects will be followed up for 3 consecutive RSV seasons in the Northern Hemisphere (NH) and at least 2 consecutive RSV seasons in the Southern Hemisphere (SH). The RSV seasons defined for this study are from October 1 to April 30 in the NH and from March 1 to September 30 in the SH. The efficacy analyses for Part 1 were case-driven. For immunogenicity, blood samples were taken from all subjects at pre-Dose 1 (Day 1) and 1 month post-Dose 1 (Day 31). Additional immunogenicity samples were planned for participants in the reactogenicity and immunogenicity subset at Visit 3 (pre-Season 2) and Visit 5 NH (pre-Season 3). For safety, solicited AEs were collected in the reactogenicity and immunogenicity subset. Unsolicited AEs were collected for four and 30 days after vaccination, respectively, while both SAEs and pIMDs were collected for six months after vaccination.

Part 1 included one interim analysis for the primary efficacy endpoint when 47 cases were accrued during Season 1, and a sample size re-assessment was also planned. However, because the interim analysis met the success criterion, there was no sample size adjustment and the datasets of the interim analysis were submitted for this BLA.

Part 2 was to be initiated when the vaccine lots for Part 1 were no longer available at the study sites, which did not occur and Part 2 was therefore not initiated.

Prior to Season 2, all subjects who received 1 of the RSVPreF3 OA vaccine lots are to be re-randomized in a 1:1 ratio into 2 subgroups (i.e., RSV Annual group and RSV 1-Dose group) to receive annual revaccination doses (Dose 2 and Dose 3 in the Northern Hemisphere [NH] and Dose 2 in the SH).

The RSV Annual group will receive an additional dose of RSVPreF3 OA vaccine before each subsequent season, while the RSV 1-Dose group will receive 1 dose of placebo at the same time points. To maintain the study blind, subjects who were initially randomized to the Placebo group will also receive additional doses of placebo at the same time points.

6.2.3 Population

Subjects \geq 60 YOA were enrolled.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study treatments consisted of a saline placebo and three consecutively produced lots of RSVPreF3 OA vaccine containing 120 mcg of RSVPreF3 OA antigen adjuvanted with AS01E per 0.5 mL dose.

6.2.6 Sites and Centers

The study was conducted at 278 centers in 17 countries.

6.2.7 Surveillance/Monitoring

Please refer to the clinical review.

6.2.8 Endpoints and Study Success Criteria

Primary Efficacy Endpoint:

1. First occurrence of RT-PCR-confirmed RSV-A and/or B-associated LRTD, according to the case definition, with the following success criterion:
 - The LL of the 2-sided CI for VE is above 20%.

Secondary Efficacy:

1. First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definition.
2. First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition.

Secondary Immunogenicity Endpoints:

1. In a subset of subjects, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Dose 3 (pre-Season 3):
 - NAb titers against RSV-A.
 - NAb titers against RSV-B.
 - RSVPreF3 OA IgG-specific Ab concentrations.

Safety Endpoints:

1. 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 (i.e., the day of vaccination and 3 subsequent days).
2. In all participants:
 - Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days).
 - 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.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Efficacy

The primary efficacy analysis in terms of occurrence of RSV-confirmed LRTD was evaluated using the conditional exact binomial method based on the Poisson model by considering the exact inference on the relative risk (RR), adjusted by age categories and regions, conditional on the total number of cases observed and time at risk. VE was defined as 1 minus the RR. Missing data were not replaced.

All events related to the efficacy endpoints were collected, but only the first event of RT-PCR-confirmed RSV-A and/or B-associated LRTD from each subject was considered for the primary efficacy analysis.

The primary efficacy analysis was performed on the modified Exposed Set (mES), which is a subset of the ES. The mES is defined as:

- mES: Subjects in the ES who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination. Subjects were analyzed according to the administered intervention.

Additionally, subgroup analyses were performed by hemisphere, region, ethnicity, race, sex, baseline frailty status, and baseline comorbidities.

Analysis of Immunogenicity

For the immunogenicity analysis, at each time point that blood samples were collected the following analyses were conducted:

- Percentages of subjects with antibody (Ab) titers/concentrations above the LLOQ and their 95% CI
- Geometric mean titers (GMT)/geometric mean concentrations (GMC) and their 95% CIs
- Distribution of Ab titers/concentrations using reverse cumulative curves
- Mean geometric increase (MGI) and their 95% CIs

The immunogenicity analyses were performed on the Per Protocol Set for Immunogenicity (PPSI) for participants included in the immunogenicity and reactogenicity subset. The PPSI is defined as:

- PPSI: All subjects who received at least the first dose of the study intervention to which they were randomized, have post-vaccination immunogenicity data available, and did not meet protocol deviations that lead to exclusion.

Analysis of Safety

All safety data were summarized descriptively. Safety analyses of reactogenicity were performed on the solicited safety set (SSS) for participants included in the

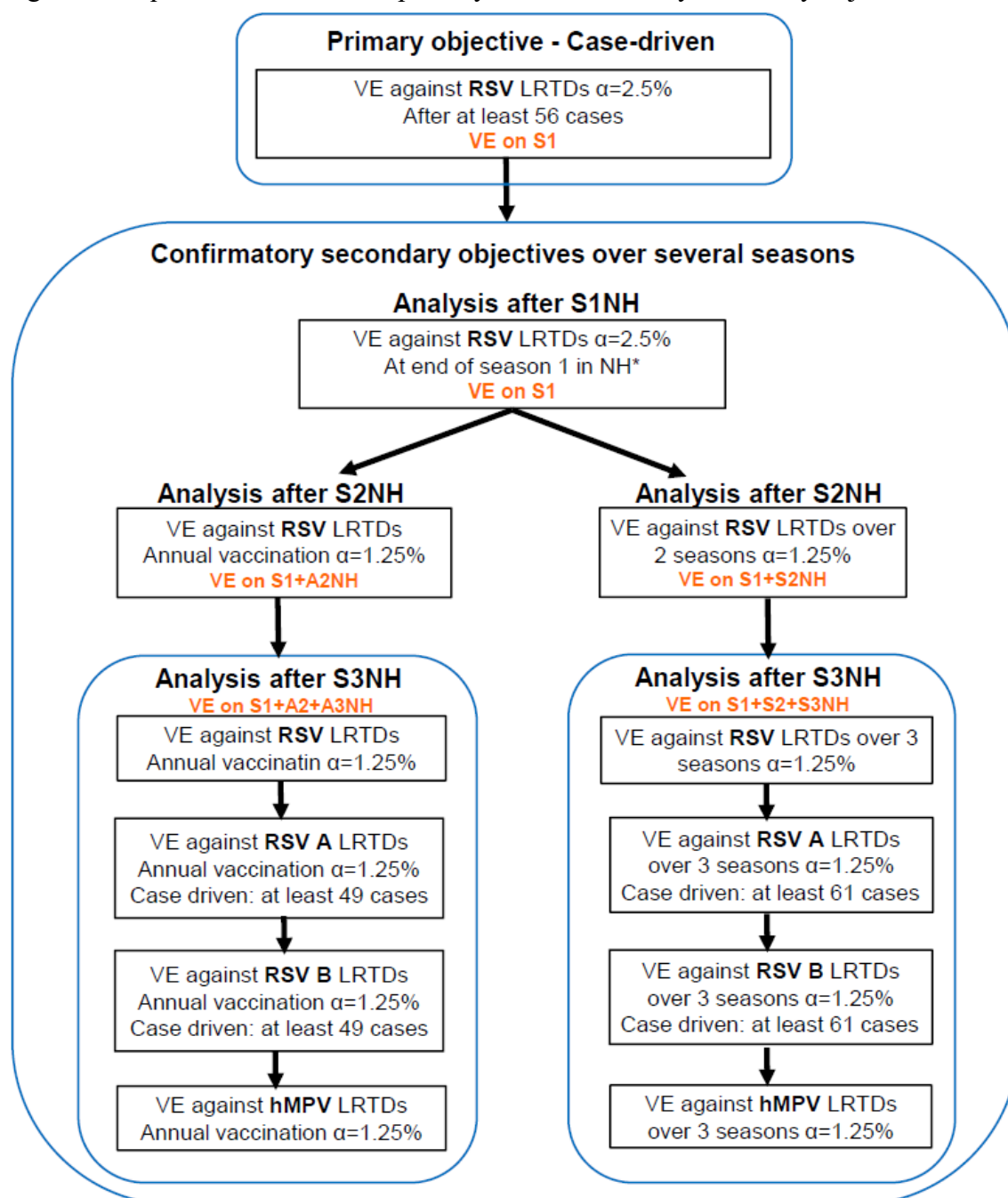
immunogenicity and reactogenicity subset and unsolicited AEs were summarized in the ES. The SSS is defined as:

- SSS: All subjects in the ES who have solicited safety data.

Multiplicity Adjustment

The family-wise Type I error rate for testing the primary efficacy endpoint was fixed at one-sided $\alpha = 0.025$. For the primary efficacy endpoint, one interim analysis was specified based on a Wang-Tsiatis stopping boundary with $\Delta = 0.3$ and information fraction = 0.80. Given that the null hypothesis for the primary endpoint was rejected at the interim analysis, the secondary endpoints will be evaluated according to a pre-specified procedure. No interim analyses were specified for the secondary efficacy endpoints. The secondary efficacy endpoints will be tested using the Fixed-Sequence Method with a Bonferroni adjustment, detailed in Figure 1 below, to preserve a family-wise Type I error rate of 0.025 (one-sided).

Figure 1: Sequential evaluation of primary and confirmatory secondary objectives



S1/S2/S3=Season 1/2/3 after a single dose; A2/A3 = Annual evaluation during Season 2/3 (after revaccination); Season 3 is only applicable in the NH.

*The end of S1NH analysis will be performed if at least 1 additional RSV-confirmed ARI has been reported since the analysis of the primary efficacy objective and if there are at least 2-3 weeks between the database cut-off dates of the 2 analyses.

Source: Figure 4 from RSV OA=ADJ-006 Clinical Study Protocol.

Sample Size Determination

Assuming an attack rate of 0.6%, a VE of 70%, a dropout rate of 10%, and a target number of 56 cases, a sample size of 16,000 (8,000 per group) enrolled subjects was calculated to yield 90% power for the 1-sided exact binomial test of the primary efficacy endpoint.

However, due to the potential impact of COVID-19 pandemic measures on the RSV circulation and the difficulty to estimate the attack rate for the first season of the study, the sample size was increased to 25,000 (12,500 per group) subjects to mitigate the risk of a lower attack rate, as shown in Table 11 below.

Table 11: Total sample size to be enrolled in the NH to ensure at least 90% power to demonstrate the primary objective depending on attack rate, assuming a non-evaluable rate of 10%

Number of cases needed for Primary Objective	Attack rate	Sample size
56 RSV-confirmed LRTD	0.6%	16,000
56 RSV-confirmed LRTD	0.55%	17,500
56 RSV-confirmed LRTD	0.5%	19,200
56 RSV-confirmed LRTD	0.45%	21,500
56 RSV-confirmed LRTD	0.42%	23,000
56 RSV-confirmed LRTD	0.4%	24,000

Source: Table 26 from RSV OA=ADJ-006 Clinical Study Protocol.

6.2.10 Study Population and Disposition

A total of 26,664 subjects were included in the Enrolled Set, of which 25,040 were randomized and 24,966 (12,467 in the RSVPreF3 group and 12,499 in the Placebo group) were included in the ES. Table 12 summarizes the demographics of the ES. Overall, no major imbalances were observed between the vaccine groups. Additionally, the demographics of the mES, SSS, and PPSI were similar to that of the ES.

Table 12: Summary of demography and baseline characteristics – ES

-	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Total N=24966	Total N=24966
-	Value or n	%	Value or n	%	Value or n	%
Age (years) at vaccination on Day 1	-	-	-	-	-	-
n	12467	-	12499	-	24966	-
Mean	69.5	-	69.6	-	69.5	-
Standard Deviation	6.5	-	6.4	-	6.5	-
Median	69.0	-	69.0	-	69.0	-
Minimum	59	-	59	-	59	-
Maximum	102	-	98	-	102	-
Age category	-	-	-	-	-	-
≥ 65 YOA	9259	74.3	9329	74.6	18588	74.5
≥ 70 YOA	5504	44.1	5519	44.2	11023	44.2
≥ 80 YOA	1017	8.2	1028	8.2	2045	8.2
60-69 YOA	6963	55.9	6980	55.8	13943	55.8
70-79 YOA	4487	36.0	4491	35.9	8978	36.0
Sex	-	-	-	-	-	-
Male	5979	48.0	6072	48.6	12051	48.3
Female	6488	52.0	6427	51.4	12915	51.7
Ethnicity	-	-	-	-	-	-
Hispanic Or Latino	682	5.5	682	5.5	1364	5.5
Not Hispanic Or Latino	11780	94.5	11811	94.5	23591	94.5
Unknown	5	0.0	6	0.0	11	0.0
Race	-	-	-	-	-	-
American Indian Or Alaska Native	44	0.4	35	0.3	79	0.3
Asian	953	7.6	956	7.6	1909	7.6
Black Or African American	1064	8.5	1101	8.8	2165	8.7
Native Hawaiian Or Other Pacific Islander	11	0.1	6	0.0	17	0.1
White	9887	79.3	9932	79.5	19819	79.4
Other	508	4.1	469	3.8	977	3.9

Table 12: Summary of demography and baseline characteristics – ES (continued)

-	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Total N=24966	Total N=24966
-	Value or n	%	Value or n	%	Value or n	%
Race (sub-category)	-	-	-	-	-	-
African	1064	8.5	1101	8.8	2165	8.7
Asian	953	7.6	956	7.6	1909	7.6
White	9887	79.3	9932	79.5	19819	79.4
Other	563	4.5	510	4.1	1073	4.3
Hemisphere	-	-	-	-	-	-
Northern hemisphere	11496	92.2	11522	92.2	23018	92.2
Southern hemisphere	971	7.8	977	7.8	1948	7.8
Type Of Residence	-	-	-	-	-	-
Community Dwelling	12306	98.7	12351	98.8	24657	98.8
Long-Term Care Facilities	161	1.3	148	1.2	309	1.2
BMI (kg/m²)	-	-	-	-	-	-
n	12457	-	12490	-	24947	-
Mean	29.1	-	29.1	-	29.1	-
Standard Deviation	6.1	-	6.0	-	6.1	-
Median	28.3	-	28.3	-	28.3	-
Minimum	12.6	-	13.1	-	12.6	-
Maximum	116.7	-	69.8	-	116.7	-
Frailty Status	-	-	-	-	-	-
Frail	189	1.5	177	1.4	366	1.5
Pre-Frail	4793	38.4	4781	38.3	9574	38.3
Fit	7464	59.9	7521	60.2	14985	60.0
Unknown	21	0.2	20	0.2	41	0.2
Smoking status for tobacco	-	-	-	-	-	-
Current smoker	1644	13.2	1665	13.3	3309	13.3
Former smoker	4311	34.6	4430	35.4	8741	35.0
Never smoker	6511	52.2	6404	51.2	12915	51.7
Unknown	1	0.0	0	0	1	0.0

Table 12: Summary of demography and baseline characteristics – ES (continued)

-	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Total N=24966	Total N=24966
-	Value or n	%	Value or n	%	Value or n	%
Smoking status for e-cigarettes	-	-	-	-	-	-
Current smoker	121	1.0	109	0.9	230	0.9
Former smoker	89	0.7	78	0.6	167	0.7
Never smoker	12256	98.3	12312	98.5	24568	98.4
Unknown	1	0.0	0	0	1	0.0
Charlson Comorbidity Index - Categories	-	-	-	-	-	-
Low/Medium risk	8235	66.1	8368	66.9	16603	66.5
High risk	4232	33.9	4131	33.1	8363	33.5
Charlson Comorbidity Index - Score	-	-	-	-	-	-
n	12467	-	12499	-	24966	-
Mean	3.2	-	3.2	-	3.2	-
Standard Deviation	1.2	-	1.2	-	1.2	-
Median	3.0	-	3.0	-	3.0	-
Minimum	2	-	2	-	2	-
Maximum	11	-	11	-	11	-
Comorbidity of interest	-	-	-	-	-	-
At least 1 pre-existing comorbidity of interest	4937	39.6	4864	38.9	9801	39.3
At least 1 pre-existing Cardiorespiratory condition	2496	20.0	2422	19.4	4918	19.7
At least 1 pre-existing Endocrinometabolic condition	3200	25.7	3236	25.9	6436	25.8

N = number of subjects.

n/% = number / percentage of subjects in a given category.

Age computed based on incomplete date of birth (only year was available).

Frailty status: Frail = Subjects with a walking speed < 0.4m/s or who were not able to perform the test; Pre-Frail = Subjects with a walking speed between 0.4-0.99 m/s; Fit = Subjects with a walking speed ≥ 1 m/s.

Charlson Comorbidity Index: Low/medium Risk = Subjects with comorbidity score at baseline less than or equal to 3; High Risk = Subjects with comorbidity score at baseline greater than 3.

Source: Table 2.3 from RSV OA=ADJ-006 Clinical Study Report.

Participant dispositions from the ES to the mES, SSS, and PPSI are presented in Tables 13 – 15, respectively. A total of $n = 24,960$ (12,466 in the RSVPreF3 group and 12,494 in the Placebo group), $n = 1,757$ (879 in the RSVPreF3 group and 878 in the Placebo group), and $n = 1,702$ (850 in the RSVPreF3 group and 852 in the Placebo group) participants were included in the mES, SSS, and PPSI, respectively.

Table 13: Summary of participant disposition from Exposed Set to modified Exposed Set

-	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Total N=24966	Total N=24966
-	n	%	n	%	n	%
Eliminations	1	0.0	5	0.0	6	0.0
Other deviation from study procedures (confirmed RSV ARI case prior to day 15 after vaccination) (2500)	1	0.0	5	0.0	6	0.0
Number of participants included in modified Exposed Set	12466	100.0	12494	100.0	24960	100.0

N = number of participants.

n/% = number / percentage of participants in a given category.

Source: Table 14.1.1.2 from RSV OA=ADJ-006 Clinical Study Report.

Table 14: Summary of participant disposition from Exposed Set to Solicited Safety Set

-	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Total N=24966	Total N=24966
-	n	%	n	%	n	%
Eliminations	11588	92.9	11621	93.0	23209	93.0
Participant not included in reactogenicity and immunogenicity subset (2600)	11567	92.8	11600	92.8	23167	92.8
No safety follow up (1160)	21	0.2	21	0.2	42	0.2
Number of participants included in Solicited Safety Set	879	7.1	878	7.0	1757	7.0

N = number of participants.

n/% = number / percentage of participants in a given category.

Source: Table 14.1.1.3 from RSV OA=ADJ-006 Clinical Study Report.

Table 15: Summary of participant disposition from Exposed Set to Per Protocol Set for Immunogenicity

-	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Total N=24966	Total N=24966
-	n	%	n	%	n	%
Withdrawals	110	0.9	109	0.9	219	0.9
Consent withdrawal, not due to an adverse event and/or a serious adverse event	68	0.5	60	0.5	128	0.5
Lost to follow-up	25	0.2	27	0.2	52	0.2
Adverse event requiring expedited reporting	13	0.1	13	0.1	26	0.1
Other	2	0.0	4	0.0	6	0.0
Unsolicited non-serious adverse event	1	0.0	4	0.0	5	0.0
Migrated / moved from the study area	1	0.0	1	0.0	2	0.0
Eliminations	11507	92.3	11538	92.3	23045	92.3
Participant not included in reactogenicity and immunogenicity subset (2600)	11467	92.0	11503	92.0	22970	92.0
Vaccine, excluded by the protocol, was administered (1040)	102	0.8	116	0.9	218	0.9
Vaccine, excluded by the protocol, was administered (C1040)	51	0.4	53	0.4	104	0.4
Randomization procedures (did not receive the correct vaccine according to the randomization allocation) (1050)	12	0.1	7	0.1	19	0.1
Randomization code broken (1060)	3	0.0	2	0.0	5	0.0
Vaccine administration not according to protocol (1070)	3	0.0	3	0.0	6	0.0
Use of study treatment impacted by a temperature excursion (1080)	40	0.3	44	0.4	84	0.3
Subject did not meet entry criteria (2010)	6	0.0	7	0.1	13	0.1
Subject did not meet entry criteria (C2010)	1	0.0	2	0.0	3	0.0
Medication, excluded by the protocol, was administered (2040)	23	0.2	13	0.1	36	0.1
Medication, excluded by the protocol, was administered (C2040)	3	0.0	6	0.0	9	0.0
Intercurrent medical condition (2050)	10	0.1	8	0.1	18	0.1
Out of window assessment for immunogenicity (2090)	308	2.5	341	2.7	649	2.6
Missed assessment (immunology) (2100)	76	0.6	72	0.6	148	0.6
Missed assessment (immunology) (C2100)	1	0.0	0	0	1	0.0
Number of participants included in Per Protocol Set for immunogenicity at Visit 2	850	6.8	852	6.8	1702	6.8

N = number of participants.

n/% = number / percentage of participants in a given category.

Elimination codes starting with 'c' indicate that the elimination is related to COVID-19.

Source: Table 14.1.1.5 from RSV OA=ADJ-006 Clinical Study Report.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Efficacy Endpoints

Overall Analysis

The overall efficacy results and by both age category and RSV subtype at the interim analysis are displayed in Table 16. For the overall efficacy, 7 and 40 cases were reported in the RSVPreF3 OA and Placebo groups, respectively, where the estimated VE was 82.58% with 2-sided 96.95% CI (57.89%, 94.08%). The alpha value of 3.05% for the 2-sided CI was derived from a Wang-Tsiatis stopping boundary with $\Delta = 0.3$ and information fraction = 0.80. Because the LL of the 2-sided CI was above the pre-defined threshold of 20%, the primary efficacy success criterion was met.

Analyses of VE by both age category and RSV subtype also showed consistently high VEs around 80%, except for VE in subjects ≥ 80 YOA. Of note, the number of cases was small in this age group (2 and 3 cases in the RSVPreF3 OA and placebo groups, respectively).

Subgroup Analyses

Across the subgroup analyses of hemisphere, region, ethnicity, race, sex, baseline frailty status, and baseline comorbidities, for subgroups for which there were a sufficient number of cases, VE was consistently greater than 70%. VEs for subgroups with an insufficient number of cases are not reported.

For hemisphere, no subgroup analysis was performed, since all RSV cases occurred in the NH.

For region, VE for participants in North America and the European Union was 93.35% with 95% CI (56.76%, 99.84%) and 80.06% with 95% CI (46.98%, 94.04%), respectively. One case occurred in Asia (in the RSVPreF3 OA group).

For ethnicity, VE for non-Hispanic participants was 82.13% with 95% CI (59.59%, 93.26%). One case occurred among Hispanic participants (in the Placebo group).

For race, VE for Caucasian participants was 87.23% with 95% CI (67.57%, 96.07%). Two cases occurred among African participants (one in the RSVPreF3 OA group and one in the Placebo group). One case occurred among Asian participants (in the RSVPreF3 OA group). No cases occurred for participants classified as "Other".

For sex, VE for male and female participants was 90.45% with 95% CI (60.92%, 98.91%) and 74.10% with 95% CI (28.27%, 92.44%), respectively.

Baseline frailty status was assessed by a gait speed test, where participants were asked to walk 3 or 4 meters. Based on walking speed, participants were categorized into frail

(walking speed < 0.4 m/s or unable to complete the test), pre-frail (walking speed between 0.4-0.99 m/s), or fit (walking speed ≥ 1 m/s) subgroups. VE for pre-frail and fit participants was 92.92% with 95% CI (53.44%, 99.83%) and 79.95% with 95% CI (46.66%, 94.00%), respectively. Two cases occurred among frail participants (one in the RSVPreF3 OA group and one in the Placebo group).

Baseline comorbidities were assessed by Charlson Comorbidity Index (CCI), where participants were categorized into low/medium ($CCI \leq 3$) or high ($CCI > 3$) risk subgroups. VE for low/medium and high risk participants was 82.39% with 95% CI (48.45%, 95.57%) and 82.88% with 95% CI (40.79%, 96.79%), respectively.

Table 16: Summary table of VE against first occurrence of RT-PCR-confirmed RSV LRTD, using Poisson method – mES

-	RSVPreF3	RSVPreF3	RSVPreF3	RSVPreF3	Placebo	Placebo	Placebo	Placebo	VE	VE	VE	VE
-	N	n	T (year)	n/T (per 1000 years)	N	n	T (year)	n/T (per 1000 years)	%	LL CI	UL CI	P-value
Overall	12466	7	6865.9	1.0	12494	40*	6857.3	5.8	82.58	57.89	94.08	<0.0001
≥ 65 YOA	9258	5	5098.7	1.0	9325	29	5132.1	5.7	82.72	54.85	94.78	<0.0001
≥ 70 YOA	5503	3	3015.0	1.0	5515	19	3020.9	6.3	84.37	46.91	97.04	0.0008
≥ 80 YOA	1016	2	551.4	3.6	1028	3	559.3	5.4	33.83	-477.68	94.47	0.9931
60-69 YOA	6963	4	3850.8	1.0	6979	21	3836.4	5.5	80.96	43.56	95.25	0.0009
70-79 YOA	4487	1	2463.6	0.4	4487	16	2461.6	6.5	93.81	60.15	99.85	0.0003
RSV-A	12466	2	6867.4	0.3	12494	13*	6868.9	1.9	84.62	32.08	98.32	0.0074
RSV-B	12466	5	6866.7	0.7	12494	26*	6862.3	3.8	80.88	49.40	94.27	0.0002

*One case was reported without RSV-A or RSV-B subtype.

N = number of subjects; n = number of subjects with at least one RT-PCR-confirmed RSV LRTD; RSV LRTD = RSV LRTD identified by Adjudication Committee.

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 years) = Incidence rate of subjects reporting at least one event.

CI = 95% CI except for overall results where CI is 96.95% CI due to adjustment of alpha level at interim using the Wang-Tsiatis method with $\Delta = 0.3$ and information fraction = 0.80.

Source: Table 2.4 from RSV OA=ADJ-006 Clinical Study Report.

6.2.11.2 Analyses of Secondary Efficacy Endpoints

Efficacy results for RT-PCR-confirmed RSV A and/or B-associated severe LRTD and ARI at the interim analysis are displayed in Tables 17 and 18, respectively. For severe LRTD, the estimated VE was 94.10% with 95% CI (62.37%, 99.86%). For ARI, the estimated VE was 71.71% with 95% CI (56.23% 82.27%).

Table 17: VE against first occurrence of RT-PCR-confirmed RSV severe LRTD, using Poisson method – mES

-	RSVPreF3	RSVPreF3	RSVPreF3	RSVPreF3	Placebo	Placebo	Placebo	Placebo	VE	VE	VE	VE
Definition	N	n	T (year)	n/T (per 1000 years)	N	n	T (year)	n/T (per 1000 years)	%	LL CI	UL CI	P-value
Any	12466	1	6867.9	0.1	12494	17	6867.7	2.5	94.10	62.37	99.86	0.0001
Definition 1: Clinical symptomology	12466	1	6867.9	0.1	12494	17	6867.7	2.5	94.10	62.37	99.86	0.0001
Definition 2: Supportive therapy	12466	0	6868.2	0.0	12494	2	6872.9	0.3	100.00	- 252.09	100.00	0.2535

N = number of subjects; n = number of subjects with at least one RT-PCR-confirmed RSV severe LRTD according to the definition;
RSV severe LRTD = RSV LRTD identified as severe by Adjudication Committee.

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 years) = Incidence rate of subjects reporting at least one event.

CI = 95% CI.

Source: Table 11.10 from RSV OA=ADJ-006 Clinical Study Report.

Table 18: VE against first occurrence of RT-PCR-confirmed RSV ARI, using Poisson method – mES

RSVPreF3	RSVPreF3	RSVPreF3	RSVPreF3	Placebo	Placebo	Placebo	Placebo	VE	VE	VE	VE
N	n	T (year)	n/T (per 1000 years)	N	n	T (year)	n/T (per 1000 years)	%	LL CI	UL CI	P-value
12466	27	6858.7	3.9	12494	95	6837.8	13.9	71.71	56.23	82.27	<0.0001

N = number of subjects; n = number of subjects with at least one RT-PCR-confirmed RSVARI.

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 years) = Incidence rate of subjects reporting at least one event.

CI = 95% CI.

Source: Table 11.11 from RSV OA=ADJ-006 Clinical Study Report.

6.2.11.3 Analyses of Secondary Immunogenicity Endpoints

Table 19 displays RSV-A/B NAb GMTs and MGIs for the RSVPreF3 and Placebo groups. At Day 1 (pre-vaccination), all participants had detectable RSV-A/B NAbs due to previous exposure to RSV.

The RSV-A NAb titers MGI at Day 31 over baseline was 10.2 with 95% CI (9.5, 11.0) in the RSVPreF3 group with little change in the Placebo group.

The RSV-B NAb titers MGI at Day 31 over baseline was 8.6 with 95% CI (8.0, 9.2) in the RSVPreF3 group with little change in the Placebo group.

Table 19: RSV-A NAb and RSV-B NAb GMTs and MGIs – PPSI

-	-	-	RSVPreF3	RSVPreF3	RSVPreF3	RSVPreF3	Placebo	Placebo	Placebo	Placebo
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI
RSV-A NAb	D1	GMT	885	918.0	865.7	973.5	892	928.6	877.5	982.6
RSV-A NAb	D31	GMT	848	9329.7	8699.3	10005.8	846	873.6	822.6	927.8
RSV-A NAb	D31 / D1	MGI	844	10.2	9.5	11.0	846	0.9	0.9	1.0
RSV-B NAb	D1	GMT	885	1195.8	1130.5	1264.8	892	1244.1	1174.4	1317.9
RSV-B NAb	D31	GMT	848	10178.9	9564.1	10833.1	846	1263.1	1185.0	1346.3
RSV-B NAb	D31 / D1	MGI	844	8.6	8.0	9.2	846	1.0	1.0	1.1

N = number of participants.

CI = 95% CI.

D1 = Pre-vaccination at Day 1; D31 = 30 days post-Dose 1.

Source: Adapted from Tables 2.10 and 2.11 from RSV OA=ADJ-006 Clinical Study Report.

Table 20 displays RSVPreF3 Specific IgG GMCs and MGIs for the RSVPreF3 and Placebo groups. At Day 1 (pre-vaccination), all participants had detectable RSVPreF3-specific IgG Abs due to previous exposure to RSV.

The RSVPreF3 Specific IgG MGI at Day 31 over baseline was 13.1 with 95% CI (12.3, 13.9) in the RSVPreF3 group with little change in the Placebo group.

Table 20: RSVPreF3-Specific IgG GMCs and MGIs – PPSI

-	-	-	RSVPreF3	RSVPreF3	RSVPreF3	RSVPreF3	Placebo	Placebo	Placebo	Placebo
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI
RSVPreF3 Specific IgG	D1	GMC	885	7041.1	6719.7	7377.8	892	7090.1	6785.6	7408.1
RSVPreF3 Specific IgG	D31	GMC	848	91729.9	87514.2	96148.7	846	7044.5	6726.5	7377.5
RSVPreF3 Specific IgG	D31 / D1	MGI	844	13.1	12.3	13.9	846	1.0	1.0	1.0

N = number of participants.

CI = 95% CI.

D1 = Pre-vaccination at Day 1; D31 = 30 days post-Dose 1.

Source: Adapted from Table 2.9 from RSV OA=ADJ-006 Clinical Study Report.

6.2.12 Analyses of Safety Endpoints

Percentages of subjects reporting solicited local and systemic reactions within 4 days after the study dose are displayed in Table 21. The percentages of subjects reporting solicited local and systemic reactions were generally higher in the RSVPreF3 group than the Placebo group. The most frequently reported solicited local reaction was pain (60.9% in the RSVPreF3 group and 9.3% in the Placebo group), while the most frequently reported solicited systemic reaction was fatigue (33.6% in the RSVPreF3 group and 16.1% in the Placebo group).

Table 21: Percentage of subjects with solicited local and systemic events within 4 days following the study dose – SSS

Local Adverse Reactions	RSVPreF3 % (n) N = 879	Placebo % (n) N = 874
Pain	60.9% (535)	9.3% (81)
Pain, Grade 3	1% (9)	0
Erythema	7.5% (66)	0.8% (7)
Erythema, > 100 mm	0.2% (2)	0
Swelling	5.5% (48)	0.6% (5)
Swelling > 100 mm	0.2% (2)	0
Systemic Adverse Reactions	N = 879	N = 878
Fatigue	33.6% (295)	16.1% (141)
Fatigue, Grade 3	1.7% (15)	0.5% (4)
Myalgia	28.9% (254)	8.2% (72)
Myalgia, Grade 3	1.4% (12)	0.3% (3)
Headache	27.2% (239)	12.6% (111)
Headache, Grade 3	1.3% (11)	0
Arthralgia	18.1% (159)	6.4% (56)
Arthralgia, Grade 3	1.3% (11)	0.6% (5)
Fever	2.0% (18)	0.3% (3)
Fever, Grade 3	0.1% (1)	0.1% (1)

n/% = number/percentage of participants presenting at least one type of event.

N = number of participants who completed the diary card.

Grade 3 pain: defined as significant pain at rest and prevents normal everyday activities.

Grade 3 fatigue, myalgia, headache, arthralgia: Defined as preventing normal activity.

Fever defined as a temperature $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ by any route (oral, axillary, or tympanic); Grade 3 fever defined as $> 39.0^{\circ}\text{C}/102.2^{\circ}\text{F}$.

Source: Adapted from Tables 12.2 and 12.3 from RSV OA=ADJ-006 Clinical Study Report.

Percentages of subjects reporting unsolicited AEs after the study dose up to the DLP of 30 April 2022 are displayed in Table 22. The percentages of subjects reporting unsolicited AEs were generally higher in the RSVPreF3 group than the Placebo group. However, the percentages of participants reporting MAAEs, SAEs, and pIMDs were similar between groups. A total of 10 and 7 subjects reported at least one related SAE up to the DLP in the RSVPreF3 and Placebo groups, respectively. A total of 7 and 5 subjects reported at least one related pIMD up to the DLP in the RSVPreF3 and Placebo groups, respectively.

A total of 107 deaths (49 in the RSVPreF3 group and 58 in the Placebo group) were reported up to the DLP. Of these, 1 (i.e., cardiopulmonary failure [TTO: 30 days]) and 2 (i.e., 'not coded' [TTO: 223 days] and pulmonary embolism [TTO: 147 days]) were assessed as related to the study intervention by the investigator in the RSVPreF3 and Placebo groups, respectively.

Table 22: Summary of subjects by unsolicited adverse event category up to DLP of 30APR2022 – ES

-	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Placebo N=12499	Placebo N=12499	Placebo N=12499
-	<i>n</i>	<i>n</i>	%	LL CI	UL CI	<i>n</i>	<i>n</i>	%	LL CI	UL CI
Any unsolicited adverse event within 30 days post-vaccination	8411	4117	33.0	32.2	33.9	3732	2229	17.8	17.2	18.5
Any Grade 1 unsolicited adverse event within 30 days post-vaccination	5873	3264	26.2	25.4	27.0	2328	1492	11.9	11.4	12.5
Any Grade 2 unsolicited adverse event within 30 days post-vaccination	2205	1392	11.2	10.6	11.7	1197	870	7.0	6.5	7.4
Any Grade 3 unsolicited adverse event within 30 days post-vaccination	336	246	2.0	1.7	2.2	207	158	1.3	1.1	1.5
Any related unsolicited adverse event within 30 days post-vaccination	5584	3105	24.9	24.1	25.7	1146	731	5.8	5.4	6.3
Any Grade 3 related unsolicited adverse event within 30 days post-vaccination	165	112	0.9	0.7	1.1	41	25	0.2	0.1	0.3
Any medically attended unsolicited adverse event within 30 days post-vaccination	879	688	5.5	5.1	5.9	871	691	5.5	5.1	5.9
Any non-serious unsolicited adverse event within 30 days post-vaccination	8312	4057	32.5	31.7	33.4	3616	2157	17.3	16.6	17.9
Any non-serious Grade 3 unsolicited adverse event within 30 days post-vaccination	275	192	1.5	1.3	1.8	128	98	0.8	0.6	1.0
Any non-serious related unsolicited adverse event within 30 days post-vaccination	5579	3102	24.9	24.1	25.7	1142	727	5.8	5.4	6.2
Any non-serious Grade 3 related unsolicited adverse event within 30 days post-vaccination	160	108	0.9	0.7	1.0	38	22	0.2	0.1	0.3

Table 22: Summary of subjects by unsolicited adverse event category up to DLP of 30APR2022 – ES

-	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Placebo N=12499	Placebo N=12499	Placebo N=12499
-	<i>n</i>	<i>n</i>	%	LL CI	UL CI	<i>n</i>	<i>n</i>	%	LL CI	UL CI
Any non-serious medically attended unsolicited adverse event within 30 days post-vaccination	782	614	4.9	4.6	5.3	758	618	4.9	4.6	5.3
Any serious adverse event up to 6 months post-vaccination	643	522	4.2	3.8	4.6	656	506	4.0	3.7	4.4
Any related serious adverse event up to DLP	12	10	0.1	0.0	0.1	7	7	0.1	0.0	0.1
Any pIMD up to 6 months post-vaccination	41	40	0.3	0.2	0.4	35	34	0.3	0.2	0.4
Any related pIMD up to DLP	7	7	0.1	0.0	0.1	5	5	0.0	0.0	0.1
Any fatal serious adverse event up to DLP	58	49	0.4	0.3	0.5	64	58	0.5	0.4	0.6

N = number of subjects.

n = number of events reported.

n/% = number/percentage of subjects presenting at least one type of adverse event.

CI = 95% CI.

Safety DLP = 30APR2022.

Source: Table 2.14 from RSV OA=ADJ-006 Clinical Study Report.

An Addendum to Integrated Summary of Safety was also submitted, which included unsolicited AE data up to a later DLP (30 September 2022) for Study RSV OA=ADJ-006. Percentages of subjects reporting unsolicited AEs after the study dose up to the DLP of 30 September 2022 are displayed in Table 23. For both groups, the distributions of the unsolicited AEs up to the DLP of 30 September 2022 were similar to that with the DLP of 30 April 2022.

A total of 11 and 7 subjects reported at least one related SAE in the RSVPreF3 and Placebo groups, respectively. A total of 5 subjects reported at least one related pIMD in both the RSVPreF3 group and Placebo groups, respectively. Due to the investigator changing the designation of some pIMDs from related to unrelated between the two DLPs, the number of related pIMDs up to the DLP of 30 September 2022 is less than up to the DLP of 30 April 2022.

A total of 183 deaths (88 in the RSVPreF3 group and 95 in the Placebo group) were reported up to the DLP of 30 September 2022. Since the previous DLP of 30 April 2022, 1 new death (i.e., unknown cause [TTO: 326 days]) in the Placebo group was assessed as related to the study intervention by the investigator.

Table 23: Summary of subjects by unsolicited adverse event category up to DLP of 30SEP2022 – ES

-	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	RSVPreF3 N=12467	Placebo N=12499	Placebo N=12499	Placebo N=12499	Placebo N=12499	Placebo N=12499
-	<i>n</i>	<i>n</i>	%	LL CI	UL CI	<i>n</i>	<i>n</i>	%	LL CI	UL CI
Any serious adverse event up to 6 months post-vaccination	665	539	4.3	4.0	4.7	692	535	4.3	3.9	4.6
Any related serious adverse event up to DLP	14	11	0.1	0.0	0.2	7	7	0.1	0.0	0.1
Any pIMD up to 6 months post-vaccination	42	41	0.3	0.2	0.4	35	34	0.3	0.2	0.4
Any related pIMD up to DLP	6	5	0.0	0.0	0.1	5	5	0.0	0.0	0.1
Any fatal serious adverse event up to DLP	100	88	0.7	0.6	0.9	103	95	0.8	0.6	0.9

N = number of subjects.

n = number of events reported.

n/*%* = number/percentage of subjects presenting at least one type of adverse event.

CI = 95% CI.

Safety DLP = 30SEP2022.

Source: Table 1 from Addendum to Integrated Summary of Safety.

6.3 Clinical Study RSV OA=ADJ-007

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

Dates:

1. Study initiation date (First Subject First Visit): 27 April 2021
2. DLP for analysis: 8 February 2022

6.3.1 Objectives

Primary Immunogenicity Objectives:

1. To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV compared to RSVPreF3 OA investigational vaccine administered alone.
2. To demonstrate the non-inferiority of FLU-QIV when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU-QIV administered alone.

Secondary Immunogenicity Objectives:

1. To evaluate the non-inferiority of FLU-QIV when co-administered with the RSVPreF3 OA investigational vaccine compared to FLU-QIV administered alone.
2. To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV or administered alone.
3. To evaluate the humoral immune response to FLU-QIV when co-administered with the RSVPreF3 OA investigational vaccine or administered alone.

Safety Objective:

1. To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and FLU-QIV, co-administered or administered alone.

6.3.2 Design Overview

Subjects were randomized with a ratio of 1:1 to either a single dose of RSVPreF3 OA investigational vaccine and a single dose of FLU-QIV on Day 1, referred to as the co-administration group (Co-Ad group), or a single dose of FLU-QIV on Day 1, followed by a single dose of the RSVPreF3 OA investigational vaccine on Day 31, referred to as the Control group. The randomization algorithm used a minimization procedure, where age category (60-69, 70-79 or ≥ 80 years), center, country, and sex were included as minimization factors.

For immunogenicity, blood samples were collected from subjects at pre-vaccination (Day 1) and 1 month post-vaccination (Day 31) in the Co-Ad group. Blood samples were collected from subjects at pre-vaccination (Day 1 for FLU-QIV/Day 31 for RSVPreF3 OA vaccine), 1 month post-FLU-QIV (Day 31), and 1 month post-RSVPreF3 OA

vaccine (Day 61) in the Control group. For safety, solicited AEs and unsolicited AEs were collected for four and 30 days after vaccination, respectively, while both SAEs and pIMDs were collected for six months after vaccination.

6.3.3 Population

Subjects ≥ 60 YOA were enrolled.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The vaccine formulations evaluated in this study consisted of 1) 120 mcg of RSVPreF3 OA antigen adjuvanted with AS01E per 0.5 mL dose; and 2) FLU Quadrivalent Influenza vaccine with 15 μ g HA per strain/dose. The influenza vaccine strains included A/Victoria/2570/2019 (H1N1), IVR-215 (15 μ g HA); A/Hong Kong/2671/2019 (H3N2), NIB-121 (15 μ g HA); B/Washington/02/2019, wild type (15 μ g HA); B/Phuket/3073/2013, wild type (15 μ g HA).

6.3.6 Sites and Centers

The study was conducted at 14 centers in 3 countries: 7 in New Zealand, 5 in Panama and 2 in South Africa.

6.3.7 Surveillance/Monitoring

Please refer to the clinical review.

6.3.8 Endpoints and Study Success Criteria

Primary Immunogenicity Endpoints:

1. RSV-A neutralization antibody titers expressed as group GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose, with the following success criterion:
 - The UL of the 2-sided CI for GMR (Control over Co-Ad) is less than 1.5.
2. HI antibody titers for each of the four FLU-QIV strains expressed as group GMT ratio, 1 month after the FLU-QIV dose, with the following success criterion:
 - The UL of the 2-sided CI for GMR (Control over Co-Ad) is less than 1.5.

Secondary Immunogenicity Endpoints:

1. HI seroconversion status for each of the four FLU-QIV strains expressed as seroconversion rate (SCR), 1 month after the FLU-QIV dose, where SCR is defined below.
 - SCR is defined as the percentage of vaccinees who have either a HI pre-dose titer $< 1:10$ and a post-dose titer $\geq 1:40$ or a pre-dose titer $\geq 1:10$ and at least a four-fold increase in post-dose titer.
2. RSV-A neutralization antibody titers expressed as MGI at 1 month after the RSVPreF3 OA investigational vaccine dose.

3. RSV-B neutralizing antibody titers expressed as group GMT ratio and MGI at 1 month after the RSVPreF3 OA investigational vaccine dose in a subset.
4. HI antibody titers for each of the FLU-QIV strains expressed as GMT, on Day 1 and Day 31.
5. HI seroconversion status for each of the FLU-QIV strains expressed as SCR, from Day 1 to Day 31.
6. HI seroprotection status for each of the FLU-QIV strains expressed as seroprotection rate (SPR), on Day 1 and Day 31, where SPR is defined below.
 - SPR is defined as the percentage of vaccinees with a serum HI titer $\geq 1:40$.
7. HI antibody titers for each of the FLU-QIV strains expressed as MGI, 1 month after the FLU-QIV dose.

Safety Endpoints:

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

6.3.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

For the primary immunogenicity analysis, ANCOVA models were fit to log₁₀-transformed antibody titers with covariates for treatment group, age category (60-69, 70-79 or ≥ 80 years), country, sex, and pre-dose log₁₀-transformed titer. Missing data were not replaced. Titers below the technical assay cut-off were replaced by half the technical assay cut-off; titers above the ULOQ were replaced by the ULOQ.

The immunogenicity analyses were performed on the PPS, defined as:

- PPS: All eligible participants who received at least 1 study intervention as per protocol, had immunogenicity results pre- and post-dose for at least 1 antigen, and complied with blood draw intervals. Contribution of participants to PPS at specific time points will be defined by time point, without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

For the secondary immunogenicity analysis, the 95% CI on group difference in seroconversion rates (Control group minus Co-Ad group) was computed based on the method of Miettinen and Nurminen. The 95% CI for the group GMT ratio in terms of RSV-B neutralizing antibody titers was computed in a subset of 425 subjects. At each time point that blood samples were collected the following analyses were performed:

- Percentages of subjects with antibody (Ab) titers/concentrations above the LLOQ and their 95% CIs
- Geometric mean titers (GMT)/geometric mean concentrations (GMCs) and their 95% CIs
- Distribution of Ab titers/concentrations using reverse cumulative curves
- Mean geometric increases (MGIs) and their 95% CIs

Analysis of Safety

All safety data were summarized descriptively. Safety analyses were performed on the ES.

Multiplicity Adjustment

For the primary immunogenicity endpoints, demonstration of non-inferiority required that all five (i.e., RSV-A and the four FLU-QIV strains) ULs of the two-sided 95% CIs for the GMRs be less than 1.5. Thus, no multiplicity adjustments were necessary.

Sample Size Determination

Assuming between-group mean differences of 0 for RSV-A and each of the four FLU-QIV strains, standard deviations of 0.45 and 0.6 for RSV-A and each of the four FLU-QIV strains, respectively, for log₁₀-transformed titer, and a dropout rate of 10%, a sample size of 880 (440 per group) subjects was calculated to yield 93.7% global power for demonstrating non-inferiority under 1.5-fold non-inferiority margins for RSV-A and all four FLU-QIV strains. A SD of 0.45 for RSV-A neutralizing titers was assumed based on the results from the RSV OA=ADJ-002 study.

6.3.10 Study Population and Disposition

A total of 976 subjects were included in the Enrolled Set, of which 890 were randomized and 885 (442 in the Co-Ad group and 443 in the Control group) were included in the ES. Table 24 displays the demographics of the ES. Overall, no major imbalances were observed between the vaccine groups. Additionally, the demographics of the PPS were similar to those of the ES.

Table 24: Summary of demography and baseline characteristics – ES

-	Co-Ad N=442	Co-Ad N=442	Control N=443	Control N=443	Total N=885	Total N=885
-	Value or n	%	Value or n	%	Value or n	%
Age (years) at first dose	-	-	-	-	-	-
n	442	-	443	-	885	-
Mean	68.4	-	68.6	-	68.5	-
Standard Deviation	6.9	-	6.9	-	6.9	-
Median	67.0	-	68.0	-	67.0	-
Minimum	59	-	59	-	59	-
Maximum	106	-	101	-	106	-
Age group	-	-	-	-	-	-
≥ 65 YOA	287	64.9	297	67.0	584	66.0
≥ 70 YOA	182	41.2	184	41.5	366	41.4
≥ 80 YOA	38	8.6	40	9.0	78	8.8
60-69 YOA	260	58.8	259	58.5	519	58.6
70-79 YOA	144	32.6	144	32.5	288	32.5
Country	-	-	-	-	-	-
New Zealand	145	32.8	145	32.7	290	32.8
Panama	153	34.6	157	35.4	310	35.0
South Africa	144	32.6	141	31.8	285	32.2
Sex	-	-	-	-	-	-
Male	214	48.4	215	48.5	429	48.5
Female	228	51.6	228	51.5	456	51.5
Ethnicity	-	-	-	-	-	-
Hispanic Or Latino	152	34.4	155	35.0	307	34.7
Not Hispanic Or Latino	290	65.6	287	64.8	577	65.2
Unknown	0	0	1	0.2	1	0.1

Table 24: Summary of demography and baseline characteristics – ES (continued)

-	Co-Ad N=442	Co-Ad N=442	Control N=443	Control N=443	Total N=885	Total N=885
-	Value or n	%	Value or n	%	Value or n	%
Race	-	-	-	-	-	-
American Indian Or Alaska Native	0	0	0	0	0	0
Asian	4	0.9	5	1.1	9	1.0
Black Or African American	72	16.3	70	15.8	142	16.0
Native Hawaiian Or Other Pacific Islander	2	0.5	1	0.2	3	0.3
White	137	31.0	135	30.5	272	30.7
Maori	7	1.6	5	1.1	12	1.4
Mixed Race	218	49.3	227	51.2	445	50.3
Other	2	0.5	0	0	2	0.2

N = number of subjects.

n/% = number / percentage of subjects in a given category.

Age computed based on incomplete date of birth (only year was available).

Source: Table 11.1 from RSV OA=ADJ-007 Clinical Study Report.

Participant dispositions from the ES to the PPS at Visit 2 for both the Co-Ad and Control groups and the ES to the PPS at Visit 3 for the Control group are presented in Tables 25 and 26, respectively. A total of n = 837 (427 in the Co-Ad group and 410 in the Control group) and n = 397 participants in the Control group were included in the PPS at Visits 2 and 3, respectively.

Table 25: Summary of participant disposition from Exposed Set to Per Protocol Set for Immunogenicity at Visit 2

-	Co-Ad N=442	Co-Ad N=442	Control N=443	Control N=443	Total N=885	Total N=885
-	n	%	n	%	n	%
Withdrawals	3	0.7	8	1.8	11	1.2
Consent Withdrawal, Not Due To An Adverse Event And/Or A Serious Adverse Event	0	0	5	1.1	5	0.6
Adverse Event Requiring Expedited Reporting	2	0.5	2	0.5	4	0.5
Lost To Follow-Up	1	0.2	0	0	1	0.1
Other	0	0	1	0.2	1	0.1
Eliminations	12	2.7	25	5.6	37	4.2
Excluded Medication, Vaccine Or Device (1040)	2	0.5	3	0.7	5	0.6
Excluded Medication, Vaccine Or Device (C1040)	3	0.7	3	0.7	6	0.7
Study Treatment Not Administered Per Protocol (1070)	0	0	9	2.0	9	1.0
Administration Of Any Medication Forbidden By The Protocol (2040)	1	0.2	1	0.2	2	0.2
Intercurrent Medical Condition (2050)	2	0.5	1	0.2	3	0.3
Out Of Window Assessment For Immunogenicity (2090)	2	0.5	0	0	2	0.2
Out Of Window Assessment For Immunogenicity (C2090)	1	0.2	8	1.8	9	1.0
Missed Assessment (2100)	1	0.2	8	1.8	9	1.0
Number of participants included in per protocol set at visit 2	427	96.6	410	92.6	837	94.6

N = number of participants.

n/% = number / percentage of participants in a given category.

Elimination codes starting with 'c' indicate that the elimination is related to COVID-19.

Source: Table 14.1.1.2 from RSV OA=ADJ-007 Clinical Study Report.

Table 26: Summary of participant disposition from Exposed Set to Per Protocol Set for Immunogenicity at Visit 3

-	Control N=443	Control N=443
-	n	%
Withdrawals	19	4.3
Consent Withdrawal, Not Due To An Adverse Event And/Or A Serious Adverse Event	8	1.8
Adverse Event Requiring Expedited Reporting	7	1.6
Lost To Follow-Up	2	0.5
Solicited Adverse Event	1	0.2
Other	1	0.2
Eliminations	27	6.1
Excluded Medication, Vaccine Or Device (1040)	3	0.7
Excluded Medication, Vaccine Or Device (C1040)	3	0.7
Study Treatment Not Administered Per Protocol (1070)	4	0.9
Administration Of Any Medication Forbidden By The Protocol (2040)	1	0.2
Intercurrent Medical Condition (2050)	2	0.5
Out Of Window Treatment Administration (2080)	2	0.5
Out Of Window Assessment For Immunogenicity (2090)	13	2.9
Out Of Window Assessment For Immunogenicity (C2090)	2	0.5
Missed Assessment (2100)	4	0.9
Number of participants included in per protocol set at visit 3	397	89.6

N = number of participants.

n/% = number / percentage of participants in a given category.

Elimination codes starting with 'c' indicate that the elimination is related to COVID-19.

Source: Table 14.1.1.3 from RSV OA=ADJ-007 Clinical Study Report.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoints

Immunogenicity results in terms of GMT, MGI, and GMT ratio for RSV-A and each of the four FLU-QIV strains are displayed in Table 27. The GMT ratio of RSV-A neutralizing antibodies between the Control group and the Co-Ad group at 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group and Day 61 for Control group) was 1.27 with 95% CI (1.12, 1.44). The GMT ratios of FLU-QIV A/H3N2, FLU-QIV A/H1N1, FLU-QIV B/Yamagata, and FLU-QIV B/Victoria strain antibodies between the Control group and the Co-Ad group at 1 month after the FLU-QIV dose (Day 31) were 1.17 with 95% CI (1.02, 1.35), 1.22 with 95% CI (1.03, 1.44), 1.17 with 95% CI (1.04, 1.32), and 1.10 with 95% CI (0.95, 1.26), respectively. Because the ULs of all 95% CIs were below the pre-defined threshold of 1.5, the co-primary immunogenicity objectives were met.

Table 27: Ratio of RSV-A Neutralizing antibody titers GMTs and Ratio of HI GMTs for each of the FLU-QIV strains between the Control group and (over) the Co-Ad group, 1 month after the RSVPreF3 OA investigational vaccine dose – PPS

-	-	-	Co-Ad	Co-Ad	Co-Ad	Co-Ad	Control	Control	Control	Control	Control vs Co-Ad	Control vs Co-Ad	Control vs Co-Ad
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI	GMR*	LL CI	UL CI
RSV-A nAb	PRE	GMT	435	1053.7	971.8	1142.5	411	951.0	873.9	1034.8	-	-	-
-	PI	GMT	427	10060.5	9126.0	11090.7	398	12255.0	11160.4	13456.9	1.27	1.12	1.44
-	-	MGI	427	9.61	8.70	10.61	397	12.95	11.75	14.28	-	-	-
FLU-QIV A/Hong Kong/2671/2019 H3N2 HI (1/DIL)	D1	GMT	435	61.4	53.8	69.9	437	63.3	55.7	71.9	-	-	-
-	D31	GMT	427	295.2	263.6	330.6	411	346.8	306.6	392.3	1.17	1.02	1.35
-	D31 / D1	MGI	427	4.81	4.22	5.48	410	5.50	4.81	6.29	-	-	-
FLU A/Victoria/2570/2019 H1N1 HI (1/DIL)	D1	GMT	435	20.0	18.0	22.3	437	19.9	17.8	22.2	-	-	-
-	D31	GMT	427	267.1	235.6	302.8	411	325.4	282.5	374.9	1.22	1.03	1.44
-	D31 / D1	MGI	427	13.36	11.58	15.42	410	16.25	14.08	18.76	-	-	-
FLU-QIV B/Phuket/3073/2013 Yamagata HI (1/DIL)	D1	GMT	435	10.4	9.5	11.3	411	10.8	9.9	11.7	-	-	-
-	D31	GMT	427	28.9	26.0	32.1	411	34.8	31.1	39.0	1.17	1.04	1.32
-	D31 / D1	MGI	427	2.82	2.55	3.12	410	3.22	2.90	3.58	-	-	-
FLU B/Washington/02/2019 Victoria HI (1/DIL)	D1	GMT	435	12.2	11.1	13.4	437	13.5	12.2	15.1	-	-	-
-	D31	GMT	427	41.6	37.1	46.6	411	47.9	41.9	54.8	1.10	0.95	1.26
-	D31 / D1	MGI	427	3.43	3.06	3.85	410	3.60	3.18	4.08	-	-	-

*Adjusted group ratio of GMT (Control group/Co-Ad group) based on an ANCOVA model applied to \log_{10} -transformed titers. The ANCOVA model included treatment group, age category (age at vaccination: 60-69, 70-79 or ≥ 80 years), country, and sex as fixed effects and pre-dose \log_{10} -transformed titer as covariate.

N = number of participants.

CI = 95% CI.

PRE = Pre-vaccination (D1 for Co-Ad group, D31 for Control group); PI = Post-vaccination (D31 for Co-Ad group, D61 for Control group).

Source: Adapted from Tables 2.5 and 2.7 from RSV OA=ADJ-007 Clinical Study Report.

6.3.11.2 Analyses of Secondary Endpoints

Immunogenicity results in terms of GMT, MGI, and GMT ratio for RSV-B neutralizing antibody are displayed in Table 28. The GMT ratio of RSV-B neutralizing antibodies between the Control group and the Co-Ad group at 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group and Day 61 for Control group) was 1.27 with 95% CI (1.08, 1.49).

Table 28: Ratio of RSV-B Neutralizing antibody titers GMTs between the Control group and (over) the Co-Ad group, 1 month after the RSVPreF3 OA investigational vaccine dose – PPS

-	-	-	Co-Ad	Co-Ad	Co-Ad	Co-Ad	Control	Control	Control	Control	Control vs Co-Ad	Control vs Co-Ad	Control vs Co-Ad
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI	GMR*	LL CI	UL CI
RSV-B nAb	PRE	GMT	214	1372.4	1232.1	1528.8	211	1570.9	1396.9	1766.7	-	-	-
-	POST	GMT	212	10518.6	9302.0	11894.3	205	14207.1	12526.5	16113.1	1.27	1.08	1.49
-	-	MGI	212	7.67	6.76	8.72	205	9.23	8.01	10.63	-	-	-

*Adjusted group ratio of GMT (Control group/Co-Ad group) based on an ANCOVA model applied to log₁₀-transformed titers. The ANCOVA model included treatment group, age category (age at vaccination: 60-69, 70-79 or ≥80 years), country, and sex as fixed effects and pre-dose log₁₀-transformed titer as covariate.

N = number of participants.

CI = 95% CI.

PRE = Pre-vaccination (D1 for Co-Ad group, D31 for Control group); PI = Post-vaccination (D31 for Co-Ad group, D61 for Control group).

Source: Adapted from Table 11.11 from RSV OA=ADJ-007 Clinical Study Report.

Immunogenicity results in terms of SCR and SPR based on the HI antibody are displayed in Table 29.

At Day 31 the percentages of participants achieving SCR based on HI antibody titers were 54.3%, 78.9%, 28.8%, and 35.6% in the Co-Ad group and 56.8%, 83.4%, 32.7%, and 35.9% in the Control group for the FLU-QIV A/H3N2, FLU-QIV A/H1N1, FLU-QIV B/Yamagata, and FLU-QIV B/Victoria strains, respectively.

At Day 1, the SPRs based on HI antibody titers were 70.8%, 35.4%, 14.3%, and 20.0% in the Co-Ad group and 70.2%, 34.4%, 14.9%, and 23.6% in the Control group for the FLU-QIV A/H3N2, FLU-QIV A/H1N1, FLU-QIV B/Yamagata, and FLU-QIV B/Victoria strains, respectively, due to previous exposure to the strains.

At Day 31 the SPRs based on HI antibody titers were 97.4%, 94.6%, 47.8%, and 59.3% in the Co-Ad group and 97.1%, 93.4%, 54.1%, and 61.2% in the Control group for the FLU-QIV A/H3N2, FLU-QIV A/H1N1, FLU-QIV B/Yamagata, and FLU-QIV B/Victoria strains, respectively.

Table 29: Percentages of participants with HI antibody titers equal to or above the cut-off for SCR and SPR for each of the 4 influenza strains – PPS

-	-	-	Co-Ad	Co-Ad	Co-Ad	Co-Ad	Control	Control	Control	Control
Antibody	Time point	-	N	%	LL CI	UL CI	N	%	LL CI	UL CI
FLU-QIV A/Hong Kong/2671/2019 H3N2 HI (1/DIL)	D31	SCR	427	54.3	49.5	59.1	410	56.8	51.9	61.7
-	D1	SPR	435	70.8	66.3	75.0	436	70.2	65.6	74.4
-	D31	SPR	427	97.4	95.4	98.7	410	97.1	94.9	98.5
FLU A/Victoria/2570/2019 H1N1 HI (1/DIL)	D31	SCR	427	78.9	74.7	82.7	410	83.4	79.5	86.9
-	D1	SPR	435	35.4	30.9	40.1	436	34.4	29.9	39.1
-	D31	SPR	427	94.6	92.0	96.6	410	93.4	90.6	95.6
FLU-QIV B/Phuket/3073/2013 Yamagata HI (1/DIL)	D31	SCR	427	28.8	24.6	33.4	410	32.7	28.2	37.5
-	D1	SPR	435	14.3	11.1	17.9	436	14.9	11.7	18.6
-	D31	SPR	427	47.8	43.0	52.6	410	54.1	49.2	59.0
FLU B/Washington/02/2019 Victoria HI (1/DIL)	D31	SCR	427	35.6	31.1	40.3	410	35.9	31.2	40.7
-	D1	SPR	435	20.0	16.3	24.1	436	23.6	19.7	27.9
-	D31	SPR	427	59.3	54.4	64.0	410	61.2	56.3	66.0

N = number of participants.

CI = 95% CI.

Source: Adapted from Tables 11.7 and 11.8 from RSV OA=ADJ-007 Clinical Study Report.

6.3.12 Analyses of Safety Endpoints

Percentages of subjects reporting solicited local and systemic reactions within 4 days after each dose are displayed in Tables 30 and 31, respectively.

For both the FLU and RSV doses, the percentages of subjects reporting solicited local reactions were generally slightly higher when the doses were co-administered at Visit 1 in the Co-Ad group than when the doses were sequentially administered at Visits 1 and 2 in the Control group. For the Co-Ad group, the percentages of subjects reporting solicited local reactions were generally higher after the RSV dose than the FLU dose at Visit 1. The most frequently reported solicited local reaction was pain (28.3% and 47.9% after the FLU and RSV doses, respectively, in the Co-Ad group at Visit 1; 20.5% after the FLU dose at Visit 1 and 39.1% after the RSV dose at Visit 2 in the Control group).

The percentages of subjects reporting solicited systemic reactions were generally higher in the Co-Ad group at Visit 1 than the Control group at either Visit 1 or Visit 2. For the Control group, the percentages of subjects reporting solicited systemic reactions were generally higher after the RSV dose at Visit 2 than after the FLU dose at Visit 1. The most frequently reported solicited systemic event was fatigue (22.4% in the Co-Ad group at Visit 1; 12.8% after the FLU dose at Visit 1 and 17.9% after the RSV dose at Visit 2 in the Control group).

Table 30: Percentage of subjects with solicited local events within 4 days following each dose – ES

Dose	Local Adverse Reactions	Co-Ad % (n) N = 438 for FLU at Visit 1 N = 438 for RSV at Visit 1	Control % (n) N = 438 for FLU at Visit 1 N = 419 for RSV at Visit 2
FLU at Visit 1	Pain	28.3% (124)	20.5% (90)
-	Pain, Grade 3	0.9% (4)	0
RSV at Visit 1	Pain	47.9% (210)	-
-	Pain, Grade 3	2.7% (12)	-
RSV at Visit 2	Pain	-	39.1% (164)
-	Pain, Grade 3	-	1.4% (6)
FLU at Visit 1	Erythema	1.1% (5)	0.5% (2)
-	Erythema, > 100 mm	0	0
RSV at Visit 1	Erythema	4.1% (18)	-
-	Erythema, > 100 mm	0	-
RSV at Visit 2	Erythema	-	2.1% (9)
-	Erythema, > 100 mm	-	0
FLU at Visit 1	Swelling	1.4% (6)	0.7% (3)
-	Swelling > 100 mm	0	0
RSV at Visit 1	Swelling	3.2% (14)	-
-	Swelling > 100 mm	0	-
RSV at Visit 2	Swelling	-	1.0% (4)
-	Swelling > 100 mm	-	0

n/% = number/percentage of participants presenting at least one type of event.

N = number of participants who completed the diary card.

Grade 3 pain: Defined as significant pain at rest and prevents normal everyday activities.

Source: Adapted from Table 12.1 from RSV OA=ADJ-007 Clinical Study Report.

Table 31: Percentage of subjects with solicited systemic events within 4 days following each dose and overall – ES

Dose	Systemic Adverse Reactions	Co-Ad % (n) N = 438 for both FLU and RSV at Visit 1	Control % (n) N = 438 for FLU at Visit 1 N = 419 for RSV at Visit 2
Visit 1	Fatigue	22.4% (98)	12.8% (56)
-	Fatigue, Grade 3	0.9% (4)	0.5% (2)
RSV at Visit 2	Fatigue	-	17.9% (75)
-	Fatigue, Grade 3	-	1.0% (4)
Visit 1	Myalgia	22.1% (97)	9.4% (41)
-	Myalgia, Grade 3	0.7% (3)	0
RSV at Visit 2	Myalgia	-	19.6% (82)
-	Myalgia, Grade 3	-	1.2% (5)
Visit 1	Headache	21.7% (95)	12.8% (56)
-	Headache, Grade 3	0.5% (2)	0.5% (2)
RSV at Visit 2	Headache	-	16.2% (68)
-	Headache, Grade 3	-	1.0% (4)
Visit 1	Arthralgia	16.2% (71)	4.8% (21)
-	Arthralgia, Grade 3	0.7% (3)	0
RSV at Visit 2	Arthralgia	-	11.2% (47)
-	Arthralgia, Grade 3	-	0.7% (3)
Visit 1	Fever	2.5% (11)	0.7% (3)
-	Fever, Grade 3	0.7% (3)	0
RSV at Visit 2	Fever	-	1.0% (4)
-	Fever, Grade 3	-	0.2% (1)

For each dose:

n/% = number/percentage of subjects presenting at least one type of symptom.

N = number of participants who completed the diary card.

Grade 3 fatigue, myalgia, headache, arthralgia: Defined as preventing normal activity.

Fever defined as a temperature $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ by any route (oral, axillary, or tympanic); Grade 3 fever defined as $> 39.0^{\circ}\text{C}/102.2^{\circ}\text{F}$.

Source: Adapted from Table 12.2 from RSV OA=ADJ-007 Clinical Study Report.

Percentages of subjects reporting unsolicited AEs after each dose are displayed in Table 32. Overall, no substantial differences were observed between the treatment groups with respect to unsolicited AEs across categories. There were two subjects in the Co-Ad group who reported both a related SAE and pIMD up to the DLP. In addition to these subjects, there was one participant in the Co-Ad group and one participant in the Control group who reported a related pIMD up to the DLP.

A total of 12 deaths (4 in the Co-Ad group and 8 in the Control group) were reported up to the DLP. Of these, 1 event of acute disseminated encephalomyelitis in the Co-Ad group was considered by the investigator to be related to the study intervention FLU-QIV.

Table 32: Summary of subjects by unsolicited adverse event category – ES

-	Co-Ad N = 442	Co-Ad N = 442	Co-Ad N = 442	Co-Ad N = 442	Control N = 443	Control N = 443	Control N = 443	Control N = 443
-	n	%	LL CI	UL CI	n	%	LL CI	UL CI
At least one unsolicited adverse event within 30 days	83	18.8	15.2	22.7	105	23.7	19.8	27.9
At least one related unsolicited adverse event within 30 days	26	5.9	3.9	8.5	15	3.4	1.9	5.5
At least one grade 3 unsolicited adverse event within 30 days	13	2.9	1.6	5.0	15	3.4	1.9	5.5
At least one related grade 3 unsolicited adverse event within 30 days	1	0.2	0.0	1.3	2	0.5	0.1	1.6
At least one medically attended unsolicited adverse event within 30 days	35	7.9	5.6	10.8	49	11.1	8.3	14.4
At least one serious unsolicited adverse event during the entire study periods	15	3.4	1.9	5.5	20	4.5	2.8	6.9
At least one related serious unsolicited adverse event during the entire study period	2	0.5	0.1	1.6	0	0	0	0.8
At least one fatal unsolicited adverse event during the entire study period	4	0.9	0.2	2.3	8	1.8	0.8	3.5
At least one pIMD during the entire study period	5	1.1	0.4	2.6	1	0.2	0.0	1.3
At least one related pIMD during the entire study period	3	0.7	0.1	2.0	1	0.2	0.0	1.3

N = number of subjects.

n/% = number/percentage of subjects presenting at least one type of adverse event.

CI = 95% CI.

Safety DLP = 08FEB2022.

Source: Table 12.3 from RSV OA=ADJ-007 Clinical Study Report.

6.4 Clinical Study RSV OA=ADJ-009

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

Dates:

1. Study initiation date (First Subject First Visit): 1 October 2021
2. DLP for analysis: 9 March 2022

6.4.1 Objectives

Primary Immunogenicity Objective:

1. To demonstrate the lot-to-lot consistency of 3 lots of RSVPreF3 OA investigational vaccine in terms of immunogenicity.

Safety Objective:

1. To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine.

6.4.2 Design Overview

Subjects were randomized with a ratio of 1:1:1 to 1 of 3 lots of RSVPreF3 OA investigational vaccine. The randomization algorithm used a minimization procedure, where both age category (60-69, 70-79 or ≥ 80 years) and center were included as minimization factors.

For immunogenicity, blood samples were collected from all subjects at pre-vaccination (Day 1) and 1 month post-vaccination (Day 31). For safety, solicited AEs and unsolicited AEs were collected for four and 30 days after vaccination, respectively, while both SAEs and pIMDs were collected for six months after vaccination.

6.4.3 Population

Subjects ≥ 60 YOA were enrolled.

6.4.4 Study Treatments or Agents Mandated by the Protocol

The vaccine formulation evaluated in this study was 120 mcg of RSVPreF3 OA antigen adjuvanted with AS01E per 0.5 mL dose.

6.4.6 Sites and Centers

The study was conducted at 19 centers in 3 countries: 7 in Canada, 3 in Sweden, and 9 in the United States.

6.4.7 Surveillance/Monitoring

Please refer to the clinical review.

6.4.8 Endpoints and Study Success Criteria

Primary Immunogenicity Endpoints:

1. RSVPreF3-specific immunoglobulin G (IgG) antibody concentrations expressed as group GMC ratio at 30 days post-vaccination (Day 31), with the following success criterion:
 - The 2-sided 95% CI of the group GMC ratios between each pair of the 3 lots (RSVPreF3 OA investigational vaccine lot divided by another RSVPreF3 OA investigational vaccine lot) is within the pre-defined thresholds of [0.67, 1.5].

Safety Endpoints:

- Percentage of participants reporting each solicited event with onset within 4 days after study intervention administration (i.e., the day of vaccination and 3 subsequent days).
- Percentage of participants reporting unsolicited adverse events (AE) within 30 days after study intervention administration (i.e., the day of vaccination and 29 subsequent days).
- Percentage of participants reporting serious AEs (SAEs) after study intervention administration (Day 1) up to study end (6 months after vaccination).
- Percentage of participants reporting potential immune-mediated diseases (pIMDs) after study intervention administration (Day 1) up to study end (6 months after vaccination).

6.4.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

For the primary immunogenicity analysis, ANCOVA models were fit to log₁₀-transformed antibody concentrations with covariates for treatment group, age category (60-69, 70-79 or ≥80 years), and pre-dose log₁₀-transformed concentration. Missing data were not replaced. Concentrations below the technical assay cut-off were replaced by half the technical assay cut-off; concentrations above the ULOQ were replaced by the ULOQ.

The immunogenicity analyses were performed on the PPS, defined as:

- PPS: All eligible 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.

For the secondary immunogenicity analysis, at each time point that blood samples were collected the following analyses were performed:

- Percentages of subjects with antibody (Ab) concentrations above the LLOQ and their 95% CIs
- Geometric mean concentrations (GMCs) and their 95% CIs
- Distribution of Ab concentrations using reverse cumulative curves
- Mean geometric increases (MGIs) and their 95% CIs

Analysis of Safety

All safety data were summarized descriptively. Safety analyses were performed on the ES.

Multiplicity Adjustment

For the primary immunogenicity endpoints, demonstration of lot-to-lot consistency required that the two-sided 95% CIs fall within [0.67, 1.5] for all pairwise comparisons of GMCs. Thus, no multiplicity adjustments were necessary.

Sample Size Determination

Assuming between-group mean differences of 0, standard deviations of 0.45 for log₁₀-transformed concentration, and a dropout rate of 10%, a sample size of 750 (250 per group) subjects was calculated to yield 91% global power for demonstrating lot-to-lot consistency under the [0.67, 1.5] equivalence margins. A SD of 0.45 was assumed based on the results from the RSV OA=ADJ-002 study.

6.4.10 Study Population and Disposition

A total of 770 subjects were included in the Enrolled Set, of which 758 were randomized and 757 (251 in Group 1, 253 in Group 2, and 253 in Group 3) were included in the ES. Table 33 displays the demographics of the ES. Overall, no major imbalances were observed between the three lots. Additionally, the demographics of the PPS were similar to those of the ES.

Table 33: Summary of demography and baseline characteristics – ES

-	Group 1 N=251	Group 1 N=251	Group 2 N=253	Group 2 N=253	Group 3 N=253	Group 3 N=253	Total N=757	Total N=757
-	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years) at first vaccination	-	-	-	-	-	-	-	-
n	251	-	253	-	253	-	757	-
Mean	69.7	-	70.1	-	69.9	-	69.9	-
Standard Deviation	6.6	-	6.6	-	6.6	-	6.6	-
Median	69.0	-	69.0	-	69.0	-	69.0	-
Minimum	60	-	60	-	60	-	60	-
Maximum	90	-	93	-	88	-	93	-
Age group	-	-	-	-	-	-	-	-
≥ 65 YOA	191	76.1	194	76.7	195	77.1	580	76.6
≥ 70 YOA	114	45.4	116	45.8	117	46.2	347	45.8
≥ 80 YOA	24	9.6	26	10.3	26	10.3	76	10.0
60-69 YOA	137	54.6	137	54.2	136	53.8	410	54.2
70-79 YOA	90	35.9	90	35.6	91	36.0	271	35.8
Country	-	-	-	-	-	-	-	-
Canada	105	41.8	105	41.5	109	43.1	319	42.1
Sweden	83	33.1	83	32.8	83	32.8	249	32.9
United States	63	25.1	65	25.7	61	24.1	189	25.0
Sex	-	-	-	-	-	-	-	-
Male	120	47.8	122	48.2	144	56.9	386	51.0
Female	131	52.2	131	51.8	109	43.1	371	49.0
Ethnicity	-	-	-	-	-	-	-	-
Hispanic Or Latino	7	2.8	9	3.6	10	4.0	26	3.4
Not Hispanic Or Latino	244	97.2	244	96.4	243	96.0	731	96.6
Race	-	-	-	-	-	-	-	-
American Indian Or Alaska Native	0	0	0	0	0	0	0	0
Asian	6	2.4	10	4.0	10	4.0	26	3.4
Black Or African American	6	2.4	3	1.2	4	1.6	13	1.7
Native Hawaiian Or Other Pacific Islander	0	0	1	0.4	0	0	1	0.1
White	231	92.0	231	91.3	233	92.1	695	91.8
Other	8	3.2	8	3.2	6	2.4	22	2.9

N = number of subjects.

n/% = number / percentage of subjects in a given category.
Age computed based on incomplete date of birth (only year was available).
Source: Table 11.1 from RSV OA=ADJ-009 Clinical Study Report.

Participant dispositions from the ES to the PPS are presented in Table 34. A total of n = 708 (234 in Group 1, 237 in Group 2, and 237 in Group 3) participants were included in the PPS.

Table 34: Summary of participant disposition from Exposed Set to Per Protocol Set

-	Group 1 N=251	Group 1 N=251	Group 2 N=253	Group 2 N=253	Group 3 N=253	Group 3 N=253	Total N=757	Total N=757
-	n	%	n	%	n	%	n	%
Withdrawals	1	0.4	1	0.4	1	0.4	3	0.4
Lost To Follow-Up	1	0.4	1	0.4	0	0	2	0.3
Adverse Event Requiring Expedited Reporting	0	0	0	0	1	0.4	1	0.1
Eliminations	16	6.4	15	5.9	15	5.9	46	6.1
Excluded Medication, Vaccine Or Device (1040)	4	1.6	3	1.2	4	1.6	11	1.5
Excluded Medication, Vaccine Or Device (C1040)	4	1.6	3	1.2	4	1.6	11	1.5
Randomization Procedures (1050)	0	0	1	0.4	0	0	1	0.1
Intercurrent Medical Condition (2050)	0	0	1	0.4	0	0	1	0.1
Out Of Window Assessment For Immunogenicity (2090)	6	2.4	6	2.4	4	1.6	16	2.1
Out Of Window Assessment For Immunogenicity (C2090)	1	0.4	0	0	2	0.8	3	0.4
Missed Assessment (2100)	2	0.8	1	0.4	1	0.4	4	0.5
Number of participants included in per protocol set at visit 2	234	93.2	237	93.7	237	93.7	708	93.5

N = number of participants.

n/% = number / percentage of participants in a given category.

Elimination codes starting with 'c' indicate that the elimination is related to COVID-19.

Source: Table 14.1.1.2 from RSV OA=ADJ-009 Clinical Study Report.

6.4.11 Analyses of Primary Immunogenicity Endpoints

Immunogenicity results of GMC ratio are displayed in Tables 35 – 37 for the three pairwise comparisons, respectively. The ratios of RSVPreF3-specific IgG antibody GMCs between Group 1 and Group 2, Group 1 and Group 3, and Group 2 and Group 3 at 1 month post-vaccination were 1.06 with 95% CI (0.94, 1.21), 0.92 with 95% CI (0.81, 1.04), and 0.87 with 95% CI (0.77, 0.99), respectively. Because each pair of LLs and ULs of the 95% CIs was within the pre-defined equivalence margins of [0.67, 1.5], the primary immunogenicity objective was met.

Table 35: Ratio of RSVPreF3 OA IgG antibody concentrations GMCs between RSVPreF3 Group 1 and (over) RSVPreF3 Group 2, 1 month after the RSVPreF3 OA investigational vaccine dose – PPS

-	-	-	Group 1	Group 1	Group 1	Group 1	Group 2	Group 2	Group 2	Group 2	Group 1 vs Group 2	Group 1 vs Group 2	Group 1 vs Group 2
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI	GMR*	LL CI	UL CI
RSVPreF3 OA IgG tot	POST	GMC	234	86039.9	78541.5	94254.3	237	80518.0	73150.0	88628.2	1.06	0.94	1.21

*Comparison is done using the adjusted group ratio of GMC (ANCOVA model applied to log₁₀-transformed titers). The ANCOVA model includes both treatment group and age category (age at vaccination: 60-69, 70-79 or ≥ 80 years) as fixed effects and pre-dose log₁₀-transformed titer as covariate.

N = number of participants.

CI = 95% CI.

Source: Table 11.3 from RSV OA=ADJ-009 Clinical Study Report.

Table 36: Ratio of RSVPreF3 OA IgG antibody concentrations GMCs between RSVPreF3 Group 1 and (over) RSVPreF3 Group 3, 1 month after the RSVPreF3 OA investigational vaccine dose – PPS

-	-	-	Group 1	Group 1	Group 1	Group 1	Group 3	Group 3	Group 3	Group 3	Group 1 vs Group 3	Group 1 vs Group 3	Group 1 vs Group 3
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI	GMR*	LL CI	UL CI
RSVPreF3 OA IgG tot	POST	GMC	234	86039.9	78541.5	94254.3	237	94260.9	86042.2	103264.7	0.92	0.81	1.04

*Comparison is done using the adjusted group ratio of GMC (ANCOVA model applied to log₁₀-transformed titers). The ANCOVA model includes both treatment group and age category (age at vaccination: 60-69, 70-79 or ≥ 80 years) as fixed effects and pre-dose log₁₀-transformed titer as covariate.

N = number of participants.

CI = 95% CI.

Source: Table 11.4 from RSV OA=ADJ-009 Clinical Study Report.

Table 37: Ratio of RSVPreF3 OA IgG antibody concentrations GMCs between RSVPreF3 Group 2 and (over) RSVPreF3 Group 3, 1 month after the RSVPreF3 OA investigational vaccine dose – PPS

-	-	-	Group 2	Group 2	Group 2	Group 2	Group 3	Group 3	Group 3	Group 3	Group 2 vs Group 3	Group 2 vs Group 3	Group 2 vs Group 3
Antibody	Time point	-	N	Value	LL CI	UL CI	N	Value	LL CI	UL CI	GMR*	LL CI	UL CI
RSVPreF3 OA IgG tot	POST	GMC	237	80518.0	73150.0	88628.2	237	94260.9	86042.2	103264.7	0.87	0.77	0.99

*Comparison is done using the adjusted group ratio of GMC (ANCOVA model applied to log₁₀-transformed titers). The ANCOVA model includes both treatment group and age category (age at vaccination: 60-69, 70-79 or ≥ 80 years) as fixed effects and pre-dose log₁₀-transformed titer as covariate.

N = number of participants.

CI = 95% CI.

Source: Table 11.5 from RSV OA=ADJ-009 Clinical Study Report.

6.4.12 Analyses of Safety Endpoints

Percentages of subjects reporting solicited local and systemic reactions within 4 days after the study dose are displayed in Table 38. Across the three groups, the percentages of subjects reporting solicited local and systemic reactions were generally similar. The most frequently reported solicited local reaction was pain (58.2%, 65.7%, and 62.7% in RSVPreF3 Groups 1 – 3, respectively), while the most frequently reported solicited systemic event was myalgia (31.3%, 34.3%, and 33.7% in RSVPreF3 Groups 1 – 3, respectively).

Table 38: Percentage of subjects with solicited local and systemic events within 4 days following the study dose – ES

Local Adverse Reactions	RSVPreF3 Group 1 % (n) N = 249	RSVPreF3 Group 2 % (n) N = 251	RSVPreF3 Group 3 % (n) N = 252
Pain	58.2% (145)	65.7% (165)	62.7% (158)
Pain, Grade 3	0.4% (1)	0.8% (2)	0.8% (2)
Erythema	13.3% (33)	12.0% (30)	14.7% (37)
Erythema, > 100 mm	0	0.4% (1)	0.8% (2)
Swelling	8.0% (20)	8.0% (20)	9.1% (23)
Swelling > 100 mm	0.4% (1)	0	0.8% (2)
Systemic Adverse Reactions	-	-	-
Fatigue	28.1% (70)	25.9% (65)	27.8% (70)
Fatigue, Grade 3	2.0% (5)	1.2% (3)	1.6% (4)
Myalgia	31.3% (78)	34.3% (86)	33.7% (85)
Myalgia, Grade 3	0	1.6% (4)	0.8% (2)
Headache	25.7% (64)	23.5% (59)	22.2% (56)
Headache, Grade 3	0.4% (1)	0.4% (1)	1.2% (3)
Arthralgia	13.3% (33)	13.9% (35)	14.7% (37)
Arthralgia, Grade 3	0	1.2% (3)	0.4% (1)
Fever	2.0% (5)	1.6% (4)	2.8% (7)
Fever, Grade 3	0.4% (1)	0	0

n/% = number/percentage of participants presenting at least one type of event.

N = number of participants who completed the diary card.

Grade 3 pain: defined as significant pain at rest and prevents normal everyday activities.

Grade 3 fatigue, myalgia, headache, arthralgia: Defined as preventing normal activity.

Fever defined as a temperature $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ by any route (oral, axillary, or tympanic); Grade 3 fever defined as $> 39.0^{\circ}\text{C}/102.2^{\circ}\text{F}$.

Source: Adapted from Tables 12.4 and 12.5 from RSV OA=ADJ-009 Clinical Study Report.

Percentages of subjects reporting unsolicited AEs after the study dose are displayed in Table 39. Overall, no substantial differences were observed between the treatment groups with respect to the reporting of unsolicited AEs. There was one participant in RSVPreF3 Group 3 who reported a related pIMD up to the DLP. A total of 3 deaths (0, 2, and 1 in RSVPreF3 Groups 1 – 3, respectively) were reported up to the DLP, but none were considered related to the study treatment by investigator.

Table 39: Summary of subjects by unsolicited adverse event category – ES

-	Group 1 N=251	Group 1 N=251	Group 1 N=251	Group 1 N=251	Group 2 N=253	Group 2 N=253	Group 2 N=253	Group 2 N=253	Group 3 N=253	Group 3 N=253	Group 3 N=253	Group 3 N=253
-	n	%	LL CI	UL CI	n	%	LL CI	UL CI	n	%	LL CI	UL CI
At least one unsolicited adverse event within 30 days after vaccination	36	14.3	10.3	19.3	37	14.6	10.5	19.6	33	13.0	9.2	17.8
At least one related unsolicited adverse event within 30 days after vaccination	11	4.4	2.2	7.7	15	5.9	3.4	9.6	12	4.7	2.5	8.1
At least one grade 3 unsolicited adverse event within 30 days after vaccination	5	2.0	0.6	4.6	6	2.4	0.9	5.1	4	1.6	0.4	4.0
At least one grade 3 related unsolicited adverse event within 30 days after vaccination	1	0.4	0.0	2.2	3	1.2	0.2	3.4	0	0	0	1.4
At least one medically attended unsolicited adverse event within 30 days after vaccination	12	4.8	2.5	8.2	11	4.3	2.2	7.6	11	4.3	2.2	7.6
At least one serious unsolicited adverse event up to DLP	3	1.2	0.2	3.5	2	0.8	0.1	2.8	2	0.8	0.1	2.8
At least one related serious unsolicited adverse event up to DLP	0	0	0	1.5	0	0	0	1.4	0	0	0	1.4
At least one fatal unsolicited adverse event up to DLP	0	0	0	1.5	2	0.8	0.1	2.8	1	0.4	0.0	2.2
At least one pIMD unsolicited adverse event up to DLP	0	0	0	1.5	0	0	0	1.4	2	0.8	0.1	2.8
At least one related pIMD unsolicited adverse event up to DLP	0	0	0	1.5	0	0	0	1.4	1	0.4	0.0	2.2

N = number of subjects.

n/% = number/percentage of subjects presenting at least one type of adverse event.

CI = 95% CI.

Safety DLP = 09MAR2022.

Source: Table 12.6 from RSV OA=ADJ-009 Clinical Study Report.

7. Integrated Overview of Efficacy

An Integrated Summary of Efficacy (ISE) was submitted, but efficacy (Study RSV OA=ADJ-006 only) and immunogenicity data were presented by individual study. No pooled immunogenicity analyses were conducted. Therefore, all efficacy and immunogenicity analyses were reviewed for the individual studies in Section 6 and no additional review of the ISE is performed.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

Safety data were summarized descriptively according to the study vaccine received. The following safety analyses were conducted:

1. Solicited AEs were analyzed individually by study, summarized over the categories of any, local, and systemic solicited AE.
 - All groups for each study were included except for the Co-Ad group from Study RSV OA=ADJ-007.
 - The safety analysis set for Study RSV OA=ADJ-006 was the SSS and the ES for all other studies.
2. Unsolicited AEs were pooled across studies.
 - All groups for each study were included except for the Placebo group from Study RSV OA=ADJ-006 and the Co-Ad group from Study RSV OA=ADJ-007.
 - The safety analysis set for each study was the ES.

8.2 Safety Database

Data from Studies RSV OA=ADJ-004, RSV OA=ADJ-006, RSV OA=ADJ-007, and RSV OA=ADJ-009 were individually included for the Solicited AEs and pooled for the Unsolicited AEs.

8.3 Pooling of Data Across Studies/Clinical Trials

One pooled dataset was generated for the Unsolicited AEs:

1. RSVPreF3: All subjects in the RSV OA=ADJ-004, RSV OA=ADJ-006, RSV OA=ADJ-007, and RSV OA=ADJ-009 studies who received RSVPreF3 and provided unsolicited AE data in the ES.

The study designs were similar with one exception: subjects received RSVPreF3 at Day 31 in the Control group of Study RSV OA=ADJ-007 instead of Day 1 in the RSVPreF3 groups for all other studies.

8.4 Safety Results

Tables 40 – 42 display solicited AE data within 4 days after the study dose across Studies RSV OA=ADJ-004, RSV OA=ADJ-006, RSV OA=ADJ-007, and RSV OA=ADJ-009. Across studies, the occurrence of both solicited local and systemic reactions was largely consistent among subjects who received RSVPreF3, except that subjects in the Control group of Study RSV OA=ADJ-007 reported relatively fewer local and systemic reactions compared to other groups that received RSVPreF3 in other studies.

Table 40: RSV OA=ADJ-006: Summary of adverse events (solicited only) within 4 days following vaccination — SSS

-	-	RSVPreF3	RSVPreF3	RSVPreF3	RSVPreF3	Placebo	Placebo	Placebo	Placebo
-	-	n	%	LL CI	UL CI	n	%	LL CI	UL CI
Vaccination*	N	879	-	-	-	878	-	-	-
-	Any adverse event	632	71.9	68.8	74.9	245	27.9	25.0	31.0
-	Local adverse event	547	62.2	58.9	65.4	88	10.0	8.1	12.2
-	Systemic adverse event	434	49.4	46.0	52.7	204	23.2	20.5	26.2

*Vaccination at Visit 1.

N = number of participants with diary card.

n/%= number/percentage of participants presenting at least one type of symptom.

CI = 95% CI.

Source: Table 9 from Integrated Summary of Safety.

Table 41: RSV OA=ADJ-004 and -007: Summary of adverse events (solicited only) within 4 days following vaccination – ES

-	-	RSV OA=ADJ-004	-	-	-	RSV OA=ADJ-007	-	-	-
-	-	Total	Total	Total	Total	Control	Control	Control	Control
-	-	n	%	LL CI	UL CI	n	%	LL CI	UL CI
RSV Dosing*	N	1646	-	-	-	419	-	-	-
-	Any adverse event	1217	73.9	71.7	76.0	212	50.6	45.7	55.5
-	Local adverse event	1024	62.2	59.8	64.6	167	39.9	35.1	44.7
-	Systemic adverse event	815	49.5	47.1	52.0	143	34.1	29.6	38.9

*RSV dosing at Visit 1 in RSV OA=ADJ-004 and Visit 2 in RSV OA=ADJ-007 study.

N = number of participants with diary card.

n/%= number/percentage of participants presenting at least one type of symptom.

CI = 95% CI.

Source: Adapted from Table 10 from Integrated Summary of Safety.

Table 42: RSV OA=ADJ-009: Summary of adverse events (solicited only) within 4 days following vaccination – ES

-	-	Group 1	Group 1	Group 1	Group 1	Group 2	Group 2	Group 2	Group 2	Group 3	Group 3	Group 3	Group 3
-	-	n	%	LL CI	UL CI	n	%	LL CI	UL CI	n	%	LL CI	UL CI
RSV Dosing*	N	249	-	-	-	251	-	-	-	252	-	-	-
-	Any adverse event	175	70.3	64.2	75.9	189	75.3	69.5	80.5	187	74.2	68.3	79.5
-	Local adverse event	150	60.2	53.9	66.4	168	66.9	60.7	72.7	162	64.3	58.0	70.2
-	Systemic adverse event	113	45.4	39.1	51.8	127	50.6	44.2	56.9	119	47.2	40.9	53.6

*RSV dosing at Visit 1.

N = number of participants with diary card.

n/%= number/percentage of participants presenting at least one type of symptom.

CI = 95% CI.

Source: Adapted from Table 10 from Integrated Summary of Safety.

Table 43 displays the aggregate unsolicited AE data after the study dose across Studies RSV OA=ADJ-004, RSV OA=ADJ-006, RSV OA=ADJ-007, and RSV OA=ADJ-009. Overall, 0.1%, 0.1%, and 0.4% of subjects reported at least one related SAE, related pIMD, and death, respectively, up to the respective DLPs. One death was considered related to the RSVPreF3 OA investigational vaccine by the investigator.

Table 43: RSV OA=ADJ-004, -006, -007 and -009: Summary of subjects by adverse event category – ES

-	RSVPreF3 N=15303	RSVPreF3 N=15303	RSVPreF3 N=15303	RSVPreF3 N=15303	RSVPreF3 N=15303
-	<i>n</i>	<i>n</i>	%	LL CI	UL CI
Any medically attended unsolicited adverse event with onset within 30 days following vaccination	1060	834	5.4	5.1	5.8
Any serious adverse event with onset within 30 days following vaccination	126	114	0.7	0.6	0.9
Any serious adverse event up to DLP	902	701	4.6	4.3	4.9
Any related serious adverse event with onset within 30 days following vaccination	6	6	0.0	0.0	0.1
Any related serious adverse event up to DLP	13	11	0.1	0.0	0.1
Any pIMD with onset within 30 days following vaccination	15	15	0.1	0.1	0.2
Any pIMD up to DLP	56	55	0.4	0.3	0.5
Any related pIMD with onset within 30 days following vaccination	4	4	0.0	0.0	0.1
Any related pIMD up to DLP	9	9	0.1	0.0	0.1
Any fatal serious adverse event with onset within 30 days following vaccination	14	14	0.1	0.1	0.2
Any fatal serious adverse event up to DLP	72	63	0.4	0.3	0.5

N = number of subjects.

n = number of events reported.

n/% = number/percentage of subjects presenting at least one type of adverse event.

CI = 95% CI.

Safety DLP = For RSV OA=ADJ-004: 11FEB2022; for RSV OA=ADJ-006: 30APR2022; for RSV OA=ADJ-007: 08FEB2022; for RSV OA=ADJ-009: 09MAR2022.

Source: Table 14.3.1.8 from Statistical Report for the Aggregated Safety Analysis.

8.5 Additional Safety Evaluations

Not applicable.

8.6 Safety Conclusions

Across studies, the occurrence of both solicited local and systemic reactions was largely consistent among subjects who received RSVPreF3, except that subjects in the Control group of Study RSV OA=ADJ-007 reported relatively fewer local and systemic reactions compared to other groups that received RSVPreF3 in other studies. Overall, 0.1%, 0.1%, and 0.4% of subjects who received RSVPreF3 reported at least one related SAE, related pIMD, and death, respectively, up to the respective DLPs. One death was considered related to the RSVPreF3 OA investigational vaccine by the investigator. The ISS did not identify any novel safety concerns.

9. Additional Statistical Issues

There are no additional statistical issues.

10. Conclusions

10.1 Statistical Issues and Collective Evidence

Efficacy, immunogenicity, and safety of the RSVPreF3 OA investigational vaccine has been evaluated across four Phase 3 clinical studies: RSV OA=ADJ-004, RSV OA=ADJ-006, RSV OA=ADJ-007, and RSV OA=ADJ-009.

Efficacy of the RSVPreF3 OA investigational vaccine was demonstrated in Study RSV OA=ADJ-006. At the interim analysis, 7 and 40 cases were reported in the RSVPreF3 OA and Placebo groups, respectively, resulting in an estimated VE of 82.58% with 2-sided 96.95% CI (57.89%, 94.08%). The alpha value of 3.05% for the 2-sided CI was derived from a Wang-Tsiatis stopping boundary with $\Delta = 0.3$ and information fraction = 0.80. Because the LL of the 2-sided CI was above the pre-defined threshold of 20%, the success criterion for the primary efficacy objective was met. Analyses of VE by both age group and RSV subtype also showed consistently high VEs around 80%, except for VE in subjects ≥ 80 YOA where there were only a small number of cases to conclude definitively.

Non-inferiority of the immune response induced by the RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV compared to when the two vaccines were administered sequentially was demonstrated in Study RSV OA=ADJ-007. The GMT ratio of RSV-A neutralizing antibodies between the Control group (sequential administration) and the Co-Ad group at 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group and Day 61 for Control group) was 1.27 (95% CI: 1.12, 1.44). The GMT ratios of FLU-QIV A/H3N2, FLU-QIV A/H1N1, FLU-QIV B/Yamagata, and FLU-QIV B/Victoria strain antibodies between the Control group and

the Co-Ad group at 1 month after the FLU-QIV dose (Day 31) were 1.17 with 95% CI (1.02, 1.35), 1.22 with 95% CI (1.03, 1.44), 1.17 with 95% CI (1.04, 1.32), and 1.10 with 95% CI (0.95, 1.26), respectively. Because the ULs of all 95% CIs were below the pre-defined non-inferiority margin of 1.5, the success criteria of the co-primary immunogenicity objectives were met.

Lot-to-lot consistency of the RSVPreF3 OA investigational vaccine was demonstrated in Study RSV OA=ADJ-009. The ratios of RSVPreF3-specific IgG antibody GMCs between Group 1 and Group 2, Group 1 and Group 3, and Group 2 and Group 3 at 1 month post-vaccination were 1.06 with 95% CI (0.94, 1.21), 0.92 with 95% CI (0.81, 1.04), and 0.87 with 95% CI (0.77, 0.99) respectively. Because all 95% CIs were within the pre-defined equivalence margins of [0.67, 1.5], the success criterion of the primary immunogenicity objective was met.

Based on safety data collected from Study RSV OA=ADJ-006, compared to placebo, the RSVPreF3 OA investigational vaccine elicited higher rates of solicited local and systemic reactions within 4 days after the study dose as well as higher rates of unsolicited AEs. No substantial differences in the rates of related SAEs and pIMDs were observed between the RSVPreF3 OA investigational vaccine and placebo groups.

Based on safety data collected from Study RSV OA=ADJ-007, when administered with FLU-QIV, the RSVPreF3 OA investigational vaccine elicited higher rates of solicited local and systemic reactions within 4 days after the study dose but generally similar rates of unsolicited AEs than when administered alone. No substantial differences in the rates of related SAEs and pIMDs were observed between the RSVPreF3 OA investigational vaccine when administered with FLU-QIV than when administered alone. No deaths occurred that were considered related to the RSVPreF3 OA investigational vaccine when administered with FLU-QIV.

The safety data collected from Studies RSV OA=ADJ-004 and RSV OA=ADJ-009 were generally consistent with the safety data collected from the RSVPreF3 group in Study RSV OA=ADJ-006 and the Control group from Study RSV OA=ADJ-007 in terms of both solicited local and systemic reactions and unsolicited AEs.

In Study RSV OA=ADJ-004, there was one participant in the RSV Flexible Revaccination group who reported a case of Guillain-Barré Syndrome (GBS), which was recorded as both a related SAE and pIMD. The VRBPAC meeting held on March 1, 2023 identified the one case of GBS as a cause for concern regarding the safety of the RSVPreF3 OA investigational vaccine.

Across the four Phase 3 studies, one death was considered related to the RSVPreF3 OA investigational vaccine by the investigator.

10.2 Conclusions and Recommendations

No major statistical issues have been identified. All pre-specified efficacy and immunogenicity objectives across the Phase 3 studies have been met. The efficacy and immunogenicity data thus support licensure of the RSVPreF3 OA investigational vaccine.