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RSVPreF3 OA

SPONSOR BRIEFING DOCUMENT

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

MEETING DATE: FEBRUARY 28-MARCH 1, 2023

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ADEM	Acute Disseminated Encephalomyelitis
ANOVA	Analysis of variance
ARI	Acute Respiratory Infection
$AS01_B$	Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21)
$AS01_E$	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
BLA	Biologics License Application
CD4	Cluster of differentiation marker 4
CD8	Cluster of differentiation marker 8
CD40L	Cluster of differentiation marker 40 ligand
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DLP	Data Lock Point
ED_{60}	Estimated Dilution 60: serum dilution giving a 60% reduction of signal compared to a control without serum
ELISA	Enzyme-Linked Immunosorbent Assay
EQ-5D	EuroQoL 5-dimension Health Questionnaire
ES	Exposed Set
F	Fusion
FDA	Food and Drug Administration, US
FLU-PRO	InFLUenza Patient-Reported Outcome
FLU-QIV	Influenza Quadrivalent Inactivated Vaccine
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline Biologicals SA
HI	Hemagglutination Inhibition
HLT	High Level Term
HRP	Horseradish Peroxidase
HRQoL	Health-Related Quality of Life
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL	Interleukin
ILI	Influenza-Like Illness
LL	Lower Limit
LRTD	Lower Respiratory Tract Disease
LRTI	Lower Respiratory Tract Illness
LS	Least Squares
L2L	Lot-to-Lot
MedDRA	Medical Dictionary for Regulatory Activities
mES	modified Exposed Set
MGI	Mean Geometric Increase
MPL	3-O-desacyl-4'-monophosphoryl lipid A
NAb	Neutralizing Antibody
NH	Northern Hemisphere
OA	Older Adult
OR	Odds Ratio
PCR	Polymerase Chain Reaction
pIMD	Potential Immune-Mediated Disease
PPSi	Per-Protocol Set for immunogenicity
PreF	Prefusion

Abbreviation	Definition
PRO	Patient-Reported Outcome
PT	Preferred Term
qRT-PCR	Quantitative Reverse Transcription Polymerase Chain Reaction
QoL	Quality of Life
QS-21	QS-21 Stimulon® (*Quillaja saponaria* Molina fraction 21) (QS-21 adjuvant is licensed from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, US corporation)
RNA	Ribonucleic Acid
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RSVPreF3 OA	RSV PreFusion protein 3 Older Adult
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SF-12	Short form 12-item survey
SH	Southern Hemisphere
SOC	System Organ Class
SSS	Solicited Safety Set
TNF-α	Tumor Necrosis Factor alpha
UL	Upper Limit
UI	Uncertainty Interval
US	United States
VE	Vaccine Efficacy
YOA	Years Of Age

1 EXECUTIVE SUMMARY

1.1 Introduction

This document supports the favorable benefit-risk profile of GlaxoSmithKline Biologicals SA (GSK) RSVPreF3 OA vaccine for the proposed indication of 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 (YOA).

The RSVPreF3 OA vaccine consists of a recombinant RSV F protein stabilized in its trimeric and prefusion (PreF) conformation, i.e., the RSVPreF3 antigen (120 μg), and the AS01$_E$ adjuvant system, which is a liposome-based adjuvant system containing 25 μg of each of the immuno-enhancers Quillaja saponaria Molina fraction 21 (QS-21, licensed from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, United States [US] corporation) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL). It is administered intramuscularly as a single dose.

1.2 Background, Unmet Need, and Expected Immune Response

RSV is a highly contagious human virus (*Pneumoviridae* family) that causes respiratory tract infections in people of all ages and is a major contributor to respiratory morbidity and mortality in infants, young children, and older adults worldwide.

There is a single RSV serotype with 2 RSV subtypes, A and B, which co-circulate in each season. In temperate climates, RSV epidemics occur yearly during late fall, winter, and early spring (lasting about 5 to 7 months). In tropical climates the patterns are less predictable and can be related to the rainy season. RSV may also persist at low levels throughout the year [Obando-Pacheco, 2018] (Section 2.1).

Adults experience multiple RSV infections over the course of their lifetime. Following natural infection with RSV, the protection is short-lived and incomplete. It is not sufficient to prevent reinfection, which occurs throughout life [Simoes, 1999; Walsh, 2004b; Falsey, 2006b; Krilov, 2011; Habibi, 2015].

RSV is the fourth most frequent cause of medically attended respiratory tract disease in adults (after influenza virus, rhinovirus, and SARS-CoV-2) [Hedberg, 2022]. Older adults are at high risk of morbidity and mortality from RSV disease due to age-related decline in immunity and underlying conditions (e.g., diabetes, chronic respiratory conditions and heart disease) [CDC, 2022b]. RSV is estimated to cause annually 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths in adults ≥65 YOA in US [CDC, 2022a]. In addition, based on a systematic literature review and meta-analysis, the estimated unadjusted annual rates for RSV-associated outpatient visits in the US were 906,882 for adults ≥65 YOA, and 721,857 for adults 50-64 YOA. However, these figures may be underestimated, as use of polymerase chain reaction (PCR) testing alone in older adults has been reported to lead to an underdetection of RSV infection by a factor of 1.4 compared with adding testing of paired serology specimens [McLaughlin, 2022].

RSV-associated infection can have a considerable impact on the functional status and quality of life (QoL) of older adults, resulting in increased care requirements, risk of further hospitalization and mortality. In a US study, RSV infection in adults ≥50 YOA was associated with substantial

impact on daily life, including impact on productivity; social or leisure activities; relationships; emotional, physical or cognitive functioning; and sleep [Curran, 2022].

Despite the significant medical need, there is currently no specific treatment or Food and Drug Administration (FDA)-approved vaccine for the prevention of RSV infection or associated disease. Treatment for RSV in older adults is limited to supportive care (Sections 2.3 and 2.4).

1.3 Product Description

The RSVPreF3 OA vaccine was designed to prevent RSV-associated LRTD in adults ≥60 YOA. Taking into consideration the pre-existing immune responses to RSV and immunosenescence-related decline in RSV-specific immunity of the target population, the vaccine was designed to provide protection against LRTD by (1) boosting the serum neutralizing antibody (NAb) response against both RSV-A and RSV-B and (2) boosting RSVPreF3 Th1 CD4+ T cells in older adults to a similar level as seen in young adults vaccinated with unadjuvanted RSVPreF3 (Section 3.2.3).

The RSVPreF3 OA vaccine is a suspension for injection supplied as a single dose vial of lyophilized RSVPreF3 antigen component to be reconstituted with the accompanying vial of AS01$_E$ adjuvant suspension component. After reconstitution, a single dose of 0.5 mL contains 120 μg of RSVPreF3 antigen adjuvanted with the liposome-based adjuvant system AS01$_E$, containing 25 μg of each of the immuno-enhancers QS-21 and MPL.

The RSVPreF3 antigen is an engineered recombinant protein, derived from the RSV fusion (F) surface glycoprotein of an RSV-A strain (RSV-A A2 strain) that has been stabilized in its trimeric and PreF conformation (Sections 3.2.1 and 3.2.2). The F protein has been selected as the vaccine antigen because it is a major surface glycoprotein of the virus, it plays a central role in RSV entry into the host cell, and it is highly conserved among RSV-A and RSV-B subtypes. The preF conformation of the F protein was selected as it is the main target of RSV NAbs in humans following natural exposure to RSV [Magro, 2012; Ngwuta, 2015; Olmsted, 1986; Smith, 2012; McLellan, 2013].

In addition, the AS01$_E$ adjuvant system was included in the RSVPreF3 OA vaccine because it has the ability to promote induction of robust specific Th1 CD4+ T cell responses, as well as rapid and durable humoral responses when combined with a protein antigen [Leroux-Roels, 2016; Garçon, 2011; Didierlaurent, 2017; Pallikkuth, 2020] (Section 3.2.3). *Shingrix,* a vaccine approved by the FDA in 2017 for the prevention of herpes zoster in adults ≥50 YOA (indication expanded in 2021 to adults aged ≥18 YOA who are or will be at increased risk of herpes zoster due to immunodeficiency or immunosuppression caused by known disease or therapy), contains the AS01$_B$ adjuvant (double quantity of each of the immuno-enhancers in comparison to AS01$_E$), and has been demonstrated to be highly efficacious with a favorable benefit-risk profile [Lal, 2015; Cunningham, 2016, López-Fauqued, 2019].

1.4 Non-clinical Data

Non-clinical pharmacology and toxicology studies in animal models showed that RSVPreF3 adjuvanted with AS01 was well tolerated and induced higher RSV NAb and specific T -cell responses compared to the unadjuvanted RSVPreF3 (Section 4). The results supported further clinical evaluation of vaccine formulations based on RSVPreF3 and AS01.

1.5 Overview of the Clinical Development Program

An overview of clinical studies conducted with RSVPreF3 OA vaccine is provided in Table 1.1, and further details can be found in Sections 1.6 to 1.10.

The clinical development program was initiated with the Phase 1/2 dose and formulation selection Study 002, which evaluated the reactogenicity, safety, and immunogenicity of several formulations of the RSVPreF3 OA vaccine. The Phase 3 program includes:

1. the immunogenicity Study 004, evaluating the humoral and cellular immunogenicity as well as the reactogenicity, safety, and persistency of the immune response to RSVPreF3 OA vaccine administered according to different revaccination schedules,
2. the pivotal efficacy Study 006, demonstrating the efficacy of a single dose and annual revaccination doses of RSVPreF3 OA vaccine in the prevention of RSV LRTD, and evaluating the humoral immunogenicity and reactogenicity in a subset of participants, as well as the safety of the vaccine,
3. the co-administration Study 007, demonstrating non-inferiority in terms of humoral immunogenicity, and evaluating the reactogenicity and safety of RSVPreF3 OA vaccine when co-administered with an unadjuvanted seasonal influenza quadrivalent inactivated vaccine (FLU-QIV), and
4. the lot-to-lot (L2L) consistency Study 009, demonstrating the consistency of 3 lots of RSVPreF3 OA vaccine in terms of humoral immunogenicity as well as evaluating the safety and reactogenicity of the 3 lots.

Across the clinical development program, safety data are available for 15,845 participants ≥60 YOA who have received at least 1 dose of RSVPreF3 OA. Of these, 15,745 participants were part of the Phase 3 clinical studies (Table 10.1).

Table 1.1 Overview of clinical studies with RSVPreF3 OA

Study	Phase and Purpose (Status)	Population (age)	Study Groups and Schedule	Participants in ES (N)
002*	Phase 1/2 Dose and formulation selection study (Completed)	**Part A:** Adults 18-40 YOA	4 parallel groups in **Part A** (1:1:1:1) receiving 2 doses of RSVPreF3 OA (30, 60 or 120 μg, unadjuvanted) or placebo† at Day 1 and Day 61	48 in Part A
		Part B: Older Adults 60-80 YOA	10 parallel groups in **Part B** (1:1:1:1:1:1:1:1:1:1) receiving 2 doses of RSVPreF3 OA (30, 60 or 120 μg, unadjuvanted or adjuvanted with $AS01_B$ or $AS01_E$) or placebo at Day 1 and Day 61	1005 in Part B, among whom 100 received the 120 μg RSVPreF3 OA adjuvanted with $AS01_E$
004	Phase 3 Immunogenicity (humoral and cellular) study (Ongoing)	Older Adults ≥ 60 YOA	3 parallel groups (3:1:1) receiving a single dose of RSVPreF3 OA at Day 1 followed by 3 possible revaccination schedules	1653

Study	Phase and Purpose (Status)	Population (age)	Study Groups and Schedule	Participants in ES (N)
006	Phase 3 Pivotal efficacy study (Ongoing)	Older Adults ≥ 60 YOA	Season 1: 2 parallel groups (1:1) receiving a single dose of either RSVPreF3 OA or placebo† at Day 1 followed by annual revaccination with either RSVPreF3 OA or placebo†	24,966 among whom 12,467 received RSVPreF3 OA
007	Phase 3 Co-administration study, with FLU-QIV (Completed)	Older Adults ≥ 60 YOA	2 parallel groups (1:1) receiving a single dose of RSVPreF3 OA either co-administered with or given 1 month apart from a single dose of FLU-QIV	885 among whom 868 received RSVPreF3 OA
009	Phase 3 Lot-to-lot consistency study (Completed)	Older Adults ≥ 60 YOA	3 parallel groups (1:1:1) receiving a single dose of RSVPreF3 OA (lot 1, lot 2, or lot 3) at Day 1 in all groups	757

$AS01_B$ = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); $AS01_E$ = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21); ES = Exposed Set; FLU-QIV = Seasonal Influenza Quadrivalent Inactivated Vaccine; N = number of participants, YOA = Years of Age.
†Placebo = saline solution, NaCl.
*Note: Study 011 was an open-label extension of Study 002, which assessed the safety and immunogenicity of a revaccination dose in adults ≥ 60 YOA. A total of 122 participants were enrolled to receive either 30, 60, or 120 µg of $AS01_E$-adjuvanted vaccine 18 months after their final dose in Study 002.

Clinical Development with RSVPreF3 in Pregnant Women

In parallel with the RSVPreF3 OA clinical development program, GSK initiated development of another RSV vaccine candidate intended for active immunization of pregnant women 18-49 YOA during the second and third trimester of pregnancy to prevent RSV-associated lower respiratory tract illness (LRTI) in infants by transfer of maternal antibodies. The RSV maternal vaccine candidate contains 120 µg of the RSVPreF3 antigen, as does the RSVPreF3 OA vaccine, however it does not include any adjuvant.

In February 2022, GSK stopped enrollment and vaccination in the Phase 3, double-blind, 2:1-randomized, placebo-controlled study to assess the safety and efficacy of the maternal vaccine candidate (RSVPreF3 Mat) administered to women 18-49 YOA in the late second or third trimester of pregnancy (RSV MAT-009) and all other ongoing RSVPreF3 Mat studies, due to the identification of safety signals emergent from the RSV MAT-009 study. The safety signals were an observed imbalance in the proportions of preterm births (before 37 weeks gestational age) and neonatal deaths (those that occur within 28 days after birth) between the vaccine and the placebo groups. The imbalance in neonatal deaths is a consequence of the imbalance in preterm births and not an independent safety signal. No other safety signal has been observed in infants or mothers, and the study remains ongoing for safety and efficacy follow-up.

GSK continues to investigate the cause of the preterm birth safety signal and currently does not have a mechanistic explanation for it.

The observed safety signal of preterm birth is specific to pregnant women. The clinical development program of RSVPreF3 OA vaccine which is presented in this document is

conducted in a different population (adults ≥60 YOA) that does not include pregnant women [Eijkemans, 2014].

1.6 Dose and Formulation Selection - Phase 1/2 Study 002

Study 002 was a Phase 1/2 randomized, placebo-controlled, observer-blind[1], multi-center study that evaluated the reactogenicity, safety, and immunogenicity of different formulations of the RSVPreF3 OA vaccine as compared to placebo, when administered according to a 0, 2-month schedule. The study was conducted in 2 parts. In Part A, the study evaluated the safety and reactogenicity of 2 doses of unadjuvanted RSVPreF3 antigen in a limited number of healthy young adults 18-40 YOA (first time in human) before evaluating the investigational vaccines in adults 60-80 YOA (Part B). In Part A, 48 young adults were equally randomized in 4 study groups to receive either 1 of the 3 vaccine formulations containing RSVPreF3 (at 30, 60 or 120 μg) unadjuvanted or placebo. In Part B, 1005 older adults were equally randomized in 10 study groups to receive either 1 of the 9 vaccine formulations containing RSVPreF3 (at 30, 60 or 120 μg) unadjuvanted or adjuvanted with AS01$_E$ or AS01$_B$ (AS01$_E$ containing half of the quantity of the immuno-enhancers in comparison to AS01$_B$) or placebo.

All vaccine formulations containing RSVPreF3 antigen (with or without adjuvant) induced humoral immune responses (as measured with RSV-A and RSV-B serum neutralization assays and RSVPreF3-binding immunoglobulin G [IgG] assay) and cellular immune responses (as measured by RSVPreF3-specific Th1 CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ) after 1 dose in young adults and in older adults 60-80 YOA. The formulations with 120 μg RSVPreF3 were the most immunogenic, inducing post-Dose 1 RSV-A and RSV-B neutralization titers that were on average, 8.0 to 10.0 times the pre-vaccination titers (fold-increase; RSV-A: 8.0 to 9.9, RSV-B: 9.2 to 10.0) (Part B) (Sections 7.2 and 7.4).

Formulations adjuvanted with AS01$_E$ or AS01$_B$ induced higher cellular responses compared to unadjuvanted formulations, and restored RSVPreF3-specific Th1 CD4+ T cells in adults 60-80 YOA almost to the level observed in young adults vaccinated with unadjuvanted RSVPreF3 (Part A), despite the lower cellular response at baseline in the older adults (Section 7.5).

Administration of a second dose 2 months after the first dose did not significantly increase immune responses compared to the first dose (Section 7.3).

The overall reactogenicity of the AS01-adjuvanted formulations was higher than that of the unadjuvanted formulations, with the highest frequencies of solicited administration site and systemic adverse events (AEs) within 7 days post-vaccination observed in the group receiving 120 μg RSVPreF3/AS01$_B$. The majority of reported solicited AEs were mild to moderate in intensity and of short duration (median ≤2 days). No apparent relationship was noted between the incidence or severity of unsolicited AEs within 30 days post-vaccination and the antigen

[1] Observer-blind: participant and the site and sponsor personnel involved in the clinical evaluation of the participants are blinded. Vaccine has been prepared and administered by qualified study personnel (unblinded) who did not participate in data collection, evaluation or review of any study endpoint (i.e., reactogenicity, safety, efficacy).

dose or the presence of AS01$_E$ or AS01$_B$ adjuvant. No safety concern has been identified for any of the 9 studied formulations (Section 7.5).

Based on immune response and reactogenicity, the 120 μg RSVPreF3/AS01$_E$ formulation with a 1 dose schedule was selected for the Phase 3 studies.

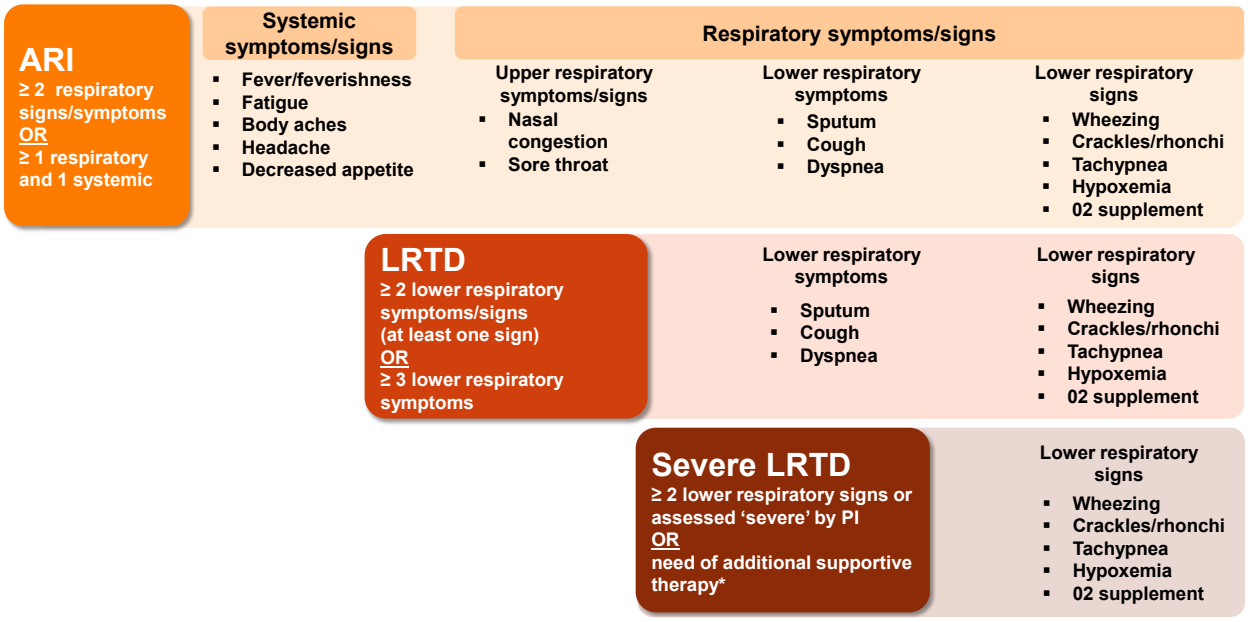
1.7 Efficacy — Pivotal Study 006

Study 006 is an ongoing Phase 3, randomized, placebo-controlled, observer-blind study to demonstrate the efficacy and evaluate the reactogenicity, safety and immunogenicity of a single dose and revaccination doses of RSVPreF3 OA in adults ≥60 YOA. It is conducted in 17 countries in the Northern hemisphere (NH, including North America, Europe, and Asia) and the Southern hemisphere (SH). Participants will be followed for 3 consecutive RSV seasons in the NH and at least 2 consecutive RSV seasons in the SH. Pre-Season 1, participants were randomized (1:1) to receive either RSVPreF3 OA vaccine (RSVPreF3 OA group) or saline solution (Placebo group). Pre-Season 2, all participants who received RSVPreF3 OA vaccine will be re-randomized in a 1:1 ratio into 2 subgroups to receive annual revaccination doses of either RSVPreF3 OA or placebo. Participants who received placebo pre-Season 1 will also receive placebo at subsequent timepoints.

The primary objective of the study was to demonstrate the efficacy of a single dose of RSVPreF3 OA in the prevention of quantitative reverse transcription polymerase chain reaction (qRT-PCR) confirmed RSV-A and/or -B LRTD (Figure 1.1) during the first season in adults ≥60 YOA.

A total of 26,664 participants were enrolled into the study, of which 25,040 were randomized, and 24,981 received the study intervention. At VE Analysis 1, fifteen participants were excluded due to invalid informed consent and 24,966 were included in the Exposed Set (ES, 12,467 in the RSVPreF3 OA group and 12,499 in the placebo group). The primary efficacy analysis population (modified Exposed Set [mES]) included 24,960 participants (12,466 in the RSVPreF3 OA group and 12,494 in the placebo group) (Section 8.1.6.2, Table 8.1 and Section 8.2.1, Figure 8.2). The study enrolled participants from different geographical areas, races, ethnicities, ages, and health statuses (including participants with underlying comorbidities, such as cardiorespiratory conditions, and endocrine and metabolic conditions, which included diabetes mellitus, type 1 or 2, and advanced liver or renal disease and are referred to as endocrinometabolic conditions) (Section 8.2.2).

Figure 1.1 Case definitions used for VE analyses in Study 006



ARI = acute respiratory infection; LRTD = lower respiratory tract disease; PI = principal investigator; VE = vaccine efficacy.
*O_2 supplementation, positive airway pressure therapy or other types of mechanical ventilation

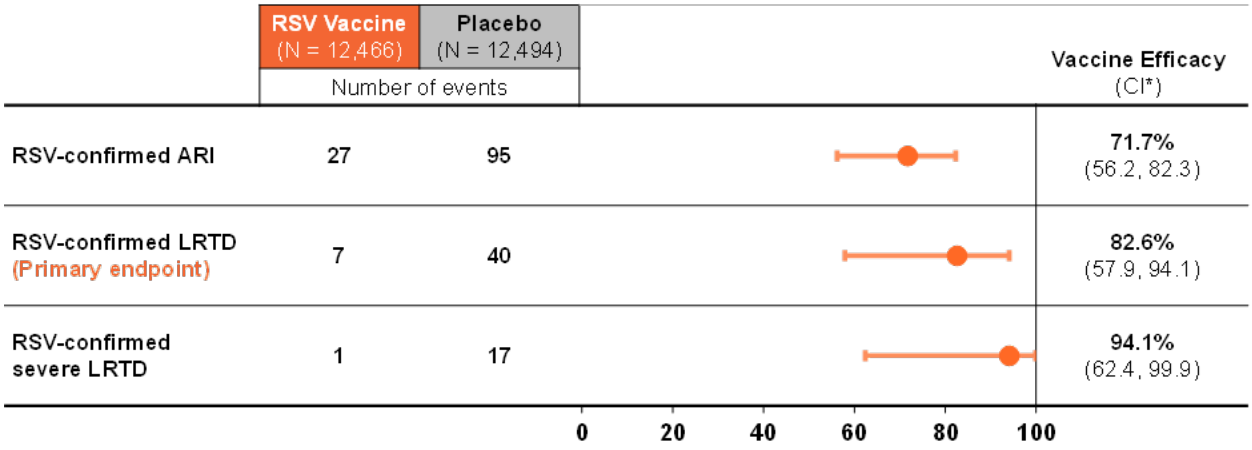
The pre-specified interim analysis of vaccine efficacy (VE) was case driven (Section 8.1.6) and performed with 47 qRT-PCR-confirmed RSV LRTD cases, adjudicated by an external Adjudication Committee, and accrued in the mES up to the efficacy data lock point (DLP) of April 11, 2022. It is referred as VE Analysis 1.

The VE against qRT-PCR-confirmed RSV LRTD was 82.6% (96.95% confidence interval [CI]: 57.9, 94.1), with 7 RSV LRTD cases observed in the RSVPreF3 OA group, compared to 40 cases in the placebo group (Figure 1.2, Section 8.2.3). As the lower limit (LL) of the CI was above the pre-specified success criterion (>20%), the primary objective was met.

The median follow-up period was 6.7 months, which covers the duration of an RSV season.

High and consistent VE was observed with RSVPreF3 OA, which protected against a spectrum of symptomatic RSV disease, from acute respiratory infection (ARI) to severe LRTD (Figure 1.2, Section 8.2.4.1).

Figure 1.2 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD, RSV ARI and RSV severe LRTD – mES



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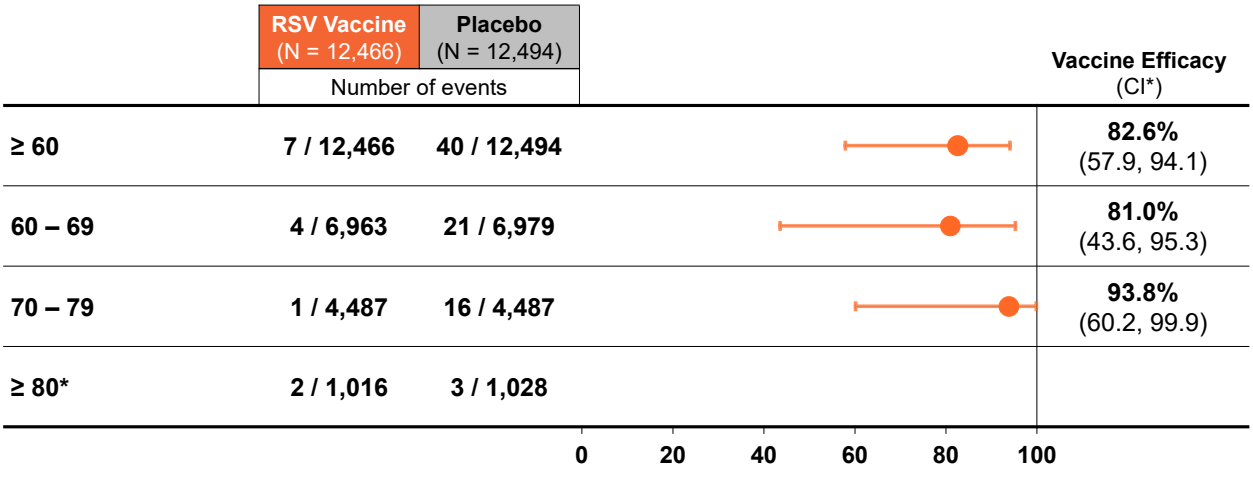
ARI = acute respiratory infection; CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy.
* 95% CI for RSV severe LRTD and RSV ARI. 96.95% for RSV LRTD.

VE against RSV LRTD was maintained when evaluated by age strata, with point estimates above 80% in participants 60-69 YOA and 70-79 YOA (Figure 1.3). In the age group of participants ≥80 YOA (representing 8.2% of participants in the mES), the VE analysis was inconclusive due to the lower number of participants and lower number of RSV LRTD cases (5 cases among 2044 participants, 2 in RSVPreF3 OA group and 3 in placebo group) in this age group (Section 8.2.4.2).

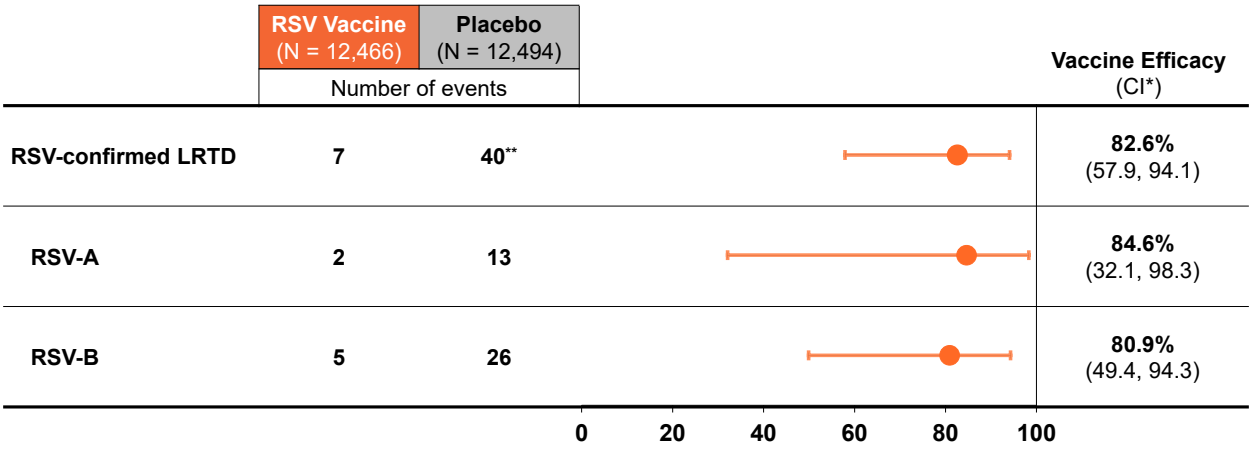
Figure 1.3 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD, by age category – mES



CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy.
*CI = 96.95% for ≥60 YOA and 95% for other age categories.
** Due to too few cases observed in adults ≥80 years of age, cannot conclude VE.

The RSVPreF3 OA vaccine provides a similar level of protection against LRTD and ARI caused by the 2 RSV subtypes, RSV-A and RSV-B (Figure 1.4, Section 8.2.4.5).

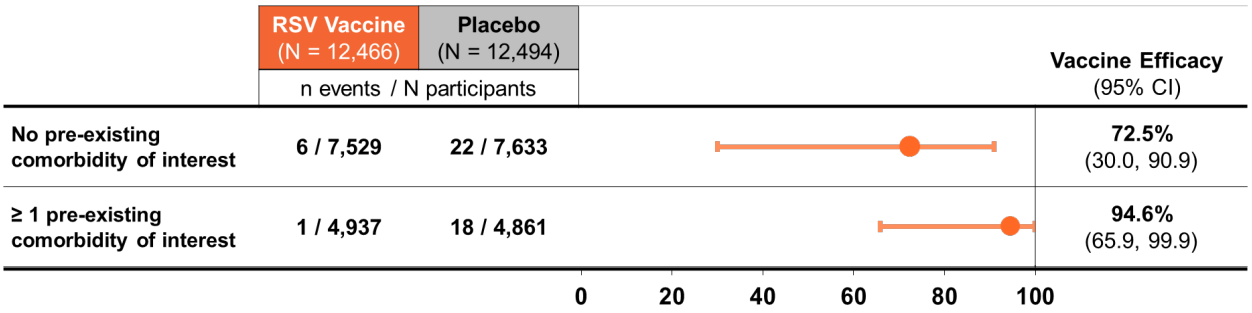
Figure 1.4 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD, by RSV subtype – mES



CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain.
*CI = 95% for RSV-A and RSV-B and 96.95% for RSV-confirmed LRTD
**Note: Out of the 40 RSV LRTD cases in the placebo group, 1 was confirmed by local testing and RSV subtype information is not available.

High VE was observed against RSV LRTD in participants with ≥1 comorbidity of interest (Figure 1.5), which included chronic obstructive pulmonary disease (COPD), asthma, any chronic respiratory/pulmonary disease, diabetes mellitus, chronic heart failure, and advanced liver or renal disease (Section 8.2.4.3).

Figure 1.5 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD by comorbidities of interest – mES



CI= confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain.
Note: Comorbidities of interest in Study 006 included chronic obstructive pulmonary disease, asthma, any chronic respiratory/pulmonary disease, diabetes mellitus, chronic heart failure, and advanced liver or renal disease.

For patient-reported outcome (PRO) measures, the InFLUenza Patient-Reported Outcome (FLU-PRO) questionnaire was used to provide a direct measure of the presence and severity of the experienced respiratory infection symptoms. The difference of the median Maximum (worst) FLU-PRO Chest/Respiratory score during the first 7 days between the RSVPreF3 (1.07) and placebo (1.86) group was statistically significant with a p-value of 0.0258. A minimally clinically important difference of 0.26 was estimated for the FLU-PRO chest score. As such, the observed

difference in medians between the study groups (i.e., 0.79) for the FLU-PRO chest score is considered clinically meaningful. These data show that participants experiencing an ARI in the RSVPreF3 OA group reported less severe chest symptoms compared to participants in the placebo group, during the first 7 days of an RSV ARI episode (Section 8.2.5).

1.8 Immunogenicity — Studies 004 and 006

Study 004 Immunogenicity

Study 004 is an ongoing Phase 3, randomized, open-label, multi-center study, evaluating the humoral and cellular immune response, as well as the reactogenicity, safety and persistence of the immune response to RSVPreF3 OA administered according to different revaccination schedules in adults ≥60 YOA.

The RSVPreF3 OA vaccine elicited high humoral immune responses as measured with RSV-A and RSV-B serum neutralization assays and RSVPreF3-binding IgG assay. One month post-vaccination titers were, on average, 10.5 (95% CI: 9.9, 11.2) and 7.8 (95% CI: 7.3, 8.3) times the pre-vaccination titers (fold-increase), for the neutralization A assay and the neutralization B assay respectively. In addition, RSVPreF3-binding IgG concentrations were 12.2 (95% CI: 11.6, 12.8) times the pre-vaccination concentrations (fold-increase). These humoral immune responses were consistent across the age categories (60-69, 70-79, and ≥80 YOA) (Figure 1.6). The observed RSV-B neutralizing titers show that the RSVPreF3 antigen (that is derived from the RSV-A subtype [RSV-A A2 strain]) elicits a functional immune response against both RSV-A and RSV-B strains.

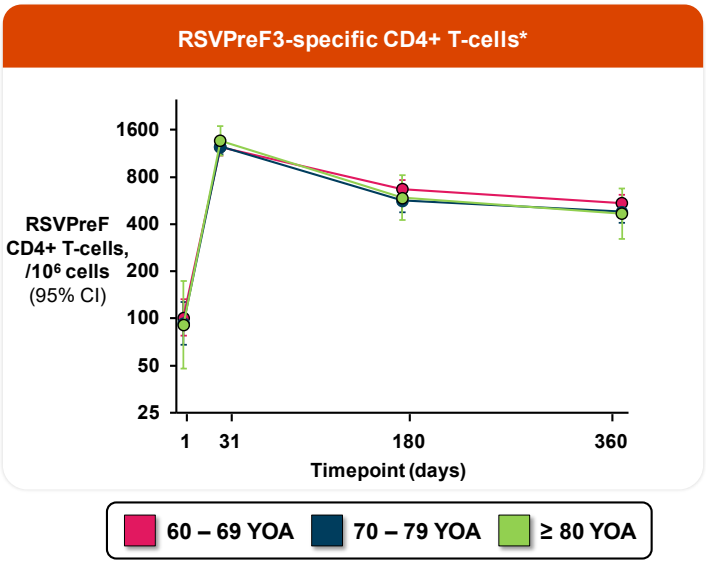
Figure 1.6 Study 004: RSV-A and RSV-B neutralizing titers by age group up to 12 months post-vaccination – PPSi

CI = confidence interval; ED = estimated dilution; GMT = geometric mean titer; NAb = neutralizing titers (referred as NAb in the figure); PPSi = per-protocol set for immunogenicity; YOA = years of age.

The RSVPreF3 OA vaccine also induced higher frequencies of RSVPreF3-specific CD4+ T cells, defined as expressing at least 2 markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-ɣ, IL-13, IL-17, at 1 month post-vaccination (median frequency: 1344)

when compared to pre-vaccination levels (median frequency: 190), with similar frequencies across age categories (Figure 1.7).

Figure 1.7 Study 004: RSVPreF3-specific CD4+ T cell response by age group up to 12 months post-vaccination – PPSi



CI = confidence interval; PPSi = per-protocol set for immunogenicity; YOA = years of age.

The humoral immune responses declined by 12 months post-vaccination but remained, on average, ≥ 2 times the pre-vaccination levels (3.1 [95% CI: 3.0, 3.3], 2.3 [95% CI: 2.2, 2.5] and 3.5 [95% CI: 3.4, 3.6] for RSV-A neutralizing titers, RSV-B neutralizing titers, and RSVPreF3-binding IgG concentrations, respectively). The decline has also been observed for cellular immune response with a median frequency of 575.5 of RSVPreF3-specific CD4+ T cells by 12 months post-vaccination (Figure 1.6, Figure 1.7, Section 9.4.1).

Study 006 Immunogenicity

In Study 006, humoral immunity was assessed in a subset of participants (Reactogenicity and Immunogenicity subset) including approximately 7% of the total study population. At 1 month post-vaccination, the RSV-A serum neutralizing titers were, on average, 10.2 (95% CI: 9.5, 11.0) times the pre-vaccination titers, RSV-B neutralizing titers were 8.6 (95% CI: 8.0, 9.2) times the pre-vaccination titers, and RSVPreF3-binding IgG concentrations were 13.1 (95% CI: 12.3, 13.9) times the pre-vaccination concentrations. The humoral immune responses were high and consistent across the different age groups (Section 9.4.2). The humoral immunogenicity data obtained in Study 006 are in line with the data observed in Study 004.

1.9 Co-Administration with Influenza Vaccine – Study 007

Study 007 was a Phase 3, randomized, controlled, multi-center, co-administration study with FLU-QIV, which aimed to demonstrate non-inferiority of the immune response to each of the co-administered vaccines as compared to sequential administration of each vaccine. In this study, participants ≥60 YOA received 1 dose of RSVPreF3 OA vaccine and FLU-QIV or 1 dose of FLU-QIV followed by a dose of RSVPreF3 OA vaccine 1 month later.

Co-administration of RSVPreF3 OA and FLU-QIV induced a statistically non-inferior immune response compared to the sequential administration of each vaccine. The criteria for non-inferiority of the immune responses in the control versus co-administration group were met, as the upper limits (ULs) of the 2-sided 95% CIs of the group GMT ratios were <1.5 (ULs ranging from 1.26 to 1.44) for RSV-A serum neutralization and hemagglutination inhibition (HI) against the strains Flu A/Hong Kong/H3N2, Flu A/Victoria/H1N1, Flu B/Phuket/Yamagata, and Flu B/Washington/Victoria, with GMT ratios for RSV-A serum neutralization and HI ranging from 1.10 to 1.27 (Section 9.4.3).

1.10 Consistency of the Manufacturing Process – Study 009

Study 009 was a Phase 3, randomized, double-blind, multi-center, L2L consistency study evaluating 3 lots of RSVPreF3 OA vaccine. Results from this study demonstrated consistency between 3 RSVPreF3 OA vaccine lots in terms of immunogenicity. The 2-sided 95% CI on the RSVPreF3-binding IgG group GMC ratios between each pair of the 3 lots (RSVPreF3 OA lot divided by another RSVPreF3 OA lot) were within the pre-defined limits of [0.67, 1.5]. The RSVPreF3-binding IgG GMCs observed at baseline and 1 month post-vaccination were similar to the GMCs observed in studies 002, 004, and 006 (Section 9.4.4).

1.11 Reactogenicity and Safety in Adults ≥60 YOA

Across the clinical development program, safety data are available for 15,845 participants who have received at least 1 dose of RSVPreF3 OA. In the Phase 3 clinical studies, 15,745 participants ≥60 YOA received at least 1 dose of the RSVPreF3 OA vaccine (Section 10.1). All available data have been used for the assessment of the overall safety profile of the RSVPreF3 OA vaccine (Table 10.2).

The assessment of reactogenicity was derived from the Solicited Safety Set (SSS) for Study 006 (i.e., participants who received either RSVPreF3 OA vaccine or placebo and who recorded solicited administration site and systemic events within 4 days post-vaccination), and the ES for the other studies (i.e., all participants with valid informed consent and at least 1 study vaccine administration documented). The analyses of unsolicited AEs, serious adverse events (SAEs), and potential immune-mediated diseases (pIMDs) were based on the ES for all studies.

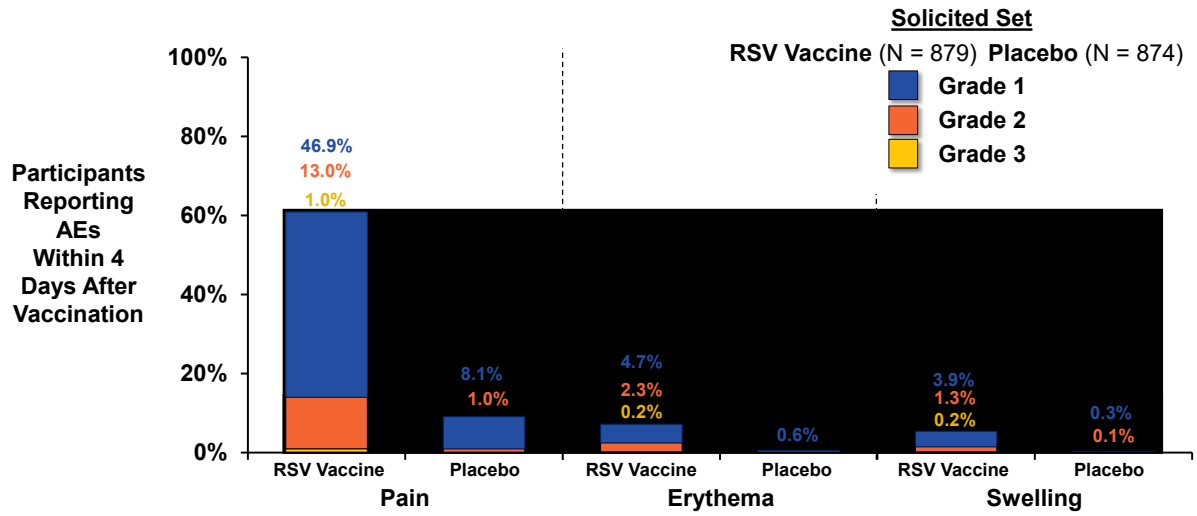
The greatest amount of data is from the large placebo-controlled, multi-regional Study 006, which evaluated reactogenicity in a subset of 1,757 participants, of whom 879 were vaccinated with RSVPreF3 OA (SSS), and safety in 24,966 participants, of whom 12,467 vaccinated with RSVPreF3 OA (ES). Median safety follow-up time from Dose 1 up to DLP of September 30, 2022 or up to Dose 2 administration (if administered before DLP) was nearly 12 months (364 days) (Section 10.3, Figure 8.2).

Solicited Safety Set – Study 006

Solicited administration site and systemic AEs were more frequently reported in the RSVPreF3 OA group, as compared with placebo (71.9% [95% CI: 68.8, 94.9] versus 27.9% [95% CI: 25.0, 31.0] for any solicited event). The most commonly reported (occurring in ≥10% of participants) solicited events within 4 days post-vaccination in the RSVPreF3 OA group were injection site pain (60.9%), fatigue (33.6%), myalgia (28.9%), headache (27.2%), and arthralgia (18.1%). The solicited events were generally mild to moderate, with few Grade 3 events (4.1% [95% CI: 2.9,

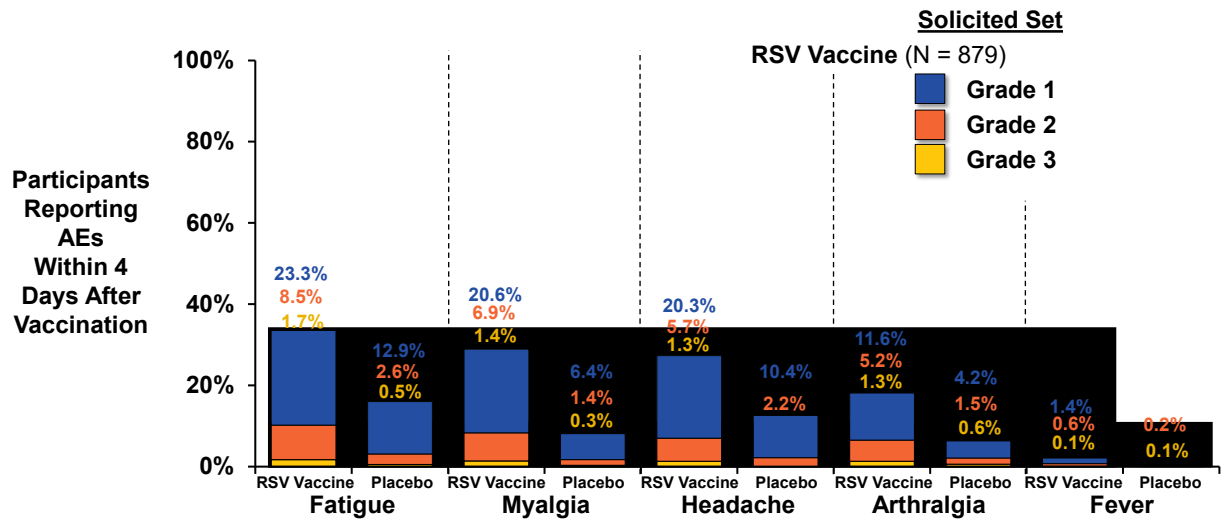
5.6] in the RSVPreF3 OA group and 0.9% [95% CI: 0.4, 1.8] in the placebo group), and of short duration (median duration between 1 and 2 days) (Figure 1.8, Figure 1.9, Section 10.3.1).

Figure 1.8 Study 006: Solicited administration site events within 4 days after either RSVPreF3 OA or placebo, by grade – SSS



AE = adverse event; SSS = Solicited Safety Set.
Events of short duration (median duration 2 days for RSVPreF3 OA group, and between 1 and 4 days in placebo group).

Figure 1.9 Study 006: Solicited systemic events within 4 days after either RSVPreF3 OA or placebo, by grade – SSS



AE = adverse event; SSS = Solicited Safety Set.
Events of short duration (median duration between 1 and 2 days for both groups).

Exposed Set – Study 006

In the ES, unsolicited AEs within 30 days post-vaccination were more frequently reported in the RSVPreF3 OA group compared with placebo (33.0% versus 17.8% for any AE [relative risk [RR]: 1.85; 95% CI: 1.8, 2.0], 2.0% versus 1.3% for Grade 3 AEs [RR: 1.6; 95% CI: 1.3, 1.9],

and 24.9% versus 5.8% for AEs assessed as related to vaccination by the investigator [RR: 4.3; 95% CI: 3.9, 4.6]). The more frequent occurrence of unsolicited AEs in the RSVPreF3 OA group in the ES was mainly driven by events reflecting vaccine reactogenicity (Section 10.3.2.1). Unsolicited AEs with a medically attended visit were balanced between RSVPreF3 OA and placebo groups (5.5% in each group) (Section 10.3.2.2).

No case of anaphylaxis to vaccine was reported (Section 10.5).

Serious adverse events reported up to 6 months post-vaccination were equally distributed between RSVPreF3 OA and placebo groups, with a frequency of 4.3%. The most frequently reported SAEs in both groups reflected common conditions in the older adult population, such as infections and infestations (0.9% in both groups), mainly of the respiratory tract, and cardiac disorders (0.8% in RSVPreF3 OA group and 0.7% in placebo group).

SAEs considered as related to vaccination by the investigator were reported for 0.1% of participants in both groups, up to the DLP of September 30, 2022.

Within the System Organ Class (SOC) “cardiac disorders”, a higher number of AEs (serious and non-serious) of atrial fibrillation was observed in the RSVPreF3 OA group (10 events) compared to placebo (4 events) within 30 days post-vaccination. Of these, 7 events in the RSVPreF3 OA group and 1 event in the placebo group were SAEs (RR: 7.02; 80% CI: 1.47, 75.62). None of these SAEs of atrial fibrillation were considered as related to vaccination by the investigator, none resulted in stroke, and none were fatal. All reported events were recorded as resolved during the follow-up period. There was no difference between groups for SAEs of atrial fibrillation at 6 months post-vaccination (14 events in the RSVPreF3 OA group versus 16 in placebo).

Atrial fibrillation is a component of the High Level Term (HLT), “supraventricular arrythmias”, which also includes atrial flutter, atrial tachycardia, sinus node dysfunction and sinus tachycardia. Medical assessment of all (serious and non-serious) events reported under this HLT within 30 days post-vaccination showed that 17 participants reported 18 events, with 12 participants [0.1%] in the RSVPreF3 OA group and 5 participants [<0.1%] in the placebo group. Of note, among the 18 events:

- One participant experienced sinus tachycardia coinciding with administration of the vaccine and an injection site reaction,
- 10 participants had pre-existing atrial fibrillation or supraventricular arrythmia, where recurrence is characteristic of the condition, and
- All participants for which a new onset event of atrial fibrillation was reported had relevant risk factors and/or precipitant medical conditions (e.g., hypertension, coronary artery disease, COPD, acute infection).

Details about these events are provided in Table 10.10, Section 10.3.2.3. When considering that all reports of supraventricular arrythmia events (excluding the case of sinus tachycardia) occurred either in participants with a known history of these arrhythmias (where intermittent recurrence of episodes is characteristic of the condition) or when new-onset, in participants with recognized risk factors for developing supraventricular arrythmia, and at an incidence not higher than background rates reported in the literature, GSK believes these cases more plausibly

reflect the epidemiology of the older adult population and the expected disease course of these events rather than a vaccine effect (consistent with investigator determination, and the recommendation from the Independent Data Monitoring Committee [IDMC] to continue with the study). Notwithstanding, GSK will continue to monitor and assess events of atrial fibrillation in clinical studies.

Fatalities, reported up to the safety DLP, occurred with a frequency of 0.7% and 0.8% in RSVPreF3 OA group and placebo group, respectively. The most frequently reported fatal SAEs (by SOC) were “cardiac disorders”, “general disorders and administration site conditions”, and “infections and infestations”.

Within the SOC “infections and infestations”, a higher number of participants experiencing COVID-19 leading to death is observed in the RSVPreF3 OA group (10 participants [0.1%]) compared to the placebo group (2 participants [<0.1%]) (RR: 5.01; 80% CI: 1.60, 21.16). All participants had concurrent medical conditions that are known risk factors for severe COVID-19 disease or for increased COVID-19 mortality (e.g., diabetes, hypertension, coronary artery disease, obesity, COPD, asthma) and 9 participants out of 12 were either not fully vaccinated (had not completed the primary series of COVID-19) or optimally protected (did not receive boosters) against COVID-19; details about these events are provided in Table 10.12. This observed imbalance in COVID-19 deaths is not accompanied by imbalances in COVID-19 and serious COVID-19. None of these fatal cases were considered as related to vaccination by the investigators.

Potential immune-mediated diseases (pIMDs) were equally distributed between the RSVPreF3 OA and placebo groups, with a frequency of 0.3% for any pIMD occurring within 6 months post-vaccination. There was no meaningful difference in type or frequency of reported pIMDs by subgroups (Section 10.3.2.5).

Aggregated analyses

Aggregated analyses for the RSVPreF3 OA group were performed for unsolicited AEs with a medically attended visit, all SAEs, and all pIMDs. The aggregated analyses included a total of 15,303 participants who received 1 dose of RSVPreF3 OA vaccine, pooled from the from the Phase 3 studies (004, 006, 007 [except when co-administered with FLU-QIV] and 009).

In the aggregated analyses, 5.4% of participants reported at least 1 unsolicited AE with a medically attended visit within 30 days after vaccination (Section 10.4.1).

Up to the DLP of the analyses, SAEs were reported for 4.6% of participants, 11 of which (<0.1%) were considered related to vaccination by the investigator. Besides those reported in Study 006, 1 SAE considered as related to RSVPreF3 OA vaccination by the investigator was reported in 1 participant in the open-label Study 004: Guillain-Barré syndrome (also a pIMD). However, the diagnosis could not be confirmed, and the case resolved within 6 months. (Details are available in Section 10.4.2).

Up to the DLP of the analyses, pIMDs were infrequently reported (0.4%). For 9 (<0.1%) participants, pIMD events were considered as related to vaccination by the investigator.

Study 007

Results from the co-administration Study 007 show that the RSVPreF3 OA vaccine has a comparable and clinically acceptable safety profile when co-administered with FLU-QIV (Section 10.6).

1.12 Benefit- Risk Summary

RSV infection is a major health concern in older adults, leading to approximately 1 million outpatients visits, 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths every year in US adults ≥65 YOA [CDC, 2022a]. Despite this significant medical need, there are currently no vaccines approved for the prevention of RSV disease or effective treatments for this population.

A single dose of the RSVPreF3 OA vaccine produced high efficacy in adults ≥60 YOA in the prevention of RSV LRTD. High VE was observed across different subgroups in terms of age (high VE observed in age categories 60-69 YOA and 70-79 YOA), pre-existing conditions (≥1 comorbidity of interest), and across a spectrum of symptomatic RSV disease - from ARI, to LRTD and severe LRTD. This protection spanned the duration of one RSV season. The immunological non-inferiority of RSVPreF3 OA co-administered with FLU-QIV compared to RSVPreF3 OA administered separately sequentially 1 month apart was demonstrated in Study 007, supporting the co-administration of both vaccines without jeopardizing the immune response.

Based on safety data from more than 15,000 RSVPreF3 OA vaccine recipients, a single dose of the RSVPreF3 OA vaccine has a clinically acceptable safety profile in adults ≥60 YOA. Solicited administration site and systemic events occurred more frequently than with placebo, and were generally mild to moderate, with few Grade 3 events, and were of short duration, with most lasting between 1 and 2 days post-vaccination. SAEs, including fatal SAEs, and pIMDs are equally distributed between RSVPreF3 OA and placebo groups.

A higher number of SAEs of atrial fibrillation was observed in the RSVPreF3 OA group compared to placebo within 30 days post-vaccination; no difference between groups was observed at 6 months post-vaccination. After thorough review of all cases, GSK believes these events more plausibly reflect the epidemiology of the older adult population and the expected disease course of atrial fibrillation rather than a vaccine effect. It is to be noted that individuals with underlying cardiac disease appear to be at increased risk of symptomatic RSV disease, resulting in increased health care utilization and morbidity. Additionally, RSV disease is associated with exacerbations of arrhythmias in individuals with and without known pre-existing cardiovascular disease [Ivey, 2018]. Notwithstanding, GSK will continue to monitor and assess events of atrial fibrillation in clinical studies.

The RSVPreF3 OA vaccine has a comparable and clinically acceptable safety profile when co-administered with FLU-QIV, compared to sequential administration of both vaccines.

Routine pharmacovigilance activities, including ongoing monitoring of participant safety during the subsequent seasons of the 006 study and other ongoing and new studies, will further characterize the safety profile of the RSVPreF3 OA vaccine post-licensure.

1.13 Overall Conclusions

The available efficacy, immunogenicity, and safety data support the favorable benefit-risk profile of the RSVPreF3 OA vaccine for the proposed indication of active immunization for the prevention of LRTD caused by RSV-A and RSV-B subtypes in adults ≥60 YOA (Section 11).

2 BACKGROUND ON RSV

Summary

- RSV is the fourth most frequent cause, after influenza virus, rhinovirus, and SARS-CoV-2, of medically attended respiratory tract disease in adults.
- Following natural infection with RSV, the protection is short-lived and incomplete. It is not sufficient to prevent reinfection, which occurs throughout life.
- Older adults are at high risk for severe disease due to age-related decline in immunity and underlying conditions (e.g., diabetes, chronic respiratory conditions and heart disease).
- RSV is estimated to cause 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths every year in US adults ≥65 YOA.
- RSV can have a considerable impact on the functional status and QoL of older adults.
- Older adults hospitalized with RSV are at greater risk of death or long-term health consequences and place a high burden on the healthcare system.
- Despite the significant medical need, there is currently no specific treatment or FDA-approved vaccine for the prevention of RSV infection or associated disease in older adults.

2.1 Epidemiology of RSV

2.1.1 RSV Overview

RSV is a highly contagious human virus that causes respiratory tract infections in people of all ages and is a major contributor to respiratory morbidity and mortality in infants, young children, older adults and adults with comorbidities worldwide. RSV infection does not confer long-term protective immunity; therefore, reinfection with RSV occurs throughout life and is common in all age groups [Simoes, 1999; Walsh, 2004b; Falsey, 2006b; Krilov, 2011; Habibi, 2015].

RSV is a member of the enveloped *Pneumoviridae* family and expresses 11 proteins encoded by 10 genes [Pandya, 2019]. There is a single RSV serotype with 2 RSV subtypes, A and B [Borchers, 2013]. The most extensive antigenic and genetic differences between and within the 2 subtypes are found in the attachment G glycoprotein [Cane, 2001; Johnson, 1987; Sullender, 2000]. The F surface glycoprotein is the major antigen for eliciting NAb responses. The F glycoprotein is highly conserved among the RSV subtypes and contemporary strains.

The 2 subtypes co-circulate in each season [Belongia, 2018], and the predominance of one over the other varies by year and geographic location [Waris, 1991; Staadegaard, 2021]. In temperate climates RSV epidemics occur yearly during late fall, winter, and early spring (lasting about 5 to 7 months). In tropical climates the patterns are less predictable and can be related to the rainy season. RSV may also persist at low levels throughout the year [Obando-Pacheco, 2018]. The ongoing COVID-19 pandemic has significantly impacted the timing and magnitude of RSV epidemics in countries across the world, due to non-pharmaceutical interventions implemented to slow the spread of COVID-19. Respiratory related potentially preventable hospitalizations were found to be considerably reduced during the pandemic period compared to the prepandemic period (adjusted RR: 0.54; 95% CI: 0.50, 0.58; p<0.001) [Becker, 2022].

Modelling data suggest that the year or years directly following the pandemic the seasonality of RSV will remain atypical, after which the viruses would return to their expected seasonality [Baker, 2020]. Eventually, SARS-CoV-2 may become an endemic coronavirus and exhibit similar seasonality patterns, which in some locations would make it overlap with the influenza and RSV seasons [Lagacé-Wiens, 2021]. This would put considerable additional strain on the healthcare system during the season. Recent data show that after a 2021-2022 season during which the US saw less RSV infections in older adults than usual, there was an early start of the 2022-2023 RSV season, with RSV hospitalization rates in older adults in November being 10 times higher than at the same point in the season in the years before the COVID-19 pandemic [CNN Health, 2022; CDC, 2022c].

2.1.2 Incidence of RSV

Older adults experience a significant burden of disease from RSV, with some studies indicating a burden comparable to that of influenza in a population vaccinated for influenza, with an average annual incidence of RSV ARI of 5.5-5.7% and incidence increasing with age and comorbidities [Falsey, 2005; Korsten, 2021].

While the incidence of RSV disease in older adults has historically been underreported, in recent years a number of prospective studies have been conducted to provide more precise estimates, mainly for seasonal attack rates[2]. Across various studies during winter seasons from 2000 to 2016 in the US, RSV ARI attack rates ranged from 0.6/1000 to 70/1000 individuals per season, with the majority of estimates between 10/1000 and 20/1000 [Falsey, 2005; McClure, 2014; Falloon, 2017a; Belongia, 2018; Jackson, 2021a; Jackson, 2021b]. Even within the same population, there can be a 3-fold difference in attack rate between seasons [Belongia, 2018]. Differences in study design and case definition may also account for part of the differences in attack rates [Saez-Lopez, 2019]. A worldwide systematic review and meta-analysis found an estimated RSV ARI incidence rate in adults ≥65 YOA of 6.7 /1000 person-years. Based on this estimate, in 2015, there were about 1.5 million episodes of RSV ARI in older adults in industrialized countries [Shi, 2020b]. A published GSK meta-analysis found an RSV ARI attack rate of 1.62% (95% CI: 0.84, 3.08) among adults ≥60 YOA [Savic, 2022].

Studies utilizing other case definitions, such as LRTD or influenza-like illness (ILI), also found attack rates within these ranges [Falloon, 2017a; Fowlkes, 2014]. A systematic analysis in 195 countries found the incidence of RSV LRTI in adults ≥70 YOA to be 6.3 /1000 individuals [GBD, 2018]. The incidence of medically attended RSV tends to increase with age, from 12.4/1000 individuals in adults 50-59 YOA up to 19.9/1000 individuals in adults ≥70 YOA [McClure, 2014].

2.1.3 Prevalence of RSV

Overall, based on all publications reporting prevalence, the median prevalence of RSV among adults ≥60 YOA with ARI in high income countries is around 6.3% (interquartile range: 3.8-9.4).

[2] Attack rate: a form of incidence that measures the proportion of persons in a population who experience an acute health event during a limited period (e.g., during an outbreak), calculated as the number of new cases of a health problem during an outbreak divided by the size of the population at the beginning of the period, usually expressed as a percentage or per 1,000 or 100,000 population.

A US outpatient study analyzing samples from the 2010-2011 season detected RSV in 4.6% of ARI cases and 7.5% of ILI cases [Fowlkes, 2014]. When assessing moderate to severe ILI episodes for adults ≥65 YOA in 14 different countries across North America, Europe and East Asia, RSV was the third most common respiratory virus (prior to the COVID-19 pandemic), detected in 7.4% of cases [Falsey, 2014]. The prevalence of RSV among patients hospitalized with respiratory infection is similar to the outpatient setting. In Canada, over the 2012-2015 influenza seasons, the prevalence of RSV among hospitalized ARI patients was 4.8% for those >60 YOA [ElSherif, 2021].

2.2 Burden and Clinical Symptomatology of RSV Disease

2.2.1 Clinical Manifestations and Complications

Although for healthy young adults, clinical presentation of RSV disease often resembles the common cold, with mild to moderate cough and nasal congestion, RSV is associated with more severe disease (i.e., LRTD) in older adults. It is estimated to cause 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths every year in US adults ≥65 YOA [CDC, 2022a] (refer also to Section 2.2.2 and 2.2.3 for more information about hospitalizations and mortality due to RSV). In addition, the estimated unadjusted annual rates for RSV-associated outpatient visits in the US were 906,882 for adults ≥65 YOA, and 721,857 for adults 50-64 YOA, in a systematic literature review and meta-analysis. These figures may be an underestimate, as PCR testing in older adults has been reported to lead to an underdetection of RSV infection by a factor of 1.4 compared with adding testing of paired serology specimens [McLaughlin, 2022].

Severe clinical manifestations of RSV in older adults may be due, in part, to immunosenescence-related decline in RSV-specific immunity in this population. Adults ≥60 YOA and those with certain comorbidities (such as diabetes, chronic respiratory conditions, and heart disease) or who are severely immunocompromised have a greater risk of severe respiratory complications [CDC, 2022b]. These include pneumonia, and comorbidity exacerbations, resulting in respiratory failure, requirement for supplemental oxygen and mechanical ventilation, prolonged hospitalization, and mortality similar to seasonal influenza.

RSV plays an important role in the development of pneumonia among older adults, which can be observed in 30% to 66% of patients hospitalized with RSV [Volling, 2014; Tseng, 2020; Lui, 2021; Boattini, 2021; Falsey, 2006a]. According to numerous studies, RSV in older adults may account for 3-15% of community-acquired pneumonia, 9-10% of hospital admissions for acute cardiorespiratory diseases, and approximately 6,500 excessive deaths during seasonal peaks [Murata, 2007; Walsh, 2011; Katsurada, 2017; Hansen, 2022].

In adults hospitalized with RSV, bacterial co-infection is common. In a retrospective study in France, bacterial co-infection occurred in 12.1% of hospitalized patients with RSV ARI, with *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* being the 2 most common bacterial isolates. [Godefroy, 2020].

2.2.2 Hospitalizations Due to RSV

RSV accounts for a significant number of hospitalizations among older adults, in some studies comparable to that of influenza in a population in which vaccination coverage for influenza is high, but the effectiveness of influenza vaccines is suboptimal [CDC, 2018; Shi, 2020a].

A US database study from 2008-2014 found that the proportion of all RSV cases requiring hospitalization increased with age: 5.8% for those 65-74 YOA, 9.7% for those 75-84 YOA and 11.8% for those ≥85 YOA [Tong, 2020]. This was also found by a study in multiple hospitals in New York state, from 2017-2020 [Sieling, 2021; Branche, 2022a]. There, hospitalization rates for those 65-75 YOA ranged from 0.8/1000 persons to 1.3/1000 persons across seasons, while for those ≥85 YOA, it ranged from 2.1/1000 persons to 6.6/1000 persons across seasons.

Among those hospitalized with RSV in the US, a larger proportion experienced a length of stay ≥7 days than among those hospitalized with influenza (odds ratio [OR]: 1.4,), including a length of stay ≥7 days among survivors (OR: 1.5), as well as a higher proportion of intensive care unit admission (OR: 1.3) [Ackerson, 2019].

A published GSK meta-analysis found an RSV hospitalization rate of 0.15% (95% CI: 0.09, 022) among adults ≥60 YOA [Savic, 2022].

2.2.3 Mortality Due to RSV

In-hospital deaths attributable to RSV among adults are largely in people aged ≥65 YOA [Schmidt, 2019; Saravanos, 2019]. However, this may not capture all deaths due to RSV, as various studies show increased mortality after discharge [Auvinen, 2022; Descamps, 2022].

The Global Burden of Disease Project reported an increase in mortality due to LRTIs among adults ≥70 YOA from 746,700 in year 2000 to 1,080,958 in 2016. RSV was found to be the second leading etiology of LRTI deaths overall, with 22,009 (95% uncertainty interval [UI]: 15,705, 30,787) estimated deaths in 2016 [GBD, 2018]. In adults ≥70 YOA, similar mortality rates due to RSV and influenza (for which there is a vaccine) were reported globally: 5.4/100,000 (95% UI: 3.9, 7.6) and 6.1/100,000 (95% UI: 4.1, 8.5), respectively [GBD, 2018].

A recent US modelling study based on death certificate data estimated up to 12,600 RSV-attributable respiratory and circulatory deaths among those ≥65 YOA per year [Hansen, 2022]. In a published GSK meta-analysis, the RSV ARI in-hospital case fatality rate in adults ≥60 YOA was estimated to be 7.13% (95% CI: 5.40, 9.36) [Savic, 2022].

2.2.4 Impact on Daily Life and Long-Term Impact of RSV

RSV can have a considerable impact on the functional status and QoL of older adults, resulting in increased care requirements, and with increased risk of further hospitalization and mortality.

In a prospective study conducted over 4 consecutive winters in the US, the mean duration of RSV illness was 16 days (standard deviation: 8) in adults ≥65 YOA, and 39% of patients were unable to perform the normal activities of daily living for at least 1 day [Falsey, 2005].

In a qualitative US study, RSV infection in adults ≥50 YOA was associated with substantial impact on daily life, including impact on productivity; social or leisure activities; relationships; emotional, physical or cognitive functioning; and sleep. Physical functioning was impaired in 83% of participants, and 63% reported symptoms lasting beyond the acute disease stage from a week to >1 month [Curran, 2022].

In a prospective study conducted over 3 consecutive winters in adults ≥60 YOA hospitalized with RSV in the US, a functional decline at 6 months post-discharge was experienced by those

living in skilled nursing facilities or in the community with assistance prior to hospitalization. Additionally, 14% required a higher level of care at discharge compared with their living situation prior to hospitalization [Branche, 2022b]. Professional home-care was required in up to 24.5% of adults ≥18 YOA hospitalized with RSV in an international prospective cohort study, and up to 26.6% required readmission within 3 months [Falsey, 2021]. Within a year of admission, the cumulative mortality rate was 25.8% among adults ≥60 YOA hospitalized with RSV in the US [Tseng, 2020].

2.2.5 Risk of RSV Infection in Individuals with Comorbidities

Several comorbidities have been shown to be risk factors for RSV, notably COPD, cardiovascular conditions, diabetes mellitus, immunocompromising conditions and frailty.

In a study among hospitalized patients ≥65 YOA in the US with ≥2 ARI symptoms or exacerbation of underlying cardiopulmonary disease, the incidence rate for RSV was between 3.5 and 13.4 times higher in those with COPD compared to those without COPD [Branche, 2022a]. Among those with diabetes, the ratio was between 2.3 and 6.4 and among those with coronary artery disease between 3.7 and 6.5. Among those with congestive heart failure, those 60-79 YOA had an incidence rate ratio between 5.9 and 7.6, while those ≥80 YOA had an incidence ratio between 4.0 and 5.4.

In another study among hospitalized adults diagnosed with RSV in the US (determined through ICD-9 and ICD-10 coding, data on laboratory results unavailable), several comorbidities such as COPD, congestive heart failure, hematologic malignancies, stroke and chronic kidney disease were significantly associated with a higher risk of hospitalization [Wyffels, 2020].

Complication rates of RSV among frail older persons have varied with rates of pneumonia ranging from 5-67% and death from 0-20% [Falsey, 1998b].

2.3 Current Treatment Options

There is currently no specific treatment or FDA-approved vaccine for the prevention of RSV infection or associated disease in older adults. Treatment for RSV in older adults is limited to supportive care, consisting of supplemental oxygen, intravenous fluids, and bronchodilators. There is no clear benefit from the use of the anti-viral drug ribavirin in adults [Avery, 2020]. Inhaled and systemic corticosteroids are often prescribed in patients with asthma or COPD [Falsey, 2019].

2.4 Unmet Medical Need

In adults, the highest disease burden is observed in older individuals and those with comorbidities, such as lung or heart disease and diabetes, and with weakened immune systems. In these patient populations, RSV can exacerbate conditions like COPD, asthma, or congestive heart failure, and lead to severe outcomes such as pneumonia, hospitalization, and death [Prasad, 2021;CDC, 2022b]. RSV can have a considerable long-term impact on the functional status and QoL of older adults, resulting in increased care requirements, and with increased risk of further hospitalization and mortality. As the global population ages, the burden of RSV in adults continues to increase [Branche, 2015].

In the context of high burden of disease and unmet medical need, prevention of respiratory disease caused by RSV using a vaccine with a suitable benefit-risk profile for older adults, including individuals with comorbidities, is an optimal approach for reducing the RSV disease burden. Compared with standard medical treatment, prevention through an effective RSV vaccine could decrease RSV-related morbidity and prescription drug use (such as treatment with antipyretics, cough suppressants, or antibiotics), as well as maintain QoL [Gessner, 2000].

3 PRODUCT DESCRIPTION

Summary

- The RSVPreF3 OA vaccine consists of 2 components: a recombinant RSV F protein stabilized in its trimeric and PreF conformation, i.e., the RSVPreF3 antigen (120 μg), and the AS01$_E$ adjuvant system (liposome-based adjuvant system containing 25 μg of each of the immuno-enhancers QS-21 and MPL).
- The RSVPreF3 OA vaccine was designed to provide protection against LRTD by (1) boosting the serum NAb response against both RSV-A and RSV-B and (2) boosting RSVPreF3 Th1 CD4+ T cells in older adults to a similar level as seen in young adults vaccinated with unadjuvanted RSVPreF3.

3.1 Proposed Indication

The RSVPreF3 OA vaccine is indicated for active immunization for the prevention of LRTD caused by RSV-A and RSV-B subtypes in adults 60 YOA and older.

3.2 Product Overview

3.2.1 RSVPreF3 OA Composition

The RSVPreF3 OA vaccine consists of 2 components: the RSVPreF3 antigen and the AS01$_E$ adjuvant system.

The RSVPreF3 antigen is an engineered version of the RSV F surface glycoprotein, derived from the RSV-A subtype (RSV-A A2 strain), and stabilized in its trimeric and preF conformation. RSVPreF3 is expressed as a soluble and secreted protein in a mammalian cell line (CHO cells).

AS01$_E$ is a liposome-based adjuvant system containing 25 μg of each of the immuno-enhancers QS-21 and MPL. The liposomes consist of dioleoylphosphatidylcholine and cholesterol.

3.2.2 Dosing and Administration

The RSVPreF3 OA vaccine consists of a 2-vial presentation composed of a freeze-dried preparation containing 120 μg RSVPreF3 antigen drug substance and excipients, filled into a 3 mL glass vial to be reconstituted with the adjuvant AS01$_E$, prior to administration.

Prior to reconstitution, both the lyophilized antigen preparation and the liquid adjuvant system must be stored refrigerated between 2 and 8°C (35.6-46.4°F), protected from light, and must not be frozen. The shelf-life of RSVPreF3 and AS01$_E$ is 24 months and 36 months, respectively, when stored between 2 and 8°C (35.6-46.4°F).

A single dose after reconstitution is 0.5 mL. The reconstituted suspension for injection is to be administered intramuscularly. After reconstitution, the vaccine should be administered immediately or stored in the refrigerator (2-8°C, 36-46°F) or at room temperature (up to 25°C [77°F]) and used within 4 hours. The reconstituted vaccine should be discarded if not used within 4 hours.

3.2.3 Mechanism of Action

Expected immune response in the older adult target population

RSV NAbs play a major role in the prevention of RSV LRTD. Older adults with low serum neutralization titers have been reported to be at greater risk of developing symptomatic RSV infection and of hospitalization than those who have high neutralization titers [Falsey, 1998a; Walsh, 2004a]. Importantly, natural immunity after infection is not long lasting and does not efficiently protect against reinfection, which occurs throughout life [Simoes, 1999; Walsh, 2004b; Falsey, 2006b; Krilov, 2011; Habibi, 2015].

Beyond the humoral response, older adults with diminished RSV-specific CD4+ and CD8+ T cell responses are at risk for infection and severe disease progression. Indeed, older adults have decreased frequencies, functionality and proliferative capacity of RSV-specific T cell responses as compared to younger adults [Looney, 2002; De Bree, 2005; Ely, 2007; Cherukuri, 2013; Cusi, 2010].

Taking into consideration the pre-existing immune responses to RSV and immunosenescence-related decline in RSV-specific immune response of the target population, the RSVPreF3 OA vaccine was designed to provide protection against LRTD by:

- boosting NAb response against both RSV-A and RSV-B. The aim of this vaccinal approach is to trigger an increase in RSV NAbs above the levels elicited by natural infection in older adults.
- boosting RSVPreF3 Th1 CD4+ T cells in older adults to a similar level as seen in young adults vaccinated with unadjuvanted RSVPreF3.

Choice of the antigen and adjuvant

Based on the expected immune response, the vaccine formulation was selected as follows:

- The F glycoprotein was selected as the vaccine antigen because it is a major surface glycoprotein of the virus, it plays a central role in RSV entry into the host cell, and it is highly conserved among RSV-A and RSV-B subtypes. Furthermore, the trimeric preF conformation of F was selected as the vaccine antigen as it is the main target of RSV NAbs in humans following natural exposure to RSV [Magro, 2012; Ngwuta, 2015; Olmsted, 1986; Smith, 2012; McLellan, 2013].
- The adjuvant AS01 facilitates the recruitment and activation of antigen presenting cells carrying vaccine-derived antigens in the draining lymph node, which in turn leads to the generation of RSVPreF3-specific Th 1 CD4+ T cells and induction of RSV-A and RSV-B neutralizing antibody responses. It was considered for inclusion in the RSVPreF3 OA vaccine because of its ability to promote induction of robust specific Th1 CD4+ T cell responses and to induce rapid and durable humoral responses when combined with a protein antigen [Leroux-Roels, 2016; Garçon, 2011; Didierlaurent, 2017]. Adjuvanted vaccines enable induction of CD4+ follicular helper T cells and memory B cells [Pallikkuth, 2020], as well as antibodies with Fc related functions, such as NK cell activation and phagocytosis [Suscovich, 2020; Das, 2021], and complement deposition. *Shingrix*, a vaccine approved by the FDA in 2017 for the prevention of herpes zoster in adults ≥50 YOA (indication expanded in 2021 to adults aged ≥18 YOA who are or will be at increased risk of

herpes zoster due to immunodeficiency or immunosuppression caused by known disease or therapy), contains AS01$_B$ (double quantity of each of the immuno-enhancers relative to AS01$_E$), and has been demonstrated to be highly efficacious with a favorable benefit-risk profile [Lal, 2015; Cunningham, 2016; López-Fauqued, 2019].

4 NON-CLINICAL DATA

The choice of the RSVPreF3 antigen and the use of AS01 were supported by data from toxicology and non-clinical pharmacology studies.

Two Good Laboratory Practice repeat-dose toxicity studies were performed in New Zealand White rabbits to investigate the local tolerance, potential local and systemic toxic effects, and acute reactions, as measured via biomarkers, induced by 3 intramuscular injections of 120 or 240 μg RSVPreF3/dose formulated with $AS01_B$, and to evaluate the persistence, delayed onset or reversibility of any effects over a 4-week treatment-free period. RSVPreF3/$AS01_B$ was well tolerated. No adverse findings were identified as all observed findings did not impact the animals' health, were limited in severity, and were considered to be the expected inflammatory reaction/immune response following the administration of an adjuvanted vaccine.

RSVPreF3 was characterized for its non-clinical immunogenicity in RSV-naïve mice. Vaccine-elicited CD4+ T cells were characterized, using a flow cytometry-based intra-cellular cytokine staining assay, as RSVPreF3-specific CD4+ T cells expressing IL-2 and/or TNF-α and/or IFN-γ. RSVPreF3 was tested either as an unadjuvanted formulation or combined with different adjuvants. When combined with AS01, it elicited the targeted RSV-specific immunity.

This immunity included both the RSV-A and RSV-B NAb and RSV F-specific CD4+ and CD8+ T cell responses. Furthermore RSVPreF3-AS01 elicited higher Ab responses against the highly neutralization-sensitive and PreF-specific antigenic site Ø, when compared to unadjuvanted RSVPreF3. Finally, RSVPreF3-AS01 elicited a high proportion of NAbs among the total elicited RSVPreF3-binding antibodies, demonstrating its capacity to elicit highly potent antibody responses.

As additional supportive pre-clinical evidence, unadjuvanted RSVPreF3 was shown to potently boost RSV F antigenic site Ø-specific Ab responses, and elicit strong RSV NAb responses in bovine RSV-primed cows, a surrogate model of RSV-primed humans [Steff, 2017].

In conclusion, the pharmacology and toxicology studies showed that, in animal models, the RSVPreF3 OA vaccine candidate was well tolerated and induced higher RSV NAb and RSV F-specific CD4+ and CD8+ T cell responses, compared to the unadjuvanted RSVPreF3. Furthermore, RSVPreF3 OA vaccine candidate induced a high proportion of NAbs among the total elicited RSVPreF3-binding antibodies, and potently induced/boosted antibodies recognizing the highly neutralization-sensitive, and PreF-specific, antigenic site Ø. Altogether these results demonstrated that the RSVPreF3 OA vaccine candidate elicited, in animal models, the desired immune response. These results thus supported further clinical evaluation of the RSVPreF3 OA vaccine candidate.

5 SUMMARY OF INTERACTIONS WITH FOOD AND DRUG ADMINISTRATION

During the clinical development of the RSVPreF3 OA vaccine, several regulatory consultations took place with the US FDA (Type B Pre-IND meeting, Type B end-of-Phase 2 meeting, and Type C meetings), and other regulatory authorities (European Medicines Agency; Pharmaceuticals and Medical Devices Agency, Japan; Federal Agency for Medicines and Health Products, Belgium).

The following main items were discussed with and deemed acceptable by the FDA:

- The choice of the immunological assays and GSK qRT-PCR to be used in the Phase 3 studies (method validation reports for all primary and secondary endpoints were shared with the FDA);
- The selected formulation, 120 μg RSVPreF3/AS01$_E$, as a 1-dose regimen for further evaluation in the Phase 3 clinical development program;
- The design of Study 006, including the success criterion for the primary endpoint, to support the assessment of RSVPreF3 OA efficacy, and use of the mES as primary cohort for the efficacy analysis;
- The ARI and LRTD case definitions used in Study 006;
- The adjudication process for RSV LRTD cases in Study 006;
- The design of Study 007, including the non-inferiority margin for evaluation of co-administration of RSVPreF3 OA with FLU-QIV;
- The design of Study 009, assessing L2L consistency;
- The safety data package to support benefit-risk assessment and initial BLA.

6 CLINICAL DEVELOPMENT WITH RSVPreF3 ANTIGEN

Summary

- Clinical development programs with RSVPreF3 have been initiated in pregnant women (unadjuvanted RSVPreF3) and in older adults (RSVPreF3 adjuvanted with AS01E).
- Clinical studies conducted with RSVPreF3 OA in adults ≥60 YOA include:
  - Study 002: a Phase 1/2, randomized, placebo-controlled, observer-blind, dose and formulation selection study.
  - Study 004: a Phase 3, randomized, open-label immunogenicity and safety study.
  - Study 006: a pivotal Phase 3, randomized, placebo-controlled, observer-blind, efficacy and safety study.
  - Study 007: a Phase 3, randomized, controlled, open-label co-administration study, with FLU-QIV.
  - Study 009: a Phase 3, randomized, double-blind, L2L consistency study.

6.1 Clinical Development with RSVPreF3 in Pregnant Women

In parallel with the RSVPreF3 OA clinical development program, GSK initiated development of another RSV vaccine candidate intended for active immunization of pregnant women 18-49 YOA during the second and third trimester of pregnancy to prevent RSV-associated LRTI in infants by transfer of maternal antibodies. The RSV maternal vaccine candidate contains 120 μg of the RSVPreF3 antigen, as does the RSVPreF3 OA vaccine, however it does not include any adjuvant.

In 2020, GSK initiated a phase 3, double-blind, 2:1-randomized, placebo-controlled study (RSV MAT-009; NCT04605159) in 24 countries to assess the safety and efficacy of a single dose of the maternal vaccine candidate (RSVPreF3 Mat) administered to 18–49-year-old women in the late second or third trimester of pregnancy.

In February 2022, the IDMC for the study RSV MAT-009 observed and imbalance in the proportion of preterm births (birth at less than 37 completed weeks of gestation) in the vaccine group versus the placebo group and recommended that study enrollment be paused. GSK voluntarily paused the enrollment, randomization, and vaccination of participants in its active pregnant women studies to investigate the safety signal. Following a review of additional unblinded data from the RSV MAT-009 study, the imbalance in preterm births was noted to be persistent across a range of risk factors, and a higher proportion of neonatal deaths (death of a live born infant within the first 28 completed days of life) reported in the vaccine group compared to the placebo group was also observed. GSK stopped enrollment and vaccination in all ongoing RSV maternal studies as a precautionary measure.

With data from 3,557 pregnant women vaccinated with RSVPreF3 Mat and 1,771 with placebo, the imbalance in preterm births is statistically significant (RR at the day 43 post-delivery interim analysis: 1.38; p=0.009; Table 6.1). The imbalance in neonatal deaths is a consequence of the imbalance in preterm births and not an independent safety signal. There were more extremely <28 weeks gestational age) and very (≥28 and <32 weeks gestational age) preterm-born infants

in the vaccine group, and no imbalance in neonatal death was observed among term-born infants. An in-depth qualitative review of the clinical information available for each neonatal death concluded that the events leading to neonatal death (e.g., very low or low birth weight, sepsis, necrotizing colitis, pneumonia, respiratory distress syndrome, hypoxic-ischemic injury) are commonly observed in preterm-born infants, particularly those who are extremely and very preterm, and there is no consistent temporal pattern of events from birth or from maternal vaccination.

No other safety signal has been observed in infants or mothers. The study remains ongoing for safety and efficacy follow-up.

Table 6.1 Summary of preterm births and neonatal deaths in study RSV MAT-009 - Infant participants - ES

Event:	RSV MAT N=3,496* n	RSV MAT N=3,496* % (95% CI)	Control N=1,739* n	Control N=1,739* % (95% CI)	Relative Risk (95% CI)
Preterm births	238	6.81 (5.99, 7.69)	86	4.95 (3.97, 6.07)	1.38 (1.08, 1.75)
Neonatal deaths	13	0.37 (0.20, 0.64)	3	0.17 (0.04, 0.50)	2.16 (0.62, 7.55)
Neonatal death in an extremely preterm birth (22 ≤ gestational age <28 weeks)	2	0.06 (0.007, 0.21)	0	0.00 (0.00, 0.21)	Not estimable (0.26, inf)**
Neonatal death in a preterm live birth (28 ≤ gestational age <37 weeks)	5	0.14 (0.05, 0.33)	0	0.00 (0.00, 0.21)	Not estimable (0.65, inf)**
Neonatal death in a term live birth (≥ 37 weeks of gestational age)	6	0.17 (0.06, 0.37)	3	0.17 (0.04, 0.50)	0.99 (0.25, 3.97)

* Participants were randomized to the RSV MAT and Control groups with a ratio of 2:1.
** a 95% CI was constructed by using Wilson-type of confidence interval [Miettinen, 1985].For Neonatal death in an extremely preterm birth (22 ≤ gestational age <28 weeks), a risk difference is 0.06% with 95% CI (-0.16%, 0.21%), while for Neonatal death in a preterm live birth (28 ≤ gestational age <37 weeks), a risk difference is 0.14% with 95% CI (-0.08%, 0.33%).RSV MAT = Participants born to vaccinated mother who received RSVPreF3 120 μg dose. Control = Participants born to vaccinated mother who received Sucrose/Placebo. N = number of participants in the corresponding category; n/% = number/percentage of participants with the corresponding event; 95% CI = exact 95% confidence interval. Data lock point: October 4, 2022.

No signal for either preterm birth or neonatal death was observed from the completed RSV MAT-004 Phase 2 study (NCT04126213) in pregnant women, and no imbalances in preterm birth or neonatal death have been observed in the RSV MAT-012 Phase 3 study (NCT04980391) in high-risk pregnancies (ongoing for safety follow-up).

Although GSK has observed an imbalance in the numbers of preterm births in the vaccine group compared with placebo in the RSV MAT-009 study, the overall incidence of preterm birth in the study is low in both groups and remains below the preterm birth background rates for the majority of the participating countries. The imbalance in preterm births was observed more with low and middle-income countries (RR: 1.57, 95% CI: 1.17, 2.10) than high-income countries (RR: 1.04, 95% CI: 0.68, 1.58). In low and middle-income countries, the preterm birth imbalance

peaked from August to December 2021 and was not observed consistently from January 2022 onward.

No association was found with the administered vaccine lot, gestational age at vaccination, time between vaccination and delivery or various risk factors for preterm birth. Investigations into the safety signal and safety follow-up of the mothers and infants are ongoing.

GSK continues to investigate the cause of the safety signal and currently does not have a mechanistic explanation for it. Data are still being collected, and further analysis to better understand the safety data from the RSV maternal trials is ongoing. GSK has initiated a study, RSV MAT-015, to describe the safety of study participants who received RSVPreF3 maternal vaccination (any dose) or control in previous RSV MAT studies during any pregnancy conceived post-vaccination or post-control.

The observed safety signal of preterm birth is specific to pregnant women. The clinical development program of RSVPreF3 OA vaccine, which is presented in this document, is conducted in a different population (adults ≥60 YOA) that does not include pregnant women [Eijkemans, 2014].

6.2 Clinical Development with RSVPreF3 in Adults ≥60 YOA

The clinical data with the RSVPreF3 OA vaccine included in the Biologics License Application (BLA) have been generated in several clinical studies, including Phase 3 studies, that evaluated the efficacy, immunogenicity, safety, co-administration, and L2L consistency of the vaccine. Table 6.2 provides an overview of these studies, including the main purpose, design, population and vaccination schedule.

The clinical program was initiated with the Phase 1/2 **Study 002**, which evaluated the reactogenicity, safety, and immunogenicity of different formulations of the vaccine as compared to placebo, when administered according to a 0, 2-month schedule. As it was a first time in human study, the safety of the RSVPreF3 OA vaccine antigen was first evaluated in healthy adults 18-40 YOA (Part A) before subsequent evaluation in the older adult population 60-80 YOA (Part B). Based on safety and immunogenicity data up to 1 month post-Dose 2, GSK selected 120 μg RSVPreF3/AS01$_E$ as the final vaccine formulation to be given according to a 1 dose regimen for further evaluation in Phase 3 studies in the target population of adults ≥60 YOA.

The Phase 3 program was initiated with the immunogenicity **Study 004**, which evaluates the humoral and cellular immune response as well as the reactogenicity, safety and persistency of the immune response to RSVPreF3 OA administered according to different revaccination schedules in adults ≥60 YOA. The study is ongoing with follow-up until 3 years post-vaccination. While data up to 6 months post-Dose 1 were included in the BLA, this document presents immunogenicity data up to 12 months post-Dose 1.

Efficacy of RSVPreF3 OA is being evaluated in the large pivotal Phase 3 **Study 006**, which is conducted in NH and SH countries. The study was designed to demonstrate the efficacy of a single dose of the RSVPreF3 OA vaccine in the prevention of RSV LRTD during the first RSV season, and assesses the humoral immunogenicity, reactogenicity and safety of the vaccine. VE is planned to be evaluated through 3 consecutive years covering 3 RSV seasons in the NH

and at least 2 seasons in the SH, following a single dose or annual revaccination doses of the RSVPreF3 OA vaccine. The interim analysis (VE1 Analysis) of the primary objective was to be triggered if at least 35 cases of RT-PCR confirmed and externally adjudicated RSV LRTD cases were accrued in the primary cohort of efficacy (mES) with data available at the end of Season 1 in the NH or later. The interim analysis was performed with 47 cases of RSV-confirmed LRTDs accrued in mES up to the efficacy DLP on April 11, 2022 included (i.e., all available data of ARI cases with ARI visit reported up to that date included), and results of this interim analysis were included in the BLA. Humoral immune response data up to 1 month post-vaccination, as well as reactogenicity and safety data up to the DLP of April 30, 2022, were also included in the initial BLA. The post-Dose 1 safety data up to the DLP of September 30, 2022 or up to Dose 2 administration for deaths, related SAEs and related pIMDs, as well as the 6-months post-Dose 1 safety data for all NH and SH participants for all SAEs and pIMDs, were also provided in the BLA.

Immunogenicity, reactogenicity and safety data on co-administration of the RSVPreF3 OA vaccine with FLU-QIV were generated in the Phase 3 **Study 007**. This study aimed to demonstrate non-inferiority of the immune responses to each of the co-administered vaccines as compared to sequential administration. The study is completed, and data up to study end were included in the BLA.

L2L consistency data were generated in the Phase 3 **Study 009**. This study aimed to demonstrate consistency of 3 lots of RSVPreF3 OA in terms of humoral immunogenicity. Safety and reactogenicity of the 3 lots were also evaluated. This study is completed, and data up to 1 month post-vaccination were included in the BLA.

Table 6.2 Details of clinical studies with RSVPreF3 OA

Study	Purpose Status	Study design Duration	Population (age)	Vaccination schedule	Study groups	Participants in ES (N)
002*	Dose and formulation selection study Completed	Phase 1/2, randomized, placebo-controlled, observer-blind‡, multi-center Study duration: 3 months for participants in Part A and 14 months for participants in Part B	**Part A:** Adults 18-40 YOA **Part B:** Older Adults 60-80 YOA	2 doses of RSVPreF3 OA or placebo at Day 1 and Day 61 depending on the group	4 parallel groups in Part A (1:1:1:1): **30-PLAIN_A** **60-PLAIN_A** **120-PLAIN_A** **Placebo_A**† 10 parallel groups in Part B (1:1:1:1:1:1:1:1:1:1): **30-PLAIN_B** **60-PLAIN_B** **120-PLAIN_B** **30-AS01E_B** **60-AS01E_B** **120-AS01E_B** **30-AS01B_B** **60-AS01B_B** **120-AS01B_B** **Placebo_B**†	 12 12 12 12 101 97 100 101 101 100 103 100 101 101
004	Immunogenicity study Ongoing	Phase 3, randomized (3:1:1), open-label, multi-center Study duration: planned to be approximately 3 years for participants in all groups	Older Adults ≥60 YOA	Single dose of RSVPreF3 OA at Day 1 followed by 3 possible revaccination schedules	3 parallel groups: **RSV_annual:** RSVPreF3 OA at Day 1, Month 12, and Month 24 **RSV_flexible revaccination:** RSVPreF3 OA at Day 1 and a revaccination dose at Month 24 **RSV_1dose:** RSVPreF3 OA at Day 1	993 329 331

Study	Purpose Status	Study design Duration	Population (age)	Vaccination schedule	Study groups	Participants in ES (N)
006	Pivotal efficacy study Ongoing	Phase 3, randomized, placebo-controlled, observer-blind‡, multi-center Study duration: planned to be approximately 3 years for participants in the NH and 2.5 to 3 years for participants in the SH	Older Adults ≥60 YOA	Single dose of either RSVPreF3 OA or placebo at Day 1 in all groups at Season 1 and annual revaccination with either RSVPreF3 OA or placebo depending on the group	Season 1 2 parallel groups (1:1): **RSVPreF3:** RSVPreF3 OA **placebo (Control)**: placebo† Season 2 and 3 3 parallel groups: **RSV_annual**: RSVPreF3 OA annual pre-season revaccination doses **RSV_1dose**: placebo† annual pre-season administration **placebo (Control)**: placebo† annual pre-season administration	12,467 12,499 Season 2: Ongoing
007	Co-administration study, with FLU-QIV Completed	Phase 3, randomized (1:1), controlled, open-label, multi-center Study duration: 6 to 7 months (i.e., 6 months after last vaccination in all groups)	Older Adults ≥60 YOA	Single dose of RSVPreF3 OA either co-administered with or given a month apart from a single dose of FLU-QIV	2 parallel groups (1:1): **Co-Ad**: FLU-QIV + RSVPreF3 OA at Day 1 **Control:** FLU-QIV at Day 1 + RSVPreF3 OA at Day 31	442 443
009	Lot-to-lot consistency study Completed	Phase 3, randomized (1:1:1), double-blind, multi-center Study duration: 6 months in all groups	Older Adults ≥60 YOA	Single dose of RSVPreF3 OA at Day 1 in all groups	3 parallel groups (1:1:1): **RSVPreF3_Grp1**: RSVPreF3 OA Lot 1 **RSVPreF3_Grp2:** RSVPreF3 OA Lot 2 **RSVPreF3_Grp3**: RSVPreF3 OA Lot 3	251 253 253

ES = Exposed Set, FLU-QIV = Seasonal Influenza Quadrivalent Inactivated Vaccine; N = number of participants in the ES; NH = Northern hemisphere; SH = Southern hemisphere; YOA = Years of Age.

*Note: Study 011 was an open-label extension of Study 002, which assessed the safety and immunogenicity of a revaccination dose in adults ≥60 YOA. A total of 122 participants were enrolled to receive either 30, 60, or 120 μg of AS01-adjuvanted vaccine 18 months after their final dose in Study 002.

†Placebo = saline solution, NaCl.

‡Observer-blind: the participant, the investigational site and sponsor personnel involved in the clinical evaluation of the participants are blinded. Vaccine has been prepared and administered by qualified study personnel (unblinded) who did not participate in data collection, evaluation or review of any study endpoint (i.e., reactogenicity, safety, efficacy).

7 DOSE AND FORMULATION SELECTION — STUDY 002

Summary

- In the Phase 1/2 Study 002, the formulations containing RSVPreF3 antigen induced humoral immune response (as measured by both RSV-A and RSV-B neutralizing assays, and RSVPreF3-binding IgG assay) as well as cellular (RSVPreF3 specific Th1 CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ) immune responses after a first dose, with no further increase after a second dose.
- The formulations including 120 μg RSVPreF3 induced the highest increase in RSV-A and RSV-B neutralizing titers 1 month post-Dose 1 over baseline, compared to formulations with lower antigen doses.
- Adjuvanted formulations induced a statistically significant higher cellular immune response, compared to unadjuvanted formulations, and restored RSVPreF3-specific Th1 CD4+ T cells in adults 60-80 YOA almost to the level observed in young adults vaccinated with unadjuvanted RSVPreF3.
- Based on immunogenicity and safety data from Study 002, the 120 μg RSVPreF3/AS01$_E$ formulation with a single dose schedule was selected for Phase 3 development.

7.1 Key Design Features

Study 002 was a Phase 1/2, randomized, placebo-controlled, observer-blind, multi-center study that evaluated the safety, reactogenicity, and immunogenicity of different formulations of the RSVPreF3 OA vaccine (adjuvanted with AS01$_E$ or AS01$_B$ or unadjuvanted), as compared to placebo (saline solution, NaCl), when administered intramuscularly according to a 0-, 2-month schedule in adults aged 18-40 or 60-80 YOA.

The study was conducted in 2 parts. In Part A, 48 young adults 18-40 YOA were equally randomized in 4 study groups (12 participants per group) to receive 1 of 3 vaccine formulations containing unadjuvanted RSVPreF3 (at 30, 60, or 120 μg) or placebo. In Part B, 1005 older adults 60-80 YOA were equally randomized into 10 study groups (~100 participants per group) to receive either 1 of the 9 vaccine formulations containing RSVPreF3 (at 30, 60 or 120 μg) unadjuvanted or adjuvanted with AS01$_B$ or AS01$_E$ or placebo (Table 7.1).

Table 7.1 Study 002: Dose formulations and numbers of participants in Parts A and B (ES)

Formulation	Part A	Part B		
Placebo	12	101		
Antigen	**Unadjuvanted**	**Unadjuvanted**	**$AS01_E$**	**$AS01_B$**
30 µg	12	101	101	103
60 µg	12	97	101	100
120 µg	12	100	100	101

$AS01_B$ = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); $AS01_E$ = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21); ES = Exposed Set; YOA = years of age. Part A included young adults aged 18-40 YOA. Part B included older adults aged 60-80 YOA.

The primary analysis of immunogenicity was based on the Per-Protocol Set for immunogenicity (PPSi). Humoral immune response (RSV-A and RSV-B neutralizing titers, RSVPreF3-binding IgG) and cellular immune response (RSVPreF3-specific Th1 CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ [referred as polypositive Th1 CD4+ T cells]) were assessed.

Once the immune response to each of the 9 investigational formulations versus placebo was evaluated, statistical comparisons were performed on the groups pooled according to adjuvant content to (1) select the regimen, (2) demonstrate the effect of the adjuvant, and (3) support selection of the adjuvant dose ($AS01_E$ or $AS01_B$). Selection of the antigen dose was done based on statistical comparisons on the individual groups and by antigen dose level. All the comparisons were performed in terms of RSV-A neutralizing titers and RSVPreF3-specific polypositive Th1 CD4+ T cells.

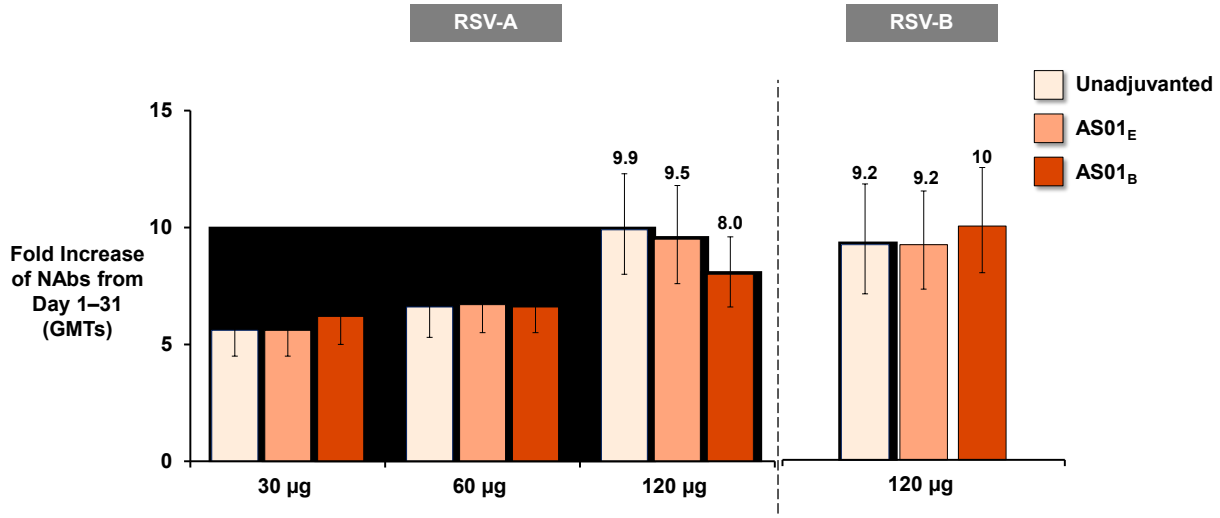
7.2 Overall Immunogenicity of the RSVPreF3 Antigen

All formulations containing RSVPreF3 (with or without adjuvant) induced both humoral and cellular responses after 1 dose.

A 5.6- to 9.9-fold increase (on average post-vaccination titers were 5.6- to 9.9 times the pre-vaccination titers [fold-increase]) in RSV-A neutralizing titers was observed 1 month post-Dose 1 (Figure 7.1) and a statistically significant difference was demonstrated (p-value < 0.025) for all treatment groups versus placebo group (Table 7.2).

Humoral responses to RSV-B were expected to be consistent with RSV-A because the prefusion F protein is highly conserved across RSV subtypes. This was demonstrated through Study 002 (Figure 7.1), Study 004 (Section 9.4.1) and Study 006 (Section 9.4.2).

Figure 7.1 Study 002: Geometric mean fold increase in RSV-A and RSV-B neutralizing titers for 30, 60, and 120 µg RSVPreF3 (with and without adjuvant) 1 month post-Dose 1 – Part B, PPSi



NAb = neutralizing titers (referred to as NAb in the figure); GMT = geometric mean titer; PPSi = Per-Protocol Set for immunogenicity.
Unadjuvanted = participants receiving unadjuvanted RSVPreF3 in Part B; $AS01_E$ = participants receiving RSVPreF3 adjuvanted with $AS01_E$ in Part B; $AS01_B$ = participants receiving RSVPreF3 adjuvanted with $AS01_B$ in Part B.
Day 1 = pre-vaccination on Day 1; Day 31 = 30 days post-Dose.
RSV-B NAb titers at Day 31 were assessed in a subset of participants.

Table 7.2 Study 002: Comparisons of the 9 RSV formulations versus placebo in terms of RSV-A neutralizing titers (ED_{60}) at 1 month post-Dose 1 (ANCOVA model, Dunnett's test) – Part B PPSi

RSVPreF3 Formulation	N	GMT Ratio (RSV over placebo)	Dunnett's p-value
Plain/unadjuvanted			
30 µg	93	6.6 (4.8, 9.0)	<0.0001
60 µg	90	8.3 (6.0, 11.4)	<0.0001
120 µg	90	11.6 (8.4, 15.9)	<0.0001
$AS01_E$ Adjuvanted			
30 µg	92	6.5 (4.8, 8.8)	<0.0001
60 µg	97	7.9 (5.9, 10.6)	<0.0001
120 µg	94	11.3 (8.4, 15.2)	<0.0001
$AS01_B$ Adjuvanted			
30 µg	95	7.3 (5.5, 9.6)	<0.0001
60 µg	95	8.1 (6.1, 10.7)	<0.0001
120 µg	93	9.8 (7.4, 13.1)	<0.0001

ANCOVA = Analysis of Covariance; $AS01_B$ = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); $AS01_E$ = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21); ED_{60} = estimated dilution 60; GMT = geometric mean titer; N = number of participants with available results;; PPSi = Per-Protocol Set for immunogenicity. RSVPreF3 formulation is considered superior to placebo if one-sided p-value <0.025. Dunnett's adjustment was applied.

The ratios of fold increase of RSVPreF3-binding IgG over RSV-A neutralization titers (estimated dilution 60 [ED_{60}]) were similar across treatment groups, ranging from 1.3 to 1.5 at Day 31 (Appendix table 2). This suggests that most antibodies induced by the 9 RSV formulations had neutralizing activity.

The median frequency of RSVPreF3-specific polypositive Th1 CD4+ T cells increased at 1 month post-Dose 1 and a statistically significant difference (p-value < 0.025) was shown for all treatment groups versus placebo.

7.3 Vaccination Regimen Selection (1-Dose Schedule)

No further increase in humoral response was observed after the second dose administered 2 months after the first dose in any of the treatment groups. The statistical comparisons of the mean responses 1 month post-Dose 2 versus 1 month post-Dose 1 in terms of RSV-A neutralizing titers did not show an effect of the second dose (Table 7.3).

Similarly, data did not show a significant effect of the second dose in terms of the frequency of RSVPreF3 specific polypositive Th1 CD4+ T cells (geometric mean ratio of approximately 1, p-value > 0.025, except for $AS01_E$, for which p= 0.0090, with a geometric mean ratio of 1.11]) (Table 7.3).

Based on these data, a single dose regimen was selected and immune responses at 1 month post-Dose 1 were considered as the basis for the selection of the antigen dose and the adjuvant.

Table 7.3 Study 002: Comparisons of the mean responses post-Dose 2 versus post-Dose 1 in terms of RSV-A neutralizing titers (ED_{60}) and RSVPreF3-specific polypositive Th1 CD4+ T cells, on groups pooled according to adjuvant content – Part B, PPSi

	RSV group	N	GMT or GMF Ratio, Day 91 over Day 31 (95% CI)	p-value
			GMT Ratio	
NAb	Unadjuvanted	290	0.70 (0.65, 0.75)	<0.0001
	$AS01_E$	294	0.69 (0.64, 0.74)	<0.0001
	$AS01_B$	295	0.72 (0.66, 0.77)	<0.0001
			GMF Ratio	
CD4+	Unadjuvanted	231	0.94 (0.86, 1.02)	0.1181
	$AS01_E$	232	1.11 (1.03, 1.20)	**0.0090**
	$AS01_B$	239	1.06 (0.98, 1.14)	0.1266

CI = confidence interval; ED_{60} = estimated dilution 60; NAb = neutralizing titers (referred to as NAb in the table); PPSi = per-protocol set for immunogenicity; Unadjuvanted=participants receiving unadjuvanted RSVPreF3 in Part B (30, 60 or 120 μg); $AS01_E$=participants receiving RSVPreF3 adjuvanted with $AS01_E$ in Part B (30, 60 or 120 μg); $AS01_B$=participants receiving RSVPreF3 adjuvanted with $AS01_B$ in Part B (30, 60 or 120 μg). N= Number of participants with both pre- and post-vaccination results available.
Post-Dose 2 Day 91 is considered as significantly higher to Post-Dose 1 Day 31 if the observed ratio is >1 and the one-sided p-value <0.025 (shown in **bold**).
GMT = Geometric mean antibody titer adjusted for covariates (ANCOVA model).
GMT: 95% CI = 95% confidence interval for the adjusted GMT (ANCOVA model: adjustment for covariates – pooled variance); ANCOVA model on the log-transformed titers with the pre-vaccination log-transformed titer as covariate, and the adjuvant content, antigen dose and age category as fixed effects.
GMF = Geometric mean antibody frequency adjusted for covariates (ANCOVA model).
GMF 95% CI = 95% confidence interval for the adjusted GMF (ANCOVA model: adjustment for covariates – delta method); ANCOVA model on the log-transformed frequencies with the pre-vaccination and the background log-transformed frequency as covariate, and the adjuvant content, antigen dose and age category as fixed effects.

7.4 Antigen Dose Selection (120 µg)

A statistically significant difference (p-value < 0.025) on humoral immune response (RSV-A neutralizing titers) with increasing antigen dose was demonstrated at Day 31 between:

- 120-Plain versus 30-Plain,
- 120-$AS01_E$ versus 30-$AS01_E$,
- 120-$AS01_E$ versus 60-$AS01_E$, and
- 120-$AS01_B$ versus 30-$AS01_B$.

The linear effect of the antigen dose was also demonstrated to be statistically significant.

The highest increases in RSV-A neutralizing titers 1 month post-Dose 1 over baseline were observed for the formulations containing 120 μg RSVPreF3, with or without adjuvant, and were

on average 8.0- to 9.9-times the pre-vaccination titers (fold-increase) (Figure 7.1), which is well above the increase reported following natural infection [Walsh, 2004a; Walsh, 2004b; Falsey, 2006b; Walsh, 2013]. This increase supports the selection of the 120 μg antigen dose in the final formulation. Additionally, 1 dose vaccination with formulations containing 120 μg RSVPreF3 brings the neutralizing level in older adults (Part B) within the same range as in young adults vaccinated with unadjuvanted RSVPreF3 OA (Part A).

7.5 Adjuvant and Adjuvant Dose Selection ($AS01_E$)

An immunologic benefit of any $AS01_E$ or $AS01_B$ formulations over unadjuvanted formulations was demonstrated in terms of RSVPreF3-specific polypositive Th1 CD4+ T cells (p-value <0.025, pre-specified analysis on the groups pooled according to their adjuvant content, i.e., $AS01_B$, $AS01_E$, or unadjuvanted). The difference in immunological response observed between the pooled $AS01_E$-based formulations and the pooled $AS01_B$-based formulations after 1 vaccine dose was limited (Table 7.4).

Importantly, formulations adjuvanted with $AS01_E$ or $AS01_B$ restored the frequencies of RSVPreF3-specific polypositive Th1 CD4+ T cells in older adults (Part B) almost to the level observed in young adults vaccinated with unadjuvanted RSVPreF3 (Part A) (Figure 7.2), despite the lower cellular response at baseline observed in the older adults.

The overall reactogenicity in terms of solicited administration site and systemic events of the AS01-adjuvanted formulations was higher than the unadjuvanted formulations. The highest frequencies of solicited administration site and systemic events were observed in the group receiving 120 μg RSVPreF3/$AS01_B$ (in 78.2% and 59.4% of participants, respectively, versus 58.0% and 34.0% of participants who received 120 μg RSVPreF3/$AS01_E$). Most solicited events were mild to moderate in intensity, with few Grade 3 events, and of short duration (median duration equal to or below 2 days). For unsolicited AEs, no clear relationship was noted between the incidence or severity of unsolicited AEs and the antigen dose or the adjuvant ($AS01_E$ or $AS01_B$). No safety concern has been identified for any of the studied formulations.

Table 7.4 Study 002: Comparisons of the RSV groups pooled* according to their adjuvant content in terms of RSV-A neutralizing titers (ED_{60}) and RSVPreF3-specific polypositive Th1 CD4+ T cells at 1 month post-vaccination (ANCOVA model) - Part B, PPSi

	Group 1 (Part B)			Group 2 (Part B)			GMT or GMF Ratio (Group 1 over Group 2)	
	Formulation	N	GMT/GMF (95% CI)	Formulation	N	GMT or GMF (95% CI)	Ratio (95% CI)	p-value
						GMT	GMT Ratio	
NAb	$AS01_E$	283	6823.6 (6148.4, 7573.0)	PLAIN	273	7192.8 (6425.4, 8051.9)	1.0 (0.8, 1.1)	0.4953
	$AS01_B$	283	6970.5 (6321.8, 7685.7)	PLAIN	273	7192.8 (6425.4, 8051.9)	1.0 (0.8, 1.1)	0.6752
	$AS01_B$	283	6970.5 (6321.8, 7685.7)	$AS01_E$	283	6823.6 (6148.4, 7573.0)	1.0 (0.9, 1.2)	0.7664
						GMF	GMF Ratio	
CD4+	$AS01_E$	201	1484.6 (1370.9, 1606.4)	PLAIN	196	1113.1 (1022.8, 1209.8)	1.3 (1.2, 1.5)	**<0.0001**
	$AS01_B$	210	1833.0 (1698.5, 1976.9)	PLAIN	196	1113.1 (1022.8, 1209.8)	1.7 (1.5, 1.8)	**<0.0001**
	$AS01_B$	210	1833.0 (1698.5, 1976.9)	$AS01_E$	201	1484.6 (1370.9, 1606.4)	1.2 (1.1, 1.4)	**0.0001**

ANCOVA = analysis of covariance; CI = confidence interval; ED_{60} = estimated dilution 60; NAb = neutralizing titers (referred to as NAb in the table); PPSi = per-protocol set for immunogenicity.

PLAIN = participants receiving unadjuvanted RSVPreF3 in Part B (30, 60 or 120 μg); $AS01_E$ = participants receiving RSVPreF3 adjuvanted with $AS01_E$ in Part B (30, 60 or 120 μg); $AS01_B$=participants receiving RSVPreF3 adjuvanted with $AS01_B$ in Part B (30, 60 or 120 μg).

* Groups were pooled to increase the chance to detect a significant difference between adjuvanted and plain formulations.

N = Number of participants with both pre- and post-vaccination results available.

GMT = geometric mean antibody titer adjusted for covariates (ANCOVA model).

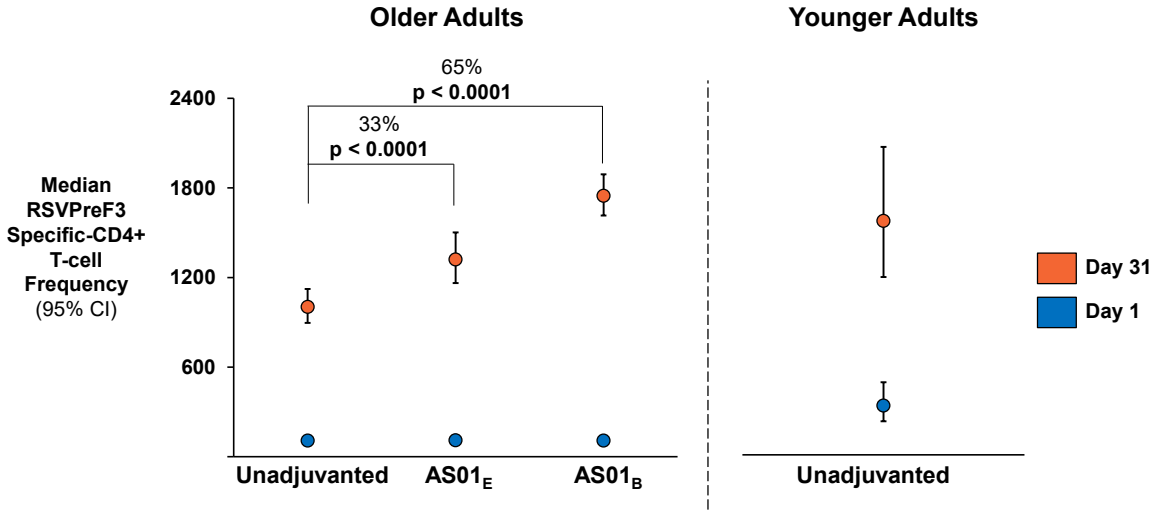
GMT: 95% CI = 95% confidence interval for the adjusted GMT (ANCOVA model: adjustment for covariates – pooled variance); ANCOVA model on the log-transformed titers with the pre-vaccination log-transformed titer as covariate, and the adjuvant content, antigen dose and age category as fixed effects

GMF = geometric mean antibody frequency adjusted for covariates (ANCOVA model).

GMF: 95% CI = 95% confidence interval for the adjusted GMF (ANCOVA model: adjustment for covariates – delta method); ANCOVA model on the log-transformed frequencies with the pre-vaccination and the background log-transformed frequency as covariate, and the adjuvant content, antigen dose and age category as fixed effects.

Group 1 is considered superior to Group 2 (GM ratio >1; no superiority margin used) if one-sided p-value <0.025 (shown in **bold**).

Figure 7.2 Study 002: Comparisons of the RSVPreF3-specific Th1 CD4+ T cell responses among $AS01_E$, $AS01_B$, and unadjuvanted formulations of RSVPreF3 at 1 month post-Dose 1 – Part A and Part B PPSi



$AS01_B$ = Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21); $AS01_E$ = Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21); CI = confidence interval; PPSi = Per-Protocol Set for immunogenicity.
Older adults: participants receiving 30, 60 or 120 µg RSVPreF3 OA unadjuvanted (plain), or adjuvanted with $AS01_E$ or $AS01_B$ in Part B. Younger adults: participants receiving unadjuvanted 30, 60 or 120 µg RSVPreF3 OA in Part A. Day 1 = pre-vaccination on Day 1; Day 31 = 30 days post-Dose.

7.6 Conclusion of Dose and Formulation Selection

Based on immunogenicity and safety data from Study 002, the 120 µg RSVPreF3/$AS01_E$ formulation administered as a single dose schedule was selected for Phase 3 development. This is based on the selected formulation's ability 1) to induce both humoral (RSV-A and RSV-B serum neutralization, and RSVPreF3-binding IgGs) and cellular responses (RSVPreF3 specific polypositive Th1 CD4+ T cells) after a single dose in the target population, 2) restore RSVPreF3-specific Th1 CD4+ T cells in adults 60-80 YOA almost to the level observed in young adults vaccinated with unadjuvanted RSVPreF3, despite lower baseline levels in the older adults, and 3) lower reactogenicity compared to $AS01_B$-adjuvanted formulations.

8 CLINICAL EFFICACY — PIVOTAL PHASE 3 EFFICACY STUDY 006

Summary

- The primary objective of Study 006 was met: RSVPreF3 OA provided high VE against qRT-PCR-confirmed RSV LRTD.
    - The RSVPreF3 OA vaccine decreased the incidence of RSV LRTD by 82.6% (96.95% CI: 57.9, 94.1), compared to placebo. There were 7 RSV LRTD cases observed in the RSVPreF3 OA group (N= 12,466) compared to 40 cases in the placebo group (N=12,494).
- High VE against RSV LRTD was observed throughout the median 6.7 months follow-up period and supports the efficacy over the course of at least one RSV season.
- The observed VE for RSVPreF3 OA against RSV LRTD was >80% for both subtypes, RSV-A and RSV-B (84.6% [95% CI: 32.1, 98.3] and 80.9% [49.4, 94.3], respectively).
- High VE was observed across a spectrum of symptomatic RSV disease, from ARI (71.7% [95% CI: 56.2, 82.3]) to severe LRTD (94.1% [95% CI: 62.4, 99.9]).
- High VE was observed in subgroups at increased risk of developing severe RSV LRTD, including adults with at least 1 comorbidity of interest (94.6% [95% CI: 65.9, 99.9]).
- Results of PROs during RSV disease show that breakthrough cases in the RSVPreF3 OA group had less intense respiratory symptoms which may lead to less impact on functioning/health-related quality of life (HRQoL), than the RSV cases in the placebo group.

8.1 Study Design

8.1.1 Overview of Study Design

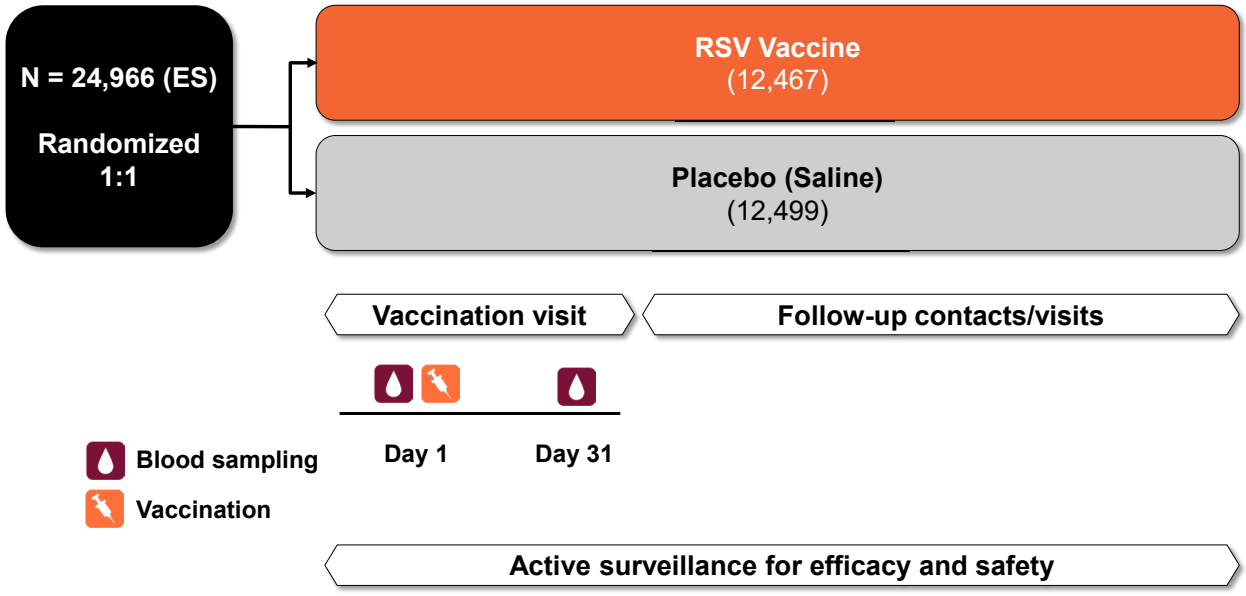
Study 006 is an ongoing Phase 3, randomized, placebo-controlled, observer-blind study to demonstrate the efficacy, and evaluate the immunogenicity, reactogenicity (in a subset), and safety of RSVPreF3 OA when administered as a single dose in adults ≥60 YOA. Pre-Season 1, participants were randomized (1:1) to receive either RSVPreF3 OA vaccine or placebo (saline solution, NaCl). Pre-Season 2, all participants who received RSVPreF3 OA vaccine will be re-randomized in a 1:1 ratio into 2 sub-groups to receive annual revaccination doses of either RSVPreF3 OA or placebo. Participants who received placebo pre-Season 1 will also receive placebo at subsequent timepoints.

This global study is being conducted in multiple centers in 17 countries across both NH and SH. Recruitment began end of May 2021 in the NH and in June 2021 in the SH, with the aim to complete vaccinations before the start of the first RSV season (i.e., October 2021 in the NH and March 2022 in the SH). Participants will be followed for 3 consecutive RSV seasons in the NH and at least 2 consecutive RSV seasons in the SH.

Surveillance for ARI is performed during the entire study, via spontaneous reporting by the study participant (starting on the day of vaccination) and via scheduled site staff contacts (starting from Day 31 onwards) with different frequencies of contact during the RSV seasons and the inter-season periods (refer to Section 8.1.7.1). Swab samples are being collected in all participants meeting pre-specified criteria for ARI case definition (refer to Section 8.1.7.2). Blood samples were taken at pre-vaccination and at Day 31 after vaccination in all participants. An overview of the study design up to the revaccination dose at Season 2 is provided in Figure 8.1.

A total of 26,664 participants were enrolled, of whom 25,040 were randomized 1:1, and 24,981 received the study intervention. At VE Analysis 1, fifteen participants were excluded due to invalid informed consent and 24,966 were included in the ES (12,467 participants in the RSVPreF3 OA group and 12,499 participants in the placebo group). The randomization algorithm used a stratification by subset (participants included in reactogenicity/immunogenicity subset or not) and a minimization procedure accounting for center, age, and region within each stratification factor (subset and non-subset). Participants were enrolled from 3 age categories (60-69, 70-79, and ≥80 YOA) with approximately 55.8%, 36.0% and 8.2% in each age category, respectively. Age groups were stratified by male and female. Participants with chronic stable medical conditions, with or without specific treatment, were allowed to participate if considered by the investigator as medically stable. Patients who were immunocompromised were excluded.

Figure 8.1 Study 006: Design overview*



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

8.1.2 Justification for the Use of Placebo

A controlled, observer-blind, randomized study design was chosen to control for potential bias. As there is currently no licensed RSV vaccine, a saline solution (NaCl) was included as a control (placebo) for the efficacy, safety/reactogenicity, and immunogenicity assessments in Study 006.

8.1.3 Independent Data Monitoring Committee

Study 006 is being monitored by an IDMC that oversees the ethical and safety interests of study participants, while protecting as far as possible the scientific validity of the data, and makes recommendations to GSK concerning the continuation, modification, or termination of the study.

To date, the IDMC has not made any recommendations for actions to be taken for safety reasons after regular unblinded data review.

8.1.4 Adjudication of LRTD Cases

An external LRTD Adjudication Committee was set up for this study with blinded qualified external experts in the respiratory medicine and/or infectious diseases. The LRTD adjudication committee reviewed all RSV qRT-PCR-confirmed cases fulfilling either the LRTD case definition or reported as LRTD by the investigator. Only adjudicated cases were considered for the efficacy endpoint analyses.

8.1.5 Description and Rationale for Firewall Team

To allow assessment of the available data, while also preserving the multi-year blind of the study at the individual participant level, an independent firewall team was established to act as an interface between the GSK study and submission teams, and the regulatory authorities. This firewall team is a restricted group of designated experts from GSK who are not involved in the RSVPreF3 OA clinical development program. This allows the reporting and submission of unblinded results (provided by the independent external statisticians) to the relevant regulatory authorities while maintaining the study blind at individual participant level for the study team (central and local), investigators, and participants until end-of-study database lock.

An independent external statistician executed all statistical analyses and shared the blinded and unblinded output with the firewall team. Following the review of these outputs, the firewall team shared the blinded statistical output with the submission team.

8.1.6 Statistical Methods

8.1.6.1 Efficacy Objectives

The primary objective of Study 006 was to demonstrate the efficacy of a single dose of the RSVPreF3 OA vaccine in the prevention of RSV-A and/or B-confirmed LRTD during the first season in adults ≥60 YOA. This objective was met if the LL of the 96.95% CI for VE was >20%.

The key secondary descriptive objectives supporting the efficacy data were:

- To evaluate the efficacy of a single dose of RSVPreF3 OA in the prevention of RSV LRTD: by age category; for each RSV subtype (A and B) separately; by baseline comorbidities of interest and baseline frailty status.
- To evaluate the efficacy of a single dose of RSVPreF3 OA in the prevention of: RSV ARI; severe RSV LRTD; hospitalization due to RSV respiratory diseases (during the RSV seasons*).

  ** The RSV seasons defined for this study are from 1 October to 30 April in NH and from 1 March to 30 September in SH.*

The key secondary objectives evaluating HRQoL via PROs were to evaluate the impact of a single dose of RSVPreF3 OA in participants with RSV ARI on: ARI total symptoms (based on FLU-PRO Total score); lower respiratory tract symptoms (based on FLU-PRO chest score); health utility score (based on EuroQoL 5-dimension Health Questionnaire [EQ-5D] utility score); and physical functioning (based on Short form 12-item survey [SF-12] physical functioning score).

8.1.6.2 Data Sets Analyzed

Analysis sets used in Study 006 are presented in Table 8.1.

Table 8.1 Analysis sets used in Study 006

Analysis Set	Description	Endpoint
Exposed Set (ES)	All participants who received at least the first dose of the study intervention and with valid informed consent. The allocation in a group was done in function of the administered intervention.	Primary population for the **VE** analysis on endpoints **not related to RSV** (hospitalization, complications, any ARI/LRTD, all-cause mortality)* Population used to complement primary analysis of primary objective** Population for analysis of **safety endpoints** (unsolicited AEs, SAEs, fatal SAEs and pIMDs)
Modified Exposed Set (mES)	All participants in the ES who did not report an RSV ARI prior to Day 15 after vaccination.	Primary population for the **VE** analysis for endpoints related to **RSV-confirmed cases**
Per-Protocol Set for efficacy (PPSe)	All participants in the mES (i.e., who did not report an RSV ARI prior to Day 15 after vaccination) who received at least the first dose of the study vaccine to which they were randomized, have data available for efficacy endpoint measures, did not have protocol deviations leading to exclusion.	Population used to complement primary analysis of primary objective**
mES RSV ARI cases	All participants in the mES who had a qRT-PCR-confirmed RSV ARI case.	Primary population for the **PRO analysis** (FLU-PRO, EQ-5D, SF-12)
mES RSV LRTD cases	All participants in the mES who had a qRT-PCR-confirmed RSV LRTD case.	Primary population for the **PRO analysis** (PGI-S, PGI-C)*
Solicited Safety Set (SSS)	All participants who received at least the first dose of the study intervention (ES) and have solicited safety data.	Population for analysis of **reactogenicity** (solicited AEs) **and safety** endpoints (unsolicited AEs)

Analysis Set	Description	Endpoint
Per-Protocol Set for Immunogenicity (PPSi)	All participants 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.	Primary population for the **immunogenicity** analysis

AE = adverse events; ARI = acute respiratory infection, EQ-5D = EuroQoL 5-dimension Health Questionnaire; ES = exposed set; FLU-PRO = InFLUenza Patient-Reported Outcome; LRTD = lower respiratory tract disease, mES = modified exposed set; PGI-C = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, pIMD = potential immune-mediated disease; PPSe = per-protocol set for efficacy; PPSi = per-protocol set for immunogenicity; PRO = patient-reported outcomes, qRT-PCR = quantitative reverse transcription polymerase chain reaction, SAE = serious adverse event; SF-12 = Short form 12-item survey; VE = vaccine efficacy.
* These analyses are not described in this document.** Additional analyses of the primary objective were performed on the PPSe and on the ES to complement the primary analysis. The VE results of the analyses on the ES and PPSe were consistent with those on the mES, and are not described in this document.

8.1.6.3 Sample size determination

The number of cases needed to trigger the final analysis of the primary endpoint was determined in order to ensure 90% power to demonstrate the primary objective (i.e., the LL of the 95% CI around the VE against RSV LRTD >20%). Assuming a VE of 70%, at least 56 cases were needed. The number of participants to be enrolled in the study was then deducted considering an attack rate of 0.42% (i.e., a low attack rate considering the COVID-19 pandemic context) and a non-evaluable rate of 10%.

With this sample size (N=23,000), should the 56 cases not be accrued by the end of the Season 1 in NH, a pre-planned case driven interim analysis could be triggered when at least 35 externally adjudicated RSV LRTD cases had been reported in the mES.

8.1.6.4 Statistical Analysis of Efficacy Endpoints

The interim VE analysis was performed with 47 cases of externally adjudicated RSV LRTDs accrued in the mES up to the efficacy DLP of April 11, 2022 (i.e., all available data of ARI cases with ARI visit reported up to that date included).

The Wang-Tsiatis approach [Wang, 1987] was used to determine the adjusted alpha levels for the interim analyses. Based on the information available at the time of VE Analysis 1 (47 cases), 96.95% Cis were computed for analysis of the primary endpoint and sensitivity analyses related to the primary endpoint. Results of VE Analysis 1 are considered final for the primary objective as the success criterion was met.

The primary analysis of VE in terms of first occurrence of RSV LRTD was evaluated using the conditional exact binomial method based on the Poisson model [Chan, 1998]. This method computed an exact CI around the rate ratio (ratio of the event rates in the vaccine versus control groups). The analysis considered the exact inference on the RR, adjusted by age categories and regions, conditionally to the total number of cases observed and time at risk. The VE was defined as 1 minus the RR.

For the primary analysis on the mES, the time at risk corresponded to the period starting on Day 15 after the first vaccination up to the first occurrence of event or up to censoring. For the analysis on the ES, the full period after the first vaccination up to the first occurrence of event or censoring was considered for the time at risk. For the throat/nasal swab samples collected at ARI visits for qRT-PCR testing, only the swab samples that were collected within 14 days after the ARI onset (i.e., up to Day 15) were considered for case counting and analysis.

In case of multiple RSV events reported for the same participant, only the first event was considered for the primary analysis of all primary/secondary VE endpoints. The first occurrence of LRTD was considered as RSV-positive case for the primary analysis if at least 1 swab sample tested positive for RSV-A and/or RSV-B by GSK qRT-PCR or by an external qRT-PCR test (non-GSK), if a GSK qRT-PCR result was not available.

For the primary analysis, a case that was positive by the qRT-PCR for RSV-A and/or RSV-B was counted as an RSV case, irrespective of the result for other respiratory viruses tested by multiplex qRT-PCR (co-infection). Any swab samples that were positive for RSV by RSV-A/B qRT-PCR were tested by a multiplex PCR (panel of viruses) for detection of potential viral co-infection.

For each group, the number of participants with RSV LRTD cases, the incidence rates, the VE with (1-α)% CI, and p-value was tabulated for primary efficacy endpoint. The p-value reported in the efficacy tables is the 2-sided exact p-value comparing incidence rates and testing the null hypothesis of VE $\leq$0%. The VE against RSV LRTD was demonstrated if the LL of the 2-sided CI of VE was above 20%. The same alpha was used for the primary endpoint and for the sensitivity analyses of the primary endpoint. For secondary endpoints and subgroups analyses 95% CIs were used. No adjustment for multiplicity was done for descriptive analysis on secondary efficacy endpoints on which no hypothesis testing was predefined.

In order to assess the robustness of the primary objective analysis, several sensitivity analyses were performed: (1) estimation of VE and its 96.95% CI using a Cox proportional hazard regression model [Cox, 1972], adjusted for the same covariates as the primary analysis: age and region, (2) analysis including all RSV LRTD cases either fulfilling case definition and/or confirmed by the study investigators, (3) analysis considering the RSV LRTD cases confirmed by the GSK qRT-PCR only, (4) analysis excluding RSV LRTD cases with viral respiratory co-infections and RSV LRTD cases without respiratory co-infections. In addition, a re-randomization test was performed to show that the randomization procedure using minimization algorithm does not impact the outcome of the primary endpoint.

In addition to subgroup analyses planned as secondary objectives (by age category, by RSV subtype, by baseline comorbidities of interest, and frailty status), VE analysis of primary efficacy endpoint was also performed according to the following subgroups: by sex (male and female), by hemisphere (NH and SH), by region (North America, Europe, Asia, and SH), by race (African, Asian, White, Other) and by ethnicity (Hispanic, not Hispanic).

ARI cases with missing qRT-PCR results were considered negative regardless of the group in which they were reported. This a conservative approach in case of a positive VE.

8.1.6.5 Statistical Analysis of QoL Endpoints

The maximum FLU-PRO scores (e.g., Chest and upper respiratory) during the first 7 days from the onset of ARI symptoms were compared between study groups using a Wilcoxon non-parametric test.

Estimated Least Squares (LS) mean FLU-PRO total score during the first 7 days from the onset of RSV ARI episode for participants with qRT-PCR-confirmed RSV, were analyzed using a repeated measures analysis of variance (ANOVA) model. The LS means estimates for time by study group and the difference in LS means and associated p-values were obtained from the ANOVA model.

The study group difference in LS means of the SF-12 physical functioning scores and EQ-5D utility score at the initial ARI visit was estimated using repeated measures mixed effects model including the timepoints: pre-season, initial ARI visit, and pre-next-season visit.

All provided p-values are 2-sided and unadjusted.

8.1.7 Methods Used to Evaluate Efficacy and Case Definitions

8.1.7.1 Surveillance for Acute Respiratory Infection

Surveillance for ARI is performed all-year around via spontaneous reporting by the study participant (starting on the day of vaccination) and by scheduled site staff contacts (starting from 1 month post-vaccination) with different frequencies of contact during the RSV seasons (bi-weekly) and the inter-season periods (monthly). The RSV seasons defined for this study are from 1 October to 30 April in NH and from 1 March to 30 September in SH.

Spontaneous reporting is the main route to capture ARI episodes and consisted of phone calls by the participants (instructed to contact the investigator/site staff promptly if they experienced an ARI as defined by protocol). For each ARI episode, 2 swab samples (self-collected nasal swab and site-collected nasal/throat swab) were to be taken in all participants meeting pre-specified criteria for ARI (see Section 8.1.7.2 for case definitions). The self-collected swabs were preferably to be done within 48 hours of ARI onset but not later than 5 days after ARI onset. Site-acquired nasal/throat swabs were to be collected during an ARI visit, that was to take place within 6 days after ARI onset (i.e., up to Day 7). In special circumstances (for example in case of suspected COVID-19 and pending SARS-CoV-2 test result, or self-quarantine) and if it was not possible to perform the ARI visit within 6 days after ARI onset, then the interval for this visit and the site swab collection could be extended up to maximum 14 days after ARI onset (i.e., until Day 15).

In addition to the participant's spontaneous reporting, the active surveillance (i.e., regular site staff contacts) helped to capture ARI cases that participants neglected to report.

8.1.7.2 Case Definitions for Acute Respiratory Infection and Lower Respiratory Tract Disease

The efficacy objectives were evaluated according to pre-defined case definitions for ARI and LRTD (Appendix table 1), which were developed based on previous experience in the RSV field (including other manufacturers' experience in clinical studies and previous RSV epidemiological studies conducted by GSK), on regulatory guidelines [EMA, 2018; FDA, 2017; WHO, 2019], on existing diagnostic and treatment guidelines for respiratory infections in adults [Beasley, 2015; Levy, 2010; O'Driscoll, 2008; Schermer, 2009], and on input from consultations with external experts. The case definitions were also discussed and agreed with regulatory agencies.

- An **ARI case** is defined as the concomitant presence of 2 respiratory symptoms/signs, or 1 respiratory and 1 systemic symptom/sign, for at least a day. The ARI case definition includes a limited number of upper and lower respiratory symptoms and signs and is expected to be of high sensitivity and low specificity. This allows easy detection of ARI by the study participant and consequently early swabbing which appears to be more sensitive in detection of RSV [Falloon, 2017b]. The presence of a systemic symptom is not mandatory to trigger swabbing and is expected to be less frequent in older than in younger adults. Particularly, fever in ARIs caused by RSV tends to be less frequent in comparison with influenza viruses [Falsey, 2014].
- An **LRTD case** is defined as the concomitant presence of lower respiratory symptoms and signs; either at least 2 lower respiratory symptoms/signs with at least 1 lower respiratory sign or at least 3 lower respiratory symptoms for at least a day. GSK considers the applied LRTD case definition to be sufficiently discriminative to distinguish LRTD from other pathologies involving sputum and cough, while still allowing for a wide range of respiratory symptoms to be considered in line with the varied presentation of LRTD in older adults.
- **Severe RSV LRTD** was defined as clinical symptomology (i.e., requiring the presence of at least 2 lower respiratory signs or assessed as "severe" by the investigator) or based on supportive therapy (i.e., requiring the need for oxygen supplementation, positive airway pressure therapy or other types of mechanical ventilation).

8.1.7.3 qRT-PCR confirmation for RSV

In Study 006, for any ARI cases identified during the ARI surveillance and with at least 1 swab available, potential RSV infection was assessed by qRT-PCR testing of swab samples at GSK. If a GSK qRT-PCR result was not available for potential RSV infection, non-GSK RT-PCR test results (i.e., an FDA-approved or CE-marked RSV RT-PCR test) performed at local laboratories which were certified and accredited from routine clinical diagnostics were considered for analysis.

The GSK RSV-A and RSV-B qRT-PCR assay was validated before the start of testing in Study 006. Details on the qRT-PCR assay are presented in Section 13.2.4.

8.1.8 Methods Used to Evaluate QoL

8.1.8.1 InFLUenza Patient-Reported Outcome (FLU-PRO)

Symptomatology/burden of an RSV ARI episode was assessed using the FLU-PRO (Version 2.0), a 32-item daily diary, which assesses influenza signs and symptoms across 6 body systems: Nose (4 items), Throat (3 items), Eyes (3 items), Chest/Respiratory (7 items), Gastrointestinal (4 items), and Body/Systemic (11 items). The FLU-PRO Total score is computed as the mean score across all 32 items. Total scores can range from 0 (symptom free) to 4 (very severe symptoms). The FLU-PRO was to be completed daily for each ARI episode to record changes from onset to resolution or for a maximum of 14 days.

The FLU-PRO has been shown to produce scores that are well defined, reliable, valid, and responsive to change in influenza-positive and influenza-negative adults [Powers, 2018a; Powers, 2018b]. The validity of this health survey as a measure of RSV symptoms in adults ≥50 YOA with PCR-confirmed RSV has recently been confirmed in a qualitative, non-interventional, cross-sectional study in the US [Curran, 2022].

8.1.8.2 Short Form 12 acute version 2 (SF-12)

The impact of an RSV ARI episode on patient's physical functioning and other HRQoL domains was assessed using the SF-12 questionnaire, a multi-purpose health survey with 12 questions. The SF-12 covers 8 HRQoL domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). From these domains, summary scores for the physical component and mental component are computed. Higher scores indicate higher functioning and/or HRQoL. The SF-12 questionnaire was to be completed by all participants at Visit 1 (Day 1) and at the ARI visit for participants with ARI.

8.1.8.3 EuroQoL-5D-3L (EQ-5D)

The impact of an RSV ARI episode on HRQoL utility values was assessed using the EQ-5D health utility questionnaire. The EQ-5D assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each on a scale of 1 (no problems) to 3 (extreme problems). The EQ-5D then generates a 5-digit number that summarizes the patient's health profile at that point in time. For example, a patient who responds 1 to all 5 items has a profile "11111." Likewise, a participant who responds with the highest level of difficulty to all items has a profile "33333." These profiles are subsequently converted to a single index utility score in which a higher score indicates a higher level of functioning and/or HRQoL.

The EQ-5D questionnaire was to be completed by all participants at Visit 1 (Day 1) and at the ARI visit for participants with ARI.

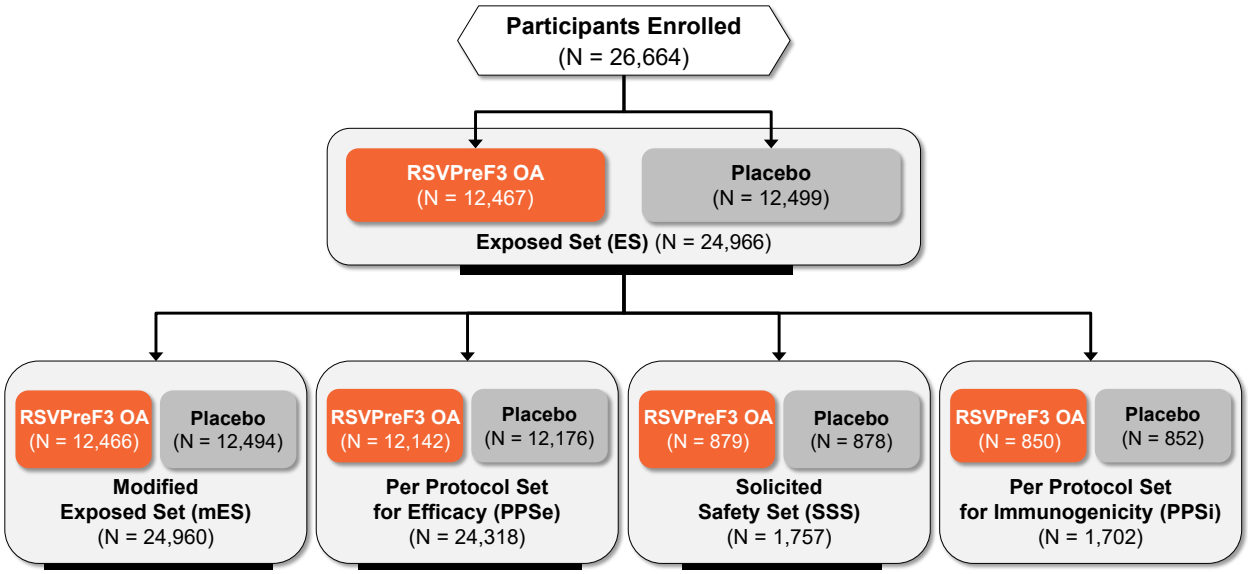
8.2 Results

8.2.1 Participant Disposition

A flowchart of disposition and analysis sets is presented in Figure 8.2.

A total of 26,664 participants were enrolled, of whom 25,040 were randomized 1:1, and 24,981 received a study intervention. At VE Analysis 1, fifteen participants were excluded due to invalid informed consent, and 24,966 were included in the Exposed Set (12,467 participants in the RSVPreF3 OA group and 12,499 participants in the placebo group). The primary efficacy analysis population (Modified Exposed Set [mES]) included 24,960 participants ≥60 YOA who received 1 dose of either RSVPreF3 OA (N=12,466) or placebo (N=12,494). Per protocol, the mES excluded 6 participants who reported RSV ARI within 15 days of vaccination (1 in the RSVPreF3 OA group and 5 in the placebo group).

Figure 8.2 Study 006: Flowchart — Disposition of participants



Reason for 6 eliminations from Exposed Set to Modified Exposed Set was participants had an acute respiratory infection within 15 days from receiving study treatment.

8.2.2 Baseline Demographics and Characteristics

Similar demographic characteristics were observed in the RSVPreF3 OA and placebo groups (Table 8.2). Overall, participants in the ES had a median age at study entry of 69.5 years, with participants with various geographic ancestries, which facilitated diversification of participant population. A total of 39.3% of participants had at least one underlying comorbidity of interest, i.e., conditions that are risk factors for RSV.

Table 8.2 Study 006: Summary of demographic and baseline characteristics — ES

Parameter	RSVPreF3 OA N=12,467 Value or n(%)	Placebo N=12,499 Value or n(%)
Age (years) at vaccination at Visit 1		
Mean	69.5	69.6
Standard deviation	6.5	6.4
Median	69.0	69.0
Age category		

Parameter	RSVPreF3 OA N=12,467 Value or n(%)	Placebo N=12,499 Value or n(%)
≥80 YOA	1,017 (8.2)	1,028 (8.2)
60-69 YOA	6,963 (55.9)	6,980 (55.8)
70-79 YOA	4,487 (36.0)	4,491 (35.9)
Sex		
Male	5,979 (48.0)	6,072 (48.6)
Female	6,488 (52.0)	6,427 (51.4)
Ethnicity		
Hispanic or Latino	682 (5.5)	682 (5.5)
Not Hispanic or Latino	11,779 (94.5)	11,811 (94.5)
Unknown	5 (<0.1)	6 (<0.1)
Race		
African	1,064 (8.5)	1,101 (8.8)
Asian	953 (7.6)	956 (7.7)
White	9,887 (79.3)	9,932 (79.5)
Other*	563 (4.5)	510 (4.1)
Hemisphere		
Northern hemisphere	11,496 (92.2)	11,522 (92.2)
Southern hemisphere	971 (7.8)	977 (7.8)
Type of residence		
Community dwelling	12,306 (98.7)	12,351 (98.8)
Long-term care facilities	161 (1.3)	148 (1.2)
BMI (kg/m²)		
n	12,457	12,490
Mean	29.1	29.1
Standard deviation	6.1	6.0
Median	28.3	28.3
Frailty status		
Frail	189 (1.5)	177 (1.4)
Pre-frail	4,793 (38.4)	4,781 (38.3)
Fit	7,464 (59.9)	7,521 (60.2)
Unknown	21 (0.2)	20 (0.2)
Comorbidity of interest		
≥ 1 pre-existing comorbidity of interest	4,937 (39.6)	4,864 (38.9)
≥ 1 pre-existing cardiorespiratory condition	2,496 (20.0)	2,422 (19.4)
≥ 1 pre-existing endocrinometabolic condition†	3,200 (25.7)	3,236 (25.9)

BMI = body-mass index; ES = Exposed Set; N = number of participants; n/% = number / percentage of participants in a given category; Value = value of the considered parameter; YOA = years of age.
* Includes Native American, Alaska Native, Native Hawaiian and other Pacific Islanders.
† Endocrinometabolic conditions include diabetes mellitus, Type 1 or Type 2, and advanced liver or renal disease.

8.2.3 Primary Efficacy Objective — Efficacy against RSV LRTD Disease in Adults ≥60 YOA

Study 006 met its primary objective to demonstrate the efficacy of a single dose of the RSVPreF3 OA vaccine in the prevention of RSV LRTD during the first RSV season in adults ≥60 YOA.

VE of a single dose of RSVPreF3 OA against RSV LRTD was 82.6% (96.95% CI: 57.9, 94.1), with 7 RSV LRTD cases observed in the RSVPreF3 OA group compared to 40 cases in the placebo group (Table 8.3). The success criterion was met (LL of the 2-sided CI above the pre-defined threshold of 20%), and the interim VE Analysis 1 is considered final for the primary objective.

Table 8.3 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD in adults ≥60 YOA – mES

	RSVPreF3 OA (N=12,466)			Placebo (N=12,494)			Vaccine Efficacy	
Endpoint	n	T (year)	Rate (per 1000)	n	T (year)	Rate (per 1000)	% Efficacy (96.95% CI)	p-value
qRT-PCR-confirmed RSV LRTD	7	6865.9	1.0	40	6857.3	5.8	82.6 (57.9, 94.1)	<0.0001

CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy; YOA = years of age. N = number of participants. N = number of participants with ≥ 1 event of qRT-PCR-confirmed RSV LRTD. RSV LRTD was 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. Rate (n/T) (per 1000) = Incidence rate of participants reporting at least one event. 96.95% CI = 96.95% confidence interval – adjustment of alpha level at interim obtained using Wang-Tsiatis method. P-value = 2-sided exact p-value conditional to number of cases comparing incidence rates.

Subgroup analyses

VE analyses of the primary efficacy endpoint by subgroups showed a high VE (i.e., around 80%) across subgroups aligned with the observations in the overall analysis, except for some subgroup analyses with not enough participants and/or cases to conclude.

8.2.4 Secondary Efficacy Objectives

8.2.4.1 Efficacy across RSV Disease Spectrum

8.2.4.1.1 Efficacy against RSV ARI

A single dose of the RSVPreF3 OA vaccine reduced the risk of developing RSV ARI by 71.7% (95% CI: 56.2, 82.3) with 27 RSV ARI cases observed in the RSVPreF3 OA group compared to 95 cases in the placebo group (Table 8.4) (see Appendix table 1 for ARI definition).

Table 8.4 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV ARI – mES

	RSVPreF3 OA (N=12,466)			Placebo (N=12,494)			Vaccine Efficacy	
Endpoint	n	T (year)	Rate (per 1000)	n	T (year)	Rate (per 1000)	% Efficacy (95% CI)	p-value
qRT-PCR-confirmed RSV ARI	27	6858.7	3.9	95	6837.8	13.9	71.7 (56.2, 82.3)	<0.0001

ARI = acute respiratory infection; CI = confidence interval; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy.
N = number of participants. N = number of participants with ≥1 event of qRT-PCR-confirmed RSV ARI. 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. Rate (n/T) (per 1000) = Incidence rate of participants reporting at least one event. P-value = 2-sided exact p-value conditional to number of cases comparing incidence rates.

8.2.4.1.2 Efficacy against Severe RSV LRTD

The RSVPreF3 OA vaccine reduced the risk of developing severe RSV LRTD by 94.1% (95% CI: 62.4, 99.9, Table 8.5), with 1 case of severe RSV-associated LRTD observed in the RSVPreF3 OA group and 17 cases in the placebo group.

Table 8.5 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV severe LRTD – mES

	RSVPreF3 OA (N=12,466)			Placebo (N=12,494)			Vaccine Efficacy	
Endpoint	n	T (year)	Rate (per 1000)	n	T (year)	Rate (per 1000)	% Efficacy (95% CI)	p-value
qRT-PCR-confirmed RSV severe LRTD	1	6867.9	0.1	17	6867.7	2.5	94.1 (62.4, 99.9)	0.0001

CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; N = number of participants. N = number of participants with ≥1 event of qRT-PCR-confirmed RSV severe LRTD. RSV severe LRTD was identified by clinical symptomology or supportive therapy and confirmed by Adjudication Committee (see Section 8.1.7.2 and Appendix table 1 for definition of severe LRTD). T (year) = sum of follow-up time (from Day 15 post-vaccination till first occurrence of the event or till the efficacy data lock point or till drop-out date) expressed in years. Rate (n/T) (per 1000) = Incidence rate of participants reporting at least one event. P-value = 2-sided exact p-value conditional to number of cases comparing incidence rates.

8.2.4.2 Efficacy by Age Category

VE analysis showed a high efficacy (>80%) across age categories except in participants ≥80 YOA for whom VE was inconclusive due to a lower number of participants (8.2% of mES) and lower number of RSV-associated LRTD cases (5 cases among 2044 participants) (Table 8.6)

Table 8.6 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD by age categories – mES

	RSVPreF3 OA (N=12,466)				Placebo (N=12,494)				Vaccine Efficacy	
Subgroup	N	n	T (year)	Rate (per 1000)	N	n	T (year)	Rate (per 1000)	% Efficacy (95% CI)	p-value
60-69 YOA	6963	4	3850.8	1.0	6979	21	3836.4	5.5	81.0 (43.6, 95.3)	0.0009
70-79 YOA	4487	1	2463.6	0.4	4487	16	2461.6	6.5	93.8 (60.2, 99.9)	0.0003
≥80 YOA	1016	2	-	-	1028	3	-	-	-*	-

CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy; YOA = years of age. N = number of participants. N = number of participants with ≥ 1 event of qRT-PCR-confirmed RSV LRTD. RSV LRTD was 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. Rate (n/T) (per 1000) = Incidence rate of participants reporting at least one event. P-value = 2-sided exact p-value conditional to number of cases comparing incidence rates.
* Due to too few cases observed in adults ≥80 years of age, cannot conclude VE.

8.2.4.3 Efficacy for Participants with Comorbidities of Interest

Participants at increased risk of RSV LRTD due to pre-existing medical conditions were identified using the following preexisting comorbidities of interest at baseline: COPD, asthma, any chronic respiratory/pulmonary disease, diabetes mellitus, chronic heart failure, and advanced liver or renal disease.

RSVPreF3 OA showed high VE against RSV LRTD for participants with ≥1 pre-existing comorbidity of interest: 94.6% (95% CI: 65.9, 99.9) (Table 8.7).

Table 8.7 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD by baseline comorbidity status – mES

	RSVPreF3 OA (N=12,466)				Placebo (N=12,494)				Vaccine Efficacy	
Subgroup	N	n	T (year)	Rate (per 1000)	N	n	T (year)	Rate (per 1000)	% Efficacy (95% CI)	p-value
No comorbidity of interest	7529	6	4094.1	1.5	7633	22	4148.1	5.3	72.5 (30.0, 90.9)	0.0040
≥1 comorbidity of interest	4937	1	2771.8	0.4	4861	18	2709.1	6.6	94.6 (65.9, 99.9)	<0.0001

CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy. N = number of participants. N = number of participants with ≥ 1 event of qRT-PCR-confirmed RSV LRTD. RSV LRTD was 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. Rate (n/T) (per 1000) = Incidence rate of participants reporting at least one event. P-value = 2-sided exact p-value conditional to number of cases comparing incidence rates.

8.2.4.4 Efficacy for Participants with Frailty/Pre-Frailty status at baseline

When analyzed by baseline frailty status assessed by Gait Speed test, VE was 92.9% (95% CI: 53.4, 99.8) for pre-frail participants and 80.0% (95% CI: 46.7, 94.0) for fit participants. It was not possible to establish VE for frail participants due to the lower number of participants and consequently lower number of RSV LRTD cases (2 cases in 366 frail participants) (Table 8.8).

Table 8.8 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD by frailty status – mES

	RSVPreF3 OA (N=12,466)				Placebo (N=12,494)				Vaccine Efficacy	
Subgroup	N	n	T (year)	Rate (per 1000)	N	n	T (year)	Rate (per 1000)	% Efficacy (95% CI)	p-value
Frail	189	1	-	-	177	1	-	-	-*	-
Pre-frail	4792	1	2577.6	0.4	4778	14	2545.3	5.5	92.9 (53.4, 99.8)	0.0009
Fit	7464	5	4182.7	1.2	7519	25	4208.5	5.9	80.0 (46.7, 94.0)	0.0003

CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy. N = number of participants. N = number of participants with ≥ 1 event of qRT-PCR-confirmed RSV LRTD. RSV LRTD was identified by Adjudication Committee. Gait Speed Test Assessment; Frail = Participants with a walking speed <0.4m/s or who were not able to perform the test; Pre-Frail = Participants with a walking speed between 0.4-0.99 m/s; Fit = Participants with a walking speed ≥1 m/s. 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. Rate (n/T) (per 1000) = Incidence rate of participants reporting at least one event. P-value = 2-sided exact p-value conditional to number of cases comparing incidence rates.
* Due to too few cases observed in frail category, cannot conclude VE.

8.2.4.5 Efficacy by RSV Subtype (A or B)

Efficacy results indicate that the RSVPreF3 OA vaccine provides a similar level of protection against LRTD and ARI caused by both RSV subtypes, RSV-A and RSV-B (Table 8.9).

Table 8.9 Study 006: VE against first occurrence of qRT-PCR-confirmed RSV LRTD and RSV ARI by RSV subtype – mES

	RSVPreF3 OA (N=12,466)			Placebo (N=12,494)			Vaccine Efficacy	
qRT-PCR-Confirmed	n	T (year)	Rate (per 1000)	n	T (year)	Rate (per 1000)	% Efficacy (95% CI)	p-value
RSV-A LRTD	2	6867.4	0.3	13	6868.9	1.9	84.6 (32.1, 98.3)	0.0074
RSV-B LRTD	5	6866.7	0.7	26	6862.3	3.8	80.9 (49.4, 94.3)	0.0002
RSV-A ARI	9	6865.2	1.3	32	6862.3	4.7	71.9 (39.7, 88.2)	0.0004
RSV-B ARI	18	6861.7	2.6	61	6849.4	8.9	70.6 (49.6, 83.7)	<0.0001

ARI = acute respiratory infection; CI = confidence interval; LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy.
N = number of participants. N = number of participants with ≥ 1 event of qRT-PCR-confirmed RSV LRTD or RSV ARI. RSV LRTD was 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 DLP or till drop-out date) expressed in years. Rate (n/T) (per 1000) = Incidence rate of participants reporting at least one event. P-value = 2-sided exact p-value conditional to number of cases comparing incidence rates. Note: for RSV cases confirmed by local testing, RSV subtype information is not available.

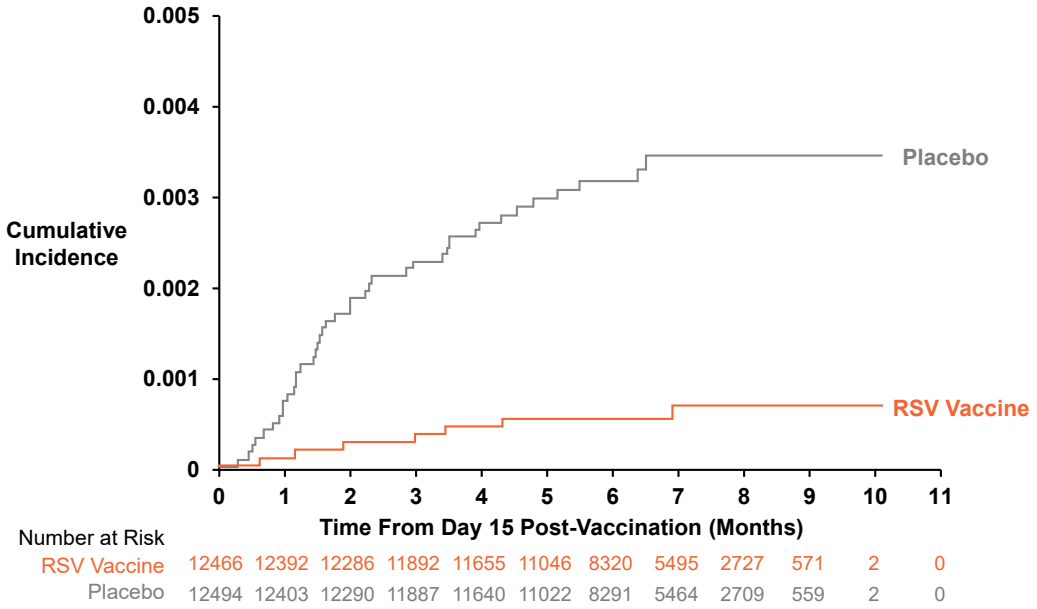
8.2.4.6 Efficacy against Hospitalizations Due to RSV Respiratory Diseases

Up to the efficacy DLP of April 11, 2022, 2 hospitalizations due to RSV respiratory disease were reported. Because of the low numbers, no conclusions could be made regarding VE of RSVPreF3 OA against hospitalization due to RSV respiratory disease.

8.2.4.7 Efficacy over Time

- The median follow-up time up to VE Analysis 1 in the mES was 6.7 months (10.1 maximum) overall, and 6.9 months for both groups in the NH, where all RSV LRTD cases occurred. Cumulative incidence curves of RSV LRTD cases reported from Day 15 post-vaccination up to VE Analysis 1 support high efficacy against RSV LRTD through the median follow-up period of 6.7 months (Figure 8.3) and supports the efficacy over the course of at least one RSV season.

Figure 8.3 Study 006: Cumulative incidence curves for qRT-PCR-confirmed RSV LRTD reported up to VE Analysis 1 – mES



LRTD = lower respiratory tract disease; mES = modified Exposed Set; qRT-PCR = quantitative reverse transcription polymerase chain reaction; VE = vaccine efficacy.

8.2.5 Results of Patient-Reported Outcomes

Results of the median Maximum FLU-PRO Chest/Respiratory score (see Section 8.1.8 for definitions) show that the RSVPreF3 OA vaccine attenuates the severity of RSV ARI in breakthrough cases. The observed reduction in symptoms translated into a reduced impact of RSV infection on physical functioning and into a better QoL.

- **Median Maximum FLU-PRO Chest/Respiratory score:** Overall, 82.0% of participants completed at least 1 FLU-PRO questionnaire during the first 7 days of the RSV ARI episode. The difference of the median Maximum (worst) FLU-PRO Chest/Respiratory score during the first 7 days between the RSVPreF3 (1.07) and placebo (1.86) group was statistically significant with a p-value of 0.0258 (Table 8.10). A minimally clinically important difference of 0.26 was estimated for the FLU-PRO chest score. As such, the observed difference in medians between the study groups (i.e., 0.79) for the FLU-PRO chest score is considered clinically meaningful. These data show that participants with breakthrough RSV ARI cases in the RSVPreF3 OA group had a reduction in intensity of respiratory symptoms versus the placebo group. Participants in the RSVPreF3 OA group reported less severe chest symptoms, such as trouble breathing, chest tightness, and frequency and severity of cough, compared to placebo during the first 7 days of the RSV ARI episode.
- **SF-12 Physical Functioning domain:** Compliance with completion of the SF-12 questionnaire was 99.2% at baseline and 73.0% for the 1 scheduled assessment during the RSV ARI. During the ARI episode, the LS Means was 7.0 (95% CI: -9.9, 23.9; p=0.4125) points higher for the RSVPreF3 OA group compared to placebo (Table 8.10). Decrease from baseline to during the RSV ARI episode was 2.0 points in the RSVPreF3 OA group and 11.4 points in the placebo group.

- **EQ-5D Utility score:** Compliance with completion of the EQ-5D questionnaire was 99.2% at baseline and 72.1% for the 1 scheduled assessment during the RSV ARI episode. During the ARI episode the LS Means was 0.079 (95% CI: -0.034, 0.191; p = 0.1695) point higher for the RSVPreF3 OA group compared to placebo (Table 8.10). There was no decrease from baseline to during the RSV ARI episode in the RSVPreF3 OA group while the mean decreased by 0.048 point in the placebo group.

The median Maximum FLU-PRO Chest/Respiratory score results and the values for the SF-12 and EQ-5D show that breakthrough cases in the RSVPreF3 OA group had less intense respiratory symptoms which may lead to less impact on functioning/HRQoL, than the RSV cases in the placebo group.

Table 8.10 Study 006: Summary statistics of maximum FLU-PRO Chest /Respiratory score, SF-12 Physical Functioning Domain score and EQ-5D Utility score – mES RSV ARI cohort

Instrument	Parameter	RSVPreF3 OA N=27	Placebo N=95	Difference	95% CI	p-value
Maximum FLU-PRO Chest/Respiratory	N with data	24	76			
	Mean	1.32	1.90	0.58	-	0.0258
	Median	1.07	1.86	0.79		
	Q1	0.29	1.43			
	Q3	2.21	2.50			
SF-12 Physical functioning domain	N with data	20	69			
	Baseline	74.2	76.6			
	During RSV ARI	72.2	65.2	7.0	-9.9, 23.9	0.4125
	Standard Error	10.0	9.8	8.5		
EQ-5D Utility score	N with data	19	69			
	Baseline	0.862	0.859			
	During RSV ARI	0.890	0.811	0.079	-0.034, 0.192	0.1695
	Standard Error	0.072	0.074	0.057		

ARI = acute respiratory infection; CI = confidence interval; EQ-5D = EuroQoL 5-dimension Health Questionnaire; FLU-PRO = InFLUenza Patient-Reported Outcome; mES = modified Exposed Set; SF-12 = Short form 12-item survey.
FLU-PRO: The maximum FLU-PRO Chest/Respiratory score is the highest score observed during the first 7 days of the first episode. The P-value is obtained from the non-parametric Wilcoxon Rank Sum test of the difference between vaccination groups. The Chest / Respiratory domain is composed of 7 items. A higher score indicates a higher level of symptoms/problems.
SF-12 and EQ-5D: SF-12 and EQ-5D questionnaires to be completed once during the episode on day of onset. LS Means (Least Squares Means) are obtained from the longitudinal model featuring the baseline assessment, the assessment during the RSV ARI episode and the assessment pre-following season including terms for vaccination group, timepoint and timepoint by vaccination group interaction term. Difference=differences in LS Means between vaccination groups. CI= 95% confidence interval of the difference. A higher score indicates a higher level of functioning/quality of life.
Note: Cases reported from vaccination up to efficacy data lock point = 11APR2022.

8.3 Efficacy Conclusions

Study 006 data show that a single dose of RSVPreF3 OA vaccine offers a high level of protection for adults ≥60 YOA against a spectrum of symptomatic RSV-A and RSV-B associated diseases.

The primary endpoint of Study 006 was met demonstrating high VE of RSVPreF3 OA vaccine against RSV-A and/or B LRTD in adults ≥60 YOA. Compared with placebo, the RSVPreF3 OA vaccine decreased the incidence of RSV-A and/or RSV-B LRTD by 82.6% (96.95% CI: 57.9, 94.1), with 7 RSV LRTD cases observed in the RSVPreF3 OA group compared to 40 cases in the placebo group.

The cumulative incidence curves illustrate high VE against RSV LRTD observed through the median follow-up period of 6.7 months. This, in addition to the high VE observed, supports that the vaccine provides protection against RSV LRTD for the duration of at least one RSV season.

A high VE was observed across subgroups by age with point estimates >80% in the age groups ≥60, 60-69, and 70-79 YOA. No conclusions could be drawn for adults ≥80 YOA due to the low number of participants/cases in this category. Nevertheless, there is no reason to believe VE would not be sustained in this subgroup since no decline in VE was observed with increasing age when analyzed per 10-year strata (60-69 YOA versus 70-79 YOA). In addition, immune responses are consistent across the different age groups (60-69 YOA, 70-79 YOA, and ≥80 YOA) (Sections 9.4.1.3 and 9.4.2.1).

High VE of 94.6% (95% CI: 65.9, 99.9) was observed for participants with at least 1 comorbidity of interest (COPD, asthma, any chronic respiratory/ pulmonary disease, diabetes mellitus, chronic heart failure, advanced liver or renal disease).

The RSVPreF3 OA vaccine reduced the risk of developing RSV ARI by 71.7% (95% CI: 56.2, 82.3) and the risk of developing severe RSV LRTD by 94.1% (95% CI: 62.4, 99.9).

The statistically and clinically meaningful difference in the median Maximum FLU-PRO Chest/Respiratory score between the RSVPreF3 OA and placebo groups and the values of SF-12 and EQ-5D show that breakthrough RSV ARI cases in the RSVPreF3 OA group have less intense respiratory symptoms, which may lead to less impact on functioning/HRQoL.

9 IMMUNOGENICITY

Summary

- Results from the immunogenicity Study 004 show that the RSVPreF3 OA vaccine is immunogenic in terms of RSV-A and RSV-B neutralizing titers, RSVPreF3-binding IgG concentrations, and frequency of RSVPreF3-specific CD4+ T cells up to at least 12 months after administration as a single dose. One month post-vaccination titers were, on average, 10.5-times, 7.8-times and 12.2-times the pre-vaccination titers (fold-increase), for the neutralization A assay, the neutralization B assay as well as RSVPreF3-binding IgG, respectively, and were consistent across age groups.
- These results are supported by immunogenicity data from Study 006, which showed at 1 month post-vaccination, the RSV-A serum neutralizing titers, on average, 10.2 times the pre-vaccination titers, RSV-B neutralizing titers 8.6 times the pre-vaccination titers, and RSVPreF3-binding IgG concentrations 13.1 times the pre-vaccination concentrations
- The immunological non-inferiority of RSVPreF3 OA co-administered with FLU-QIV compared to RSVPreF3 OA administered sequentially 1 month apart was demonstrated in Study 007.
- L2L consistency was demonstrated between 3 RSVPreF3 OA vaccine lots in terms of RSVPreF3-binding IgG concentration at 1 month post-vaccination, in Study 009.

9.1 Key Features of Phase 3 Immunogenicity Studies

9.1.1 Study 004 Design and Key Features

Study 004 is a Phase 3, randomized, open-label immunogenicity study to evaluate the immunogenicity of the RSVPreF3 OA vaccine when administered as a 1-dose regimen in adults ≥60 YOA followed until 3 years post-vaccination. In addition, the study is designed to evaluate the immunogenicity of different revaccination schedules (with one group receiving 2 revaccinations, at Months 12 and 24, and a second group receiving a single revaccination at Month 24). The immunogenicity data of the RSVPreF3 OA vaccine to support initial filling and the immunogenicity claims in the prescribing information are based on data up to 6 months post-Dose 1, including:

- Humoral immune response in terms of RSV-A and RSV-B neutralizing titers (primary objective) and RSVPreF3-binding IgG concentrations (secondary objective), in the *Humoral Immunity Subset*.
- Cell-mediated immune response in terms of frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, hereafter referred to as polypositive CD4+ and/or CD8+ T cells (secondary objective), in the *Cell-Mediated Immunity Subset*).

Immunogenicity data at 12 months post-vaccination are also presented in this document.

Study 004 and 006 enrolled populations of same age range and with the same inclusion/exclusion criteria.

9.1.2 Study 006 Immunogenicity Assessment

The pivotal Phase 3 Study 006 also assessed humoral immunogenicity response in a subset of participants via blood samples collected pre-vaccination and at 1 month post-vaccination (see Section 8.1 for additional details on design of Study 006).

9.1.3 Study 007 Design and Key Features

Study 007 was a Phase 3, randomized, controlled, open-label co-administration study, which aimed to demonstrate non-inferiority of the immune response to each of the co-administered vaccines as compared to sequential administration of each vaccine 1 month apart. In this study, the non-inferiority of the immune response to each of the co-administered RSVPreF3 OA and FLU-QIV vaccines (in terms of RSV-A neutralizing titers and serum HI titers for each of the flu strains, respectively) as compared to the sequential administration of the FLU-QIV and RSVPreF3 OA vaccines were evaluated as co-primary objectives.

9.1.4 Study 009 Design and Key Features

Study 009 was a Phase 3, randomized, double-blind, L2L consistency study. This study aimed to demonstrate the consistency of 3 lots of RSVPreF3 OA vaccine administered as a single dose in adults ≥60 YOA in terms of RSVPreF3-binding IgG GMCs at 1 month post-vaccination. Evaluation was done on 3 randomly selected RSVPreF3 drug product lots extemporaneously reconstituted with 3 randomly selected AS01$_E$ adjuvant lots, resulting in 3 unique random combinations, as per FDA request.

9.2 Methods Used to Evaluate Immunogenicity

The humoral immune response was evaluated by serum RSV-A and RSV-B neutralization assays for determination of serum neutralization titers against RSV-A and RSV-B, and by RSVPreF3-binding IgG enzyme-linked immunosorbent assay (ELISA) for measurement of IgG antibodies binding to the RSVPreF3 protein. The cellular immune response was evaluated using an intracellular cytokine staining (ICS) assay performed on peripheral blood mononuclear cells samples stimulated with a PreF3 peptide pool. All assays were validated before the start of the Phase 3 testing. Details on process of immunogenicity testing and variability of assays are presented in Sections 13.2.1, 13.2.2, and 13.2.3.

9.3 Statistical Methods

9.3.1 Immunogenicity Endpoints

The main immunogenicity endpoints presented and discussed in this document are (Table 9.1):

- Humoral immune response in terms of:
    - Neutralizing titers (referred as NAb hereafter) against RSV-A and RSV-B.
    - RSVPreF3-binding IgG concentrations.

  - Serum HI titers (referred as HI Ab hereafter) for each of the FLU-QIV vaccine strains.

- Cell-mediated immune response in terms of frequency of RSVPreF3-specific polypositive CD4+ T cells.

Table 9.1 Overview of primary and secondary immunogenicity endpoints in Phase 3 studies

	Study 004	Study 006	Study 007	Study 009
Primary – Humoral immune response				
RSVPreF3 OA: NAb titers against RSV-A and RSV-B	GMT and MGI at **Days 1 and 31, Months 6** and 12 post-Dose 1, in a subset of participants	-	GMT ratio for RSV-A[1] 1 month after RSVPreF3 OA (Control group **Day 61** divided by Co-Ad group **Day 31**); Success criteria for NI: The UL of the 2-sided 95% CI is ≤1.5.	
RSVPreF3 OA: RSVPreF3-binding IgG concentrations				GMC ratio at **Day 31**; Success criteria for L2L: The 2 sided 95% CI of the GMC ratios between each pair of the 3 lots is within the pre-defined clinical limit of [0.67, 1.5].
FLU-QIV: HI Ab titers for each of the FLU-QIV vaccine strains	-	-	GMT ratio at **Day 31** after FLU-QIV (Control group divided by Co-Ad group); Success criteria for NI: The UL of the 2-sided 95% CI is ≤1.5.	
Secondary – Humoral immune response				
RSVPreF3 OA: NAb titers against RSV-A and RSV-B	GMT and MGI 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 participants	GMT and MGI at **Days 1, 31**, pre-Season 2 and pre-Season 3 in a subset of participants	GMT and MGI at **Day 61** in the Control group and **Day 31** in the Co-Ad group (1 month after RSVPreF3 OA): MGI (RSV-A), GMT ratio and MGI (RSV-B, in a subset of participants).	
RSVPreF3 OA: RSVPreF3-binding IgG concentrations	GMC and MGI at **Days 1 and 31, Months 6**, 12, 18, 24, 30 and 36 post-Dose 1, and at 1 month after each revaccination dose (Months 13 and 25), in a subset of participants	GMC and MGI at **Days 1, 31**, pre-Season 2 and pre-Season 3 in a subset of participants		MGI at **Day 31**
FLU-QIV: HI Ab titers for each of the FLU-QIV vaccine strains	-	-	**Day 31** after FLU-QIV: SCR and MGI, **Days 1 and 31:** GMT, SPR	-

	Study 004	Study 006	Study 007	Study 009
Secondary – Cellular immune response				
RSVPreF3 OA: Frequency of RSVPreF3-specific polypositive CD4+ and/or CD8+ T cells[2]	**Days 1 and 31, Months 6**, 12, 18, 24, 30 and 36 post-Dose 1, and at 1 month after each revaccination dose (Months 13 and 25), in a subset of participants	-	-	-

Ab = antibody; CI = confidence interval; FLU-QIV = Seasonal Influenza Quadrivalent Inactivated Vaccine; GMC = geometric mean concentration; GMT = geometric mean titer; HI = hemagglutination inhibition; IgG = Immunoglobulin G; L2L = lot-to-lot consistency; MGI = mean geometric increase; NAb = neutralizing antibody; NI = non-inferiority; SCR = seroconversion rate; SPR = seroprotection rate; UL = upper limit.
Timepoints indicated in **bold** are included in the Biologics License Application.
[1] RSV-B NAb titers were assessed as a secondary endpoint in Study 007.
[2] RSVPreF3-specific polypositive CD4+/CD8+ T cells expressing at least 2 activation markers including at least 1 cytokine among CD40L, IL-2, TNF-α, IFN-γ and also including IL-13, IL-17 and 4-1BB in the Phase 3 study.

9.3.2 Data Sets Analyzed

In all studies, the primary analysis of immunogenicity was based on the PPSi.

In Study 004, immune response evaluations were performed in a subset of participants (*Humoral Immunity Subset*, including approximately 60% of the total study population, and *Cell-Mediated Immunity Subset*, including approximately 35% of the total study population).

In Study 006, assessment of the humoral immune response was performed in a subset including approximately 7% of the total study population (*Reactogenicity and Immunogenicity Subset*). The participants contributing to this subset were recruited from a selected number of countries and of sites, in which the first participants in each age category were allocated to the subset until the allocated target was reached.

9.3.3 Statistical Analysis of Immunogenicity Endpoints

Descriptive analysis

The humoral immune response was assessed by any of: RSV-A and RSV-B neutralizing titers expressed as GMT, RSVPreF3-binding IgG expressed as GMC, and MGI from baseline. Cell-mediated immune responses (RSVPreF3-specific polypositive CD4+ and/or CD8+ T cells response expressed as median frequency and geometric mean) were analyzed using descriptive statistics. RSV-A and -RSV-B serum neutralization titers are expressed in ED_{60}.

The immunogenicity analysis was also performed by age category (≥65, ≥70, ≥80, 60-69, and 70-79 YOA). Additional subgroup analyses were performed by sex (Study 004), hemisphere (Study 006), and region (studies 004 and 006).

Confirmatory inferential analyses

In Study 007 (co-administration with FLU-QIV), non-inferiority analyses in terms of RSV-A neutralization and HI antibody titers were performed using a likelihood-based analysis of covariance model, including the treatment group, the age category (60-69, 70-79, or ≥80 YOA), country, and sex as fixed effects, and the pre-dose log_{10}-transformed titer as covariate. Non-inferiority was demonstrated if the UL of the 2-sided 95% CI on the group GMT ratio (group receiving sequential administration of RSVPreF3 OA and FLU-QIV vaccines, divided by group receiving the vaccines concomitantly administered) was ≤1.5 for RSVPreF3 OA vaccine and each of the FLU-QIV strains.

In Study 009 (L2L consistency), the 3 RSVPreF3 OA lots were compared in terms of RSVPreF3-binding IgG concentrations at 1 month post-vaccination, with a 1-sided alpha of 2.5%. L2L consistency was demonstrated if the 2-sided 95% CI of the GMC ratios between each pair of the 3 lots was within the pre-defined clinical limit of [0.67, 1.5]. A sensitivity analysis was performed to compare titers induced in different groups (analysis of covariance model), which included the vaccine group, age category, and center as fixed effects, and the pre-dose log_{10}-transformed titer as covariate.

9.4 Immunogenicity Results from Phase 3 Studies

9.4.1 Study 004 — Characterization of Immune Response and Persistence up to 12 Months Post-Vaccination

9.4.1.1 Humoral Immune Response

The RSVPreF3 OA vaccine elicited higher humoral immune responses (i.e., RSV-A and RSV-B serum neutralization GMT and RSVPreF3-binding IgG GMC) at 1 month post-Dose 1 compared to pre-vaccination (Table 9.2). The humoral immune responses declined by 12 months post-vaccination but remained well above pre-vaccination levels.

Table 9.2 Study 004: Humoral immune response up to 12 months post-vaccination – Humoral PPSi (pooled)

	GMT or GMC		MGI (Fold Increase before vs after Vaccination)	
Time Point	**N**	**Value (95% CI)**	**N**	**Value (95% CI)**
RSV-A neutralization titers (ED_{60})				
Day 1	985	863.4 (819.7, 909.4)		
Day 31	937	9096.5 (8509.0, 9724.5)	937	10.5 (9.9, 11.2)
Month 6	924	3749.0 (3532.0, 3979.5)	923	4.4 (4.2, 4.6)
Month 12	870	2667.2 (2505.5, 2839.4)	869	3.1 (3.0, 3.3)
RSV-B neutralization titers (ED_{60})				
Day 1	986	1235.0 (1171.2, 1302.1)		
Day 31	937	9627.0 (9084.7, 10201.6)	937	7.8 (7.3, 8.3)
Month 6	924	4295.7 (4069.5, 4534.4)	924	3.5 (3.4, 3.7)
Month 12	870	2886.1 (2724.2, 3057.7)	870	2.3 (2.2, 2.5)
RSVPreF3-binding IgG (ELU/mL)				
Day 1	985	7486.9 (7194.9, 7790.7)		
Day 31	937	91123.5 (87326.7, 95085.3)	936	12.2 (11.6, 12.8)
Month 6	924	35162.8 (33679.8, 36711.2)	923	4.7 (4.5, 5.0)
Month 12	870	26161.1 (25098.1, 27269.1)	870	3.5 (3.4, 3.6)

CI = confidence interval, ED_{60} = estimated dilution 60; ELISA = enzyme-linked immunosorbent assay; ELU/mL = ELISA units per milliliter; GMC = geometric mean concentration, GMT = geometric mean titer, IgG = immunoglobulin G, MGI = mean geometric increase, PPSi = Per-Protocol Set for immunogenicity.
Day 1 = pre-vaccination on Day 1; Day 31 = 30 days post-Dose 1; Month 6 = 6 months post-Dose 1; Month 12 = 12 months post-Dose 1.

9.4.1.2 Cellular Immune Response

The RSVPreF3 OA vaccine induced higher frequencies of RSVPreF3-specific polypositive CD4+ T cells, at 1 month post-Dose 1 compared to pre-vaccination levels (Table 9.3).

The cell-mediated immune responses declined by 12 months post-vaccination but remained above pre-vaccination levels. No change in the RSVPreF3-specific polypositive CD8+ T cell response was observed at analyzed timepoints.

Table 9.3 Study 004: RSVPreF3-specific polypositive CD4+ T cell response up to 12 months post-vaccination – Cellular PPSi (pooled groups)

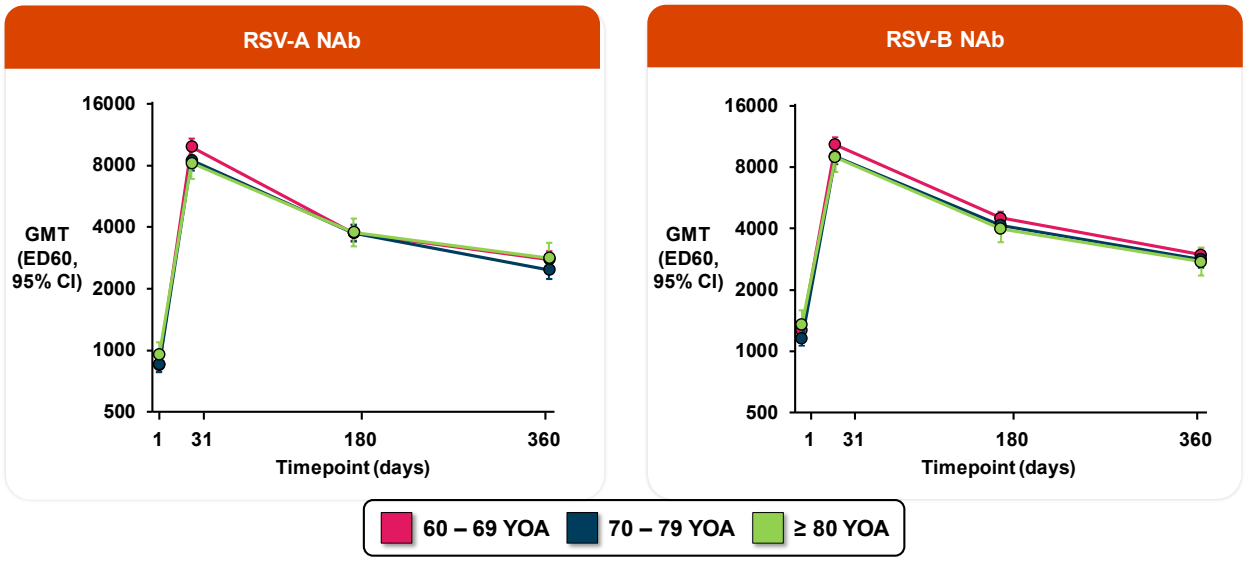
Time Point	N	Median Frequency (Q1, Q3)	Geometric mean
Day 1	471	190.0 (71.0, 364.0)	96.7
Day 31	408	1344.0 (825.5, 2142.0)	1262.1
Month 6	436	669.0 (428.0, 1049.5)	617.9
Month 12	438	575.5 (348.0, 927.0)	509.1

N = number of participants with available results. Q1 and Q3 = 25th and 75th percentiles; PPSi = per-protocol set for immunogenicity. Day 1 = pre-vaccination on Day 1; Day 31 = 30 days post-Dose 1; Month 6 = 6 months post-Dose 1; Month 12 = 12 months post-Dose 1.

9.4.1.3 Subgroup Analyses (By Age Group, Sex and Region)

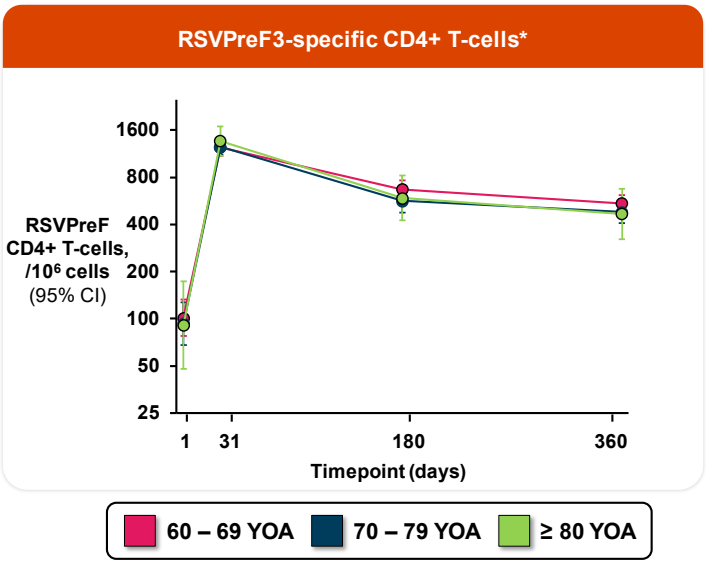
In the PPSi for Study 004, the humoral immune response (RSV-A and RSV-B neutralizing titers), as well as the cellular immune response were high and consistent across the different age groups (Figure 9.1 and Figure 9.2).

Figure 9.1 Study 004: Humoral response by age group up to 12 months after vaccination – PPSi



CI = confidence interval; ED = estimated dilution; GMT = geometric mean titer; NAb = neutralizing titers (referred as NAb in the figure); PPSi = per-protocol set for immunogenicity; YOA = years of age.

Figure 9.2 Study 004: Cellular immune response by age group up to 12 months after vaccination – PPSi



CI = confidence interval; PPSi = per-protocol set for immunogenicity; YOA = years of age.

No trend in humoral or cellular immune response by sex was observed in Study 004.

When RSV-A and RSV-B neutralizing titers were analyzed by region, although a lower MGI tended to be observed at Day 31 in Asia and Europe than in North America, results remained well above pre-vaccination values at all timepoints in all regions.

9.4.2 Study 006 — Humoral Immune Response in Pivotal Phase 3 Study

The humoral immunogenicity data in terms of serum RSV-A and RSV-B neutralizing titers, and RSVPreF3-binding IgG concentrations obtained in Study 006 are in line with the data observed in Study 004.

Robust increases in RSV-A and RSV-B neutralizing titers, both above the -increase following natural infection in older adults [Walsh, 2004a; Walsh, 2004b; Falsey, 2006b; Walsh, 2013], were observed. Similarly, an increase in RSVPreF3-binding IgG concentrations was observed at Day 31 (Table 9.4).

Table 9.4 Study 006: Humoral immune response up to 1 month post-vaccination – PPSi

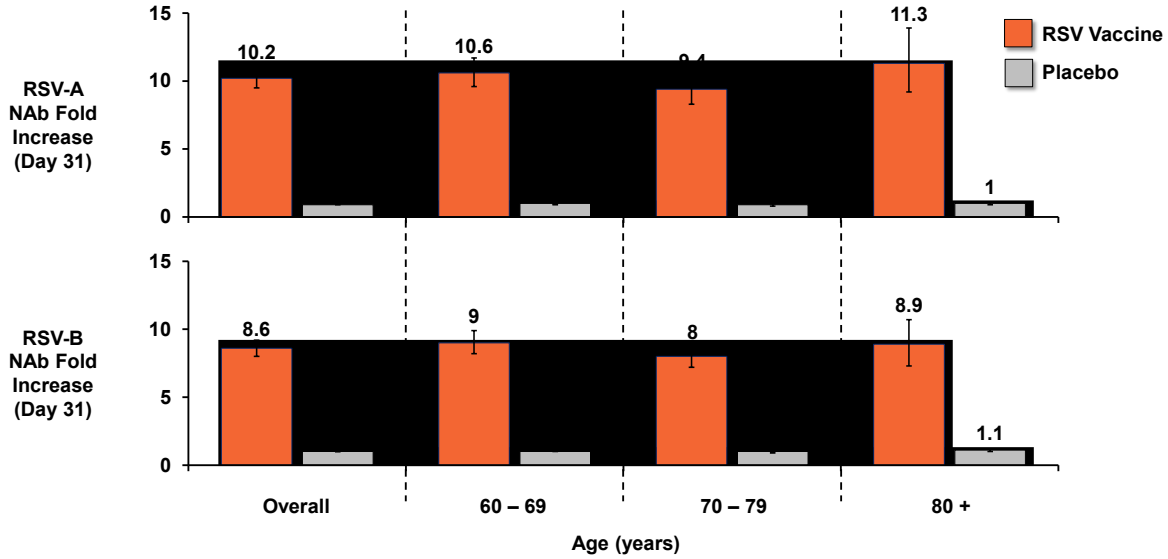
Time Point	GMT or GMC for RSVPreF3 OA group		MGI (Fold Increase before vs after Vaccination)	
	N	Value (95% CI)	N	Value (95% CI)
RSV-A neutralizing titers (ED_{60})				
Day 1	885	918.0 (865.7, 973.5)		-
Day 31	848	9329.7 (8699.3, 10005.8)	844	10.2 (9.5, 11.0)
RSV-B neutralizing titers (ED_{60})				
Day 1	885	1195.8 (1130.5, 1264.8)		-
Day 31	848	10178.1 (9564.1, 10833.1)	844	8.6 (8.0, 9.2)
RSVPreF3-binding IgG (ELU/mL)				
Day 1	885	7041.1 (6719.7, 7377.8)		-
Day 31	848	91729.9 (87514.2, 96148.7)	844	13.1 (12.3, 13.9)

CI = confidence interval; ED_{60} = estimated dilution 60; ELISA = enzyme-linked immunosorbent assay; ELU/mL = ELISA units per milliliter; GMC = geometric mean concentration; GMT = Geometric mean antibody titers; IgG = immunoglobulin G; MGI = mean geometric increase; N = number of participants with available results; PPSi = per-protocol set for immunogenicity.
Day 1 = pre-vaccination on Day 1; Day 31= 30 days post-Dose 1.

9.4.2.1 Subgroup Analyses (By Age Group, Hemisphere and Region)

In the PPSi for Study 006, the humoral response (RSV-A and RSV-B neutralizing titers) at 1 month post-vaccination was high and consistent across the different age groups (Figure 9.3).

Figure 9.3 Study 006: Humoral immune response by age group at 1 month post-vaccination – PPSi



NAb = neutralizing titers (referred as NAb in the figure); PPSi = per-protocol set for immunogenicity. Day 31 = 30 days post-Dose 1.

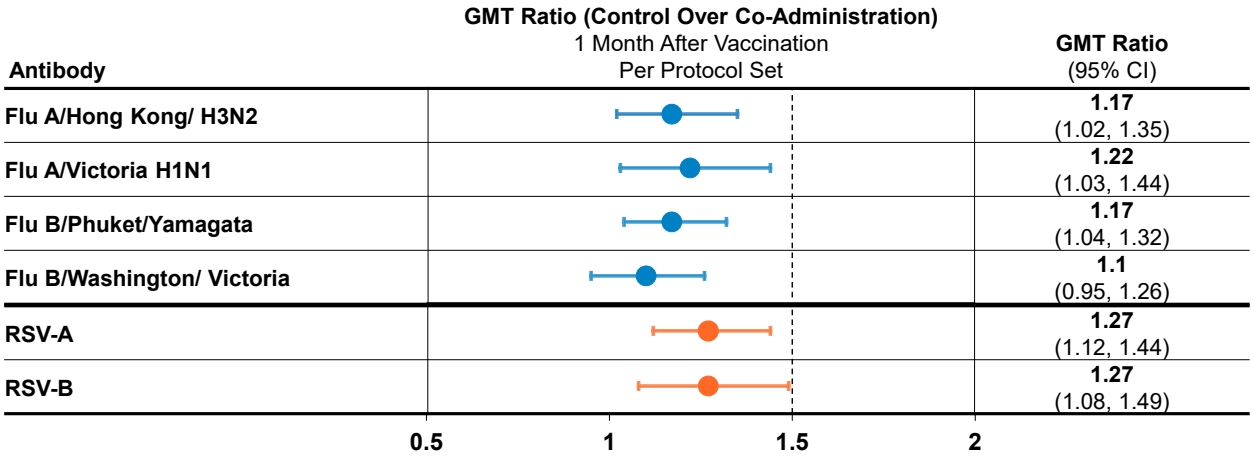
Subgroup analyses by hemisphere and by region of RSV-A, RSV-B neutralizing titers and RSVPreF3-binding IgG concentrations were consistent with the overall data from Study 006. Of note, the pre-vaccination levels of RSV-A, RSV-B neutralizing titers and RSVPreF3-binding IgG concentrations in Asia were lower than in other regions, although the MGI was high and consistent with other subgroups.

9.4.3 Study 007 — Immune Response when Co-Administered with Seasonal Influenza Vaccine

Both co-primary objectives of the co-administration Study 007 were met:

- RSVPreF3 OA co-administered with FLU-QIV demonstrated non-inferiority to RSVPreF3 OA administered alone with respect to RSV-A serum neutralization GMTs (ED_{60}): the UL of the 95% CI for the GMT ratio (Control:Co-Ad Groups) was ≤1.5 (Figure 9.4).
- FLU-QIV co-administered with RSVPreF3 OA demonstrated non-inferiority to FLU-QIV administered alone with respect to HI GMTs for each of the 4 strains: the ULs of the 95% CIs for the GMT ratios (Control:Co-Ad Groups) were ≤ 1.5 (Figure 9.4).

Figure 9.4 Study 007: Ratio of RSV-A serum neutralization GMTs and HI GMTs between Control group and Co-Ad group, 1 month post-vaccination - PPSi



CI = confidence interval; Co-Ad = co-administration; GMT = geometric mean titer; HI = hemagglutination inhibition; PPSi = per-protocol set for immunogenicity.
Note: Non-inferiority was demonstrated if the UL of the 2 sided 95% CI on the group GMT ratio (Control group divided by Co-Ad group) was ≤1.5 for RSVPreF3 OA vaccine and each of the FLU-QIV strains. RSV-B neutralizing titers were assessed as secondary descriptive endpoint in a subset of participants.

9.4.4 Study 009 — Lot-to-Lot Consistency

The primary objective of the L2L consistency Study 009 was met. L2L consistency (3 lots) of the RSVPreF3 OA vaccine administrated as a single dose in adults ≥60 YOA has been demonstrated in terms of RSVPreF3-binding IgG GMCs 1 month post-vaccination, since the 2-sided 95% CI of the GMC ratios between each pair of the 3 lots was within the pre-defined clinical limit of [0.67, 1.5] (Table 9.5).

Table 9.5 Study 009: Ratio of RSVPreF3-binding IgG GMCs between groups, 1 month post-vaccination – PPSi

Parameter:	RSVPreF3 OA Lot		Ratio (95% CI)
	Lot 1	Lot 2	
N GMC	234 86039.9	237 80518.0	1.06 (0.94, 1.21)
	Lot 1	**Lot 3**	
N GMC	234 86039.9	237 94260.9	0.92 (0.81, 1.04)
	Lot 2	**Lot 3**	
N GMC	237 80518.0	237 94260.9	0.87 (0.77, 0.99)

CI = confidence interval; GMC = geometric mean concentration; IgG = immunoglobulin G; PPSi = per-protocol set for immunogenicity. N = number of participants with available results Comparison is done using the adjusted group ratio of GMCs (ANCOVA model applied to the logarithm- transformed titers). The ANCOVA model includes the treatment group and the age category (age at vaccination: 60-69, 70-79 or ≥80 years) as fixed effects and the pre-dose log-10 titer as covariate

The RSVPreF3-binding IgG GMCs observed at baseline and at Day 31 post-vaccination were similar to the GMCs observed in studies 002, 004, and 006 (Table 9.6).

Table 9.6 Study 009: Humoral immune response in terms of RSVPreF3-binding IgG (ELU/mL) 1 month post-vaccination – PPSi (pooled groups)

Time point	GMC		MGI (Fold Increase before vs after Vaccination)	
	N	Value (95% CI)	N	Value (95% CI)
Day 1	749	7380.6 (6994.0, 7788.7)		-
Day 31	708	86760.8 (82236.7, 91533.8)	708	11.9 (11.1, 12.7)

CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; ELU/mL = ELISA units per milliliter; GMC = geometric mean concentration; IgG = immunoglobulin G; MGI = mean geometric increase; PPSi = per-protocol set for immunogenicity.
N = number of participants with available results; N for MGI = number of participants with available results at both time points. Day 1 = pre-vaccination on Day 1; Day 31= 30 days post-Dose 1.

9.5 Immunogenicity Conclusions

A single dose of RSVPreF3 OA vaccine induced strong humoral and cellular immune responses in adults ≥60 YOA, which remained above pre-vaccination levels up to at least 12 months post-vaccination.

The immunogenicity data obtained following a single dose of the RSVPreF3 OA vaccine in the Phase 3 multi-country studies confirm the ability of the RSVPreF3 antigen to elicit serum neutralizing titers against both RSV-A and RSV-B strains, and cell-mediated immune response as observed in the earlier Phase 1/2 Study 002.

In the Phase 3 immunogenicity Study 004, the RSVPreF3 OA vaccine was found to be immunogenic in terms of RSV-A and RSV-B neutralizing titers, RSVPreF3-binding IgG concentrations and frequency of RSVPreF3-specific polypositive CD4+ T cells up to at least 12 months after administration as a single dose in adults ≥60 YOA. One month post-vaccination titers were, on average, 10.5-times, 7.8-times and 12.2-times the pre-vaccination titers (fold-increase), for the neutralization A assay, the neutralization B assay as well as RSVPreF3-binding IgG. The increases in RSV-A and RSV-B neutralizing titers were both above the increase following natural infection in older adults [Walsh, 2004a; Walsh, 2004b; Falsey, 2006b; Walsh, 2013], and were observed across all age groups.

Humoral immunogenicity data from the pivotal Phase 3 efficacy Study 006 support findings from Study 004. At 1 month post-vaccination, the RSV-A serum neutralizing titers were, on average, 10.2 times the pre-vaccination titers, RSV-B neutralizing titers 8.6 times the pre-vaccination titers, and RSVPreF3-binding IgG concentrations 13.1 times the pre-vaccination concentrations. These increases were observed across all age groups.

The immunological non-inferiority of RSVPreF3 OA co-administered with FLU-QIV compared to RSVPreF3 OA administered sequentially 1 month apart was demonstrated in Study 007, supporting the co-administration of both vaccines without jeopardizing the immune response.

10 CLINICAL SAFETY

Summary

- The main source of safety data is the pivotal Phase 3 Study 006, which includes reactogenicity data for 1,757 participants (of whom 879 were vaccinated with RSVPreF3 OA) and safety data in 24,966 participants (of whom 12,467 were vaccinated with RSVPreF3 OA), with a median follow-up of nearly 12 months.
    - Higher reactogenicity was reported in the RSVPreF3 OA group as compared to the placebo group (71.9% versus 27.9% for any solicited events).
    - Most reported solicited events were mild to moderate in intensity, with few Grade 3 events (<2%), and of short duration (median duration between 1 and 2 days).
    - The most commonly reported solicited events within 4 days post-vaccination were pain at the injection site, fatigue, myalgia, headache, and arthralgia.
    - In the ES, which included also participants for which solicited events following vaccination were not collected, unsolicited AEs were more frequently reported in the RSVPreF3 OA group compared to placebo. This difference was mainly driven by events reflecting vaccine reactogenicity.
    - SAEs (including fatal SAEs) and pIMDs occurring within 6 months post-vaccination, as well as fatalities reported up to the safety DLP were balanced between RSVPreF3 OA and placebo groups.
    - A higher number of AEs and SAEs of atrial fibrillation were observed in the RSVPreF3 OA group compared to placebo within 30 days post-vaccination; no difference in serious events of atrial fibrillation between groups was observed at 6 months post-vaccination. GSK believes these events more plausibly reflect the epidemiology of the older adult population and the expected disease course of atrial fibrillation rather than a vaccine effect.
- No case of anaphylaxis to vaccine was reported in any of the studies.
- Results from the co-administration Study 007 show that the RSVPreF3 OA vaccine has an overall clinically acceptable safety profile when co-administered with FLU-QIV.

The safety data from the pivotal, placebo-controlled Phase 3 efficacy Study 006, which represents nearly 80% of the overall exposure (12,467 participants in Study 006 out of 15,745 participants receiving RSVPreF3 OA in all Phase 3 studies; refer also to Section 10.1), was used as the main source to support the benefit-risk profile of the RSVPreF3 OA vaccine in the target population of adults ≥60 YOA.

The safety and reactogenicity data from the Study 006 (refer to Section 10.3) are supported by:

- Data from the 3 additional Phase 3 studies (004, 007, and 009), as well as supportive data from the Phase 1/2 dose selection Study 002. The results from these studies are in line with the data obtained in Study 006 and are therefore not provided in this document, except for co-administration data from Study 007 (refer to Section 10.5).
- Data pooled across the Phase 3 studies (004, 006, 007, and 009). Aggregated analyses for the RSVPreF3 OA group were performed for unsolicited AEs with a medically attended visit, SAEs, and non-serious or serious pIMDs (refer to Section 10.4).

For the ongoing studies 004 and 006 in which revaccination doses are administered, only events following administration of the first dose of RSVPreF3 OA vaccine were considered in the individual safety analyses and aggregated analyses.

10.1 Extent of Exposure to RSVPreF3 OA vaccine

Across the clinical development program, safety data are available for 15,845 participants which have received at least 1 dose of RSVPreF3 OA. In the Phase 3 clinical studies, 15,745 participants ≥60 YOA received at least 1 dose of the RSVPreF3 OA vaccine (Table 10.1).

In Study 006 12,467 participants received RSVPreF3 OA vaccine, and 12,499 participants received placebo, and were included in the ES. Among participants receiving the RSVPreF3 OA vaccine, 4,704 participants were from North America (including 3,469 participants from the US), 5,916 participants were from Europe, 876 participants were from Asia, and 971 participants were from the SH. The median safety follow-up time, from Dose 1 up to DLP of September 30, 2022 or up to Dose 2 administration (if administered before DLP), was nearly 12 months (364 days). At the time of DLP, 76.2% of participants, all from the NH, had attended their Visit 3 (Pre-Season 2 visit), which occurred approximately 12 months post-Dose 1.

The aggregated analyses across all Phase 3 studies considered all data following administration of 1 dose of RSVPreF3 OA vaccine, except in case of co-administration with FLU-QIV. 15,303 participants were included: 5,645 participants from North America (US, Canada and Mexico), 6,892 participants from Europe, 1,369 participants from Asia and 1,397 participants from the SH. The median safety follow-up duration was 7.9 months.

The aggregated analysis used the same DLP (see Table 10.2) as for the individual study analyses, except for Study 006. For this study, a first safety analysis was performed at the time of the interim efficacy analysis (VE Analysis 1) with a DLP of April 30, 2022. The aggregated analysis includes data up to the DLP of this first analysis. A second safety analysis was performed with a DLP of September 30, 2022. Individual safety data from Study 006 are shown up to the DLP of this second analysis.

Table 10.1 Number of participants evaluated for safety in studies presented in this document

Study	Age	Number of participants in each study (ES) (RSVPreF3 OA)
Phase 3 studies		
Study 006	≥60 YOA	12,467
Study 004		1,653
Study 007		868
Study 009		757
Total (Phase 3)		**15,745**
Phase 1/2 study		
Study 002 (Part B)	60–80 YOA	100
Total (Phase 1/2 and Phase 3)		**15,845**

ES = Exposed Set; YOA = years of age.

10.2 Methods Used to Evaluate Safety

In the Phase 3 studies, AEs reflecting reactogenicity (administration site events: pain, erythema and swelling, and systemic events: fever, headache, fatigue, myalgia, and arthralgia) were actively solicited for 4 days after vaccination (i.e., day of vaccination and 3 subsequent days) using paper diary cards (collected only for participants in the Reactogenicity subset in Study 006).

In addition to these solicited events, all other AEs that occurred within 30 days after vaccination (i.e., day of vaccination and 29 subsequent days) were collected as unsolicited AEs.

As for all vaccines containing adjuvant systems, pIMDs, which are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology, were collected. AEs to be recorded and reported as pIMDs are those listed in Appendix table 3. In addition, events not included in the pre-defined list of pIMDs but identified as per investigator judgment were collected as pIMDs.

In all Phase 3 studies, all pIMDs and SAEs were collected up to 6 months post-vaccination. In the Phase 3 studies 004 and 006, which have a duration of longer than 6 months, collection of pIMDs and SAEs considered as related to vaccination (according to the investigator), as well as fatal SAEs, is performed throughout the duration of the studies (Table 10.2).

Events were classified by Medical Dictionary for Regulatory Activities (MedDRA) PT. Using clinical judgment, the investigator assessed the intensity of each event and the presence or absence of a possible causal relationship to study vaccination according to criteria specified in the study protocols. The intensity of each event was graded on a 3-point scale (Appendix table 4 and Appendix table 5).

Table 10.2 Reporting periods for safety events in the Phase 3 studies

Phase 3 Study	Follow-up Time				DLP for safety (follow-up in months post RSVPreF3 OA vaccination)
	Solicited AEs	Unsolicited AEs	SAEs/ pIMDs	SAEs/pIMDs with causal relationship to vaccination and fatal SAEs	
004	4 days post-vaccination	30 days post-vaccination	6 months post-vaccination	Entire study period*	February 11, 2022 (at least 6 months for all participants)
006					September 30, 2022 (12 months**)
007					February 8, 2022*** (6 months)
009					March 9, 2022 (at least 1 month for all participants)

AE = adverse event; DLP = data lock point; pIMD = potential immune-mediated disease; SAE = serious adverse event.
*Note that for studies 007 and 009, the entire study period equals 6 months post RSVPreF3 OA vaccination. For studies 004 and 006, the entire study period equals approximately 3 years.
**12 months (364 days) refers to the median safety follow-up time in Study 006, when considering the DLP of September 30, 2022. Note: for the aggregated analysis the DLP of April 30, 2022, corresponding to the first safety analysis in Study 006, was used.
*** February 8, 2022 corresponds to the date of the last participant's last contact for this completed study. Database freeze date is March 18, 2022.

10.2.1 Analyses of Safety Endpoints

Safety was assessed as a secondary objective in all Phase 3 studies, with the following descriptive safety endpoints:

- Occurrence of each solicited administration site and systemic event within a 4-day period after vaccination (collected for a subset of participants in Study 006).
- Occurrence of unsolicited AEs within a 30-day period after vaccination.
- Occurrence of SAEs and pIMDs (serious and non-serious) from vaccination up to 6 months.
- Occurrence of SAEs and pIMDs (serious and non-serious) with causal relationship to vaccination (as per investigator's assessment) from vaccination up to study end or next vaccination.
- Occurrence of fatal SAEs, regardless of causality assessment, from vaccination up to study end or next vaccination.

The safety analyses per study are provided in Table 10.3.

Table 10.3 Safety analyses for individual Phase 3 studies

Safety analyses	Study 004	Study 006		Study 007	Study 009
	Exposed Set	Exposed Set	Solicited Safety Set	Exposed Set	Exposed Set
Summary of AEs (solicited only or solicited and unsolicited) within solicited follow-up period or within 30 days following vaccination, including Grade 3, Grade 3 non-serious and with a medically attended visit*	●	●	●	●	●
Number and percentage of participants with solicited administration site/systemic events during the solicited follow-up period, including Grade 3 solicited events	●		●	●	●
Number and percentage of participants with unsolicited AEs during the 30-day post-vaccination period, including Grade 3 unsolicited AEs, unsolicited AEs with relationship to vaccination**, Grade 3 unsolicited AEs with relationship to vaccination** and with a medically attended visit**	●	●	●*	●	●
Number and percentage of participants reporting [any/Grade 3] unsolicited AEs within 4 days following vaccination*		●	●		
All SAEs during the safety follow-up period	6 months post-vaccination	6 months post-vaccination		up to study end	until DLP
All pIMDs during the safety follow-up period	6 months post-vaccination	6 months post-vaccination		up to study end	until DLP
All SAEs/pIMDs with causal relationship to vaccination and fatal SAEs	until 6 months post-vaccination and until DLP	until 6 months post-vaccination and until DLP		up to study end	until DLP
Duration of solicited events during the follow-up period	●		●	●	●
Duration of solicited events ongoing beyond the solicited follow-up period	●		●	●	●

AE = adverse event; DLP = data lock point; pIMD = potential immune-mediated disease; SAE = serious adverse event.
*The results for these analyses are not presented in this document.
**Any and Grade 3 unsolicited AEs with relationship to vaccination and with a medically attended visit were only assessed for the Exposed Set in Study 006.
● Indicates safety analyses performed for the study.

10.2.2 Study Cohorts Evaluated

10.2.2.1 Reactogenicity

The analysis of reactogenicity was performed on the:

- SSS for Study 006 (i.e., participants included in the Reactogenicity subset who received either RSVPreF3 OA vaccine or the placebo and who recorded solicited safety data),
- ES for studies 004, 007 and 009 (i.e., all participants with valid informed consent and at least 1 study vaccine administration documented).

10.2.2.2 Unsolicited AEs, SAEs, and pIMDs

In each individual study, the analysis of unsolicited AEs, SAEs, and pIMDs was based on the ES.

The aggregated analysis performed across all Phase 3 studies for unsolicited AEs with medically attended visit, SAEs, and non-serious or serious pIMDs considered all data post-vaccination with RSVPreF3 OA in the ES, except in case of co-administration with FLU-QIV (for which only the safety data following RSVPreF3 OA administration in the Control group were considered).

10.3 Safety Findings from Study 006

The available safety database consists of:

- 1,757 participants in the SSS, of whom 879 vaccinated with RSVPreF3 OA were included for the characterization of the reactogenicity profile within 4 days post-vaccination,
- 24,966 participants in the ES, of whom 12,467 vaccinated with RSVPreF3 OA were included for the characterization of the safety profile in terms of unsolicited AEs, SAEs, and pIMDs (Figure 8.2). *Note: The ES includes the 1,757 participants in the SSS.*

10.3.1 Solicited Safety Set

10.3.1.1 Solicited Administration Site and Systemic Events

Overall, higher reactogenicity was reported in the RSVPreF3 OA group compared to placebo group (71.9% versus 27.9% for any solicited event).

- Solicited administration site events in the SSS within 4 days following vaccination were reported in 62.2% participants in the RSVPreF3 OA group and 10.0% participants in the placebo group. Pain was the most frequently reported solicited administration site event. Most administration site events were mild to moderate in intensity, with a low incidence (<2%) of Grade 3 or medically attended events (Table 10.4).
- Solicited systemic events in the SSS within 4 days following vaccination were reported in 49.4% participants in the RSVPreF3 OA group and 23.2% participants in the placebo group. The most frequently reported solicited systemic events were fatigue, myalgia, headache, and arthralgia. Most systemic events were mild to moderate in intensity, with a low incidence (<2%) of Grade 3 or medically attended events (Table 10.5).

Regardless of treatment group, most solicited events, including Grade 3 events, were of short duration. The median duration of solicited administration site and systemic events was between 1 and 2 days in the RSVPreF3 OA group and between 1 and 4 days in the placebo group. Few participants experienced solicited events lasting longer than 4 days.

Table 10.4 Study 006: Percentage of participants with solicited administration site events within 4 days post-vaccination – SSS

Adverse Event		RSVPreF3 OA (N=879) n (%)	Placebo (N=874) n (%)
Erythema	Any	66 (7.5)	7 (0.8)
	Grade 3 (>100 mm)	2 (0.2)	0 (0)
Pain	Any	535 (60.9)	81 (9.3)
	Grade 3	9 (1.0)	0 (0)
Swelling	Any	48 (5.5)	5 (0.6)
	Grade 3 (>100 mm)	2 (0.2)	0 (0)

N = number of participants with completed diary card for solicited administration site events; n (%) = number (percentage) of participants presenting at least one type of event; SSS = Solicited Safety Set.

Table 10.5 Study 006: Percentage of participants with solicited systemic events within 4 days post-vaccination — SSS

Adverse Event		RSVPreF3 OA (N=879) n (%)	Placebo (N=878) n (%)
Arthralgia	Any	159 (18.1)	56 (6.4)
	Grade 3	11 (1.3)	5 (0.6)
Fatigue	Any	295 (33.6)	141 (16.1)
	Grade 3	15 (1.7)	4 (0.5)
Fever	≥38.0 °C	18 (2.0)	3 (0.3)
	Grade 3 (>39.0 °C)	1 (0.1)	1 (0.1)
Headache	Any	239 (27.2)	111 (12.6)
	Grade 3	11 (1.3)	0 (0)
Myalgia	Any	254 (28.9)	72 (8.2)
	Grade 3	12 (1.4)	3 (0.3)

N = number of participants with completed diary card for solicited systemic events; n (%) = number (percentage) of participants presenting at least one type of event; SSS = Solicited Safety Set.

Subgroup analyses

When analyzed by age category, the percentage of participants reporting administration site pain was lower in the ≥80 YOA category (42.1%) compared to the 60-69 YOA category (67.5%). Similarly, the percentage of participants with headache was lower in the ≥80 YOA (15.9%) category compared to the 60-69 YOA (30.9%) category.

In subgroup analyses by race, hemisphere, and region, the percentage of participants reporting administration site pain was lower for participants of African heritage (36.1%) compared to other races (62.2% in the white category, 65.2% in other races and 67.3% in the Asian category), and it was lower in the SH (40.7%) compared to the NH (63.1%). These trends were not observed for solicited systemic events.

When analyzed by sex, the observed percentage of participants with at least 1 solicited administration site or solicited systemic event tended to be higher in female versus male participants.

No difference in reactogenicity was observed in terms of baseline frailty status or ethnicity.

10.3.2 Exposed Set

The summary of AEs in the ES in Study 006 is presented in Table 10.6.

Table 10.6 Study 006: Summary of AEs – ES

Adverse Event Category	RSVPreF3 OA N=12,467 n (%)	Placebo N=12,499 n (%)
Any unsolicited AE within 30 days post-vaccination	4,117 (33.0)	2,229 (17.8)
Any Grade 3 unsolicited AE within 30 days post-vaccination	246 (2.0)	158 (1.3)
Any related unsolicited AE within 30 days post-vaccination	3,105 (24.9)	731 (5.8)
Any Grade 3 related unsolicited AE within 30 days post-vaccination	112 (0.9)	25 (0.2)
Any medically attended unsolicited AE within 30 days post-vaccination	688 (5.5)	691 (5.5)
Any SAE up to 6 months post-vaccination	539 (4.3)	535 (4.3)
Any related SAE up to DLP	11 (0.1)	7 (0.1)
Any pIMD up to 6 months post-vaccination	41 (0.3)	34 (0.3)
Any related pIMD up to DLP	5 (<0.1)	5 (<0.1)
Any fatal SAE up to DLP	88 (0.7)	95 (0.8)

N = number of participants; n (%) = number (percentage) of participants presenting at least one type of adverse event; AE = adverse event; DLP = data lock point; ES = Exposed Set; pIMD = potential immune-mediated disease; SAE = serious adverse event; Safety DLP = 30SEP2022.

10.3.2.1 All Unsolicited AEs

In the ES, the incidence of unsolicited AEs within 30 days post-vaccination (any, Grade 3, and related) was higher in the RSVPreF3 OA group compared to placebo (Table 10.6 and Table 10.7).

The most frequently reported unsolicited AEs in the RSVPreF3 OA group were from the System Organ Class (SOC) “General disorders and administration site conditions”. For participants who were not included in the SSS, all events following vaccination were recorded as unsolicited events, including those reactions that were solicited in the SSS (i.e., injection site erythema, swelling, and pain; fatigue, headache, fever, myalgia, and arthralgia). Therefore, the more frequent occurrence of unsolicited AEs in the RSVPreF3 OA group in the ES is mainly driven by

those PTs corresponding to the reactogenicity of the vaccine, reported by participants not included in the SSS.

Other frequently reported unsolicited AEs by SOC in the RSVPreF3 OA group were “Nervous system disorders” and “Musculoskeletal and connective tissue disorders” (Table 10.7).

Within the SOC “Musculoskeletal and connective disorders”, imbalances are observed for the PTs “pain in extremity”, “arthralgia”, myalgia” and “muscle spasms”. Following medical review of the cases, “pain in extremity” and “muscles spasms” were not considered as related to vaccination:

- Pain in extremity was not taking place at the injection site;
- Muscle spasms were co-reported with myalgia or not temporally associated with vaccination.

Arthralgia and myalgia are part of the solicited systemic events.

Table 10.7 Study 006: Unsolicited AEs within 30 days post-vaccination (SOCs for which unsolicited AEs occurred in at least 1% of participants in the RSVPreF3 OA group) – ES

System Organ Class	RSVPreF3 OA (N=12,467) n (%)	Placebo (N=12,499) n (%)	Relative Risk (95% CI)
Any unsolicited adverse event	4,117 (33.0)	2,229 (17.8)	1.9 (1.8, 2.0)
General disorders and administration site conditions	2,929 (23.5)	572 (4.6)	5.1 (4.7, 5.6)
Nervous system disorders	803 (6.4)	485 (3.9)	1.7 (1.5, 1.9)
Musculoskeletal and connective tissue disorders	553 (4.4)	328 (2.6)	1.7 (1.5, 1.9)
Respiratory, thoracic, and mediastinal disorders	502 (4.0)	437 (3.5)	1.2 (1.0, 1.3)
Infections and infestations	484 (3.9)	506 (4.0)	1.0 (0.8, 1.1)
Gastrointestinal disorders	326 (2.6)	260 (2.1)	1.3 (1.1, 1.5)
Injury, poisoning and procedural complications	134 (1.1)	131 (1.0)	1.0 (0.8, 1.3)
Skin and subcutaneous tissue disorders	126 (1.0)	87 (0.7)	1.5 (1.1, 1.9)

AE = adverse event; CI = confidence interval; ES = Exposed Set; N = number of participants; n (%) = number (percentage) of participants presenting at least one type of adverse event; SOC = System Organ Class.
Note: SOCs for which unsolicited AEs occurred in ≥ 1% of participants in RSVPreF3 OA group are included in this table.

The unsolicited AEs occurring within 30 days post-vaccination (by PT) for which the LL of the 95% CI around the RR was above 1.0 are shown in Table 10.8. The PTs reported most frequently are reflecting vaccine reactogenicity.

Table 10.8 Study 006: Any unsolicited AE within 30 days post-vaccination by PT with statistically significant difference – ES

Preferred Term	RSVPreF3 OA N=12,467 n (%)	Placebo N=12,499 n (%)	Relative Risk (95% CI)
Any unsolicited adverse event	4,117 (33.0)	2,229 (17.8)	1.9 (1.8, 2.0)
Injection site pain	1,967 (15.8)	174 (1.4)	11.3 (9.7, 13.3)
Headache	651 (5.2)	362 (2.9)	1.8 (1.6, 2.1)
Injection site erythema	452 (3.6)	27 (0.2)	16.8 (11.4, 25.8)
Injection site swelling	319 (2.6)	19 (0.2)	16.8 (10.6, 28.3)
Fatigue	318 (2.6)	133 (1.1)	2.4 (2.0, 3.0)
Pyrexia	215 (1.7)	38 (0.3)	5.7 (4.0, 8.2)
Myalgia	152 (1.2)	53 (0.4)	2.9 (2.1, 4.0)
Rhinorrhea	141 (1.1)	108 (0.9)	1.3 (1.0, 1.7)
Arthralgia	128 (1.0)	93 (0.7)	1.4 (1.1, 1.8)
Pain	116 (0.9)	33 (0.3)	3.5 (2.4, 5.4)
Vaccination site pain	115 (0.9)	6 (<0.1)	19.2 (8.6, 53.5)
Chills	85 (0.7)	29 (0.2)	2.9 (1.9, 4.7)
Nausea	85 (0.7)	32 (0.3)	2.7 (1.8, 4.1)
Pain in extremity	83 (0.7)	36 (0.3)	2.3 (1.6, 3.5)
Injection site pruritus	80 (0.6)	16 (0.1)	5.0 (2.9, 9.2)
Injection site warmth	79 (0.6)	5 (<0.1)	15.8 (6.5, 50.1)
Injection site joint pain	65 (0.5)	5 (<0.1)	13.0 (5.3, 41.5)
Malaise	58 (0.5)	14 (0.1)	4.15 (2.3, 8.1)
Injection site reaction	53 (0.4)	12 (0.1)	4.4 (2.3, 9.1)
Administration site pain	49 (0.4)	4 (<0.1)	12.3 (4.5, 46.9)
Asthenia	49 (0.4)	19 (0.2)	2.6 (1.5, 4.7)
Feeling hot	38 (0.3)	7 (0.1)	5.4 (2.4, 14.4)
Body temperature increased	32 (0.3)	3 (<0.1)	10.7 (3.4, 54.6)
Rash	31 (0.2)	10 (0.1)	3.1 (1.5, 7.1)
Injection site discomfort	26 (0.2)	4 (<0.1)	6.5 (2.3, 25.7)
Muscle spasms	24 (0.2)	8 (0.1)	3.0 (1.3, 7.7)
Abdominal pain	23 (0.2)	9 (0.1)	2.6 (1.1, 6.3)
Lethargy	21 (0.2)	5 (<0.1)	4.2 (1.6, 14.3)
Vaccination site erythema	18 (0.1)	1 (<0.1)	18.1 (2.9, 751.9)
Injection site induration	18 (0.1)	2 (<0.1)	9.0 (2.2, 80.2)
Lymphadenopathy	15 (0.1)	4 (<0.1)	3.8 (1.2, 15.6)
Somnolence	15 (0.1)	5 (<0.1)	3.0 (1.0, 10.6)
Discomfort	14 (0.1)	3 (<0.1)	4.7 (1.3, 25.4)
Feeling cold	13 (0.1)	3 (<0.1)	4.3 (1.2, 23.8)
Injection site movement impairment	12 (0.1)	1 (<0.1)	12.0 (1.8, 514.3)

Preferred Term	RSVPreF3 OA N=12,467 n (%)	Placebo N=12,499 n (%)	Relative Risk (95% CI)
Anxiety	10 (0.1)	2 (<0.1)	5.0 (1.1, 47.1)
Injection site inflammation	9 (0.1)	1 (<0.1)	9.0 (1.3, 395.5)

AE = adverse event; CI = confidence interval; ES = Exposed Set; N = number of participants; n (%) = number (percentage) of participants presenting at least one type of adverse event; PT = Preferred Term.
Note: PTs with statistically significant difference are included in this table.

For Grade 3 related unsolicited AEs, statistically significantly higher rates were observed in the RSVPreF3 OA group compared to placebo group for injection site pain, injection site erythema, injection site swelling, pyrexia, and headache, i.e., events reflecting vaccine reactogenicity. They occurred with a frequency of <0.3%.

10.3.2.2 Unsolicited AEs with a Medically Attended Visit

Based on the ES in Study 006, unsolicited AEs with a medically attended visit reported within 30 days post-vaccination were balanced between RSVPreF3 OA and placebo groups (Table 10.6).

10.3.2.3 Serious Adverse Events

A narrower CI (80%, without multiplicity adjustment) was applied for SAEs to facilitate identification of events for further medical review and assessment. This approach, while improving the ability to detect potential safety signals, increases the probability of a false positive finding.

Based on the ES in Study 006:

- The incidence of SAEs up to 6 months post-vaccination in the RSVPreF3 OA and placebo groups was balanced (Table 10.9). The most frequently reported SAEs up to 6 months post-vaccination in both groups were reported in the SOCs “Infection and infestations” (mainly infections of the respiratory tract) and “Cardiac disorders”, both reflecting the study population and the period when the study was conducted (COVID-19 pandemic).

Table 10.9 Study 006: SAEs within 6 months post-vaccination (SOCs for which SAEs occurred in at least 0.5% of participants in the RSVPreF3- OA group) – ES

System Organ Class	RSVPreF3 OA (N=12,467) n (%)	Placebo (N=12,499) n (%)	Relative Risk, % (80% CI)
Any SAE within 6 months after vaccination	539 (4.3)	535 (4.3)	1.0 (1.0, 1.1)
Infections and infestations	111 (0.9)	117 (0.9)	0.9 (0.8, 1.1)
Cardiac disorders	94 (0.8)	92 (0.7)	1.0 (0.8, 1.3)
Neoplasms, benign, malignant, and unspecified	69 (0.6)	65 (0.5)	1.1 (0.8, 1.4)
Nervous system disorders	63 (0.5)	67 (0.5)	0.9 (0.7, 1.2)
Injury, poisoning, and procedural complications	60 (0.5)	61 (0.5)	1.0 (0.8, 1.3)

CI = confidence interval; ES = exposed set; N = number of participants; n (%) = number (percentage) of participants presenting at least one type of adverse event; SAE = serious adverse event; SOC = System Organ Class.
Note: SOCs for which SAEs occurred in ≥0.5% of participants in RSVPreF3 OA group are included in this table

Within the SOC "cardiac disorders", a higher number of participants in the RSVPreF3 OA group (12 participants [0.1%]) compared to the placebo group (5 participants [<0.1%]) reported AEs in the HLT "supraventricular arrythmias" (RR: 2.4; 95% CI: 0.8, 8.7) within 30 days post-vaccination (Table 10.10). The 17 participants reported a total of 18 events (serious and non-serious).

- Of the 18 events reported, more SAEs were reported from the RSVPreF3 OA group (8 events) compared to the placebo group (2 events) (RR: 4.01; 80% CI: 1.23, 17.38). None of these SAEs were considered related to vaccination by the investigator, and none were fatal. Eleven (11) SAEs reported in this HLT occurred in participants with an established history of these arrythmias, therefore reflecting the expected course of these conditions, which is characterized by recurrent episodes of symptomatic events.
- Among the 18 events, 1 is a new onset of sinus tachycardia (non-serious) that occurred within 30 minutes after vaccination and was associated with local injection site reaction (bruising) and which resolved within the day.
- 3 events are other supraventricular arrhythmic events (2 serious events, atrial flutter and sinus node dysfunction; and 1 non serious event, atrial tachycardia).

Atrial fibrillation is a component of the HLT, "supraventricular arrythmias", which also includes atrial flutter, atrial tachycardia, sinus node dysfunction and sinus tachycardia. Events of atrial fibrillation account for the majority of the HLT events (14 atrial fibrillation events in total [serious and non-serious]; 8 SAEs). Among the 8 atrial fibrillation SAEs, 7 were reported from participants in the RSVPreF3 OA group versus 1 in the placebo group (RR: 7.02; 80% CI: 1.5, 75.6). Details about these events are provided in Table 10.10.

- 6 events (reported by 6 participants) correspond to new onset of atrial fibrillation (3 serious events and 3 non-serious events). The participants, in addition to their age, all had relevant predisposing/concurrent medical conditions and important risk factors (e.g., chronic conditions such as hypertension, coronary artery disease, or COPD, or an intercurrent acute

infection) for development of atrial fibrillation. There was no pattern in the time to onset after vaccination among these events.

- 11 events (reported by 10 participants) correspond to recurrence of pre-existing atrial fibrillation (3 non-serious and 5 serious events) or other supraventricular arrhythmic events (2 serious events, atrial flutter and sinus node dysfunction) and 1 non-serious event, atrial tachycardia). The recurrence of atrial fibrillation / supraventricular arrhythmic events is to be expected as part of the natural progression of the disorders. Atrial fibrillation and supraventricular arrhythmic events typically have recurrences (even after ablation), and it is therefore expected that those individuals with established atrial fibrillation and supraventricular arrhythmic events exhibited events during the course of the study. There was no pattern in the time to onset among these events.
- None of the participants who experienced atrial fibrillation or other supraventricular arrhythmias were reported to have had RSV illness, which might have triggered the arrhythmia. None of the events resulted in stroke.

Table 10.10 Study 006: Serious and non-serious supraventricular arrythmias within 30 days post-vaccination – ES

Age / Sex	TTO (days)	Serious (Y/N)	Event	Pre-Existing Condition	Risk Factors/ comorbidities/medical conditions
New onset of SVA events					
76/F	1	No	Sinus Tachycardia		Local injection site reactions
77/F	1	No	AFib		HTN, COPD
75/M	22	No	AFib		CAD, onset in the framework of a worsening of heart failure
75/F	30	No	AFib		Onset in the framework of URTI
64/F	12	Yes	AFib		HTN, mild valve regurg. (mitral, aortic, tricuspid), event considered related to overdose of losartan
64/M	24	Yes	AFib		HTN, CAD, diabetes
71/F	24	Yes	AFib		Graves' disease, hypothyroidism; event occurred in context of an acute MI
Recurrence of SVA events					
76/M	3	No	AFib	AFib	HTN, COPD
71/F	18	No	AFib	AFib	HTN
89/M	27	No	AFib	AFib	CAD, Heart failure, HTN
74/M	11	No	Atrial tachycardia	Sinus node dysfunction	Mild valvular regurg. (mitral, tricuspid), angina pectoris; participant had decrease in exercise tolerance and chest pressure for several months prior to study enrollment
		Yes	Sinus node dysfunction		
62/M	1	Yes	AFib	AFib (Holter monitor)	HTN
76/M	5	Yes	AFib	AFib (pacemaker)	HTN
68/M	12	Yes	AFib	AFib	Heart Failure, CAD, MI, type 2 diabetes
68/F	16	Yes	AFib	Atrial flutter	HTN, COPD
64/M	21	Yes	AFib	AFib, Ventricular extrasystoles	HTN, ventricular extrasystoles
75/M	28	Yes	Atrial flutter	Atypical atrial flutter (ablation)	HTN, COPD, Sleep apnea

AFib = atrial fibrillation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; F = female; HTN = hypertension; M = male; meds = medication; MI = myocardial infarction; N = no; regurg = regurgitation; SVA = supraventricular arrythmia; TTO = time to onset, URTI = upper respiratory tract infection.

- The incidence of atrial fibrillation reported in the literature for adults over 70 YOA is 9.7 per 1.000 person/years. Cardiac comorbidities, such as ischemic heart disease and hypertension (as observed in participants experiencing new-onset atrial fibrillation in Study 006) are recognized causal risk factors for the development of atrial fibrillation [Krahn, 1995].
- In summary, most SAEs reported for supraventricular arrythmia occurred in participants with an established history of these arrythmias, therefore reflecting the expected course of these conditions, which is characterized by recurrent episodes of symptomatic events. GSK believes these cases more plausibly reflect the epidemiology of the older adult population and the expected disease course of these events rather than a vaccine [Krahn, 1995]. New onset atrial fibrillation SAEs occurred in participants with relevant risk factors and predisposing/concurrent medical conditions, who are at high underlying risk of developing atrial fibrillation. This is further supported when comparing the observed incidence of atrial fibrillation in Study 006 to the incidence in relevant older adult populations reported in the literature, where the rates observed in the RSVPreF3 OA group in Study 006 are not higher than the expected background rates [Krahn, 1995]. This is consistent with the investigators determining that none of the serious atrial fibrillation events were considered related to vaccination, and the conclusion of the IDMC, which recommended continuation of the study as planned after a focused review of unblinded data of supraventricular arrythmia events. Based on the totality of information, GSK believes these cases more plausibly reflect the epidemiology of the older adult population and the expected disease course of these events rather than a vaccine effect. Notwithstanding, GSK will continue to monitor and assess events of atrial fibrillation events for the remainder of the ongoing 006 study.
- No imbalance was observed for SAEs of atrial fibrillation reported within 6 months post-vaccination (14 events in the RSVPreF3 OA group versus 16 events in the placebo group) or up to DLP of September 30, 2022 (19 events in the RSVPreF3 OA group versus 22 events in the placebo group).

Serious adverse events considered as related by the investigator

The incidence of SAEs considered as causally related to vaccination by the investigator up to DLP of September 30, 2022 was balanced between the groups (Table 10.6). Many of these SAE cases described a long time to onset or presence of pre-existing risk factors and predisposing medical conditions that could explain the events.

Subgroup analyses

The percentage of participants with at least 1 SAE was similar between the RSVPreF3 OA and placebo groups when analyzed by age, region, ethnicity, race and sex. By age category, the observed percentage was highest in participants ≥80 YOA, in both groups, as expected. By hemisphere, the observed percentage of participants with at least 1 SAE was lower in SH compared to NH.

10.3.2.4 Deaths

Overall, data show no imbalance in reporting of fatal SAEs between the RSVPreF3 OA group and placebo. Based on the ES in Study 006:

- Up to 6 months following vaccination, at least 1 fatal SAE was reported in 43 (0.3%) participants in the RSVPreF3 OA group and in 56 (0.4%) participants in the placebo group.
- Up to the DLP of September 30, 2022, the proportion of participants with at least one fatal SAE was generally balanced between the RSVPreF3 OA group and the placebo group. The most frequently reported fatal SAEs (by SOC) were “cardiac disorders”, “general disorders and administration site conditions”, and “infections and infestations” (Table 10.11).

Table 10.11 Study 006: Fatal SAEs up to data lock point by SOC – ES

System Organ Class	RSVPreF3 OA (N=12,467) n (%)	Placebo (N=12,499) n (%)
Any fatal SAE	88 (0.7)	95 (0.8)
Cardiac disorders	23 (0.2)	26 (0.2)
Infections and infestations	20 (0.2)	12 (0.1)
General disorders and administration site conditions	14 (0.1)	24 (0.2)
Nervous system disorders	10 (0.1)	11 (0.1)
Respiratory, thoracic, and mediastinal disorders	7 (<0.1)	8 (<0.1)
Neoplasms, benign, malignant, and unspecified	7 (<0.1)	6 (<0.1)
Hepatobiliary disorders	3 (<0.1)	2 (<0.1)
Injury, poisoning and procedural complications	3 (<0.1)	2 (<0.1)
Gastrointestinal disorders	3 (<0.1)	1 (<0.1)
Renal and urinary disorders	3 (<0.1)	1 (<0.1)
Vascular disorders	2 (<0.1)	3 (<0.1)
Blood and lymphatic system disorders	*1* (<0.1)	
Metabolism and nutrition disorders	*1* (<0.1)	
Not coded	*1* (<0.1)	

ES = Exposed Set; N = number of participants; n (%) = number (percentage) of participants presenting at least one type of adverse event; SAE = serious adverse event; SOC = System Organ Class.
x= events reported in 1 group only, group not disclosed to avoid to unblinding

Within the SOC “infections and infestations”, a higher number of participants experiencing COVID-19 leading to death is observed in the RSVPreF3 OA group (10 participants [0.1%]) compared to the placebo group (2 participants [<0.1%]) (RR: 5.01; 80% CI: 1.60, 21.16). None of these fatal cases were considered related to vaccination by the investigators. A thorough medical assessment of these fatal COVID-19 cases has been performed and details of these cases are presented in Table 10.12. All participants had concurrent medical conditions that are known risk factors for severe COVID-19 disease or for increased COVID-19 mortality (e.g., diabetes, hypertension, coronary artery disease, obesity, COPD, asthma) and 9 participants out of 12 were either not fully

vaccinated (had not completed the primary series) or optimally protected (did not receive boosters) against SARS-CoV-2; details about these events are provided in Table 10.12. This observed imbalance in COVID-19 deaths is not accompanied by similar imbalances in COVID-19 (serious and non-serious), supporting that the fatal COVID-19 imbalance could be based on chance. Up to 30 days post-vaccination, 40 participants [0.3%] in the RSVPreF3 OA group and 41 participants [0.3%] in the placebo group reported COVID-19 (RR: 0.98; 95% CI: 0.62, 1.55) and up 6 months post-vaccination, 33 participants [0.3%] in the RSVPreF3 OA group and 30 participants [0.2%] in the placebo group reported a serious SARS-CoV-2 infection (RR: 1.10; 80% CI: 0.77, 1.57).

It is important to note that a higher number of participants who died from unknown cause (HLT “General disorders and administration site conditions” or due to pulmonary embolism (HLT “Respiratory, thoracic and mediastinal disorders”) is observed in the placebo group (18 deaths and 5 fatal pulmonary embolisms) compared to RSVPreF3 OA group (11 deaths and 1 fatal pulmonary embolism). Although no information about potential SARS-CoV-2 infection is provided for these events, this possibility cannot be excluded.

Table 10.12 Study 006: Fatal COVID-19 cases up to DLP – ES

Country	Age/ Sex	TTO	Event	Related	Comorbidities	Complication during hospitalization	Reported cause of death	Vaccinated against COVID			TTO COVID-19 vaccine/ event (days)
								Yes/No	Brand/ type	Number of doses received	
UK	68/F	12	COVID-19 pneumonia	No	Chronic kidney disease, hypertension	Acute renal failure	Covid-19 pneumonitis and chronic kidney disease	Yes	Pfizer, Pfizer	2	177
US	73/M	35	COVID-19 pneumonia	No	Hyperlipidemia, morbid obesity	Respiratory failure multiorgan failure	Covid-19 pneumonia respiratory failure and multi-organ failure	Yes	Pfizer, Pfizer	2	187
Germany	66/M	84	COVID-19 pneumonia	No	Atrial F brillation, Coronary artery disease, angina pectoris, hypertension, sleep apnea. Former tobacco smoker (10Y)	Respiratory failure Refused invasive therapy	Covid-19 pneumonia	Yes	AstraZeneca AstraZeneca	2	145
Mexico	62/M	90	COVID-19	No	Coronary artery disease, Chronic kidney disease Diabetes Type 2		Covid-19	Yes	AstraZeneca	1	120
Mexico	65/F	101	COVID-19 pneumonia	No	Diabetes Type 2 Hypertension Obesity Grade I. Former tobacco smoker (14Y)	Hypoxia	COVID-19 pneumonia	None reported	No COVID vaccination received	NA	NA
Germany	79/M	106	COVID-19 pneumonia recovered with sequela	No	Coronary artery disease, Chronic renal insufficiency, Diabetes Type 1 Hypertension, Pulmonary fibrosis. Former tobacco smoker (20Y)	Hypoxia	Covid-19 pneumonia	Yes	AstraZeneca AstraZeneca	2	182
Poland	62/M	112	COVID-19	No	HTA, Hyperlipidemia, Glucose tolerance impaired Former tobacco smoker (23Y)		Covid-19	Yes	AstraZeneca AstraZeneca	2	145

Country	Age/ Sex	TTO	Event	Related	Comorbidities	Complication during hospitalization	Reported cause of death	Vaccinated against COVID			TTO COVID-19 vaccine/ event (days)
								Yes/No	Brand/ type	Number of doses received	
US	86/M	115	COVID-19 pneumonia	No	Atrial Fibrillation, Coronary artery disease, asthma, Hyperlipidemia, hypertension Ventricular tachycardia Implantable defibrillator user	Acute renal failure Bilateral pneumonia	COVID-19 pneumonia	Yes	Moderna, Moderna	2	256
Poland	68/M	12	COVID-19	No	Diabetes type 2, Hypertension Obstructive sleep apnea. Former tobacco smoker (5Y)		Covid-19	Yes	COVID-19 (unspecified), COVID-19 (unspecified	2	190
US	74/M	153	COVID-19	No	Atrial Fibrillation, Coronary artery disease, hypertension sleep apnea, COPD O2 dependent neurofibromatosis	Respiratory failure, heart failure, pulmonary embolism	Covid-19, congestive cardiac failure aggravated and pulmonary embolism	Yes	Moderna, Moderna	2	306
UK	72/M	360	COVID-19	No	Metastatic colorectal cancer CT TAP Progressive metastatic malignancy. Former tobacco smoker (46Y)		Metastatic colorectal cancer COVID-19	Yes	AstraZeneca, AstraZeneca	2	446
Belgium	≥90/ M	391	COVID-19	No	Atrial Fibrillation, Congestive heart failure, End stage renal disease. Former tobacco smoker (20Y)	Angor	Acute COVID-19	Yes	Pfizer 4 times	4	198

F = female; M = male; UK = United Kingdom; US = United States; Y = years

Fatal SAEs considered as related by the investigator

Four participants in Study 006 had a fatal SAE considered as related to vaccination by the investigator (2 deaths within 6 months: pulmonary embolism and cardiopulmonary failure) and 2 additional deaths [unknown cause] up to DLP of September 30, 2022).

- Pulmonary embolism: A 70-year-old male with past medical history of asthma who, 147 days after receiving RSVPreF3 OA or placebo (treatment groups remain blinded), died due to pulmonary embolism.
- Cardiopulmonary failure: A 63-year-old male who, 30 days after receiving RSVPreF3 OA or placebo, had a cardiorespiratory arrest with a fatal outcome. No autopsy was performed. The events triggering the cardiorespiratory arrest were not provided.
- Death of unknown cause: A 64-year-old male with medical history of diabetes Type II, hyperlipidemia, hypertension, benign prostatic hyperplasia and fatty liver disease died of an unknown cause, 223 days after receiving RSVPreF3 OA or placebo.
- Death of unknown cause: A 71-year-old female with comorbid conditions including anxiety, asthma, depression, tension headaches, glaucoma, hyperlipidemia, insomnia, nephrolithiasis, osteoarthritis, osteoporosis, gastroesophageal reflux disease, mild chronic kidney disease, obstructive sleep apnea and diabetes Type II, died of an unknown cause 326 days after receiving RSVPreF3 OA or placebo.

10.3.2.5 Potential Immune-Mediated Diseases

- Overall, data show no imbalance in reporting of pIMDs between the RSVPreF3 OA and placebo groups (Table 10.13). Based on the ES in Study 006, the incidence of pIMDs up to 6 months post-vaccination was similar in both groups. The most frequently reported pIMDs in both groups were in the SOCs “Metabolism and nutrition disorders”, “Musculoskeletal and connective tissue disorders” and “Skin and subcutaneous tissue disorders.” At PT level, the most frequently reported pIMDs in both groups were gout (12 participants [0.1%] and 11 participants [0.1%] in RSVPreF3 OA and placebo groups, respectively), and polymyalgia rheumatica (5 participants [<0.1%] and 2 participants [<0.1%] in RSVPreF3 OA and placebo groups, respectively).

Table 10.13 Study 006: pIMDs within 6 months post-vaccination (SOCs for which pIMDs occurred in at least 4 participants in the RSVPreF3 OA group) – ES

System Organ Class	RSVPreF3 OA (N=12,467) n (%)	Placebo (N=12,499) n (%)
Any pIMD	41 (0.3)	34 (0.3)
Metabolism and nutrition disorders	12 (0.1)	11 (0.1)
Musculoskeletal and connective tissue disorders	12 (0.1)	7 (0.1)
Skin and subcutaneous tissue disorders	4 (<0.1%)	4 (<0.1%)
Nervous system disorders	4 (<0.1%)	2 (<0.1%)
Gastrointestinal disorders	4 (<0.1%)	1 (<0.1%)

ES = Exposed Set; N = number of participants; n (%) = number (percentage) of participants presenting at least one type of adverse event; pIMD = potential immune-mediated disease; SOC = System Organ Class.
Note: SOCs for which pIMDs occurred in ≥4 participants in the RSVPreF3 OA group are included in this table.

Potential immune-mediated disorders considered as related by the investigator

- The incidence of pIMDs considered related vaccination by the investigator, up to DLP of September 30, 2022, was balanced between both groups, with 5 participants reporting at least 1 event in each group (Table 10.6). The pIMDs considered as related by the investigator to either RSVPreF3 OA or placebo (treatment groups remain blinded) were rheumatoid arthritis (non-serious), trigeminal neuralgia (non-serious), gout (non-serious), psoriasis (non-serious), polyarthritis (non-serious), Bell's palsy (2 events; 1 serious and 1 non-serious), thrombocytopenia (serious, reported in a participant who previously reported Bell's palsy), immune thrombocytopenia (serious), giant cell arteritis (serious), and myasthenia gravis (non-serious).
- No imbalance was observed for pIMDs and pIMDs assessed to be causally related to vaccination by the investigator when analyzed by SOC or PT.

10.4 Safety Findings from Aggregated Analyses of Studies 004, 006, 007, and 009

The aggregated analyses included a total of 15,303 participants who received 1 dose of RSVPreF3 OA vaccine, pooled from the Phase 3 studies (004, 006 [with a DLP of the first safety analysis of April 30, 2022], 007, and 009). Analyses were performed on the following categories: unsolicited AEs with medically attended visit, SAEs, and pIMDs and included all data post-vaccination, except in case of co-administration with FLU-QIV.

10.4.1 Unsolicited AEs with a Medically Attended Visit

In the aggregated analyses, 834 (5.4%) of participants experienced at least one unsolicited AE with a medically attended visit reported within 30 days after vaccination. The most frequently reported unsolicited AEs resulting in medically attended visit (by SOC) were "Infections and infestations" (1.6% participants), followed by "Musculoskeletal and connective tissue disorders" (0.7% participants) and "Injury, poisoning and procedural complications" (0.7% participants).

10.4.2 Serious Adverse Events

Up to the DLP of the analyses, at least 1 SAE was reported for 701 participants (4.6%). The most frequently reported SAEs by SOC were "Infections and infestation" (141 [0.9%] participants), followed by "Cardiac disorders" (129 [0.8%] participants) and "Neoplasm benign, malignant and unspecified" (101 [0.7%] participants).

For 11 (<0.1%) participants, SAEs were considered as related vaccination by the investigator. In addition to those reported in Study 006 (Section 10.3.2.3), 1 SAE considered as related to RSVPreF3 OA vaccination by the investigator was reported by 1 participant in the open-label Study 004: Guillain-Barré syndrome (also a pIMD; Section 10.4.3). This participant experienced symptoms of muscular weakness beginning 9 days after vaccination, which is within the risk window for Guillain-Barré syndrome as a vaccine-related reaction. However, neither a neurological consultation nor electrophysiologic testing were reported, and because the reported clinical signs and serological parameters may be present in other neurological disorders, the reported

information is insufficient to confirm the diagnosis (as per Brighton Collaboration Working Group case definition). Additionally, it was not reported if alternative causes for the participant's symptoms were investigated and excluded. The event was considered as resolved after approximately 6 months.

10.4.3 Potential Immune-Mediated Diseases

Up to the DLP of the analyses, pIMDs were infrequently reported (55/15,303 participants, 0.4%). The most frequently reported pIMDs (by SOC) were "Metabolism and nutrition disorders" (13 [0.1%] participants), "Musculoskeletal and connective tissue disorders" (13 [0.1%] participants), and "Nervous system disorders" (8 [0.1%] participants).

For 9 (<0.1%) participants, pIMD events were considered as related to vaccination by the investigator. In addition to those reported in Study 006 (Section 10.3.2.5), pIMDs considered as related to vaccination by the investigator were reported in:

- 1 participant in Study 004: Guillain-Barré syndrome (SAE), described in Section 10.4.2,
- 1 participant in Study 009: worsening of psoriasis (inter-digital lesions) (non-serious) occurring 14 days after vaccination. The event resolved after 166 days.

10.5 Hypersensitivity (Including Anaphylaxis)

In the clinical studies with RSVPreF3 OA, participants with known hypersensitivity to any component of the vaccine were excluded from enrollment.

To identify potential cases of hypersensitivity reactions, including anaphylaxis, searches of the unsolicited AEs (non-serious and serious) reported within 30-days post-vaccination in the ES in Study 006 were performed using the Standardized MedDRA Queries (SMQs) "Hypersensitivity reactions" and "Anaphylaxis" (MedDRA v.25.0 SMQ, narrow scope). The hypersensitivity search retrieved 88 cases (0.7%) in the RSVPreF3 OA group versus 49 cases (0.4%) in the placebo group (RR: 1.8 [95% CI: 1.3, 2.6]). Most of the events (31 [0.2%] in the RSVPreF3 OA group) were rashes. One case of anaphylaxis to food was reported 18 days after vaccination in Study 006, considered as not related to vaccination by the investigator. Importantly, no case of anaphylaxis to vaccine was identified. One case of anaphylaxis to food was reported 18 days after vaccination, considered as not related to vaccination by the investigator.

Overall, no case of anaphylaxis to vaccine was reported in any of the RSVPreF3 OA studies.

10.6 Safety Findings when Co-Administered with Seasonal Influenza Vaccine — Study 007

Overall, the RSVPreF3 OA vaccine had a clinically acceptable safety profile when co-administered with FLU-QIV. The summary of AEs in Study 007 is presented in Table 10.14.

Table 10.14 Study 007: Safety of RSVPreF3 OA vaccine when co-administered with FLU-QIV - ES

AE Category	Co-Ad Group (N=442*) RSVPreF3 OA+FLU-QIV n (%)	Control Group (N=443*) FLU-QIV n (%)	Control Group (N=443*) RSVPreF3 n (%)
Within 4 days of vaccination*			
Any solicited administration site AE	234 (53.4)	91 (20.8)	167 (39.9)
Any solicited systemic AE	176 (40.2)	108 (24.7)	143 (34.1)
Within 30 days of vaccination			
Any unsolicited AE	83 (18.8)	105 (23.7)	
During entire study period			
Any medically attended AE	35 (7.9)	49 (11.1)	
pIMD	5 (1.1)	1 (0.2)	
SAE	15 (3.4)	20 (4.5)	
Fatal SAE	4 (0.9)	8 (1.8)	

AE = adverse event; ES = Exposed Set; N = number of participants; n (%) = number (percentage) of participants presenting at least one type of adverse event; pIMD = potential immune-mediated disease; SAE = serious adverse event. Co-Ad group = Participants receiving a single dose of RSVPreF3 OA investigational vaccine and a single dose of FLU-QIV vaccine at Visit 1 (Day 1); Control group = Participants receiving a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).
* For solicited events within 4 days of vaccination, N = 438 for both groups (i.e., 438 participants in each group completed the diary cards and had information on solicited events).

The reactogenicity profile of the Co-Ad group was predominantly influenced by the RSVPreF3 OA vaccine component, with an observed percentage of participants reporting solicited administration site events that was higher in the Co-Ad group (who received RSVPreF3 OA and FLU-QIV at the same visit) than in the Control group (who received RSVPreF3 OA and FLU-QIV 1 month apart) (Table 10.15). Pain was the most frequently reported solicited administration site event and the most frequent Grade 3 event during the 4-day post-vaccination period in both groups (Table 10.15).

Table 10.15 Study 007: Percentage of participants with solicited administration site events within 4 days following each dose – ES

Adverse Event			Co-Ad Group n (%)	Control Group n (%)
Erythema	FLU Dosing at visit 1	N	438	438
		Any	5 (1.1)	2 (0.5)
		Grade 3	0	0
	RSV Dosing at visit 1	N	438	-
		Any	18 (4.1)	-
		Grade 3	0	-
	RSV Dosing at visit 2	N	-	419
		Any	-	9 (2.1)

Adverse Event			Co-Ad Group n (%)	Control Group n (%)
		Grade 3	-	0
Pain	FLU Dosing at visit 1	N	438	438
		Any	124 (28.3)	90 (20.5)
		Grade 3	4 (0.9)	0
	RSV Dosing at visit 1	N	438	-
		Any	210 (47.9)	-
		Grade 3	12 (2.7)	-
	RSV Dosing at visit 2	N	-	419
		Any	-	164 (39.1)
		Grade 3	-	6 (1.4)
Swelling	FLU Dosing at visit 1	N	438	438
		Any	6 (1.4)	3 (0.7)
		Grade 3	0	0
	RSV Dosing at visit 1	N	438	-
		Any	14 (3.2)	-
		Grade 3	0	-
	RSV Dosing at visit 2	N	-	419
		Any	-	4 (1.0)
		Grade 3	-	0

ES = Exposed Set; Co-Ad group = Participants receiving a single dose of RSVPreF3 OA investigational vaccine and a single dose of FLU-QIV vaccine at Visit 1 (Day 1); Control group = Participants receiving a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).
For each dose: N = number of participants; n (%) = number (percentage) of participants presenting at least one type of symptom whatever the dose administered.

The percentage of participants reporting solicited systemic events was higher following concomitant administration of both vaccines in the Co-Ad group than following administration of FLU-QIV alone. However, it was not higher compared to administration of RSVPreF3 OA alone (Table 10.16). Fatigue, myalgia, and headache were the most frequently reported solicited systemic events during the 4-day post-vaccination. Grade 3 events were infrequent (≤1%) in both treatment groups.

Table 10.16 Study 007: Percentage of participants with solicited systemic events within 4 days following each dose and overall – ES

Adverse Event			Co-Ad Group n (%)	Control Group n (%)
Arthralgia	Dosing at visit 1	N	438	438
		Any	71 (16.2)	21 (4.8)
		Grade 3	3 (0.7)	0
	Dosing at visit 2	N	-	419
		Any	-	47 (11.2)

Adverse Event			Co-Ad Group n (%)	Control Group n (%)
		Grade 3	-	3 (0.7)
	Per participant	N	438	438
		Any	71 (16.2)	58 (13.2)
		Grade 3	3 (0.7)	3 (0.7)
Fatigue	Dosing at visit 1	N	438	438
		Any	98 (22.4)	56 (12.8)
		Grade 3	4 (0.9)	2 (0.5)
	Dosing at visit 2	N	-	419
		Any	-	75 (17.9)
		Grade 3	-	4 (1.0)
	Per participant	N	438	438
		Any	98 (22.4)	105 (24.0)
		Grade 3	4 (0.9)	6 (1.4)
Fever	Dosing at visit 1	N	438	438
		≥38.0 °C	11 (2.5)	3 (0.7)
		Grade 3	3 (0.7)	0
	Dosing at visit 2	N	-	419
		≥38.0 °C	-	4 (1.0)
		Grade 3	-	1 (0.2)
	Per participant	N	438	438
		≥38.0 °C	11 (2.5)	6 (1.4)
		Grade 3	3 (0.7)	1 (0.2)
Headache	Dosing at visit 1	N	438	438
		Any	95 (21.7)	56 (12.8)
		Grade 3	2 (0.5)	2 (0.5)
	Dosing at visit 2	N	-	419
		Any	-	68 (16.2)
		Grade 3	-	4 (1.0)
	Per participant	N	438	438
		Any	95 (21.7)	98 (22.4)
		Grade 3	2 (0.5)	6 (1.4)
Myalgia	Dosing at visit 1	N	438	438
		Any	97 (22.1)	41 (9.4)
		Grade 3	3 (0.7)	0
	Dosing at visit 2	N	-	419
		Any	-	82 (19.6)
		Grade 3	-	5 (1.2)
	Per participant	N	438	438

Adverse Event		Co-Ad Group n (%)	Control Group n (%)
	Any	97 (22.1)	100 (22.8)
	Grade 3	3 (0.7)	5 (1.1)

ES = Exposed Set; Co-Ad group = Participants receiving a single dose of RSVPreF3 OA investigational vaccine and a single dose of FLU-QIV vaccine at Visit 1 (Day 1); Control group = Participants receiving a single dose of FLU-QIV vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).
For dose and per participant: N = number of participants; n/% = number/percentage of participants presenting at least one type of symptom whatever the study dose administered

The percentage of participants reporting unsolicited AEs during the 30-day post-vaccination follow-up period was lower in the Co-Ad group than the Control group (Table 10.14). The most frequently reported unsolicited AEs by PT were headache (2.3%) and cough (2.0%) in the Co-Ad group, and upper respiratory tract infection (2.3%) and headache (2.0%) in the Control group.

The percentages of participants reporting SAEs (including fatal SAEs) or pIMDs were similar between the Co-Ad and Control groups (Table 10.14).

- SAEs considered by the investigator to be possibly related to FLU-QIV were reported in 2 (0.5%) participants in the Co-Ad group (both SAEs were acute disseminated encephalomyelitis [ADEM], also considered as pIMDs, one of which was fatal). Both events occurred within a plausible risk window for ADEM as a vaccine-related reaction. However, there is insufficient evidence in both cases to confirm the diagnosis (as per Brighton Collaboration Working Group case definition); alternative diagnoses could be considered, and 2 vaccines were co-administered. None of the participants in the Control group reported SAEs considered by the investigator to be possibly related to vaccination.
- pIMDs considered by the investigator to be related to vaccination were reported for 3 participants in the Co-Ad group, including 2 participants with ADEM considered as related to FLU-QIV (serious events, described as SAEs above) and 1 participant with gout (non-serious) considered as related to both RSVPreF3 OA and FLU-QIV. The case of gout occurred in a 66-year-old male with a medical history of diabetes, hyperlipidemia, and gout. The event occurred 1 day after the participant received RSVPreF3 OA vaccine and FLU-QIV co-administered. In the Control group, 1 participant reported gout (non-serious) considered as related to FLU-QIV.

10.7 Pharmacovigilance Plan

A pharmacovigilance plan has been developed to address the potential risks and missing information for RSVPreF3 OA vaccine.

pIMDs are a theoretical risk for the RSVPreF3 OA vaccine, as for any vaccine using an adjuvant system. The occurrence of pIMDs following vaccination with the RSVPreF3 OA vaccine is monitored in ongoing clinical studies. In the post-licensure setting, GSK's established pharmacovigilance activities, including the use of targeted follow-up

questionnaires to ensure collection of structured information on pIMDs, and the custom MedDRA query for pIMD signal detection, will be used for surveillance.

Aggregated information emerging from various sources including safety reports within the GSK safety database and other databases, global scientific literature, clinical study data, and pre-clinical information will further characterize the safety profile for events including atrial fibrillation. All new information from these surveillance activities that potentially alters the benefit-risk balance will be communicated promptly to regulatory authorities, as well as through periodic safety reports.

The persistence of immunogenicity and efficacy will be further assessed in studies 004 and 006, and safety monitoring will also continue in these studies. In addition, several other studies are ongoing, including co-administration studies with a high dose quadrivalent influenza vaccine, and an adjuvanted quadrivalent influenza vaccine, and a study in adults 50-59 YOA, comprising adults at increased risk of RSV LRTD.

10.8 Safety Conclusions

In more than 15,000 participants ≥60 YOA who received the RSVPreF3 OA vaccine across multiple Phase 3 studies, a single dose of RSVPreF3 OA vaccine was generally well tolerated with an acceptable safety profile.

The main safety analyses were derived from the large placebo-controlled, multi-regional Study 006, including reactogenicity data for a subset of 1,757 participants, of whom 879 were vaccinated with RSVPreF3 OA (SSS), and safety data in 24,966 participants, of whom 12,467 vaccinated with RSVPreF3 OA (ES). The median safety follow-up time in Study 006 was nearly 12 months.

AEs reflecting administration site and systemic reactogenicity were more frequently reported in the RSVPreF3 OA group compared to placebo.

The most commonly reported (≥10%) solicited events within 4 days post-vaccination were pain at the injection site, fatigue, myalgia, headache, and arthralgia. The solicited events were generally mild to moderate, with few Grade 3 events (<2%), and were of short duration with a median duration between 1 and 2 days.

In the ES, unsolicited AEs within 30 days post-vaccination were more frequently reported in the RSVPreF3 OA group compared to placebo. This was mainly driven by events reflecting vaccine reactogenicity.

No case of anaphylaxis related to RSVPreF3 OA vaccine has been reported.

SAEs, including fatalities and SAEs considered related to vaccination by the investigator, were balanced between RSVPreF3 OA and placebo groups. The most frequently reported SAEs were infections and infestations (mainly of the respiratory tract) followed by cardiac disorders, which are common conditions found in the older adult population.

Within the SOC “cardiac disorders”, a higher number of AEs (serious and non-serious) of supraventricular arrhythmia events, primarily events of atrial fibrillation, were reported within 30 days post-vaccination in the RSVPreF3 OA group compared to the placebo

group. None of the events resulted in stroke, and none was fatal. When considering that all reports of supraventricular arrythmia events (excluding the case of sinus tachycardia) occurred either in participants with a known history of these arrhythmias (where intermittent recurrence of episodes is characteristic of the condition) or when new-onset, in participants with recognized risk factors for developing supraventricular arrythmia, and at an incidence not higher than background rates reported in the literature, GSK believes these cases more plausibly reflect the epidemiology of the older adult population and the expected disease course of these events rather than a vaccine effect (consistent with investigator determination, and the recommendation from the IDMC to continue with the study). Notwithstanding, GSK will continue to monitor and assess the events of atrial fibrillation in clinical studies.

Within the SOC “infections and infestations”, a higher incidence of participants experiencing SARS-CoV-2 infection leading to death is observed in the RSVPreF3 OA group (10 participants) compared to the placebo group (2 participants). None of these fatal cases was considered as related by the investigators. All participants had concurrent medical conditions that are known risk factors for severe COVID-19 disease or for increased COVID-19 mortality (e.g., diabetes, hypertension, coronary artery disease, obesity, COPD, asthma) and the majority were not fully vaccinated (primary vaccination or booster) against SARS-CoV-2. Fatal COVID-19 cases will be monitored through routine pharmacovigilance.

As for all vaccines using an adjuvant system, pIMDs are considered theoretical risks for RSVPreF3 OA. The available data show that pIMDs are uncommon and equally distributed between the treatment groups.

The overall percentages of SAEs and pIMDs considered related to either RSVPreF3 OA vaccine or placebo by the investigator, occurring within 6 months after vaccination and up to the DLP of September 30, 2022, are balanced between groups.

11 BENEFIT-RISK CONCLUSIONS

11.1 Therapeutic Context and Unmet Need

RSV is increasingly recognized as an important cause of morbidity and mortality in older adults, leading to approximately 1 million outpatients visits, 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths every year in US adults ≥65 YOA. Despite the significant medical need, there are currently no vaccines approved for the prevention of RSV disease or effective treatments for this population. Treatment for RSV in older adults is limited to supportive care, consisting of supplemental oxygen, intravenous fluids, and bronchodilators.

The prevention of respiratory disease caused by RSV using a vaccine with a favorable benefit-risk profile for older adults, including those with comorbidities, is an optimal approach for limiting RSV disease burden. Approval of an effective RSV vaccine for older adults would significantly decrease RSV-related burden in this population.

11.2 Efficacy and Immunogenicity Benefits

A single dose of RSVPreF3 OA vaccine has been demonstrated to be efficacious against RSV LRTD in adults ≥60 YOA, for the duration of at least one RSV season. VE by RSV subtype (A or B) is consistent, confirming the ability of the PreF antigen to protect against RSV LRTD, irrespective of the predominant circulating subtype.

Although an immunological correlate of protection for RSV is not yet established, a single dose of RSVPreF3 OA vaccine induced a strong functional humoral response against RSV-A and RSV-B, as well as a strong RSVPreF3-specific cellular immune response in adults ≥60 YOA, persisting up to at least 12 months and consistent across age categories.

The Phase 3 studies evaluating RSVPreF3 OA included a diverse older adult population (i.e., from different geographic areas, races/ethnicities, ages, and health statuses, including participants with underlying comorbidities). High VE was observed across different cohorts of population in terms of age (high VE observed in age categories 60-69 YOA [81.0%] and 70-79 YOA [93.8%]), pre-existing conditions (at least 1 comorbidity of interest [94.6%]), and across a spectrum of symptomatic RSV disease, from ARI (71.7%) to LRTD (82.6%) and severe LRTD (94.1%). Based on the currently available data, it is expected that this vaccine will prevent the majority of the RSV-associated LRTD cases in the vulnerable older adult population, resulting in a significant reduction in RSV disease burden.

In addition, RSVPreF3 OA has a comparable and clinically acceptable safety profile when co-administered with a seasonal quadrivalent influenza vaccine, when compared to sequential administration of the vaccines, allowing programmatic flexibility and practicality when prophylactically treating older adults.

11.3 Risks

The safety profile of RSVPreF3 OA vaccine in adults ≥60 YOA is well characterized, with safety data available for 15,845 individuals which have received at least 1 dose of RSVPreF3 OA vaccine.

In the large placebo-controlled Study 006, the primary source of safety data, administration site and systemic reactogenicity was higher in the RSVPreF3 OA group compared to placebo. The common (frequency ≥10%) solicited events observed in the 4 days after vaccination included local symptoms at the site of injection (pain) and systemic symptoms (myalgia, fatigue, arthralgia, and headache). The solicited events were mostly mild to moderate in intensity and of short duration (median duration between 1 and 2 days). These findings are in line with reactogenicity data generated in the Phase 1/2 Study 002 and in other Phase 3 studies (004, 007, and 009).

The more frequent occurrence of unsolicited AEs in the RSVPreF3 OA group in the ES was mainly driven by events reflecting vaccine reactogenicity.

SAEs, including fatal SAEs, are equally distributed between RSVPreF3 OA and placebo groups. The most frequently reported SAEs were infections and infestations (mainly of the respiratory tract) followed by cardiac disorders, which are conditions commonly encountered in the older adult population. Although at the PT level the observed incidence of serious atrial fibrillation was statistically higher in the vaccine group compared to placebo group, within 30 days post-vaccination, none of these events were considered as related by the investigator, and GSK believes these cases more plausibly reflect the epidemiology of the older adult population (in a US study the prevalence of atrial fibrillation increased from 0.1% among adults younger than 55 YOA to 9.0% in persons ≥80 YOA [Go, 2001]) and the expected disease course of the event. Notwithstanding, GSK will continue to monitor and assess the event of atrial fibrillation in clinical studies.

pIMDs following vaccination are considered important theoretical risks for RSVPreF3 OA vaccine, as for all adjuvanted vaccines. In Study 006 pIMDs are equally distributed between the RSVPreF3 OA and placebo groups, with a frequency of 0.3% in both groups for any pIMDs. For pIMDs considered by investigator as related to vaccination, rates were <0.1% in both groups. Routine pharmacovigilance activities, including the use of targeted follow-up questionnaires to ensure collection of structured information on pIMDs, and the custom MedDRA query for pIMD signal detection, will be used to further characterize reported events of pIMDs.

No case of anaphylaxis related to RSVPreF3 OA has been reported.

Based on the safety data from over 15,000 RSVPreF3 OA vaccine recipients, a single dose of the RSVPreF3 OA vaccine has a clinically acceptable safety profile in adults ≥60 YOA.

11.4 Benefit-Risk Assessment

A single dose of the RSVPreF3 OA vaccine produced high efficacy in adults ≥60 YOA against RSV LRTD. This protection was observed regardless of RSV disease severity (ARI, LRTD, severe LRTD), advancing age, presence of at least 1 underlying comorbidity of interest, and against both RSV-A and B strains for the duration of at least one RSV season.

Based on the available safety data from more than 15,000 RSVPreF3 OA vaccine recipients, a single dose of the RSVPreF3 OA vaccine has a clinically acceptable safety and reactogenicity profile in adults ≥60 YOA. GSK will use routine pharmacovigilance activities to monitor the emerging post-licensure safety profile, with close monitoring of atrial fibrillation, anaphylaxis and pIMDs. All new information that may alter the favorable benefit-risk profile will be shared promptly with regulatory authorities, as well as through periodic aggregate reports.

The available efficacy, immunogenicity, and safety data support the favorable benefit-risk profile of the RSVPreF3 OA vaccine administered as a single dose to adults ≥60 YOA to protect against RSV-A and RSV-B associated disease.

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13 APPENDICES

13.1 Supplemental Efficacy Information

Appendix table 1 Case definitions used for VE analyses in Study 006

<table>
<tr><th>Endpoint</th><th>Case definition</th></tr>
<tr><td>ARI
(Trigger for swabbing)</td><td>Presence of:
• at least 2 respiratory symptoms/signs for at least 24 hours
OR
• at least 1 respiratory symptom/sign + 1 systemic symptom/sign for at least 24 hours
Respiratory symptoms and signs
- Nasal congestion/rhinorrhea
- Sore throat
- New or increased sputum
- New or increased cough
- New or increased dyspnea (shortness of breath)
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]
Systemic symptoms and signs
- Fever[1]/feverishness[2]
- Fatigue
- Body aches
- Headache
- Decreased appetite</td></tr>
<tr><td>qRT-PCR-confirmed RSV ARI[5]</td><td>An event meeting the case definition of ARI with at least 1 RSV-positive swab detected by qRT-PCR.[6]</td></tr>
<tr><td>LRTD</td><td>Presence of:
• at least 2 lower respiratory symptoms/signs for at least 24 hours including at least 1 lower respiratory SIGN
OR
• at least 3 lower respiratory symptoms for at least 24 hours
Lower respiratory symptoms
- New or increased sputum
- New or increased cough
- New or increased dyspnea (shortness of breath)
Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
<tr><td>qRT-PCR-confirmed RSV LRTD [5]</td><td>An event meeting the case definition of LRTD with at least 1 RSV-positive swab detected by qRT-PCR.[6]</td></tr>
<tr><td>qRT-PCR-confirmed severe RSV LRTD – Definition 1 “Clinical symptomology” [5]</td><td>Presence of a LRTD with at least one of the following criteria:
• at least 2 lower respiratory SIGNS
• an LRTD episode assessed as ‘severe’ by the investigator[7][5]
AND
• with at least 1 RSV-positive swab detected by qRT-PCR
Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]</td></tr>
</table>

Endpoint	Case definition
	- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4] - Need for oxygen supplementation[4]
qRT-PCR-confirmed **severe** RSV LRTD – Definition 2 "Supportive therapy"[5]	Presence of a LRTD with at least one of the following criteria[8]: • Need for oxygen supplementation[4] • Need for positive airway pressure therapy (e.g., CPAP) • Need for other types of mechanical ventilation AND • with at least 1 RSV-positive swab detected by qRT-PCR

ARI = acute respiratory infection; LRTD = lower respiratory tract disease; RSV: respiratory syncytial virus; qRT-PCR = reverse transcription polymerase chain reaction

1. Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route.
2. Feverishness is defined as the feeling of having fever without objective measurement.
3. Reported by study participant or investigator.
4. Reported by investigator. Peripheral arterial oxygen saturation (SpO2%) was assessed using pulse oximetry at each protocol defined visit and each ARI visit. For the purpose of the study, the same validated oxygen saturation device has been provided to each study site.
5. Throat and/or nasal swab samples collected at ARI visits for qRT-PCR testing were collected within 6 days after ARI onset (i.e., up to Day 7). In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it was not possible to perform the ARI visit within 6 days after ARI onset (i.e., within Day 3 to Day 7), then the interval for this visit and the site swab collection could be extended up to maximum 14 days after ARI onset (i.e., until Day 15).
6. A case that was positive by the quantitative qRT-PCR for RSV-A and/or RSV-B was counted as an RSV case, whatever the result for RSV-A/B tested by multiplex qRT-PCR, for other respiratory virus tested by multiplex qRT-PCR (co-infection).
7. The investigator graded each ARI/LRTD as mild, moderate or severe based on a grading scale. An ARI/LRTD event was graded as severe by the investigator if it prevented normal, everyday activities. Such an event could, for example, have prevented attendance at work and could have necessitated the administration of corrective therapy.
8. In case the participant was already receiving any of these for treating/controlling any pre-existing condition, any significant change or adaptation in the used therapy was to be taken into account.

13.2 Supplemental Immunogenicity Information

Appendix table 2 Study 002: Geometric mean ratios of the fold increase (post over pre-vaccination) between RSVPreF3-binding IgG concentrations and RSV-A neutralizing titers (ED_{60}) at 1 month post-vaccination – Part B, PPSi

Formulation	N	RSVPreF3 IgG GM Fold Increase (95% CI)	RSV-A NAb GM Fold Increase (95% CI)	GM Ratio of Fold Increase (95% CI)
Post-Dose 1 at Day 31 / Pre-vaccination				
Unadjuvanted				
30 μg	93	7.2 (6.2, 8.5)	5.6 (4.5, 6.8)	1.3 (1.1, 1.5)
60 μg	90	10.2 (8.4, 12.3)	6.6 (5.3, 8.4)	1.5 (1.3, 1.8)
120 μg	90	12.8 (11.0, 14.9)	9.9 (8.0, 12.3)	1.3 (1.1, 1.5)
$AS01_E$				
30 μg	92	8.2 (6.8, 9.8)	5.6 (4.5, 6.9)	1.5 (1.3, 1.7)
60 μg	97	8.6 (7.2, 10.2)	6.7 (5.5, 8.2)	1.3 (1.1, 1.5)
120 μg	94	12.4 (10.2, 15.0)	9.5 (7.6, 11.8)	1.3 (1.1, 1.5)
$AS01_B$				
30 μg	95	7.8 (6.6, 9.3)	6.2 (5.0, 7.6)	1.3 (1.1, 1.5)
60 μg	95	9.5 (7.9, 11.5)	6.6 (5.5, 8.1)	1.4 (1.2, 1.7)
120 μg	93	11.5 (9.7, 13.5)	8.0 (6.6, 9.6)	1.4 (1.2, 1.7)
Placebo	92	1.0 (1.0, 1.0)	0.9 (0.8, 1.0)	1.1 (1.0, 1.2)

CI = confidence interval; ED_{60} = estimated dilution 60; GM = geometric mean; N = Number of participants with available results at the 2 considered time points (post and pre) for both RSVPreF3-binding IgG and RSV-A NAb = neutralizing titers (referred to as NAb in the table); PPS = per-protocol set for immunogenicity.

13.2.1 RSV-A and RSV-B Neutralization Assays

Assay Description

The serum neutralization assay is a functional assay that measures the ability of serum antibodies to neutralize RSV entry and replication in a host cell line. Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a monolayer of Vero cells (African Green Monkey, kidney, Cercopitheus aethiops, ATCC CCL 81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell monolayer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (Polyclonal anti-RSV-A/B IgG) and a secondary antibody conjugated to horseradish peroxidase (HRP), allowing the visualization of plaques after coloration with TrueBlue peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with a Reading software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing titer is expressed in ED_{60} and corresponds to the inverse of the interpolated serum dilution that

yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others [Barbas, 1992; Bates, 2014]. Titers are also expressed in International Units per milliliter (IU/mL). Secondary standard calibrated against the international reference (NIBSC 16/284) is included in the runs.

Variability of the Two Assays

RSV-A neutralization assay: intermediate precision: 32.0%

RSV-B neutralization assay: intermediate precision: 37.2%

For neutralization assays, coefficients of variation between 30 and 40% are expected. The common maximum target put in the validation protocol is 50%. For such an assay, a global variability below 30% is quite rare. Therefore, the assays utilized present an expected variability.

13.2.2 RSVPreF3-binding IgG ELISA

Assay Description

Binding antibodies to the RSVPreF3 antigen were evaluated by an indirect ELISA allowing the detection and the quantification of antigen-binding IgG antibodies in human serum samples. The principle of these assays is as follows: RSVPreF3 protein antigen is adsorbed onto a 96-well polystyrene microplate. After washing and blocking steps, dilutions of serum samples, controls and standards are added to the coated microplate. A reference standard curve is prepared using a pool of commercial human serum containing anti-RSV antibodies. After incubation, the microplate is washed to remove unbound primary antibodies. Binding IgG are detected by the addition of a secondary anti-human antibody (total IgG binding), conjugated to HRP. Binding antibodies are quantified by the addition of the HRP substrate, tetramethylbenzidine and hydrogen peroxide, whereby a colored product develops proportionally to the amount of anti-RSVPreF3 protein total IgG antibodies present in the serum sample. The optical density of each sample dilution is then interpolated on the reference standard. The corresponding antibody concentration, corrected for the dilution factor, is expressed in arbitrary ELISA Laboratory Units per milliliter (ELU/mL).

Variability of the ELISA

The coefficient of variation of the assay is 8.2% which is within the acceptable range for an ELISA, and can even be considered a low variability (high accuracy). Maximum variability accepted in a validation protocol is 30%, and most of ELISAs have a variability between 15-25%.

13.2.3 ICS 10p

Assay Description

The ICS was used to assess RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-γ, IFN-γ, IL-13, IL-17. As previously described [Moris, 2011], thawed peripheral

blood mononuclear cells are stimulated in vitro in the presence of anti-CD28 and anti-CD49d antibodies either with pools of 15-mer peptides overlapping by 11 amino acids and spanning the sequence of the RSVPreF3 protein, or with medium. After 2 hours of incubation at 37°C, Brefeldin A is added to inhibit cytokine secretion during an additional overnight incubation at 37°C. Cells are subsequently harvested, stained for surface markers (CD4+ and CD8+) and then fixed. Fixed cells are then permeabilized and stained with labeled antibodies specific for the following immune markers:

- CD3+: phenotyping T cells;
- CD40L (CD154), expressed on activated CD4+ T cells, [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006];
- IL-2: key for the development, survival and function of T cells [Boyman, 2012];
- TNF-α: anti-viral/intracellular factor, pro-inflammatory cytokine, cytotoxicity [Sedger, 2014];
- IFN-γ: anti-viral factor, associated with the Th1-like profile [Schoenborn, 2007];
- 4-1BB (CD137), expressed on activated CD4+ and CD8+ T cells [Wölfl, 2008];
- IL-13: associated with the Th2-like profile [Bao, 2015];
- IL-17: associated with the Th17-like profile [Korn, 2009].

After staining with the markers above, the cellular samples are analyzed by flow cytometry allowing to determine the frequency of CD4+ and/or CD8+ T cells expressing the marker(s) of interest per million of CD4+ and/or CD8+ T cells.

Variability of the ICS10P

Global variability is <25% over the analytical range, which is much lower than biological variability (variability between subjects). The maximum variability allowed to succeed the validation is ≤40%. So, the ICS10P used is within an acceptable range, with respect to variability.

13.2.4 qRT-PCR able to discriminate RSV-A and RSV-B subtypes

RSV-A and RSV-B ribonucleic acids (RNAs) extracted from the swab samples were detected in a duplex qRT-PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process involved nucleic acids extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real-time RT-PCR reaction using a calibration curve (absolute quantitation). The RSV viral load was reported as copies of RSV RNA per mL of sample (assay positivity cut-off was set at the limit of detection: 304 copies per mL for RSV-A and 475 copies per mL for RSV-B).

13.3 Supplemental Safety Information

Appendix table 3 Pre-defined list of potential immune-mediated diseases (pIMDs)

Blood disorders and coagulopathies	Cardio-pulmonary inflammatory disorders	Endocrine disorders

- Antiphospholipid syndrome
- Autoimmune aplastic anemia
- Autoimmune hemolytic anemia, including:
  - Warm antibody hemolytic anemia
  - Cold antibody hemolytic anemia
- Autoimmune lymphoproliferative syndrome (ALPS)
- Autoimmune neutropenia
- Autoimmune pancytopenia
- Autoimmune thrombocytopenia
  - Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", "primary immune thrombocytopenia".
- Evans syndrome
- Pernicious anemia
- Thrombosis with thrombocytopenia syndrome (TTS)
- Thrombotic thrombocytopenic purpura
  - Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"
	- Idiopathic Myocarditis/Pericarditis, including:
	  - Autoimmune / Immune-mediated myocarditis
	  - Autoimmune / Immune-mediated pericarditis
	  - Giant cell myocarditis
	- Idiopathic pulmonary fibrosis, including:
	  - Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis)
	  - Pleuroparenchymal fibroelastosis (PPFE)
	- Pulmonary alveolar proteinosis (PAP)
	  - Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"
		- Addison's disease
		- Autoimmune / Immune-mediated thyroiditis, including:
		  - Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)
		  - Atrophic thyroiditis
		  - Silent thyroiditis
		  - Thyrotoxicosis
		- Autoimmune diseases of the testis and ovary, including:
		  - Autoimmune oophoritis
		  - Autoimmune ovarian failure
		  - Autoimmune orchitis
		- Autoimmune hyperlipidemia
		- Autoimmune hypophysitis
		- Diabetes mellitus type I
		- Grave's or Basedow's disease, including:
		  - Marine Lenhart syndrome
		  - Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
		- Insulin autoimmune syndrome
		- Polyglandular autoimmune syndrome, including:
		  - Polyglandular autoimmune syndrome type I, II and III

Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**

- Ocular Autoimmune / Immune-mediated disorders, including:
  - Acute macular neuroretinopathy (also known as acute macular outer retinopathy)
  - Autoimmune/Immune-mediated retinopathy
	- Autoimmune / Immune-mediated pancreatitis
	- Celiac disease
	- Inflammatory Bowel disease, including:
	  - Crohn's disease
	  - Microscopic colitis
	  - Terminal ileitis
		- Autoimmune cholangitis
		- Autoimmune hepatitis
		- Primary biliary cirrhosis
		- Primary sclerosing cholangitis

- Autoimmune/Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia - Cogan's syndrome: an oculo-audiovestibular disease - Ocular pemphigoid - Ulcerative keratitis - Vogt-Koyanagi-Harada disease	- Ulcerative colitis - Ulcerative proctitis	
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**

- Gout, including:
  - Gouty arthritis
- Idiopathic inflammatory myopathies, including:
  - Dermatomyositis
  - Inclusion body myositis
  - Immune-mediated necrotizing myopathy
  - Polymyositis
- Mixed connective tissue disorder
- Polymyalgia rheumatica (PMR)
- Psoriatic arthritis (PsA)
- Relapsing polychondritis
- Rheumatoid arthritis, including:
  - Rheumatoid arthritis associated conditions
  - Juvenile idiopathic arthritis
  - Palindromic rheumatism
  - Still's disease
  - Felty's syndrome
- Sjogren's syndrome
- Spondyloarthritis, including:
  - Ankylosing spondylitis
  - Juvenile spondyloarthritis
  - Keratoderma blenorrhagica
  - Psoriatic spondylitis
  - Reactive Arthritis (Reiter's Syndrome)
  - Undifferentiated spondyloarthritis
- Systemic Lupus Erythematosus, including:
  - Lupus associated conditions (eg, Cutaneous lupus erythematosus, Lupus nephritis, etc.)
  - Complications such as shrinking lung syndrome (SLS)
	- Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants, including:
	  - Acute necrotising myelitis
	  - Bickerstaff's brainstem encephalitis
	  - Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)
	  - Myelin oligodendrocyte glycoprotein antibody-associated disease
	  - Neuromyelitis optica (also known as Devic's disease)
	  - Noninfective encephalitis/ encephalomyelitis / myelitis
	  - Postimmunization encephalomyelitis
	- Guillain-Barré syndrome (GBS)*, including:
	  - Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
	- Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including:
	  - Cranial nerve neuritis (eg, Optic neuritis)
	  - Idiopathic nerve palsies/paresis (eg, Bell's palsy)
	  - Melkersson-Rosenthal syndrome
	  - Multiple cranial nerve palsies/paresis
	- Multiple Sclerosis (MS), including:
	  - Clinically isolated syndrome (CIS)
	  - Malignant MS (the Marburg type of MS)
	  - Primary-progressive MS (PPMS)
	  - Radiologically isolated syndrome (RIS)
		- Autoimmune/Immune-mediated glomerulonephritis, including:
		  - IgA nephropathy
		  - IgM nephropathy
		  - C1q nephropathy
		  - Fibrillary glomerulonephritis
		  - Glomerulonephritis rapidly progressive
		  - Membranoproliferative glomerulonephritis
		  - Membranous glomerulonephritis
		  - Mesangioproliferative glomerulonephritis
		  - Tubulointerstitial nephritis and uveitis syndrome

- Systemic Scleroderma (Systemic Sclerosis), including:
  - Reynolds syndrome (RS)
  - Systemic sclerosis with diffuse scleroderma
  - Systemic sclerosis with limited scleroderma (also known as CREST syndrome)
	- Relapsing-remitting MS (RRMS)
	  - Secondary-progressive MS (SPMS)
	  - Uhthoff's phenomenon
	- Myasthenia gravis, including:
	  - Ocular myasthenia
	  - Lambert-Eaton myasthenic syndrome
	- Narcolepsy (with or without presence of unambiguous cataplexy)
	- Peripheral inflammatory demyelinating neuropathies and plexopathies, including
	  - Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy)
	  - Antibody-mediated demyelinating neuropathy
	  - Chronic idiopathic axonal polyneuropathy (CIAP)
	  - Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (eg, multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)
	  - Multifocal motor neuropathy (MMN)
	- Transverse myelitis (TM), including:
	  - Acute partial transverse myelitis (APTM)
	  - Acute complete transverse myelitis (ACTM)	

Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**

- Alopecia areata
- Autoimmune / Immune-mediated blistering dermatoses, including:
  - Bullous Dermatitis
  - Bullous Pemphigoid
  - Dermatitis herpetiformis
  - Epidermolysis bullosa acquisita (EBA)
  - Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease
  - Pemphigus
- Erythema multiforme
- Erythema nodosum
	- Large vessels vasculitis*, including:
	  - Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)
	  - Giant cell arteritis (also called temporal arteritis)
	  - Takayasu's arteritis
	- Medium sized and/or small vessels vasculitis*, including:
	  - Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)
	  - Behcet's syndrome
	  - Buerger's disease (thromboangiitis obliterans)
		- Anti-synthetase syndrome
		- Capillary leak syndrome
		  - Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
		- Goodpasture syndrome
		  - Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"
		- Immune-mediated enhancement of disease, including:

- Lichen planus, including:
  - Liquen planopilaris
- Localised Scleroderma (Morphoea)
  - Eosinophilic fasciitis (also called Shulman syndrome)
- Psoriasis
- Pyoderma gangrenosum
- Reactive granulomatous dermatitis, including:
  - Interstitial granulomatous dermatitis
  - Palisaded neutrophilic granulomatous dermatitis
- Stevens-Johnson Syndrome (SJS), including:
  - Toxic Epidermal Necrolysis (TEN)
  - SJS-TEN overlap
- Sweet's syndrome, including:
  - Acute febrile neutrophilic dermatosis
- Vitiligo
	- Churg–Strauss syndrome (allergic granulomatous angiitis)
	- Erythema induratum (also known as nodular vasculitis)
	- Henoch-Schonlein purpura (also known as IgA vasculitis)
	- Microscopic polyangiitis
	- Necrotizing vasculitis
	- Polyarteritis nodosa
	- Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)
	- Wegener's granulomatosis
		- Vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)
		- Immunoglobulin G4 related disease
		- Langerhans' cell histiocytosis
		- Multisystem inflammatory syndromes, including:
		  - Kawasaki's disease
		  - Multisystem inflammatory syndrome in adults (MIS-A)
		  - Multisystem inflammatory syndrome in children (MIS-C)
		- Overlap syndrome
		- Raynaud's phenomenon
		- Sarcoidosis, including:
		  - Loefgren syndrome
		- Susac's syndrome

Appendix table 4 Intensity scales for solicited events in adults in Phase 3 studies

Event	Intensity grade	Parameter
Pain at the injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities
	2	Moderate: Painful when limb is moved and interferes with every day activities
	3	Severe: Significant pain at rest. Prevents normal every day activities
Erythema at the injection site		Record greatest surface diameter in mm
Swelling at the injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	Normal
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

*Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route. The route for measuring temperature could be oral, axillary, or tympanic.

Appendix table 5 Intensity scale for local injection site erythema/swelling and fever

Intensity grade	Erythema/Swelling	Fever
0	≤ 20 mm	< 38.0°C (100.4°F)
1	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2	> 50 - ≤ 100 mm	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3	> 100 mm	> 39.0°C (102.2°F)