RESPIRATORY SYNCYTIAL VIRUS STABILIZED BIVALENT PREFUSION F SUBUNIT VACCINE (RSVPREF / ABRYSVO)

BRIEFING DOCUMENT FOR VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE MEETING 28 FEBRUARY 2023 – 01 MARCH 2023

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LIST OF ABBREVIATIONS

Abbreviations	Term
ACIP	Advisory Committee on Immunization Practices
ADR	adverse drug reaction
AEs	adverse events
$Al(OH)_3$	aluminum hydroxide
anti-GQ1b	antibody (IgG) to GQ1b ganglioside (diagnostic marker of Miller Fisher Syndrome)
AMI	acute myocardial infarction
ARI	acute respiratory illness
ARI-RSV	respiratory syncytial virus associated acute respiratory illness
AUC	area under the curve
BLE	bilateral lower extremity
CBER	Center for Biologics Evaluation and Research
CD4+	cluster of differentiation 4 positive
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIPD	chronic inflammatory demyelinating polyneuropathy
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CpG	CpG 24555 (cytosine-guanine nucleotides)
CRP	C-reactive protein
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DS-Cav1	incompletely stabilized RSV F
e-diary	electronic diary
EHR	electronic health record
FDA	Food and Drug Administration
FIH	first in human
GBS	Guillain-Barre syndrome
GLP	Good Laboratory Practices
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titre
HAI	hemagglutination inhibition assay
ICU	intensive care unit
IgG	immunoglobulin G
LBCI	lower bound confidence interval
LLOD	lower limit of detection
LLOQ	lower limit of quantification
LPLV	last participant last visit
LRTI	lower respiratory tract illness
LRTI-RSV	respiratory syncytial virus associated lower respiratory tract illness
MAE	medically attended adverse event
mITT	modified intent to treat
NAAT	nucleic acid amplification test
NDCMC	newly diagnosed chronic medical condition
NIH	National Institutes of Health
OTC	over the counter
P	number of RSVpreF cases divided by the total number of cases
PCR	polymerase chain reaction
PDUFA	Prescription Drug User Fee Act
PT	Preferred Term

Abbreviations	Term
PYO	person-years observation
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV-ARI	respiratory syncytial virus associated acute respiratory illness
RSV B	respiratory syncytial virus subgroup B
RSV F	respiratory syncytial virus fusion (F) glycoprotein
RSVpreF	respiratory syncytial virus bivalent stabilized prefusion F subunit vaccine
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SIIV	seasonal inactivated influenza vaccine
sLRTI-RSV	severe respiratory syncytial virus associated lower respiratory tract illness
SOC	System Organ Class
T4	bacteriophage T4
TH1	T-cell helper type 1
Tris	tris(hydroxymethyl)aminomethane
TSS	total symptom score
US	United States
VE	vaccine efficacy
VL-AUC	viral load-area under the curve
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WBC	white blood cell

EXECUTIVE SUMMARY

On September 30, 2022 Pfizer submitted a Biologics License Application to support licensure of RSVpreF (Abrysvo), a respiratory syncytial virus (RSV) bivalent stabilized prefusion F subunit vaccine indicated for the prevention of acute respiratory disease and lower respiratory tract illness (LRTI) caused by RSV in individuals 60 years of age and older. RSVpreF is administered intramuscularly, as a single 0.5-mL injection. The Prescription Drug User Fee Act (PDUFA) action date for the BLA is May 31, 2023. Licensure is being sought based on the totality of clinical data which demonstrates that RSVpreF is a highly efficacious against moderate and more severe LRTI-RSV (based on number of symptoms), well-tolerated and safe vaccine, with a benefit-to-risk ratio that is favorable. These data are summarized herein. Note, a separate BLA is under Food and Drug Administration (FDA) review for the same RSVpreF dose and formulation for use in pregnant individuals to protect their infants from RSV.

Unmet Need

Despite more than 50 years of vaccine-development efforts, no vaccine to protect against RSV disease in any population has been authorized. Prevention of RSV disease in young infants and older adults is a significant unmet need, globally. RSV is the leading cause of bronchiolitis and viral pneumonia and can lead to fatal respiratory distress in infants with underlying cardiopulmonary disease, or in the absence of effective health care systems.[1,2] RSV infection is essentially universal by 2 years of age.[3] In adults, RSV illness occurs more commonly with increasing age and among those with existing comorbidities, which are exacerbated due to RSV exposure.[4,5] Similar to influenza, RSV is also a common cause of LRTI causing substantial disease burden in these populations.[6,7] In the US, RSV is responsible for approximately 60,000 – 160,000 hospitalizations and 6,000 – 13,000 deaths annually in adults ≥65 years of age.[8,9,10,11] Furthermore, in the US there are 120,000 emergency department visits and approximately 1.36 million RSV-associated acute respiratory illness (ARI-RSV) outpatient visits among adults ≥65 years of age.[8] In industrialized countries, a recent meta-analysis found the case fatality rate of medically attended ARI-RSV was 8.2% among older adults (>70% included events were hospitalizations).[12] Finally, a substantial burden of non-medically attended ARI is experienced by older adults, comprising 72–83% of all ARI-RSV[4,13], which would correspond to an estimated additional 3.5 to 6.5 million illnesses annually.

The RSVpreF older adult indication was granted Breakthrough Therapy Designation (2022) by the United States (US) FDA, confirming that RSVpreF is intended to treat a serious condition and has the potential to address an unmet medical need for a preventative measure against acute respiratory disease and LRTI caused by RSV in older adults.

Vaccine Design and Scientific Rationale

The F glycoprotein on the surface of the virus has 2 very different conformations – prefusion and postfusion. Prefusion F is inherently unstable and spontaneously rearranges to postfusion F. Prefusion F displayed on the surface of the virus is required to infect the respiratory tract and antibodies specific to this conformation most effectively neutralize RSV[14], partly explaining failures of postfusion F vaccine studies in adults.[14-18] Pfizer's bivalent stabilized

prefusion F subunit vaccine (RSVpreF) is based on a breakthrough scientific development—the determination of the crystal structure of prefusion RSV F in complex with an antibody fragment.[19] That structure provided the critical information needed to stabilise prefusion F through structural engineering so that it can be used as a vaccine antigen. The premise of Pfizer's RSVpreF is that F antigens structurally engineered for stability in the prefusion conformation elicit higher neutralizing titers and should confer better protection than postfusion F antigens.

RSVpreF contains equal amounts of RSV subgroup A and subgroup B fusion glycoprotein (F) antigens engineered for stability in the prefusion conformation. These 2 major RSV subgroups, A and B, cocirculate, often alternating in predominance from season-to-season,[20] and both cause severe disease.[1] Subgroup-specific amino acid-sequence differences between surface-exposed parts of mature RSV F glycoproteins are concentrated in prefusion-specific epitopes.[14,21] To cover RSV diversity optimally, Pfizer's RSVpreF is bivalent.

The total dose of the RSV drug product is 120 µg of the RSV prefusion F antigen (60 µg subgroup A, 60 µg subgroup B). The vaccine does not contain an adjuvant.

Overview of the Clinical Development Program (CDP) for the Older Adult Indication

The extensive clinical development program designed to support the RSVpreF older adult indication includes the C3671013 pivotal Phase 3 safety and efficacy study (ongoing) and 5 supportive studies.

Phase 1/2 studies evaluated various dose levels and formulations and supported the final candidate vaccine selection for the pivotal Phase 3 efficacy study in older adults ≥60 years of age (C3671013).

Unadjuvanted RSVpreF 120 µg (60 µg subgroup A, 60 µg subgroup B) was selected for the pivotal Phase 3 study based on prior clinical data showing no benefit of an adjuvanted formulation (with CpG 24555 (cytosine-guanine nucleotides) [CpG]/ aluminum hydroxide [$Al(OH)_3$]), and that unadjuvanted RSVpreF had high efficacy in a RSV human challenge model and a favorable safety and tolerability profile.[22,23,15]

C3671013 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to assess the safety, immunogenicity, and **efficacy** of RSVpreF in the prevention of RSV-associated LRTI (LRTI-RSV) in up to 45,000 adults 60 years of age and older during the first RSV season and the long-term immunogenicity and efficacy of RSVpreF across 2 RSV seasons. This is an event-driven study which has a target of at least 59 first episode evaluable LRTI-RSV cases with ≥2 symptoms (primary endpoint).

Key Efficacy Results from the Pivotal Phase 3 Study C3671013

The evidence for robust RSVpreF clinical efficacy in older adults is based on results from an interim analysis from the pivotal Phase 3 Study C3671013, an ongoing, multicenter, randomized, double-blinded, placebo-controlled study in which older adults were administered RSVpreF 120 µg or placebo (1:1 randomization).

The interim efficacy analysis from Study C3671013 was conducted when 44 first-episode LRTI-RSV cases with ≥2 symptoms had accrued in the first RSV season through the ARI surveillance cutoff date of 08 July 2022. After the Data Monitoring Committee (DMC) declared success of first-episode LRTI-RSV cases with ≥2 symptoms and with 16 first-episode LRTI-RSV cases with ≥3 symptoms accrued (meeting minimum requirement for interim analyses), this endpoint was included in the interim analysis. These analyses demonstrated statistically significant efficacy for RSVpreF for the primary efficacy endpoints of LRTI-RSV cases with ≥2 symptoms and LRTI-RSV cases with ≥3 symptoms (lower bound of the vaccine efficacy (VE) confidence interval [CI] >20% for first-episode cases for both endpoints). The results showed that in adults ≥60 years of age, a single dose of RSVpreF 120 µg was:

- 66.7% (96.66% CI: 28.8%, 85.8%) efficacious in preventing LRTI-RSV (first episode) with ≥2 symptoms in the first RSV season.

- 85.7% (96.66% CI: 32.0%, 98.7%) efficacious in preventing LRTI-RSV (first episode) with ≥3 symptoms in the first RSV season.

Further, RSVpreF 120 µg was 62.1% (95% CI: 37.1%, 77.9%) efficacious in preventing ARI-RSV (first episode) in the first RSV season.

Study C3671013 did not accumulate enough RSV severe cases to determine VE against this outcome. However, as described by the Advisory Committee on Immunization Practices (ACIP) RSV older adult working group, efficacy against more severe outcomes is expected to be at least as high as efficacy against lower respiratory tract disease/illness cases.[11] Thus, for RSVpreF, the VE for severe disease would be expected to be similar or higher than that observed for cases with ≥3 symptoms (85.7%). These cases all experienced ≥1 of the more severe LRTI symptoms (wheezing, tachypnea, and shortness of breath) versus cases with ≥2 symptoms, which may have experienced only cough and sputum production.

Safety Profile of RSVpreF Based on Pivotal Phase 3 C3671013 Study

As of the data cutoff date of 14 July 2022 (nasal swab collection, AE collection), safety data from 17,215 participants who received RSVpreF 120 µg in the pivotal Phase 3 C3671013 study demonstrated that the vaccine is safe and well tolerated when administered to adults ≥60 years of age, based on:

- Local reactions and systemic events to RSVpreF 120 µg were mostly mild to moderate in severity.

- The incidences of adverse events (AEs) and AEs assessed by the investigator as related to study intervention within 1 month of vaccination were similar between the RSVpreF 120 µg group and placebo group.

- The incidences of newly diagnosed chronic medical conditions (NDCMCs), serious adverse events (SAEs), life threatening AEs, and AEs leading to withdrawal were similar between the RSVpreF 120 µg group and placebo group.

- AEs leading to death were reported in 52 (0.3%) RSVpreF recipients and 49 (0.3%) placebo recipients, none of which were considered related to vaccination.

Benefit/Risk Conclusions

The pivotal Phase 3 C3671013 study, and the totality of data from the RSVpreF clinical development program for older adults, provides robust evidence that RSVpreF is highly efficacious against LRTI-RSV with ≥2 and ≥3 symptoms and ARI-RSV and is well-tolerated, with a benefit-to-risk ratio that is highly favorable and that supports the proposed indication for prevention of acute respiratory disease and lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

1. BACKGROUND INFORMATION

1.1. RSV Disease in Adults

RSV is a major cause of respiratory infection in both infants and older adults. Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall.[24] RSV has 2 major subgroups, A and B, which cocirculate. Either can cause severe disease.[25]

In the US, RSV is responsible for approximately 60,000 – 160,000 hospitalizations and 6,000 – 13,000 deaths annually in adults 65 years of age and older.[8,9,10,11] Furthermore, in the US, there are 120,000 emergency department visits and approximately 1.36 million RSV-associated ARI-RSV outpatient visits among adults age ≥65 years of age.[8] Finally, a substantial burden of non-medically attended ARI is experienced by older adults, comprising 72–83% of all ARI-RSV[4,13], which would correspond to an estimated additional 3.5 to 6.5 million illnesses annually. However, the burden of adult RSV disease is under appreciated since testing for RSV is less common in older adults than in children. RSV disease in adults is also difficult to diagnose based on clinical signs and symptoms alone, and, before the recent broader use of more sensitive detection methods, laboratory confirmation of RSV in adults was challenging because of lower levels of virus viral shedding compared to children.[26]

Adults 60 years of age and older are at increased risk of RSV illness, which can trigger exacerbations of underlying comorbid conditions, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF).[26] RSV infection has been associated with up to 22% of acute COPD exacerbations in prospective cohort studies and 11% of wintertime hospitalizations for COPD exacerbations.[26] In industrialized countries, a recent meta-analysis found the case fatality rate of medically attended ARI-RSV (>70% subjects inpatients) was 8.2% (95% CI: 5.5–11.9%) among older adults and 9.9% (95% CI: 6.7-14.4%) among adults with comorbidities (community and medically attended events combined).[12] Further, in the same report, 5% of medically attended RSV among older adults were admitted to the intensive care unit (ICU) and 27% for adults with comorbidities.[12] Overall, adults with comorbidities have a higher risk of experiencing medically significant ARI-RSV infection and a poorer outcome.[8,12] A higher incidence of RSV-associated hospitalization among adults has been documented in census-tracts with higher poverty levels, particularly when comparing neighborhoods with the lowest levels of crowding with neighborhoods with the highest levels of crowding, even in developed countries.[27]

The pathogenesis of severe RSV disease in older adults is not well understood, but there are common risk factors in the elderly for severe disease.[28] Immunosenescence, as a consequence of aging, can result in a weakened immune response to pathogens and suboptimal response to vaccines. In addition, lung expansion in older adults is compromised because of decreased strength of the respiratory muscle and diaphragm. Older adults may also have decreased protective mucus levels, lung compliance, and elastin.[29-31] RSV may lead to hospitalization or even death among the elderly, despite some preexisting immunity and limited viral replication.

1.2. Proposed Indication

The proposed indication for RSVpreF (120 µg) is:

Prevention of acute respiratory disease and lower respiratory tract disease caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older by active immunization.

1.3. General Product Information

Pfizer's bivalent RSVpreF is comprised of equal quantities of 2 recombinant RSV F antigens representing the 2 major subgroups A and B, each structurally engineered for enhanced stability in the prefusion conformation. The total dose of the RSV drug product is 120 µg of the RSV prefusion F antigen (60 µg subgroup A, 60 µg subgroup B). The unadjuvanted formulation was selected based on clinical data showing no benefit of an adjuvanted formulation (with CpG/$Al(OH)_3$), and that unadjuvanted RSVpreF had high efficacy in a RSV human challenge model and a favorable safety and tolerability profile (Section 4).

The RSVpreF drug product is presented as a sterile lyophilized powder at the target strength of 240 mg/mL upon reconstitution and is filled in a 2 mL Type 1 glass vial. Each vial of the lyophilized vaccine is reconstituted with 0.65 mL of sterile water diluent.

The bulk drug product formulation contains 20 mM Tris (tromethamine), 50 mM sodium chloride, 0.2 mg/mL polysorbate 80, 30 mg/mL sucrose and 60 mg/mL mannitol.

RSVpreF is administered intramuscularly, as a single 0.5-mL injection.

2. UNMET MEDICAL NEED

2.1. Current Strategies to Prevent or Treat RSV Disease

Currently, there is no authorized vaccine to prevent RSV disease. In older adults, RSV disease is associated with increased morbidity and mortality either caused by the virus itself, due to bacterial superinfection, or deterioration of already existing chronic medical conditions.[32] Older adults hospitalized due to RSV infection have a high morbidity and health-resource utilization.[33]

Treatment of RSV disease consists primarily of supportive care (eg, fluids, supplemental oxygen, hydration and suctioning of secretions, mechanical ventilation).[34,35] Comprehensive hygiene measures are helpful and cost-effective in limiting the spread of RSV, and should always be advocated as a prophylactic measure, however, they are not sufficiently efficacious to prevent the disease burden. In patients diagnosed with RSV, infection may be treated with aerosolized ribavirin; however, ribavirin is rarely used to treat RSV, except in the context of severe immunosuppression, because of inconvenient administration, questionable benefit in immunocompetent patients, teratogenicity concerns based on nonhuman animal data, and high cost.[36-38] Ribavirin has also not resulted in a meaningful impact upon clinically relevant outcomes, including reductions in mortality, duration of hospitalization, need for mechanical ventilation, and ICU admission.[39-41] Paracetamol and over the counter (OTC) cold medications may be used to relieve milder symptoms.

2.2. Scientific Rationale for RSVpreF Vaccine

The trimeric RSV F surface glycoprotein is the primary target of neutralizing antibodies and is the basis for the engineered antigens in Pfizer's vaccine candidate. During RSV entry into cells, F rearranges from a prefusion to a postfusion conformation. As it rearranges, F fuses the viral and host cell membranes. Structural data show that the postfusion F conformation used in many prior failed vaccine approaches is very different from the predominant prefusion conformation that is present on virions. The structural difference between conformations results in antigenic differences. In contrast to postfusion F, prefusion F is in an inherently unstable conformation that needs to be stabilized to be useful as an improved vaccine antigen.[19,42] Based on this new understanding, Pfizer has developed 2 structurally engineered, stabilized prefusion F vaccine antigens, one for each RSV subgroup. The Pfizer RSV vaccine program is based on the premise that prefusion F antigens will elicit higher neutralizing antibody titers and better protection than the postfusion F antigens in previous vaccine candidates.[43-45]

In 2013, the breakthrough determination of the crystal structure of prefusion RSV F in complex with an antibody fragment that prevented rearrangement from the prefusion to the postfusion conformation enabled a National Institutes of Health (NIH) laboratory to engineer a partially stabilized RSV F, termed DS-Cav1. This construct elicited approximately 10-fold higher neutralizing antibody titers than postfusion F in laboratory animals.[19,46] Building on

the prefusion F crystal structure, Pfizer engineered RSV F constructs stabilized in the prefusion conformation. The constructs are RSV F ectodomains "locked" in the prefusion conformation by C-terminal bacteriophage T4 (T4) fibritin foldon trimerization domains and internal stabilizing mutations. The stabilized prefusion F subunit construct, on which the antigens in Pfizer's vaccine candidate are based, elicits >50-fold higher neutralizing titers than a postfusion F antigen in rhesus macaques.

RSV F has approximately 90% amino acid identity between the 2 subgroups. Unlike types of polioviruses or types and subtypes of influenza, RSV subgroups are not serotypes, and some cross-neutralization occurs between RSV subgroups A and B. However, there are antigenic differences between the subgroups that could lead to differences in protective efficacy. Most of the sequence differences between the mature F glycoproteins of the subgroups are concentrated in the prefusion-specific epitopes that elicit the most potent RSV-neutralizing and protective antibody responses.[14,47] Therefore, to cover current RSV diversity optimally, the Pfizer RSV vaccine candidate is based on recently circulating strains rather than a standard laboratory strain, and it is bivalent, with 1 F antigen (genotype Ontario) from subgroup A (preF A) and another (genotype Buenos Aires) from subgroup B (preF B). The prefusion F stabilizing mutations were introduced into each of these background F sequences. In cotton rats, immunization with the bivalent mixture elicited higher overall neutralizing titers than the constituent monovalent components.

3. SUMMARY OF KEY NONCLINICAL STUDIES

Nonclinical studies in mice, cotton rats, and rhesus macaques supported selection of the RSV subgroup A and subgroup B stabilized prefusion F antigens for RSVpreF. The in vivo data demonstrated, in RSV-naïve experimental animals, that immunization with stabilized prefusion F elicits much higher neutralizing titers than immunization with postfusion F. In the cotton rat model, immunization with the vaccine candidate protected cotton rats from RSV shedding and did not enhance respiratory pathology upon infectious RSV challenge.

To support the clinical development, RSVpreF in representative clinical formulations were tested in a Good Laboratory Practices (GLP)-compliant repeat-dose toxicity study in rats and a GLP-compliant combined fertility and pre- and postnatal developmental toxicity study in pregnant and lactating rabbits.

In both studies, RSVpreF was administered at 120 µg preF A and 120 µg of preF B (240 µg total antigen per dose), or 2 times the recommended clinical dose by IM injections. Repeat-dose administrations of RSVpreF (1 dose every 3 or 2 weeks for a total of 3 doses), with or without $Al(OH)_3$, to Wistar Han rats were tolerated without evidence of systemic toxicity, and produced a functional antibody response and anticipated, nonadverse, local inflammatory reactions. RSVpreF, with or without $Al(OH)_3$, administered to female rabbits for a total of 4 doses (twice during premating and twice during gestation) had no effects on mating performance or fertility in female rabbits or on embryo-fetal or postnatal survival, growth, or development in the F1 offspring.

4. OVERVIEW OF CLINICAL STUDIES

Pfizer developed RSVpreF to protect against RSV disease for 2 indications: one for prevention in adults 60 years of age and older by active immunization (Section 1.2), and one for prevention in infants from birth up to 6 months of age by active immunization of pregnant individuals.

Table 1 lists the studies for the clinical development plan for the Pfizer older adult RSV vaccine, including the C3671013 pivotal Phase 3 study (ongoing) and 5 supportive studies. For each of the studies, the study designs and primary and secondary endpoints are summarized in Table 11 (Appendix), and the key results in the sections below.

The final dose and formulation of RSVpreF (120 µg, unadjuvanted) selected for use in older adults were based on the safety and immunogenicity data from Studies C3671001 and C3671002 and the efficacy evaluation in Study WI257521, which collectively showed no benefit of an adjuvanted formulation (with CpG/Al(OH)$_3$) and that unadjuvanted RSVpreF had high efficacy in a RSV human challenge model and a favorable safety and tolerability profile.

Table 1. Studies in the RSVpreF Clinical Development Program for the Older Adult Indication

Study / Status	Brief Description	Age Group
C3671001 / completed (Section 4.1.1)	Phase 1/2 first in human • Dose ranging • +/- Al(OH)$_3$ • +/- Influenza vaccine • Revaccination	18-85 years
C3671002 / completed (Section 4.1.2)	Phase 1/2 CpG/Al(OH)$_3$ adjuvant safety and immunogenicity	65-85 years
WI257521 / completed (Section 4.1.3)	Phase 2a human challenge study	18-50 years
C3671014 / completed (Section 4.1.4)	Phase 3 lot consistency study	18-49 years
C3671013 / ongoing (Section 4.2)	Phase 3 pivotal efficacy study	≥60 years
C3671006 / clinically completed (Section 4.3.1)	Phase 3 concomitant influenza vaccine study	≥65 years

Abbreviations: Al(OH)$_3$ = aluminum hydroxide; CpG = CpG 24555.
Note: Studies in the RSVpreF clinical development program to support the maternal indication are not included.

Key Agreements with the FDA

Throughout the development of RSVpreF, Pfizer sought input from regulatory agencies on the clinical development plan for the older adult indication, and on the design of the pivotal

Phase 3 C3671013 study endpoints that would support licensure. The key agreements from these interactions are summarized below.

Center for Biologics Evaluation and Research (CBER) agreed that for the pivotal Phase 3 C3671013 study, a VE with a lower bound confidence interval (LBCI) of >20% for the 95% CI for the primary endpoint would support licensure. CBER was also in agreement with case definitions of LRTI-RSV with 2 and 3 symptoms and objective criteria for severe LRTI-RSV (sLRTI-RSV) (Table 2); inclusion in the label of sequential primary endpoints (LRTI-RSV evaluating VE with at least 2 and 3 symptoms); and a key secondary endpoint (sLRTI-RSV), if primary endpoints were met, to evaluate VE as 2 or 3 symptoms plus at least 1 of the severe objective criteria that was agreed with CBER. CBER also agreed with the proposal to conduct an interim analysis when at least 29 first-episode cases with ≥2 symptoms of LRTI-RSV had accrued.

4.1. Supportive Studies Completed in the Older Adult Clinical Development Program

4.1.1. Study C3671001 – Phase 1/2 First in Human

The completed first in human (FIH) dose-finding Study C3671001 (Table 11) evaluated the safety, tolerability, and immunogenicity of RSVpreF with and without concomitant seasonal inactivated influenza vaccine (SIIV) administration in 1235 nonpregnant female and male participants 18 to 85 years of age, divided into age subgroups of 18-49 and 50-85 years of age to support the maternal and the older adult indications. Three dose levels of RSVpreF (60 µg, 120 µg, and 240 µg) were evaluated in formulations with and without $Al(OH)_3$. Analyses were performed for a Sentinel Cohort (participants 18-49 or 50-85 years of age) and an Expanded Cohort (participants 18-49 or 65-85 years of age) as specified in Table 11.

Of the 1235 participants randomized, 1233 were vaccinated and 1135 (91.9%) completed the 12 month follow up visit. In the Sentinel Cohort, 84 participants were vaccinated in the 18-49 year age group and 84 were vaccinated in the 50-85 year age group. In the Expanded Cohort, 533 participants were vaccinated in the 18-49 year age group and 532 were vaccinated in the 65-85 year age group.

In both age groups, RSVpreF elicited robust neutralizing responses against RSV subgroup A (RSV A) and RSV subgroup B (RSV B) 1 month after vaccination across all vaccine dose levels and formulations (Figure 1 [RSV A]; similar results for RSV B are shown in Figure 7). The inclusion of $Al(OH)_3$ showed no benefit in enhancing immune responses at any dose level and the frequency and severity of local reactions trended higher in the groups receiving $AL(OH)_3$ containing formulations, noticeably in the younger (18–49 year) age group. Immune responses trended higher in the younger age group and in females. RSV A– and RSV B–neutralizing titer geometric mean fold rises (GMFRs) remained 2.5- to 5.2-fold higher at 12 months after vaccination compared to before vaccination, indicating good antibody persistence. RSV A– and RSV B–neutralizing titer geometric mean titres (GMTs) were higher through 12 months after vaccination compared to participants who received placebo (Figure 8 [RSV A] and Figure 9 [RSV B]). These results were consistent between age groups, across dose levels, and for formulations with or without $Al(OH)_3$.

Coadministration of RSVpreF with SIIV did not affect RSV immunogenicity, regardless of dose level or formulation. One month postvaccination, immune responses to SIIV as measured by hemagglutination inhibition assay (HAI) GMTs trended lower when RSVpreF was coadministered with SIIV compared with SIIV alone. However, as this was a dose-ranging, hypothesis-generating study designed primarily to evaluate safety, a separate non-inferiority study evaluating concomitant use with SIIV was performed and recently completed (C3671006; Section 4.3.1). Results will be shared when available.

Additionally, analyses of local reaction, systemic event, and AEs endpoints (listed in Table 11) in both cohorts demonstrated that RSVpreF was safe and well tolerated when administered alone or with SIIV, with no major differences observed across all dose levels, formulations and age groups.

Revaccination

At approximately 12 months after Vaccination 1, participants in the Expanded Cohort who received an initial 240 µg dose of RSVpreF (with or without $Al[OH]_3$) were revaccinated at the same dose and formulation with concomitant SIIV or placebo (Vaccination 3 and 4) and followed for 12 months. The SIIV or placebo assignment and the vaccination scheme was the same as for the initial vaccination. As a control, the placebo group was also revaccinated with placebo alone and then followed by SIIV alone. As discussed above in Section 4, this part of the study was conducted before the final dose selection for older adults.

Revaccination after 12 months increased neutralizing titer levels, but increases were lower than increases observed after Vaccination 1; data for the older age group (65 – 85 years) are presented in Figure 2 for RSV A (similar results for RSV B are shown in Figure 10). Although RSVpreF neutralizing titer decreased over time, titers remained higher than prevaccination across the 2 RSVpreF formulation groups, administered with and without concomitant SIIV, for RSV A or B through Month 12.

Figure 1. RSV A Neutralizing GMTs and GMFRs at 1 Month After Vaccination 1 (Age Group: 65 – 85 Years) – Expanded Cohort – Evaluable RSV Immunogenicity Population, Study C3671001

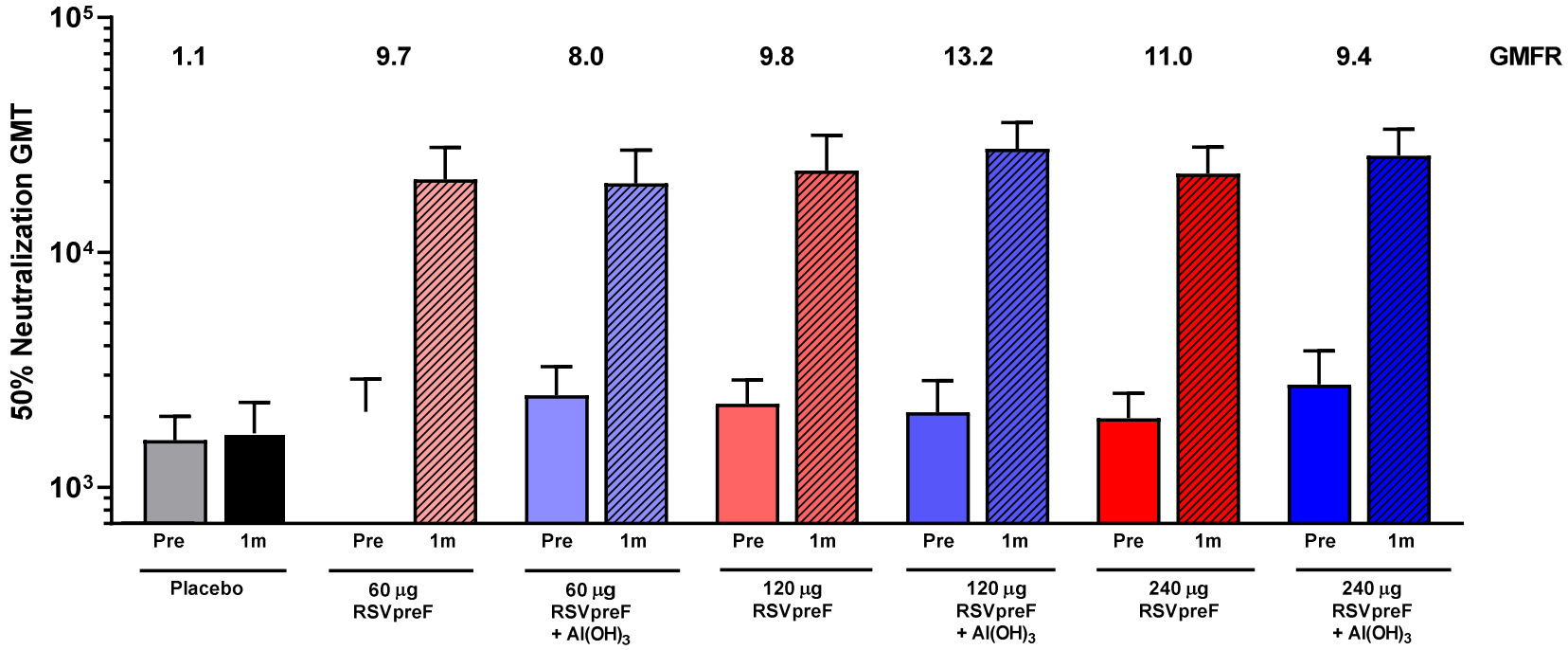
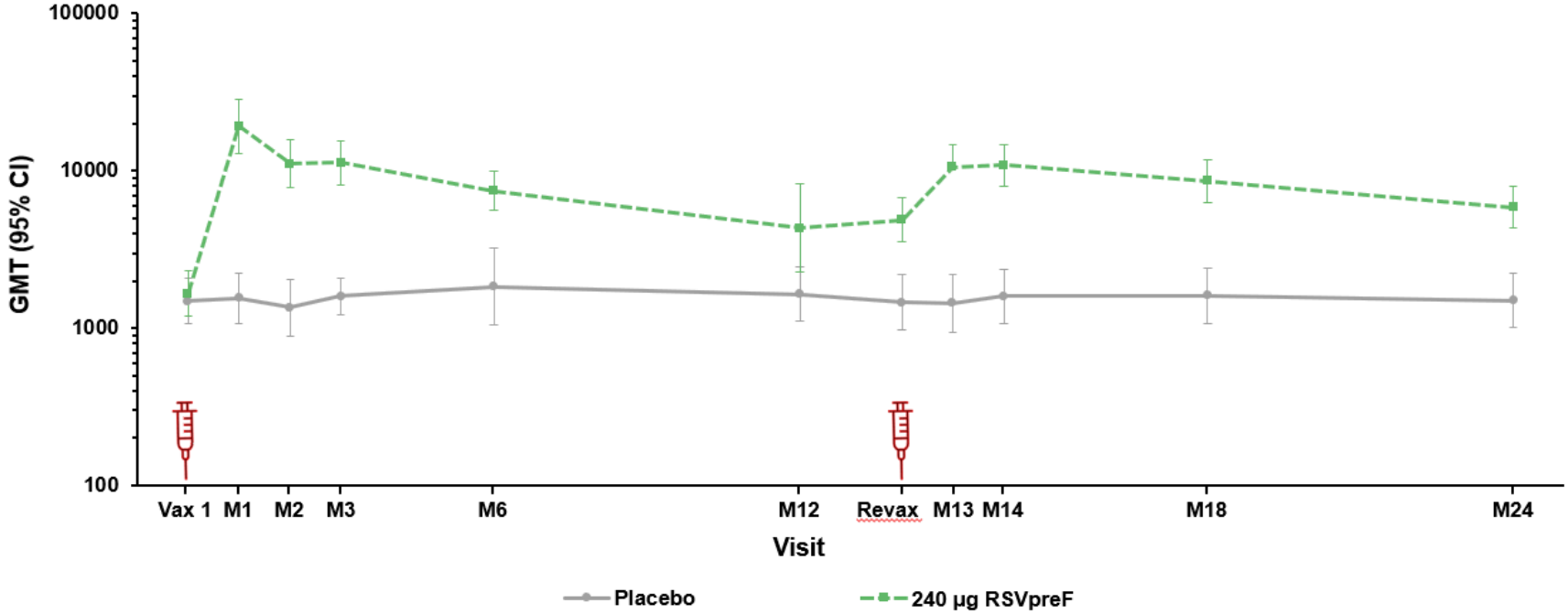


Figure 2. Kinetics Plot of RSV A Neutralizing GMTs (Age Group: 65 – 85 Years) – Expanded Cohort for Revaccination – Evaluable RSV Immunogenicity Population, Study C3671001



4.1.2. Study C3671002 – Phase 1/2 Adjuvant Safety and Immunogenicity

The completed Phase 1/2, multicenter, randomized, placebo-controlled, observer-blind, dose- and formulation-finding Study C3671002 (Table 11) in participants 65-85 years of age described the safety, tolerability, and immunogenicity of 7 RSVpreF formulations at 3 antigen dose levels of 60 µg, 120 µg, and 240 µg of the prefusion F antigens formulated with $Al(OH)_3$ or $CpG/Al(OH)_3$, or RSVpreF with the prefusion F antigens alone at a single antigen dose level when administered concomitantly with SIIV. In addition to the Primary Cohort evaluations, the 240 µg RSVpreF formulated with $CpG/Al(OH)_3$ was evaluated when administered in a Month-0, Month-2 Cohort without concomitant SIIV.

Two hundred fifty (250) participants in the Primary Cohort received 1 of 3 dose levels of RSVpreF (60 µg, 120 µg, or 240 µg) with $Al(OH)_3$ or $CpG/Al(OH)_3$, or 240 µg RSVpreF with RSV A and B antigens alone, given as a single dose concomitantly with SIIV, or SIIV only. In total, 63 participants in the Month-0, Month-2 Cohort received at least 1 dose of 240 µg of RSVpreF with $CpG/Al(OH)_3$ and 57 participants received 2 doses administered 2 months apart without concomitant SIIV.

All RSVpreF doses and formulations elicited robust, persistent neutralizing responses when administered alone or concomitantly with SIIV. In the Primary Cohort, all RSVpreF doses and formulations elicited high RSV A and RSV B neutralizing antibody GMTs 1 month after vaccination (GMFRs ranging from 4.8 to 11.6 and 4.5 to 14.1, respectively). As shown in Figure 11 (RSV A) and Figure 12 (RSV B), GMTs in all groups declined but remained higher than baseline (before vaccination) and placebo (SIIV only) at 12 months after vaccination (GMFRs ranging from 2.1 to 3.5 and 2.2 to 4.3, respectively). The inclusion of $CpG/Al(OH)_3$ showed no benefit in enhancing the immune response compared to RSVpreF formulations with $Al(OH)_3$ at any dose level or compared to RSVpreF alone at the 240 µg dose level. In the Month-0, Month-2 Cohort, no increase in GMTs was observed from before Vaccination 2 to 1 month after Vaccination 2 (GMFR of 0.9). However, RSV A and RSV B neutralizing titer GMTs remained higher than baseline (before vaccination) and placebo levels 6 months after Vaccination 2.

Additionally, analyses of local reaction, systemic event, and AE endpoints (listed in Table 11) demonstrated that RSVpreF was safe and well tolerated when administered alone or concomitantly with SIIV, with no major differences observed across dose levels or formulations.

4.1.3. Study WI257521 - Phase 2a RSV Human Challenge

The completed Study WI257521 (Table 11) evaluated the safety, immunogenicity, and efficacy of a single dose of 120 µg RSVpreF in an infectious virus challenge model in healthy adults 18–50 years of age.

A total of 70 participants were randomized and received study vaccine/placebo; there were 35 participants in each group. Challenge virus was received by 62 participants, 31 per group. Participants ranged in age between 19 and 50 years.

RSVpreF immunization was highly effective against symptomatic RSV infection and prevented shedding of infectious virus in healthy adults, as demonstrated by (Table 12):

- VE against quantitative reverse transcription polymerase chain reaction (qRT-PCR) confirmed symptomatic RSV infection confirmed by any 2 detectable qRT-PCR results over at least 2 consecutive days (primary endpoint) was 86.7% (95% CI: 53.8%–96.5%).

- VE of 100% (95% CI: 72.8%–100%) was also observed for symptomatic RSV infection confirmed by any 2 quantifiable viral RNA results on ≥2 consecutive days.

- Symptomatic RSV infection confirmed by culture (1 quantifiable culture result) yielded an observed VE of 100% (95% CI: 67.7%–100%).

- Efficacy against RSV infection, regardless of presence, absence, or severity of symptoms, was 75% (95% CI: 38.4%–90.6%) for any 2 quantifiable qRT-PCR results on 2 consecutive days and 100% (95% CI: 72.8%–100%) for any 1 quantifiable culture-confirmed infection.

- Viral load area under the curve (AUC) (primary endpoint) and the peak viral load was markedly lower in the RSVpreF group than in the placebo group, and the duration of the viral load was much shorter in the RSVpreF group than in the placebo group.

- The sum total symptom score (TSS), peak TSS over duration of quarantine, and TSS AUC were all substantially lower for the RSVpreF group than the placebo group.

- The increase in nonvaccine RSV antigen-binding antibody after challenge of placebo recipients, but not RSVpreF recipients, confirmed vaccine-mediated protection from RSV infection.

Immunogenicity results showed that RSVpreF elicited large increases in neutralizing titers (Figure 13 [RSV A] and Figure 14 [RSV B]) and a substantial increase in the RSV F-specific cluster of differentiation 4 positive (CD4+) T-cell helper type 1 (TH1) response at 1 month after immunization, similar to those observed in previous clinical studies.

- RSVpreF elicited robust neutralizing responses against RSV A and RSV B 1 month after vaccination.

- RSVpreF elicited increases in TH1 CD4+ T-cell responses that were sustained above prevaccination levels at 1-month after vaccination. Similar to the nonvaccine RSV antigen-binding antibody results, an increase in RSV F- and M-specific CD4+ T-cell response was noted post-challenge in the placebo group, but not in RSVpreF indirectly indicating protective efficacy.

RSVpreF was safe and well-tolerated, consistent with previous clinical studies.

Overall, immunization with a single RSVpreF dose had a good safety profile and provided essentially complete protection against symptomatic RSV infection in a viral challenge

model. The high RSVpreF observed efficacy exceeds that reported by other candidate RSV vaccines in the same challenge model.[48]

4.1.4. Study C3671014 – Phase 3 Lot Consistency

The completed Phase 3, multicenter, parallel-group, randomized, double-blind, placebo-controlled Study C3671014 (Table 11) examined the immune response and the safety and tolerability profiles across 3 manufactured lots of RSVpreF when administered as a single 120 µg dose level to healthy adults 18 through 49 years of age, to demonstrate lot equivalence in the manufacturing of RSVpreF.

Across all vaccine lots, 745 participants were randomized and vaccinated with RSVpreF 120 µg, and 247 participants were randomized and vaccinated with placebo. In total, 97.7% of participants completed the study.

The primary immunogenicity objective of the study was achieved. For both RSV A and RSV B, each pair of between-lot comparisons from the 3 vaccine lots met the predefined 1.5-fold equivalence criterion (2 sided 95% CI for each between lot geometric mean ratio (GMR) was contained in the interval 0.667 to 1.5) for the evaluable immunogenicity population (Table 13). Results were similar in the modified intent to treat (mITT) population. Subgroup analyses by sex showed similar results for females and males for both RSV A and RSV B.

Overall, RSVpreF was safe and well tolerated, with safety profiles that were similar across the 3 RSVpreF vaccine lots and consistent with previous studies.

4.2. Pivotal Phase 3 Efficacy Study C3671013 (Ongoing)

4.2.1. Study C3671013 Background

C3671013 Study Design and Methodology

C3671013 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study (Table 11) designed to assess the safety, immunogenicity, and **efficacy** of RSVpreF in the prevention of LRTI-RSV in adults 60 years of age and older during the first RSV season and the long-term immunogenicity and efficacy of RSVpreF across 2 RSV seasons. This is an event-driven study which has a target of at least 59 first episode evaluable LRTI-RSV cases with ≥2 symptoms (primary endpoint). Up to 45,000 participants would be randomized to receive RSVpreF or placebo in a 1:1 ratio. Site-based randomization is used to assign individuals to different groups, and the randomization is stratified by age group (60-69 years [at least 6,000 participants], 70-79 years [at least 6,000 participants], and 80 years and older [at least 800 participants]). All participants are followed for ARI-related symptoms for 2 RSV seasons.

Both healthy adults and adults with stable chronic diseases were included. Approximately 10% of participants were to be enrolled with stable chronic cardiopulmonary conditions such as COPD, asthma, or CHF.

Per protocol, approximately 6000 participants from a subset of sites in the US and approximately 450 participants from a subset of sites in Japan would be included in the reactogenicity subset. Local reaction and systemic event data were collected in an electronic diary (e-diary) for 7 days after study vaccination (Days 1 through 7, where Day 1 is the day of vaccination).

For all participants, AEs[1] were collected from informed consent through 1 month following study intervention administration, and NDCMCs and SAEs were collected from informed consent throughout study participation. In addition, AEs occurring up to 48 hours after blood draws or collection of nasal swabs related to study procedures were collected.

Starting on Day 15 (where Day 1 is the day of vaccination), all participants were prompted to complete a screening questionnaire (approximately weekly) using an e-diary or equivalent technology. They were also instructed to complete a questionnaire if at any time they develop symptoms of an ARI (see Table 2 for efficacy endpoints and definitions) until the end of the first RSV season. The same procedure repeated starting from the beginning of the second RSV season through the end of the RSV season.

If the participant experienced 1 or more of the ARI symptoms, the participant collected midturbinate nasal swabs optimally on ARI-Day 2 and ARI-Day 3 (but within 7 days) after the onset of the ARI symptom(s) (where ARI-Day 1 is the day of onset of symptoms), and an unplanned respiratory illness visit was initiated and could be performed as telephone, telehealth, clinic, or home visit. In person visits were conducted if the investigator deemed it necessary for the participant to be seen in person and when this was the case another swab was obtained. The swabs were collected by the site and sent to Pfizer for reverse transcription-polymerase chain reaction (RT-PCR) testing.

This study used a DMC, which was independent of the study team and included only external members.

The Study C3671013 efficacy and safety data included in this Vaccines and Related Biological Products Advisory Committee (VRBPAC) briefing document are based on an enrollment start of 31 August 2021 and the data cutoff dates for the interim efficacy analysis (described below). The efficacy data included are from first-episode cases in the first RSV season only, as of the data cutoff date. Immunogenicity data will be included in a subsequent end of Season 1 analysis.

[1] Includes: any AE; severe AEs; life-threatening AEs; immediate AEs; AEs leading to withdrawal from the study; related AEs; SAEs; death; AEs by PT and SOC; NDCMCs.

Table 2. Study C3671013 Efficacy Endpoint Assessments and Definitions

Study Endpoints/Assessments	Study Definitions
ARI	An illness involving 1 or more of the following 7 respiratory illness symptoms, lasting more than 1 day: • New or increased sore throat • New or increased cough • New or increased nasal congestion • New or increased nasal discharge • New or increased wheezing • New or increased sputum production • New or increased shortness of breath
RSV-positive test	RSV RT-PCR–positive test result by Pfizer central laboratory **OR** RSV-positive test result by certified laboratory with nucleic acid amplification test (NAAT) for RSV, if RSV RT-PCR test result by Pfizer central laboratory is not available.
ARI-RSV	ARI-RSV will be defined as an ARI with RT-PCR–confirmed RSV infection within 7 days of ARI symptom onset.
LRTI	LRTI will be defined as an ARI with ≥2 or ≥3 of the following LRTI signs/symptoms during the illness • New or increased cough • New or increased wheezing • New or increased sputum production • New or increased shortness of breath • Tachypnea (≥25 breaths/min or ≥15% increase from resting baseline)
LRTI-RSV with at least 2 symptoms	LRTI-RSV with at least 2 symptoms will be defined as an ARI with ≥2 of the 5 LRTI signs/symptoms lasting more than 1 day during the same illness, **plus** RT-PCR–confirmed RSV infection within 7 days of ARI symptom onset.
LRTI-RSV with at least 3 symptoms	LRTI-RSV with at least 3 symptoms will be defined as an ARI with ≥3 of the 5 LRTI signs/symptoms lasting more than 1 day during the same illness, **plus** RT-PCR–confirmed RSV infection within 7 days of ARI symptom onset.

Table 2. Study C3671013 Efficacy Endpoint Assessments and Definitions

Study Endpoints/Assessments	Study Definitions
sLRTI-RSV	LRTI-RSV criteria plus at least 1 of the following: • Hospitalization due to LRTI-RSV • New/increased oxygen supplementation • New/increased mechanical ventilation, including continuous positive airway pressure (CPAP)

Interim Efficacy Analysis

Per protocol, the C3671013 efficacy study is event-driven, with a target of 59 first-episode evaluable LRTI-RSV with ≥2 symptoms cases. An interim analysis could be performed when the total number of evaluable first episode LRTI-RSV cases with ≥2 symptoms is at least 29. The interim analysis would utilize Pocock boundary based on actual cases at interim analysis among a total of 59 cases.

Per protocol, if the total number of evaluable first episode LRTI-RSV cases with ≥3 symptoms is at least 15, this endpoint would be included in the interim analysis. Additionally, if the total number of evaluable first episode sLRTI-RSV cases is at least 12, this endpoint would be included in the interim analysis.

A preplanned interim efficacy analysis was conducted when 44 first-episode LRTI-RSV cases with ≥2 symptoms had accrued in the first RSV season through the ARI surveillance cutoff date of 08 July 2022. After the DMC had declared success of first-episode LRTI-RSV cases with ≥2 symptoms and with 16 first-episode LRTI-RSV cases with ≥3 symptoms accrued, this endpoint was included in the interim analysis. The minimum number of first episode sLRTI-RSV cases had not accrued as of this cutoff date, and therefore, the interim analysis of this endpoint was not conducted; an analysis of this endpoint will be part of a subsequent end of Season 1 analysis provided that sufficient cases of severe disease are accrued. Because the secondary endpoint of ARI-RSV is descriptive without type-I error spending, analysis of ARI-RSV was included.

The interim analysis of Study C3671013 was based on the ARI surveillance cutoff of 08 July 2022 (first ARI symptom, ARI Day 1) and the nasal swab collection cutoff of 14 July 2022 (nasal swab collection could occur up to ARI Day 7). The AE collection cutoff was 14 July 2022.

As of the data cutoff date (14 July 2022), 34,383 participants were randomized to receive RSVpreF or placebo. Most randomized participants (99.7%) received study intervention.

All study participants remain in blinded follow-up after the interim analysis.

Statistical Analyses

For the efficacy and safety analyses presented:

- The evaluable efficacy population was the primary population for efficacy analyses. The analyses were repeated on the mITT efficacy population.

- Analyses of reactogenicity were based on the e-diary subset safety population. Analyses of AEs were based on the safety population.

The following analyses were also performed:

- For the primary endpoint, analyses were performed for RSV A+ and RSV B+, separately. These subset analyses were also performed for ARI-RSV.

- Selected efficacy endpoints (first episode of LRTI-RSV cases with ≥2 and ≥3 symptoms and ARI-RSV cases), local reactions, systemic events, and AEs were analyzed by age group (60-69 years, 70-79 years, and ≥80 years), sex, race, ethnicity, risk status, and country.

Hypotheses and Decision Rules

Per protocol, for the primary efficacy objective and key secondary objective, RSVpreF would be compared to placebo, testing the following 3 hypotheses:

1. H_0: VE ≤20% vs H_a: VE >20% against first episode of LRTI-RSV with ≥2 symptoms (as defined by ≥2 of the 5 LRTI signs/symptoms in the first RSV season)

2. H_0: VE ≤20% vs H_a: VE >20% against first episode of LRTI-RSV with ≥3 symptoms (as defined by ≥3 of the 5 LRTI signs/symptoms in the first RSV season)

3. H_0: VE ≤20% vs H_a: VE >20% against first episode of sLRTI-RSV in the first RSV season

where H_0 and H_a represent the null and alternative hypotheses, respectively. VE was defined as VE = 100 × (1 - risk ratio). Risk ratio was calculated as the ratio of the case count of first-episode confirmed cases in the RSVpreF group to the corresponding case count in the placebo group.

The 3 hypothesis tests specified above would be tested sequentially as ordered, with an overall type I error of 5% (2-sided), or a 1-sided alpha of 2.5%.

The primary efficacy objective would be achieved if the lower bound of the VE CI is >20% for LRTI-RSV with ≥2 symptoms, either with Pocock-adjusted CI (if interim analysis was conducted) or with 95% CI (if no interim analysis was conducted) at the final analysis.

4.2.2. Study C3671013 Efficacy Results

The Study C3671013 efficacy results (using the endpoint definitions in Table 2) for the preplanned interim analysis presented in this briefing document are through the ARI surveillance cutoff date in the first RSV season (08 July 2022). In the evaluable efficacy population of 32,614 participants (16,306 RSVpreF; 16,308 placebo), the average ARI surveillance was 6.78 months. Note, the study was conducted during the COVID pandemic; nonpharmaceutical associations led to the reduced transmission of RSV and shifts of typical RSV seasonality in many geographies,[49] and the number of cases in the study perhaps is lower that what would have been expected from prior seasons.

Overall, VE of RSVpreF 120 µg compared to placebo met the predefined success criteria for the primary efficacy objective, and RSVpreF offered strong protection against LRTI-RSV with ≥2 symptoms and ≥3 symptoms and ARI-RSV in participants 60 years of age and older. For RSV Subgroups A and B, the VEs were consistent across all efficacy endpoints analyzed. Results based on the mITT population were also consistent. An ad hoc analysis of 2 symptoms versus ≥3 symptoms LRTI-RSV supports that the ≥3 symptom group represents a more specific and severe subset of the ≥2 symptom LRTI-RSV group. Additionally, RSVpreF offered strong protection against medically attended LRTI-RSV with ≥2 symptoms and ≥3 symptoms, with VEs similar to those observed for the main endpoint analyses. Medically attended ARI-RSV VE was slightly higher than overall ARI-RSV VE.

For all subgroups analyzed, including sex, age group, race, ethnicity, country, and prespecified significant conditions, the RSV cases (although limited for several subgroups) were predominantly reported in the placebo group, and there were no clinically meaningful differences from the main analyses or between subgroups.

Demographics of the Evaluable Efficacy Population

Demographic and baseline characteristics in the evaluable efficacy population were well balanced between the RSVpreF and placebo groups and similar to those of the safety population. Participants were mostly White (77.6%), followed by Black or African American (13.2%), and Asian (8.2%); 65.1% non-Hispanic/non-Latino and 34.4% Hispanic/Latino; and mostly located in the US (61.9%), followed by Argentina (18.7%) and Japan (7.1%). The median age of participants was 67.0 years, with 62.4% aged 60-69 years, 31.9% aged 70-79 years, and 5.7% aged ≥80 years. The number of participants in each age category met the stratification targets specified in the protocol (Section 4.2).

4.2.2.1. Primary Efficacy Endpoint: First Episode of LRTI-RSV with ≥2 Symptoms in RSV Season 1

As of the ARI surveillance cutoff date of 08 July 2022, there were 11 first episode LRTI-RSV cases with ≥2 symptoms in the RSVpreF group and 33 in the placebo group in the evaluable efficacy population that occurred from Day 15 through the cutoff date, corresponding to a VE of 66.7% (96.66% CI: 28.8%, 85.8%) for RSVpreF (Table 3 and Figure 3).[2]

For RSV A, VE for LRTI-RSV with ≥2 symptoms was 88.9% (96.66% CI: 10.6%, 99.8%) based on 1 case in the RSVpreF group and 9 cases in the placebo group. For RSV B, VE for LRTI-RSV with ≥2 symptoms was 56.5% (96.66% CI: -0.7%, 82.8%) based on 10 cases in the RSVpreF group and 23 cases in the placebo group (Table 3).

Analysis of this primary efficacy endpoint based on the mITT population yielded similar results; the mITT population had 1 additional first episode LRTI-RSV case ≥2 symptoms reported before Day 15 (from Day 1 [vaccination date]) in the placebo group.

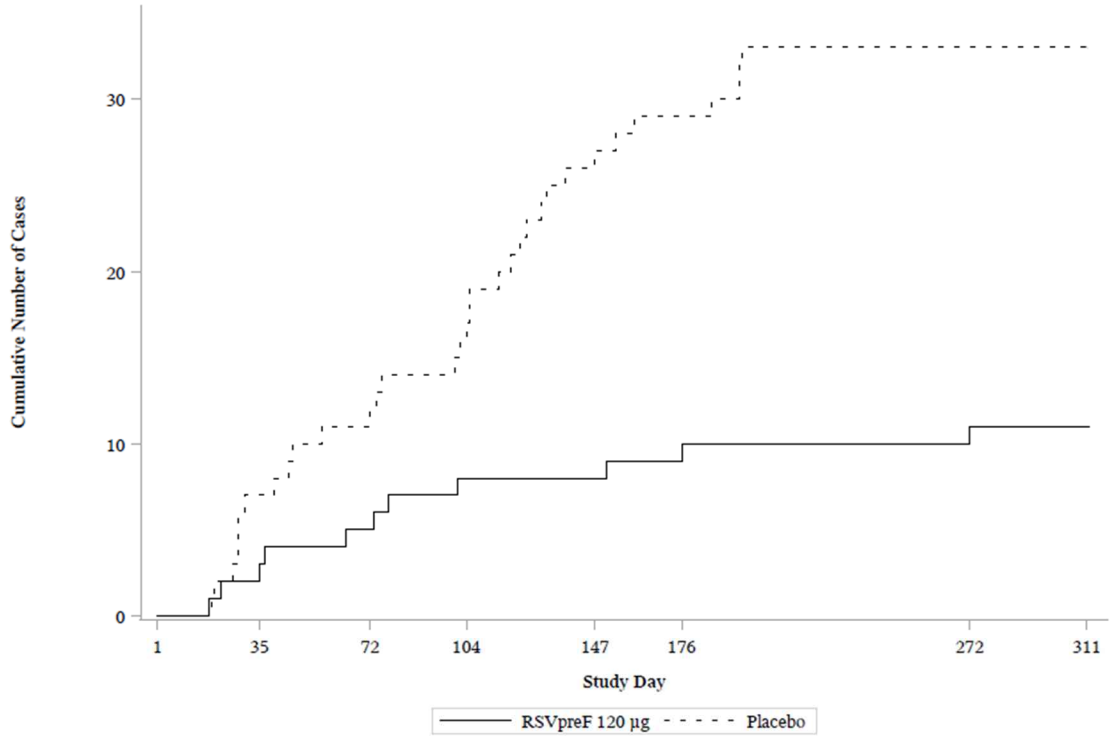
[2] 1 participant (placebo group) reported 2 episodes of LRTI-RSV cases. The first episode was included in the analysis of LRTI-RSV cases with ≥2 symptoms and ARI-RSV; the second episode met the definition of LRTI-RSV cases with ≥3 symptoms and was the first episode of this endpoint, thus it was included in the analysis of this endpoint.

Table 3. Vaccine Efficacy of RSVpreF Against First Episode of LRTI-RSV With ≥2 Symptoms – Evaluable Efficacy Population, Study C3671013

Efficacy Endpoint	RSVpreF 120 µg N=16306	Placebo N=16308	VE[a], % (96.66% CI)
First episode of LRTI-RSV with ≥2 symptoms, n (%)	11 (0.07)	33 (0.20)	66.7 (28.8, 85.8)
Incidence Rate (per 1000 PYO[b])	1.19	3.58	
First episode of LRTI-RSV with ≥2 symptoms, Subgroup A, n (%)	1 (0.01)	9 (0.06)	88.9 (10.6, 99.8)
Incidence Rate (per 1000 PYO[b])	0.11	0.98	
First episode of LRTI-RSV with ≥2 symptoms, Subgroup B, n (%)	10 (0.06)	23 (0.14)	56.5 (-0.7, 82.8)
Incidence Rate (per 1000 PYO[b])	1.08	2.50	

Source: Adapted from STN 0000 Study C3671013, Clinical Study Report, Table 10.
Abbreviations: LRTI-RSV = lower respiratory tract illness associated with RSV; N = total number of participants in each vaccine group; n = number of participants meeting the efficacy endpoint case definition from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022), followed by the calculated percentage in parentheses (%); PYO = person-years observation; RSV = respiratory syncytial virus; VE = vaccine efficacy.
The evaluable efficacy population included all study participants who were eligible for the study; received study intervention to which they were randomized (RSVpreF or placebo); with a minimum follow-up through Day 15 after vaccination (Day 1 is the day of vaccination); and without major protocol violations before the symptom onset date of the confirmed ARI or LRTI case.
a. VE is defined as 1 - Risk Ratio, and calculated as 1-(P/[1-P]), where P is the number of first episode of LRTI-RSV with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of LRTI-RSV with ≥2 symptoms cases. CI is obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending.
b. PYO is defined as the total ARI surveillance duration days across all participants at risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from vaccination date through death/discontinuation/surveillance cutoff date/major protocol deviation, whichever is earlier.
Subgroup A means the swab sample is positive for RSV subgroup A; and Subgroup B means the swab sample is positive for RSV subgroup B.
Note: Positive RSV test result was based on the Pfizer central laboratory test on those nasal swabs collected within 7 days after symptom onset. In the event that no nasal swabs from the central laboratory are available (either the swab was not obtained or the swab was taken outside of the 7-day window), results from a certified laboratory with nucleic acid amplification test (NAAT) for RSV can be used.
One positive RSV polymerase chain reaction (PCR) test from local lab without subgroup information is included in the count of LRTI-RSV (but not included in any subgroup rows), as there was no swab within 7 days of symptom onset for central lab testing available.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (13:52) Source Data: adtte Table Generation: 04DEC2022 (22:54)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_FDA/adtte_s01_lrti2_eval

Figure 3. Cumulative Case Accrual Curve From Day of Vaccination, First Episode of LRTI-RSV With ≥2 Symptoms - Evaluable Efficacy Population, Study C3671013



Cumulative Number of Events								
RSVpreF 120 µg	0	3	5	8	8	10	11	11
Placebo	0	7	12	17	27	29	33	33

Abbreviation(s): LRTI-RSV = lower respiratory tract illness associated with respiratory syncytial virus.
Note: First episode of LRTI-RSV cases with symptom onset from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022) were included.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (14:52) Source Data: adtte Table Generation: 23AUG2022 (03:57)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_Primary/adtte_fx01_eval

4.2.2.2. Primary Efficacy Endpoint: First Episode of LRTI-RSV with ≥3 Symptoms in RSV Season 1

As of the ARI surveillance cutoff date of 08 July 2022, there were 2 first episode LRTI-RSV cases with ≥3 symptoms in the RSVpreF group and 14 in the placebo group in the evaluable efficacy population that occurred from Day 15 through the cutoff date, corresponding to a VE of 85.7% (96.66% CI: 32.0%, 98.7%) for RSVpreF (Table 4 and Figure 4).

For RSV A, VE for LRTI-RSV with ≥3 symptoms was 66.7% (96.66% CI: -393.7%, 99.6%) based on 1 case in the RSVpreF group and 3 cases in the placebo group. For RSV B, VE for LRTI-RSV with ≥3 symptoms was 90.0% (96.66% CI: 21.8%, 99.8%) based on 1 case in the RSVpreF group and 10 cases in the placebo group (Table 4).

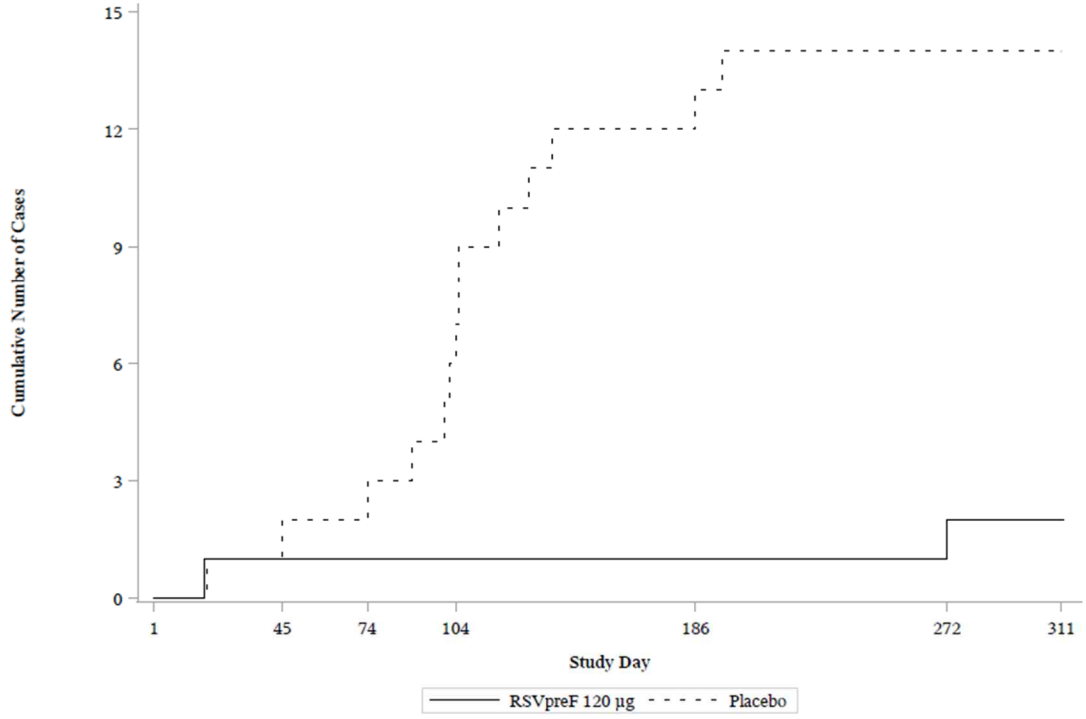
Analysis of this primary efficacy endpoint based on the mITT population yielded similar results; the mITT population had 1 additional first episode LRTI-RSV case ≥3 symptoms reported before Day 15 (from Day 1 [vaccination date]) in the placebo group.

Table 4. Vaccine Efficacy of RSVpreF Against First Episode of LRTI-RSV With ≥3 Symptoms – Evaluable Efficacy Population, Study C3671013

Efficacy Endpoint	RSVpreF 120 µg N=16306	Placebo N=16308	VE[a], % (96.66% CI)
First episode of LRTI-RSV with ≥3 symptoms, n (%)	2 (0.01)	14 (0.09)	85.7 (32.0, 98.7)
Incidence Rate (per 1000 PYO[b])	0.22	1.52	
First episode of LRTI-RSV with ≥3 symptoms, Subgroup A, n (%)	1 (0.01)	3 (0.02)	66.7 (-393.7, 99.6)
Incidence Rate (per 1000 PYO[b])	0.11	0.33	
First episode of LRTI-RSV with ≥3 symptoms, Subgroup B, n (%)	1 (0.01)	10 (0.06)	90.0 (21.8, 99.8)
Incidence Rate (per 1000 PYO[b])	0.11	1.09	

Source: Adapted from STN 0000 Study C3671013, Clinical Study Report, Table 11.
Abbreviations: LRTI-RSV = lower respiratory tract illness associated with RSV; N = total number of participants in each vaccine group; n = number of participants meeting the efficacy endpoint case definition from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022), followed by the calculated percentage in parentheses (%); PYO = person-years observation; RSV = respiratory syncytial virus; VE = vaccine efficacy.
The evaluable efficacy population included all study participants who were eligible for the study; received study intervention to which they were randomized (RSVpreF or placebo); with a minimum follow-up through Day 15 after vaccination (Day 1 is the day of vaccination); and without major protocol violations before the symptom onset date of the confirmed ARI or LRTI case.
a. VE is defined as 1 - Risk Ratio, and calculated as 1-(P/[1-P]), where P is the number of first episode of LRTI-RSV with ≥3 symptoms cases in RSVpreF group divided by the total number of first episode of LRTI-RSV with ≥3 symptoms cases. CI is obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending.
b. PYO is defined as the total ARI surveillance duration days across all participants at risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from vaccination date through death/discontinuation/surveillance cutoff date/major protocol deviation, whichever is earlier.
Subgroup A means the swab sample is positive for RSV subgroup A; and Subgroup B means the swab sample is positive for RSV subgroup B.
Note: Positive RSV test result was based on the Pfizer central laboratory test on those nasal swabs collected within 7 days after symptom onset. In the event that no nasal swabs from the central laboratory are available (either the swab was not obtained or the swab was taken outside of the 7-day window), results from a certified laboratory with nucleic acid amplification test (NAAT) for RSV can be used.
One positive RSV polymerase chain reaction (PCR) test from local lab without subgroup information is included in the count of LRTI-RSV (but not included in any subgroup rows), as there was no swab within 7 days of symptom onset for central lab testing available.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (13:52) Source Data: adtte Table Generation: 04DEC2022 (22:56)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_FDA/adtte_s01_lrti3_eval

Figure 4. Cumulative Case Accrual Curve From Day of Vaccination, First Episode of LRTI-RSV With ≥3 Symptoms - Evaluable Efficacy Population, Study C3671013



Cumulative Number of Events

RSVpreF 120 µg	0	1	1	1	1	2	2
Placebo	0	2	3	7	13	14	14

Abbreviation(s): LRTI-RSV = lower respiratory tract illness associated with respiratory syncytial virus.
Note: First episode of LRTI-RSV cases with symptom onset from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022) were included.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (14:52) Source Data: adtte Table Generation: 23AUG2022 (03:54)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_Primary/adtte_fx01_eval_lr3

The C3671013 study did not accumulate enough severe cases using the stringent predefined objective criteria (hospitalization, increased/new oxygen supplementation or increased or increased/new mechanical ventilation) to determine VE against this outcome. However, it is likely that cases with ≥3 symptoms in Study C3671013 represent a more severe subset of the broader set of cases with ≥2 symptoms. To confirm this, specific symptom distribution within the categories of 2 symptoms versus ≥3 symptoms LRTI-RSV was evaluated in an *ad hoc* analysis. Per the study protocol, 5 symptoms were included in the definition of LRTI: new onset or worsening cough, sputum production, wheezing, tachypnea, and shortness of breath. The first two were considered potentially milder because they could reflect solely upper respiratory disease. Of 29 total LRTI-RSV cases with only 2 symptoms in Study C3671013, 25 (86.2%) had only cough and sputum production, while 2 each had cough and wheezing or cough and shortness of breath (Table 5). Of 16 total LRTI-RSV cases with ≥3 symptoms, by definition none experienced only cough and sputum production, 5 (31.3%) experienced 1 of the 3 more severe symptoms with or without sputum or cough, 7 (43.8%) experienced 2 of these symptoms, and 4 (25.0%) experienced all 3.

Additionally, compared to LRTI-RSV cases with ≥2 symptoms, LRTI-RSV cases with ≥3 symptoms more frequently presented more severe symptoms, such as wheezing and shortness of breath. Of the 16 first episode LRTI-RSV cases with ≥3 symptoms in Study C3671013, there were 4 participants with pneumonia or bronchopneumonia, including 2 who were hospitalized and 1 who required oxygen supplementation. There were also 4 participants with bronchitis, all requiring corticosteroid treatment.

Together these data support that the ≥3 symptom group represents a more specific and severe subset of the ≥2 symptom LRTI-RSV group.

Table 5. Distribution of LRTI Symptom Combinations for LRTI-RSV Cases From Day 15 Through the Surveillance Cutoff Date (08Jul2022) – Evaluable Efficacy Population, Study C3671013

	LRTI-RSV With ≥2 Symptoms n (%)	LRTI-RSV With ≥3 Symptoms n (%)	LRTI-RSV With 2 Symptoms Only n (%)
Total Cases[a]	45	16	29
Symptom combination			
Cough + Sputum	25 (55.6)	0	25 (86.2)
Cough + Sputum + Wheezing	4 (8.9)	4 (25.0)	0
Cough + Sputum + Wheezing + Shortness of Breath	5 (11.1)	5 (31.3)	0
Cough + Sputum + Wheezing + Shortness of Breath + Tachypnea	2 (4.4)	2 (12.5)	0
Cough + Sputum + Tachypnea	1 (2.2)	1 (6.3)	0
Cough + Wheezing	2 (4.4)	0	2 (6.9)
Cough + Wheezing + Shortness of Breath	1 (2.2)	1 (6.3)	0
Cough + Wheezing + Shortness of Breath + Tachypnea	2 (4.4)	2 (12.5)	0
Cough + Shortness of Breath	2 (4.4)	0	2 (6.9)
Sputum + Wheezing + Shortness of Breath	1 (2.2)	1 (6.3)	0
No additional symptoms (Wheezing, Shortness of Breath, or Tachypnea) beyond Cough or Sputum	25 (55.6)	0	25 (86.2)
1 additional symptom (Wheezing, Shortness of Breath, or Tachypnea) beyond Cough or Sputum	9 (20.0)	5 (31.3)	4 (13.8)
2 additional symptoms (Wheezing, Shortness of Breath, or Tachypnea) beyond Cough or Sputum	7 (15.6)	7 (43.8)	0
3 additional symptoms (Wheezing, Shortness of Breath, and Tachypnea) beyond Cough or Sputum	4 (8.9)	4 (25.0)	0

a. These values are the denominators for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (13:52) Source Data: adeff Table Generation: 02FEB2023 (20:51)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_Adhoc/adeff_s999_1

4.2.2.3. Secondary Efficacy Endpoint: First Episode of ARI-RSV in RSV Season 1

As of the ARI surveillance cutoff date, there were 22 first episode ARI-RSV cases in the RSVpreF group and 58 in the placebo group in the evaluable efficacy population that

occurred from Day 15 through the cutoff date,[3] corresponding to a VE of 62.1% (95% CI: 37.1%, 77.9%) for RSVpreF (Table 6).

For RSV A, VE for ARI-RSV was 66.7% (95% CI: -10.0%, 92.2%) based on 4 cases in the RSVpreF group and 12 cases in the placebo group. For RSV B, VE for ARI-RSV was 60.0% (95% CI: 29.5%, 78.2%) based on 18 cases in the RSVpreF group and 45 cases in the placebo group (Table 6).

Analysis of this secondary efficacy endpoint using the mITT Population yielded similar results; the mITT population had 2 additional first-episode ARI-RSV cases reported before Day 15 (from Day 1 [vaccination date]) in the placebo group.

Table 6. Vaccine Efficacy of RSVpreF Against First Episode of ARI-RSV – Evaluable Efficacy Population, Study C3671013

Efficacy Endpoint	RSVpreF 120 µg N=16306	Placebo N=16308	VE[a], % (95% CI)
First episode of ARI-RSV, n (%)	22 (0.13)	58 (0.36)	62.1 (37.1, 77.9)
Incidence Rate (per 1000 PYO[b])	2.38	6.30	
First episode of ARI-RSV, Subgroup A, n (%)	4 (0.02)	12 (0.07)	66.7 (-10.0, 92.2)
Incidence Rate (per 1000 PYO[b])	0.43	1.30	
First episode of ARI-RSV, Subgroup B, n (%)	18 (0.11)	45 (0.28)	60.0 (29.5, 78.2)
Incidence Rate (per 1000 PYO[b])	1.95	4.89	

Source: Adapted from STN 0000 Study C3671013, Clinical Study Report, Table 12.
Abbreviations: ARI-RSV = acute respiratory illness associated with RSV; N = total number of participants in each vaccine group; n = number of participants meeting the efficacy endpoint case definition from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022), followed by the calculated percentage in parentheses (%); PYO = person-years observation; RSV = respiratory syncytial virus; VE = vaccine efficacy.
The evaluable efficacy population included all study participants who were eligible for the study; received study intervention to which they were randomized (RSVpreF or placebo); with a minimum follow-up through Day 15 after vaccination (Day 1 is the day of vaccination); and without major protocol violations before the symptom onset date of the confirmed ARI or LRTI case.
a. VE is defined as 1 - Risk Ratio, and calculated as 1-(P/[1-P]), where P is the number of first episode of ARI-RSV cases in RSVpreF group divided by the total number of first episode of ARI-RSV cases. Nominal 95% CI is obtained using the conditional exact test based on the binomial distribution of P.
b. PYO is defined as the total ARI surveillance duration days across all participants at risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from vaccination date through death/discontinuation/surveillance cutoff date/major protocol deviation, whichever is earlier.
Subgroup A means the swab sample is positive for RSV subgroup A; and Subgroup B means the swab sample is positive for RSV subgroup B.
Note: Positive RSV test result was based on the Pfizer central laboratory test on those nasal swabs collected within 7 days after symptom onset. In the event that no nasal swabs from the central laboratory are available (either the swab was not

[3] Because not all nasal swabs collected from ARI visits were tested for RSV positivity at the time of the interim analysis, the actual case count for ARI-RSV may be higher. The proportion of swabs tested among total swabs collected within 7-days of ARI symptom onset was the same in the vaccine and placebo groups (74%). Swabs collected within 7 days after symptom onset based on ARI visits that met LRTI with at least 2 symptoms were prioritized for testing for the primary endpoint analysis.

Table 6. Vaccine Efficacy of RSVpreF Against First Episode of ARI-RSV – Evaluable Efficacy Population, Study C3671013

Efficacy Endpoint	RSVpreF 120 µg N=16306	Placebo N=16308	VE[a], % (95% CI)

obtained or the swab was taken outside of the 7-day window), results from a certified laboratory with nucleic acid amplification test (NAAT) for RSV can be used.
One positive RSV polymerase chain reaction (PCR) test from local lab without subgroup information is included in the count of ARI-RSV (but not included in any subgroup rows), as there was no swab within 7 days of symptom onset for central lab testing available.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (13:52) Source Data: adtte Table Generation: 04DEC2022 (22:56)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_FDA/adtte_s01_ari_eval

4.2.2.4. Efficacy Subgroup Analyses: First Episode of LRTI-RSV and ARI-RSV in RSV Season 1

VEs against first-episode LRTI-RSV with ≥2 symptoms and with ≥3 symptoms and first episode ARI-RSV (from Day 15 through the surveillance data cutoff date) were evaluated by age group, sex, race, ethnicity, country, and prespecified significant conditions in the evaluable efficacy population. Overall, for subgroups with enough cases and participants for VE analyses, VEs were generally similar to those observed in the main analyses above and did not identify any clinically meaningful differences across subgroups. However, these results should be interpreted with caution as several subgroups (eg, for race, country) included a limited number of cases and participants, which contributed to wide CIs around the point estimates.

4.2.2.5. Health Care Visits: Medically Attended (First Episode) LRTI-RSV and ARI-RSV in RSV Season 1

Table 7 presents VE based on first episode cases of LRTI-RSV with ≥2 symptoms and ≥3 symptoms and ARI-RSV that were medically attended, requiring any outpatient or inpatient visit such as hospitalization, ER visit, urgent care visit, home healthcare services, primary care physician office visit, pulmonologist office visit, specialist office visit, or telehealth contact, not including a visit to the study site.

Overall, RSVpreF offered strong protection against medically attended LRTI-RSV with ≥2 symptoms and ≥3 symptoms with VEs similar to those observed for all first episode cases (in the main analyses above). Medically attended ARI-RSV VE was slightly higher than overall ARI-RSV VE.

As of the ARI surveillance cutoff date of 08 July 2022:

- For LRTI-RSV with ≥2 symptoms, there were 7 first episode cases in the RSVpreF group and 20 in the placebo group in the evaluable efficacy population that occurred from

Day 15 through the cutoff date, corresponding to a VE of 65.1% (95% CI: 14.0%, 87.5%) for RSVpreF.

- For LRTI-RSV with ≥3 symptoms, there were 2 first episode cases in the RSVpreF group and 10 in the placebo group in the evaluable efficacy population that occurred from Day 15 through the cutoff date, corresponding to a VE of 80.0% (95% CI: 6.3%, 97.9%) for RSVpreF.

- For ARI-RSV, there were 8 first episode cases in the RSVpreF group and 26 in the placebo group in the evaluable efficacy population that occurred from Day 15 through the cutoff date, corresponding to a VE of 69.3% (95% CI: 30.1%, 88.0%) for RSVpreF.

Table 7. Medically Attended LRTI-RSV or ARI-RSV Starting 14 Days After Vaccination, Evaluable Efficacy Population, Study C3671013

Endpoint	RSVpreF N=16306 Cases n (%) Incidence rate per 1000 person-years	Placebo N=16308 Cases n (%) Incidence rate per 1000 person-years	VE[a], % (95% CI)
Medically attended LRTI-RSV with ≥2 symptoms	7 (0.04) 0.76	20 (0.12) 2.17	65.1 (14.0, 87.5)
Medically attended LRTI-RSV with ≥3 symptoms	2 (0.01) 0.22	10 (0.06) 1.09	80.0 (6.3, 97.9)
Medically attended ARI-RSV	8 (0.05) 0.87	26 (0.16) 2.82	69.3 (30.1, 88.0)

Abbreviation(s): ARI-RSV = acute respiratory illness associated with RSV; LRTI-RSV = lower respiratory tract illness associated with RSV; N = total number of participants in the specified group; n = number of first episode of each specified endpoint with symptom onset from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022); RSV = respiratory syncytial virus; VE = vaccine efficacy.
The evaluable efficacy population included all study participants who were eligible for the study; received study intervention to which they were randomized (RSVpreF or placebo); with a minimum follow-up through Day 15 after vaccination (Day 1 is the day of vaccination); and without major protocol violations before the symptom onset date of the confirmed ARI or LRTI case.
Medically attended = any outpatient or inpatient visit such as hospitalization, ER visit, urgent care visit, home healthcare services, primary care physician office visit, pulmonologist office visit, specialist office visit, or telehealth contact, not including a visit to the study site.
Note: Positive RSV test result was based on the Pfizer central laboratory test on those nasal swabs collected within 7 days after symptom onset. In the event that no nasal swabs from the central laboratory are available (either the swab was not obtained or the swab was taken outside of the 7-day window), results from a certified laboratory with nucleic acid amplification test (NAAT) for RSV can be used.
One positive RSV polymerase chain reaction (PCR) test from local lab without subgroup information is included in the count of ARI-RSV or LRTI-RSV, as there was no swab within 7 days of symptom onset for central lab testing available.
a. VE adjusted for follow-up time is calculated as 1-(hP/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases and h is the ratio of total follow-up time in the placebo group to the total follow-up time in the RSVpreF group. Nominal 95% CI is obtained using the conditional exact test based on the binomial distribution of P adjusted by person-time follow-up.
PFIZER CONFIDENTIAL SDTM Creation: 11AUG2022 (13:52) Source Data: adtte Table Generation: 28DEC2022 (01:58)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_FDA/adtte_sx3

4.2.3. Study C3671013 Safety Results

As of the data cutoff date, the Study C3671013 safety population included 34,284 participants who received study intervention (17,215 RSVpreF; 17,069 placebo). Of these, 13,273 (77.1%) and 13,122 (76.9%) participants in the RSVpreF and placebo groups, respectively, completed the 6-month safety follow-up visit.

Overall, RSVpreF 120 µg was safe and well tolerated in participants 60 years of age and older, with a profile that was consistent with prior studies.

Subgroup analyses by sex, age group, race, ethnicity, country, and prespecified significant conditions suggested no clinically meaningful differences in safety events for most subgroups. Local reaction reporting was higher in females vs males in the RSVpreF group (Section 4.2.3.1.1), and systemic event reporting was higher in females vs males in the RSVpreF and placebo groups (Section 4.2.3.1.2). These observations are consistent with literature reports of gender differences in reporting of reactogenicity for other vaccines.[50,51]

Demographics of the Safety Populations

Demographic and baseline characteristics of the safety population were well balanced between the RSVpreF and placebo groups. Participants were mostly White (78.3%), followed by Black or African American (12.9%), and Asian (7.8%); 62.6% non-Hispanic/non-Latino and 36.9% Hispanic/Latino; and mostly located in the US (59.8%), followed by Argentina (21.3%) and Japan (6.8%). The median age of participants was 67.0 years, with 62.5% aged 60-69 years, 31.8% aged 70-79 years, and 5.6% aged ≥80 years.

Among 7169 participants in the e-diary subset safety population, 3630 participants received RSVpreF and 3539 participants received placebo. Demographics and baseline characteristics of the e-diary subset safety population were mostly similar to those of the safety population; however, per protocol (Section 4.2), participants that comprised this subset were only located in the US (93.6%) or Japan (6.4%).

4.2.3.1. Reactogenicity

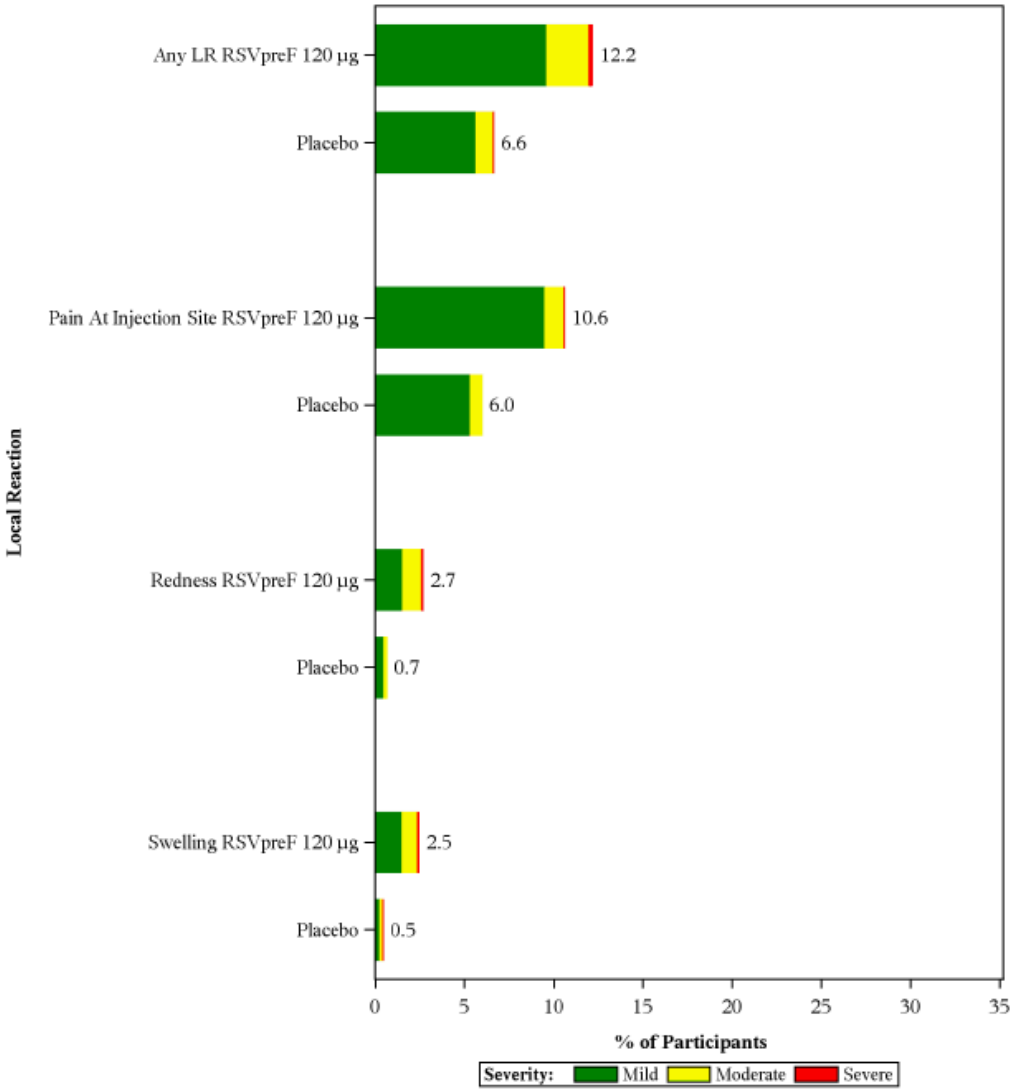
4.2.3.1.1. Local Reactions

The proportions of participants who reported local reactions within 7 days after vaccination were higher in the RSVpreF group (12.2%) compared to the placebo group (6.6%) (Figure 5, Table 14). The most frequently reported local reaction in both groups was pain at the injection site, reported by 10.6% of participants in the RSVpreF group and 6.0% of participants in the placebo group. Most local reactions were mild or moderate in severity and were short-lived (resolved with median durations between 1 to 1.5 days). A total of 8 (0.2%) and 2 (<0.1%) participants in the RSVpreF and placebo groups, respectively, reported severe local reactions. The most frequently reported severe local reactions were swelling and redness (≤0.1% across both groups).

Subgroup Analyses – Local Reactions

Local reactions within 7 days after vaccination were evaluated by sex, age group, race, ethnicity, country, and prespecified significant conditions. Overall, for most subgroups, observations within each subgroup were similar for the RSVpreF and placebo groups and suggested no clinically meaningful differences by subgroup. For sex subgroups, 15.9% of females vs 8.8% of males in the RSVpreF group reported any local reaction, whereas results were similar by sex subgroup in the placebo group (6.4% of females vs 6.9% of males). Similarly, the proportions were higher for females than males in the RSVpreF group for each type of local reaction. However, these results for any and severe local reactions should be interpreted with caution, as several subgroups included a limited number of events and participants.

Figure 5. Local Reactions, by Maximum Severity, Within 7 Days After Vaccination - E-Diary Subset Safety Population, Study C3671013



Abbreviation(s): LR = local reaction.
Note: Local reactions were collected in the e-diary from Day 1 to Day 7 after vaccination for a subset of study participants from selected sites.

Note: For participants who received multiple vaccinations due to multiple enrollments, the vaccine group RSVpreF 120 µg was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations; across vaccinations, the highest severity of local reactions reported from the time of the first dose of RSVpreF (RSVpreF group) or placebo (placebo group) was included in the analysis.
Note: Any reactogenicity reported as related adverse events within 7-day of vaccination from ediary subset safety population are included.
PFIZER CONFIDENTIAL SDTM Creation: 23DEC2022 (04:09) Source Data: adfacevd Table Generation: 17JAN2023 (11:25)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_suppFlag_FDA/adce_fx01

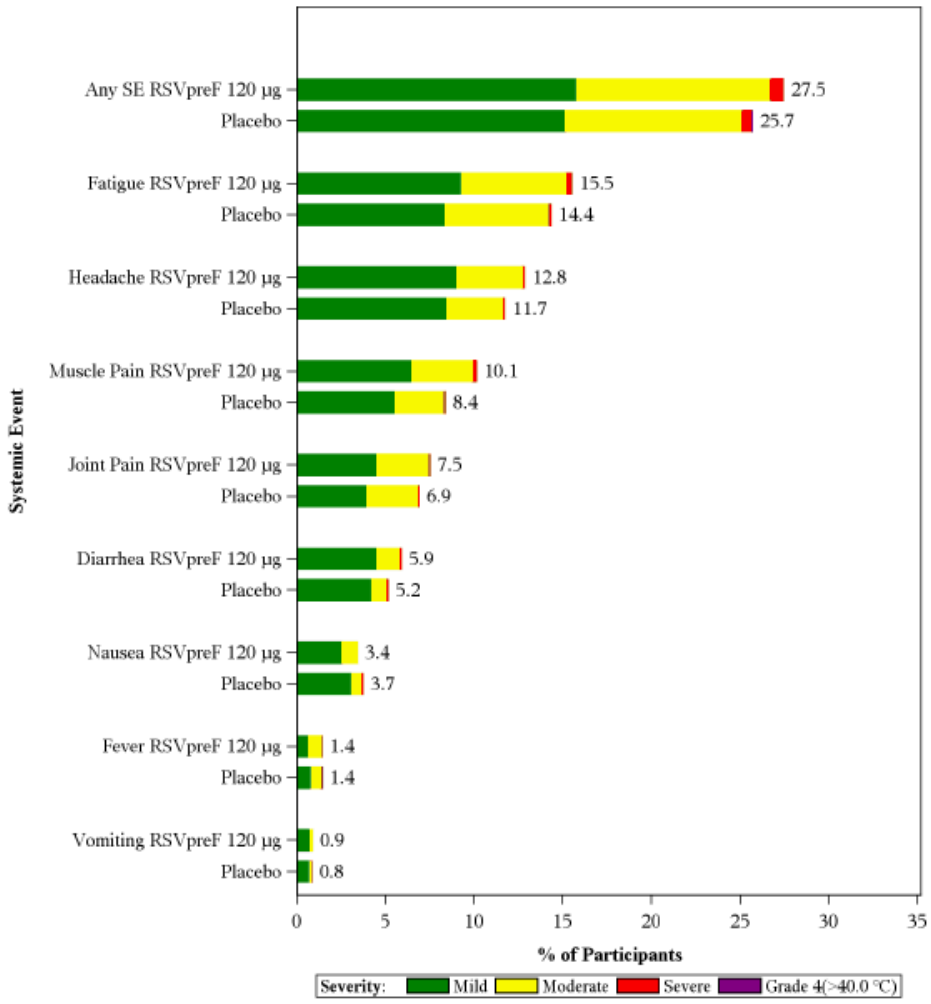
4.2.3.1.2. Systemic Events

The proportions of participants who reported systemic events within 7 days after vaccination were similar in the RSVpreF (27.5%) and placebo (25.7%) groups (Figure 6, Table 15). The most frequently reported systemic event was fatigue, reported by 15.5% of participants in the RSVpreF group and 14.4% of participants in the placebo group. Most systemic events were mild or moderate in severity and were short-lived (resolved with median durations between 1 to 2 days). The proportions of participants with severe systemic events were similar in the RSVpreF (0.7%) and placebo (0.6%) groups. The most frequently reported severe systemic event in both groups was fatigue (≤0.3% across both groups). The incidence of fevers was low (1.4% of participants in each group), and most events were mild (≥38.0°C to 38.4°C) or moderate (>38.4°C to 38.9°C) in severity.

Subgroup Analyses – Systemic Events

Systemic events within 7 days after vaccination were evaluated by sex, age group, race, ethnicity, country, and prespecified significant conditions. Overall, for most subgroups, observations within each subgroup were similar for the RSVpreF and placebo groups and suggested no clinically meaningful differences by subgroup. As observed for reporting of any local reaction (Section 4.2.3.1.1), in the RSVpreF group reporting of any systemic event was higher for females (32.7%) than males (22.7%); however, this was also observed in the placebo group (29.8% of females vs 21.6% of males). Results by sex subgroup for each type of systemic event were also similar for the RSVpreF and placebo groups. However, these results for any and severe systemic events should be interpreted with caution, as several subgroups included a limited number of events and participants.

Figure 6. Systemic Events, By Maximum Severity, Within 7 Days After Vaccination - E-Diary Subset Safety Population, Study C3671013



Abbreviation(s): SE = systemic event.
Note: Systemic events were collected in the e-diary from Day 1 to Day 7 after vaccination for a subset of study participants from selected sites.

Note: For participants who received multiple vaccinations due to multiple enrollments, the vaccine group RSVpreF 120 µg was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations; across vaccinations, the highest severity of systemic events reported from the time of the first dose of RSVpreF (RSVpreF group) or placebo (placebo group) was included in the analysis.
Note: Only an investigator or qualified designee is able to classify a participant's fever as Grade 4, after clinical evaluation of the participant, review of documentation from another medically qualified source, or contact with the participant. While this figure provides a summary of participants who reported a temperature at Grade 4 level in their e-diary, not all of the e-diary reports have been classified as Grade 4 fevers per the protocol.
Note: Any reactogenicity reported as related adverse events within 7-day of vaccination from ediary subset safety population are included.
PFIZER CONFIDENTIAL SDTM Creation: 23DEC2022 (04:09) Source Data: adfacevd Table Generation: 17JAN2023 (11:30)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_suppFlag_FDA/adce_fx01_1

4.2.3.2. Adverse Events

4.2.3.2.1. Overview of Adverse Events by Category

An overview of AEs reported within 1 month after vaccination is shown in Table 8. Note that only participants in the reactogenicity subset used an e-diary to record local reactions or systemic events occurring within 7 days of vaccination; thus, for the majority of participants all such events were reported as AEs.

The proportions of participants reporting any AEs within 1 month after vaccination were similar in the RSVpreF (8.9%) and the placebo (8.5%) groups (Table 8). Most AEs were mild or moderate in severity; severe AEs were reported in ≤0.4% across both groups. AEs assessed as related by the investigator were reported in 1.3% of the RSVpreF group and 0.9% of the placebo group. SAEs, AEs leading to death, life-threatening AEs, AEs leading to withdrawal, immediate AEs, and NDCMCs were reported in ≤0.6% across both groups.

For AEs reported from vaccination through the data cutoff date (Table 9), the proportions of participants reporting any AEs were similar for the RSVpreF group (12.9%) and placebo group (12.8%). Most AEs were mild or moderate in both groups (≤1.4% reported as severe). AEs assessed as related by the investigator were reported in 1.3% of the RSVpreF group and 0.9% of the placebo group. Across both groups, SAEs and NDCMCs were reported in ≤2.3% and ≤1.8%, respectively; AEs leading to death, life-threatening AEs, AEs leading to withdrawal, and immediate AEs were reported in ≤0.6% each.

Subgroup Analyses – Adverse Events by Category

AEs, by category, reported from vaccination through the 1-month follow-up visit were evaluated by sex, age group, race, ethnicity, country, and prespecified significant conditions. Overall, for most subgroups, results in both the RSVpreF and placebo groups suggested no clinically meaningful differences across subgroups. For age subgroups, in the RSVpreF group the proportions of participants reporting SAEs were higher for those ≥80 years (1.3%) than 60-69 years (0.5%) and 70-79 years (0.7%), whereas in the placebo group SAE reporting was similar by age subgroup (range: 0.4% - 0.6%). No SAEs were assessed as related in participants ≥80 years in either group. However, these results for any and related AEs, by category, should be interpreted with caution, as several subgroups included a limited number of events and participants.

Table 8. Adverse Events, by Category, Reported From Vaccination Through the 1-Month Follow-Up Visit – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=17215)		Placebo (N[a]=17069)	
Adverse Event Category	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any Event	1537 (8.9)	(8.5, 9.4)	1451 (8.5)	(8.1, 8.9)
Serious	103 (0.6)	(0.5, 0.7)	81 (0.5)	(0.4, 0.6)
AE leading to death	11 (<0.1)	(0.0, 0.1)	8 (<0.1)	(0.0, 0.1)
Severe	65 (0.4)	(0.3, 0.5)	51 (0.3)	(0.2, 0.4)
Life-threatening	24 (0.1)	(0.1, 0.2)	19 (0.1)	(0.1, 0.2)
Related	230 (1.3)	(1.2, 1.5)	159 (0.9)	(0.8, 1.1)
AE leading to withdrawal	3 (<0.1)	(0.0, 0.1)	2 (<0.1)	(0.0, 0.0)
Immediate AE[d]	35 (0.2)	(0.1, 0.3)	31 (0.2)	(0.1, 0.3)
Newly diagnosed chronic medical condition (NDCMC)	81 (0.5)	(0.4, 0.6)	83 (0.5)	(0.4, 0.6)

Note: For participants who received multiple vaccinations due to multiple enrollments, the vaccine group RSVpreF 120 µg was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations; adverse events reported from Day 1 (vaccination day for each dose) through Day 31 after any vaccination, beginning with the first dose of RSVpreF (RSVpreF group) or the first dose of placebo (placebo group) were included in the analysis.
Note: Any reactogenicity reported as related adverse events within 7-day of vaccination from ediary subset safety population are excluded in this table.
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. Each participant was counted once.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Immediate AE refers to an AE reported in the 30-minute post vaccination observation period.
PFIZER CONFIDENTIAL SDTM Creation: 03JAN2023 (16:57) Source Data: adae Table Generation: 13JAN2023 (10:56)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_suppFlag_FDA/adae_s015_1m

Table 9. Adverse Events, by Category, Reported From Vaccination Through Data Cutoff (14Jul2022) – Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=17215)		Placebo (N[a]=17069)	
Adverse Event Category	n[b] (%)	(95% CI[c])	n[b] (%)	(95% CI[c])
Any Event	2227 (12.9)	(12.4, 13.4)	2179 (12.8)	(12.3, 13.3)
Serious	396 (2.3)	(2.1, 2.5)	387 (2.3)	(2.0, 2.5)
AE leading to death	52 (0.3)	(0.2, 0.4)	49 (0.3)	(0.2, 0.4)
Severe	246 (1.4)	(1.3, 1.6)	218 (1.3)	(1.1, 1.5)
Life-threatening	101 (0.6)	(0.5, 0.7)	103 (0.6)	(0.5, 0.7)
Related	231 (1.3)	(1.2, 1.5)	160 (0.9)	(0.8, 1.1)
AE leading to withdrawal	10 (<0.1)	(0.0, 0.1)	6 (<0.1)	(0.0, 0.1)
Immediate AE[d]	35 (0.2)	(0.1, 0.3)	31 (0.2)	(0.1, 0.3)
Newly diagnosed chronic medical condition (NDCMC)	301 (1.7)	(1.6, 2.0)	313 (1.8)	(1.6, 2.0)

Note: For participants who received multiple vaccinations due to multiple enrollments, the vaccine group RSVpreF 120 µg was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations; any adverse events reported from the first dose of RSVpreF (RSVpreF group) or the first dose of placebo (placebo group) through data cutoff date (14Jul2022) were included in the analysis.
Note: Any reactogenicity reported as related adverse events within 7-day of vaccination from ediary subset safety population are excluded in this table.
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event category. Each participant was counted once.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Immediate AE refers to an AE reported in the 30-minute post vaccination observation period.
PFIZER CONFIDENTIAL SDTM Creation: 03JAN2023 (16:57) Source Data: adae Table Generation: 13JAN2023 (11:09)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_suppFlag_FDA/adae_s015_dc

Adverse Events by System Organ Class and Preferred Term

AEs from vaccination through the 1-month follow-up visit that were most frequently reported (≥1%) for the RSVpreF and placebo groups were in the System Organ Classes (SOCs) of Infections and infestations (2.3% vs 2.2%), Respiratory, thoracic and mediastinal disorders (2.2% vs 2.4%), and general disorders and administration site conditions (1.8% vs 1.2%). By Preferred Term (PT), the most frequently reported AE in the RSVpreF group was cough (0.6%), which was also reported in 0.6% of the placebo group.

4.2.3.2.2. Immediate Adverse Events

Participants with immediate AEs reported within 30 minutes postvaccination were low in frequency (0.2% in each group; Table 8). Most immediate AEs were in the SOC of General

disorders and administration site conditions for both the RSVpreF (0.2%) and placebo group (0.1%), and were primarily injection site reactions. By PT, all immediate AEs were reported in <0.1% of participants in either group, with Injection site pain most frequently reported (14 RSVpreF vs 12 placebo). Immediate AEs were assessed as related in 0.2% of participants in each group.

4.2.3.2.3. Related Adverse Events

The proportions of participants who reported AEs from vaccination through the 1-month follow-up visit that were assessed as related were 1.3% and 0.9% in the RSVpreF and placebo groups (Table 8), with 1.2% and 0.8%, respectively, reported within 7 days after vaccination. The most frequently-reported related AEs in the RSVpreF and placebo groups were in the SOC of General disorders and administration site conditions (1.0% vs 0.5%) and were mostly reactogenicity events (eg, injection site reactions, fatigue, pyrexia).

From vaccination to the data cutoff date, proportions of participants with AEs that were assessed by the investigator as related were 1.3% in the RSVpreF group and 0.9% in the placebo group (Table 9), which included non-serious AEs reported after the 1-month follow-up visit for 2 participants: cough (mild severity) in RSVpreF group, cataract (moderate severity) in placebo group.

There were no participants with AEs leading to death or withdrawal that were assessed as related. In both groups, <0.1% of participants had SAEs, severe or life-threatening AEs, and NDCMCs that were assessed as related, and 0.2% had immediate AEs that were assessed as related.

4.2.3.2.4. Severe or Life-Threatening Adverse Events

From vaccination through the 1-month follow-up visit, for the RSVpreF and placebo groups few severe AEs (0.4% vs 0.3%) or life-threatening AEs (0.1% vs 0.1%) were reported (Table 8). Those assessed as related by the investigator included 2 severe events (non-serious AE of viral infection in placebo group, SAE of Miller Fisher syndrome in RSVpreF group), and 1 life-threatening event (SAE of Guillain-Barre syndrome [GBS] in the RSVpreF group); see Section 4.2.3.2.5 for further details for SAEs assessed as related.

Severe or life-threatening events were most frequently reported in the SOC of Infections and infestations for participants in the RSVpreF group (17 [<0.1%]) and placebo group (19 [0.1%]). By PT, all severe or life-threatening events were reported in <0.1% of participants in either group. In the RSVpreF group, the most frequently reported (4 participants each) were Sepsis, Fall, and COPD.

4.2.3.2.5. Serious Adverse Events

The proportion of SAEs reported from vaccination through the 6-month follow-up visit was similar in the RSVpreF (1.9%) and placebo (1.7%). The most frequently reported SOCs in the RSVpreF group were Infections and infestations, Cardiac disorders, and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (0.4%, 0.3%, and 0.3%, respectively), which were reported similarly in the placebo group (0.3% in each SOC). By PT, all SAEs were reported in <0.1% of participants in either group.

From vaccination through the data cutoff date of 14 July 2022, SAEs were reported in 2.3% of participants in each group. The most frequently reported SOCs in the RSVpreF group were Cardiac disorders and Infections and infestations (0.5% each), which were reported similarly in the placebo group (0.5% and 0.4%, respectively). By PT, all SAEs were reported in <0.1% of participants in either group. The most frequently reported SAEs by PT in the RSVpreF group were Coronary artery disease, Acute myocardial infarction, Atrial fibrillation, and Ischemic stroke (11 participants each), which were reported similarly in the placebo group.

Serious Adverse Events Assessed as Related by the Investigator

To the data cutoff date, 3 SAEs were assessed as related by the investigator, which occurred in 3 participants in the RSVpreF group (none in the placebo group). These 3 events of hypersensitivity, GBS, and Miller Fisher syndrome are briefly summarized below. Note: no additional AEs of GBS or Miller Fisher syndrome were reported in the study within 6 months post-vaccination or in any of the other studies in the RSV program.

- **Hypersensitivity** (characterized as a delayed allergic reaction, not anaphylaxis) of moderate severity was reported in a participant (Argentina; 60-69 year-old age group) with a medical history that included allergies to non-vaccine medications. Symptom onset was approximately 8 hours after receipt of RSVpreF (Day 1). The participant experienced shortness of breath and chest pain, which resulted in syncope with loss of consciousness. The participant was transferred to a primary care center; all laboratory tests were normal. The event resolved on Day 5.

  The investigator considered there is a reasonable possibility that the event was related to blinded study intervention.

- **GBS** (life-threatening; Section 4.2.3.2.4) was reported in a participant (US; 60-69 year-old age group), with symptom onset 7 days after receiving RSVpreF (Day 8). The participant, who had a medical history that included hypertension, first presented with acute myocardial infarction (AMI) on Day 7 and underwent angioplasty. On Day 8 (1 day after AMI), the participant experienced lower back pain and on Day 14 bilateral lower extremity (BLE) weakness. Worsening of symptoms resulted in hospitalization on Day 37 (discharged with updated medications list, walker, and physical therapy) and Day 45. Diagnostic examinations including nerve conduction and cerebrospinal fluid (CSF) results supported the diagnosis of GBS. In the following months, the participant reported fluctuation of the symptomatology and the diagnosis was changed to chronic inflammatory demyelinating polyneuropathy (CIPD). According to the last follow up (December 2022), the participant reported improving symptomatology and was continuing physical therapy.

  After discussion with the participant's neurologist, the investigator considered that there is a possibility that the patient's GBS was related to blinded study intervention,

considering the BLE weakness onset on Day 14. The case met Level 1 of the Brighton Criteria[4] (highest level of diagnostic certainty of GBS diagnosis).

- **Miller Fisher Syndrome** (severe; Section 4.2.3.2.4) was reported in a participant (Japan; 60-69 year-old age group) with a medical history that included diabetes. Symptom onset occurred 8 days after receiving RSVpreF (Day 9), and included feeling tired (Day 9) and a mild sore throat (Day 10). Symptoms subsequently reported included ataxic gait (Day 11) and dizziness and loss of appetite (Day 18), and on Day 19 antibiotic treatment was started. Two days later (Day 21), the participant returned to the hospital with diplopia (ophthalmologist revealed ophthalmoplegia and eyelid ptosis). The participant also had paresthesia in both palms and the soles of both feet. Additional physical examination and work up performed on Day 22 revealed normal findings (head CT, labs, thyroid ultrasounds, gastroscopy, colonoscopy) aside from minimal elevation of blood values (C-reactive protein [CRP], white blood cell [WBC]) suggesting possible infection. On Day 41, when most of the symptoms were resolved, a neurologist made a retrospective diagnosis of Miller Fisher Syndrome based on clinical course and symptoms, although an anti-GQ1b antibody test[5] (to GQ1b ganglioside) was negative. As of the participant's last study visit, all symptoms had resolved (diplopia spontaneously resolved by Day 40, the paresthesia in the palms on Day 44, and paresthesia in the soles of the feet on Day 100).

  Considering the clinical course, rareness of this disease, and diagnosis made by a neurologist, the investigator considered that there is a reasonable possibility that the event was related to blinded study intervention, although some other test results as supportive evidence were missing. The case met Level 4 of the Brighton Criteria (reported event of Fisher Syndrome with insufficient evidence to meet the case definition).

The case reporting GBS has a potentially confounding factor with symptoms starting 1 day after the AMI. The case reporting Miller Fisher Syndrome also has a potential alternative etiology (ie, preceded by upper respiratory infection symptoms). Both entities, GBS/Miller Fisher Syndrome, are rare diseases with an incidence rate that increases with age and differ between countries (incidence rates 4.6-7.8 per 100,000 among adults, ≥60 years of age, in the general population).[52,53,54,55] Using a Pfizer internal historical safety standing cohort (unpublished) to examine background rates for potential AEs of special interest using a large US-based electronic health record (EHR) database (Optum) that included trial-similar inclusion/exclusion criteria as Study C3671013, an incidence rate of 10.2 per 100,000 among adults ≥60 years of age was observed.

4.2.3.2.6. Deaths

As of the data cutoff (14 July 2022), AEs leading to death were reported in 52 (0.3%) RSVpreF recipients and 49 (0.3%) placebo recipients (Table 9). None of these deaths were

[4] The Brighton Criteria are used as a tool to aid in early and prompt diagnosing of GBS.

[5] Testing for the presence of the anti-GQ1b antibody in serum is used as a diagnostic marker of Miller Fisher Syndrome.

assessed as related to study intervention. The primary causes of death most frequently reported were in the SOC of Cardiac disorders for participants in the RSVpreF (20 [0.1%]) and placebo (19 [0.1%]) groups.

4.2.3.2.7. Discontinuations from Study Due to Adverse Events

AEs leading to withdrawal from the study through the data cutoff date were similar in the RSVpreF and placebo groups: 10 (<0.1%) and 6 (<0.1%) participants, respectively (Table 9). By PT, for both groups all events were reported in 1 participant each except for Depression (3 participants in the RSVpreF group). None of the events were assessed as related.

4.2.3.2.8. Newly Diagnosed Chronic Medical Conditions

As of the data cutoff (14 July 2022), NDCMCs reported after vaccination were balanced for the RSVpreF and placebo groups (1.7% vs 1.8% overall; Table 9); none of the events in the RSVpreF group and 1 in the placebo group were assessed as related. NDCMCs were most frequently reported (0.3% in each group) in the SOCs of Metabolism and nutrition disorders and Musculoskeletal and connective tissue disorders.

4.2.3.2.9. Adverse Drug Reactions

This section contains adverse drug reactions (ADRs) which are AEs for which there is a reason to conclude that the drug caused the event(s). The Sponsor determines ADRs following a thorough assessment of available evidence from non-clinical, clinical, and post-marketing information (if applicable). Factors considered in the determination of ADRs may include (but not be limited to) temporal relationship, frequency of occurrence, drug mechanism of action, biological plausibility, dose response, drug class effects, lack of confounding factors, dechallenge and rechallenge information, and an investigator's assessment of relatedness. ADRs in this section may be non-serious or serious.

ADRs identified in Study C3671013 included vaccination site pain (very common; ≥10%), vaccination site redness (common; ≥1% and <10%), vaccination site swelling (common; ≥1% and <10%), and hypersensitivity (very rare; <0.01%) (Table 10).

Table 10. Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC, Study C3671013

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to <1/10	Very rare <1/10,000
Immune system disorders			Hypersensitivity
General disorders and administration site conditions	Vaccination site pain	Vaccination site redness, vaccination site swelling	

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(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_Adhoc/adr_ns020

4.3. Other Studies Supporting the Older Adult Clinical Development Program

4.3.1. Study C3671006 – Phase 3 Concomitant Influenza

C3671006 is a clinically complete study (Table 11) to assess the safety and immunogenicity of RSVpreF when coadministered with SIIV compared to sequential administration of the vaccines when given 1 month apart (SIIV followed by RSVpreF). This Phase 3, multicentre, placebo-controlled, randomized, double-blind study was conducted in Australia and included approximately 1400 healthy adults 65 years of age and older that were randomized 1:1 to either the coadministration group (RSVpreF + SIIV)/placebo or the sequential-administration group (placebo + SIIV)/RSVpreF. Primary immunogenicity objectives are: 1) to demonstrate that the immune responses elicited by RSVpreF when coadministered with SIIV (RSVpreF + SIIV) are noninferior to those elicited by RSVpreF alone when administered 1 month after SIIV; 2) to demonstrate that the immune responses elicited by SIIV when coadministered with RSVpreF (RSVpreF + SIIV) are noninferior to those elicited by SIIV alone.

Data from this study will be available in Quarter 2 of 2023 and are planned to be submitted to regulatory agencies.

5. PHARMACOVIGILANCE

At this time, Pfizer has not identified any safety concerns from the clinical trial safety data and the vaccine reactogenicity profile is well tolerated in all studied age groups.

Post-marketing safety surveillance will include review of safety data from all sources for detection and evaluation of potential safety signals in a timely manner and per applicable regulations.

Pfizer will conduct a post-marketing safety study in the older adult population to further assess GBS and immune-mediated demyelinating conditions. To determine the safety of Abrysvo in immunocompromised older adult participants, Pfizer will conduct a post-marketing safety study.

6. BENEFIT/RISK ASSESSMENT

6.1. Benefits

RSV is a serious or life-threatening condition that causes an estimated 60,000 – 160,000 hospitalizations and 6,000 – 13,000 deaths annually among adults in the US.[8,9,10,11] Furthermore, in the US there are 120,000 emergency department visits and approximately 1.36 million RSV-associated ARI-RSV outpatient visits among adults age ≥65 years of age.[8] A substantial burden of non-medically attended ARI is experienced by older adults, comprising 72–83% of all ARI-RSV,[4,13] which would correspond to an estimated additional 3.5 to 6.5 million illnesses annually.

The pivotal study C3671013 demonstrated that RSVpreF, when administered as a single dose of 120 µg to adults ≥60 years of age, was 66.7% (96.66% CI: 28.8%, 85.8%) efficacious in preventing LRTI-RSV (first episode) with ≥2 symptoms, and 85.7% (96.66% CI: 32.0%, 98.7%) efficacious in preventing LRTI-RSV (first episode) with ≥3 symptoms in the first RSV season. Further, a single dose of RSVpreF 120 µg conferred 62.1% (95% CI: 37.1%, 77.9%) efficacy against ARI-RSV (first episode) in the first RSV season.

Study C3671013 did not accumulate enough RSV severe cases to determine VE against this outcome. However, it is likely that cases with ≥3 symptoms in Study C3671013 represent a more severe subset of the broader set of cases with ≥2 symptoms. An ad hoc analysis demonstrated that among the LRTI-RSV cases with ≥2 symptoms, cough and sputum production were the most common symptoms reported; symptoms consistent with more severe disease (wheezing, shortness of breath, tachypnea) were more frequently reported for cases involving ≥3 LRTI symptoms.

While evidence suggests persons with ≥3 LRTI symptoms had more severe disease than those with 2 symptoms, it is nevertheless the case that RSV-related emergency department visits, hospitalizations, and deaths represent a more severe outcome than LRTI-RSV with ≥3 symptoms. Based on the assumption that more severe outcomes should have at least as high a VE as less severe outcomes,[11] the observed RSVpreF VE of 85.7% against LRTI-RSV with ≥3 symptoms (Study C3671013) was applied to estimate potentially preventable emergency department visits, hospitalizations, and deaths in the US older adult population.

In this case, assuming a 100% uptake rate, a single dose of RSVpreF 120 µg has the potential to prevent up to 136,000 hospitalizations, 100,000 emergency department visits, and 11,000 deaths annually in the US population ≥65 years of age, and a higher number in the population ≥60 years of age (no burden data are available specifically for the population ≥60 years of age). Furthermore, the observed RSVpreF VE of 62.1% against ARI-RSV (Study C3671013) could potentially (assuming 100% uptake in the target population) prevent 845,000 ARI-RSV-related outpatient visits and 2 to 4 million non-medically attended ARI illnesses annually in the US population ≥65 years of age. The mean RSV-attributable expenditures during the acute phase of the illness were $35,338 for hospitalization, $2,077 for emergency department visits, and $665 for outpatient visit.[56] The 1 year RSV-attributable expenditures per case (in the US population ≥18 years of age) for adult disease leading to hospitalization, emergency department visits, and outpatient visits have been estimated at $42,009, $13,758, and $12,636, respectively.[56]

To yield the positive population-based overall health outcomes described, high acceptability and uptake of the vaccine will be needed. The favorable safety and tolerability profile of RSVpreF with a systemic event profile similar to placebo will favor vaccine uptake and the realization of the health benefits. Regardless of uptake, though, the benefit in terms of health and economic value per person vaccinated will be substantial. Overall, we estimate the vaccination of approximately 219 persons would prevent 1 RSV-related hospitalization among adults ≥65 years of age on average, assuming a 2-year duration of protection.[57] Analogously, approximately 35 older adults would need to be vaccinated to prevent 1 RSV-related outpatient visit.

In summary, the robust evidence of clinical efficacy from the Phase 3 study C3671013 demonstrates that RSVpreF is a first-in-class bivalent vaccine that will address an unmet medical need for a preventive measure against acute respiratory disease and lower respiratory tract disease caused by RSV in older adults, a disease for which there are currently no prophylactic or therapeutic options.

6.2. Risks

A total of 17,215 adult participants ≥60 years of age received RSVpreF 120 µg in the pivotal Phase 3 C3671013 study.

No important identified or potential safety risks were detected for RSVpreF when administered as a single 120 µg dose in adults ≥60 years of age. Local reactions and systemic events following RSVpreF 120 µg administration were generally mild to moderate in severity. The incidence of AEs, related AEs, NDCMCs, SAEs, life threatening AEs, and AEs leading to withdrawal were similar between the RSVpreF and placebo groups. None of the deaths in the Phase 3 C3671013 study were considered vaccine-related.

Overall, RSVpreF was well tolerated in adults ≥60 years of age.

6.3. Benefit/Risk Assessment

The pivotal Phase 3 C3671013 study, and the totality of data from the RSVpreF clinical development program for older adults, provides robust evidence that RSVpreF is an efficacious, well tolerated and safe vaccine, with a benefit-to-risk ratio that is highly favorable and that supports the proposed indication for prevention of acute respiratory disease and lower respiratory tract disease caused by RSV in adults 60 years of age and older.

7. APPENDICES

7.1. Studies in the RSVpreF Clinical Development Program for the Older Adult Indication

Table 11. Summary of Studies in the RSVpreF Older Adult Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 1/2 **Study C3671001** **(Completed)** Title: A Phase 1/2, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding, First in human Study to Describe the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus Vaccine (RSV Vaccine) in Healthy Adults	The study assessed the safety, tolerability, and immunogenicity of 6 RSVpreF bivalent formulations (RSV A and B) at 3 escalating dose levels of 60 µg (30 µg A and 30 µg B), 120 µg (60 µg A and 60 µg B), and 240 µg (120 µg A and 120 µg B) of the prefusion RSV F antigen, with or without $Al(OH)_3$, when administered alone or concomitantly with SIIV. (US Study)	This study utilized a sentinel cohort (Phase 1) and an expanded cohort (Phase 2). One thousand two hundred thirty-five nonpregnant female and male participants 18 to 85 years of age were randomised. **Participants in the Phase 1**: Male and female participants 18 to 49 years of age. Male and female participants 50 to 85 years of age. **Participants in the Phase 2:** Male and female participants 18 to 49 years of age. Male and female participants 65 to 85 years of age. The age groups were run in parallel.	**Sentinel and expanded cohorts:** Local reactions within 14 days after Vaccination 1. Systemic events within 14 days after Vaccination 1. AEs within 1 month after Vaccination 1. Medically attended AEs and SAEs through 12 months after Vaccination 1. **Expanded cohort:** AEs within 1 month after Vaccination 2.	**Sentinel cohort:** RSV A– and RSV B–neutralizing titers measured before Vaccination 1, and 2 weeks and 1, 2, 3, and 6 months after Vaccination 1. **Expanded cohort:** RSV A and RSV B antibody titers measured before Vaccination 1, and 1, 2, 3, and 6 months after Vaccination 1. **Expanded cohort:** HAI titers for all strains and neutralization titers for the H3N2 strain in the SIIV measured before and 1 month after SIIV administration.

Table 11. Summary of Studies in the RSVpreF Older Adult Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 1/2 Study C3671002 (Completed) Title: A Phase 1/2, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding First in human Study to Describe the Safety, Tolerability, and Immunogenicity of an Adjuvanted Respiratory Syncytial Virus (RSV) Vaccine in Healthy Older Adults	The study assessed the safety, tolerability, and immunogenicity of 7 RSVpreF formulations at 3 antigen dose levels of 60 µg, 120 µg, and 240 µg of the prefusion F antigens formulated with $Al(OH)_3$ or $CpG/Al(OH)_3$, or RSVpreF with the prefusion F antigens alone at a single antigen dose level when administered concomitantly with SIIV. (Australian Study)	Three hundred seventeen nonpregnant female and male participants 65 to 85 years of age were randomized.	**Stage 1:** Local reactions within 14 days after Vaccination 1. Systemic events within 14 days after Vaccination 1. AEs within 1 month after Vaccination 1. Medically attended AEs and SAEs through 12 months after Vaccination 1 (from Visit 1 through Visit 5).	**Stage 1:** RSV A– and RSV B–neutralizing titers measured before and 1 month after Vaccination 1. HAI titers for all strains in the SIIV measured before and 1 month after Vaccination 1.

Phase 2a **Study WI257521** **(Completed)** Title: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Immunogenicity and Efficacy of A Respiratory Syncytial Virus Vaccine (RSVpreF) in A Virus Challenge Model in Healthy Adults	The study assessed the safety, immunogenicity, and efficacy of RSVpreF against RSV-A Memphis 37b infection in healthy adults who received a single dose vaccination with either 120 µg RSVpreF or placebo 1 month prior to challenge with RSV-A Memphis 37b. (United Kingdom Study)	Seventy nonpregnant female and male participants 18 to 50 years of age have been vaccinated with RSVpreF or placebo.	Reduction in 1 or more of the following: Viral load-AUC (VL-AUC) of RSV-A Memphis 37b as determined by qRT PCR on nasal samples collected twice daily starting 2 days post-viral challenge up to discharge from quarantine. Symptomatic RSV infection confirmed by any detectable viral RNA on at least 2 consecutive days. Sum total symptoms diary card score: sum total clinical symptoms (TSS).	Reduction in: Symptomatic RSV infection confirmed by any quantifiable viral RNA on at least 2 consecutive days. Culture lab-confirmed reduction of symptomatic RSV infection. Peak viral load of RSV-A Memphis 37b as defined by the maximum viral load determined by quantifiable qRT PCR and viral culture measurements in nasal samples starting 2 days post-viral challenge up to discharge from quarantine. Duration of RSV-A Memphis 37b quantifiable qRT-PCR and RSV viral culture measurements in nasal samples starting 2 days post-viral challenge up to discharge from quarantine. VL-AUC of RSV-A Memphis 37b as determined by quantitative viral culture on nasal samples starting 2 days post-viral challenge up to discharge from quarantine. TSS-AUC of total clinical symptoms (TSS). Peak symptoms diary card score: peak total clinical symptoms (TSS). Peak daily symptom score: Individual maximum daily sum of Symptom score starting 1 day post-viral challenge up to the end of quarantine. Number (%) of participants with Grade 2 or higher symptoms.

				Occurrence of at least 2 positive quantifiable (≥lower limit of quantification [LLOQ]) qRT-PCR and detectable (≥lower limit of detection [LLOD]) measurements in nasal samples at different timepoints reported on 2 or more consecutive days starting 2 days post-viral challenge up to discharge from quarantine. Occurrence of at least 1 positive quantitative (≥LLOQ) cell culture measurement in nasal samples starting 2 days post-viral challenge up to discharge from quarantine. Total weight of mucus produced, and total number of tissues used by participants starting 1 day post-viral challenge up to discharge from quarantine. The incidence of: Occurrence of solicited local reactions and systemic events within 7 days, unsolicited AEs within 30 days after vaccination, medically attended AEs (MAEs), and SAEs from vaccination up to study end, unsolicited AEs within 30 days post-viral challenge up to Day +28 follow up, SAEs related to the viral challenge from the viral challenge up to Day +28 follow up, and hematological and biochemical laboratory abnormalities during the quarantine period. Use of concomitant medications within 30 days post-viral challenge.

Table 11. Summary of Studies in the RSVpreF Older Adult Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 3 **Study C3671014 (Completed)** Title: A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of 3 lots of respiratory syncytial virus (RSV) prefusion F subunit vaccine in healthy adults	The study is assessing the safety, tolerability, and immunogenicity across 3 manufactured lots of RSVpreF when administered to healthy adults to demonstrate lot equivalence in manufacturing of RSVpreF. Participants are randomized in a 1:1:1:1 ratio to receive 1 of 3 lots of RSVpreF or placebo. (US Study)	Approximately 1000 healthy participants, 18 through ≤49 years of age, are randomized to receive 1 of 3 lots of RSVpreF or placebo.	**Immunogenicity:** RSV A and RSV B NTs **Safety:** Local reactions for 7 days after vaccination Systemic events for 7 days after vaccination AEs through study completion SAEs through study completion	N/A

Table 11. Summary of Studies in the RSVpreF Older Adult Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 3 **Study C3671013 (Ongoing)** Title: A Phase 3 Study To Evaluate the Efficacy, Immunogenicity, And Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults	The study is assessing the safety, immunogenicity, and efficacy of RSVpreF in participants 60 years or older. Participants are being randomised in a 1:1 ratio to receive a single dose of RSVpreF 120 µg or placebo, in 3 age strata (60-69 years, 70-79 years, and ≥80 years). (Global Study)	Approximately 45,000 participants, both healthy and those with stable chronic cardiopulmonary disease including COPD, asthma, and CHF, at risk conditions will be vaccinated.	**Primary Efficacy:** LRTI-RSV cases in the first season **Primary Safety:** Prompted local reactions (pain at the injection site, redness, and swelling) Prompted systemic events (fever, vomiting, nausea, diarrhoea, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain) AEs NDCMCs SAEs	**Key secondary efficacy**: sLRTI RSV cases in the first season **Secondary efficacy**: LRTI-RSV cases (multiple seasons) ARI RSV cases (each and multiple seasons) sLRTI RSV cases (each and multiple seasons) **Secondary Immunogenicity**: RSV neutralizing titer RSVpreF-binding immunoglobulin G (IgG)

Phase 3 Study C3671006 (Clinically Completed; last participant last visit [LPLV] 12 Oct 2022) Title: A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of respiratory syncytial virus prefusion F subunit vaccine when coadministered with seasonal inactivated influenza vaccine in adults ≥65 years of age	The study assessed the safety and immunogenicity of RSVpreF when coadministered with SIIV compared **to** sequential administration of the vaccines when given 1 month apart (SIIV followed by RSVpreF)**.** Participants were randomized 1:1 to either the coadministration group (RSVpreF + SIIV)/placebo or the sequential-administration group (placebo + SIIV)/RSVpreF. (Australia study)	Approximately 1400 healthy adults 65 years of age and older, randomized to either the coadministration group or the sequential-administration group	**Primary Safety**: Local reactions (redness, swelling, and pain at the injection site) self-reported on e-diaries for 7 days after vaccination Systemic events (fever, fatigue, headache, nausea, vomiting, diarrhea, muscle pain, and joint pain) self-reported on e-diaries for 7 days after vaccination AEs SAEs **Primary RSV Immunogenicity**: (To demonstrate that the immune responses elicited by RSVpreF when coadministered with SIIV (RSVpreF + SIIV) are noninferior to those elicited by RSVpreF alone when administered 1 month after SIIV) RSV A and RSV B neutralizing titers **Primary SIIV Immunogenicity**: (To demonstrate that the immune responses elicited by SIIV when coadministered with RSVpreF (RSVpreF + SIIV) are noninferior to those elicited by SIIV alone)	**Secondary RSV Immunogenicity:** (To describe immune responses elicited by RSVpreF when coadministered with SIIV or when administered alone) RSV A and RSV B neutralizing titers **Secondary SIIV Immunogenicity:** (To describe immune responses elicited by SIIV when coadministered with RSVpreF or when administered alone) Strain-specific HAI titers H3N2-neutralizing antibody titers (if interpretable H3N2-HAI titers cannot be obtained)

Table 11. Summary of Studies in the RSVpreF Older Adult Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
			Strain-specific HAI titers H3N2-neutralizing antibody titers (if interpretable H3N2-HAI titers cannot be obtained)	

7.2. Additional Data from Supportive Studies in the RSVpreF Clinical Development Program for Older Adults

7.2.1. Study C3671001 (First in Human) Neutralizing GMTs after Vaccination and Revaccination

Figure 7. RSV B Neutralizing GMTs and GMFRs at 1 Month After Vaccination 1 (Age Group: 65 – 85 Years) – Expanded Cohort – Evaluable RSV Immunogenicity Population, Study C3671001

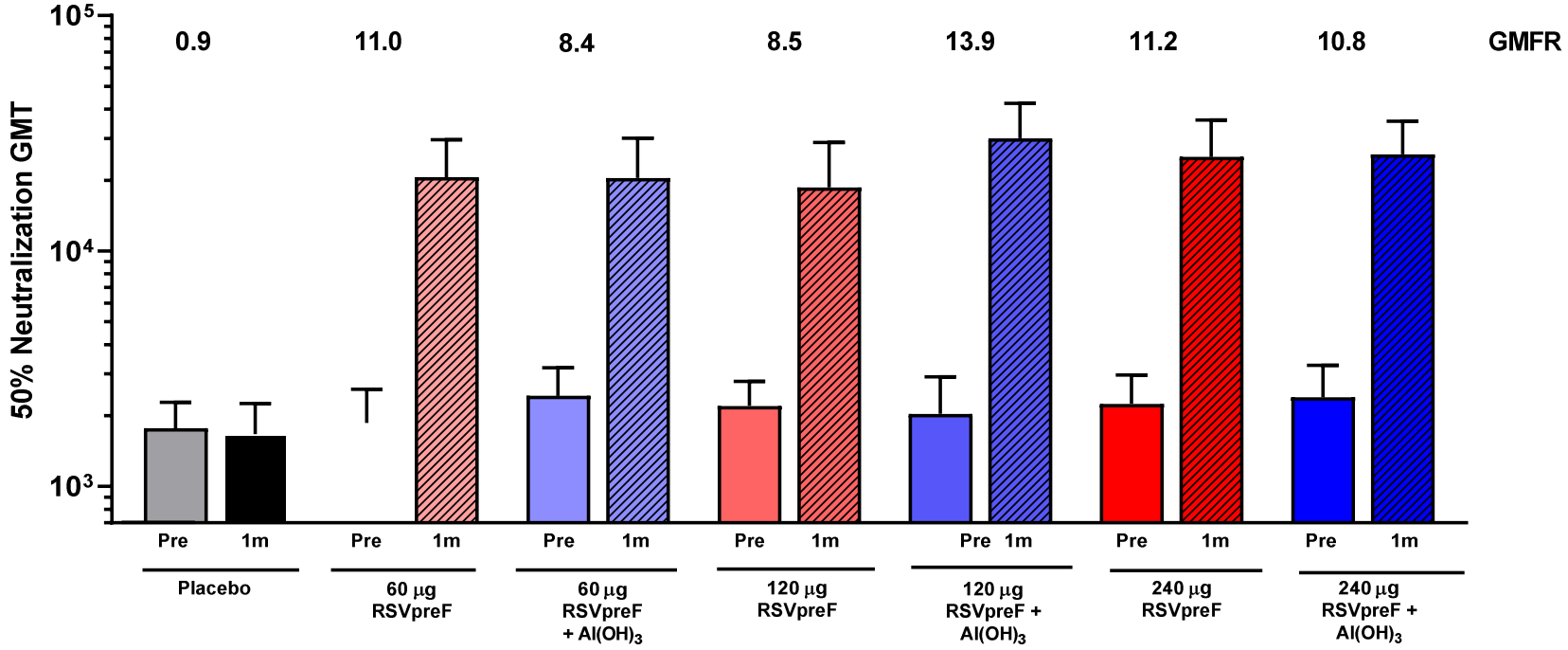


Figure 8. Kinetics Plot of RSV A Neutralizing GMTs (Age Group: 65 - 85 Years) –Expanded Cohort – Evaluable RSV Immunogenicity Population, Study C3671001

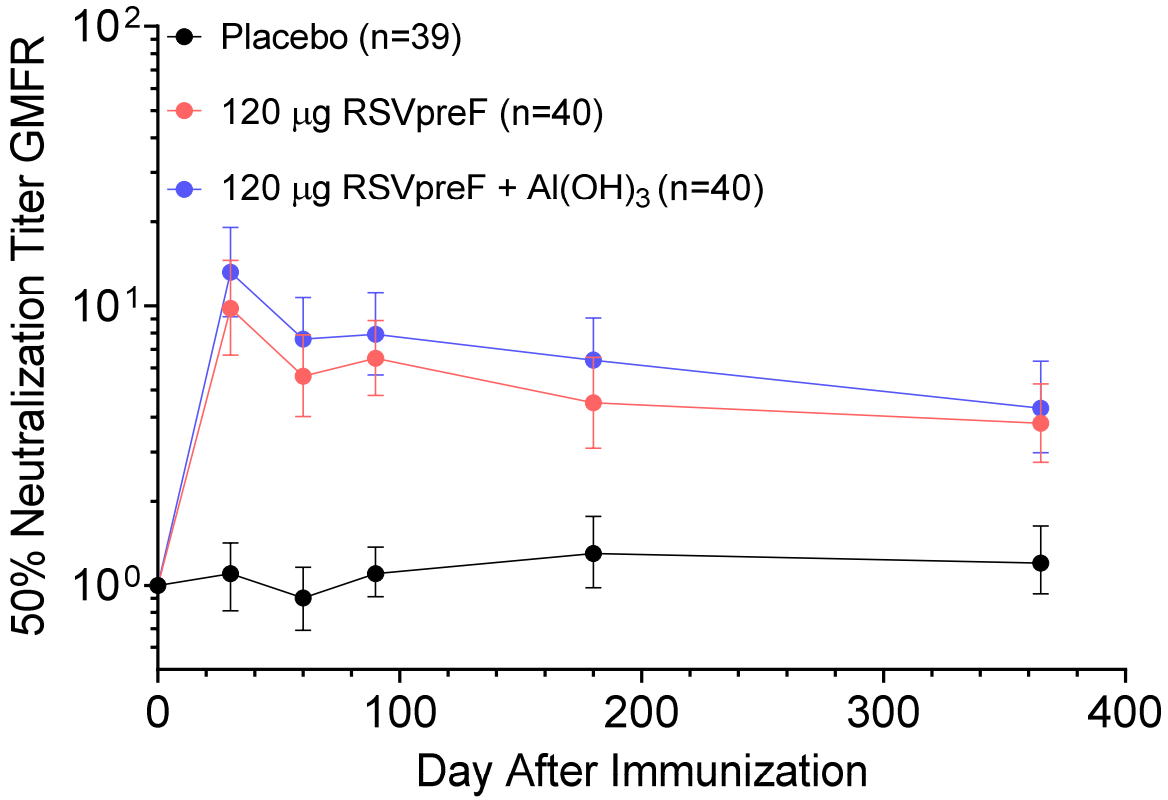


Figure 9. Kinetics Plot of RSV B Neutralizing GMTs (Age Group: 65 - 85 Years) –Expanded Cohort – Evaluable RSV Immunogenicity Population, Study C3671001

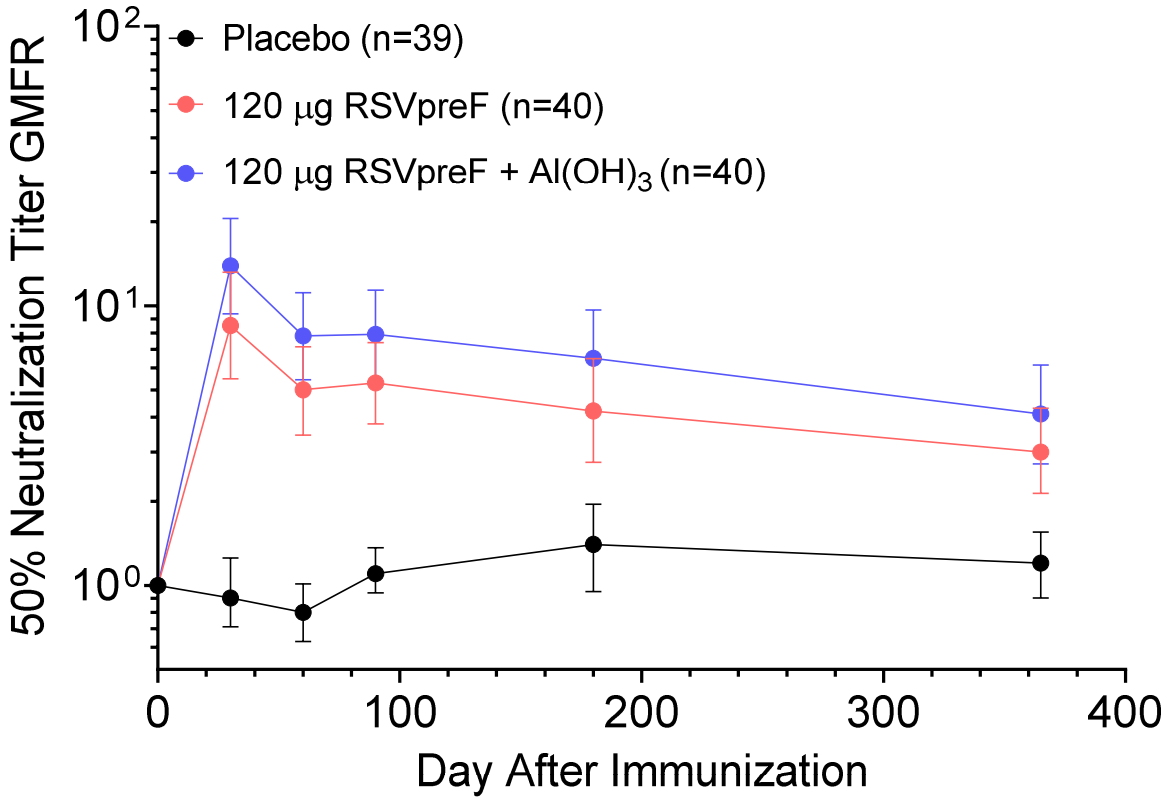
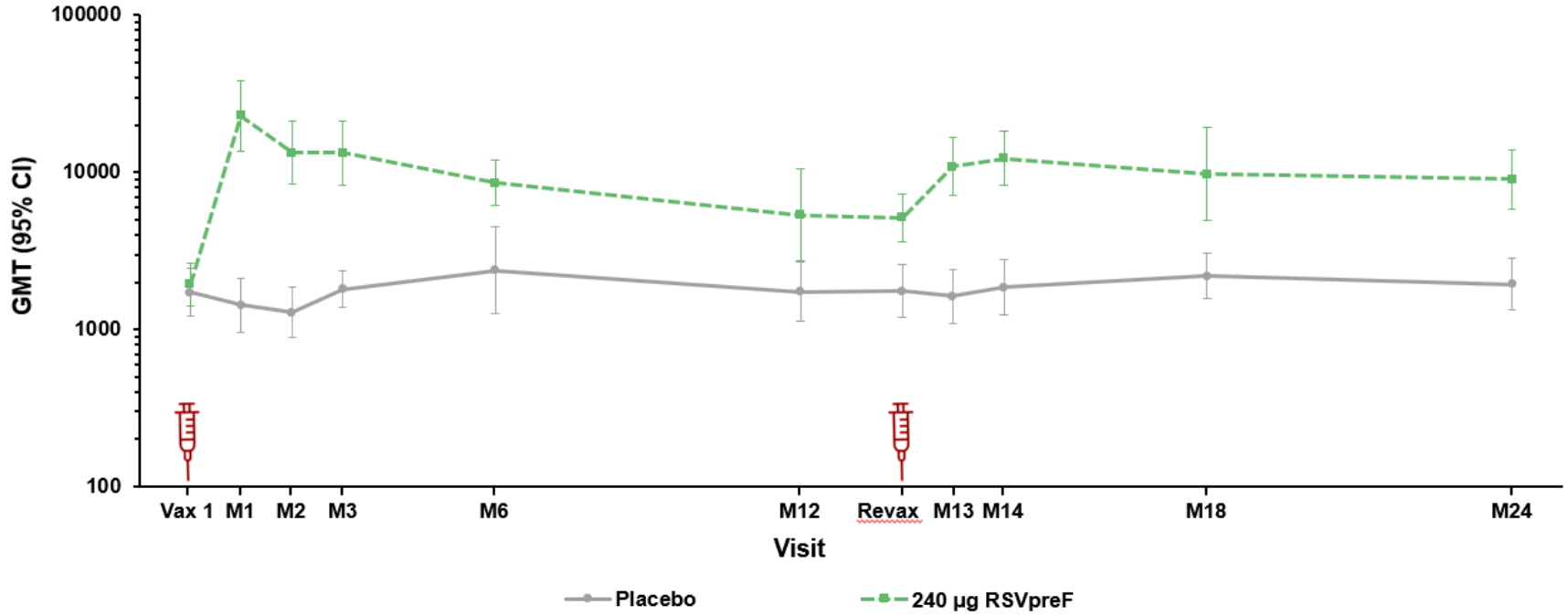
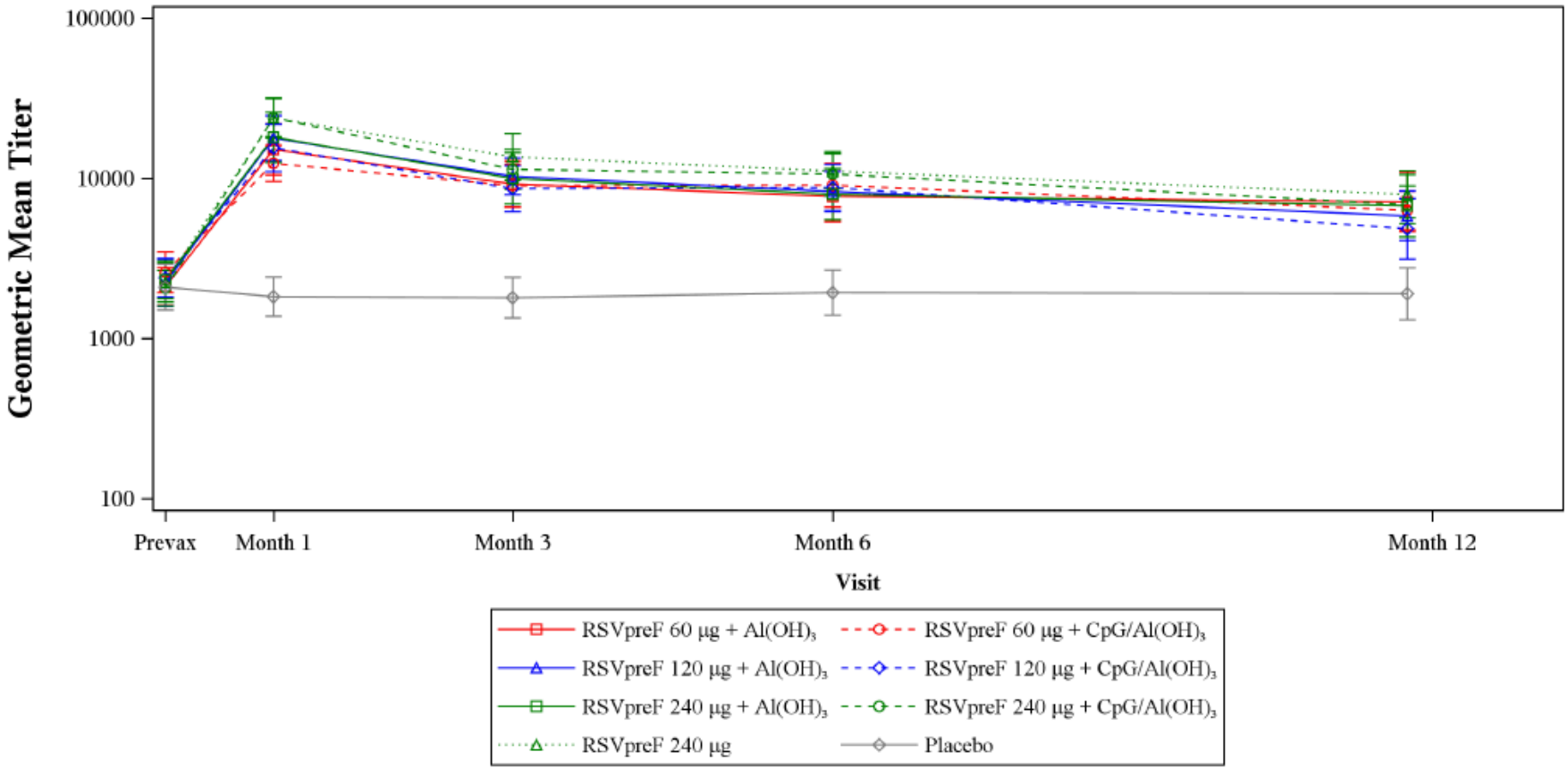


Figure 10. Kinetics Plot of RSV B Neutralizing GMTs (Age Group: 65 – 85 Years) – Expanded Cohort for Revaccination – Evaluable RSV Immunogenicity Population, Study C3671001



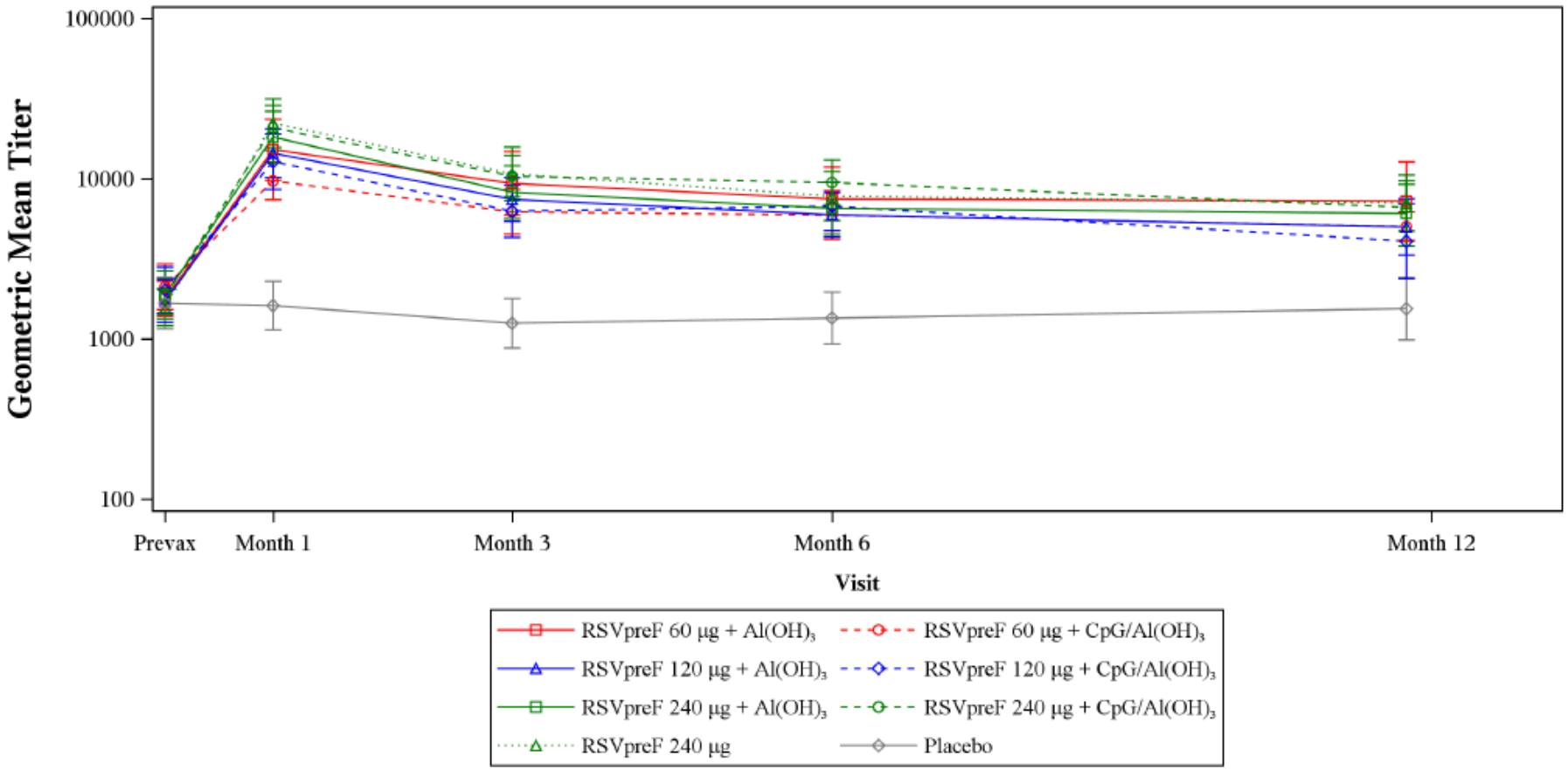
7.2.2. Study C3671002 (Adjuvant Safety and Immunogenicity) Neutralizing GMTs

Figure 11. Kinetics Plot of RSV A Neutralizing GMTs – Primary Cohort – Evaluable Immunogenicity Population, Study C3671002



Abbreviations: GMT = geometric mean titer; Prevax = Prevaccination; RSV = respiratory syncytial virus; RSV A = respiratory syncytial virus subgroup A.
Note: Error bars represent 95% CI for GMT.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2021 (21:39) Source Data: adva Output File: ./nda1/C3671002_CSR/adva_f003_kc_a
Date of Generation: 08FEB2021 (10:16)

Figure 12. Kinetics Plot of RSV B Neutralizing GMTs – Primary Cohort – Evaluable Immunogenicity Population, Study C3671002



Abbreviations: GMT = geometric mean titer; Prevax = Prevaccination; RSV = respiratory syncytial virus; RSV B = respiratory syncytial virus subgroup B.
Note: Error bars represent 95% CI for GMT.
PFIZER CONFIDENTIAL SDTM Creation: 25JAN2021 (21:39) Source Data: adva Output File: ./nda1/C3671002_CSR/adva_f003_kc_c
Date of Generation: 08FEB2021 (10:16)

7.2.3. Study WI257521 (Human Challenge) Efficacy and Immunogenicity Results

Table 12. Study WI257521 Efficacy Results

Efficacy Endpoints	n (%)		Comparison
	RSVpreF (N=31)	Placebo (N=31)	VE (95% CI)
qRT-PCR-confirmed symptomatic RSV infection (Variant 1)[a] *Any 2 detectable (≥LLOD) qRT-PCR results from nasal swabs obtained on 2 or more consecutive days from Day 2 to Day 12 AND symptoms from 2 different categories (URT, LRT, systemic) or any grade 2 symptom (bothersome but not interfering with daily activity)*	2 (6.5)	15 (48.4)	86.7% (53.8, 96.5)
qRT-PCR-confirmed symptomatic RSV infection *Any 2 quantifiable (≥LLOQ) RT-PCR results from nasal swabs obtained on 2 or more consecutive days from Day 2 to Day 12 AND symptoms from 2 different categories (URT, lower LRT, systemic) or any grade 2 symptom (bothersome but not interfering with daily activity)*	0	13 (41.9)	100% (72.8, 100)
Culture lab-confirmed symptomatic RSV infection *Any lab-confirmed culturable RSV infection (one quantifiable (≥LLOQ) viral culture measurement from Day 2 to Day 12 AND symptoms from 2 different categories (URT, LRT, systemic) or any grade 2 symptom (bothersome but not interfering with daily activity)*	0	11 (35.5)	100% (67.7, 100)
Lab confirmed qRT-PCR infection *Any 2 quantifiable (≥LLOQ) results from swabs obtained on 2 or more consecutive days from Day 2 to 12, regardless of symptoms*	4 (12.9)	16 (51.6)	75.0% (38.4, 90.6)
Culture lab confirmed infection *Any 1 quantifiable (≥LLOQ) viral culture measurement from Day 2 to Day 12, regardless of symptoms*	0	13 (41.9)	100% (72.8, 100)
	Median (Q1-Q3)	**Median (Q1-Q3)**	**P-Value (Wilcoxon)**
VL-AUC by qRT-PCR (hrs*log$_{10}$ copies/mL)[a]	0.0 (0.0, 19.0)	96.7 (0.0, 675.3)	<0.001 (two-sided)
Peak viral load (highest value during Day 2-Day 12) by qRT-PCR (log$_{10}$ copies/mL)	0.0 (0.0, 3.1)	4.2 (0.0, 7.0)	Not Calculated
Duration of viral load by qRT-PCR from first quantifiable until the first confirmed unquantifiable assessment after which no further virus is detected (Kaplan-Meier estimate) (hours)	18.0 (11.8, 54.4)	131.6 (72.1, non-estimable)	Not Calculated

Table 12. Study WI257521 Efficacy Results

Efficacy Endpoints	n (%)		Comparison VE (95% CI)
	RSVpreF (N=31)	Placebo (N=31)	
	Geometric Mean	Geometric Mean	Ratio (95% CI)
Sum of total symptom scores by graded symptom scoring[a]	2.1	10.8	0.26 (0.12, 0.56)
Peak total symptoms scores over the duration of quarantine (Day 1- Day 12)	0.8	2.6	0.49 (0.33, 0.73)
AUC for total symptom scores by graded symptom scoring	6.7	56.7	0.13 (0.042, 0.43)

a. Protocol defined primary endpoints. All other endpoints are secondary.

Figure 13. RSV A Neutralizing GMTs and GMFRs, Study WI257521

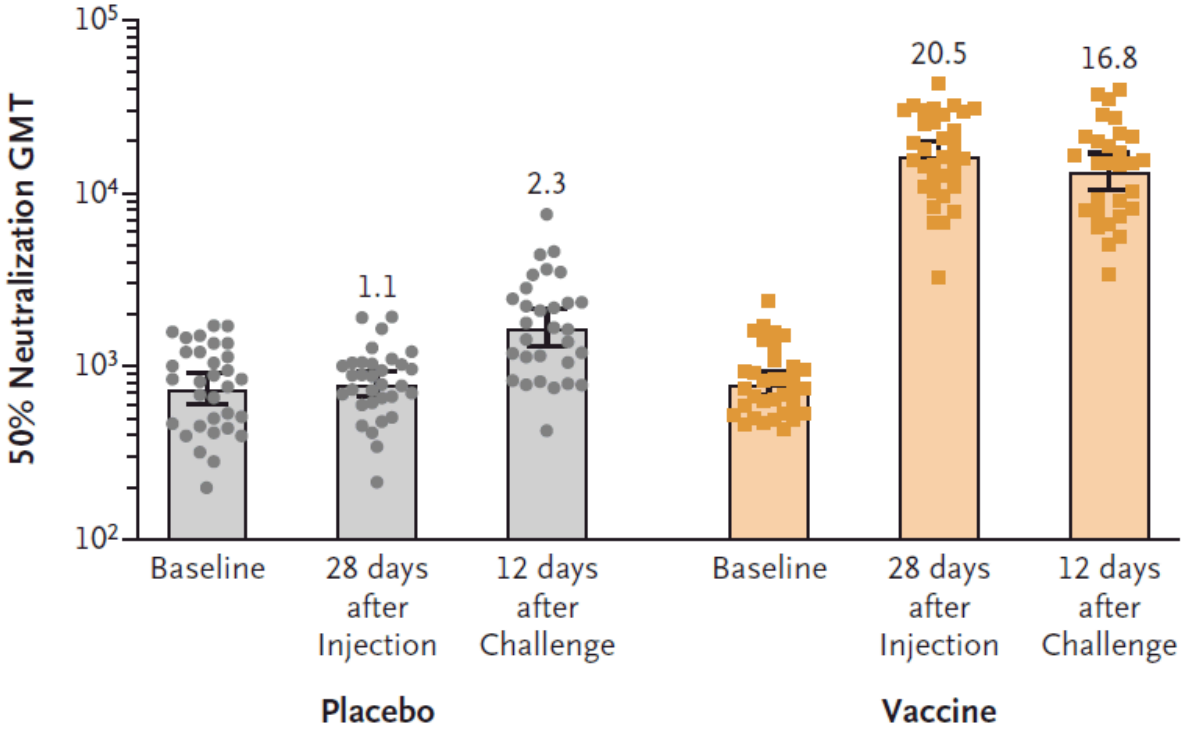
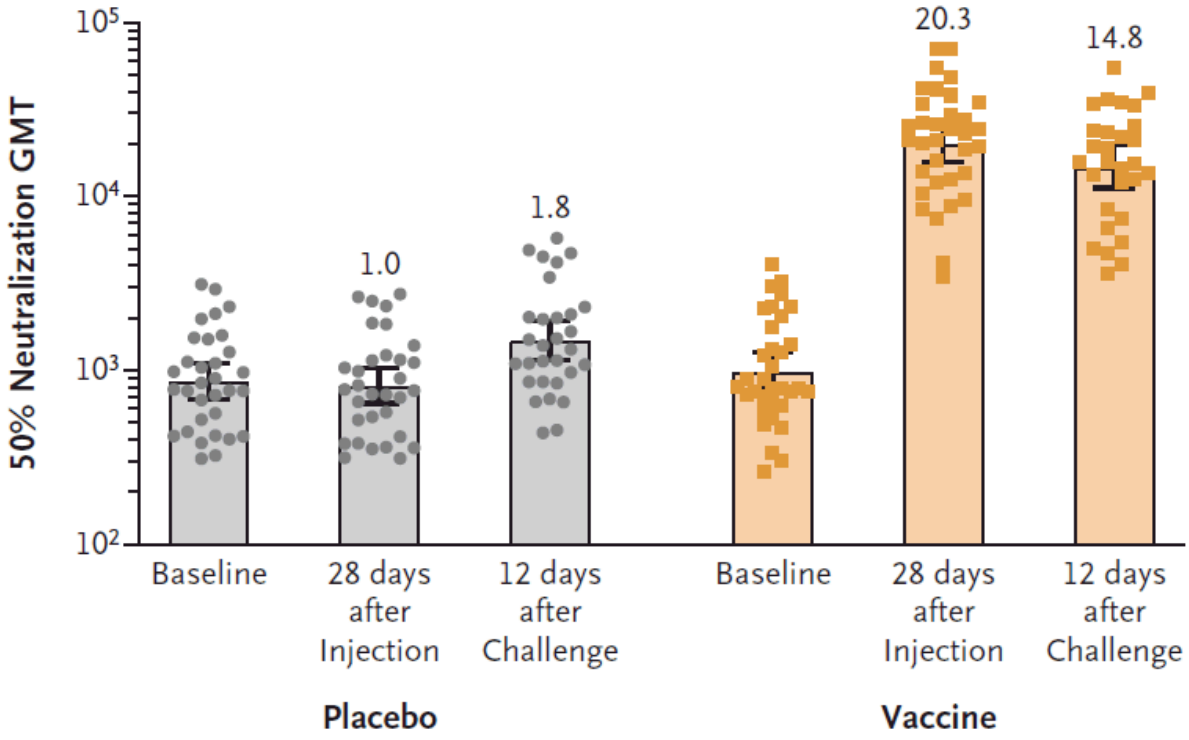


Figure 14. RSV B Neutralizing GMTs and GMFRs, Study WI257521



7.2.4. Study C3671014 (Lot Consistency) Ratios of Neutralizing Geometric Mean Titers

Table 13. Ratio of 50% Neutralizing Geometric Mean Titers Between Individual RSVpreF Lots at 1 Month After Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)								
	Group 1 RSVpreF Lot 1		Group 2 RSVpreF Lot 2		Group 3 RSVpreF Lot 3		Comparison GMR[a] (95% CI[a])		
RSV Subgroup	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	Group 1 RSVpreF Lot 1 / Group 2 RSVpreF Lot 2	Group 1 RSVpreF Lot 1 / Group 3 RSVpreF Lot 3	Group 2 RSVpreF Lot 2 / Group 3 RSVpreF Lot 3
A	236	25238.1 (22867.7, 27854.2)	236	25207.5 (22360.8, 28416.6)	238	24130.9 (21536.3, 27038.1)	1.00 (0.858, 1.169)	1.05 (0.900, 1.215)	1.04 (0.886, 1.232)
B	236	21701.9 (19433.1, 24235.6)	236	20317.3 (17944.4, 23003.9)	238	19238.1 (16920.0, 21873.9)	1.07 (0.905, 1.261)	1.13 (0.953, 1.336)	1.06 (0.884, 1.262)

Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
a. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in LS means and corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling timepoint.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 18MAY2022 (11:31) Table Generation: 18MAY2022 (11:31) (Database snapshot date : 05May2022) Output File: ./nda_oa/C3671014_CSR/adva_s007_gmr_evimm

7.3. Additional Data from Pivotal Phase 3 Study C3671013

7.3.1. Study C3671013 Local Reactions and Systemic Events, by Maximum Severity

Table 14. Local Reactions, by Maximum Severity, Within 7 Days After Vaccination – E-Diary Subset Safety Population, Study C3671013

	Vaccine Group (as Administered)					
	RSVpreF 120 µg			Placebo		
Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Pain at injection site[d]						
Any	3621	385 (10.6)	(9.6, 11.7)	3539	212 (6.0)	(5.2, 6.8)
Mild	3621	343 (9.5)	(8.5, 10.5)	3539	188 (5.3)	(4.6, 6.1)
Moderate	3621	40 (1.1)	(0.8, 1.5)	3539	24 (0.7)	(0.4, 1.0)
Severe	3621	2 (<0.1)	(0.0, 0.2)	3539	0	(0.0, 0.1)
Redness[e]						
Any	3619	97 (2.7)	(2.2, 3.3)	3532	23 (0.7)	(0.4, 1.0)
Mild	3619	55 (1.5)	(1.1, 2.0)	3532	16 (0.5)	(0.3, 0.7)
Moderate	3619	38 (1.1)	(0.7, 1.4)	3532	7 (0.2)	(0.1, 0.4)
Severe	3619	4 (0.1)	(0.0, 0.3)	3532	0	(0.0, 0.1)
Swelling[e]						
Any	3619	89 (2.5)	(2.0, 3.0)	3532	16 (0.5)	(0.3, 0.7)
Mild	3619	54 (1.5)	(1.1, 1.9)	3532	8 (0.2)	(0.1, 0.4)
Moderate	3619	31 (0.9)	(0.6, 1.2)	3532	6 (0.2)	(0.1, 0.4)
Severe	3619	4 (0.1)	(0.0, 0.3)	3532	2 (<0.1)	(0.0, 0.2)
Any local reaction[f]						
Any	3621	441 (12.2)	(11.1, 13.3)	3539	235 (6.6)	(5.8, 7.5)
Mild	3621	347 (9.6)	(8.6, 10.6)	3539	199 (5.6)	(4.9, 6.4)
Moderate	3621	86 (2.4)	(1.9, 2.9)	3539	34 (1.0)	(0.7, 1.3)
Severe	3621	8 (0.2)	(0.1, 0.4)	3539	2 (<0.1)	(0.0, 0.2)

Note: Local reactions were collected in the e-diary from Day 1 to Day 7 after vaccination for a subset of study participants from selected sites.
Note: For participants who received multiple vaccinations due to multiple enrollments, the vaccine group RSVpreF 120 µg was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations; across vaccinations, the highest severity of local reactions reported from the time of the first dose of RSVpreF (RSVpreF group) or placebo (placebo group) was included in the analysis.
Note: Any reactogenicity reported as related adverse events within 7-day of vaccination from ediary subset safety population are included in this table.
a. N = number of participants with at least 1 day of e-diary data. This value is the denominator for the percentage calculations. Caliper units were not distributed to 9 participants included in the e-diary subset thus the denominator for 'Redness' and 'Swelling' excluded the 9 participants.

Table 14. Local Reactions, by Maximum Severity, Within 7 Days After Vaccination – E-Diary Subset Safety Population, Study C3671013

	Vaccine Group (as Administered)					
	RSVpreF 120 µg			Placebo		
Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])

b. n = Number of participants reporting in e-diary any reaction or with maximum severity of mild, moderate, or severe based on the severity scales. Each participant was counted once.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
e. Mild: 2.5 cm to 5.0 cm; moderate: >5.0 cm to 10.0 cm; severe: >10.0 cm or grading scale as reported in AE.
f. Any local reaction: any pain at the injection site, redness, or swelling of at least mild severity.
PFIZER CONFIDENTIAL SDTM Creation: 23DEC2022 (04:09) Source Data: adfacevd Table Generation: 18JAN2023 (12:47)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_suppFlag_FDA/adce_s010

Table 15. Systemic Events, by Maximum Severity, Within 7 Days After Vaccination – E-Diary Subset Safety Population, Study C3671013

	Vaccine Group (as Administered)					
	RSVpreF 120 µg			Placebo		
Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Fever						
Any	3619	52 (1.4)	(1.1, 1.9)	3532	51 (1.4)	(1.1, 1.9)
Mild	3619	23 (0.6)	(0.4, 1.0)	3532	27 (0.8)	(0.5, 1.1)
Moderate	3619	28 (0.8)	(0.5, 1.1)	3532	21 (0.6)	(0.4, 0.9)
Severe	3619	1 (<0.1)	(0.0, 0.2)	3532	2 (<0.1)	(0.0, 0.2)
Grade 4 (>40.0°C)[d]	3619	0	(0.0, 0.1)	3532	1 (<0.1)	(0.0, 0.2)
Fatigue[e]						
Any	3621	562 (15.5)	(14.4, 16.7)	3539	508 (14.4)	(13.2, 15.6)
Mild	3621	335 (9.3)	(8.3, 10.2)	3539	296 (8.4)	(7.5, 9.3)
Moderate	3621	215 (5.9)	(5.2, 6.8)	3539	207 (5.8)	(5.1, 6.7)
Severe	3621	12 (0.3)	(0.2, 0.6)	3539	5 (0.1)	(0.0, 0.3)
Headache[e]						
Any	3621	465 (12.8)	(11.8, 14.0)	3539	415 (11.7)	(10.7, 12.8)
Mild	3621	326 (9.0)	(8.1, 10.0)	3539	299 (8.4)	(7.6, 9.4)
Moderate	3621	135 (3.7)	(3.1, 4.4)	3539	113 (3.2)	(2.6, 3.8)
Severe	3621	4 (0.1)	(0.0, 0.3)	3539	3 (<0.1)	(0.0, 0.2)
Muscle Pain[e]						

Table 15. Systemic Events, by Maximum Severity, Within 7 Days After Vaccination – E-Diary Subset Safety Population, Study C3671013

	Vaccine Group (as Administered)					
	RSVpreF 120 µg			Placebo		
Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
Any	3621	367 (10.1)	(9.2, 11.2)	3539	297 (8.4)	(7.5, 9.4)
Mild	3621	234 (6.5)	(5.7, 7.3)	3539	196 (5.5)	(4.8, 6.3)
Moderate	3621	125 (3.5)	(2.9, 4.1)	3539	98 (2.8)	(2.3, 3.4)
Severe	3621	8 (0.2)	(0.1, 0.4)	3539	3 (<0.1)	(0.0, 0.2)
Joint Pain[e]						
Any	3621	272 (7.5)	(6.7, 8.4)	3539	244 (6.9)	(6.1, 7.8)
Mild	3621	163 (4.5)	(3.8, 5.2)	3539	139 (3.9)	(3.3, 4.6)
Moderate	3621	106 (2.9)	(2.4, 3.5)	3539	103 (2.9)	(2.4, 3.5)
Severe	3621	3 (<0.1)	(0.0, 0.2)	3539	2 (<0.1)	(0.0, 0.2)
Nausea[e]						
Any	3621	124 (3.4)	(2.9, 4.1)	3539	132 (3.7)	(3.1, 4.4)
Mild	3621	92 (2.5)	(2.1, 3.1)	3539	108 (3.1)	(2.5, 3.7)
Moderate	3621	32 (0.9)	(0.6, 1.2)	3539	21 (0.6)	(0.4, 0.9)
Severe	3621	0	(0.0, 0.1)	3539	3 (<0.1)	(0.0, 0.2)
Vomiting[e]						
Any	3621	32 (0.9)	(0.6, 1.2)	3539	30 (0.8)	(0.6, 1.2)
Mild	3621	26 (0.7)	(0.5, 1.1)	3539	24 (0.7)	(0.4, 1.0)
Moderate	3621	6 (0.2)	(0.1, 0.4)	3539	4 (0.1)	(0.0, 0.3)
Severe	3621	0	(0.0, 0.1)	3539	2 (<0.1)	(0.0, 0.2)
Diarrhea[e]						
Any	3621	214 (5.9)	(5.2, 6.7)	3539	183 (5.2)	(4.5, 6.0)
Mild	3621	162 (4.5)	(3.8, 5.2)	3539	148 (4.2)	(3.5, 4.9)
Moderate	3621	48 (1.3)	(1.0, 1.8)	3539	31 (0.9)	(0.6, 1.2)
Severe	3621	4 (0.1)	(0.0, 0.3)	3539	4 (0.1)	(0.0, 0.3)
Any systemic event[f]						
Any	3621	994 (27.5)	(26.0, 28.9)	3539	909 (25.7)	(24.3, 27.2)
Mild	3621	570 (15.7)	(14.6, 17.0)	3539	536 (15.1)	(14.0, 16.4)
Moderate	3621	397 (11.0)	(10.0, 12.0)	3539	352 (9.9)	(9.0, 11.0)
Severe	3621	27 (0.7)	(0.5, 1.1)	3539	20 (0.6)	(0.3, 0.9)
Grade 4 (fever >40.0°C)[d]	3621	0	(0.0, 0.1)	3539	1 (<0.1)	(0.0, 0.2)

Note: Events were collected in the e-diary from Day 1 to Day 7 after vaccination for a subset of study participants from selected sites.
Note: For participants who received multiple vaccinations due to multiple enrollments, the vaccine group RSVpreF 120

Table 15. Systemic Events, by Maximum Severity, Within 7 Days After Vaccination – E-Diary Subset Safety Population, Study C3671013

	Vaccine Group (as Administered)					
	RSVpreF 120 µg			Placebo		
Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])

µg was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations; across vaccinations, the highest severity of systemic events reported from the time of the first dose of RSVpreF (RSVpreF group) or placebo (placebo group) was included in the analysis.
Note: Any reactogenicity reported as related adverse events within 7-day of vaccination from ediary subset safety population are included in this table.
a. N = number of participants with at least 1 day of e-diary data. This value is the denominator for the percentage calculations. Thermometer was not distributed to 9 participants included in the e-diary subset thus the denominator for 'Fever' excluded the 9 participants.
b. n = Number of participants reporting in e-diary any event or with maximum severity of mild, moderate, or severe based on the severity scales. Each participant was counted once.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Only an investigator or qualified designee is able to classify a participant's fever as Grade 4, after clinical evaluation of the participant, review of documentation from another medically qualified source, or contact with the participant. While this table provides a summary of participants who reported a temperature at Grade 4 level in their e-diary, not all of the e-diary reports have been classified as Grade 4 fevers per the protocol.
e. For fever (e-diary)– mild:38.0-38.4°C; moderate:>38.4-38.9°C; severe:>38.9°C; for vomiting (e-diary) – mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration. For diarrhea (e-diary) – mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours. For other systemic events (e-diary) and all related AEs – mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily routine activity.
f. Any systemic event: any fever ≥38.0°C, or any fatigue, headache, muscle pain, joint pain, nausea, vomiting, or diarrhea.
PFIZER CONFIDENTIAL SDTM Creation: 23DEC2022 (04:09) Source Data: adfacevd Table Generation: 19JAN2023 (09:21)
(Data cutoff date : 14JUL2022 Database snapshot date : 05AUG2022) Output File: ./oa_1013/C3671013_CSR_suppFlag_FDA/adce_s020

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