BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA)
STN	125769/0
CBER Received Date	September 30, 2022
PDUFA Goal Date	May 31, 2023
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Nadine Peart Akindele, MD Clinical Review Staff, DVRPA, OVRR, CBER Alaina Halbach, MD Clinical Review Staff, DVRPA, OVRR, CBER
Review Completion Date / Stamped Date	May 31, 2023
Supervisory Concurrence	Rachel Zhang, MD Team Leader, Clinical Review Staff, DVRPA, OVRR, CBER Anuja Rastogi, MD, MHS Branch Chief, Clinical Review Staff, DVRPA, OVRR, CBER Douglas Pratt, MD, MPH Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	Pfizer Inc.
Established Name	Respiratory Syncytial Virus Vaccine
(Proposed) Trade Name	Abrysvo
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.5 mL dose contains 120 µg of RSV stabilized prefusion F protein (60 µg RSV-A and 60 µg RSV-B)
Dosage Form(s) and Route(s) of Administration	Solution for intramuscular injection, supplied as a single dose vial of lyophilized powder that is reconstituted with sterile water provided in a pre-filled syringe
Dosing Regimen	Single 0.5 mL dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARD	acute respiratory disease
RSV-ARD	RSV-associated acute respiratory disease
BIMO	bioresearch monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DMC	data monitoring committee
ERD	enhanced respiratory disease
FI-RSV	formalin-inactivated RSV
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	Hemagglutinin-inhibition
HD	high dose
LRTD	lower respiratory tract disease
RSV-LRTD	RSV-associated lower respiratory tract illness
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Miller Fisher syndrome
NAAT	nucleic acid amplification test
NDCMC	Newly Diagnosed Chronic Medical Condition
NT	neutralizing titer
PFS	pre-filled syringe
PREA	Pediatric Research Equity Act
PT	preferred term
PVP	pharmacovigilance plan
RSV	respiratory syncytial virus
RSV-sLRTD	RSV-associated severe lower respiratory tract disease
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SIIV	seasonal inactivated influenza vaccine
SMQ	standardized MedDRA query
SOC	system organ class
US	United States
USPI	US Prescribing Information
VE	vaccine efficacy
WFI	Water for Injection

1. EXECUTIVE SUMMARY

On September 30, 2022, Pfizer, Inc. (the Applicant) submitted a Biologics License Application (BLA) to the United States Food and Drug Administration (FDA) to support licensure of RSVpreF (Abrysvo), with the proposed indication of "prevention of acute respiratory disease and lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in individuals 60 years of age and older." RSVpreF is a recombinant protein subunit vaccine which consists of equal amounts of stabilized prefusion F (preF) antigens from the two major RSV subgroups: RSV A and RSV B. The proposed dosing regimen is a single intramuscular injection at the dose level of 120 µg.

Data from 6 clinical studies were submitted in support of the BLA. The primary data to support the safety and efficacy of RSVpreF in individuals 60 years of age and older consist of data from an ongoing multi-national Phase 3 randomized, double-blind and placebo-controlled trial (Study C3671013, referred to as Study 1013 throughout this document) in 34,284 participants who received a dose of RSVpreF (n=17,215) or placebo (n=17,069).

Efficacy

The primary objective of Study 1013 was to demonstrate the efficacy of RSVpreF in preventing RSV-LRTD in the first RSV season. Efficacy of RSVpreF was demonstrated in Study 1013 after a successful protocol-specified interim analysis (considered the primary analysis) that evaluated primary efficacy endpoints of laboratory-confirmed RSV-associated lower respiratory tract disease (RSV- LRTD) with ≥2 symptoms and ≥3 symptoms with onset at least 14 days after vaccination. Vaccine efficacy (VE) in preventing laboratory-confirmed RSV-LRTD with ≥2 symptoms was 66.7% (96.66% confidence interval [CI] 28.8, 85.8), with 11 cases in the vaccine group and 33 cases in the placebo group. VE in preventing laboratory-confirmed RSV-LRTD with ≥3 symptoms was 85.7% (96.66% CI 32.0, 98.7), with 2 cases in the vaccine group and 14 cases in the placebo group. A planned descriptive analysis of a secondary endpoint of VE against RSV-associated acute respiratory disease (RSV- ARD) demonstrated a VE of 67.9% (95% CI 49.1, 80.4). VE analysis for RSV-associated severe lower respiratory tract disease (RSV-sLRTD) was not performed at the time of the final analysis for the primary objective, as the minimum number of first episode RSV-sLRTD cases had not accrued; there were 2 cases of RSV-sLRTD in the placebo group and no cases in the RSVpreF groups.

Safety

Safety data from Study 1013 through the July 14, 2022, data cutoff included 34,284 vaccinated participants (17,215 RSVpreF recipients and 17,069 placebo recipients), of which 26,395 participants (77.0%) had at least 6 months of follow-up post-vaccination. Data on solicited local and systemic adverse reactions (ARs) within 7 days following vaccination were collected from a subset of study participants (n=7,196). The most reported (>10%) solicited ARs among RSVpreF recipients were fatigue (15.5%), headache (12.8%), injection site pain (10.6%), and muscle pain (10.1%); these were predominately mild and moderate, with 0.2% and 0.7% of local and systemic solicited ARs, respectively, reported as grade 3 in severity. Unsolicited adverse events (AEs) were followed in the entire Safety Population (N=34,284) through 1 month following vaccination. There were no meaningful imbalances in the overall rates of unsolicited adverse events within 1 month following vaccination between vaccine and placebo recipients in the Safety Population. A numerical imbalance was noted in the specific adverse event of atrial fibrillation with 10 events in the RSVpreF group and 4 events in the placebo group. As of the data cut-off, serious adverse events (SAEs) were balanced between study groups (2.3% in both groups). Three SAEs, all of which were in the RSVpreF group, were considered possibly related

to study vaccine by the FDA, in agreement with the investigator's assessment: an event of hypersensitivity, not classified as anaphylaxis, beginning 8 hours after vaccination; a case of Guillain-Barré syndrome (GBS) with onset 7 days after vaccination; and a case of Miller Fisher syndrome (considered a variant of GBS) with onset 8 days after vaccination. Deaths occurred in 52 (0.3%) RSVpreF recipients and 49 (0.3%) placebo recipients. None of the deaths were considered related to study intervention.

After the data cutoff date, one case of a sensory-motor axonal polyneuropathy was reported that was not considered by the investigator to be related to the vaccination; however, FDA has determined that a causal association cannot be excluded.

In the additional 5 supporting clinical studies submitted to the BLA, a total of 2,727 participants received varying dose levels and formulations of RSVpreF. Review of the safety data from these studies did not reveal any additional safety concerns. Across the 5 supporting studies, there were no SAEs assessed as related to study vaccine and no events of GBS or other polyneuropathies reported post-vaccination.

Lot Consistency

Clinical lot consistency was demonstrated in Study C3671014, with the 2-sided 95% CIs for geometric mean ratios (GMRs) of neutralizing antibodies at 1 month after vaccination for each pair of individual vaccine lots (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) remaining contained within the prespecified interval (0.667, 1.5).

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed.

Efficacy

Study 1013 was conducted in multiple regions and countries. In descriptive analyses of the primary endpoints by subgroup, no notable differences were observed in VE point estimates by country, age, sex, race, ethnicity and pre-specified conditions. VE estimates for participants in the United States (US) were comparable to those of the overall study population. The VE point estimates for vaccine recipients in each of the age stratifications enrolled were also similar to those of the overall population of the study and vaccine efficacy appeared to be preserved among participants ≥80 years of age. VE point estimates were also preserved among those with at least one at-risk condition for severe RSV. Interpretation of the subgroup analyses however is limited by small sample sizes and low case numbers for these subgroups.

Safety

In study 1013, descriptive summaries of safety data were reported by age, sex, race, ethnicity, and country. In general, there were no suggestions of clinically relevant differences of the reactogenicity profile between sex, race, ethnicity, or country. By age, in general, solicited ARs were reported more commonly in the younger age subgroup (60-69 years) compared to the older age subgroups. This observation was consistent with the overall higher reactogenicity reported in Study 1014 which enrolled a younger population of participants. No other notable differences were reported by subgroup in the 4 remaining studies.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

Data Submitted in the Application

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

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

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Respiratory syncytial virus (RSV) is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. The severity of RSV disease increases with age and comorbidities (e.g., chronic obstructive pulmonary disease, congestive heart failure, asthma) (Falsey et al, 2005). RSV disease among adults 65 years of age and older results in an average of 177,000 hospitalizations in the United States (US) each year; during 1999-2018, the highest mortality among all age groups was seen in among adults 65 years of age and older with a mortality rate of 14.7 per 100,000 (CDC, 2022; Hansen et al, 2022).

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

RSV strains are grouped within a single serotype but are separated into 2 major phylogenetic lineages (subgroups RSV A and RSV B) originally determined by cross neutralization studies and confirmed to be due mainly to antigenic differences in the RSV glycoprotein G. Currently, RSV A and RSV B strains are differentiated by sequences within the N-terminal 270 nucleotides of the RSV glycoprotein G gene. Glycoprotein G and glycoprotein F are the primary targets of neutralizing antibodies. While glycoprotein G shows significant genetic diversity between the two subgroups, glycoprotein F is relatively antigenically conserved. Both subgroups tend to co-circulate during each season, however, the prevalence of the RSV subgroup dominating local annual outbreaks is variable and unpredictable.

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

High risk populations include infants and young children, elderly, immunocompromised individuals (hematologic malignancies, hematopoietic stem cell transplant recipients, lung transplant recipients), and those with underlying cardiopulmonary conditions. In older adults, RSV infections can lead to severe disease, requiring hospitalization for respiratory support, including supplemental oxygen, intubation, and/or mechanical ventilation.

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

Treatment for RSV infection is limited to supportive care.

Palivizumab (Synagis; MedImmune), is a monoclonal antibody approved by the FDA for prevention of severe RSV disease in high-risk infants.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, only one vaccine has been approved by the FDA for prevention of lower respiratory tract disease caused by RSV. On May 3, 2023, FDA approved the adjuvanted RSV vaccine (trade name Arexvy) manufactured by GlaxoSmithKline Biologicals, SA for use in adults 60 years of age and older. Information regarding the safety and effectiveness of Arexvy is described in the US Prescribing Information (USPI).

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

Currently, RSVPreF is not licensed in any country.

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

Regulatory Pathway to Licensure:

The basis of the licensure approach relied on establishing acceptable safety and efficacy in preventing lower respiratory tract disease due to RSV after administration of RSVpreF as compared to placebo.

Major Regulatory Activity:

The following timeline provides the major regulatory activity associated with this BLA-

- March 21, 2022: Received Breakthrough Therapy Designation
- August 31, 2022: Response to pre-BLA Questions
    - CBER provided guidance on studies to be included in the BLA submission
    - CBER confirmed integrated summary of effectiveness and integrated summary of safety are not needed
- November 29, 2022: Received Priority Review Status

2.6 Vaccine-Associated Enhanced Respiratory Disease

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

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized to accommodate the conduct of a complete review without unreasonable difficulty. Initially, incomplete data for the analyses of RSV-ARD through the data cutoff date in Study 1013 was submitted. These complete data were obtained in a timely manner for review through an information request.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Safety, efficacy and immunogenicity data from six studies were provided in this application to support licensure of RSVpreF. All clinical trials were approved by Ethics Committees; followed the International Council on Harmonisation-Good Clinical Practice (GCP) guidelines; conformed to the Declaration of Helsinki; and informed, written consent was obtained from all participants as per GCP requirements and contained all the essential elements as stated in 21 CFR 50.25. Potential or actual issues regarding the conduct of the study were investigated and, where possible, corrective and preventive actions were taken.

Bioresearch monitoring (BIMO) inspections were issued for 3 clinical study sites that participated in the conduct of Study 1013. The inspections did not reveal substantive issues that impact the data submitted in this application.

3.3 Financial Disclosures

Covered clinical studies: C3671001, C3671002, C3671004, C3671013, C3671014, WI257521
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 2,372
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1 Is an attachment provided with details of the disclosable financial interests/arrangements? ☒ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☒ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 52 Is an attachment provided with the reason? ☒ Yes ☐ No (Request explanation from applicant)

Reviewer Comment

Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators, includes a list of 52 of 2,372 clinical investigators for whom required financial information could not be obtained. According to Pfizer's procedures for obtaining financial information all investigators are assessed for equity interest, significant payments of other sorts, other compensation by the Applicant and propriety interest. All significant payments of other sorts are checked via internal Pfizer procedures. The Applicant conducted a due diligence process where additional attempts were performed (via mail, phone, fax, and/or e-mail) to meet the recommendations mentioned within the FDA's Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators for certifying Due Diligence. No additional financial concerns were identified by the BIMO reviewer. It is not expected that financial bias impacted the studies performed to support licensure of RSVpreF.

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

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing were reviewed and determined to support licensure. Facility information and data provided in the BLA were reviewed by CBER CMC reviewers and found to be sufficient and acceptable.

4.2 Assay Validation

The relative prefusion content (potency) tests for the final drug product and clinical serologic assays were adequate to support licensure as determined by CBER Product and Assay reviewers.

4.3 Nonclinical Pharmacology/Toxicology

The CBER Toxicology reviewer considered the nonclinical toxicology data to be adequate to support licensure.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

RSV fusion (F) protein can exist in two antigenically distinct forms – prefusion and postfusion. Prefusion F (preF) is the active form of the protein and is capable of mediating fusion of virus and host cell membranes during cell entry. Serum neutralizing antibodies against the F protein are associated with reduced risk of RSV disease. RSVpreF vaccine induces an immune response against preF that protects against lower respiratory tract disease caused by RSV.

4.5 Statistical

The CBER statistical reviewer confirmed the key statistical analyses for safety and efficacy and found no major statistical issues that would impact the interpretation of the data and conclusions.

4.6 Pharmacovigilance

Pfizer will perform routine pharmacovigilance for all adverse events and must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). Pfizer will also perform enhanced pharmacovigilance activities for GBS and supraventricular arrhythmias, which includes expedited (15-day) reporting regardless of seriousness and a summary and analysis of cumulative data in the Periodic Adverse Experience Report (PAER). GBS and supraventricular arrhythmia reports must be submitted as 15-day expedited reports for 3 years following the date of product licensure. In addition, the Applicant is required to conduct a postmarketing, retrospective cohort study utilizing Centers for Medicare and Medicaid Services (CMS) claims data, to evaluate the serious risk of GBS among 1.5 million older adults vaccinated with Abrysvo in the United States, as a postmarketing requirement (PMR). The sponsor commits to evaluating the potential risk of atrial fibrillation in an active surveillance study among older adults vaccinated with Abrysvo, utilizing data from the Veterans Affairs Health System, as a postmarketing commitment (PMC). The sponsor also plans to conduct an active surveillance safety study among immunocompromised adults vaccinated with Abrysvo, utilizing data from the Veterans Affairs Health System, as a voluntary sponsor study.

The DPV reviewer has reviewed the final PVP submitted by the Applicant and has found it to be acceptable.

4.7 Devices

The terminally sterilized 1 mL standard glass ungraduated pre-filled syringe (PFS) containing sterile water for reconstitution was reviewed by the Office of Medical Products and Tobacco reviewer and was found to be an acceptable device for administration of the vaccine.

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

5.1 Review Strategy

This BLA included clinical data from Study 1013 to support efficacy and safety of RSVpreF in adults 60 years of age and older. Supportive data from 5 additional trials were also submitted to the BLA and are outlined in Table 1 and individually summarized in Section 6.

The clinical, labeling, and financial disclosure information sections of the application were reviewed with detailed analyses of the main trials' study reports and pertinent line listings, case report forms, and datasets.

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

The following amendments were reviewed in support of this application (listed by modules):

- Amendment 0: Modules 1, 2, and 5 (Original submission and Priority Review Designation request)
- Amendment 3: Modules 1 and 5
- Amendment 6: Modules 1 and 5
- Amendment 7: Module 1
- Amendment 8: Modules 1 and 5
- Amendment 9: Modules 1 and 5
- Amendment 10: Modules 1 and 5
- Amendment 11: Module 1
- Amendment 12: Module 1 and 5
- Amendment 13: Module 1
- Amendment 14: Modules 1 and 5
- Amendment 15: Modules 1 and 5
- Amendment 16: Module 1
- Amendment 17: Modules 1 and 5
- Amendment 20: Module 1
- Amendment 23: Modules 1 and 5
- Amendment 24: Module 1
- Amendment 27: Module 1
- Amendment 29: Module 1
- Amendment 33: Module 1
- Amendment 36: Modules 1 and 5
- Amendment 37: Modules 1 and 5
- Amendment 38: Module 1
- Amendment 39: Module 1
- Amendment 40: Module 1
- Amendment 41: Module 1
- Amendment 42: Module 1 and 5
- Amendment 43: Module 1
- Amendment 44: Module 1
- Amendment 45: Module1
- Amendment 48: Module 1
- Amendment 49: Module 1
- Amendment 50: Module 1

- Amendment 60: Module 1
- Amendment 63: Module 1
- Amendment 64: Module 1
- Amendment 66: Module 1
- Amendment 67: Module 1 and 5
- Amendment 69: Module 1
- Amendment 70: Module 1
- Amendment 71: Module 1
- Amendment 72: Module 1
- Amendment 73: Module 1

5.3 Table of Studies/Clinical Trials

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of RSVpreF

Study Number	**Study Type**	**Total Randomized (N) Total Final RSVpreF (n) Age Group**	**Test Product(s)***
C3671013	Phase 3 Efficacy, Immunogenicity, Safety	N=34,383 n=17,215 Adults ≥60 years	RSVpreF 120 µg (final)
C3671014	Phase 3, Lot-to-Lot, Safety, Immunogenicity	N=993 n=745 Adults 18-49 years	RSVpreF 120 µg (final)
C3671001	Phase 1/2 First-in-human, Dose-finding, Safety, Immunogenicity	N=1,235 n=186 Adults 18-85 years	RSVpreF 120ug (final), RSVpreF (60 µg, 120 µg, 240 µg) with $Al(OH)_3$ adjuvant, or without adjuvant. Subset: co-ad with SIIV; Subset: re-vaccination at 1 year
C3671002	Phase 1 Dose-finding, Safety, Immunogenicity	N=317 n=0 Adults 65-85 years	RSVpreF (60 µg, 120 µg, 240 µg) with $Al(OH)_3$ adjuvant, or with CpG/$Al(OH)_3$ adjuvant, or without adjuvant (240 µg only). Subset with co-ad with SIIV
C3671004	Phase 2 Safety, Immunogenicity	N=713 n=282 Non-pregnant women 18-49 years	RSVpreF 120 µg (final), RSVpreF (120 µg, 240 µg) with $Al(OH)_3$ adjuvant, or without adjuvant Subset with co-ad with Tdap
WI257521	Phase 2 Human Challenge Study; Safety, Immunogenicity, Efficacy	N=70 n=35 Adults 18-50 years	RSVpreF 120 µg (final)

Source: STN 125769/0 tabular-listing.pdf, Table 5 in response to FDA IR #12
Abbreviations: $Al(OH)_3$=aluminum hydroxide; SIIV=seasonal inactivated influenza vaccine; co-ad=concomitant administration; n=number of participants who received at least 1 dose of final RSVpreF; final=final formulation of RSVpreF (120 µg without adjuvant)
*Only the active vaccine(s) is listed. Each of the studies also included a placebo group

5.4 Consultations

5.4.1 Advisory Committee Meeting

The Vaccine and Related Biological Products Advisory Committee convened on February 28, 2023, to discuss and vote on whether the available efficacy and safety data support licensure of Abrysvo for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older. When asked whether the available data were adequate to support the safety of Pfizer's candidate RSV vaccine in adults 60 years of age and older, of 12 committee members, 7 voted yes, 4 voted no and 1 abstained. When asked whether the available data were adequate to support the effectiveness of Pfizer's candidate RSV vaccine in adults 60 years of age and older, of 12 committee members, 7 voted yes, 4 voted no, and 1 abstained. The committee noted limitations of the clinical development of RSVpreF including limited efficacy data in elderly individuals older than 80 years of age or individuals with major risk factors for RSV, lack of data on the immune response to RSVpreF after concomitant administration with other vaccines for the target population, and lack of safety and effectiveness data after revaccination. The committee also noted that the potential safety signal of GBS detected in two participants, one of which was life-threatening, and the imbalance in cases of atrial fibrillation between the two groups. Despite the limitations and concerns, the committee generally agreed that the available data was supportive of the proposed indication.

5.5 Literature Reviewed

Acosta, P et al. (2016). Brief history and characterization of enhanced respiratory syncytial virus disease. Clinical and Vaccine Immunology. March 7;23(3):189-195. doi: 10.1128/CVI.00609-15

Centers for Disease Control and Prevention (CDC). (2022). RSV Research and Surveillance. Accessed October 10, 2022.

Chin, J et al. (1969). Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. American Journal of Epidemiology. Apr;89(4):449-63. doi: 10.1093/oxfordjournals.aje.a120957.

Falsey, AR, Hennessey, PA, Formica, MA, Cox, C., & Walsh, EE. (2005). Respiratory syncytial virus infection in elderly and high-risk adults. The New England Journal of Medicine, 352(17), 1749–1759. doi: 10.1056/NEJMoa043951.

Falsey, AR; Singh, HK; Walsh EE. (2006). Serum antibody decay in adults following natural respiratory syncytial virus infection. J.Med. Virol., 78(11), 1493-1497.

Fulginiti, VA et al. (1969). Respiratory virus immunization. I. A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. American Journal of Epidemiology. Apr;89(4):435-48. doi: 10.1093/oxfordjournals.aje.a120956.

Hall, CB, Walsh, EE, Long, CE, & Schnabel, KC. (1991). Immunity to and frequency of reinfection with respiratory syncytial virus. The Journal of Infectious Diseases, 163(4), 693–698. doi: 10.1093/infdis/163.4.693.

Hansen CL, Chaves SS, Demont C, Viboud C. (2022). Mortality associated with influenza and respiratory syncytial virus in the US, 1999-2018. JAMA Netw Open.;5(2):e220527. doi:10.1001/jamanetworkopen.2022.0527.

Johnson KM, Bloom HH, Mufson MA, and Chanock RM. (1962). Natural reinfection of adults by respiratory syncytial virus. Possible relation to mild upper respiratory disease. The New England Journal of Medicine, 267, 68–72. doi: 10.1056/NEJM196207122670204.

Kapikian et al. (1969). An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. American Journal of Epidemiology. Apr;89(4):405-21. doi: 10.1093/oxfordjournals.aje.a120954.

Kampmann, et al. (2023). Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. The New England journal of medicine, 388(16),1451–1464. doi: 10.1056/NEJMoa2216480

Kim, H et al. (1969). Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. American Journal of Epidemiology. Apr;89(4):422-34. doi: 10.1093/oxfordjournals.aje.a120955.

Sejvar, JJ, Baughman, AL, Wise, M, & Morgan, OW. (2011). Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology, 36(2), 123–133. doi: 10.1159/000324710.

Yen C, Wei K, Wang W, Huang Y, Chang Y. (2022). Risk of Guillain-Barré Syndrome among older adults receiving influenza vaccine in Taiwan. JAMA Netw Open.;5(9):e2232571. doi:10.1001/jamanetworkopen.2022.32571.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study C3671013

NCT05035212
Title: “A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults”

Study Overview: This study is an ongoing, multi-country study designed to evaluate the efficacy, immunogenicity, and safety of RSVpreF in prevention of lower respiratory tract disease due to RSV (RSV-LRTD) in healthy individuals 60 years of age and older, as compared to placebo. The study was initiated August 31st, 2021, and is planned to be conducted through 2 RSV seasons. This BLA submission contains efficacy and safety data from the first RSV season, based on the protocol pre-specified interim analysis. Only study objectives and results available at the time of this BLA submission are described below.

6.1.1 Objectives

Primary Objectives

1. Efficacy: To demonstrate the efficacy of RSVpreF in preventing RSV-LRTD in the first RSV season following vaccination.
   Endpoint: RSV-LRTD cases (see Table 2 for case definitions)
   a. VE, defined as the relative risk reduction of first-episode RSV-LRTD cases with ≥2 LRTD signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination).

- ***Statistical Criterion for Success:*** Lower bound of the VE CI[1] is >20% against first episode of RSV-LRTD with ≥2 symptoms (as defined by ≥2 of the 5 LRTD signs/symptoms in the first RSV season)

b. VE, defined as the relative risk reduction of first-episode RSV-LRTD cases with ≥3 LRTD signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination).
   - ***Statistical Criterion for Success:*** Lower bound of the VE CI[1] is VE >20% against first episode of RSV-LRTD with ≥3 symptoms (as defined by ≥3 of the 5 LRTD signs/symptoms in the first RSV season)

2. Safety: To describe the safety profile of RSVpreF as measured by the percentage of participants reporting local reactions, systemic events, AEs, and SAEs.
   Endpoint:
   a. The proportion of participants reporting solicited local reactions within 7 days following study intervention administration in a subset of participants.
   b. The proportion of participants reporting solicited systemic events within 7 days following study intervention administration in a subset of participants.
   c. The proportion of participants reporting AEs through 1 month following study intervention administration.
   d. The proportion of participants reporting NDCMCs throughout the study.
   e. The proportion of participants reporting SAEs throughout the study

Secondary Objectives

1. Efficacy: To describe the efficacy of RSVpreF in preventing RSV-ARD
   Endpoint: RSV-ARD cases
   a. VE, defined as the relative risk reduction of first-episode RSV-ARD cases in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination)

Additional secondary objectives evaluated vaccine efficacy in preventing LRTD, severe RSV-LRTD (RSV-sLRTD), and ARD at each RSV season and across 2 RSV seasons following vaccination, and immunogenicity (neutralizing and binding antibody responses) from 1-month post-vaccination through end-of-Season 2. These analyses will be conducted with the end-of-Season 1 analysis and/or the end-of-study analysis and will not be discussed in this memorandum.

6.1.2 Design Overview

Study 1013 is an ongoing, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of RSVpreF in individuals 60 years of age and older. Participants were randomized 1:1 to receive a single intramuscular injection of RSVpreF or placebo, with randomization stratified by age group:

- 60-69 years (at least 6,000 participants)
- 70-79 years (at least 6,000 participants)
- 80 years and older (at least 800 participants)

[1] The primary efficacy objective was considered met if the lower bound of the VE CI was >20% for RSV-LRTD 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.

Both healthy adults and adults with stable chronic diseases were enrolled, including participants with stable chronic cardiopulmonary conditions such as chronic obstructive pulmonary disease (COPD), asthma, or congestive heart failure. The study is designed to be conducted through 2 RSV seasons, with the primary efficacy analysis to be assessed during the first RSV season.

All study participants had 5 study visits that had the following major study activities-

- Visit 1: Day 1
  - Blood sampling, single vaccination with RSVpreF or placebo
- Visit 2: Days 28-36 post-vaccination
  - 1 month follow up-blood sampling, e-Diary card transcription, collection of mid-turbinate nasal swabs if ≥1 ARD symptoms are present
- Visit 3: Day 175-189 post-vaccination
  - 6 month follow up- e-Diary card transcription, collection of mid-turbinate nasal swabs if ≥1 ARD symptoms are present
- Visit 4: Prior to the start of season 2
  - Blood sampling, e-Diary card transcription, collection of mid-turbinate nasal swabs if ≥1 ARD symptoms are present
- Visit 5: At 4 weeks post-end of season 2
  - e-Diary card transcription, collection of mid-turbinate nasal swabs if ≥1 ARD symptoms are present

6.1.3 Population

Eligibility Criteria

Individuals were eligible for inclusion if they met all the following criteria: males and females (not of childbearing potential), ≥60 years of age who were healthy (those with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, could be included).

Individuals were not eligible for inclusion in the study if they met any of the following exclusion criteria:

- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- History of severe AR associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention(s) or any related vaccine.
- Serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the participant from participating in the study.
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
- Participation in other studies involving an investigational product within 28 days prior to consent and/or through and including the 6-month follow-up visit (Visit 3). Note: This criterion does not apply to participants who are participating in a follow-up period for another study involving a study intervention that is an investigational drug or vaccine, if receipt of the last dose was at least 6 months prior to consenting for this study and there

is no further dosing anticipated from the previous study during the participant's participation in this study.
- Individuals who receive chronic systemic treatment with immunosuppressive therapy, including cytotoxic agents, monoclonal antibodies, systemic corticosteroids, or radiotherapy, e.g., for cancer or an autoimmune disease, from 60 days before study intervention administration or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled in the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intra-bursal, or topical (skin or eyes) corticosteroids are permitted.
  Note: Participants with COPD or asthma were enrolled if chronic corticosteroids do not exceed a dose equivalent to 10 mg/day of prednisone.
- Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration.
- Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation.
- Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

6.1.4 Study Treatments or Agents Mandated by the Protocol

RSVpreF: investigational RSV vaccine

- Dose and route of administration: 1 mL intramuscular
- Formulation: Equal amounts of two stabilized RSV prefusion F antigens derived from virus subgroups A and B. The total dose of the RSV drug product was 120 µg of the RSV prefusion F antigen.
- Presentation: Lyophilized white powder in a glass vial with a PFS containing diluent of sterile Water for Injection (WFI)
- Lots: EN3320

Placebo: a lyophile match to the vaccine, which consists of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients. The physical appearance of the reconstituted RSVpreF and placebo were similar.

- Lots: DC8153, FF4813

Diluent: sterile WFI

- Lot: EF0408

6.1.5 Directions for Use

For this study RSVpreF was supplied as a lyophilized white powder in a glass vial; for reconstitution, a PFS containing diluent of sterile WFI, and a vial adapter were used.

6.1.6 Sites and Centers

There were 240 sites in the United States (US), South Africa, Japan, Canada, Finland, the Netherlands, and Argentina with a Safety population of 34,284 participants. There were 158 US sites with a Safety population of 20,501 US participants.

6.1.7 Surveillance/Monitoring

Study Monitoring

Study oversight included Institutional Review Board or Independent Ethics Committee review and approval of the study protocol, any amendments, the informed consent, and other pre-approval information. This study used a data monitoring committee (DMC), which was independent of the study team and included only external members to review unblinded cumulative safety data throughout the study and the interim analysis for efficacy. A separate unblinded external vendor performed case split(s) between RSVpreF and placebo at the interim analysis and communicated the results to the DMC (which used a reporting statistician who was independent of the Applicant). Additionally, an unblinded Pfizer clinician met with the DMC. Per protocol, after DMC declared study success of first-episode RSV-LRTD cases with ≥2 symptoms, the unblinded clinician communicated internally so that the study was unblinded to specific Applicant staff for this interim analysis. Study centers were monitored by Pfizer and (b) (4), a clinical research organization.

Safety Monitoring

E-Diaries were used to record safety data. In a subset of participants (e-diary subset safety population), solicited reactions were recorded. Solicited local ARs (pain, redness, or swelling at injection site) were recorded from Day 0 to Day 7. Solicited systemic ARs of fatigue, headache, muscle pain, joint pain, nausea, vomiting, diarrhea, and fever were collected from Day 0 to Day 7. In all participants, all unsolicited AEs occurring from Day 0 through 1 month after vaccination as well as through study end were recorded. Newly Diagnosed Chronic Medical Condition (NDCMCs), and SAEs were collected and recorded from the first receipt of study vaccine throughout the entire study. SAEs that were related to the study vaccine(s) were collected and recorded from the time of the first study vaccination throughout the entire study.

Investigators followed participants with SAEs or participants who were withdrawn as result of an AE until the event had resolved, stabilized, or until the event was otherwise explained, or the participant was lost to follow-up. Those with other non-serious AEs were followed until resolution or study end unless they were lost to follow-up.

Efficacy Monitoring

Starting 14 days after study vaccination (Study Day 15), all participants were actively monitored for onset of acute respiratory disease (ARD) symptoms. If the participant experienced 1 or more ARD symptoms (defined in Table 2), the participant was instructed to self-collect mid-turbinate nasal swabs, optimally on both ARD-Day 2 and ARD-Day 3 (where ARD-Day 1 is the date of onset of symptoms). An illness visit was to be conducted within 7 days of onset of symptoms. The swabs were collected by the study site and sent to a central laboratory for reverse transcription polymerase chain reaction (RT-PCR) testing for RSV. Participants were monitored for onset of RSV-associated lower respiratory tract disease (RSV-LRTD) that was defined as ARD with ≥2 or ≥3 LRTD signs/symptoms lasting more than 1 day during the same illness (defined in Table 2).

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1 above and Section 6.1.9 below.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

Target enrollment was approximately 45,000 participants to be randomized to receive either RSVpreF or placebo in a 1:1 ratio. This was an event-driven study with a target of 59 first-episode evaluable RSV-LRTD cases with ≥2 symptoms.

Methods

For the primary efficacy objective and key secondary objective, RSVpreF was compared to placebo, testing the following 3 hypotheses, where H_0 and H_a represent the null and alternative hypotheses, respectively:

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

VE was defined as VE = 100 × (1 - risk ratio). The 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 were 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 was considered met if the lower bound of the VE CI was >20% for RSV-LRTD 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.

Case Definitions

The case definition for the efficacy endpoints for Study 1013 are shown in Table 2. The definition of laboratory-confirmed RSV infection includes RSV RT-PCR–positive test result by Pfizer central laboratory, or an 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 was not available. Testing results were based on samples taken within 7 days after symptoms onset.

Table 2. Case Definitions, Study 1013

Study Endpoint	Study Definition
RSV-ARD	An illness involving 1 or more of the following 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 **AND** laboratory-confirmed RSV infection within 7 days of ARD symptom onset
RSV-LRTD with ≥2 symptoms	ARD with ≥2 of the following LRTD signs/symptoms lasting more than 1 day during the same 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) **AND** laboratory-confirmed RSV infection within 7 days of ARD symptom onset.
RSV-LRTD with ≥3 symptoms	ARD with ≥3 of the following LRTD signs/symptoms lasting more than 1 day during the same 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) **AND** laboratory-confirmed RSV infection within 7 days of ARD symptom onset.
RSV-sLRTD	Meeting RSV-LRTD criteria plus at least 1 of the following: • Hospitalization due to RSV-LRTD • New/increased oxygen supplementation • New/increased mechanical ventilation, including continuous positive airway pressure

Source: STN 125769/0 Study C3671013 Clinical Study Report Table 3
Abbreviations: ARD=acute respiratory disease; RSV-ARD=RSV-associated acute respiratory disease; LRTD=lower respiratory tract disease; RSV-LRTD=RSV-associated lower respiratory tract disease; RSV=respiratory syncytial virus; RSV-sLRTD=severe RSV-LRTD

Analysis Timing

The primary efficacy objective evaluated the efficacy of RSVpreF to prevent RSV-associated RSV-LRTD (see Table 2) with ≥2 symptoms starting at least 14 days after vaccination across the first RSV season. The study design was event driven with the primary analysis originally planned to be conducted following the occurrence of 59 evaluable first-episode RSV-LRTD cases with ≥2 symptoms. An interim analysis of the primary endpoint was planned to be conducted following the occurrence of at least 29 evaluable first-episode RSV-LRTD cases with ≥2 symptoms. The primary efficacy objective would be achieved if the lower bound of the CI for VE against RSV-LRTD with ≥2 symptoms is >20% at either the interim or primary analysis based on the Pocock-adjusted CI controlling the Type I error rate at a one-sided 2.5%.

At the interim analysis, if there were at least 15 evaluable first-episode RSV-LRTD cases with ≥3 symptoms, then this second primary endpoint would also be evaluated as part of the interim analyses. In addition, if there were at least 12 evaluable first-episode severe RSV-LRTD cases in the 1st RSV season, then this secondary endpoint would also be evaluated.

Additional protocol-specified analyses include the end-of-Season 1 analysis, to be conducted after the first RSV season ends for all participants included in the study, and the end-of-study analysis, to be conducted after all participants have completed the study.

Reviewer Comment

1. For this study, an interim analysis was conducted when 44 first-episode LRTD RSV cases with ≥2 symptoms occurred in the first RSV season through the ARD surveillance cutoff date of July 8, 2022. There were 16 first-episode RSV-LRTD cases with ≥3 symptoms using the same cutoff date; therefore, the interim analysis of this second primary endpoint was also conducted.

2. The minimum number of first-episode severe RSV-LRTD cases had not accrued as of the cutoff date, and therefore, this key secondary endpoint was not included with the interim analysis. Not all participants had reached end-of-Season 1 as of the data cutoff date, thus the end-of-Season 1 analysis and the end-of-study analysis have not yet been conducted. All participants will remain in blinded follow-up through study completion. Additional analyses that are planned to be conducted include the following secondary and exploratory objectives: efficacy in prevention of RSV-sLRTD, immunogenicity, rates, descriptions of LRTD associated healthcare resource utilization, and vaccine efficacy across both 1 and 2 seasons. The approach to submission of data in support of the BLA was discussed with the Applicant and was agreed upon with FDA prior to the submission of the application.

Sensitivity Analyses/Subgroup Analyses

The following analyses were also performed:

- Two statistical methods were used as sensitivity analysis on the VE and the corresponding CI:
  - One method adjusted the follow-up time (1-incidence ratio), and the other method utilized the time to the first episode of case onset (1-hazard ratio).
- For the primary endpoint, analyses were performed for RSV A positive and RSV B positive, separately. These subset analyses were also performed for RSV-ARD.
- Selected efficacy endpoints (first episode of RSV-LRTD cases with ≥2 and ≥3 symptoms and RSV-ARD cases), local reactions, systemic events, and AEs were summarized by age group (60-69 years, 70-79 years, and ≥80 years), sex, race, ethnicity, risk status, and country.

Protocol Amendments

The original protocol was dated July 7, 2021.

Protocol Amendment 1 (November 23, 2021) included the following relevant changes:

- Updated the US IND number and added the ClinicalTrials.gov identification number. To file with other studies in older adults.
- Added a paragraph describing the role of a group of internal blinded case reviewers for efficacy endpoint blinded data review to clarify their role.
- Updated RSV positive test definition to remove “(Any positive result, either from testing at the central laboratory or from a local NAAT in a certified laboratory, will be considered an RSV-positive result, regardless of whether the results are the same or not).”
- Added a definition for RSV-ARD.

- Additional clarifications, updates, and typographical edits were made.

Protocol Amendment 2 (March 23, 2022) included the following relevant changes:

- Updated the participant enrollment wording from "~30,000" to "up to 45,000," because the enrollment could go up to 45,000 participants to achieve the required number of cases.
- Clarified the risk of study procedures associated with nasal swab for efficacy study.
- Removed the bullet referring to monitoring cases of COVID-19 as adverse events of special interest (AESIs) as these will not be captured as AESIs.
- Updated the AESI section to remove the requirement of collecting positive SARS-CoV-2 as an AESI.
- Updated the first paragraph to provide clarification that the swabs collected within 7 days after symptom onset will be tested, and local test results will be used only when central laboratory results are not available.
- Added the multiplicity adjustment due to the additional 2 hypothesis tests.
- Added RSV-LRTD with ≥3 LRTD symptoms.
- Clarified severe RSV-LRTD as a key secondary objective.
- Clarified the primary estimands used for the interim analysis.
- Additional clarifications, updates, and typographical edits were made.

Protocol Amendment 3 (July 7, 2022) included the following relevant changes:

- Given the short time interval between interim analysis and the end-of-Season 1 analysis, the analysis of exactly 59 cases was removed.
- Removed Season 3 as the study will end at the end of Season 2.
- Additional clarifications, updates, and typographical edits were made.

Changes in the Conduct of the Study and Planned Analyses

Issues related to study conduct included the following:

- Due to a low compliance rate of study conduct at 1 study site (Site 1227), additional sensitivity analyses that excluded this site were performed for the safety evaluations of local reactions, systemic events, AEs at 1 month and AEs at data cut-off. These analyses showed similar results as the full study analyses. As no RSV cases were reported at this site, the Applicant reports there was no impact to the efficacy analyses.

  Reviewer Comment
  Based on the sensitivity analyses performed by the Applicant, the inclusion of participants enrolled in this study site is not likely to affect the overall conclusions of the study.

6.1.10 Study Population and Disposition

A total of 35,971 participants were enrolled in the study. This BLA submission consists of data from the start of enrollment on August 31, 2021, through data cutoff date of July 14, 2022, for safety and data cutoff date of July 8, 2022, for efficacy (ARD surveillance cutoff, plus additional 6 days allowed for nasal swab collection). The first participant was enrolled on August 31, 2021.

6.1.10.1 Populations Enrolled/Analyzed

Populations used for the study analyses are defined in Table 3. The Evaluable Efficacy Population was the primary population used for the analyses of efficacy. The e-Diary Subset Safety Population was used for the analyses of solicited safety and the Safety Population was used for all remaining safety analyses.

Table 3. Analysis Populations

Population	Description
Safety Population	All enrolled participants who received the study intervention.
Modified Intent-to-treat (mITT) Efficacy Population	All participants who were randomized and received study intervention.
Evaluable Efficacy Population	All study participants who met the following criteria: • Were eligible for the study. • Received study intervention to which they were randomized (RSVpreF or placebo). • A minimum follow-up through Day 15 after vaccination (Day 1 is the day of vaccination). • Had no major protocol violations before the symptom onset date of the confirmed ARD or LRTD case.
e-Diary Subset Safety Population	All participants included in the reactogenicity subset who received the study intervention and with at least 1 day of e-diary data transferred.

Source: STN 125769/0 Study C3671013 Clinical Study Report Table 4

6.1.10.1.1 Demographics

The demographics of participants in the Safety Population are shown in Table 4. The median age of participants in the Safety Population was 67 years, with 31.8% of participants between the ages of 70-79 years and 5.6% of participants ≥80 years of age at the time of study vaccination. Overall, most participants were White (78.3%), non-Hispanic/Latino (62.6%), and located in the US (59.8%). The demographic characteristics were similar between the vaccine and placebo groups. The demographics of the Safety Population also generally reflected what was observed in the Evaluable Efficacy Population (not shown) and the eDiary Subset Safety Population (not shown).

Table 4. Demographic and Baseline Characteristics, Safety Population, Study 1013

Characteristic	RSVpreF N=17215	Placebo N=17069
Sex, n (%)	--	--
Male	8800 (51.1)	8601(50.4)
Female	8415 (48.9)	8468 (49.6)
Age[a], years	--	--
Mean age (SD)	68.3 (6.14)	68.3 (6.18)
Median age (min, max)	67 (59, 95)	67 (60, 97)
60-69 years	10756 (62.5)	10680 (62.6)
70-79 years	5488 (31.9)	5431 (31.8)
≥80 years	970 (5.6)	958 (5.6)

Characteristic	RSVpreF N=17215	Placebo N=17069
Race, n (%)	--	--
African American/Black	2206 (12.8)	2207 (12.9)
American Indian or Alaska Native	44 (0.3)	36 (0.2)
Asian	1352 (7.9)	1333 (7.8)
Native Hawaiian or other Pacific Islander	10 (<0.1)	15 (<0.1)
White	13475 (78.3)	13360 (78.3)
Multiracial	44 (0.3)	36 (0.2)
Unknown	28 (0.2)	32 (0.2)
Not reported	56 (0.3)	50 (0.3)
Ethnicity, n (%)	--	--
Hispanic/Latino	6384 (37.1)	6260 (36.7)
Not Hispanic/Latino	10740 (62.4)	10715 (62.8)
Not reported	91 (0.5)	94 (0.6)
Country, n (%)	--	--
USA	10319 (59.9)	10182 (59.7)
Argentina	3660 (21.3)	3657 (21.4)
Japan	1159 (6.7)	1156 (6.8)
The Netherlands	687 (4.0)	681 (4.0)
Canada	509 (3.0)	506 (3.0)
South Africa	495 (2.9)	497 (2.9)
Finland	386 (2.2)	390 (2.3)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 8
Abbreviations: N=total number of participants in the specified group, or the total sample; includes one participant who received RSVpreF at the age of 59 years; n=number of participants with the specified characteristic; SD=standard deviation
The Safety Population included all enrolled participants who received the study intervention;
Note: Participants were allocated to the vaccine groups as received; 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.
a. For participants who received multiple vaccinations due to multiple enrollments, analysis was based on the first participant ID at receipt of RSVpreF (RSVpreF group), or first participant ID at receipt of placebo (placebo group).

One participant in the RSVpreF group did not meet the study inclusion criteria of being ≥60 years of age and was 59 years old at the time of study vaccination. This participant was excluded from the analyses of efficacy and reactogenicity but was included in the analyses of unsolicited safety.

> Reviewer Comment
> Given the proximity of age to the inclusion criteria (participant was vaccinated 3 days before turning 60) and given the large study size, inclusion of this individual is not expected to affect the overall study conclusions.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of participants in the Safety Population (51.6%) had ≥1 pre-specified at-risk condition, the most common of which was diabetes (19%). Among all participants, 15.3% had ≥1 chronic cardiopulmonary condition, the most common of which was asthma (8.9%). The proportions and types of at-risk conditions were balanced between the RSVpreF and placebo groups.

Table 5. Baseline At Risk Conditions, Safety Population, Study 1013

Prespecified At-Risk Condition[a]	RSVpreF N=17215 n (%)	Placebo N=17069 n (%)
With ≥1 prespecified significant condition	8867 (51.5)	8831 (51.7)
Current tobacco use	2642 (15.3)	2571 (15.1)
Diabetes	3224 (18.7)	3284 (19.2)
Lung disease[b]	1956 (11.4)	2040 (12.0)
Heart disease[c]	2221 (12.9)	2233 (13.1)
Liver disease	335 (1.9)	329 (1.9)
Renal disease	502 (2.9)	459 (2.7)
With ≥1 chronic cardiopulmonary condition	2595 (15.1)	2640 (15.5)
Asthma	1541 (9.0)	1508 (8.8)
Chronic obstructive pulmonary disease (COPD)	1012 (5.9)	1080 (6.3)
Congestive heart failure (CHF)	293 (1.7)	307 (1.8)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 8
Abbreviations: N = total number of participants in the specified group, or the total sample; includes one participant who received RSVpreF at the age of 59 years; n = number of participants with the specified characteristic.
The Safety Population included all enrolled participants who received the study intervention
Note: Participants were allocated to the vaccine groups as received; 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.
a. For participants who received multiple vaccinations due to multiple enrollments, any reported prespecified medical conditions from all participant IDs were included.
b. Includes COPD and other lung disease.
c. Includes CHF and other heart disease.

6.1.10.1.3 Participant Disposition

Disposition of Study 1013 participants who contributed to the analyses of efficacy are presented in Table 6. Of the 35,971 enrolled participants, 34,383 were randomized to receive RSVpreF (n=17,197) or placebo (n=17,186). The mITT Efficacy Population included a total of 33,987 participants. The most common reason for exclusion from the mITT Efficacy Population was due to vaccination after the July 8, 2022, efficacy cutoff date for ARD surveillance (0.9% of all randomized participants).

The Evaluable Efficacy Population, used for the primary analyses of efficacy, included a total of 32,614 participants, with 16,306 RSVpreF recipients and 16,308 placebo recipients. The percentages of participants excluded and reasons for exclusion from the Evaluable Efficacy Population were similar between the two treatment groups. The most common reason for exclusion (4.0% in both groups) was efficacy surveillance duration of less than 15 days, mostly due to participants receiving the vaccine after or ≤14 days before the efficacy cutoff date of July 8, 2022.

In the study, 213 participants received multiple study vaccinations (i.e., RSVpreF or placebo) due to multiple enrollments at different investigational sites. The proportion of those who received multiple vaccinations were as follows: 75.6% (n=161) received two vaccinations, 18.3% (n=39) received three vaccinations, 5.6% (n=12) received four vaccinations, and 0.5% (n=1) received six vaccinations. Of these 213 participants, 173 (81.2%) received at least one dose of RSVpreF and 40 (18.8%) received only doses of placebo. Participants who received multiple study vaccinations were excluded from the Evaluable Efficacy Population.

Table 6. Participant Disposition, All Randomized, Study 1013

Population	RSVpreF N=17197 n (%)	Placebo N=17186 n (%)
Randomized Set	17197 (100.0)	17186 (100.0)
Modified Intent-To-Treat (mITT) Efficacy Population	16999 (98.8)	16988 (98.8)
Excluded from mITT efficacy population	198 (1.2)	198 (1.2)
Reason for exclusion	--	--
Did not receive study vaccine	49 (0.3)	50 (0.3)
Vaccinated after surveillance cutoff date (July 8, 2022)[a]	149 (0.9)	148 (0.9)
Evaluable Efficacy Population	16306 (94.8)	16308 (94.9)
Excluded from the Evaluable Efficacy Population	891 (5.2)	878 (5.1)
Reason for exclusion[b]	--	--
Not eligible for this study	42 (0.2)	41 (0.2)
Did not receive study vaccine	49 (0.3)	50 (0.3)
Received study vaccine but not as randomized	112 (0.7)	110 (0.6)
Received multiple vaccinations due to multiple enrollments at different sites	109 (0.6)	104 (0.6)
Efficacy surveillance duration was less than 15 days (<14 days after vaccination)[c]	693 (4.0)	687 (4.0)
≥1 Important protocol deviation prior to symptom onset date of confirmed RSV-ARD case	72 (0.4)	68 (0.4)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 6 & 7.
Abbreviations: RSV-ARD=acute respiratory disease associated with respiratory syncytial virus; mITT=modified intent to treat; N=total number of participants randomized to the group; one participant who received RSVpreF at the age of 59 was included in the randomized set and mITT efficacy population, but excluded from the evaluable efficacy population; n=number of participants with the specified characteristic; percentages based on all randomized
a. Due to data cutoff for efficacy (ARD surveillance) of July 8, 2022
b. Participants may have been excluded for more than 1 reason
c. Including participants vaccinated after surveillance cutoff date of July 8, 2022
The mITT efficacy population included all participants who were randomized and received study intervention.
The evaluable efficacy population included all study participants who were elig ble 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 ARD or LRTD case.

Disposition of Study 1013 participants who contributed to the analyses of safety are presented in Table 7. A total of 34,284 (99.7%) of the randomized participants received study intervention and were included in the Safety population, consisting of 17,215 participants in the RSVpreF group and 17,069 participants in the placebo group. Of these participants, 77.0% (13,273 in the RSVpreF group and 13,122 in the placebo group) have completed at least 6 months of follow-up post vaccination. The eDiary Subset Safety Population, used for the analyses of solicited safety, included 3,630 and 3,539 participants in the RSVpreF and placebo groups, respectively.

A total of 1,810 participants (5.3%) withdrew from the study after receipt of study intervention. The reasons for withdrawal and proportions of participants withdrawn were similar between the RSVpreF and placebo groups. Common reasons for withdrawal from the study after vaccination were withdrawal by the participant (2.6%) and lost to follow up (1.9%). Death during the study led to the withdrawal of 0.3% of participants in both groups. Study withdrawal due to non-fatal

adverse events were rare and occurred in <0.1% of participants in each group. Details about these AEs leading to withdrawal are further discussed in Section 6.1.12.7.

The 213 participants who received multiple vaccinations due to multiple enrollments were included in the Safety Population. For these participants, the vaccine group RSVpreF was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations.

> Reviewer Comment
> To address the issue of multiple enrollments, The Applicant performed sensitivity analyses for all safety analyses excluding the participants who received multiple enrollments from the Safety population to determine the impact multiple enrolments may have had on the study results. Sensitivity analyses performed did not demonstrate differences from the results of the entire Safety population. The FDA BIMO reviewers performed an inspection of Site 1121, the study site with the highest frequency of multiple enrollments. No substantive issues that impact the data submitted in this Application were identified.

Table 7. Participant Disposition, Safety Population, Study 1013

Population	RSVpreF N=17215 n (%)	Placebo N=17069 n (%)
Safety Population	17215	17069
Completed 6 months safety follow-up	13273 (77.1)	13122 (76.9)
Participants withdrawn after vaccination	869 (5.0)	941 (5.5)
Reason for withdrawal	--	--
Withdrawal by participant	413 (2.4)	492 (2.9)
Lost to follow-up	332 (1.9)	322 (1.9)
Death	52 (0.3)	49 (0.3)
Physician decision	14 (<0.1)	26 (0.2)
Other[a]	24 (0.1)	14 (<0.1)
Refused further study procedures	11 (<0.1)	15 (<0.1)
Protocol deviation	11 (<0.1)	11 (<0.1)
Adverse event	10 (<0.1)	6 (<0.1)
No longer meets eligibility criteria	2 (<0.1)	6 (<0.1)
Reactogenicity subset[b]	3820 (22.2)	3708 (21.7)
eDiary subset safety population	3630 (95.0)	3539 (95.4)
Excluded from eDiary subset safety population[c]	190 (5.0)	169 (4.6)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 6 & 7.
Abbreviations: N=number of participants in safety population, includes one participant who received RSVpreF at the age of 59 years; n=number of participants with the specified characteristic; percentages based on the safety population
a. Other reasons included: behavior issue (n=1); conflicting schedule (n=5); family opposition (n=1); inconsistent and unreliable reporting of medical history (n=1), noncompliant per investigator feedback (n=5); relocation (n=24); withdrawn in error (n=1)
b. A subset of study participants from select sites were included. The values in this row are the denominators for the percentage calculations for the rows below
c. Due to no eDiary data transferred
Note: For participants who received multiple vaccinations due to multiple enrollments, the last vaccination participant ID was used to assign withdrawal reason.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

The BLA submission includes data from the pre-specified interim analysis of the primary efficacy endpoints (considered the primary analysis) which includes cases of first-episode lower respiratory tract disease due to RSV (RSV-LRTD) for the first RSV season through the acute respiratory illness (ARD) surveillance cutoff date of July 8, 2022. In the Evaluable Efficacy Population, the study population used for the primary efficacy analyses, the median duration of ARD surveillance was 211 days in both the RSVpreF and the placebo groups. For the 32,614 participants included in the evaluable efficacy population, 66.3% (n=21,617) completed season 1 surveillance at the time of the data cutoff.

The two primary efficacy endpoints, tested sequentially, were (1) vaccine efficacy (VE) in preventing first-episode RSV-LRTD with 2 or more symptoms with onset at least 14 days after vaccination and (2) VE in preventing first-episode RSV-LRTD with 3 or more symptoms with onset at least 14 days after vaccination.

Primary Endpoint 1: RSV-LRTD with ≥2 Symptoms

As of the data cutoff date of July 8, 2022, there were 44 cases of first-episode RSV-LRTD with ≥2 symptoms occurring after Day 15 (14 days after vaccination). The case split was 11 cases in the RSVpreF group compared to 33 cases in the placebo group, with a VE of 66.7% (96.66% CI: 28.8, 85.8), which met the pre-specified success criterion (Table 8).

Primary Endpoint 2: RSV-LRTD with ≥3 Symptoms

As of the data cutoff date of July 8, 2022, there were 16 cases of first-episode RSV-LRTD with ≥3 symptoms occurring after Day 15. The case split was 2 cases in the RSVpreF group compared to 14 cases in the placebo group, with a VE of 85.7% (96.66% CI: 32.0, 98.7), which met the pre-specified success criterion (Table 8).

Table 8. Vaccine Efficacy of RSVpreF Against First Episode of RSV-LRTD With ≥2 or ≥3 Symptoms Starting 14 Days After Vaccination, Evaluable Efficacy Population, Study 1013

Efficacy Endpoint	RSVpreF N=16306 Cases, n (%)	Placebo N=16308 Cases, n (%)	VE[a], % (96.66% CI)
First episode of RSV-LRTD with ≥2 symptoms	11 (0.07)	33 (0.2)	66.7 (28.8, 85.8)
First episode of RSV-LRTD with ≥3 symptoms	2 (0.01)	14 (0.09)	85.7 (32.0, 98.7)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 10, Table 11.
Abbreviations: RSV-LRTD=lower respiratory tract disease 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 (%); RSV=respiratory syncytial virus; VE=vaccine efficacy
a. VE is defined as 1 - Risk Ratio, and calculated as 1-(P/[1-P]), where P is the number of first episode of RSV-LRTD with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of RSV-LRTD with ≥2 symptoms cases. CI is obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending. Vaccine efficacy is demonstrated if the lower limit of this CI exceeds 20%.
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 were used.

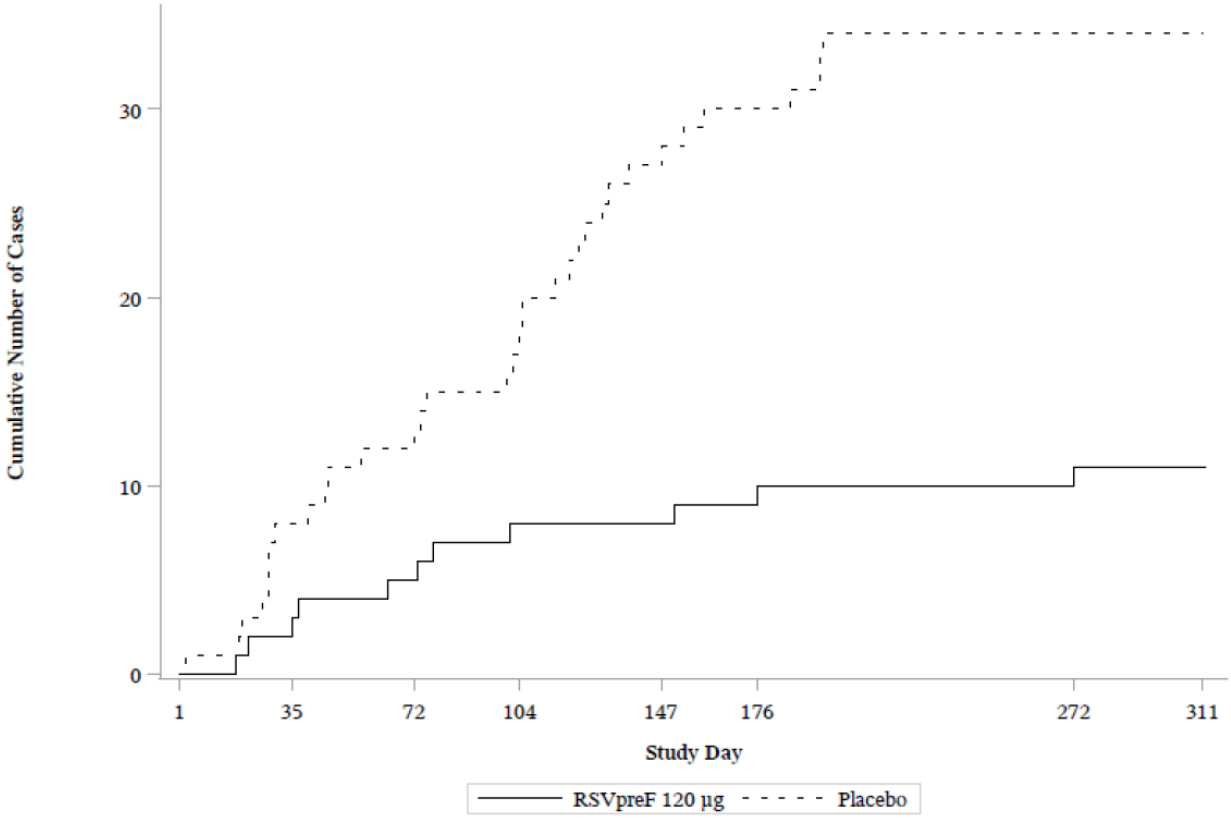
Analyses of the primary endpoints based on the mITT population, including cases which occurred prior to Day 15 (n=1), yielded similar results as those shown above.

The median duration of symptoms of RSV-LRTD cases with ≥2 symptoms was comparable between the RSVpreF group (12 days) and placebo group (11.5 days). For RSV-LRTD cases with ≥3 symptoms, the median duration of symptoms was slightly shorter in the RSVpreF group (10.5 days) compared to the placebo group (15.5 days), though this was based on a small number of cases (2 cases RSVpreF, 14 cases placebo).

Cumulative Case Accrual Curve

The cumulative case accrual curve for RSV-LRTD with ≥2 symptoms starting the day of vaccination, in the mITT Efficacy Population, is shown in Figure 1. Starting approximately 1 month after vaccination, the curves diverge, with more cases accumulating in the placebo group than the RSVpreF group. Cases continued to accrue at a faster rate in the placebo group compared to the RSVpreF group through approximately 7 months following vaccination, which was around the median duration of follow-up for participants in the study at the time of the data cutoff. The cumulative case accrual curve for RSV-LRTD with ≥3 symptoms (not shown) generally followed a similar pattern as that for RSV-LRTD with ≥2 symptoms but was based on a smaller number of cases.

Figure 1. Cumulative Case Accrual Curve From Day of Vaccination, First Episode of RSV-LRTD With ≥2 Symptoms, mITT Efficacy Population, Study 1013



Cumulative Number of Events								
RSVpreF 120 µg	0	3	5	8	8	10	11	11
Placebo	0	8	13	18	28	30	34	34

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Supplemental Figure 14.1
Abbreviations: RSV-LRTD=RSV associated lower respiratory tract disease; mITT=modified intent to treat
Note: First episode of RSV-LRTD cases with symptom onset from Day 1 (vaccination date) through surveillance cutoff date (July 8, 2022) were included.

Note: For participants included in the mITT efficacy population who received multiple vaccinations due to multiple enrollments, the assigned "vaccine group (as randomized)" was based on the randomization group assigned to the first vaccination participant ID.

Reviewer comment:
The cumulative case accrual curve demonstrates an initial increase of cases in the placebo group as compared to the RSVpreF group. Interpretation regarding the durability of vaccine effectiveness is limited by the lack of continued case accrual after Day 176.

6.1.11.2 Subgroup Analyses of Vaccine Efficacy

The estimation of VE by demographic subgroups was limited by the small number of cases for many of the subgroups and needs to be interpreted with caution. The study was not powered to assess VE by demographic subgroups. VE against RSV-LRTD with ≥2 symptoms were generally similar for each subgroup when compared to the overall study population, however the lower bound of the confidence interval crossed zero for most subgroup analyses (Table 9). Although the VE point estimate appeared to trend higher with increasing age, the small numbers of enrolled participants and RSV cases in the older age subgroups (especially participants ≥80 years) led to wide confidence intervals which limit the interpretation of these results.

Table 9. Vaccine Efficacy of RSVpreF Against First Episode of RSV-LRTD With ≥2 Symptoms Starting 14 Days After Vaccination, Evaluable Efficacy Population, Study 1013

Subgroup	RSVpreF Cases n/N	Placebo Cases n/N	VE[a], % (96.66% CI)
Age at vaccination	--	--	--
60-69 years	8/10176	19/10191	57.9 (-7.4, 85.3)
70-79 years	2/5207	9/5196	77.8 (-18.7, 98.1)
≥80 years	1/923	5/921	80.0 (-104.3, 99.7)
Sex	--	--	--
Male	6/8327	17/8225	64.7 (-0.6, 89.7)
Female	5/7979	16/8083	68.8 (3.9, 92.0)
Race	--	--	--
White	8/12654	30/12652	73.3 (36.9, 90.3)
Black or African American	3/2131	2/2162	-50.0 (-2143.8, 85.5)
Asian	0/1341	1/1330	100.0 (-5788.0, 100.0)
Ethnicity	--	--	--
Hispanic/Latino	1/5603	7/5601	85.7 (-25.1, 99.8)
Non-Hispanic/non-Latino	10/10614	26/10616	61.5 (12.8, 84.6)
Country[b]	--	--	--
United States	7/10093	19/10097	63.2 (2.2, 88.0)
Canada	0/509	1/505	100.0 (-5788.0, 100.0)
The Netherlands	1/660	2/654	50.0 (-1105.6, 99.4)
South Africa	2/467	6/469	66.7 (-109.5, 97.4)
Argentina	1/3041	5/3042	80.0 (-104.3, 99.7)

Subgroup	RSVpreF Cases n/N	Placebo Cases n/N	VE[a], % (96.66% CI)
Prespecified at-risk condition	--	--	--
With no prespecified at-risk condition	5/7992	17/7912	70.6 (10.7, 92.4)
With ≥1 prespecified at-risk condition	6/8314	16/8396	62.5 (-8.4, 89.1)
With ≥1 chronic cardiopulmonary condition	4/2420	6/2498	33.3 (-213.7, 87.9)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 14.16.
Abbreviations: RSV-LRTD=RSV-associated lower respiratory tract disease; 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), RSV=respiratory syncytial virus; VE=vaccine efficacy
a. VE is defined as 1 - Risk Ratio, and calculated as 1-(P/[1-P]), where P is the number of first episode of RSV-LRTD with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of RSV-LRTD 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. No cases of LRTD with ≥2 symptoms occurred in Japan or Finland

Due to fewer participants meeting the criteria for RSV-LRTD with ≥3 symptoms than for RSV-LRTD with ≥2 symptoms, results of subgroup analyses based on this endpoint yielded wider confidence intervals and less reliable vaccine effectiveness estimates, though followed similar trends.

6.1.11.3 Secondary Efficacy Analyses

First Episode of RSV-ARD

As of the data cutoff date, there were 103 cases of first-episode RSV-ARD reported occurring after Day 15, with 25 cases in the RSVpreF group compared to 78 in the placebo group. In a descriptive analysis of vaccine efficacy, the VE for this endpoint was 67.9% (95% CI: 49.1, 80.4) (Table 10).

Table 10. Vaccine Efficacy of RSVpreF Against First Episode of RSV-ARD, Evaluable Efficacy Population, Study 1013

Efficacy Endpoint	RSVpreF N=16306 Cases, n (%)	Placebo N=16308 Cases, n (%)	VE[a], % (95% CI)[e]
First episode of RSV-ARD	25 (0.15%)	78 (0.48%)	67.9% (49.1, 80.4)

Source: Adapted from STN 125769/0 Study C3671013, Amendment 43, Module 5, Table 40.19.
Abbreviation(s): RSV-ARD=acute respiratory disease associated with RSV; N = number of participants (at risk) in the specified vaccine group. These values are the denominators for the percentage calculations; n = Total number of cases of the specified endpoint; RSV=respiratory syncytial virus; VE=vaccine efficacy.
a. VE is defined as 1 - Risk Ratio and calculated as 1-(P/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases. Nominal 95% CI is obtained using the conditional exact test based on the binomial distribution of P.
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 were used. The median duration of symptoms of RSV-ARD cases was 8.5 days in the RSVpreF group and 11 days in the placebo group.

Reviewer Comment

At the time of the BLA submission, due to the large number of swab samples collected during the study, the central laboratory prioritized testing of samples from cases which met criteria for LRTD with at least 2 symptoms to support the evaluation of the primary efficacy endpoints. As a result, not all ARD cases with swabs collected within 7 days of symptom onset were tested and reported at the time of the interim

analysis. In a response to an FDA Information Request, under Amendment 43 to the BLA, the Applicant submitted analyses of this secondary endpoint inclusive of all swabs that were obtained in ARD cases; these data are reflected in the table above.

As described in Table 2, many of the clinical symptoms used to support the ARD case definition were also used to support the LRTD case definition. As a result, most participants who met criteria for ARD also met the case definition for LRTD, confounding the interpretation of efficacy of RSVpreF against all cases of acute respiratory disease caused by RSV, particularly those that involve upper respiratory tract symptoms. In addition, the ARD analysis was descriptively evaluated without formal hypothesis testing. Therefore, while the primary efficacy analyses support RSVpreF product labeling that includes the prevention of LRTD caused by RSV, available secondary efficacy analysis evaluating the prevention of ARD caused by RSV are not as rigorous.

Severe RSV-LRTD

Because the pre-specified number of first-episode severe RSV-LRTD cases (12 cases) had not accrued as of the July 8, 2022, surveillance cutoff date for efficacy, an interim analysis of this secondary objective was not conducted. As of the data cutoff, there were 2 cases of severe RSV-LRTD reported, both among placebo recipients; both participants were hospitalized and one required supplemental oxygen.

6.1.11.4 Exploratory

Vaccine Efficacy by RSV Subgroup

In addition to the primary and secondary efficacy analyses evaluating RSVpreF, vaccine efficacy against RSV subgroups A and B were also individually calculated (Table 11).

Table 11. Vaccine Efficacy of RSVpreF Against First Episode of RSV-LRTD With ≥2 or ≥3 Symptoms and RSV-ARD Starting 14 Days after Vaccination, By RSV Subgroup, Evaluable Efficacy Population, Study C3671013

Endpoint	RSVpreF N=16306 Cases n (%)	Placebo N=16308 Cases n (%)	VE[a], % (96.66 CI)
First episode of RSV-LRTD with ≥2 symptoms	--	--	--
RSV Subgroup A	1 (0.01)	9 (0.06)	88.9 (10.6, 99.8)
RSV Subgroup B	10 (0.06)	23 (0.14)	56.5 (-0.7, 82.8)
First episode of RSV-LRTD with ≥3 symptoms	--	--	--
RSV Subgroup A	1 (0.01)	3 (0.02)	66.7 (-393.7, 99.6)
RSV Subgroup B	1 (0.01)	10 (0.06)	90.0 (21.8, 99.8)

Endpoint	RSVpreF N=16306 Cases n (%)	Placebo N=16308 Cases n (%)	VE[a], % (96.66 CI)
First episode of RSV-ARD	--	--	--
RSV Subgroup A	6 (0.04)	22 (0.1)	72.7 (30.6, 91.0)[b]
RSV Subgroup B	19 (0.1)	56 (0.3)	66.1 (42.0, 81.0)[b]

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 10, 11, 12 and Amendment 43, Module 5, Table 40.19 .
Abbreviations: RSV-LRTD=RSV-associated lower respiratory tract disease; 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 (%); RSV=respiratory syncytial virus; VE=vaccine efficacy.
The evaluable efficacy population included all study participants who were elig ble 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 ARD or LRTD 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 RSV-LRTD with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of RSV-LRTD 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. 95% CI
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 were used.
One positive RSV polymerase chain reaction (PCR) test from local lab without subgroup information is included in the count of RSV-LRTD (but not included in any subgroup rows), as there was no swab within 7 days of symptom onset for central lab testing available.

Reviewer Comment
The overall number of RSV-LRTD and RSV-ARD cases were mostly due to RSV subgroup B. Few cases in each subgroup led to wide confidence intervals and greater imprecision around the VE point estimate for these analyses.

6.1.11.5 Post-hoc analyses

Medically Attended RSV-LRTD

A medically attended RSV case was defined as an episode with 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 illness visits to the study site. Descriptive analyses of vaccine efficacy against medically attended RSV, by each of the RSV-LRTD endpoints, are shown in Table 12. The VE point estimates were similar to those obtained in the primary efficacy analyses for the two RSV-LRTD endpoints (with ≥2 and ≥3 symptoms). The majority of the overall RSV-LRTD cases with ≥3 symptoms were medically attended: 2 out of 2 cases in the RSVpreF group and 10 out of 14 cases in the placebo group. In contrast, a lower proportion of RSV-LRTD cases ≥2 symptoms were medically attended: 7 out of 11 cases in the RSVpreF group and 20 out of 33 cases in the placebo group.

Table 12. Medically Attended RSV-LRTD Starting 14 Days After Vaccination, Evaluable Efficacy Population, Study 1013

Endpoint	RSVpreF N=16306 Cases n (%) Incidence Rate per 1000 Person-Years[b]	Placebo N=16308 Cases n (%) Incidence Rate per 1000 Person-Years[b]	VE[a], % (95% CI)
Medically attended RSV-LRTD with ≥2 symptoms	7 (<0.1) 0.8	20 (0.1) 2.2	65.1 (14.0, 87.5)
Medically attended RSV-LRTD with ≥3 symptoms	2 (<0.1) 0.2	10 (0.1) 1.1	80.0 (6.3, 97.9)

Source: Adapted from STN 125769/0 Study C3671013, Amendment 12, Module 5, Table 3
Abbreviation(s): RSV-ARD=acute respiratory disease associated with RSV; RSV-LRTD=RSV-associated lower respiratory tract disease; 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
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 were used.
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.
b. Person-years is defined as the total ARD surveillance duration days across all participants at-risk within each vaccine group, then divided by 365.25. ARD surveillance duration is from vaccination date through death /discontinuation/ surveillance cutoff date/major protocol deviation, whichever is earlier.

6.1.12 Safety Analyses

There were 34,284 participants included in the Safety Population, of which 26,395 participants (77.0%) completed at least 6 months of safety follow-up post-vaccination (13,273 RSVpreF recipients and 13,122 placebo recipients) by the data cutoff date of July 14, 2022.

6.1.12.1 Methods

See Section 6.1.7 above.

6.1.12.2 Overview of Adverse Events

Safety Overview

Table 13 provides an overview of the rates of adverse events in the RSVpreF group compared to the placebo group during the study period. The rates of solicited local reactions were higher among RSVpreF recipients compared to placebo recipients, though the rates of solicited systemic reactions and unsolicited adverse events were similar across groups. AEs leading to withdrawal from the study occurred in <0.1% of participants in each group. SAEs were reported by 2.3% of participants in both the RSVpreF and placebo groups, with 3 SAEs, all in the RSVpreF group, considered by investigators to be related to the study intervention (see Section 6.1.9 for case definitions). At the time of the data cutoff, AEs that led to death occurred in 52 (0.3%) RSVpreF recipients and 49 (0.3%) placebo recipients. None of these deaths were considered related to study intervention by FDA in agreement with the investigator's assessment.

Table 13. Proportion of Participants Reporting at Least One Adverse Event Following Vaccination, Safety Population, Study 1013

AE Type: Monitoring Period[a]	RSVpreF % (n/N)	Placebo % (n/N)
Immediate: 30 minutes	0.2 (37/17215)	0.2 (31/17069)
Solicited local reaction[b] at the injection site: Day 1-7	12.1 (438/3621)	6.6 (235/3539)
Grade 3 or above solicited local	0.2 (8/3621)	<0.1 (2/3539)
Solicited systemic reaction[c]: Day 1-7	27.4 (993/3621)	25.7 (909/3539)
Grade 3 or above solicited systemic	0.7 (27/3621)	0.6 (20/3539)
Unsolicited: Through the 1-month follow-up visit[d]	9.0 (1544/17215)	8.5 (1453/17069)
Severe unsolicited AEs	0.4 (65/17215)	0.3 (51/17069)
Related unsolicited AEs	1.4 (239/17215)	1.0 (163/17069)
Newly diagnosed chronic medical condition: Entire study period	1.7 (301/17215)	1.8 (313/17069)
AEs leading to study withdrawal: Entire study period	<0.1 (10/17215)	<0.1 (6/17069)
SAEs: Entire study period	2.3 (396/17215)	2.3 (387/17069)
Related SAEs: Entire study period	<0.1 (3/17215)	0
Deaths: Entire study period	0.3 (52/17215)	0.3 (49/17069)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Tables 13, 14, 15, 14.21, and 14.34.
Abbreviations: AE=Adverse Event; N=total number of participants in the specified group, or the total sample; for solicited local/systemic, N = number of participants with at least 1 day of e-diary data; n= number of participants who experienced the event; SAE=serious adverse event; w/d=withdrawal.
The Safety population included all enrolled participants who received the study intervention. One participant received RSVpreF at the age of 59 years; this participant was not evaluated for solicited local/systemic and did not report any unsolicited AE.
Note: Participants were allocated to the vaccine groups as received; 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.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination.
b. Solicited local reactions included pain, redness, and swelling at injection site.
c. Solicited systemic reactions included fever ≥38.0℃, fatigue, headache, muscle pain, joint pain, nausea, vomiting, and diarrhea.
d. For participants with multiple vaccinations, AEs 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.

Safety Review of Participants with Multiple Vaccinations

There were 213 participants who received multiple vaccinations due to multiple study site enrollments. For these participants, study group assignment to RSVpreF group was applied when at least one dose of RSVpreF was administered and study group assignment to placebo group was applied when placebo was administered for all vaccinations. Compared to the overall Safety Population, the proportion of participants with multiple vaccination was low, therefore inclusion of participants with multiple vaccinations in safety analyses is not anticipated to impact the interpretation of safety data.

Solicited Adverse Reactions

Solicited local and systemic ARs with onset within 7 days after vaccination were assessed in a subset of study participants from selected sites. The eDiary Subset Safety Population included a total of 7,169 participants, consisting of 3,630 RSVpreF recipients and 3,539 placebo recipients. Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema and swelling) and systemic reactions (fatigue, headache, muscle pain, joint pain, nausea, vomiting, diarrhea, and fever defined as an axillary temperature of ≥38.0º C [100.4ºF]).

Solicited Local Adverse Reactions

Table 14 includes the proportions of RSVpreF and placebo participants who reported any solicited local AR, by maximum severity. Within 7 days post-vaccination, the proportion of participants reporting any local reaction was higher in the RSVpreF group (12.2%) compared to the placebo group (6.6%). 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. Severe (Grade 3) solicited local reactions were reported by 8 (0.2%) and 2 (<0.1%) participants in the RSVpreF and placebo groups, respectively.

Among those who received RSVpreF, the median day of onset of local reactions after vaccination was 2 days for pain and 3 days for redness and swelling. Solicited local reactions had a median duration of 1 to 1.5 days.

Table 14. Proportion of Participants Reporting at Least One Solicited Local Adverse Reaction Within 7 Days Following Vaccination, by Maximum Severity, E-Diary Subset Safety Population, Study C3671013

Solicited Adverse Reaction	RSVpreF % (n/N)	Placebo % (n/N)
Any local reaction	12.1 (438/3621)	6.6 (235/3539)
Grade 1	9.5 (344/3621)	5.6 (199/3539)
Grade 2	2.4 (86/3621)	1.0 (34/3539)
Grade 3	0.2 (8/3621)	<0.1 (2/3539)
Pain[a]	--	--
Any	10.5 (382/3621)	6.0 (212/3539)
Grade 1	9.4 (340/3621)	5.3 (188/3539)
Grade 2	1.1 (40/3621)	0.7 (24/3539)
Grade 3	<0.1 (2/3621)	0
Erythema	--	--
Any	2.7 (97/3619)	0.7 (23/3532)
Grade 1 (2.5 cm to 5.0 cm)	1.5 (55/3619)	0.5 (16/3532)
Grade 2 (>5.0 cm to 10.0 cm)	1.1 (38/3619)	0.2 (7/3532)
Grade 3 (>10.0 cm)	0.1 (4/3619)	0
Swelling	--	--
Any	2.4 (88/3619)	0.5 (16/3532)
Grade 1 (2.5 cm to 5.0 cm)	1.5 (53/3619)	0.2 (8/3532)
Grade 2 (>5.0 cm to 10.0 cm)	0.9 (31/3619)	0.2 (6/3532)
Grade 3 (>10.0 cm)	0.1 (4/3619)	<0.1 (2/3532)

Source: Adapted from STN 125769/0 Phase 3 study C3671013, Clinical Study Report, Table 14.21, 14.34.
Abbreviations: N=number of participants with at least 1 day of e-diary data for the specific solicited local/systemic in the group; n=Number of participants who experienced the event, or with maximum severity of grade 1, grade 2, or grade 3.
Note: Solicited local/systemic 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: Participants were allocated to the vaccine groups as received; 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 reactions reported from the time of the first dose of RSVpreF (RSVpreF group) or placebo (placebo group) was included in the analysis.
a. Grade 1: does not interfere with activity; grade 2: interferes with activity; grade 3: prevents daily activity.

Solicited Systemic Adverse Reactions

Table 15 includes the percentages of RSVpreF and placebo participants who reported any solicited systemic AR, by maximum severity. Overall, the incidences of systemic reactions within 7 days post-vaccination were similar between the RSVpreF (27.5%) and placebo (25.7%) groups. Fatigue was the most frequently reported systemic AR (RSVpreF 15.5%; placebo 14.4%), followed by headache (RSVpreF 12.8%; placebo 11.7%) and muscle pain (RSVpreF

10.1%; placebo 8.4%). Fever was reported in 1.4% of participants in each group. Fever with maximum temperature between 38.9 - 40.0°C were reported by 1 (<0.1%) and 2 (<0.1%) participants in the RSVpreF and placebo groups, respectively. Fever >40.0°C within 7 days post-vaccination was only reported by one placebo participant (measured 40.1°C, on day of vaccination only). Overall, severe (Grade 3 or above) systemic ARs were reported in 0.7% of RSVpreF recipients and 0.6% of placebo recipients.

Among those who received RSVpreF, the median day of onset of solicited systemic ARs was between 2-3 days post-vaccination and the median duration was 1 to 2 days.

Table 15. Proportion of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days Following Vaccination, by Maximum Severity, E-Diary Subset Safety Population, Study C3671013

Solicited Adverse Reaction	RSVpreF % (n/N)	Placebo % (n/N)
Any systemic reaction	27.4 (993/3621)	25.7 (909/3539)
Grade 1	15.7 (569/3621)	15.1 (536/3539)
Grade 2	11.0 (397/3621)	9.9 (352/3539)
Grade 3	0.7 (27/3621)	0.6 (20/3539)
Grade 4 (fever >40.0°C)[b]	0	<0.1 (1/3539)
Fatigue[c]	--	--
Any	15.5 (562/3621)	14.4 (508/3539)
Grade 1	9.3 (335/3621)	8.4 (296/3539)
Grade 2	5.9 (215/3621)	5.8 (207/3539)
Grade 3	0.3 (12/3621)	0.1 (5/3539)
Headache[c]	--	--
Any	12.8 (465/3621)	11.7 (415/3539)
Grade 1	9.0 (326/3621)	8.4 (299/3539)
Grade 2	3.7 (135/3621)	3.2 (113/3539)
Grade 3	0.1 (4/3621)	<0.1 (3/3539)
Muscle Pain[c]	--	--
Any	10.1 (367/3621)	8.4 (297/3539)
Grade 1	6.5 (234/3621)	5.5 (196/3539)
Grade 2	3.5 (125/3621)	2.8 (98/3539)
Grade 3	0.2 (8/3621)	<0.1 (3/3539)
Joint Pain[c]	--	--
Any	7.5 (272/3621)	6.9 (244/3539)
Grade 1	4.5 (163/3621)	3.9 (139/3539)
Grade 2	2.9 (106/3621)	2.9 (103/3539)
Grade 3	<0.1 (3/3621)	<0.1 (2/3539)
Nausea[c]	--	--
Any	3.4 (124/3621)	3.7 (132/3539)
Grade 1	2.5 (92/3621)	3.1 (108/3539)
Grade 2	0.9 (32/3621)	0.6 (21/3539)
Grade 3	0	<0.1 (3/3539)
Vomiting[c]	--	--
Any	0.9 (32/3621)	0.8 (30/3539)
Grade 1	0.7 (26/3621)	0.7 (24/3539)
Grade 2	0.2 (6/3621)	0.1 (4/3539)
Grade 3	0	<0.1 (2/3539)

Solicited Adverse Reaction	RSVpreF % (n/N)	Placebo % (n/N)
Diarrhea[c]	--	--
Any	5.9 (213/3621)	5.2 (183/3539)
Grade 1	4.4 (161/3621)	4.2 (148/3539)
Grade 2	1.3 (48/3621)	0.9 (31/3539)
Grade 3	0.1 (4/3621)	0.1 (4/3539)
Fever (temperature ≥38°C)	--	--
Any Fever	1.4 (51/3619)	1.4 (51/3532)
≥38.0-38.4°C	0.6 (22/3619)	0.8 (27/3532)
>38.4-38.9°C	0.8 (28/3619)	0.6 (21/3532)
>38.9-40.0°C	<0.1 (1/3619)	<0.1 (2/3532)
>40.0°C	0	<0.1 (1/3532)

Source: Adapted from STN 125769/0 Phase 3 study C3671013, Clinical Study Report, Table 14.21, 14.34.
Abbreviations: N=number of participants with at least 1 day of e-diary data for the specific solicited local/systemic in the group; n=Number of participants who experienced the event, or with maximum severity of grade 1, grade 2, or grade 3.
Temperature 38.0°C =100.4°F.
Note: Solicited local/systemic 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: Participants were allocated to the vaccine groups as received; 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 reactions reported from the time of the first dose of RSVpreF (RSVpreF group) or placebo (placebo group) was included in the analysis.
b. 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.
c. For vomiting – grade 1: 1 to 2 times in 24 hours; grade 2: >2 times in 24 hours; grade 3: requires intravenous hydration. For diarrhea – grade 1: 2 to 3 loose stools in 24 hours; grade 2: 4 to 5 loose stools in 24 hours; grade 3: 6 or more loose stools in 24 hours. For other systemic reactions– grade 1: does not interfere with activity; grade 2: some interference with activity; grade 3: prevents daily routine activity.

Reviewer comment

Events synonymous with reactogenicity events were also collected by investigators and reported as adverse events. The sponsor performed a sensitivity analysis of these investigator assessed reactogenicity events. The analysis demonstrated similar results as the solicited ARs as reported in e-diary, which are displayed in the tables above.

Subgroup Analyses

Solicited local and systemic ARs were reported more frequently among female RSVpreF recipients (15.9% and 32.7%, respectively) compared to male RSVpreF recipients (8.8% and 22.7%, respectively). In the placebo group, systemic ARs were also reported at a higher rate among female participants as compared to males, but local ARs were reported by a similar proportion of female and male placebo recipients. Among RSVpreF recipients, the proportions of participants reporting solicited ARs were inversely related to increasing age, with a higher rate of solicited local and systemic reactions reported in the 60-69 years of age group (14.0% and 30.2%, respectively) as compared to the 70-79 (10.4% and 24.1%, respectively) and ≥80 (3.6% and 19.1%, respectively) years of age groups.

Unsolicited AEs

Immediate AEs

Unsolicited adverse events within 30 minutes of vaccination were reported infrequently and at similar frequencies between the RSVpreF and placebo groups (0.2% in each group). These events consisted primarily of injection site reactions.

There was one event that was clinically concerning for anaphylaxis that occurred in a 67-year-old female participant. The event occurred 3 hours and 15 minutes after vaccination with RSVpreF with the development of lip and eye swelling, vomiting and diarrhea, dizziness, tachycardia and hypotension. No treatment was administered, and all symptoms resolved within 24 hours of onset. The events were considered related to the study vaccination by FDA in agreement with the investigator.

Unsolicited AEs Within 1 Month After Vaccination

The proportions of participants who reported unsolicited AEs within 1 month after vaccination were similar across groups (8.9% RSVpreF and 8.5% placebo). Unsolicited AEs reported by ≥1% of participants in either the RSVpreF group or placebo group were under the following Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC): *Infections and infestations* (2.3% and 2.2%, respectively), *Respiratory, thoracic and mediastinal disorders* (2.2% and 2.4%, respectively), and *General disorders and administration site conditions* (1.8% and 1.2%, respectively). By MedDRA preferred term (PT), the most frequently reported AE was cough (0.6% in both groups).

Adverse events that were assessed as related to study intervention by the investigator were reported in 1.3% of RSVpreF recipients and 0.9% of placebo recipients. These AEs primarily represented reactogenicity events and were mostly reported within 7 days of vaccination.

Within 1 month of vaccination, AEs assessed as severe or life-threatening were reported in 0.4% and 0.1%, respectively, of RSVpreF recipients and 0.3% and 0.1%, respectively, of placebo recipients. By MedDRA most of these events were in the SOC *Infections and Infestations*, reported by 17 RSVpreF recipients (<0.1%) and 19 placebo recipients (0.1%). By MedDRA PT, the most frequently reported severe or life-threatening AE among RSVpreF recipients were Sepsis (n=4), Fall (n=4), and Congestive Obstructive Pulmonary Disease, COPD (n=4). By PT, the most frequently reported severe or life-threatening AE among placebo recipients were COVID-19 (n=4) and COVID-19 pneumonia (n=4). There were 2 severe AEs assessed as related to the study intervention: an SAE of Miller Fisher syndrome (variant of GBS, see Section 6.1.12.4) in the RSVpreF group and a non-serious event of viral infection in a placebo recipient. There was one life-threatening AE assessed as related to the study intervention, which was an SAE of GBS in the RSVpreF group (see Section 6.1.12.4).

Standard MedDRA Queries

FDA conducted standardized MedDRA queries (SMQs) using FDA-developed software to evaluate the Safety Population for constellations of unsolicited adverse events with onset following vaccination through the July 14, 2022, data cutoff. The SMQs were conducted on adverse event Preferred Terms that could represent various conditions, including but not limited to allergic, cardiac, neurologic, inflammatory, and autoimmune disorders.

Based on the FDA's review of available information, the SMQ for GBS identified 2 events in the RSVpreF group (discussed in Section 6.1.12.4) and none in the placebo group.

Within 1 month after vaccination, there was a numerical imbalance observed in events under the SMQ *Cardiac arrythmia*, with 21 events reported by 17 participants (0.1%) in the RSVpreF group and 8 events reported by 7 participants (<0.1%) in the placebo group. This imbalance was primarily driven by events of atrial fibrillation (10 events in 10 participants [<0.1%] in RSVpreF group compared to 4 events in 4 participants [<0.1%] in placebo group), of which 4 in the RSVpreF group and 3 in the placebo group were serious adverse events. Event onset ranged from 18 to 30 days post-vaccination, for cases occurring within 1 month after

vaccination. Among participants who reported atrial fibrillation, a medical history of atrial fibrillation was reported by 6 (60%) RSVpreF recipients and 2 (50%) placebo recipients. Among all study participants, a baseline medical history of atrial fibrillation was documented in 60 (0.3%) RSVpreF recipients and 43 (0.3%) placebo recipients. Through data cutoff, atrial fibrillation was reported by 25 RSVpreF recipients (0.1%) and 22 placebo recipients (0.1%). None of the events of atrial fibrillation were considered related to study intervention by the investigators.

No other notable imbalances observed in other queries, including for the SMQ *Immune-mediated/autoimmune disorders,* were considered clinically relevant by the FDA.

> Reviewer Comment
> Although none of the cases of atrial fibrillation (AF) were considered related to the vaccine by study investigators, an imbalance of AF cases across groups reported within 30 days of vaccination suggests that an association with study vaccination cannot be excluded. However, based on available information on the reported AF cases, as well as current clinical understanding of AF onset, causality due to RSVpreF vaccination cannot be established. FDA recommends and the Applicant agrees to conduct a postmarketing study to evaluate the risk of atrial fibrillation following vaccination.

Newly Diagnosed Chronic Medical Conditions

NDCMCs were monitored for the entire study duration through the data cutoff. NDCMCs were reported in 1.7% of RSVpreF recipients and 1.8% of placebo recipients. None of the events in the RSVpreF group and one event of headache in the placebo group, were assessed as related to study intervention by the investigator. The most frequently reported NDCMCs in the RSVpreF group were hypertension (0.2%), dyslipidemia (<0.1%), and hypercholesterolemia (<0.1%), all of which are common chronic medical condition in older adult populations. The types and proportions of NDCMCs were balanced across groups.

Subgroup Analyses

Analyses of unsolicited adverse events by demographic subgroup, including age, do not demonstrate imbalances; however, small sample sizes limit the interpretability of these analyses.

Unsolicited Adverse Events of Clinical Interest: After Data Cut-Off

After the data cutoff date of July 14, 2022, one case of polyneuropathy was reported:

- A 68-year-old female with a past medical history of arterial hypertension, hypothyroidism, dyslipidemia, lower limbs venous insufficiency, right Achilles tendon rupture followed by surgical repair developed a sensory-motor axonal polyneuropathy, with symptom onset 21 days (Day 22) after receipt of RSVpreF. The event was preceded by an episode of urticaria which occurred 1 day after vaccination (Day 2) and resolved 7 days after vaccination. On Day 22, she developed step instability and paresthesia in all four limbs, predominantly in the lower limbs and was evaluated by a neurologist. Electromyogram performed on Day 29 demonstrated bilateral focal lesions of the median nerve at the level of the wrist with moderate motor-sensory involvement and motor sensory axonal polyneuropathy predominantly in the lower limbs. She was started on treatment with Thioctic Acid, L-Acetylcarnitine, and Gabapentin on Day 103. An autonomic evaluation of the peripheral nervous system on Day 163 revealed no autonomic alterations of the cardiac parasympathetic system. She was diagnosed with

a sensory-motor axonal polyneuropathy with a predominance of the lower limbs. Her symptoms improved; however, the participant continues to experience symptoms of paresthesia in the upper limbs that do not interfere with daily activities at the time of the last available report, approximately 7 months after symptom onset. The event was considered as unrelated to study vaccination by the investigator.

Reviewer comment
This case of a sensory-motor polyneuropathy was reported to have onset of symptoms that occurred after the data cutoff for safety. The event described was not reported to be a case of GBS based on a diagnosis made by the participant's neurologist. Based on the temporal relationship with RSVpreF vaccination and available information submitted to the BLA (which does not include a neurologic exam, medication history or additional laboratory data that might further elucidate the etiology of her symptoms) a causal association cannot be excluded.

6.1.12.3 Deaths

Through the data cutoff, there were 52 (0.3%) deaths among RSVpreF recipients and 49 (0.3%) deaths among placebo recipients. In general, the causes of death among study participants were representative of the most common causes of death among the elderly adult population. The most frequently reported causes of death were in the SOC Cardiac disorders for participants in both the RSVpreF (20 participants, 0.1%) and placebo (19 participants, 0.1%) groups. By PT, these most commonly were described as cardiorespiratory arrest in the RSVpreF group (n=6) and acute myocardial infarction in the placebo group (n=5). None of the deaths were assessed as related to study intervention by the study investigators. Based on independent review of event narratives, FDA agrees with the investigators' assessments of causality.

6.1.12.4 Serious Adverse Events

Through the data cutoff, SAEs were reported in 2.3% of participants in both the RSVpreF (n=396) and placebo (n=387) groups. SAEs were most frequently reported in the SOCs Cardiac disorders (RSVpreF 0.5%; placebo 0.5%) and Infections and infestations (RSVpreF 0.5%; placebo 0.4%). There were three SAEs in the RSVpreF group that were assessed as related by the investigator and none in the placebo group. The case narratives for the 3 related SAEs in the RSVpreF group include the following:

- A 61-year-old female experienced hypersensitivity of moderate severity that began 8 hours after receipt of RSVpreF. The participant developed shortness of breath and chest pain, had loss of consciousness, and required hospitalization. She received a diagnosis of allergic drug reaction and her symptoms resolved 5 days after onset.
- A 66-year-old male with a past medical history of hypertension developed GBS, graded as life-threatening in severity, with symptom onset 7 days (Day 8) after receipt of RSVpreF. Prior to the onset of these symptoms, the participant had experienced a non-ST elevation myocardial infarction, not considered related to vaccination, on Day 7. He was hospitalized on Days 7-8 for cardiac catheterization and angioplasty and on Day 8 developed lower back pain. On Day 14, he developed bilateral lower extremity weakness, and due to a fall, he was hospitalized. Physical exam and laboratory findings were consistent with the diagnosis of GBS. He was treated with intravenous immune globulin, and 5 sessions of plasmapheresis. Symptoms improved and the event of GBS was resolving at the time of the last available report, approximately 6 months after symptom onset.

- A 66-year-old female with a past medical history of type 2 diabetes mellitus developed Miller Fisher syndrome, graded as severe, with symptom onset 8 days (Day 9) after receipt of RSVpreF. The participant symptoms included fatigue on Day 9, sore throat on Day 10, and ataxia on Day 11. On Day 19, she was hospitalized for severe fatigue and unstable movements, and later developed diplopia, ataxia, and paresthesia of bilateral palms and soles. Ophthalmoplegia was seen on exam. Her symptoms started to resolve on Day 40, without treatment. On Day 41, she was retrospectively diagnosed with Miller Fisher syndrome based on clinical course. The participant's symptoms resolved completely approximately 3 months after symptom onset.

For all the cases listed above, the event was assessed as possibly related to study vaccine by the investigators but assessed as unrelated by the Applicant. Given the temporal association and biological plausibility, FDA agrees with the assessments of the investigators that these events were possibly related to study vaccine.

6.1.12.5 Adverse Events Leading to Study Withdrawal

AEs leading to withdrawal from the study were reported in <0.1% of participants in both the RSVpreF (n=10) and placebo (n=6) groups. None of these AEs were assessed as related to the study intervention. By PT, the only AE leading to withdrawal reported by >1 participant was depression, reported by 3 RSVpreF recipients and no placebo recipient. See Section 6.1.10.1.3 for a complete overview of participants included in the Safety population and reasons for study withdrawal.

6.1.13 Study Summary

Study 1013 contributed the primary evidence to support the safety and efficacy of RSVpreF in individuals 60 years of age and older. Data submitted to the BLA are based on the protocol-specified interim analysis (considered the primary analysis), with a data cutoff of July 8, 2022, and a median follow-up for efficacy of approximately 7 months. Vaccine efficacy (VE) to prevent first-episode RSV-associated lower respiratory tract disease (RSV-LRTD) with ≥2 and ≥3 symptoms were 66.7% (96.66% CI 28.8, 85.8) and 85.7% (96.66% CI 32.0, 98.7), respectively. The majority of RSV-LRTD cases accrued in the study were RT-PCR confirmed to be RSV subgroup B. Descriptive analysis of the secondary endpoint of vaccine efficacy against RSV-associated acute respiratory disease (RSV-ARD) demonstrated a VE of 67.9% (95% CI 49.1, 80.4); however, most participants who met criteria for ARD also met the case definition for LRTD. As of the data cutoff, there were only 2 cases of severe RSV-LRTD in the study, both among placebo recipients. Descriptive analyses of VE against medically attended RSV-LRTD with ≥2 or ≥3 symptoms were similar to those evaluating the primary efficacy endpoints.

Descriptive subgroup analyses of efficacy estimates based on baseline demographic characteristics were generally consistent with the overall findings of the primary analyses but were limited by small subpopulation sizes. Although vaccine efficacy appears to be preserved among the oldest age subgroup of participants ≥80 years and among participants with at least one at-risk condition for severe RSV, the wide confidence intervals around the VE point estimates reflect the uncertainties of these analyses.

Safety data from Study 1013 are available from 34,284 vaccinated participants (17,215 RSVpreF recipients and 17,069 placebo recipients), of which 26,395 participants (77.0%) have had at least 6 months of follow-up as of July 14, 2022, data cutoff for safety.

Data on solicited local and systemic ARs within 7 days after vaccination were collected in participants from a subset of sites in Japan and the US (n=7,169). Solicited local ARs were reported by a higher proportion of RSVpreF recipients compared to placebo; solicited systemic ARs were reported at similar rates among the two groups. The most reported (>10%) solicited ARs among RSVpreF recipients were fatigue (15.5%), headache (12.8%), injection site pain (10.6%), and muscle pain (10.1%). Among RSVpreF recipients, Grade 3 ARs were reported by 0.2% and 0.7% of participants for local and systemic solicited ARs, respectively. Overall, solicited reactions were reported more commonly in the younger age subgroup (60-69 years) compared to the older age subgroups.

There were no meaningful imbalances in the overall rates of unsolicited adverse events within 1 month following vaccination between vaccine and placebo recipients in the Safety Population, however a numerical imbalance was noted in events of atrial fibrillation with 10 events in the RSVpreF group and 4 events in the placebo group. The available information on reports of atrial fibrillation in study participants is insufficient to determine a causal relationship to the vaccine. Given the risk for cardiac events in the population intended to receive the vaccine, this imbalance in events of atrial fibrillation has been included under Adverse Reactions in the USPI and a postmarketing study to evaluate the risk of atrial fibrillation after vaccination has been requested by FDA and agreed to by the Applicant.

As of the July 14, 2022, data cutoff, death occurred in 52 (0.3%) RSVpreF recipients and 49 (0.3%) placebo recipients. These deaths were due to events that occurred at rates that are expected in the general population of individuals ≥60 years of age and none were judged as related to RSVpreF. Serious adverse events were infrequent and balanced between the RSVpreF and placebo groups (2.3% in both groups). Three SAEs (i.e., hypersensitivity, GBS, and Miller Fisher Syndrome) were assessed by FDA as possibly related to RSVpreF, in agreement with the Investigator's assessment. After the data cutoff date of July 14, 2022, one case of a sensory-motor axonal polyneuropathy was reported that was not considered by the investigator to be related to the vaccination; however, FDA has determined that a causal association cannot be excluded, and additional information is being requested. Given the context of a background rate of 1.5-3 cases per 100,000 people per year for GBS in the US among adults >60 years of age (Yen et al, 2022; Sejvar et al, 2011), postmarketing assessments will be required to better understand whether an association between RSVpreF and GBS and/or other polyneuropathies exists.

6.2 Study C3671014

NCT05096208

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."

Study Overview: This study was designed to evaluate the lot consistency, immunogenicity, and safety of 3 lots of RSVpreF in healthy individuals 18 through 49 years of age, as compared to placebo. The study was conducted in the US with a total duration of approximately 1 month for each participant.

6.2.1 Objectives

Primary Objectives

1. Immunogenicity: To demonstrate that the immune responses induced by 3 RSVpreF lots (Groups 1, 2, and 3) 1 month after vaccination are equivalent.
   Endpoint:
   a. Neutralizing GMT Ratios 1 month after vaccination for every pair of RSVpreF lots (Group 1/Group 2, Group 1/Group 3, Group 2/Group 3) for RSV A and RSV B neutralization assays
      Statistical Criterion for success: 2-sided 95% CI for the ratio of neutralizing GMTs for every pair of RSVpreF lots was contained in the (0.667, 1.5) margin for both RSV A and RSV B.

2. Safety: To evaluate the safety and tolerability profiles of 3 RSVpreF lots (Groups 1, 2, and 3).
   Endpoints:
   a. The proportion of participants reporting solicited local reactions within 7 days following study intervention.
   b. The proportion of participants reporting solicited systemic reactions within 7 days following study intervention.
   c. The proportion of participants reporting AEs throughout the study.
   d. The proportion of participants reporting SAEs throughout the study.

The study included an exploratory objective to further evaluate the immune responses induced by the 3 RSVpreF lots. The exploratory endpoints included assessment of the geometric mean of the neutralizing titer (NT) for RSV A and B and RSVpreF-binding IgG for RSV A and B pre- and post-vaccination. Results from these exploratory endpoints will not be discussed in this review as they do not contribute substantially to the overall conclusions.

6.2.2 Design Overview

Study 1014 was a Phase 3 multicenter, parallel-group, randomized, double-blind, placebo-controlled study in healthy adults 18 through 49 years of age. Up to 1,000 participants were planned to be enrolled and randomized 1:1:1:1 to receive one of three RSVPreF manufacturing lots (Group 1, Group 2, and Group 3) or placebo.

All participants had 2 study visits that had the following major study activities:

- Visit 1/Day 1:
  - Blood sampling, single vaccination with RSVpreF or placebo
- Visit 2/Day 28-36 post-vaccination:
  - 1 month follow up- Blood sampling, e-Diary card transcription, collection of mid-turbinate nasal swabs if ≥1 ARD symptoms are present

The study duration for each participant was approximately 1 month after vaccination.

6.2.3 Population

Eligibility Criteria

Individuals were eligible for inclusion if they met all the following criteria: healthy males or nonpregnant, non-breastfeeding females between the ages of 18 and ≤49 years, inclusive, at Visit 1 (Day 1); participants who are willing and able to comply with scheduled visits, laboratory

tests, lifestyle considerations, and other study procedures, including daily completion of the e-diary for 7 days after study vaccination; healthy participants as determined by medical history, physical examination (if required), and the clinical judgment of the investigator to be eligible for inclusion in the study; participants with preexisting chronic medical conditions determined to be stable in the clinical judgment of the investigator may be included; capable of giving signed informed consent.

Individuals were not eligible for inclusion in the study if they met of the exclusion criteria as described in Section 6.1.3, with the following specifications/additions:

- Unstable chronic medical condition or disease requiring significant change in therapy or hospitalization for worsening disease within 3 months before receipt of study intervention.
- Known infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus
- Current alcohol abuse or illicit drug use. Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales.
- Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s).
- Pregnant females; breastfeeding females; and women of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in the protocol for the duration of the study.
- Men who are unwilling to comply with contraception methods as outlined in the protocol for the duration of the study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

RSVpreF: see Section 6.1.4.

- Lots:
  - Lot 1: EN3327
  - Lot 2: EN3313
  - Lot 3: EN3329

Placebo: see Section 6.1.4.

- Lots: DC8153

6.2.5 Directions for Use

See Section 6.1.5.

6.2.6 Sites and Centers

The study was conducted in 17 sites in the United States.

6.2.7 Surveillance/Monitoring

Surveillance

Study oversight included Institutional Review Board or Independent Ethics Committee review and approval of the study protocol, any amendments, the informed consent, and other pre-approval information. Study centers were monitored by Pfizer and (b) (4), a Clinical Research Organization.

Safety Monitoring

As described in Section 6.1.7.

Immunogenicity Monitoring

Serum samples (collected prior to study vaccination [Visit 1] and 1 month after vaccination [Visit 2]) were assayed for RSV A and RSV B serum neutralizing titers (NT) and RSVpreF-binding IgG levels. RSV A and RSV B serum 50% NTs were determined and reported. IgG levels were determined against both RSV A and RSV B prefusion F antigens in a (b) (4) (b) (4) and reported as RSVpreF-binding IgG concentrations. All assays were performed at a Pfizer central Laboratory.

6.2.8 Endpoints and Criteria for Study Success

See Section 6.2.1, above, and Section 6.2.9, below.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The target to enroll approximately 1,000 participants assumed a 10% non-evaluable rate which would result in an evaluable population of 900 participants, with an estimated 225 participants in each study group. Overall power to declare immunologic consistency for RSV A and RSV B simultaneously was 93.3%.

Methods

Immunogenicity: For all the immunogenicity endpoints, the analysis was based on the evaluable immunogenicity population. Participants were summarized according to the vaccine group to which they were randomized.

Safety: The descriptive safety analyses were based on the safety population. Participants were summarized by vaccine group according to the study intervention they actually received.

Analysis Timing

Only a final analysis was performed.

Protocol Amendments

The original protocol was dated August 23, 2021.

Protocol Amendment 1 (February 8, 2022) included the following relevant changes:

- In response to CBER feedback, sample size was increased, and the estimated enrollment period was removed. Statistical methods, including sample size, and power calculations, were updated and lot consistency thresholds modified.

Changes in the Conduct of the Study and Planned Analyses

All analyses were performed as planned in the protocol except for the lot consistency thresholds which were modified in response to CBER feedback.

Please see the statistical review for further discussion.

6.2.10 Study Population and Disposition

A total of 1028 participants were enrolled in the study. The first participant was enrolled on October 21, 2021, and the last study visit was April 4, 2022.

6.2.10.1 Populations Enrolled/Analyzed

The Safety Population included all randomized participants who receive study intervention.

The Evaluable Immunogenicity Population included all participants who met the following criteria:

- Were eligible for the study
- Received the study intervention to which they were randomized at Visit 1
- Have a valid and determinate immunogenicity result from the blood sample collected within 27 to 42 days after vaccination
- Have no major protocol violations.

6.2.10.1.1 Demographics

The demographics of participants in the Safety Population are shown in Table 16. Among all participants in the Safety Population, the median age was 34 years, and the majority of participants were White (70.9%) and non-Hispanic/Latino (73.4%). The demographic characteristics were similar between the 3 vaccine lots and placebo groups. The demographics of the Safety Population also generally reflected what was observed in the Evaluable Immunogenicity Population (not shown).

Table 16. Demographic and Baseline Characteristics, Safety Population, Study 1014

Characteristic	RSVpreF Lot 1 N=249	RSVpreF Lot 2 N=247	RSVpreF Lot 3 N=249	RSVpreF Pooled Lots N=745	Placebo N=247
Sex, n (%)	--	--	--	--	--
Male	111 (44.6)	89 (36.0)	92 (36.9)	292 (39.2)	107 (43.3)
Female	138 (55.4)	158 (64.0)	157 (63.1)	453 (60.8)	140 (56.7)
Age, years	--	--	--	--	--
Mean age (SD)	34.2 (8.58)	33.8 (9.02)	33.9 (9.02)	34.0 (8.86)	34.5 (8.73)
Median age	35.0	33.0	34.0	34.0	35.0
Age range	(18, 49)	(18, 49)	(18, 49)	(18, 49)	(18, 49)
Race, n (%)	--	--	--	--	--
African American/Black	53 (21.3)	53 (21.5)	50 (20.1)	156 (20.9)	48 (19.4)
American Indian or Alaska Native	2 (0.8)	2 (0.8)	2 (0.8)	6 (0.8)	2 (0.8)
Asian	16 (6.4)	7 (2.8)	9 (3.6)	32 (4.3)	6 (2.4)
Native Hawaiian or other Pacific Islander	0	1 (0.4)	4 (1.6)	5 (0.7)	1 (0.4)
White	169 (67.9)	177 (71.7)	179 (71.9)	525 (70.5)	178 (72.1)
Multiracial	4 (1.6)	5 (2.0)	1 (0.4)	10 (1.3)	7 (2.8)
Unknown	1 (0.4)	0	2 (0.8)	3 (0.4)	1 (0.4)
Not reported	4 (1.6)	2 (0.8)	2 (0.8)	8 (1.1)	4 (1.6)

Characteristic	RSVpreF Lot 1 N=249	RSVpreF Lot 2 N=247	RSVpreF Lot 3 N=249	RSVpreF Pooled Lots N=745	Placebo N=247
Ethnicity, n (%)	--	--	--	--	--
Hispanic/Latino	65 (26.1)	68 (27.5)	55 (22.1)	188 (25.2)	60 (24.3)
Not Hispanic/Latino	180 (72.3)	174 (70.4)	189 (75.9)	543 (72.9)	185 (74.9)
Not reported	4 (1.6)	5 (2.0)	5 (2.0)	14 (1.9)	2 (0.8)

Source: Adapted from STN 125769/0 Study C3671014, Clinical Study Report, Table 6
Abbreviations: N=total number of participants in the specified vaccine group as administered, or the total sample; n=number of participants with the specified characteristic; SD=standard deviation

6.2.10.1.2 Participant Disposition

Disposition of Study 1014 participants are presented in Table 17. Of the 1,028 enrolled participants, 993 were randomized to receive one of three lots of RSVpreF (n=746) or placebo (n=247).

The Evaluable Immunogenicity Population, used for the primary analyses of immunogenicity, included a total of 948 participants, with 710 participants receiving one of three lots of RSVpreF and 238 participants receiving placebo. The percentages of participants excluded and reasons for exclusion from the Evaluable Efficacy Population were similar between the two treatment groups. The most common reason for exclusion (2.5% overall) was not having valid and determinate assay results from Visit 2 blood draw.

A total of 992 (99.9%) of the randomized participants received study intervention and were included in the Safety population, consisting of 745 participants in the RSVpreF groups and 247 participants in the placebo group. Of these participants, 97.7% (727 in the RSVpreF groups and 243 in the placebo group) completed the study.

A total of 22 participants (2.2%) withdrew from the study after receipt of study intervention. The reasons for withdrawal and proportions of participants withdrawn were similar between the three RSVpreF groups and the placebo group. Common reasons for withdrawal from the study after vaccination were lost to follow up (1.5%) and withdrawal by the participant (0.5%). There were no study withdrawals due to adverse events.

Table 17. Participant Disposition, All Enrolled, Study 1014

Population	RSVpreF Lot 1 N=249 n (%)	RSVpreF Lot 2 N=247 n (%)	RSVpreF Lot 3 N=250 n (%)	RSVpreF Pooled Lots N=746 n (%)	Placebo N=247 n (%)
Randomized Set	249 (100.0)	247 (100.0)	250 (100.0)	746 (100.0)	247 (100.0)
Safety population	249	247	249	745	247
Evaluable immunogenicity population	236 (94.8)	236 (95.5)	238 (95.2)	710 (95.2)	238 (96.4)
Total number of participants excluded from the Evaluable immunogenicity population	13 (5.2)	11 (4.5)	12 (4.8)	36 (4.8)	9 (3.6)

Population	RSVpreF Lot 1 N=249 n (%)	RSVpreF Lot 2 N=247 n (%)	RSVpreF Lot 3 N=250 n (%)	RSVpreF Pooled Lots N=746 n (%)	Placebo N=247 n (%)
Reason for exclusion					
Not eligible for this study	0	0	0	0	1 (0.4)
Did not receive study vaccine	0	0	1 (0.4)	1 (0.1)	0
Received study vaccine but not as randomized	1 (0.4)	1 (0.4)	0	2 (0.3)	0
Visit 2 blood draw outside 27-42 days after vaccination window	5 (2.0)	2 (0.8)	5 (2.0)	12 (1.6)	4 (1.6)
Had no valid and determinate assay results from Visit 2 blood draw	7 (2.8)	8 (3.2)	6 (2.4)	21 (2.8)	4 (1.6)
Participants withdrawn after vaccination	6 (2.4)	8 (3.2)	4 (1.6)	18 (2.4)	4 (1.6)
Reason for withdrawal					
Withdrawal by subject	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.7)	0
Lost to follow-up	5 (2.0)	5 (2.0)	2 (0.8)	12 (1.6)	3 (1.2)
No longer meets eligibility criteria	0	0	0	0	1 (0.4)
Other[a]	0	1 (0.4)	0	1 (0.1)	0
Completed the study	243 (97.6)	239 (96.8)	245 (98.0)	727 (97.5)	243 (98.4)

Source: Adapted from STN 125769/0 Study C3671014, Clinical Study Report, Tables 4 and 5.
Abbreviations: mITT=modified intent to treat; N=total number of participants randomized to the group; n=indicates number of participants fulfilling the item followed by the calculated percentage in parentheses (%).
Because Safety population is presented by vaccine group as administered, not as randomized, % was not presented.
a. Other reasons included: Relocation(n=1)

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoint

The primary immunogenicity endpoint was to demonstrate that the immune responses induced by 3 RSVpreF lots (Groups 1, 2, and 3) 1 month after vaccination were equivalent based on a 1.5-fold equivalence margin for both RSV A and RSV B antigens.

Primary Endpoint 1: Lot to Lot Consistency

Lot consistency across the 3 RSVpreF lots was achieved in the evaluable immunogenicity population and for both RSV A and RSV B. The 2-sided 95% CIs for the ratio of neutralizing GMTs (GMRs) at 1 month after vaccination for each pair of individual vaccine lots (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) were contained within the prespecified interval (0.667, 1.5) (Table 18).

Table 18. Ratio of 50% Neutralizing Geometric Mean Titers Between Individual RSVpreF Lots at 1 Month After Vaccination, Evaluable Immunogenicity Population, Study 1014

RSV Subgroup	RSVpreF Lot 1 to Lot 2 GMR[a] (95% CI[a])	RSVpreF Lot 1 to Lot 3 GMR[a] (95% CI[a])	RSVpreF Lot 2 to Lot 3 GMR[a] (95% CI[a])
RSV A	1.0 (0.9, 1.2)	1.1 (0.9, 1.2)	1.0 (0.9, 1.2)
RSV B	1.1 (0.9, 1.3)	1.1 (1.0, 1.3)	1.1 (0.9, 1.3)

Source: Adapted from STN 125769/0 Study C3671014, Clinical Study Report, Table 8.
Abbreviations: GMR=geometric mean ratio; LLOQ=lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
The evaluable immunogenicity population included all study participants who were eligible for the study; received study intervention to which they were randomized (each RSVpreF lot or placebo); with a valid and determinate immunogenicity result from the blood sample collected within 27 to 42 days after vaccination; and without major protocol violations.
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.

6.2.11.2 Subpopulation Analyses

The evaluation of lot consistency by sex was overall similar to that of the primary analysis, however for two comparisons (Lot 1/Lot 3, and Lot 2/Lot 3), when analyzed by male sex, the upper bound of the confidence interval of the GMR marginally crossed 1.5 for both RSV A (1.541 and 1.508, respectively) and RSV B (1.539 and 1.655, respectively). The small samples sizes limit the interpretability of these results.

6.2.12 Safety Analyses

There were 992 participants included in the Safety Population, of which 970 participants (97.7%) completed the study (727 RSVpreF recipients and 243 placebo recipients). For the discussion of safety analyses below, only the RSVpreF pooled lots will be shown instead of each of the 3 individuals lots as the safety profile was comparable across the 3 lots.

6.2.12.1 Methods

See Section 6.2.7 above.

6.2.12.2 Overview of Adverse Events

Table 19 provides an overview of the rates of adverse events in the pooled RSVpreF lots group compared to the placebo group during the study period. As expected, the rates of solicited local and systemic reactions were higher among RSVpreF recipients compared to placebo recipients. The rates of solicited unsolicited adverse events were similar across groups. There were no AEs leading to withdrawal from the study, no SAEs, and no deaths that occurred in either group throughout the entire study period of 1-month post-vaccination.

Table 19. Proportion of Participants Reporting at Least One Adverse Event Following Vaccination, Safety Population, Study 1014

AE Type: Monitoring Period[a]	RSVpreF Pooled Lots % (n/N)	Placebo % (n/N)
Immediate: 30 minutes	0.1 (1/745)	0
Solicited local reactions[b] at the injection site: Day 1-7	39.1 (290/742)	11.7 (29/247)
Grade 3 or above solicited local	0.5 (4/742)	0
Solicited systemic reactions[c]: Day 1-7	60.9 (452/742)	47.8 (118/247)
Grade 3 or above solicited systemic	1.3 (10/742)	1.2 (3/247)
Unsolicited: Through 1-month	5.5 (41/745)	6.1 (15/247)
Severe unsolicited AEs	0.5 (4/745)	0
Related unsolicited AEs	1.2 (9/745)	0

AE Type: Monitoring Period[a]	RSVpreF Pooled Lots % (n/N)	Placebo % (n/N)
Newly diagnosed chronic medical condition: through 1-month	0	0
AEs leading to study withdrawal: through 1-month	0	0
SAEs: through 1-month	0	0
Deaths: through 1-month	0	0

Source: Adapted from STN 125769/0 Study C3671014, Clinical Study Report, Tables 10, 14.14, and 14.18.
Abbreviations: AE=Adverse Event; N=total number of participants in the specified vaccine group as administered, or the total sample; for solicited local/systemic, N=number of participants with at least 1 day of e-diary data; n= number of participants who experienced the event; SAE=serious adverse event.
The Safety population included all enrolled participants who received the study intervention.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination.
b. Solicited local included pain, redness, and swelling at injection site.
c. Solicited systemic included fever ≥38.0°C, fatigue, headache, muscle pain, joint pain, nausea, vomiting, and diarrhea.

Solicited Adverse Reactions

Solicited local and systemic ARs with onset within 7 days after vaccination were assessed in all participants daily and were recorded by study participants using eDiaries. These included the assessment of local injection site reactions (pain, erythema and swelling) and systemic reactions (fatigue, headache, muscle pain, joint pain, nausea, vomiting, diarrhea, and fever defined as an axillary temperature of ≥38.0º C [100.4º F).

Solicited Local Adverse Reactions

Within 7 days post-vaccination, the proportion of participants reporting any local reaction was higher in the RSVpreF group (39.1%) compared to the placebo group (11.7%). The most frequently reported local reaction in both groups was pain at the injection site, reported by 36.9% of participants in the pooled RSVpreF lots group and 11.3% of participants in the placebo group. Severe (Grade 3) solicited local reactions were rare, reported by 4 (0.5%) and 0 participants in the RSVpreF and placebo groups, respectively.

Among those who received RSVpreF, the median day of onset of local reactions after vaccination was 2-3 days. Solicited local reactions had a median duration of 2 days.

Solicited Systemic Adverse Reactions

Overall, the incidences of systemic reactions within 7 days post-vaccination were higher in the pooled RSVpreF lots (60.9%) group as compared to the placebo (47.8%) group. Fatigue was the most frequently reported systemic AR (RSVpreF 42.7%; placebo 33.2%), followed by headache (RSVpreF 36.3%; placebo 28.3%) and muscle pain (RSVpreF 29.6%; placebo 10.9%). Fever was reported in 2% of participants in the pooled RSVpreF lots group and 0.8% in the placebo group. Fever with maximum temperature between 38.9 - 40.0°C were reported by 2 (0.3%) and 0 participants in the pooled RSVpreF lot and placebo groups, respectively. There were no reported cases of Fever >40.0°C that occurred within 7 days post-vaccination in any group. Overall, severe (Grade 3 or above) systemic ARs were reported in 1.3% of RSVpreF recipients and 1.2% of placebo recipients.

Among those who received RSVpreF, the median day of onset of solicited systemic ARs was between 2-3 days post-vaccination and the median duration was 1 to 2 days.

Unsolicited AEs

Immediate AEs

Unsolicited adverse events within 30 minutes of vaccination were reported by one participant who received RSVpreF Lot 2. These events were injection site erythema and injection site swelling, both assessed as moderate in severity. These events were considered related to the study vaccination by the investigator. Each event lasted for 3 days before completely resolving. There were no events clinically concerning for anaphylaxis.

Unsolicited AEs Within 1 Month After Vaccination

The proportions of participants who reported unsolicited AEs within 1 month after vaccination were similar across groups (5.5% pooled RSVpreF lots and 6.1% placebo). Adverse events that were assessed as related to study intervention by the investigator were reported in 1.2% of pooled RSVpreF lots recipients, while reported in none of the placebo recipients. The most common AEs considered related to RSVpreF was lymphadenopathy, reported by 5 (0.7%) vaccine recipients. The remainder of the related AEs primarily represented reactogenicity events.

6.2.12.3 Deaths

There were no deaths reported in this study.

6.2.12.4 Serious Adverse Events

There were no SAEs reported in this study.

6.2.12.5 AEs that Led to Study Withdrawal

There were no AEs that led to study withdrawal reported in this study.

6.2.13 Study Summary

Study 1014 was designed as a lot-to-lot consistency, immunogenicity, and safety study in healthy adults ages of 18 and ≤49 years. Participants received 1 dose of one of 3 lots of RSVpreF or placebo and were followed for 1 month after vaccination.

The primary immunogenicity endpoint of lot consistency was demonstrated for both RSV A and RSV B, with the resultant 2-sided 95% CIs for GMRs at 1 month after vaccination for each pair of individual vaccine lots (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) contained within the prespecified interval (0.667, 1.5).

Safety data from Study 1014 are available from 745 RSVpreF recipients and 238 placebo recipients, of which 970 participants (97.7%) completed the total study duration of 1-month post-vaccination. Solicited local and systemic ARs were mostly mild to moderate and of short duration. There were no meaningful imbalances in the overall rates of unsolicited adverse events within 1 month following vaccination between vaccine and placebo recipients. There were no deaths or serious adverse events reported in the study.

6.3 Study C3671001

NCT0359773
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 (RSV) Vaccine in Healthy Adults”

6.3.1 Objectives

Primary Objective and Endpoints:

1. To describe the safety and tolerability of RSVpreF given alone or concomitantly with seasonal inactivated influenza vaccine (SIIV).
   Endpoints
   a. Local and systemic ARs within 14 days after Vaccination 1
   b. AEs within 1 month after Vaccination 1
   c. Medically attended AEs and SAEs through 12 months after Vaccination 1
   d. AEs within 1 month after Vaccination 2

Secondary Objectives and Endpoints:

1. To describe the immune responses elicited by RSVpreF alone or with SIIV
   Endpoints
   a. RSV A– and RSV B–neutralizing Ab titers measured before Vaccination 1, and 2 weeks and 1, 2, 3, and 6 months after Vaccination 1

2. To describe the immune responses elicited by SIIV alone or with RSVpreF
   Endpoints
   a. Hemagglutinin-inhibition (HAI) titers for all strains in the SIIV measured before and 1 month after SIIV administration.
   b. H3N2-neutralizing Ab titers measured before and 1 month after SIIV administration.

Exploratory Objectives and Endpoints:

1. To describe the safety and tolerability of a second dose of RSVpreF given alone or concomitantly with SIIV
   Endpoints
   a. Local and systemic ARs within 14 days after Vaccination 3
   b. AEs within 1 month after Vaccination 3
   c. Medically attended AEs and SAEs through 12 months after Vaccination 3

2. To describe the immune responses elicited by a second dose of RSVpreF given alone or concomitantly with SIIV
   Endpoints
   a. RSV A– and RSV B–neutralizing Ab titers measured before Vaccination 3, and 1, 2, 6 and 12 months after Vaccination 3
   b. HAI titers for all strains in the SIIV measured before and 1 month after SIIV administration.

All endpoints were descriptive with no hypothesis testing planned.

Reviewer Comment
See Section 6.3.2 for study intervention at Vaccination 1, Vaccination 2, and Vaccination 3. Additional exploratory endpoints evaluated in this study included IgG titers against prefusion F and to nonvaccine RSV antigens at scheduled time points, H3N2-specific neutralizing Ab titers measured 1 month after SIIV administration, and RT-PCR positivity for RSV A and B pre-vaccination. Results from these less relevant endpoints will not be discussed in this review as they do not contribute substantially to the overall study conclusions.

6.3.2 Design Overview

Study C3671001 was a Phase 1/2 placebo-controlled, randomized and observer blind first-in-human dose-finding study designed to assess the safety and immunogenicity of different doses of RSVpreF with and without adjuvant in healthy adults ages 18-85 years old, to evaluate for immune interference when administered concomitantly with seasonal inactivated influenza vaccine (SIIV), and to assess the safety, tolerability and immunogenicity of a second dose of RSVpreF given alone or concomitantly with SIIV in a subset of the participants. This study was conducted from April 2018 to November 2019 at 36 sites in the US.

Participants were enrolled into two age subgroups (18-49 years and 50-85 years) and were randomized to receive RSVpreF at 3 escalating dose levels of 60 µg, 120 µg, and 240 µg, with or without aluminum hydroxide ($Al[OH]_3$), administered alone or concomitantly with SIIV, or placebo (Vaccination 1). This study utilized a sentinel cohort and an expanded cohort for each dose level in each age group. The age groups ran in parallel but independently from each other.

At one month after Vaccination 1 (Vaccination 2), a dose of placebo was administered to participants who received SIIV concomitantly with RSVpreF. For participants who received RSVpreF alone or placebo, a dose of SIIV was administered for Vaccination 2. At approximately 12 months after Vaccination 1, participants in the 240 µg dose group of the expanded cohort who received an initial dose of RSVpreF with or without $Al(OH)_3$ adjuvant were revaccinated with the same dose and formulation of the RSV vaccine alone or concomitantly with SIIV (Vaccination 3). At one month after Vaccination 3, a dose of placebo or SIIV was administered (Vaccination 4), depending on whether the participant received concomitant SIIV at Vaccination 3 or RSVpreF alone, respectively.

6.3.3 Population

Inclusion Criteria (in summary): Healthy (or with stable preexisting disease) male and female participants between 18 through 85 years of age

Exclusion Criteria (in summary): Significant or unstable preexisting disease or laboratory abnormality; pregnant or lactating; previous vaccination with any licensed or investigational RSV vaccine before enrollment or throughout the study; known systemic hypersensitivity to vaccine components; history of or active autoimmune disease including GBS; congenital or acquired immunodeficiency or immunosuppression; receipt of blood/plasma products within 60 days of investigational product administration; vaccination with any influenza vaccine within 6 months before investigational product administration

6.3.4 Study Treatments or Agents Mandated by the Protocol

RSVpreF:

- Dose: 60 µg, 120 µg, or 240 µg total dose of RSVpreF per injection in 0.5mL total injection volume.
- Formulation/Presentation: each lyophilized vial of RSVpreF investigational product was supplied as a mixture of equal quantities of 2 stabilized RSV prefusion F antigens, one from each of the RSV subgroups A and B. The lyophilized powder was reconstituted by diluent with either sterile water for injection or a sterile suspension of $Al(OH)_3$ in water for injection.
- Lots (Vaccination 1 and 3):
    - 60 µg RSVpreF: Lot 17-004158

- 120 µg RSVpreF: Lot 17-004209
- 240 µg RSVpreF: Lot 17-004063
- For formulations which contained $Al(OH)_3$: adjuvant aluminum hydroxide 0.4mg/mL; Lot 17-002894

Seasonal Inactivated Influenza Vaccine (SIIV):

- Quadrivalent SIIV was used for participants 18-49 years of age and high dose (HD) trivalent SIIV or quadrivalent SIIV was used for participants 65-85 years of age.
- For the 2018-2019 flu season (Vaccination 1 or 2):
  - HD trivalent SIIV (Fluzone HD) contained A/Michigan, A/Singapore, and B/Colorado strains; Lot UI981AA
  - Quadrivalent SIIV (Fluzone Quadrivalent) contained the 3 strains above plus the B/Phuket strain; Lot UI980AA
- For the 2019-2020 flu season (Vaccination 3 or 4)
  - HD trivalent SIIV (Fluzone HD) contained A/Brisbane, A/Kansas, and B/Colorado strains; Lot UJ236AA
  - Quadrivalent SIIV (Fluzone Quadrivalent) contained the 3 strains above plus the B/Phuket strain; Lot UJ257AC

Placebo: a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose)

6.3.5 Study Population and Disposition

A total of 1,235 participants were randomized and 1,233 received Vaccination 1. Of the vaccinated participants, 1,135 (91.9%) completed the 12-month follow up visit.

Demographics

In the overall safety population, the median age was 34 years for the 18-49 years age group and 70 years for the 50-85 years age group. The majority of participants were White (79.3%) and non-Hispanic (90.2%). Demographic characteristics were generally similar across vaccine groups.

> Reviewer Comment
> Compared to the 18-49 years age group, the 50-85 years age group had a higher proportion of men, a higher proportion of participants who identified as White, and higher proportion of participants who reported former tobacco use.

Disposition

All 1,233 vaccinated participants were included in the safety population. A total of 1,196 (96.8%) were included in the evaluable RSV immunogenicity population.

A total of 1,135 participants (91.9%) completed at least 12 months of follow-up after Vaccination 1. Of the participants who withdrew after the Vaccination 1, the most common reasons for withdrawal were lost to follow-up (39 [3.2%] participants) and withdrawal by participant (32 [2.6%] participants).

Of the 267 participants who consented for revaccination, 263 (98.5%) completed Vaccination 3 and 248 (92.9%) completed 12 months of follow-up after Vaccination 3.

Reviewer Comment
A total of 39 participants (3.2%) were excluded from the evaluable immunogenicity population, the majority due to not having blood test collected at the appropriate time. As the proportion of excluded participants was similar between the study groups, it is unlikely that these missing data would bias the study findings or impact the overall immunogenicity conclusions.

6.3.6 Immunogenicity Analyses

RSV Neutralizing Titers, for RSV Vaccination Alone, With and Without Adjuvant

RSV neutralizing titer (NT) geometric mean fold rise (GMFR) across the 6 RSVpreF dose level and formulation groups for RSV A and RSV B for the 50-85 years age group are shown in Table 20. Immunogenicity results for the younger age group of participants 18-49 years are not shown as they are not relevant to the proposed indication, but there was a general trend towards higher GMFRs in the younger age group compared to the older age group across all dose levels. These immune responses in RSVpreF vaccine recipients remained elevated compared to in placebo recipients through 12 months after Vaccination 1. For participants in both age groups, inclusion of $Al(OH)_3$ in the vaccine formulations resulted in no notable enhancement of the immune response compared to formulations without $Al(OH)_3$ at any antigen dose level.

Table 20. RSV 50% Neutralizing Titer GMFRs Compared to Before Vaccination 1, Sentinel and Expanded Cohorts – Evaluable RSV Immunogenicity Population (Age Group: 50 Through 85 Years), Study 1001

Subgroup and Timepoint	RSVpreF 60 µg (N=52) GMFR (n) (95% CI)	RSVpreF 60 µg + $Al(OH)_3$ (N=52) GMFR (n) (95% CI)	RSVpreF 120 µg (N=52) GMFR (n) (95% CI)	RSVpreF 120 µg + $Al(OH)_3$ (N=52) GMFR (n) (95% CI)	RSVpreF 240 µg (N=50) GMFR (n) (95% CI)	RSVpreF 240 µg + $Al(OH)_3$ (N=55) GMFR (n) (95% CI)	Placebo (N=50) GMFR (n) (95% CI)
RSV A	--	--	--	--	--	--	--
1 Month after Vaccination 1	10.0 (52) (7.40, 13.61)	8.9 (52) (6.69, 11.92)	10.1 (52) (7.39, 13.95)	12.6 (52) (9.17, 17.23)	11.4 (50) (8.62, 15.04)	11.5 (55) (8.63, 15.28)	1.1 (50) (0.85, 1.39)
6 Months after Vaccination 1	5.9 (51) (4.47, 7.71)	4.7 (51) (3.61, 6.21)	4.8 (52) (3.60, 6.52)	6.1 (50) (4.54, 8.33)	4.5 (50) (3.66, 5.59)	4.5 (54) (3.52, 5.74)	1.2 (49) (0.92, 1.51)
12 Months after Vaccination 1	4.0 (50) (3.00, 5.38)	3.8 (49) (2.86, 5.08)	3.9 (51) (3.01, 5.06)	4.4 (47) (3.24, 6.11)	2.5 (48) (1.49, 4.09)	3.1 (53) (2.18, 4.41)	1.2 (48) (0.92, 1.48)
RSV B	--	--	--	--	--	--	--
1 Month after Vaccination 1	11.0 (52) (8.02, 15.04)	10.1 (52) (7.36, 13.98)	9.5 (52) (6.60, 13.76)	13.5 (51) (9.69, 18.95)	12.1 (50) (8.94, 16.25)	13.1 (55) (9.85, 17.48)	1.0 (50) (0.79, 1.32)
6 Months after Vaccination 1	6.2 (51) (4.50, 8.57)	5.6 (51) (4.16, 7.59)	4.8 (52) (3.36, 6.82)	6.6 (49) (4.65, 9.28)	4.3 (50) (3.42, 5.46)	4.8 (54) (3.82, 6.15)	1.2 (49) (0.91, 1.64)
12 Months after Vaccination 1	4.1 (50) (2.90, 5.78)	3.9 (49) (3.20, 4.82)	3.4 (51) (2.55, 4.59)	4.2 (46) (3.02, 5.93)	2.5 (48) (1.58, 4.10)	3.2 (53) (2.18, 4.71)	1.1 (48) (0.88, 1.38)

Source: Adapted from STN 125769/0 Study C3671001, Clinical Study Report, Table 14.33
Abbreviations: GMFR=geometric mean fold rise; LLOQ=lower limit of quantitation; n=Number of subjects with valid and determinate assay results both before vaccination (Day 1) and at the specified time point; N=total number of participants in each vaccine group.
Note: The evaluable RSV immunogenicity population included all study participants who were eligible for the study; received study intervention as randomized at Visit 1; with a valid and determinate immunogenicity result from the blood sample collected within 27 to 42 days after Vaccination 1; and without major protocol violations as determined by the study clinician.
Note: The neutralizing titer LLOQ values were: A=50 and B=70. Assay values below LLOQ were set to 0.5 × LLOQ for analysis, with the exception of calculating the fold-rise when a before Vaccination 1 assay value was below LLOQ but a corresponding after vaccination assay value was LLOQ or above, where LLOQ was set for before Vaccination 1.
Note: For each vaccine dose and formulation group or placebo, the sentinel cohort and the group without SIIV from the expanded cohort are combined.
Note: GMFRs, relative to before Vaccination 1, and the corresponding 2-sided CIs were calculated by exponentiating the mean logarithm of the fold rises and the corresponding CIs (based on the Student t distr bution).

Reviewer Comment
The GMFR for RSV neutralizing antibodies for participants receiving the RSV vaccine alone (no SIIV coadministration) were higher in the younger age group than the older age group. This may be due in part to generally higher neutralizing antibody titers at baseline in the older age group compared to the younger age group. The GMFRs were generally comparable between RSV A and B. There was some dose effect seen in the younger age group with higher neutralizing antibody GMFR with the higher RSVpreF doses, but this was not observed in the older age group. There was no consistent improvement in GMFR with the addition of the $Al(OH)_3$ adjuvant in either age group.

RSV Neutralizing Titers After Administration of RSVpreF With and Without Concomitant SIIV

RSV neutralizing antibody geometric mean titer (GMT) were compared between participants vaccinated with RSVpreF and concomitant SIIV to those in participants vaccinated with RSVpreF alone (RSVpreF + placebo). RSV neutralizing antibody GMTs varied across dose levels, formulations, and age groups, with no consistent trend observed.

Hemagglutination Inhibition Assay Titers After Administration of RSVpreF With and Without Concomitant SIIV

Hemagglutination inhibition assay (HAI) titers against all influenza strains contained in the SIIV were compared between participants vaccinated with RSVpreF and concomitant SIIV to those in participants vaccinated with SIIV alone at Vaccination 2. In general, immune responses to SIIV trended lower for participants in either age group who received RSVpreF concomitantly with SIIV compared to participants who received SIIV alone at Vaccination 2. There was more notable interference with immune responses to SIIV at increased RSVpreF dose levels in participants in the 18 through 49 year age group. In contrast, no consistent dose-dependent effect was observed in the 65 through 85 years age group.

Rates of HI seroprotection (defined as HAI titers ≥1:40) 1 month after administration of SIIV for participants who received RSVpreF concomitantly with SIIV were generally lower when compared to participants who received SIIV alone at Vaccination 2, for all influenza strains tested. A similar trend was observed for the rates of seroconversion, defined as either a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40 or a prevaccination HAI titers ≥1:10 and a minimum 4-fold rise in postvaccination HAI titer.

Reviewer Comment
RSVpreF interference with SIIV immune responses was more notable in the younger age group than the older age group. The addition of the $Al(OH)_3$ adjuvant to the RSVpreF formulation did not have a consistent impact on SIIV immune responses. However, this study was not powered to formally evaluate for immune interference, given the small sample size of ~40 participants in each vaccine group.

Revaccination at 12 Months after Vaccination 1

For those participants who were revaccinated with RSVpreF (240 µg, with or without adjuvant) 12 months after Vaccination 1, RSV neutralizing titers increased at 1 month after revaccination, but the increase was lower than that observed after Vacciation 1. The RSV NT rate of decline was slower after revaccination compared to after Vaccination 1.

Reviewer Comment
All participants in the revaccination population received a higher dose level of RSVpreF for the initial vaccination and at 12 months after initial vaccination, compared to the 120

µg dose level proposed for licensure. Thus, the data obtained from the revaccination portion of this study is of unclear relevance.

6.3.7 Safety Analyses

Solicited local and systemic ARs were reported more frequently in the younger age group compared to the older age group. Solicited local ARs were more frequently reported in participants who received $Al(OH)_3$ adjuvant-containing formulations; however, no notable increase in systemic ARs were observed in participants receiving adjuvant-containing formulations. Most solicited local ARs were mild or moderate in severity. Among participants in the older age group, there was no consistent trend in differences in the rate of solicited systemic ARs in the groups which received RSVpreF concomitantly with SIIV compared to the groups which received RSVpreF alone. For those participants who were revaccinated 1 year after initial RSVpreF vaccination, the frequency and severity of solicited local and systemic ARs were similar to those seen after Vaccination 1.

The proportions of participants reporting any unsolicited AE within 1 month after Vaccination 1 and within 1 month after Vaccination 3 were generally similar across vaccine groups for both age groups and was slightly higher compared to in the placebo groups. There were no SAEs and no deaths in the study assessed by the investigator or by the FDA as related to the investigational product.

Reviewer Comment
Overall, the younger age group experienced greater reactogenicity compared to the older age group. There were no safety concerns observed in this study after either RSVpreF Vaccination 1 or 2 and no safety concerns associated with concomitant RSVpreF and SIIV administration.

6.3.8 Study Summary

RSVpreF elicited robust RSV neutralizing antibody responses without notable dose-dependent or adjuvant-dependent response. Immune responses to SIIV trended lower when concomitantly administered with RSVpreF across the vaccine groups, though this was less noticeable in the older age group compared to the younger age group. Additional data evaluating immune responses to SIIV when concomitantly administered with RSVpreF may be needed to address uncertainties associated with immune interference. Reactogenicity trended higher in the younger age group and with adjuvanted vaccine formulations. There were no safety concerns identified in this study. Based on these results, the 120 µg non-adjuvanted formulation of the vaccine was chosen for further clinical development.

6.4 Study C3671002

NCT03572062
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"

Study 1002 was a Phase 1/2, multicenter, randomized, placebo-controlled, observer-blind, dose- and formulation-finding study to describe the safety, tolerability, and immunogenicity of different formulations and dose levels of RSV candidate vaccine in adults 65 through 85 years of age. The study evaluated 3 dose levels RSVpreF (60 µg, 120 µg, and 240 µg) formulated with either aluminum hydroxide ($Al[OH]_3$) adjuvant alone or CpG (b) (4) and aluminum hydroxide [$(CpG)/Al(OH)_3$] adjuvants. A 240 µg RSVpreF vaccine candidate without any adjuvant was also

evaluated. All of the above RSVpreF vaccine candidates were administered concomitantly with seasonal inactivated influenza vaccine (SIIV). In addition, the 240 µg RSVpreF vaccine formulated with CpG/Al$(OH)_3$ adjuvant was evaluated when administered in a Month-0, Month-2 schedule without concomitant administration of SIIV. The study was conducted from June 2018 to August 2020 at 12 sites in Australia.

A total of 313 participants were vaccinated in the study (252 active vaccine and 61 placebo). There was no notable increase in RSV neutralizing antibody titers for RSVpreF formulations that contained CpG/Al$(OH)_3$ compared to RSVpreF formulations with Al$(OH)_3$ at any antigen dose level, or when compared to the RSVpreF 240 µg without adjuvant. In the cohort of participants who received two doses of vaccine administered in a Month-0, Month-2 schedule, there was no notable increase in immune response observed with revaccination 2 months after the first dose. These data supported the selection of the unadjuvanted formulation of RSVpreF, administered as a single dose, for further clinical development in Phase 3. Additional immunogenicity results from this study will not be discussed in this review as the study did not assess the final dose level and formulation of RSVpreF (120 µg, unadjuvanted) proposed for licensure.

Local reactions and systemic events were reported at similar frequencies across the RSVpreF groups with no clear association with dose level or formulation. The overall incidence of unsolicited AEs was similar across the vaccine and placebo groups. There were no SAEs and no deaths assessed by the investigator or by the FDA as related to the investigational product.

> Reviewer Comment
> There were no safety concerns identified in this study. All RSVpreF vaccine candidates elicited an immune response against RSV when administered alone or concomitantly with SIIV. There did not appear to be an added benefit to the addition of a CpG-containing adjuvant or to the administration of a second dose of RSVpreF 2 months after the first dose. These results when taken in conjunction with those from Study 1001, justified further development of the 120 µg non-adjuvanted formulation of the vaccine.

6.5 Study C3671004

NCT04071158
Title: “A Phase 2b, Placebo-Controlled, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine When Administered Concomitantly With Tetanus, Diphtheria, and Acellular Pertussis Vaccine (Tdap) in Healthy Nonpregnant Women 18 Through 49 Years of Age”

This Phase 2 study was designed to evaluate the safety and tolerability of concomitantly administered RSVpreF and Tdap and to demonstrate that the immune responses induced by Tdap and RSVpreF when administered concomitantly are noninferior to the immune responses induced by Tdap or RSVpreF alone in healthy non-pregnant women 18 through 49 years of age. A total of 709 participants were vaccinated in the study, at 16 sites in the US. Two different dose levels (120 µg and 240 µg), with and without Al$(OH)_3$, were evaluated in the study. The immunogenicity results will not be described in this review as the population studied differed from the proposed indicated population.

Most reported local and systemic ARs were mild or moderate in intensity, with generally higher rates of severe solicited systemic ARs in participants who received concomitant administration of RSVpreF and Tdap compared to those who received Tdap alone. There were no SAEs considered related to vaccine by the investigator or FDA.

Reviewer Comment
No new safety concerns were identified in this study.

6.6 Study WI257521

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"

Study WI257521 was a randomized, Phase 2, double-blind, placebo-controlled infectious human challenge study in healthy adult participants 18 through 50 years of age. The study enrolled 70 participants who met protocol-specified "sero-suitability" status (low RSV NT levels to the RSV-A Memphis 37b challenge virus), who were randomized 1:1 to receive either 120 µg RSVpreF or placebo via intramuscular injection one month prior to being challenged with RSV-A Memphis 37b (~4.5 Log_{10} plaque forming units) intranasally. Participants were admitted to a quarantine unit for 12 days after RSV challenge where they were monitored for symptoms, RSV shedding and for immune response. This study took place from September 2020 to August 2021 at a single site in the United Kingdom.

The proportion of participants with RT-PCR confirmed symptomatic RSV infection in the 12 days after challenge was lower in the RSVpreF group (6.5%) compared to the placebo group (48.4%), with vaccine efficacy (VE) point estimate of 86.7% (95% CI 53.8, 96.5). Similar results were seen for laboratory-culture confirmed symptomatic RSV infection. Viral load AUCs were also significantly lower in RSVpreF recipients compared to placebo recipients.

Pre-vaccination RSV A and RSV B neutralizing titers were comparable in RSVpreF and placebo groups. Pre-challenge (1 month after vaccination) and Day 12 post-challenge titers were notably higher in the RSVpreF than the placebo group. Both RSV A and RSV B titers continued to be higher in the RSVpreF group than the placebo group at the end of study follow-up on Day 155.

The frequency and severity of solicited local and systemic reactions through 7 days post vaccination were similar to those seen in prior studies with RSVpreF. The frequency of unsolicited AEs in the month after vaccination was similar in the RSVpreF and placebo groups. There were no SAEs assessed by the investigator or by the FDA as related to the study vaccine. One SAE was assessed by the investigator and the FDA to be related to the viral challenge: an event of subclinical myocarditis in a 21 year old male placebo recipient with onset 11 days after RSV viral challenge. The participant was found on routine lab work during the quarantine phase to have elevated troponins which down trended without intervention. He had no clinical symptoms, no electrocardiogram changes, but had a follow-up cardiac magnetic resonance imaging that was consistent with prior myocarditis. The participant continues to be clinically well and asymptomatic from the event of myocarditis as of the last follow-up visit at 6 months after viral challenge.

Reviewer Comment
In this human challenge study, RSVpreF immunization demonstrated efficacy against symptomatic RSV illness in healthy adults, with reduced viral loads detectable by RT-PCR. There were no new safety signals identified after administration of RSVpreF consistent with previous clinical studies. One case of subclinical myocarditis was observed in a placebo recipient after viral challenge. Myocarditis is a known rare complication of viral infections, including after natural RSV infection, and thus the occurrence of this adverse event was not unexpected.

7. INTEGRATED OVERVIEW OF EFFICACY

An Integrated Summary of Efficacy is not applicable to this review as Study 1013 was the only study with clinical efficacy evaluation of RSVpreF in the relevant age population.

8. INTEGRATED OVERVIEW OF SAFETY

Study 1013 contributed most study participant safety data for the final RSVpreF 120 µg formulation in the target population for licensure (adult participants ≥60 years of age). In the remaining 5 studies submitted to this BLA, only 88 participants ≥60 years of age received the final dose level and formulation of RSVpreF. The overall safety conclusions for RSVpreF are sufficiently characterized by data from Study 1013 and reflect the safety findings from the other supportive studies. Therefore, an integrated overview of safety is not applicable to this review.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The application did not contain data from clinical studies specifically addressing whether the vaccine is safe for use in pregnancy.

In a randomized controlled clinical trial (NCT04424316), 3,682 pregnant individuals received ABRYSVO and 3,676 received placebo at 24 through 36 weeks' gestation. The infant safety population included 3,568 and 3,558 infants born to individuals in the ABRYSVO or placebo group, respectively. Among the infants born to individuals in the ABRYSVO group and in the placebo group, 202 (5.7%) and 169 (4.7%), respectively, were born prematurely and 174 (4.9%) and 203 (5.7%), respectively, had reported congenital malformations or anomalies. There were 10 (0.3%) fetal deaths in the ABRYSVO group and 8 (0.2%) in the placebo group. (Kampmann et al, 2023).

9.1.2 Use During Lactation

The application did not contain data from clinical studies specifically addressing whether the vaccine is safe for use in lactating individuals. The following language is proposed for inclusion in the RSVpreF prescribing information:

"It is not known whether ABRYSVO is excreted in human milk. Data are not available to assess the effects of ABRYSVO on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ABRYSVO and any potential adverse effects on the breastfed child from ABRYSVO or from the underlying maternal condition. For preventative vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine. ABRYSVO is not approved for use in individuals younger than 60 years of age."

9.1.3 Pediatric Use and PREA Considerations

Safety and effectiveness of RSVpreF in individuals younger than 18 years of age have not been established.

As specified in the Pediatric Research Equity Act (PREA), the Applicant requested that the assessment of RSVpreF in individuals less than 18 years of age be deferred based on the following sections of the Food, Drug, and Cosmetics Act (FD&C Act):

Age group: 0 to <2 years of age

- Statutory reason:
  - Section 505B(a)(4)(A)(i)(II): Pediatric studies should be delayed until additional safety or effectiveness data have been collected.

Age group: 2 to <18 years of age

- Statutory reason:
  - Section 505B(a)(4)(A)(i)(I): The drug or biological product is ready for approval for use in adults before pediatric studies are complete.

The Applicant's request for deferred studies in individuals less than 18 years of age was reviewed by the FDA's Pediatric Review Committee (PeRC). PeRC agreed with the deferral request on April 4, 2023.

9.1.4 Immunocompromised Patients

The application did not contain data from clinical studies specifically addressing whether the vaccine is safe and effective for use in immunocompromised individuals. The following language is proposed for inclusion in the RSVpreF prescribing information:

"Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to Abrysvo."

9.1.5 Geriatric Use

Abrysvo is approved for use in individuals 60 years of age and older. In Study 1013, of the 17,215 recipients who received ABRYSVO 62% (n=10,756) were aged 60-69 years of age, 32% (n=5,488) were 70-79 years of age and 6% (n=970) were ≥80 years of age.

10. CONCLUSIONS

The BLA contains data from six clinical studies. The primary data to support the safety and effectiveness of RSVpreF was from Study 1013, in which 17,215 participants ≥60 years of age received RSVpreF.

Efficacy of RSVpreF in prevention of RSV-LRTD in individuals ≥60 years of age was demonstrated in Study 1013. At the primary analysis, with a median follow-up of 7 months post-vaccination, vaccine efficacy against laboratory-confirmed RSV-LRTD with ≥2 and ≥3 symptoms were 66.7% (96.66% CI 28.8, 85.8) and 85.7% (96.66% CI 32.0, 98.7), respectively. Vaccine efficacy was preserved in subgroup analyses by demographic and baseline characteristics, including in individuals ≥80 years of age and those with pre-specified significant conditions. A planned descriptive analysis of a secondary endpoint of VE against RSV-ARD demonstrated a VE of 67.9% (95% CI 49.1, 80.4). Most participants who met criteria for ARD also met the case definition for LRTD, confounding the interpretation of efficacy of RSVpreF against ARD alone. This secondary efficacy analysis will not be considered supportive of the additional indication proposed by the Applicant for prevention of acute respiratory disease caused by RSV. VE analysis for RSV-associated severe lower respiratory tract disease (RSV-sLRTD) was not performed at the time of the final analysis for the primary objective, as the minimum number of first episode RSV-sLRTD cases had not accrued; there were 2 cases of RSV-sLRTD in the placebo group and no cases in the RSVpreF groups.

The most frequently reported (>10%) solicited ARs among RSVpreF recipients were fatigue (15.5%), headache (12.8%), injection site pain (10.6%), and muscle pain (10.1%). The rates of grade 3 (severe) reactions were low, at 0.2% and 0.7% of local and systemic solicited adverse reactions, respectively. Within 1 month after vaccination, a numerical imbalance was noted in events of atrial fibrillation, with 10 events in the RSVpreF group and 4 events in the placebo group. Currently available information on the reports of atrial fibrillation by study participants is insufficient to determine a causal relationship with the vaccine. Rates of SAEs were balanced between study groups (2.3% in both groups). Three SAEs were considered to be possibly related to RSVpreF by the study investigator and FDA: an event of hypersensitivity, not classified as anaphylaxis, beginning 8 hours after vaccination; a case of Guillain-Barré syndrome (GBS) with onset 7 days after vaccination; and a case of Miller Fisher syndrome (considered a variant of GBS) with onset 8 days after vaccination. After the data cutoff date of July 14, 2022, one case of a sensory-motor axonal polyneuropathy was reported with onset of neurologic symptoms 21 days after vaccination. Review of the safety data from the 5 supportive studies did not reveal any additional safety concerns, however, the safety data in the populations enrolled in the supportive studies do not necessarily represent the safety experience of the target population for the proposed indication.

Study 1014 provided clinical evidence of manufacturing consistency.

Overall, the data provided in the application support the safety and effectiveness of RSVpreF for the indication of prevention of LRTD caused by RSV in individuals 60 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 21. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• RSV is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. • Among adults 65 years of age and older, RSV disease results in an average of 177,000 hospitalizations in the US per year with a mortality rate of 14.7 per 100,000. • RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans.	• LRTD due to RSV infection in older adults is a serious and life-threatening condition and can be associated with significant morbidity and mortality.
Unmet Medical Need	• Treatment for RSV infection is limited to supportive care. • During the BLA review for RSVpreF, an adjuvanted RSV vaccine was approved by the FDA for the prevention of LRTD caused by RSV in individuals ≥60 years of age. There are no other licensed vaccines available for the prevention of RSV disease.	• Currently, there is only one licensed vaccine for the prevention of LRTD caused by RSV.
Clinical Benefit	• In a population of >34,000 participants 60 years of age and older enrolled in an ongoing randomized placebo-controlled Phase 3 trial, vaccine efficacy against LRTD associated with RSV with at least 2 and at least 3 symptoms were 66.7% (96.66% CI 28.8, 85.8) and 85.7% (96.66% CI 32.0, 98.7), respectively. In this study, the median duration of follow-up for efficacy was 7 months. • Subgroup analyses of vaccine efficacy suggest that VE is preserved across demographic subgroups and among participants with co-morbidities associated with increased risk of more severe RSV disease. • Uncertainties in clinical benefit include the following: the duration of vaccine effectiveness; VE in immunocompromised and frail elderly individuals; VE in preventing severe LRTD cases; concomitant administration with vaccines routinely recommended for use in this population.	• The effectiveness of RSVpreF was supported by the demonstration of vaccine efficacy against LRTD associated with RSV in Study 1013. • The Applicant committed to further evaluate durability of protection through 2 RSV seasons, vaccine effectiveness after re-vaccination, and vaccine effectiveness in immunocompromised individuals. • The Applicant has an ongoing study evaluating concomitant administration of RSVpreF with a seasonal influenza vaccine.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most commonly reported (>10%) solicited ARs among RSVpreF recipients were fatigue (15.5%), headache (12.8%), injection site pain (10.6%), and muscle pain (10.1%); The rates of grade 3 (severe) reactions were low, at 0.2% and 0.7% of local and systemic solicited adverse reactions, respectively. • Within 1 month following vaccination, a numerical imbalance was noted in events of atrial fibrillation, with 10 events in the RSVpreF group and 4 events in the placebo group. • One case of sensory-motor axonal polyneuropathy was reported in Study 1013 with onset 21 days following administration of RSVpreF. • Two cases of Guillain-Barré syndrome (GBS) were reported in Study 1013, with onset 7 and 8 days following administration of RSVpreF.	• The data submitted adequately characterizes the reactogenicity of RSVpreF in adults 60 years of age and older. • Currently available information on atrial fibrillation is insufficient to determine a causal relationship with the vaccine. Further evaluations in postmarketing studies are needed to assess atrial fibrillation following vaccination. • Two cases of GBS among approximately 17,000 vaccine recipients is above the expected background rate for GBS in this age group. Further evaluations in postmarketing studies are needed to assess Guillain-Barre syndrome and polyneuropathies following vaccination. • The safety of RSVpreF is acceptable for its intended use.
Risk Management	• See “Clinical Benefit” and “Risk” sections above.	• The safety data provided in the prescribing information adequately describes the risks. • The Applicant’s proposed pharmacovigilance plan will evaluate the risk of GBS, atrial fibrillation and other uncommon adverse events that may be associated with RSVpreF vaccination.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of RSVpreF in individuals 60 years of age and older in preventing RSV-associated LRTD is favorable compared to the risks associated with vaccination. Data submitted to this BLA establish the safety and effectiveness of RSVpreF among individuals 60 years of age and older. The safety of RSVpreF is adequately described in the prescribing information and the Applicant’s pharmacovigilance plan is adequate for monitoring AEs and evaluating identified safety concerns, including risk of GBS, in postmarketing studies.

11.3 Discussion of Regulatory Options

The Applicant originally proposed an indication of prevention of acute respiratory disease and lower respiratory tract disease. Due to the overlap in case definitions between the lower respiratory tract disease and acute respiratory disease endpoints, and the descriptive analysis of ARD, FDA determined that the available data would most appropriately support the more clinically relevant indication limited to prevention of lower respiratory tract disease due to RSV (see Section 6.1 and in Section 10).

Data provided in the application did not adequately address the duration of vaccine effectiveness, VE in immunocompromised and frail elderly individuals, and VE in preventing severe LRTD cases. The interpretation of efficacy in individuals ≥80 years of age was limited by the small number of individuals in this subgroup. In addition, the safety and immunogenicity data regarding concomitant administration with vaccines routinely recommended for use in adults ≥60 years of age need further evaluation. Overall, the data provided in the application support the safety and effectiveness of RSVpreF for the indication of prevention of LRTD caused by RSV in individuals 60 years of age and older.

11.4 Recommendations on Regulatory Actions

Based on the clinical data provided in the application, the clinical reviewer recommends approval of RSVpreF for the prevention of lower respiratory tract disease caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older.

11.5 Labeling Review and Recommendations

The proprietary name Abrysvo was reviewed by the Advertising and Promotional Labeling Branch and found acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

The Applicant will conduct passive and active surveillance activities for continued vaccine safety monitoring, including routine pharmacovigilance.

The Applicant has identified immunocompromised older adults as an area of missing information and has proposed to conduct a postmarketing safety study in this population.

Based on review of the submission, the FDA has determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the Federal Food, Drug, and cosmetic Act (FDCA) will not be sufficient to assess a signal of a serious risk of Guillain-Barré syndrome (GBS). Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk. Therefore, the Applicant is required to conduct the following study as a postmarketing requirement (PMR) safety study:

- A postmarketing retrospective cohort study utilizing Centers for Medicare and Medicaid Services (CMS) claims data, to evaluate the serious risk of Guillain-Barré syndrome (GBS) among approximately 1.5 million older adults vaccinated with ABRYSVO in the United States (Study C3671031).

To further evaluate the important potential risk of atrial fibrillation, the Applicant has proposed the following post-marketing study to be conducted as safety-related postmarketing commitment:

- A Post-Marketing Active Surveillance Safety Study of Atrial Fibrillation Following ABRYSVO Among Older Adults in The Veterans Affairs Health System (Study C3671037).

The Applicant has identified immunocompromised older adults as an area of missing information and has proposed the following post-marketing study to be conducted as a voluntary study:

- An Active Safety Surveillance Study among Immunocompromised Adults Aged ≥ 60 Years Receiving Respiratory Syncytial Virus Prefusion F Vaccine in the US