Vaccines and Related Biological Products Advisory Committee Meeting
February 28, 2023

FDA Briefing Document

Respiratory Syncytial Virus Vaccine
(Proposed Trade Name: Abrysvo)

Applicant:
Pfizer, Inc.

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Glossary

AE	adverse event
ARI	acute respiratory illness
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
eDiary	electronic diary
ERD	enhanced respiratory disease
FDA	US Food and Drug Administration
FI-RSV	formalin-inactivated RSV
GBS	Guillain-Barré Syndrome
LB	lower bound
LRTI	lower respiratory tract infection
LRTI-RSV	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
PASS	post-authorization safety study
PCR	polymerase chain reaction
preF	prefusion F protein
PT	MedDRA preferred term
PVP	pharmacovigilance plan
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SIIV	seasonal inactivated influenza vaccine
sLRTI-RSV	severe RSV-associated lower respiratory tract illness
SMQ	standard MedDRA query
SOC	system organ class
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On September 30, 2022, Pfizer, Inc. (the Applicant) submitted a Biologics License Application (BLA) to the US 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 caused by Respiratory Syncytial Virus (RSV) in individuals 60 years of age and older." RSVpreF is a bivalent 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 were randomized to receive a single dose of RSVpreF (n=17,215) or placebo (n=17,069). Submission of the BLA followed a successful protocol-specified interim analysis (considered the primary analysis) that evaluated primary efficacy endpoints of laboratory-confirmed RSV-associated lower respiratory tract illness (LRTI-RSV) with ≥2 symptoms and ≥3 symptoms with onset at least 14 days after vaccination. As of the July 8, 2022 data cutoff, the median duration of follow-up for efficacy was approximately 7 months.

Vaccine efficacy (VE) in preventing laboratory-confirmed LRTI-RSV 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 LRTI-RSV 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 analysis of a secondary endpoint of VE against RSV-associated acute respiratory infection (ARI-RSV) demonstrated a VE of 62.1% (95% CI 37.1, 77.9), however, not all swabs collected from ARI cases have been tested as of the data cutoff. As of the data cutoff, there were 2 cases of severe LRTI-RSV in the study, both among placebo recipients. While vaccine efficacy appears to be preserved among participants ≥80 years of age, and among participants with at least one at-risk condition for severe RSV, interpretation is limited by small sample size and low case numbers for these subgroups.

Data are not currently available on the following: the duration of vaccine effectiveness; VE in immunocompromised and frail elderly individuals; and VE in preventing severe LRTI cases. Only limited data on VE in individuals ≥80 years of age are included in subgroup analyses submitted to this BLA. Data on the durability of the immune response and safety and immunogenicity data regarding concomitant administration with vaccines routinely recommended for use in this population are also not available

Safety data from Study 1013 through the July 14, 2022, data cutoff for safety 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 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%); these were predominately mild and moderate, with 0.2% and 0.7% of local and systemic solicited adverse reactions, respectively, reported as grade 3 in severity. In general, solicited ARs were reported more commonly in the younger age

subgroup (60-69 years) compared to the older age subgroups. Most solicited ARs resolved within 1 to 2 days post-vaccination.

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, 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. Overall, there were no specific safety concerns identified in subgroup analyses by age, sex, race, ethnicity, country, or predefined at-risk condition.

As of the data cut-off, non-fatal 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 to be 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.

Adverse events that warrant postmarketing surveillance were considered during the FDA review. There were 2 GBS cases among 19,942 vaccinated participants in the clinical studies submitted to the BLA. In 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), the FDA has requested that the Applicant includes GBS and other immune-mediated demyelinating conditions in its Pharmacovigilance Plan (PVP) as an Important Potential Risk. To assess the risk of GBS and other immune-mediated demyelinating conditions among RSVpreF recipients post-licensure, FDA has requested that the Applicant propose a postmarketing safety study.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and vote on whether available safety and efficacy data support the licensure of RSVpreF to prevent lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

2. Background

2.1 General Product Information

Product name: Respiratory Syncytial Virus Vaccine

Proposed trade name: Abrysvo

Product description: Abrysvo is a bivalent recombinant stabilized prefusion F protein subunit vaccine (RSVpreF). It consists of equal amounts of prefusion F antigens from the two major RSV subgroups: RSV subgroup A prefusion F (60 µg) and RSV subgroup B prefusion F (60 µg).

Proposed indication: (Pfizer proposal) - Abrysvo is a bivalent vaccine indicated for the prevention of acute respiratory disease and lower respiratory tract disease caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older by active immunization.

Proposed dosage and administration: Abrysvo is a solution for injection supplied as a single dose vial of lyophilized powder containing 120 µg of RSV stabilized prefusion F protein (60 µg A and 60 µg B antigens) that is reconstituted with sterile water (diluent) provided in a prefilled syringe. A single dose after reconstitution is 0.5 mL. Abrysvo is administered as a single 0.5 mL dose injected intramuscularly.

2.2 Epidemiology

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 was seen in this age group 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 and threshold widely accepted as predictive of protection against RSV. The durability of naturally acquired immunity after RSV infection is also not well understood. Studies of immune response after RSV infection indicate an initial rise in serum antibody levels, with a return to baseline by 16-20 months post-infection (Falsey et al, 2006). Although high rates of re-infection and short durability of protection after infection were observed in an RSV human challenge study in young adults (Hall et al, 1991), another study among elderly individuals suggest that natural re-infection with RSV was rarely observed over two consecutive years (Johnson et al, 1962).

RSV strains are grouped within a single serotype but are separated into 2 major phylogenetic lineages (subtypes RSV-A and RSV-B) originally determined by cross neutralization studies and confirmed to be due mainly to antigenic differences in the RSV glycoprotein G. Currently, RSV-A and RSV-B strains are differentiated by sequences within the N-terminal 270 nucleotides of the RSV glycoprotein G gene. Both subtypes tend to co-circulate during each season, however, the prevalence of the RSV subtype dominating local annual outbreaks is variable and unpredictable.

2.3 Clinical Manifestations, Diagnosis, and Treatment

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. For older adults, treatment for RSV infection is limited to supportive care.

Palivizumab (Synagis; MedImmune), is a monoclonal antibody approved by the FDA for prevention of severe RSV disease in high-risk infants. Currently, there is no vaccine available for prevention of RSV disease.

2.4 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 priming by prior natural RSV infection (Acosta et al, 2016).

On May 17, 2017, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened to discuss the data needed to support clinical trials of candidate RSV vaccines in RSV-naïve infants, with a particular focus on mitigating the risk of ERD. The consensus among committee members was that although studies in adults and RSV-experienced infants would not necessarily predict subsequent risk of ERD for an RSV-naïve infant population, immunogenicity and safety data from these populations could be supportive of evaluation of RSV vaccine candidates in RSV-naïve infants.

3. FDA Review of Clinical Safety and Efficacy Data

3.1 Overview of Clinical Studies

Data from six clinical studies with RSVpreF were submitted to support the current Biologics License Application (BLA), summarized in Table 1 below. Study 1013 is an ongoing Phase 3 efficacy, immunogenicity and safety study with a single-dose regimen of 120 µg of RSVpreF in participants 60 years of age and older and is the focus of the BLA review. Results from Study 1013 are discussed in detail in Section 3.2. The remaining studies will not be discussed in this briefing document beyond this section.

Study C3671014 (referred to as Study 1014 throughout this document) is a Phase 3 lot-to-lot immunogenicity study intended to support manufacturing consistency; this study met the predefined study success criteria for demonstration of similar immune responses across 3 lots of RSVpreF. The safety database included 745 healthy adults 18 through 49 years of age who received one dose of RSVpreF. There were no SAEs and no deaths reported during this study, and no concerning safety events were observed.

Study C3671001 (referred to as Study 001 throughout this document) was a Phase 1/2 dose-finding study evaluating 3 dose levels of RSVpreF, with and without aluminum hydroxide adjuvant, in adults 18-85 years of age. Safety and immunogenicity data from Study 001 supported the selection of the 120-µg dose level of RSVpreF without adjuvant, as the final formulation to be tested in later phase studies, including Study 1013. At 12 months after initial study vaccination, a total of 212 participants in the 240-µg dose groups for RSVpreF (with or without adjuvant) were revaccinated with the same respective formulations of RSVpreF at the same dose level, with no concerning safety signals identified. This study also included study groups which received concomitant administration of RSVpreF and seasonal inactivated

influenza vaccine (SIIV); however, the immunogenicity endpoints were exploratory and only a small number of participants received the final RSVpreF formulation co-administered with SIIV. The Applicant is currently conducting a larger study to formally evaluate the safety and immunogenicity of RSVpreF when co-administered with SIIV.

Studies C3671002, C3671004, and WI257521 are supportive Phase 2 studies that do not evaluate the final formulation of RSVpreF and/or the age population (≥60 years) relevant to this BLA.

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	RSV preF 120ug (final), RSVpreF (60 µg, 120 ug, 240 µg) with $Al(OH)_3$ adjuvant, or without adjuvant. Subset: co-ad with SIIV; Subset: re-vaccination at 1 yr
C3671002	Phase 1 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 ug (final), RSVpreF 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

3.2 Study 1013

Study Title: A Phase 3 study to evaluate the efficacy, immunogenicity, and safety of respiratory syncytial virus (RSV) prefusion F subunit vaccine in adults.

3.2.1 Objectives

Primary Objectives

1. Efficacy: To demonstrate the efficacy of RSVpreF in preventing LRTI-RSV in the first RSV season following vaccination.
   Endpoint: LRTI-RSV cases
   a. VE, defined as the relative risk reduction of first-episode LRTI-RSV cases with ≥2 LRTI signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination).
   b. VE, defined as the relative risk reduction of first-episode LRTI-RSV cases with ≥3 LRTI signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination).

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. To describe the safety profile of RSVpreF as measured by the proportion of participants reporting local reactions and systemic events (7 days), AEs (1 month), and newly diagnosed chronic medical conditions (NDCMCs) and SAEs throughout the study

Secondary Objectives

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

Secondary objectives evaluated vaccine efficacy in preventing LRTI, severe LRTI-RSV (sLRTI-RSV), and ARI 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 briefing document.

3.2.2 Design

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. The study is being conducted in 240 sites in the United States (US), South Africa, Japan, Canada, Finland, the Netherlands, and Argentina. A target of 45,000 participants were to be enrolled and randomized 1:1 to receive a single intramuscular injection of RSVpreF or placebo,[1] with randomization stratified by age group: 60-69 years, 70-79 years, and 80 years and older. 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.

1 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.

Starting 14 days after study vaccination (study Day 15), all participants were actively monitored for onset of acute respiratory illness (ARI) symptoms. If the participant experienced 1 or more ARI symptoms (defined in Table 2), the participant was instructed to self-collect mid-turbinate nasal swabs, optimally on both ARI-Day 2 and ARI-Day 3 (where ARI-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 transcriptase polymerase chain reaction (RT-PCR) testing for RSV. Participants were monitored for onset of RSV-associated lower respiratory tract illness (LRTI-RSV) that was defined as ARI with ⩾2 or ≥3 LRTI signs/symptoms lasting more than 1 day during the same illness (defined in Table 2).

The primary efficacy objective evaluated the efficacy of RSVpreF to prevent RSV-associated LRTI-RSV (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 LRTI-RSV 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 LRTI-RSV cases with ≥2 symptoms. The primary efficacy objective would be achieved if the lower bound of the CI for VE against LRTI-RSV 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 LRTI-RSV 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 sLRTI-RSV 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.

For this study, an interim analysis was conducted when 44 first-episode LRTI-RSV cases with ≥2 symptoms occurred in the first RSV season through the ARI surveillance cutoff date of July 8, 2022. There were 16 first-episode LRTI-RSV cases with ≥3 symptoms using the same cutoff date; therefore, the interim analysis of this second primary endpoint was also conducted. The minimum number of first-episode severe LRTI-RSV 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 sLRTI-RSV, immunogenicity, rates and descriptions of LRTI associated healthcare resource utilization, and vaccine efficacy across both 1 and 2 seasons.

This study used a Data Monitoring Committee (DMC) to review unblinded cumulative safety data throughout the study and the interim analysis for efficacy. The DMC was independent of the study team and included only external members.

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 a 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.[2] Testing results were based on samples taken within 7 days after symptoms onset.

Table 2. Case Definitions for Study 1013

Study Endpoint	Study Definition
ARI-RSV	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 ARI symptom onset
LRTI-RSV with ≥2 Symptoms	ARI with ≥2 of the following LRTI 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 ARI symptom onset.
LRTI-RSV with ≥3 symptoms	ARI with ≥3 of the following LRTI 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 ARI symptom onset.
sLRTI-RSV	Meeting LRTI-RSV criteria plus at least 1 of the following: • Hospitalization due to LRTI-RSV • New/increased oxygen supplementation • New/increased mechanical ventilation, including continuous positive airway pressure

Source: STN 125769/0 Study C3671013 Clinical Study Report Table 3

2 RSV testing performed locally as part of routine care was considered valid when analyzed under the following conditions: a) A NAAT result positive for RSV was obtained using an FDA-cleared assay or b) A NAAT result was obtained in a laboratory that is currently CLIA-certified or has the equivalent US certification/accreditation (e.g., College of American Pathologists) or ex-US certification

Primary Efficacy Endpoint

The primary efficacy objective was to demonstrate the efficacy of RSVpreF in preventing LRTI-RSV in the first RSV season following vaccination. The following primary efficacy endpoints were evaluated:

1. Vaccine efficacy (VE), defined as the relative risk reduction of first-episode LRTI-RSV cases with ≥2 LRTI signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season, starting 14 days after study vaccination.

   Statistical Criterion for Success: Lower bound (LB) of the VE CI is >20%, with Pocock-adjusted CI.

2. VE, defined as the relative risk reduction of first-episode LRTI-RSV cases with ≥3 LRTI signs/symptoms in the RSVpreF group compared to the placebo group in the first RSV season, starting 14 days after study vaccination.

   Statistical Criterion for Success: LB of the VE CI is >20%, with Pocock-adjusted CI.

Vaccine efficacy definition: 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 2 primary endpoints 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 for the study was considered met if the statistical success criterion was met for the first primary efficacy endpoint of VE against LRTI-RSV with ≥2 symptoms.

Secondary Efficacy Endpoint

A secondary efficacy objective for the study was to describe the efficacy of RSVpreF in preventing ARI-RSV in the first RSV season following vaccination. The only secondary efficacy endpoint evaluated at the interim analysis was:

- VE, defined as the relative risk reduction of first-episode ARI-RSV cases in the RSVpreF group compared to the placebo group in the first RSV season, starting 14 days after study vaccination

No statistical success criterion was pre-specified for this secondary endpoint.

Additional secondary and exploratory efficacy endpoints were specified in the protocol but will not be discussed in this briefing document as they were not included in the interim analysis submitted to this BLA. Analyses of these additional endpoints, including the secondary endpoint of sLRTI-RSV, secondary endpoints of immunogenicity, and efficacy in prevention of LRTI over seasons 1 and 2, will be conducted with the end-of-Season 1 analysis and/or the end-of-study analysis.

Evaluation of Immunogenicity

Analyses of immunogenicity endpoints have not yet been conducted and were not included in the submission reviewed**.** Immunogenicity analyses will be included in the end-of-season-1 analysis, expected to occur around the end of February 2023.

Evaluation of Safety

The primary safety objective was to describe the safety profile of RSVpreF as measured by the percentage of participants reporting solicited local and systemic adverse reactions, unsolicited AEs, and SAEs. Solicited safety data were collected from the Reactogenicity Subset, consisting of participants from a subset of sites in the US and Japan selected based on projected recruitment and representativeness of the respective populations, and included local and systemic adverse reactions through 7 days following vaccination that were recorded using an electronic diary (eDiary). Digital thermometers and a measuring device were provided to measure temperature, redness and swelling. In all study participants, unsolicited AEs were collected from vaccination through 1 month after vaccination. NDCMCs, SAEs and AEs leading to study discontinuation will be collected from vaccination through the end of the study.

Analysis Populations

Populations used for the study analyses are displayed in Table 3 below. The Evaluable Efficacy Population was the primary population used for the analyses of efficacy. The eDiary 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 ARI or LRTI case.
eDiary Subset Safety Population	All participants included in the Reactogenicity Subset who received the study intervention and with at least 1 day of eDiary data transferred.

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

3.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition of 1013 participants who contributed to the analyses of efficacy are presented in Table 4 below. 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 ARI 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 4. Disposition, All Randomized Participants, 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 ARI-RSV case	72 (0.4)	68 (0.4)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 6 & 7.
Abbreviations: ARI-RSV=acute respiratory illness 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 (ARI 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

Disposition of 1013 participants who contributed to the analyses of safety are presented in Table 5. 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 3.2.6.

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.

Table 5. 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.

3.2.4 Demographics and Other Baseline Characteristics

The demographics of participants in the Safety Population are shown in Table 6. 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, the majority of 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 6. 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)
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 (%)	--	--
United States	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 characteristi
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).

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 7. 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
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.

3.2.5 Vaccine Efficacy

3.2.5.1 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 illness due to RSV (LRTI-RSV) for the first RSV season through the acute respiratory illness (ARI) 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 ARI surveillance was 211 days in both the RSVpreF and the placebo groups.

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

Primary Endpoint 1: LRTI-RSV with ≥2 Symptoms

As of the data cutoff date of July 8, 2022, there were 44 cases of first-episode LRTI-RSV 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: LRTI-RSV with ≥3 Symptoms

As of the data cutoff date of July 8, 2022, there were 16 cases of first-episode LRTI-RSV 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 LRTI-RSV With ≥2 or ≥3 Symptoms Starting 14 Days after Vaccination, Evaluable Efficacy Population, Study 1013

Efficacy 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], % (96.66% CI)
First episode of LRTI-RSV with ≥2 symptoms	11 (0.1) 1.2	33 (0.2) 3.6	66.7 (28.8, 85.8)
First episode of LRTI-RSV with ≥3 symptoms	2 (<0.1) 0.2	14 (0.1) 1.5	85.7 (32.0, 98.7)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 10, Table 11.
Abbreviations: LRTI-RSV=lower respiratory tract illness associated with RSV; N=total number of participants in each vaccine group; n=number of participants meeting the efficacy endpoint case definition from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022), followed by the calculated percentage in parentheses (%); 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 LRTI-RSV with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of LRTI-RSV with ≥2 symptoms cases. CI is obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending. Vaccine efficacy is demonstrated if the lower limit of this CI exceeds 20%.
b. person-years is defined as the total ARI surveillance duration days across all participants at-risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from vaccination date through death/ discontinuation/ surveillance cutoff date/major protocol deviation, whichever is earlier.
Note: Positive RSV test result was based on the Pfizer central laboratory test on those nasal swabs collected within 7 days after symptom onset. In the event that no nasal swabs from the central laboratory are available (either the swab was not obtained or the swab was taken outside of the 7-day window), results from a certified laboratory with nucleic acid amplification test (NAAT) for RSV can be used.

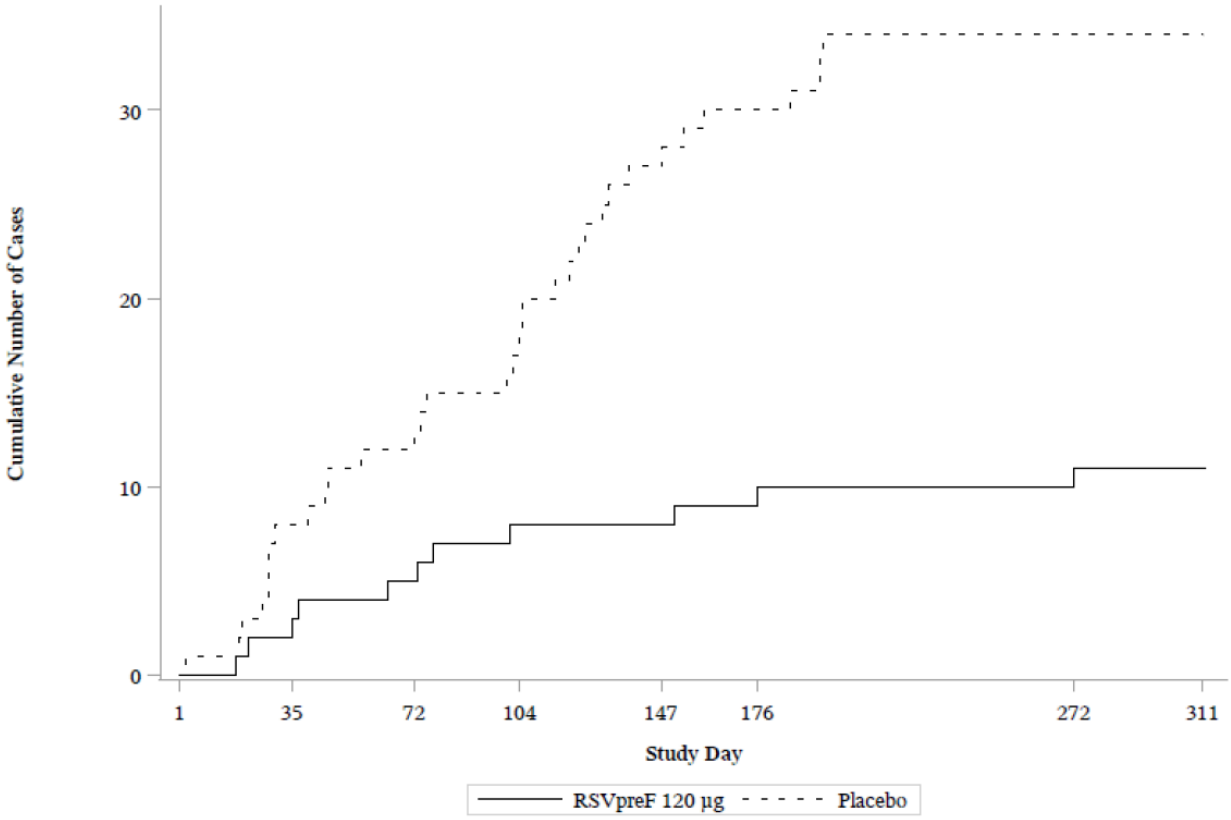
Analyses of the primary endpoints based on the mITT population, including cases which occurred prior to Day 15, yielded similar results as those shown above.

The median duration of symptoms of LRTI-RSV cases with ≥2 symptoms was comparable between the RSVpreF group (12 days) and placebo group (11.5 days). For LRTI-RSV 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 LRTI-RSV 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 LRTI-RSV with ≥3 symptoms (not shown) generally followed a similar pattern as that for LRTI-RSV 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 LRTI-RSV 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: LRTI-RSV=lower respiratory tract illness associated with RSV; mITT=modified intent to treat
Note: First episode of LRTI-RSV 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 poulation 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.

3.2.5.2 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 LRTI-RSV 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 the majority of the subgroup analyses (Table 9). In particular, 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 LRTI-RSV With ≥2 Symptoms Starting 14 Days After Vaccination, By Subgroup, 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	8/10,176	19/10,191	57.9 (-7.4, 85.3)
70-79 years	2/5,207	9/5,196	77.8 (-18.7, 98.1)
≥80 years	1/923	5/921	80.0 (-104.3, 99.7)
Sex	--	--	--
Male	6/8,327	17/8,225	64.7 (-0.6, 89.7)
Female	5/7,979	16/8,083	68.8 (3.9, 92.0)
Race	--	--	--
White	8/12,654	30/12,652	73.3 (36.9, 90.3)
Black or African American	3/2,131	2/2,162	-50.0 (-2143.8, 85.5)
Asian	0/1,341	1/1,330	100.0 (-5788.0, 100.0)
Ethnicity	--	--	--
Hispanic/Latino	1/5,603	7/5,601	85.7 (-25.1, 99.8)
Non-Hispanic/non-Latino	10/10,614	26/10,616	61.5 (12.8, 84.6)
Country[b]	--	--	--
United States	7/10,093	19/10,097	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	1/3,041	5/3,042	80.0 (-104.3, 99.7)
Prespecified at-risk condition	--	--	--
With no prespecified at-risk condition	5/7,992	17/7,912	70.6 (10.7, 92.4)
With ≥1 prespecified at-risk condition	6/8,314	16/8,396	62.5 (-8.4, 89.1)
With ≥1 chronic cardiopulmonary condition	4/2,420	6/2,498	33.3 (-213.7, 87.9)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 14.16.
Abbreviations: LRTI-RSV=lower respiratory tract illness associated with RSV; N=total number of participants in each vaccine group; n=number of participants meeting the efficacy endpoint case definition from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022), 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 LRTI-RSV with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of LRTI-RSV with ≥2 symptoms cases. CI is obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending.
b. No cases of LRTI with ≥2 symptoms occurred in Japan or Finland

Due to fewer participants meeting the criteria for LRTI-RSV with ≥3 symptoms than for LRTI-RSV 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.

3.2.5.3 Secondary Efficacy Analyses

First Episode of ARI-RSV

As of the data cutoff date, there were 80 cases of first-episode ARI-RSV reported occurring after Day 15, with 22 cases in the RSVpreF group compared to 58 in the placebo group. In a descriptive analysis of vaccine efficacy, the VE for this endpoint was 62.1% (95% CI: 37.1, 77.9) (Table 10).

Table 10. Vaccine Efficacy of RSVpreF Against First Episode of ARI-RSV 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)
First episode of ARI-RSV	22 (0.1) 2.4	58 (0.4) 6.3	62.1 (37.1, 77.9)

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 12.
Abbreviations: ARI-RSV=acute respiratory illness associated with RSV; N=total number of participants in each vaccine group; n=number of participants meeting the efficacy endpoint case definition from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022), followed by the calculated percentage in parentheses (%); 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 ARI-RSV cases in RSVpreF group divided by the total number of first episode of ARI-RSV cases. Nominal 95% CI is obtained using the conditional exact test based on the binomial distribution of P.
b. Person-years is defined as the total ARI surveillance duration days across all participants at-risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from vaccination date through death/ discontinuation/ surveillance cutoff date/major protocol deviation, whichever is earlier.
Note: Positive RSV test result was based on the Pfizer central laboratory test on those nasal swabs collected within 7 days after symptom onset. In the event that no nasal swabs from the central laboratory are available (either the swab was not obtained or the swab was taken outside of the 7-day window), results from a certified laboratory with nucleic acid amplification test (NAAT) for RSV can be used.

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 LRTI with at least 2 symptoms to support the evaluation of the primary efficacy endpoints. As a result, not all ARI cases with swabs collected within 7 days of symptom onset were tested and reported at the time of the interim analysis. The actual case count may be higher than the number reported in the analysis above, therefore at this time, the results of the analysis may not be reliable.

The median duration of symptoms of ARI-RSV cases was 8.5 days in the RSVpreF group and 11 days in the placebo group.

Severe LRTI-RSV

Because the pre-specified number of first-episode sLRTI-RSV 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 sLRTI-RSV reported, both among placebo recipients; both participants were hospitalized and one required supplemental oxygen.

3.2.5.4 Exploratory Analyses

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 LRTI-RSV With ≥2 or ≥3 Symptoms and ARI-RSV Starting 14 Days after Vaccination, By RSV Subgroup, 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], % (96.66 CI)
First episode of LRTI-RSV with ≥2 symptoms	--	--	--
RSV Subgroup A	1 (<0.1) 0.1	9 (0.1) 1.0	88.9 (10.6, 99.8)
RSV Subgroup B	10 (0.1) 1.1	23 (0.1) 2.5	56.5 (-0.7, 82.8)
First episode of LRTI-RSV with ≥3 symptoms	--	--	--
RSV Subgroup A	1 (<0.1) 0.1	3 (<0.1) 0.3	66.7 (-393.7, 99.6)
RSV Subgroup B	1 (<0.1) 0.1	10 (0.1) 1.1	90.0 (21.8, 99.8)
First episode of ARI-RSV	--	--	--
RSV Subgroup A	4 (<0.1) 0.4	12 (0.1) 1.3	66.7 (-10.0, 92.2)[c]
RSV Subgroup B	18 (0.1) 2.0	45 (0.3) 4.9	60.0 (29.5, 78.2)[c]

Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 10, 11, 12.
Abbreviations: LRTI-RSV=lower respiratory tract illness associated with RSV; N=total number of participants in each vaccine group; n=number of participants meeting the efficacy endpoint case definition from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022), followed by the calculated percentage in parentheses (%); 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 LRTI-RSV with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of LRTI-RSV with ≥2 symptoms cases. CI is obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending.
b. Person-years is defined as the total ARI surveillance duration days across all participants at-risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from vaccination date through death /discontinuation/ surveillance cutoff date/major protocol deviation, whichever is earlier.
c. 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 can be used.
One positive RSV polymerase chain reaction (PCR) test from local lab without subgroup information is included in the count of LRTI-RSV (but not included in any subgroup rows), as nasal swab was not colected within 7 days of symptom onset required for central testing.

Medically Attended LRTI-RSV

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 LRTI-RSV endpoints, are shown in Table 12. The VE point estimates were similar to those obtained in the primary efficacy analyses for the two LRTI-RSV endpoints (with ≥2 and ≥3 symptoms). The vast majority of the overall LRTI-RSV 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 LRTI-RSV 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 LRTI-RSV 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 LRTI-RSV with ≥2 symptoms	7 (<0.1) 0.8	20 (0.1) 2.2	65.1 (14.0, 87.5)
Medically attended LRTI-RSV 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, Table 3 in Appendix 1 of response to FDA IR #10
Abbreviation(s): ARI-RSV=acute respiratory illness associated with RSV; LRTI-RSV=lower respiratory tract illness associated with RSV; N=total number of participants in the specified group; n=number of first episode of each specified endpoint with symptom onset from Day 15 (14 days after vaccination) through surveillance cutoff date (08Jul2022); RSV=respiratory syncytial virus; VE=vaccine efficacy
Medically attended = any outpatient or inpatient visit such as hospitalization, ER visit, urgent care visit, home healthcare services, primary care physician office visit, pulmonologist office visit, specialist office visit, or telehealth contact, not including a visit to the study site.
Note: Positive RSV test result was based on the Pfizer central laboratory test on those nasal swabs collected within 7 days after symptom onset. In the event that no nasal swabs from the central laboratory are available (either the swab was not obtained or the swab was taken outside of the 7-day window), results from a certified laboratory with nucleic acid amplification test (NAAT) for RSV can be used.
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 ARI surveillance duration days across all participants at-risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from vaccination date through death /discontinuation/ surveillance cutoff date/major protocol deviation, whichever is earlier.

3.2.6 Safety

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.

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 3.2.6.3 for case descriptions). 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.

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 (35/17215)	0.2 (31/17069)
Solicited local[b] at the injection site: Day 1-7	12.2 (441/3621)	6.6 (235/3539)
Grade 3 or above solicited local	0.2 (8/3621)	<0.1 (2/3539)
Solicited systemic[c]: Day 1-7	27.4 (994/3621)	25.7 (909/3539)
Grade 3 or above solicited systemic	0.7 (27/3621)	0.6 (21/3539)
Unsolicited: Through the 1-month follow-up visit[d]	8.9 (1537/17215)	8.5 (1451/17069)
Related unsolicited AEs	1.3 (230/17215)	0.9 (159/17069)
Severe unsolicited AEs	0.4 (65/17215)	0.3 (51/17069)
Life-threatening unsolicited AEs	0.1 (24/17215)	0.1 (19/17069)
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	<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; based on updated dataset submitted Jan 6, 2023
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 who received vaccine (unsolicited) or with at least 1 day of eDiary data (solicited); n=number of participants who experienced the event; SAE=serious adverse event
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 included pain, redness, and swelling at injection site either reported in eDiary or AE CRF.
c. Solicited systemic included fever ≥38.0℃, fatigue, headache, muscle pain, joint pain, nausea, vomiting, and diarrhea either reported in eDiary or AE CRF.
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 the purpose of study group assignment, RSVpreF was assigned when at least one dose of RSVpreF was administered and placebo was assigned when placebo was administered for all vaccinations. When compared to the overall Safety Population, the proportion of participants with multiple vaccination was low, therefore inclusion of these participants in the safety analyses is not expected to significantly impact interpretation of safety data.

3.2.6.1 Solicited Adverse Reactions

Solicited local and systemic adverse reactions (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 [100.4º F).

Solicited Local Adverse Reactions

Table 14 includes the proportion of RSVpreF and placebo participants who reported any solicited local adverse reaction, 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 rare, 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, eDiary Subset Safety Population, Study 1013

Solicited Adverse Reaction	RSVpreF % (n/N)	Placebo % (n/N)
Any local reaction	12.2 (441/3621)	6.6 (235/3539)
Grade 1	9.6 (347/3621)	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	10.6 (385/3621)	6.0 (212/3539)
Grade 1	9.5 (343/3621)	5.3 (188/3539)
Grade 2	1.1 (40/3621)	0.7 (24/3539)
Grade 3	<0.1 (2/3621)	0
Erythema[b]	--	--
Any	2.7 (97/3619)	0.7 (23/3532)
Grade 1	1.5 (55/3619)	0.5 (16/3532)
Grade 2	1.1 (38/3619)	0.2 (7/3532)
Grade 3	0.1 (4/3619)	0
Swelling[b]	--	--
Any	2.5 (89/3619)	0.5 (16/3532)
Grade 1	1.5 (54/3619)	0.2 (8/3532)
Grade 2	0.9 (31/3619)	0.2 (6/3532)
Grade 3	0.1 (4/3619)	<0.1 (2/3532)

Source: Adapted from STN 125769/0 Phase 3 Study C3671013, Clinical Study Report, Table 14.21; based on updated dataset submitted Jan 6, 2023
Abbreviations: N=number of participants with at least 1 day of eDiary data for the specific solicited local reaction in the group; n=Number of participants who experienced the event, or with maximum severity of grade 1, grade 2, or grade 3 based on the severity scales. Each participant was counted once
Note: Any reactogenicity reported in the eDiary or as related adverse events within 7-day of vaccination from eDiary subset safety population are included in this table.
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
b. Grade 1: 2.5 cm to 5.0 cm; Grade 2: >5.0 cm to 10.0 cm; Grade: >10.0 cm or grading scale per footnote a if reported outside of eDiary.

Solicited Systemic Adverse Reactions

Table 15 includes the percentages of RSVpreF and placebo participants who reported any solicited systemic adverse reaction, 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, eDiary Subset Safety Population, Study 1013

Solicited Adverse Reaction	RSVpreF % (n/N)	Placebo % (n/N)
Any systemic reaction	27.5 (994/3621)	25.7 (909/3539)
Grade 1	15.7 (570/3621)	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)[a]	0	<0.1 (1/3539)
Fatigue[b]	--	--
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[b]	--	--
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[b]	--	--
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[b]	--	--
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[b]	--	--
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)

Solicited Adverse Reaction	RSVpreF % (n/N)	Placebo % (n/N)
Vomiting[b]	--	--
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)
Diarrhea[b]	--	--
Any	5.9 (214/3621)	5.2 (183/3539)
Grade 1	4.5 (162/3621)	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℃)	--	--
Any Fever	1.4 (52/3619)	1.4 (51/3532)
≥38.0-38.4°C	0.6 (23/3619)	0.8 (27/3532)
>38.4-38.9℃	0.8 (28/3619)	0.6 (21/3532)
>38.9-40.0℃	<0.1 (1/3619)	<0.1 (2/3532)
>40.0℃	0	<0.1 (1/3532)

Source: Adapted from STN 125769/0 Phase 3 Study C3671013, Clinical Study Report, Table 14.34; based on updated dataset submitted Jan 6, 2023
Abbreviations: N=number of participants with at least 1 day of eDiary data for the specific solicited systemic reaction 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 systemic reactions include data collected in the eDiary and related AE from Day 1 to Day 7 after vaccination for a subset of study participants from selected sites.
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. 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 eDiary, not all of the eDiary reports have been classified as Grade 4 fevers per the protocol.
b. For vomiting (eDiary) – grade 1: 1 to 2 times in 24 hours; grade 2: >2 times in 24 hours; grade 3: requires intravenous hydration. For diarrhea (eDiary) – 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 (eDiary) and all related AEs– grade 1: does not interfere with activity; grade 2: some interference with activity; grade 3: prevents daily routine activity.

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.

3.2.6.2 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 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 (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 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 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. The majority 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 preferred term (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 3.2.6.3) 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 3.2.6.3).

Standard MedDRA queries

FDA conducted standard 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 3.2.6.3) 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. FDA review of these cases is ongoing.

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

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.

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 the 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.

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.

3.2.6.3 Serious Adverse Events

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.

Non-fatal SAEs

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 narrative 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 onset of symptoms 7 days 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 onset 8 days after receipt of RSVpreF. The participant reported 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 of 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. The background rate for GBS in the US among adults >60 years of age is approximately 1.5-3 cases per 100,000 people per year (Yen et al, 2022; Sejvar et al, 2011). Therefore, GBS is being considered an important potential risk.

3.3 Safety Review of Supporting Studies Submitted to the BLA

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

4. Pharmacovigilance Plan (PVP)

The applicant did not include any important identified or important potential risks in its pharmacovigilance plan (PVP). The applicant reported cases of GBS (n=1) and a GBS variant, Miller Fisher syndrome (MFS) (n=1), in RSVpreF-exposed participants in its pivotal Phase 3 study (Study 1013). Given the uncertain relationship between RSVpreF and GBS (including MFS) and other immune-mediated demyelinating conditions, FDA is recommending that the Applicant:

1. Add GBS and other immune-mediated demyelinating conditions to its PVP as an important potential risk;
2. Submit a proposal for a postmarketing safety study to assess the risk of GBS and other immune-mediated demyelinating conditions among individuals vaccinated with RSVpreF;

3. Conduct enhanced pharmacovigilance activities including expedited reporting (i.e., submission of 15-day reports) for all cases of GBS and other immune-mediated demyelinating conditions, regardless of label status or seriousness; and
4. Submit a summary and analysis of all cases of GBS and other immune-mediated demyelinating conditions in its Periodic Adverse Experience Report.

Additionally, FDA noted that allergic reactions (including anaphylaxis) is included in the applicant's proposed label (under Warnings and Precautions) but is omitted from its PVP. FDA is requesting that the applicant add allergic reactions to its PVP as an important potential risk.

In its PVP, the applicant included use in immunocompromised older adults as missing information, which the Applicant plans to address through a postmarketing study. For the postmarketing study, the Applicant aims to use real-world claims and/or electronic health record data to compare safety outcomes in RSVpreF-exposed and RSVpreF-unexposed immunocompromised adults aged ≥60 years.

5. Summary

Study 1013 contributed the primary data 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 illness (LRTI-RSV) 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. A majority of LRTI-RSV cases accrued in the study were RT-PCR confirmed to be RSV subgroup B. Analysis of the secondary endpoint of vaccine efficacy against RSV-associated acute respiratory illness (ARI-RSV) demonstrated a VE of 62.1% (95% CI 37.1, 77.9); however, not all swabs collected from ARI cases have been tested as of the data cutoff. As of the data cutoff, there were only 2 cases of severe LRTI-RSV in the study, both among placebo recipients. Descriptive analyses of VE against medically-attended LRTI-RSV with ≥2 or ≥3 symptoms were similar to those obtained for 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.

Data are not currently available on the following: the duration of vaccine effectiveness; VE in immunocompromised and frail elderly individuals; and VE in preventing severe LRTI cases. Estimation of VE in individuals ≥80 years of age was limited by the small number of individuals in this subgroup. Data on the durability of the immune response and safety and immunogenicity data regarding concomitant administration with vaccines routinely recommended for use in this population are also not available.

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 adverse reactions (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 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%). Among RSVpreF recipients, Grade 3 ARs reported by 0.2% and 0.7% of participants for local and systemic solicited adverse reactions, 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. 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. Non-fatal 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. Review of safety data from the 5 supportive clinical studies submitted to the BLA did not reveal any other cases of GBS or other immune-mediate demyelinating condition post-vaccination, or any other safety signal. Given the higher than background rate of GBS observed in the Phase 3 study, FDA will recommend a postmarketing study and enhanced surveillance for further evaluation of GBS and other immune-mediated demyelinating conditions with postmarketing use.

6. Topics for VRBPAC Discussion

The VRBPAC will convene 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.

7. References

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