Application Type	Original BLA
STN	125769/0
CBER Received Date	September 30, 2022
PDUFA Goal Date	May 31, 2023
Division / Office	DVRPA/OVRR
Clinical Reviewer(s)	Nadine Peart-Akindele, MD
Project Manager	Goutam Sen, PhD Paul Keller, PhD Laura Montague Vera Stupina, PhD
Priority Review	Yes
Reviewer Name	Rositsa B Dimova, PhD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Ye Yang, PhD Team Lead, VEB/DB/OBPV
	Tsai-Lien Lin, PhD Branch Chief, VEB/DB/OBPV
	John Scott, PhD Director, DB/OBPV
Applicant	Pfizer Inc.
Established Name	Respiratory Syncytial Virus (RSV) Bivalent Stabilized Prefusion F Subunit Vaccine
(Proposed) Trade Name	ABRYSVO
Pharmacologic Class	Respiratory Syncytial Virus (RSV) vaccine
Formulation(s), including Adjuvants, etc	120 micrograms (mcg) of RSV stabilized prefusion F protein (60 mcg A and 60 mcg B antigens)
Dosage Form(s) and Route(s) of Administration	0.5 mL dose administered intramuscularly
Dosing Regimen	A single 0.5 mL dose
Indication(s) and Intended Population(s)	Prevention of lower respiratory tract disease caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older by active immunization.

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GLOSSARY

AE	Adverse Event
ARI	Acute respiratory illness
ARI-RSV	Acute respiratory illness due to RSV
BLA	Biologics License Application
CBER	Center for Biologics Evaluation, Research and Review
CI	Confidence Interval
CSR	Clinical Study Report
FDA	Food and Drug Administration
IR	Information Request
LRTI	Lower respiratory tract illness
LRTI-RSV	Lower respiratory tract illness due to RSV
RCT	Randomized Controlled Trial
RSV	Respiratory Syncytial Virus
RSVpreF	Respiratory Syncytial Virus Prefusion F Subunit Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
sLRTI-RSV	Severe lower respiratory tract illness due to RSV
UK	United Kingdom
US	United States
VE	Vaccine Efficacy

1. Executive Summary

Pfizer, Inc. submitted an original Biologics License Application (BLA) on September 30, 2022 (STN 125769/0) for their Respiratory Syncytial Virus (RSV) stabilized prefusion F subunit vaccine ABRYSVO (also referred to as RSVpreF in this document) for the indication of prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

In this submission, the applicant submitted data and results of the ongoing pivotal phase 3 study C3671013, entitled "A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults." C3671013 is a multicenter, randomized, double-blind, placebo-controlled study in adults 60 years of age and older. The primary efficacy objective of the study is to demonstrate the efficacy of RSVpreF in preventing lower respiratory tract illness due to RSV (LRTI-RSV) in the first RSV season following vaccination. The primary safety objective is to describe the safety profile of RSVpreF as measured by the percentage of participants reporting local reactions, systemic events, adverse events (AEs), and serious adverse events (SAEs). The key secondary efficacy objective is to demonstrate the efficacy of RSVpreF in preventing severe lower respiratory tract illness due to RSV (sLRTI-RSV) in the first RSV season following vaccination. The data and analyses submitted in this application are based on data cutoff dates of July 8, 2022 (first acute respiratory illness symptom onset, for efficacy analyses) and July 14, 2022 (nasal swab collection, for efficacy analyses; safety analyses). The submitted Clinical Study Report (CSR) includes a completed analysis for the primary efficacy endpoints (LRTI-RSV), and interim analyses of the secondary efficacy endpoint of acute respiratory illness due to RSV (ARI-RSV) and of safety endpoints.

In study C3671013, up to 45,000 participants ≥60 years of age were planned to be randomized to receive a single dose of RSVpreF or placebo in a 1:1 ratio, with randomization stratified by age group (60-69 years, 70-79 years, and 80 years and older). Each participant was planned to participate in the study for up to 2 consecutive RSV seasons. The duration of each season was estimated to be between 6 and 9 months.

The study is event-driven with a target of 59 first-episode evaluable LRTI-RSV cases with ≥2 symptoms starting on or after Day 15 (after vaccination). An interim analysis was planned when the number of evaluable first-episode LRTI-RSV cases with ≥2 symptoms (primary endpoint) was at least 29. Interim analyses of first-episode LRTI-RSV with ≥3 symptoms and first-episode sLRTI-RSV were conducted if there were at least 15 and 12 evaluable cases, respectively. The interim analysis was planned to utilize a Pocock boundary based on actual cases at interim analysis among the total of 59 cases.

During the study, all participants were asked to complete a questionnaire (approximately weekly) using an e-diary starting on Day 15 after vaccination and at any time they develop symptoms of an acute respiratory illness (ARI) through the first and second RSV seasons. Nasal swabs from participants who experienced ARI symptoms were collected and sent to Pfizer for RT-PCR testing.

The study interim efficacy analysis was conducted when 44 first-episode LRTI-RSV cases with ≥2 symptoms had accrued in the first RSV season. The analyses also included 16 first-episode LRTI-RSV cases with ≥3 symptoms. The minimum number of first-episode sLRTI-RSV cases had not accrued as of the data cutoff date, and therefore analysis for this endpoint was not conducted. All study participants remained in blinded follow-up after the interim analysis.

By the time of the data cutoff date, there were 34,383 participants randomized to receive RSVpreF (n=17,197) or placebo (n=17,186). Among the 44 cases of LRTI-RSV with ≥2 symptoms starting on or after Day 15 after vaccination, 11 were in the RSVpreF group and 33 were in the placebo group, corresponding to an estimated vaccine efficacy (VE) of 66.7%, 96.66% CI (28.8%, 85.8%), meeting the prespecified study success criterion of the lower bound of the CI >20%. Among the 16 cases of LRTI-RSV with ≥3 symptoms starting on or after Day 15 after vaccination, 2 were in the RSVpreF group and 14 were in the placebo group, corresponding to a VE of 85.7%, 96.66% CI (32.0%, 98.7%), meeting the prespecified success criterion of the lower bound of the CI >20%. The applicant additionally included a descriptive interim analysis for the secondary endpoint of ARI-RSV, where a total of 103 (25 in the RSVpreF group and 78 in the placebo group) first episodes of ARI-RSV starting from Day 15 were accumulated, corresponding to a VE of 67.9%, 95% CI (49.1%, 80.4%).

The Safety Population included 17,215 RSVpreF recipients and 17,069 placebo recipients. As of the data cutoff date, 2227 (12.9%, 95%CI [12.4%, 13.4%]) RSVpreF recipients and 2179 (12.8%, 95% CI [12.3%, 13.3%]) placebo recipients reported at least 1 AE. Of these, 231 (1.3%, 95% CI [1.2%, 1.5%]) RSVpreF recipients and 160 (0.9%, 95% CI [0.8%, 1.1%]) placebo recipients reported events that were assessed as related to study intervention by the investigator. The majority of these events were reactogenicity-related. In addition, 396 (2.3%, 95% CI [2.1%, 2.5%]) RSVpreF recipients and 387 (2.3%, 95% CI [2.0%, 2.5%]) placebo recipients reported an SAE. There was 1 (0.0058%) RSVpreF recipient who experienced an SAE of Guillain-Barre syndrome and 1 (0.0058%) RSVpreF recipient who experienced an SAE of Miller Fisher syndrome. There were 52 (0.3%) deaths among RSVpreF recipients and 49 (0.3%) deaths among placebo recipients. However, none of the deaths were assessed as related to the study intervention by the investigator.

Local reactions were reported by 12.2% of the participants in the RSVpreF group and by 6.6% of the participants in the placebo group, with pain at the injection site being the most commonly reported reaction (10.6% versus 6%, respectively). At least one systemic event was reported by 27.5% of the participants in the RSVpreF group and by 25.7% of the participants in the placebo group. The most commonly reported systemic events after RSVpreF vaccination were fatigue (15.5%) and headache (12.8%). Please refer to the clinical review memo for details on the safety and conclusions.

A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held on February 28, 2023. The two questions posed to the committee for voting were: (1) “Are the available data adequate to support the safety of ABRYSVO

(RSVpreF) when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV?" and (2) "Are the available data adequate to support the effectiveness of ABRYSVO (RSVpreF) for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older?". Out of the 12 voting committee members, 7 voted "Yes", 4 voted "No", and 1 abstained to each of the two questions.

The applicant's statistical analyses were appropriate and consistent with those prespecified in the study protocol and Statistical Analysis Plan (SAP). I verified the key results presented in this application.

In conclusion, the submitted data suggest that RSVpreF is efficacious with respect to prevention of LRTI-RSV with ≥2 symptoms and LRTI-RSV with ≥3 symptoms during the first RSV season. The applicant described the safety profile of the vaccine for the safety follow-up period as of the data cut-off date.

2. Clinical and Regulatory Background

RSV may cause severe respiratory disease and lead to hospitalization and serious outcomes in older adults, especially among those with underlying medical conditions. The RSV seasonality in the United States lasts approximately 6 months with a peak during the winter months. Currently, there is no licensed vaccine for the prevention of RSV disease. Current treatments consist primarily of supportive care.

Pfizer, Inc. submitted an original BLA on September 30, 2022 (STN 125769/0) for their RSVpreF vaccine for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older.

The pivotal phase 3 study C3671013 entitled "A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults" serves as the primary evidence of effectiveness and safety for the sought indication. Additionally, the submission includes the Clinical Study Report (CSR) and datasets for the lot consistency study C3671014, as well as for the early phase studies C3671001, C3671002, and C3671004, and for the UK phase 2 human challenge study WI257521, which are intended to serve as supportive evidence for RSVpreF (Table 1, Section 5.3). As discussed with the applicant, integrated summary of safety was not required for this BLA due to the large sample size for the pivotal study C3671013, and the small number of participants of age ≥ 60 years old included in the supportive studies who received the final vaccine formulation.

A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to discuss Pfizer's application was held on February 28, 2023 (see Section 5.4).

2.1 Disease or Health-Related Condition Studied

RSV causes respiratory tract infections in individuals of all age groups. It may cause higher severity of RSV disease in older adults and those with comorbidities, such as congestive heart failure and chronic obstructive pulmonary disease (Shi et al., 2020). In

the US, for the period between 1999 and 2018, the mean mortality rate per 100 000 population due to RSV among adults aged 65 years or older had been estimated to be 14.7 (95% CI, 13.8-15.5) for RSV (Hansen et al., 2022).

References:
Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, Campbell H, Demont C, Nyawanda BO, Chu HY, Stoszek SK, Krishnan A, Openshaw P, Falsey AR, Nair H, RESCEU Investigators. (2020). Global Disease Burden Estimates of Respiratory Syncytial Virus–Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. *The Journal of Infectious Diseases*, Volume **222**, Issue Supplement_7, 1 November 2020, Pages S577–S583, https://doi.org/10.1093/infdis/jiz059

Hansen CL, Chaves SS, Demont C, Viboud C. (2022). Mortality Associated with Influenza and Respiratory Syncytial Virus in the US, 1999-2018. *JAMA Network Open*; **5(2)**:e220527; doi:10.1001/jamanetworkopen.2022.0527.

3. Submission Quality and Good Clinical Practices

Deficiencies related to the data standards format in the initial submission of the datasets were identified by the data standards reviewer. The issues were subsequently resolved with the submission of updated datasets on January 6, 2023 (STN 125769/0/10). Additionally, the data on the secondary endpoint of RSV-associated acute respiratory illness (ARI-RSV) in the initial and in the updated datasets were incomplete since the RSV test results were not available for all acute respiratory illness (ARI) events at the time of the submissions. The applicant explained that for RSV testing, priority was given to those ARI events that corresponded to the primary endpoints. The applicant subsequently submitted, on March 23, 2023, the updated Microbiology Specimen Study Data Tabulation Model (SDTM) dataset MB which contained the missing RSV test results as of the data cut-off date. The final submission quality is acceptable.

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

Please refer to the reviews by the corresponding discipline reviewers.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This review focuses on the efficacy and safety data from the pivotal Phase 3 study C3671013 collected up to the data cutoff of July 14, 2022.

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

This review is based on the revised datasets submitted to STN 125769/0/10 on January 6, 2023. The Clinical Study Report (CSR) and supporting documents (such as study protocol, SAP, etc.) were submitted under STN 125769/0/0 on September 30, 2022. Revisions to the datasets (submitted to STN 125769/0/10) led to changes in the safety

results. The updated tables, listings, and figures (TLFs) for unsolicited AEs were submitted to STN 125769/0/15 on January 17, 2023, and the updated TLFs for solicited AEs were submitted to STN 125769/0/17 on January 20, 2023. As noted above, data on the secondary endpoint of ARI-RSV submitted to STN 125769/0/10 were incomplete. An updated MB SDTM dataset with the missing RSV test results for assessment of ARI-RSV was submitted to STN 125769/0/42 on March 23, 2023.

5.3 Table of Studies/Clinical Trials

Studies conducted to support the licensure of RSVpreF are summarized in Table 1. Study C3671013 serves as the primary evidence of safety and effectiveness of RSVpreF for the proposed indication. The rest of the studies are considered supportive.

Table 1. Clinical Studies Included in the Biologics License Application.

Study (Country) **Study Start/Status**	**Study Design**	**Study Population**	**Treatment Groups / No. of Randomized Participants**
C3671013 (Global study: US, Canada, Finland, Japan, the Netherlands, South Africa, Argentina) August 31, 2021 Ongoing	A Phase 3 study to evaluate the efficacy, immunogenicity, and safety of RSVpreF vaccine in adults.	Healthy male and female participants ≥60 years of age	Placebo N=17,186 RSVpreF 120 µg N=17,197
C3671001 (US study) April 18, 2018 Completed: November 20, 2019 Expanded Cohort (Revaccination): April 18, 2018 Completed: December 28, 2020	A Phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding, first-in-human study to describe the safety, tolerability, and immunogenicity of RSVpreF vaccine in healthy adults.	Healthy male and female participants 18-85 years of age	**Sentinel Cohort (Vaccination 1)** RSVpreF 60 µg: N=24 RSVpreF 60 µg + Al(OH)3: N=24 RSVpreF 120 µg: N=24 RSVpreF 120 µg + Al(OH)3: N=24 RSVpreF 240 µg: N=24 RSVpreF 240 µg + Al(OH)3: N=24 Placebo: N=24
C3671002 (Australian study) June 5, 2018 Completed June 23, 2020	A Phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding, first-in-human study to describe the safety, tolerability, and immunogenicity of an adjuvanted RSVpreF vaccine in healthy older adults.	Healthy male and female participants 65-85 years of age	**Primary Cohort (with concomitant SIIV)** RSVpreF 60 µg + Al(OH)3: N=32 RSVpreF 60 µg + CpG/Al(OH)3: N=32 RSVpreF 120 µg + Al(OH)3: N=32 RSVpreF 120 µg +CpG/Al(OH)3: N=31 RSVpreF 240 µg + Al(OH)3: N=32 RSVpreF 240 µg +CpG/Al(OH)3: N=32 RSVpreF 240 µg: N=32 Placebo: N=31

Study (Country) Study Start/Status	Study Design	Study Population	Treatment Groups / No. of Randomized Participants
			Month-0, Month -2 Cohort (without concomitant SIIV) RSVpreF 240 µg +CpG/Al(OH)3: N=32 Placebo: N=31
WI257521 (UK study) September 21, 2020 Completed April 8, 2021	A Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, immunogenicity and efficacy of RSVpreF vaccine in a virus challenge model in healthy adults.	Healthy male and/or female participants 18-50 years of age	Placebo 35 RSVpreF 120 µg 35
C3671004 (US study) October 1, 2019 Completed December 11, 2019	A Phase 2b, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of RSVpreF vaccine when administered concomitantly with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy nonpregnant women 18 through 49 years of age.	Healthy nonpregnant female participants 18-49 years of age	RSVpreF 120 µg + Placebo: N=143 RSVpreF 120 µg + Tdap: N=143 RSVpreF 240 µg + Al(OH)3 + Placebo: N=143 RSVpreF 240 µg + Al(OH)3 + Tdap: N=143 Placebo + Tdap: N=141
C3671014 (US study) October 21, 2021 Completed April 4, 2022	A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of 3 lots of RSVpreF vaccine in healthy adults.	Healthy male and female participants 18 49 years of age	Placebo: N=247 RSVpreF 120 µg Lot 1: N=249 RSVpreF 120 µg Lot 2: N=247 RSVpreF 120 µg Lot 3: N=250

Abbreviations: M = Male; F = Female; W/B/O = White/Black/Other; Min/max = Minimum/maximum; Al(OH)3 = Aluminum hydroxide.
Source: Adapted from Tabular Listing of Clinical Studies Included in STN 125769/0.

5.4 Consultations

5.4.1 Advisory Committee Meeting

A VRBPAC meeting to discuss Pfizer's application was held on February 28, 2023. There was, particularly, a discussion among the committee members on the safety of the vaccine due to the observed 1 SAE of Guillain-Barre syndrome and 1 SAE of Miller Fisher syndrome in the RSVpreF group. The two questions posed to the committee for voting were: (1) "Are the available data adequate to support the safety of ABRYSVO

(RSVpreF) when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV?" and (2) "Are the available data adequate to support the effectiveness of ABRYSVO (RSVpreF) for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older?". Out of the 12 voting committee members, 7 voted "Yes", 4 voted "No", and 1 abstained to each of the two questions.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C3671013

Study C3671013 is ongoing. The data and analyses submitted in this application are based on data cutoff dates of July 8, 2022 (first acute respiratory illness symptom onset, for efficacy analyses) and July 14, 2022 (nasal swab collection, for efficacy analyses; safety analyses). In the submitted CSR, is a completed analysis for the primary efficacy endpoints (LRTI-RSV), and interim analyses of the secondary efficacy endpoint of ARI-RSV and of safety endpoints.

6.1.1 Objectives

The study objectives, endpoints, and estimands are given in Table 2. The endpoints definitions are given in Table 3.

Table 2. Study Objectives, Endpoints, and Population-level Summaries.

Objectives	Endpoints	Population-level Summaries
Primary Efficacy:	**Primary Efficacy:**	**Primary Efficacy:**
To demonstrate the efficacy of RSVpreF in preventing LRTI-RSV in the first RSV season following vaccination.	LRTI-RSV cases.	In participants in compliance with the key protocol criteria (Evaluable Efficacy Population): 1. 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). 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 on Day 15 after study vaccination).
Primary Safety:	**Primary Safety:**	**Primary Safety:**

Objectives	Endpoints	Population-level Summaries
To describe the safety profile of RSVpreF as measured by the percentage of participants reporting local reactions, systemic events, AEs, and SAEs.[a]	• Prompted local reactions (pain at the injection site, redness, and swelling). • Prompted systemic events (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain). • AEs. • NDCMCs. • SAEs.	In participants receiving study intervention: 1. The proportion of participants reporting prompted local reactions within 7 days following study intervention administration in a subset of participants. 2. The proportion of participants. reporting prompted systemic events within 7 days following study intervention administration in a subset of participants. 3. The proportion of participants reporting AEs through 1 month following study intervention administration. 4. The proportion of participants reporting NDCMCs throughout the study. [a] 5. The proportion of participants reporting SAEs throughout the study. [a]
Key Secondary Efficacy:	**Key Secondary Efficacy:**	**Key Secondary Efficacy:**
To demonstrate the efficacy of RSVpreF in preventing sLRTI-RSV in the first RSV season following vaccination.[c]	sLRTI-RSV cases.	In participants in compliance with the key protocol criteria (Evaluable Efficacy Population): VE, defined as the relative risk reduction of first-episode sLRTI-RSV cases in the RSVpreF group compared to the placebo group in the first RSV season (starting on Day 15 after study vaccination).
Secondary Efficacy:	**Secondary Efficacy:**	**Secondary Efficacy:**

Objectives	Endpoints	Population-level Summaries
To describe the efficacy of RSVpreF in preventing LRTI-RSV across 2 RSV seasons following vaccination. [c]	LRTI-RSV cases.	In participants in compliance with the key protocol criteria (Evaluable Efficacy Population): 1. 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, starting on Day 15 after study vaccination through 2 RSV seasons. 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, starting on Day 15 after study vaccination through 2 RSV seasons.
To describe the efficacy of RSVpreF in preventing LRTI-RSV in the second RSV season. [c]	LRTI-RSV cases.	In participants in compliance with the key protocol criteria (Evaluable Efficacy Population): 1. 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 second RSV season. 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 second RSV season.
To describe the efficacy of RSVpreF in preventing ARI-RSV at each RSV season and across 2 RSV seasons following vaccination.[a] [c]	ARI-RSV cases.	In participants in compliance with the key protocol criteria (Evaluable Efficacy Population): 1. 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) and in the second RSV season.a 2. VE, defined as the relative risk reduction of first-episode ARI-RSV cases in the RSVpreF group compared to the placebo group, starting on Day 15 after study vaccination through the first 2 RSV seasons.

Objectives	Endpoints	Population-level Summaries
To describe the efficacy of RSVpreF in preventing sLRTI-RSV across 2 RSV seasons following vaccination.[c]	sLRTI-RSV cases.	In participants in compliance with the key protocol criteria (Evaluable Efficacy Population): VE, defined as the relative risk reduction of first-episode sLRTI- RSV cases in the RSVpreF group compared to the placebo group, starting on Day 15 after study vaccination through 2 RSV seasons.
To describe the efficacy of RSVpreF in preventing sLRTI-RSV in the second RSV season.[c]	sLRTI-RSV cases.	In participants in compliance with the key protocol criteria (Evaluable Efficacy Population): VE, defined as the relative risk reduction of first-episode sLRTI- RSV cases in the RSVpreF group compared to the placebo group, in the second RSV season.
Secondary Immunogenicity[b]:	**Secondary Immunogenicity[b]:**	**Secondary Immunogenicity[b]:**
To describe the immune responses induced by RSVpreF following vaccination. [c]	RSV NT.	In the immunogenicity subset, participants in compliance with the key protocol criteria (Evaluable Immunogenicity Population): 1. GMT of NT for RSV A and RSV B at each time point after vaccination. 2. GMT of NT for RSV A and RSV B before vaccination. 3. GMFR of NT for RSV A and RSV B from before vaccination to each time point after vaccination.
Exploratory:	**Exploratory:**	**Exploratory:**
To describe the rate of LRTI and associated healthcare resource utilization. [c]	LRTI cases.	
To describe healthcare resource utilization associated with LRTI-RSV. [c]	LRTI-RSV cases.	
To describe the efficacy of RSVpreF in preventing sLRTI.[c]	sLRTI cases.	
To further describe the immune responses induced by RSVpreF following vaccination.[c]	RSVpreF-binding IgG.	

a. Results are for the first RSV season after vaccination up to the data cutoff dates.
b. There are no primary immunogenicity objectives, endpoints, or estimands in this study.
c. The results for these objectives will be reported by the applicant at a later time.
Abbreviations: NDCMC - newly diagnosed chronic medical condition.
Source: Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Table 1, p. 17.

Table 3. Study Endpoints Definitions.

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

Source: Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Table 3, p. 25.

6.1.2 Design Overview

Study C3671013 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety, immunogenicity, and efficacy of RSVpreF vaccine in adults 60 years of age and older. Up to 45,000 participants were to be randomized to receive RSVpreF or placebo in a 1:1 ratio, with randomization stratified by age group: 60-69 years (at least 6,000 participants), 70-79 years (at least 6,000 participants), and 80 years and older (at least 800 participants). Each participant was planned to participate in the study for up to two consecutive RSV seasons. The duration of each season was estimated to be six to nine months.

This was an event-driven study with a target of 59 first-episode evaluable LRTI-RSV cases (meeting the case definition in the Evaluable Efficacy Population). An interim analysis was planned when the total number of evaluable first-episode LRTI-RSV cases with ≥2 symptoms (primary endpoint) was at least 29. If the total number of evaluable

first-episode LRTI-RSV cases with ≥3 symptoms was at least 15, this endpoint would be included in the interim analysis. Additionally, if the total number of evaluable first-episode sLRTI-RSV cases was at least 12, this endpoint would be included in the interim analysis. The interim analysis would utilize a Pocock boundary based on actual cases at interim analysis among the total of 59 cases.

All participants were asked to complete a questionnaire (approximately weekly) using an e-diary starting on Day 15 after vaccination (where Day 1 is the day of vaccination). They were also instructed to complete a questionnaire at any time they develop symptoms of an ARI until the end of the first RSV season. The same procedure was planned to be used through the second RSV season.

If a participant experienced at least 1 of the ARI symptoms (Table 2), the participant was instructed to collect nasal swabs up to ARI-Day 7 (preferably on ARI-Day 2 and ARI-Day 3) after the onset of the ARI symptom(s) (where ARI-Day 1 is the day of onset of symptoms), return the swabs as instructed, and contact the site as soon as possible to arrange an unplanned respiratory illness visit. The swabs were collected by the site and sent to Pfizer for RT-PCR testing.

Approximately 600 participants from sites in the US and approximately 450 participants from sites in Japan were planned to be included in the immunogenicity subset. For these participants, blood samples were planned to be collected before vaccination, 1 month after vaccination, and prior to the start of the second RSV season for evaluation of immunogenicity.

Approximately 6000 participants from a subset of sites in the United States and approximately 450 participants from a subset of sites in Japan were planned to be included in the reactogenicity subset for assessment of solicited reactogenicity reactions after vaccination. This included collection of local and systemic reactions through an e-diary for 7 days after study vaccination (Days 1 through 7, where Day 1 is the day of vaccination).

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

For the present report, the interim efficacy analysis was conducted when 44 first-episode LRTI-RSV cases with ≥2 symptoms had accrued in the first RSV season through the ARI surveillance cutoff date of July 8, 2022. After the Data Monitoring Committee (DMC) declared success of first-episode LRTI-RSV cases with ≥2 symptoms, there were 16 first-episode LRTI-RSV cases with ≥3 symptoms using the same cutoff date; therefore, the interim analysis of that endpoint was conducted. The minimum number of 12 first-episode sLRTI-RSV cases had not accrued as of this cutoff date; therefore, the interim

analysis of this endpoint was not conducted. All study participants remained in blinded follow-up after the interim analysis.

6.1.3 Population

The study population consisted of male and female participants ≥60 years of age. Both healthy individuals and individuals with stable chronic cardiopulmonary conditions, such as chronic obstructive pulmonary disease (COPD), asthma, or congestive heart failure (CHF), were planned to be included.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study intervention includes a single intramuscular injection into the deltoid muscle of RSVpreF vaccine (120 μg) or placebo (matching the physical appearance of the vaccine).

6.1.6 Sites and Centers

As of the data cutoff date (July 14, 2022), this study was conducted at 240 sites in: the United States (158), South Africa (20), Japan (18), Canada (15), Finland (13), the Netherlands (12), and Argentina (4).

6.1.8 Hypotheses and Criteria for Study Success

For the primary efficacy objective and the key secondary objective, RSVpreF was to be compared to placebo, testing the following three hypotheses sequentially with an overall type I error rate of 2.5% (one-sided):

1. H0: VE ≤20% vs Ha: VE >20% against first episode of LRTI-RSV with ≥2 symptoms (as defined by ≥2 of the 5 LRTI signs/symptoms in the first RSV season);
2. H0: VE ≤20% vs Ha: VE >20% against first episode of LRTI-RSV with ≥3 symptoms (as defined by ≥3 of the 5 LRTI signs/symptoms in the first RSV season);
3. H0: VE ≤20% vs Ha: VE >20% against first episode of sLRTI-RSV in the first RSV season,

where H0 and Ha represent the null and alternative hypotheses, respectively. VE was defined as VE = 100 × (1 - risk ratio). Risk ratio was calculated as the ratio of the case count of first-episode confirmed cases in the RSVpreF group to the corresponding case count in the placebo group.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for study C3671013 (version 4, dated July 22, 2022) was pre-specified and was submitted with the application in STN 125769/0. A brief overview of the SAP is presented below.

Analysis populations: The definitions of the study Analysis Populations are shown in Table 4. The primary population for efficacy analyses was the Evaluable Efficacy

Population. Supplementary analyses were planned using the modified Intent-to-Treat (mITT) Efficacy Population.

Table 4. Analysis Populations.

Population	Description
Safety Population	All enrolled participants who receive the study intervention.
mITT Efficacy Population	All participants who were randomized and received study intervention.
Evaluable Efficacy Population	All study participants who meet the following criteria: 1. Are eligible for the study. 2. A minimum follow-up through Day 15 after vaccination (surveillance end date – vaccination date ≥14 days.). 3. Received study intervention to which they were randomized (RSVpreF or placebo). Participants who received multiple vaccinations due to multiple enrollments from different sites are considered as having NOT met this criterion. 4. Had no major protocol violations before the symptom onset date of the confirmed ARI or LRTI case.
E-diary Subset Safety Population	All participants included in the reactogenicity subset who received the study intervention and with at least 1 day of e-diary data transferred.

Source: Statistical Analysis Plan for Protocol C3671013, Version 4, dated July 22, 2022, p. 35-36.

Analyses for the Primary Efficacy Endpoints and the Key Secondary Efficacy Endpoint:

Primary Analyses

VE was estimated based on the case count ratio. This method assumes that the cases follow a Poisson distribution and assumes equal person-time of follow-up.

(b) (4)

where:

C_v = number of cases in the RSVpreF group
C_p = number of cases in the placebo group
P = number of cases in the RSVpreF group divided by the total number of cases (combined RSVpreF and placebo)

The CIs for VE were derived from the conditional exact test based on the binomial distribution of P (the number of cases in the RSVpreF group, given the total number of cases in both groups).

Participants who discontinued from the study because of either loss to follow-up or death were assumed to have no cases after the discontinuation for the analysis of efficacy-related endpoints. Additional analyses with follow-up time adjusted or time-to-event hazard ratio (HR) were conducted to assess the impact of such assumption.

Sensitivity/supportive Analyses: Person-time follow-up adjusted VE and VE based on hazard ratio (using Cox regression). Analyses in the mITT Efficacy Analysis Population was also planned.

Subgroup analysis: For the primary endpoints, exploratory subset analysis was planned for RSV A, RSV B, and RSV A and B cases. Additionally, subgroup analyses by age

group (60-69 years, 70-79 years, and ≥80 years), sex, race, ethnicity, risk status, and country were also planned.

Analyses for the Primary Safety Endpoints:
Participants were summarized by vaccine group according to the study interventions they actually received (Safety Population, E-diary Subset Safety Population). The proportion of participants reporting each event and the respective 95% CIs based on the Clopper-Pearson method were reported. The 95% CI for the difference in the proportions (between study intervention group) were computed using the Miettinen and Nurminen method.

Interim Analyses (IA): According to the protocol, an IA may be performed when the total number of evaluable first episode LRTI-RSV cases with ≥2 symptoms is at least 29. A total of 3 analyses were planned.

1. First IA:
    a. If the total number of evaluable first-episode LRTI-RSV cases with ≥2 symptoms at that time is at least 59, the first analysis will be conducted as the final analysis of the primary objective, and all type I errors of the primary endpoint will be spent in this analysis. The primary objective will be demonstrated if the lower bound (LB) of the 95% CI for VE against LRTI-RSV with ≥2 symptoms is >20%.
    b. If the total number of evaluable first-episode LRTI-RSV cases with ≥2 symptoms is between 29 and 58 at the IA and the LB of the Pocock-adjusted CI for VE against LRTI-RSV with ≥2 symptoms is >20% at this IA, this analysis will be considered as the final analysis of the primary study objective. In order to include LRTI-RSV with ≥3 symptoms in the IA, the total evaluable case count on this endpoint should be at least 15. In order to include sLRTI-RSV in the IA, the total evaluable case count on this endpoint should be at least 12. If the total number of evaluable first-episode LRTI-RSV cases with ≥2 symptoms is between 29 and 58 at the IA, and the LB of the Pocock-adjusted CI for VE against LRTI-RSV with ≥2 symptoms is <20%, the final analysis of the primary objective will be performed when the total number of cases reaches 59, and the VE will be summarized with the same Pocock-adjusted CI. If at the end of the first RSV season the total number of cases has not reached 59, the final analysis for all study hypothesis endpoints will be performed after the first RSV season ends (ie, at the time of the second analysis).

2. Second IA (end-of-Season 1 analysis): will be conducted after the first RSV season ends for all participants. If all hypothesis-testing estimands were included in the final analysis of the primary objective, all efficacy estimations will be descriptively summarized with 95% CIs in this end-of-Season 1 analysis. Otherwise, if the final analysis of the primary objective was performed after a successful IA, the type I error will be spent for those untested hypothesis estimands as described below, and all other non–hypothesis-testing endpoints will be descriptively summarized with 95% CIs.

a. If a successful IA is performed on only LRTI-RSV with ≥2 symptoms with the Pocock-adjusted type I error, the 5% type I error will be spent sequentially for LRTI-RSV with ≥3 symptoms and sLRTI-RSV at this end-of-Season 1 analysis. That is, if the LB of the 95% CI for VE against LRTI-RSV with ≥3 symptoms is >20% in this end-of-Season 1 analysis, the hypothesis will then be tested on sLRTI-RSV. If the LB of the 95% CI for VE against sLRTI-RSV is >20%, the key secondary objective is achieved.
b. If an IA is performed on both LRTI-RSV with ≥2 symptoms and LRTI-RSV with ≥3 symptoms with the Pocock-adjusted type I error, and the LB of the Pocock-adjusted VE CI is >20% for both at the IA, the 5% type I error will be spent on sLRTI-RSV in this end-of-Season 1 analysis. If the LB of the 95% CI of VE against sLRTI-RSV is >20%, the key secondary objective is achieved.
c. If an IA is performed on both LRTI-RSV with ≥2 symptoms and LRTI-RSV with ≥3 symptoms with the Pocock-adjusted type I error, but the LB of the Pocock-adjusted VE CI is >20% for LRTI-RSV with ≥2 symptoms only and the Pocock-adjusted VE CI is <20% for LRTI-RSV with ≥3 symptoms at IA, the same Pocock-adjusted type I error will be spent on LRTI-RSV with ≥3 symptoms in this end-of-Season 1 analysis. If the LB of the Pocock-adjusted VE against LRTI-RSV with ≥3 symptoms is >20% at this end-of-Season 1 analysis, the sLRTI-RSV will be tested with the 5% type I error at this end-of-Season 1 analysis. If the LB of the 95% CI for VE against sLRTI-RSV is >20%, the key secondary objective is achieved.
d. If an IA is performed for all 3 hypothesis-testing estimands with the Pocock-adjusted type I error, but the LB of the Pocock-adjusted VE CI is <20% for sLRTI-RSV only, the same Pocock-adjusted type I error will be spent for sLRTI-RSV in this end-of-Season 1 analysis. If the LB of the Pocock-adjusted VE against sLRTI-RSV is >20% at this end-of-Season 1 analysis, the key secondary objective is achieved.
e. If an IA is performed on LRTI-RSV with ≥2 symptoms only, but the LB of the Pocock-adjusted VE CI is <20% at IA, the same Pocock type I error will be spent on all 3 hypothesis-testing endpoints at this end-of Season 1 analysis. If the LB of the Pocock-adjusted VE CI is >20% for LRTI-RSV with ≥2 symptoms at this end-of-Season 1, the study primary objective is achieved. If the LB of the Pocock-adjusted VE against sLRTI-RSV is >20% at this end-of-Season 1 analysis according to the fixed sequence testing order (Section 6.1.8 above), the key secondary objective is achieved.

3. End-of-study analysis: the last analysis will be conducted after all participants have finished the study. All safety data reported since the end-of-season analysis, in addition to cumulative immunogenicity and LRTI/ARI cases occurring from all participants during this study, will be included in this analysis. All efficacy estimations will be descriptively summarized with 95% CIs.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

In the study, 34,383 participants were randomized to receive RSVpreF (n=17,197) or placebo (n=17,186), as shown in Table 5. The majority of the randomized participants (99.7%) received the study intervention. As of the data cutoff date (July 14, 2022), 13,222 (76.9%) participants in the RSVpreF group and 13,173 (76.6%) participants in the placebo group have completed the 6-month safety follow-up visit.

Table 5. Disposition of Participants.

Population	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
Enrolled	-	-	35971
Randomized	17197	17186	34383
Not vaccinated	49 (0.3)	50 (0.3)	99 (0.3)
Vaccinated	17148 (99.7)	17136 (99.7)	34284 (99.7)
Ongoing	16286 (94.7)	16188 (94.2)	32474 (94.4)
Withdrawn after vaccination	862 (5.0)	948 (5.5)	1810 (5.3)
Reason for withdrawal:	-	-	-
Withdrawal by subject	410 (2.4)	495 (2.9)	905 (2.6)
Lost to follow-up	330 (1.9)	324 (1.9)	654 (1.9)
Death	52 (0.3)	49 (0.3)	101 (0.3)
Physician decision	13 (<0.1)	27 (0.2)	40 (0.1)
Refused further study procedures	11 (<0.1)	15 (<0.1)	26 (<0.1)
Protocol deviation	10 (<0.1)	12 (<0.1)	22 (<0.1)
Adverse event	10 (<0.1)	6 (<0.1)	16 (<0.1)
No longer meets eligibility criteria	2 (<0.1)	6 (<0.1)	8 (<0.1)
Other	24 (0.1)	14 (<0.1)	38 (0.1)
Completed the 6-month safety follow-up visit	13222 (76.9)	13173 (76.6)	26395 (76.8)

Source: Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Table 5, p. 31.

The analysis populations are given in Table 6. There were 213 (0.6%) participants who received multiple vaccinations due to multiple enrollments at different sites. These participants were excluded from the Evaluable Efficacy Population but were included in the mITT Efficacy Population and in the Safety Population. For the Safety Population, a participant was assigned to the RSVpreF group when at least one dose of RSVpreF was administered and was assigned to the placebo group when placebo was administered for all vaccinations. Among the 213 participants who received multiple vaccinations, 161 (75.6%) received 2 vaccinations, 39 (18.3%) received 3 vaccinations, 12 (5.6%) received 4 vaccinations, and 1 (0.5%) received 6 vaccinations.

Table 6. Analysis Populations.

Analysis Populations	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
Safety Population[a]	17215	17069	34284
Vaccinated	17215 (100.0)	17069 (100.0)	34284 (100.0)
Safety Population with 6-month follow-up visit	13273 (77.1)	13122 (76.9)	26395 (77.0)
Reactogenicity subset[b]	3820 (22.2)	3708 (21.7)	7528 (22.0)
e-Diary Subset Safety Population[c]	3630 (95.0)	3539 (95.4)	7169 (95.2)
Excluded from e-diary Subset Safety Population:	-	-	-
With no e-diary data transferred	190 (5.0)	169 (4.6)	359 (4.8)
Efficacy Analysis Populations	-	-	-
Randomized[d]	17197	17186	34383
mITT Efficacy Population	16999 (98.8)	16988 (98.8)	33987 (98.8)
Excluded from mITT Efficacy Population	198 (1.2)	198 (1.2)	396 (1.2)
Reason for exclusion:	-	-	-
Did not receive study vaccine	49 (0.3)	50 (0.3)	99 (0.3)
Vaccinated after surveillance cutoff date (July 8, 2022)	149 (0.9)	148 (0.9)	297 (0.9)
Evaluable Efficacy Population	16306 (94.8)	16308 (94.9)	32614 (94.9)
Excluded from Evaluable Efficacy Population	891 (5.2)	878 (5.1)	1769 (5.1)
Reason for exclusion[e]:	-	-	-
Not eligible for this study	42 (0.2)	41 (0.2)	83 (0.2)
Did not receive study vaccine	49 (0.3)	50 (0.3)	99 (0.3)
Received study vaccine but not as randomized	112 (0.7)	110 (0.6)	222 (0.6)
Received multiple vaccinations due to multiple enrollments at different sites	109 (0.6)	104 (0.6)	213 (0.6)
Efficacy surveillance duration was less than 15 days (<14 days after vaccination)[f]	693 (4.0)	687 (4.0)	1380 (4.0)
Had other major protocol violation(s) prior to symptom onset date of confirmed ARI-RSV case	72 (0.4)	68 (0.4)	140 (0.4)

a. The values in this row are the denominators for the percentage calculations for the Safety Population.
b. A subset of study participants from selected sites were included. The values in this row are the denominators for the percentage calculations for the reactogenicity subsets.
c. The e-diary Subset Safety Population includes those in the reactogenicity subset who received the study intervention and have e-diary data transmitted; if data for temperature, local reactions, or systemic events are reported for any day of Days 1 through 7, where Day 1 is the day of vaccination, the e-diary is considered transmitted.
d. The values in this row are the denominators for the percentage calculations for the Efficacy Analysis Populations.
e. Participants may have been excluded for more than 1 reason.
f. Including participants vaccinated after surveillance cutoff date (July 8, 2022).

Source: Adapted from Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Tables 6-7, p. 33-34.

6.1.10.1.1 Demographics

Table 7 shows the demographic and baseline characteristics by study group for the Safety Population. The characteristics were comparable between the study groups. For the Evaluable Efficacy Population, the demographic and baseline characteristics were similar to those in the Safety Population and were balanced between the study groups.

Table 7. Demographic and Baseline Characteristics (Safety Population).

Characteristics	**RSVpreF 120 µg (N=17215) n (%)**	**Placebo (N=17069) n (%)**	**Total (N=34284) n (%)**
Sex	-	-	-
Male	8800 (51.1)	8601 (50.4)	17401 (50.8)
Female	8415 (48.9)	8468 (49.6)	16883 (49.2)
Race	-	-	-
White	13475 (78.3)	13360 (78.3)	26835 (78.3)
Black or African American	2206 (12.8)	2207 (12.9)	4413 (12.9)
Asian	1352 (7.9)	1333 (7.8)	2685 (7.8)
Not reported	56 (0.3)	50 (0.3)	106 (0.3)
American Indian or Alaska Native	44 (0.3)	36 (0.2)	80 (0.2)
Multiracial	44 (0.3)	36 (0.2)	80 (0.2)
Unknown	28 (0.2)	32 (0.2)	60 (0.2)
Native Hawaiian or Other Pacific Islander	10 (<0.1)	15 (<0.1)	25 (<0.1)
Ethnicity	-	-	-
Non-Hispanic/non-Latino	10740 (62.4)	10715 (62.8)	21455 (62.6)
Hispanic/Latino	6384 (37.1)	6260 (36.7)	12644 (36.9)
Not reported	91 (0.5)	94 (0.6)	185 (0.5)
Age at Vaccination[a]	-	-	-
<60 Years	1 (<0.1)	0	1 (<0.1)
60-69 Years	10756 (62.5)	10680 (62.6)	21436 (62.5)
70-79 Years	5488 (31.9)	5431 (31.8)	10919 (31.8)
≥80 Years	970 (5.6)	958 (5.6)	1928 (5.6)
Mean (SD)	68.3 (6.14)	68.3 (6.18)	68.3 (6.16)
Median	67.0	67.0	67.0
(Min, max)	(59, 95)	(60, 97)	(59, 97)
Country	-	-	-
USA	10319 (59.9)	10182 (59.7)	20501 (59.8)
Argentina	3660 (21.3)	3657 (21.4)	7317 (21.3)
Japan	1159 (6.7)	1156 (6.8)	2315 (6.8)
The Netherlands	687 (4.0)	681 (4.0)	1368 (4.0)
Canada	509 (3.0)	506 (3.0)	1015 (3.0)
South Africa	495 (2.9)	497 (2.9)	992 (2.9)
Finland	386 (2.2)	390 (2.3)	776 (2.3)
Prespecified significant conditions[b]	-	-	-
With ≥1 prespecified significant condition	8867 (51.5)	8831 (51.7)	17698 (51.6)

Characteristics	RSVpreF 120 µg (N=17215) n (%)	Placebo (N=17069) n (%)	Total (N=34284) n (%)
Current tobacco use	2642 (15.3)	2571 (15.1)	5213 (15.2)
Diabetes	3224 (18.7)	3284 (19.2)	6508 (19.0)
Lung disease[c]	1956 (11.4)	2040 (12.0)	3996 (11.7)
Heart disease[d]	2221 (12.9)	2233 (13.1)	4454 (13.0)
Liver disease	335 (1.9)	329 (1.9)	664 (1.9)
Renal disease	502 (2.9)	459 (2.7)	961 (2.8)
With ≥1 chronic cardiopulmonary condition	2595 (15.1)	2640 (15.5)	5235 (15.3)
Asthma	1541 (9.0)	1508 (8.8)	3049 (8.9)
Chronic obstructive pulmonary disease (COPD)	1012 (5.9)	1080 (6.3)	2092 (6.1)
Congestive heart failure (CHF)	293 (1.7)	307 (1.8)	600 (1.8)
With no prespecified significant conditions	8348 (48.5)	8238 (48.3)	16586 (48.4)
Respiratory rate at baseline (breaths/min)[a]:	-	-	-
n	17188	17050	34238
Mean (SD)	15.7 (2.14)	15.7 (2.24)	15.7 (2.19)
Median	16.0	16.0	16.0
(Min, max)	(8, 29)	(6, 92[e])	(6, 92[e])

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).
b. For participants who received multiple vaccinations due to multiple enrollments, any reported prespecified medical conditions from all participant IDs were included.
c. Includes COPD and other lung disease.
d. Includes CHF and other heart disease.
e. Respiratory rate 92 confirmed by investigator to not be clinically significant and accurate to the source document.

Source: Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Table 8, p. 35-37.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The study included both healthy adults and adults with stable chronic conditions (including cardiopulmonary diseases, such as COPD, asthma, or CHF) aged 60 years or older. In the Safety Population, 51.6% had at least 1 prespecified significant condition (Table 7).

6.1.11 Efficacy Analyses

The application included data and results from the prespecified first interim analysis during the first RSV season through the ARI surveillance cutoff date of July 8, 2022. According to the requirements for the interim analysis (Section 6.1.9), the interim analysis included LRTI-RSV cases with ≥2 and ≥3 symptoms. Analysis of sLRTI-RSV was not performed as there was an insufficient number of cases at the time. The applicant also included a descriptive analysis of ARI-RSV.

6.1.11.1 Analyses of Primary Endpoints

The mean length of ARI surveillance was 201 days (standard deviation [SD] = 65.14) as of the ARI surveillance cutoff date.

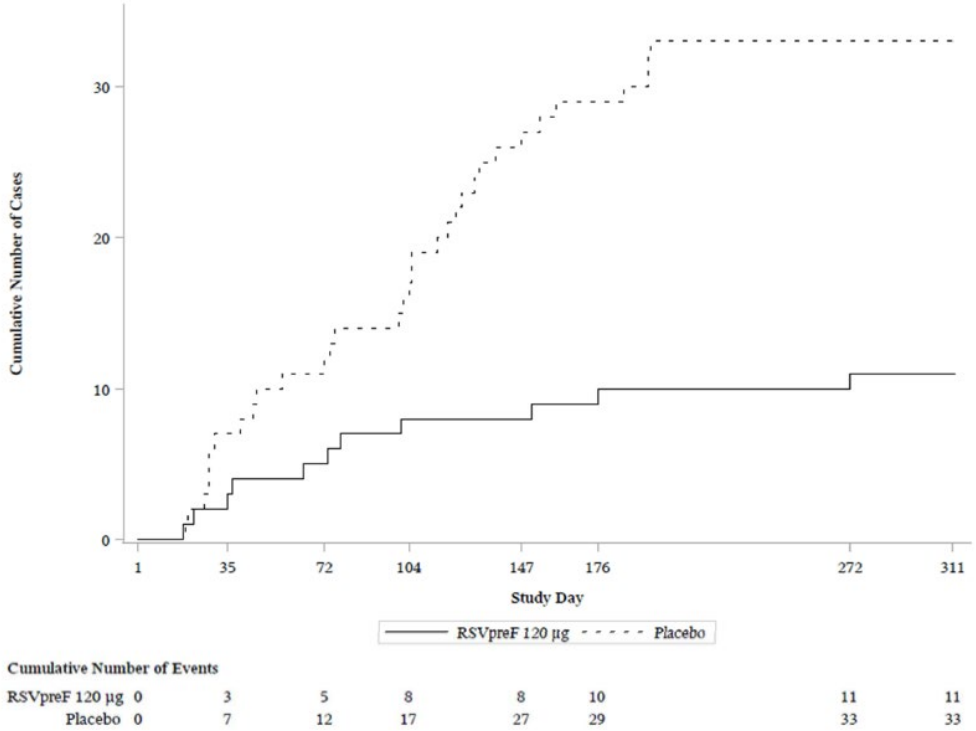
LRTI-RSV cases with ≥2 symptoms

In the Evaluable Efficacy Population, there were 45 participants with 46 episodes of LRTI-RSV with ≥2 symptoms after vaccination, of which one episode was reported before Day 15. Figure 1 shows the cumulative case accrual of first episodes of LRTI-RSV cases with ≥2 symptoms during the observation period. Thus, there were 44 first episodes of LRTI-RSV with ≥2 symptoms starting on or after Day 15. Of these, 11 were in the RSVpreF group and 33 were in the placebo group, corresponding to a VE of 66.7%, 96.66% CI (28.8%, 85.8%) based on the risk ratio (Table 8), meeting the study success criterion as the lower bound of the 96.66% CI was >20%. Therefore, according to the applicant's plan, this represents the final analysis for this endpoint. Additional analyses for this primary endpoint at later times will be descriptive..

The applicant additionally conducted sensitivity analyses using the mITT Efficacy Population, which yielded VE of 67.6%, 96.66% CI (31.1%, 86.2%) based on the risk ratio. Additional sensitivity analyses included analyses based on the incidence rate (IR) ratio (VE: 66.7%, 96.66% CI [28.9%, 85.8%]) and the hazard ratio (VE: 66.7%, 96.66% CI [32.8%, 85.0%]).

Reviewer's comment: The results of the sensitivity analyses were consistent with that of the primary analysis for this endpoint.

Figure 1. Cumulative Case Accrual of First Episode of LRTI-RSV With ≥2 Symptoms – Evaluable Efficacy Population



Source: Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Figure 1, p. 44.

Table 8. Vaccine Efficacy of RSVpreF – Evaluable Efficacy Population.

Efficacy Endpoint	**RSVpreF N = 16306 n (%)**	**RSVpreF PYO[a] = 9226 IR[b] (per 1000 PYO)**	**Placebo N = 16308 n (%)**	**Placebo PYO[a] = 9211 IR[b] (per 1000 PYO)**	**VE = 1 - RR VE[c] % (96.66% CI)**	**VE = 1 - IRR VE[d] % (96.66% CI)**	**VE = 1 - HR VE[e] % (96.66% CI)**
First episode of LRTI-RSV with ≥2 symptoms	11 (0.07)	1.19	33 (0.20)	3.58	66.7 (28.8, 85.8)	66.7 (28.9, 85.8)	66.7 (32.8, 85.0)
First episode of LRTI-RSV with ≥3 symptoms	2 (0.01)	0.22	14 (0.09)	1.52	85.7 (32.0, 98.7)	85.7 (32.1, 98.7)	85.7 (43.9, 98.2)

Abbreviations: IR = Incidence Rate; PYO = Person-Years Observation; VE = Vaccine Efficacy; RR = Risk Ratio; IRR = Incidence Rate Ratio; HR = Hazard Ratio.

a. PYO is defined as the total ARI surveillance duration days across all participants at risk within each vaccine group, divided by 365.25. ARI surveillance duration is from vaccination date through death/discontinuation/surveillance cutoff date/major protocol deviation, whichever is earlier. Minimum required surveillance duration is 15 days (14 days after vaccination) for the primary endpoint cases for Evaluable Efficacy Population.

b. IR per 1000 PYO is defined as the (number of cases / PYO) * 1000.
c. VE (primary analysis) based on case count ratio is calculated as 1-(P/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases.
d. VE (sensitivity analysis) 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.
e. VE (sensitivity analysis) based on the hazard ratio from the Cox regression model to estimate VE. Any participants without a case are censored at the time of data cutoff, death, major protocol violation, or discontinuation from the study.

Source: Adapted from Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Table 10, p. 42-43, Table 11, p. 47-48.

The applicant additionally conducted an exploratory analysis of VE with respect to RSV A and RSV B subtypes in the Evaluable Efficacy Population. For RSV A, VE against LRTI-RSV with ≥2 symptoms was 88.9%, 96.66% CI (10.6%, 99.8%) based on one case in the RSVpreF group and nine cases in the placebo group. For RSV B, VE was 56.5%, 96.66% CI (-0.7%, 82.8%) based on 10 cases in the RSVpreF group and 23 cases in the placebo group.

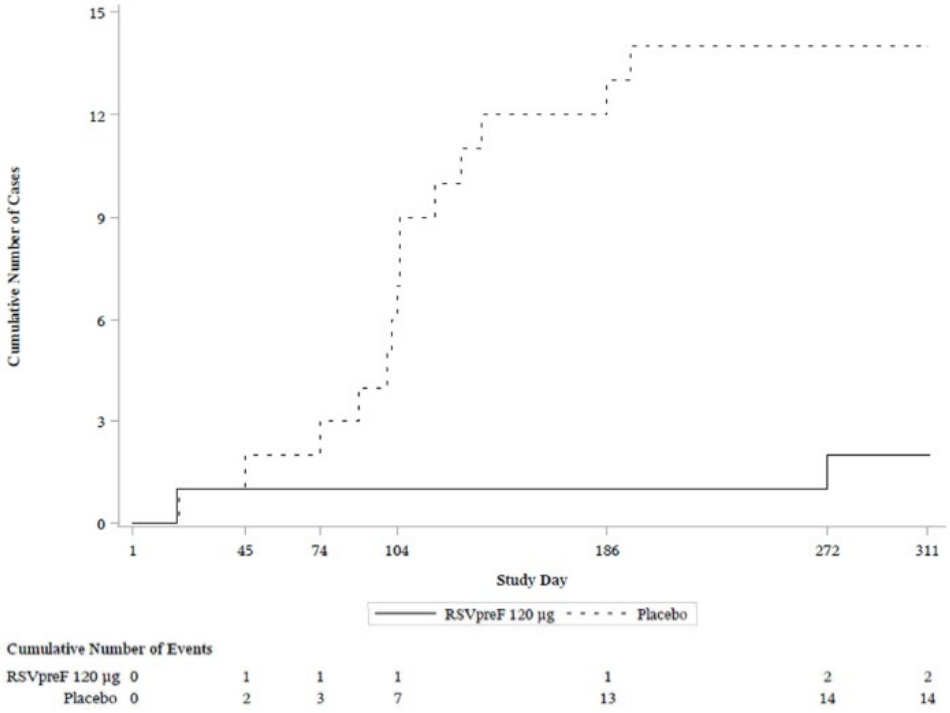
LRTI-RSV cases with ≥3 symptoms

As of the data cutoff date, in the Evaluable Efficacy Population, there were 17 individuals with 17 episodes of LRTI-RSV with ≥3 symptoms, of which 1 episode occurred before Day 15. Thus, there were 16 first episodes of LRTI-RSV with ≥3 symptoms occurring on or after Day 15, of which 2 were in the RSVpreF group and 14 were in the placebo group (Figure 2), corresponding to a VE of 85.7%, 96.66% CI (32.0%, 98.7%), as shown in Table 8. Thus, the success criterion for this endpoint was met, as the lower bound of the 96.66% CI was >20%, and respectively this represents the final analysis for this endpoint.

The applicant additionally conducted sensitivity analyses using the mITT Efficacy Population, which yielded VEs of 86.7%, 96.66% CI (37.4%, 98.8%) based on the risk ratio, 85.7%, 96.66% CI (32.1%, 98.7%) based on the IR ratio, and 85.7%, 96.66% CI (43.9%, 98.2%) based on the hazard ratio.

Reviewer's comment: The results of the sensitivity analyses were consistent with that of the primary analysis for this endpoint.

Figure 2. Cumulative Case Accrual of First Episode of LRTI-RSV With ≥3 Symptoms – Evaluable Efficacy Population.



Source: Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Figure 1, p. 49.

The applicant additionally conducted an exploratory analysis of VE with respect to RSV A and RSV B subtypes in the Evaluable Efficacy Population. For RSV A, VE against LRTI-RSV with ≥3 symptoms was 66.7%, 96.66% CI (-393.7%, 99.6%) based on 1 case in the RSVpreF group and 3 cases in the placebo group. For RSV B, VE was 90.0%, 96.66% CI (21.8%, 99.8%) based on one case in the RSVpreF group and 10 cases in the placebo group.

6.1.11.2 Analyses of Secondary Endpoints

Key secondary endpoint of sLRTI-RSV

As of the data cutoff date, there were only 2 sLRTI-RSV cases reported among the study participants. Thus, the minimum number of 12 first-episode sLRTI-RSV cases was not accrued and the interim analysis for this endpoint was not conducted.

Reviewer's comment: This endpoint will be tested at the end-of-Season 1 analysis.

Secondary endpoint of ARI-RSV

This endpoint was planned to be assessed descriptively in the study at each RSV season and across two RSV seasons. Thus, there was no multiplicity adjustment for this endpoint. As of the data cutoff date, in the Evaluable Efficacy Population, there was a total of 103 first episodes of ARI-RSV starting on or after Day 15, of which 25 were in

the RSVpreF group and 78 were in the placebo group. The corresponding VE based on the risk ratio was 67.9%, 95% CI (49.1%, 80.4%).

Reviewer's comment: There was no prespecified success criterion for this endpoint, as it was planned as a secondary endpoint to be assessed descriptively. Thus, the results for this endpoint should be considered as supportive evidence of efficacy.

Other secondary endpoints
The rest of the secondary efficacy endpoints, as well as the immunogenicity endpoints, were not assessed at this interim analysis.

6.1.11.3 Subpopulation Analyses

Exploratory subgroup analyses are presented in Table 9 for VE against LRTI-RSV with ≥2 symptoms by demographic characteristics such as age group (60-69 years, 70-79 years, and ≥80 years), sex, race, ethnicity, risk status, and country.

Table 9. Exploratory Subgroup Analyses of VE Against LRTI-RSV with ≥2 Symptoms by Subject Characteristics – Evaluable Efficacy Population

Characteristics	**Total Cases**	**RSVpreF Cases n**	**Placebo Cases n**	**VE % (1 - Risk Ratio)**	**96.66% CI**
Sex	-	-	-	-	-
Male	23	6	17	64.7	(-0.6, 89.7)
Female	21	5	16	68.8	(3.9, 92.0)
Race	-	-	-	-	-
White	38	8	30	73.3	(36.9, 90.3)
Black or African American	5	3	2	-50.0	(-2143.8, 85.5)
Asian	1	0	1	100.0	(-5788.0, 100.0)
Ethnicity	-	-	-	-	-
Non-Hispanic/non-Latino	8	1	7	85.7	(-25.1, 99.8)
Hispanic/Latino	36	10	26	61.5	(12.8, 84.6)
Age at Vaccination	-	-	-	-	-
60-69 Years	27	8	19	57.9	(-7.4, 85.3)
70-79 Years	11	2	9	77.8	(-18.7, 98.1)
≥80 Years	6	1	5	80.0	(-104.3, 99.7)
Country	-	-	-	-	-
USA	26	7	19	63.2	(2.2, 88.0)
Canada	1	0	1	100.0	(-5788.0, 100.0)
The Netherlands	3	1	2	50.0	(-1105.6, 99.4)
South Africa	8	2	6	66.7	(-109.5, 97.4)
Argentina	6	1	5	80.0	(-104.3, 99.7)
Prespecified significant conditions	-	-	-	-	-
With no prespecified significant conditions	22	5	17	70.6	(10.7, 92.4)

Characteristics	Total Cases	RSVpreF Cases n	Placebo Cases n	VE % (1 - Risk Ratio)	96.66% CI
With ≥1 prespecified significant condition	22	6	16	62.5	(-8.4, 89.1)
With ≥1 chronic cardiopulmonary condition	10	4	6	33.3	(-213.7, 87.9)

Source: Adapted from Final Full Clinical Study Report for Protocol C3671013, dated September 22, 2022, Table 14.16, p. 197.

Reviewer's comment: The VE analyses are of limited value in many of the subgroups due to the small numbers of cases accrued. Therefore, these results should be considered of descriptive nature and should be interpreted with caution. Likewise, subgroup VE against LRTI-RSV with ≥3 symptoms are not presented due to the limited number of cases.

6.1.11.4 Dropouts and/or Discontinuations

Table 5 shows the study discontinuation rates and their reasons. The rates were balanced between the two groups, with 5% in the RSVpreF group and 5.5% in the placebo group. The proportion of participants excluded from the Evaluable Efficacy Population was similar between the two groups, with 5.2% in the RSVpreF group and 5.1% in the placebo group. The most frequent reason for exclusion from this population was having an efficacy surveillance duration of <15 days (4.0% for both groups).

6.1.12 Safety Analyses

This section summarizes the main safety analysis results. The data cut-off date for the safety assessments was July 14, 2022. The safety analyses were descriptive, and no hypothesis was tested. For a more detailed discussion, please refer to Dr. Nadine Peart-Akindele's clinical review memo.

The rates of unsolicited AEs by category are shown in Table 10. Overall, 2227 (12.9%, 95% CI [12.4%, 13.4%]) RSVpreF recipients and 2179 (12.8%, 95% CI [12.3%, 13.3%]) placebo recipients experienced at least one AE. Of these, 231 (1.3%, 95% CI [1.2%, 1.5%]) RSVpreF recipients and 160 (0.9%, 95% CI [0.8%, 1.1%]) placebo recipients reported events that were assessed as related to study intervention by the investigator. The majority of these events were assessed as reactogenicity events.

There were 396 (2.3%, 95% CI [2.1%, 2.5%]) participants in the RSVpreF group and 387 (2.3%, 95% CI [2.0%, 2.5%]) in the placebo group who reported an SAE. The most common SAEs were cardiac disorders, with 81 (0.5%, 95% CI [0.4%, 0.6%]) in the RSVpreF group and 84 (0.5%, 95% CI [0.4%, 0.6%]) in the placebo group. There was one (0.0058%) participant in the RSVpreF group who experienced an SAE of Guillain-Barre syndrome and one (0.0058%) participant in the RSVpreF group who experienced an SAE of Miller Fisher syndrome. There were 52 (0.3%) deaths among RSVpreF recipients and 49 (0.3%) deaths among placebo recipients. None of the deaths were assessed as related to the study intervention by the investigator.

Through 1 month after vaccination (from Day 1 through Day 31), there were 10 (0.058%) events of atrial fibrillation in the RSVPreF vaccine group, compared to 4 (0.023%) events in the placebo group.

Table 10. Adverse Events by Category from Vaccination through Data Cutoff (July 14, 2022) – Safety Population.

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

a. For participants who received more than 1 vaccine dose due to enrollments at multiple sites, the vaccine group RSVpreF was assigned when at least one dose of the RSVpreF vaccine was received, and the placebo group was assigned when placebo was received at all vaccinations.
b. Number of participants reporting at least 1 occurrence of the specified adverse event category.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Immediate AE refers to an AE reported in the 30-minute post vaccination observation period.
Source: Adapted from STN 125769/0/15, Unsolicited Safety Tables, Table 14.

Solicited local (pain at the injection site, redness, and swelling) and systemic (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) reactions were collected for 7 days after vaccination among the E-Diary Subset Safety Population. Tables 11 and 12 show the rates of reported solicited adverse reactions by maximum severity. Local reactions were reported by 12.2% of the participants in the RSVpreF group and by 6.6% of the participants in the placebo group, with pain at the injection site being the most commonly reported reaction (10.6% versus 6%, respectively). At least one systemic event was reported by 27.5% of the participants in the RSVpreF group and by 25.7% of the participants in the placebo group. The most commonly reported systemic events after the RSVpreF vaccination were fatigue (15.5%) and headache (12.8%).

Table 11. Solicited Local Reactions, by Maximum Severity, within 7 Days after Vaccination – E-Diary Subset Safety Population

Local Reactions	RSVpreF N[a]	RSVpreF n[b] (%)	RSVpreF (95% CI[c])	Placebo N[a]	Placebo n[b] (%)	Placebo (95% CI[c])
Pain at injection site[d]	-	-	-	-	-	-
Any	3621	385 (10.6)	(9.6, 11.7)	3539	212 (6.0)	(5.2, 6.8)
Mild	3621	343 (9.5)	(8.5, 10.5)	3539	188 (5.3)	(4.6, 6.1)
Moderate	3621	40 (1.1)	(0.8, 1.5)	3539	24 (0.7)	(0.4, 1.0)
Severe	3621	2 (<0.1)	(0.0, 0.2)	3539	0	(0.0, 0.1)
Redness[e]	-	-	-	-	-	-
Any	3619	97 (2.7)	(2.2, 3.3)	3532	23 (0.7)	(0.4, 1.0)
Mild	3619	55 (1.5)	(1.1, 2.0)	3532	16 (0.5)	(0.3, 0.7)
Moderate	3619	38 (1.1)	(0.7, 1.4)	3532	7 (0.2)	(0.1, 0.4)

Local Reactions	RSVpreF N[a]	RSVpreF n[b] (%)	RSVpreF (95% CI[c])	Placebo N[a]	Placebo n[b] (%)	Placebo (95% CI[c])
Severe	3619	4 (0.1)	(0.0, 0.3)	3532	0	(0.0, 0.1)
Swelling[e]	-	-	-	-	-	-
Any	3619	89 (2.5)	(2.0, 3.0)	3532	16 (0.5)	(0.3, 0.7)
Mild	3619	54 (1.5)	(1.1, 1.9)	3532	8 (0.2)	(0.1, 0.4)
Moderate	3619	31 (0.9)	(0.6, 1.2)	3532	6 (0.2)	(0.1, 0.4)
Severe	3619	4 (0.1)	(0.0, 0.3)	3532	2 (<0.1)	(0.0, 0.2)
Any local reaction[f]	-	-	-	-	-	-
Any	3621	441 (12.2)	(11.1, 13.3)	3539	235 (6.6)	(5.8, 7.5)
Mild	3621	347 (9.6)	(8.6, 10.6)	3539	199 (5.6)	(4.9, 6.4)
Moderate	3621	86 (2.4)	(1.9, 2.9)	3539	34 (1.0)	(0.7, 1.3)
Severe	3621	8 (0.2)	(0.1, 0.4)	3539	2 (<0.1)	(0.0, 0.2)

a. Number of participants with at least 1 day of e-diary data. This value is the denominator for the percentage calculations. Caliper units were not distributed to 9 participants included in the e-diary subset thus the denominator for 'Redness' and 'Swelling' excluded the 9 participants.
b. Number of participants reporting in e-diary any reaction or with maximum severity of mild, moderate, or severe based on the severity scales. Reactogenicity events reported as related adverse events within 7-day of vaccination from the e-Diary Subset Safety Population were included in the table.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
e. Mild: 2.5 cm to 5.0 cm; moderate: >5.0 cm to 10.0 cm; severe: >10.0 cm.
f. Any local reaction: any pain at the injection site, redness, or swelling of at least mild severity.
Source: Adapted from STN 125769/0/17, Solicited Safety Tables, Table 14.21.

Table 12. Solicited Systemic Reactions, by Maximum Severity, within 7 Days after Vaccination – E-Diary Subset Safety Population

Systemic Reactions	RSVpreF N[a]	RSVpreF n[b] (%)	RSVpreF (95% CI[c])	Placebo N[a]	Placebo n[b] (%)	Placebo (95% CI[c])
Fever	-	-	-	-	-	-
Any	3619	52 (1.4)	(1.1, 1.9)	3532	51 (1.4)	(1.1, 1.9)
Mild	3619	23 (0.6)	(0.4, 1.0)	3532	27 (0.8)	(0.5, 1.1)
Moderate	3619	28 (0.8)	(0.5, 1.1)	3532	21 (0.6)	(0.4, 0.9)
Severe	3619	1 (<0.1)	(0.0, 0.2)	3532	2 (<0.1)	(0.0, 0.2)
Grade 4 (>40.0°C)[d]	3619	0	(0.0, 0.1)	3532	1 (<0.1)	(0.0, 0.2)
Fatigue[e]	-	-	-	-	-	-
Any	3621	562 (15.5)	(14.4, 16.7)	3539	508 (14.4)	(13.2, 15.6)
Mild	3621	335 (9.3)	(8.3, 10.2)	3539	296 (8.4)	(7.5, 9.3)
Moderate	3621	215 (5.9)	(5.2, 6.8)	3539	207 (5.8)	(5.1, 6.7)
Severe	3621	12 (0.3)	(0.2, 0.6)	3539	5 (0.1)	(0.0, 0.3)
Headache[e]	-	-	-	-	-	-
Any	3621	465 (12.8)	(11.8, 14.0)	3539	415 (11.7)	(10.7, 12.8)
Mild	3621	326 (9.0)	(8.1, 10.0)	3539	299 (8.4)	(7.6, 9.4)
Moderate	3621	135 (3.7)	(3.1, 4.4)	3539	113 (3.2)	(2.6, 3.8)
Severe	3621	4 (0.1)	(0.0, 0.3)	3539	3 (<0.1)	(0.0, 0.2)
Muscle Pain[e]	-	-	-	-	-	-
Any	3621	367 (10.1)	(9.2, 11.2)	3539	297 (8.4)	(7.5, 9.4)
Mild	3621	234 (6.5)	(5.7, 7.3)	3539	196 (5.5)	(4.8, 6.3)
Moderate	3621	125 (3.5)	(2.9, 4.1)	3539	98 (2.8)	(2.3, 3.4)
Severe	3621	8 (0.2)	(0.1, 0.4)	3539	3 (<0.1)	(0.0, 0.2)
Joint Pain[e]	-	-	-	-	-	-
Any	3621	272 (7.5)	(6.7, 8.4)	3539	244 (6.9)	(6.1, 7.8)
Mild	3621	163 (4.5)	(3.8, 5.2)	3539	139 (3.9)	(3.3, 4.6)

Systemic Reactions	RSVpreF N[a]	RSVpreF n[b] (%)	RSVpreF (95% CI[c])	Placebo N[a]	Placebo n[b] (%)	Placebo (95% CI[c])
Moderate	3621	106 (2.9)	(2.4, 3.5)	3539	103 (2.9)	(2.4, 3.5)
Severe	3621	3 (<0.1)	(0.0, 0.2)	3539	2 (<0.1)	(0.0, 0.2)
Nausea[e]	-	-	-	-	-	-
Any	3621	124 (3.4)	(2.9, 4.1)	3539	132 (3.7)	(3.1, 4.4)
Mild	3621	92 (2.5)	(2.1, 3.1)	3539	108 (3.1)	(2.5, 3.7)
Moderate	3621	32 (0.9)	(0.6, 1.2)	3539	21 (0.6)	(0.4, 0.9)
Severe	3621	0	(0.0, 0.1)	3539	3 (<0.1)	(0.0, 0.2)
Vomiting[e]	-	-	-	-	-	-
Any	3621	32 (0.9)	(0.6, 1.2)	3539	30 (0.8)	(0.6, 1.2)
Mild	3621	26 (0.7)	(0.5, 1.1)	3539	24 (0.7)	(0.4, 1.0)
Moderate	3621	6 (0.2)	(0.1, 0.4)	3539	4 (0.1)	(0.0, 0.3)
Severe	3621	0	(0.0, 0.1)	3539	2 (<0.1)	(0.0, 0.2)
Diarrhea[e]	-	-	-	-	-	-
Any	3621	214 (5.9)	(5.2, 6.7)	3539	183 (5.2)	(4.5, 6.0)
Mild	3621	162 (4.5)	(3.8, 5.2)	3539	148 (4.2)	(3.5, 4.9)
Moderate	3621	48 (1.3)	(1.0, 1.8)	3539	31 (0.9)	(0.6, 1.2)
Severe	3621	4 (0.1)	(0.0, 0.3)	3539	4 (0.1)	(0.0, 0.3)
Any systemic event[f]	-	-	-	-	-	-
Any	3621	994 (27.5)	(26.0, 28.9)	3539	909 (25.7)	(24.3, 27.2)
Mild	3621	570 (15.7)	(14.6, 17.0)	3539	536 (15.1)	(14.0, 16.4)
Moderate	3621	397 (11.0)	(10.0, 12.0)	3539	352 (9.9)	(9.0, 11.0)
Severe	3621	27 (0.7)	(0.5, 1.1)	3539	20 (0.6)	(0.3, 0.9)
Grade 4 (fever >40.0°C)[d]	3621	0	(0.0, 0.1)	3539	1 (<0.1)	(0.0, 0.2)

a. Number of participants with at least 1 day of e-diary data. This value is the denominator for the percentage calculations. Thermometer was not distributed to 9 participants included in the e-diary subset, and therefore the denominator for 'Fever' excluded the 9 participants.
b. Number of participants reporting in e-diary any event or with maximum severity of mild, moderate, or severe based on the severity scales. Reactogenicity events reported as related adverse events within 7-day of vaccination from the e-Diary Subset Safety Population were included in the table.
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.
d. Grade 4 fever was classified by an investigator or qualified designee only.
e. For fever (e-diary) – mild: 38.0-38.4°C; moderate: >38.4-38.9°C; severe: >38.9°C; for vomiting (e-diary) – mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration. For diarrhea (e-diary) – mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours. For other systemic events (e-diary) and all related AEs – mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily routine activity.
f. Any systemic event: any fever ≥38.0°C, or any fatigue, headache, muscle pain, joint pain, nausea, vomiting, or diarrhea.

Source: Adapted from STN 125769/0/17, Solicited Safety Tables, Table 14.34.

7. INTEGRATED OVERVIEW OF EFFICACY

There was no integrated analysis of efficacy in this application.

8. INTEGRATED OVERVIEW OF SAFETY

There was no integrated analysis of safety in this application.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Results of the ongoing pivotal Phase 3 study C3671013, entitled "A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults," are summarized as follows:

- A total of 34,383 participants were randomized to receive RSVpreF (n=17,197) or placebo (n=17,186). At the interim analysis, which occurred before the end of Season 1, there were 44 cases of LRTI-RSV with ≥2 symptoms starting on or after Day 15 (11 in the RSVpreF group and 33 in the placebo group) and 16 cases of LRTI-RSV with ≥3 symptoms starting on or after Day 15 (2 in the RSVpreF group and 14 in the placebo group), corresponding to VEs of 66.7% (96.66% CI: 28.8% to 85.8%) and 85.7% (96.66% CI: 32.0% to 98.7%), respectively, both meeting the success criterion for the lower bound of the CI >20%. There were only 2 cases of sLRTI-RSV in the placebo arm at the interim look, and therefore the analysis for the key secondary objective was not conducted.

- In a descriptive analysis of the secondary endpoint of ARI-RSV, there were a total of 103 first episodes of ARI-RSV starting from Day 15, of which 25 were in the RSVpreF group and 78 were in the placebo group. The corresponding VE based on the risk ratio was 67.9%, 95% CI (49.1%, 80.4%).

- There were 2227 (12.9%, 95% CI [12.4%, 13.4%]) RSVpreF recipients and 2179 (12.8%, 95% CI [12.3%, 13.3%]) placebo recipients who reported at least 1 AE. Of these, 231 (1.3%, 95% CI [1.2%, 1.5%]) RSVpreF recipients and 160 (0.9%, 95% CI [0.8%, 1.1%]) placebo recipients reported events that were assessed as related to study intervention by the investigator. The majority of these events were assessed as reactogenicity events.

- There were 396 (2.3%, 95% CI [2.1%, 2.5%]) RSVpreF recipients and 387 (2.3%, 95% CI [2.0%, 2.5%]) placebo recipients who reported any SAE. Of these, one (0.0058%) RSVpreF recipient experienced Guillain-Barre syndrome and one (0.0058%) RSVpreF recipient experienced Miller Fisher syndrome.

- There were 52 (0.3%) deaths among RSVpreF recipients and 49 (0.3%) deaths among placebo recipients; however, none of these were assessed as related to the study intervention by the investigator.

- Local reactions were reported by 12.2% of the participants in the RSVpreF group and by 6.6% of the participants in the placebo group, with pain at the injection site being the most commonly reported reaction (10.6% versus 6%, respectively). At least one systemic event was reported by 27.5% of the participants in the RSVpreF group and by 25.7% of the participants in the placebo group. The most commonly reported systemic events after the RSVpreF vaccination were fatigue

(15.5%) and headache (12.8%). Please refer to the review by the clinical reviewer (Dr. Nadine Peart-Akindele) for details on the safety analyses.

- The statistical methods used by the applicant were appropriate and corresponded to those prespecified in the study protocol and in the SAP. The results were verified based on data submitted in the SDTM format.

10.2 Conclusions and Recommendations

In conclusion, the primary efficacy objective of the study was met and the safety profile of the RSVpreF vaccine as of the data cutoff date during the first RSV season was described. There were no safety issues identified in the data from the statistical perspective; interpretation of the one observed case each of Guillain-Barre syndrome and Miller Fisher syndrome in the RSVpreF group is deferred to the clinical review team. The study demonstrated that the RSVpreF vaccine is efficacious in preventing LRTI-RSV with ≥2 and ≥3 symptoms.