Summary Basis for Regulatory Action

Date:	May 31, 2023
From:	Goutam Sen, Ph.D. Review Committee Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA STN:	125769
Applicant:	Pfizer Inc.
Submission Receipt Date:	September 30, 2022
Action Due Date:	May 31, 2023
Proper Name:	Respiratory Syncytial Virus Vaccine
Proprietary Name:	ABRYSVO
Indication:	Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC	
• CMC Product (Product Office and OCBQ/DBSQC)	Christian Sauder, Ph.D. OVRR/DVP Judy Beeler, M.D., OVRR/DVP Ewan Plant, Ph.D. OVRR/DVP Eric Peng, Ph.D., OVRR/DBPAP
• Facilities review (OCBQ/DMPQ)	Hector Carrero, OCBQ/DMPQ Zainab Mansaray-Storms, OCBQ/DMPQ
• QC, Test Methods, Product Quality (OCBQ/DBSQC)	Emnet Yitbarek, Ph.D., OCBQ/DBSQC Esmeralda Alvarado, OCBQ/DBSQC Claire Wernly, Ph.D. OCBQ/DBSQC Jing Lin, Ph.D., OCBQ/DBSQC George Kastanis, OCBQ/DBSQC
Clinical	
• Clinical (Product Office)	Nadine Peart Akindele, M.D., OVRR/DVRPA Alaina Halbach, M.D., OVRR/DVRPA
• Postmarketing safety Pharmacovigilance review (OBPV/DPV)	Phillip Blanc, M.D., M.P.H., OBPV/DPV
• BIMO	CDR Peter Lenahan, Ph.D., OCBQ/DIS/BMB
Statistical	
• Clinical data (OBPV/DB)	Rositsa Dimova, Ph.D., OBPV/DB
• CMC data (OBPV/DB)	Helen (Hairong) Shi, Ph.D., OBPV/DB
Non-clinical/Pharmacology/Toxicology	
• Toxicology	Nabil Al-Humadi, Ph.D., OVRR/DVRPA
• Animal pharmacology	Judy Beeler, M.D., OVRR/DVRPA
Labeling	
• Promotional (OCBQ/APLB) • PNR (OCBQ/APLB) • Carton & Container	Oluchi Elekwachi, RPh., OCBQ/DCM/APLB Oluchi Elekwachi, RPh., OCBQ/DCM/APLB Daphne Stewart, OVRR/DVRPA Ching Yim-Banzuelo, OVRR/DVRPA
Other Review(s) not captured above categories, for example: • Consults • Devices • Consults	Brenda Baldwin, Ph.D., OVRR/DVRPA Andrea Gray, Ph.D., CBER/ORO/DROP/RPB Harry Houghton, MS., OBPV/DB

• Regulatory Review	RPM: Paul Keller, Ph.D., Vera Stupina, Ph.D., Laura Montague
Advisory Committee Summary	Vaccines and Related Biological Products Committee (VRBPAC) meeting was convened on February 28, 2023. A majority of the Committee voted affirmatively (7 out of 12 votes) for the safety and effectiveness of ABRYSVO for prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus in individuals 60 years of age and older.

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GLOSSARY

AE	adverse event
AR	adverse reaction
ARI	acute respiratory infection
ARI-RSV	RSV-associated acute respiratory infection
BIMO	bioresearch monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
COPD	chronic obstructive pulmonary disease
GBS	Guillain-Barré syndrome
GMC	geometric mean concentration
GMR	geometric mean ratio
HAI	Hemagglutinin-inhibition
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract illness
LRTI-RSV	RSV-associated lower respiratory tract illness
MedDRA	Medical Dictionary for Regulatory Activities
NAAT	nucleic acid amplification test
NT	neutralizing titer
PI	package insert
PFS	pre-filled syringe
PREA	Pediatric Research Equity Act
PVP	pharmacovigilance plan
RSV	respiratory syncytial virus
RSVpreF	respiratory syncytial virus fusion surface glycoprotein in prefusion conformation
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SIIV	seasonal inactivated influenza vaccine
SMQ	standardized MedDRA query
SOC	system organ class
US	United States
VE	vaccine efficacy

1. Introduction

Pfizer Inc. (Pfizer) submitted Biologics License Application (BLA) 125769 for licensure of their Respiratory Syncytial Virus (RSV) vaccine on September 30, 2022. The proprietary name of the vaccine is ABRYSVO. The proposed indication is for active immunization for the prevention of lower respiratory tract disease caused by RSV in adults 60 years of age and older.

ABRYSVO consists of 120 mcg of lyophilized, recombinant antigen derived from the RSV fusion (F) surface glycoproteins of the two RSV subgroups, RSV-A (60 mcg) and RSV-B (60 mcg) stabilized in the pre-fusion trimeric conformation (RSVpreF) and is administered intramuscularly (IM) as a single dose (0.5 mL). ABRYSVO is supplied in cartons of 1, 5, and 10 kits, with each kit containing a vial of RSVpreF lyophilized antigen component, a pre-filled syringe containing sterile water diluent component, and a vial adapter. The RSVpreF lyophilized antigen component is reconstituted with sterile water diluent component at the time of use to form ABRYSVO.

Each dose of ABRYSVO also contains 0.11 mg tromethamine, 1.04 mg tromethamine hydrochloride, 11.3 mg sucrose, 22.5 mg mannitol, 0.08 mg polysorbate 80, and 1.1 mg sodium chloride per 0.5 mL. After reconstitution, ABRYSVO is a sterile, clear, and colorless solution.

The dating period for the RSVpreF lyophilized antigen component of ABRYSVO is 18 months from the date of manufacture when stored at 2°C to 8ºC. The dates of manufacture of the RSVpreF lyophilized antigen component and the sterile water diluent component are defined as the dates of filling into final containers. The expiration date for the packaged product is determined by the earliest expiration date of either component.

2. Background

RSV is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. Symptoms consistent with an upper respiratory tract infection can include rhinorrhea, pharyngitis, cough, headache, fatigue, and fever. Symptomatic RSV re-infections are common and continue throughout adulthood, manifested as acute upper respiratory tract infections. In older adults, RSV is also a common cause of lower respiratory tract disease and re-infections can lead to severe disease. Those who are hospitalized may require oxygen, intubation, and/or mechanical ventilation.

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). Adults 60 years of age and older are at increased risk of RSV illness and death (Thompson et al, 2003), which can trigger exacerbations of underlying comorbid conditions, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) (Murata et al, 2007). RSV infection has been associated with up to 22% of acute COPD exacerbations in

prospective cohort studies and 11% of wintertime hospitalizations for COPD exacerbations (Murata et al, 2007). The severity of RSV disease increases with age and comorbidities (e.g., chronic obstructive pulmonary disease, congestive heart failure, asthma) (Falsey et al, 2005; Walsh et al, 2004; Korsten et al, 2021; McClure et al, 2014; Branche et al, 2022).

RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans. There is currently no immune marker 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 suggests that natural re-infection with RSV was rarely observed over two consecutive years (Johnson et al, 1962). Although RSV disease represents a serious condition in individuals 65 years of age and older there are no specific treatment options for RSV disease among adults. AREXVY, a recombinant RSV vaccine was recently approved by FDA for prevention of LRTD caused by RSV in individuals 60 years of age and older.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	June 7, 2017
2. IND submission	January 31, 2018
3. Fast Track designation granted	November 5, 2018
4. Breakthrough Therapy designation granted	March 21, 2022
5. Request for comments and advice in lieu of Pre-BLA meeting	May 17, 2022 August 30, 2022
6. BLA 125769/0 submission	September 30, 2022
7. BLA filed	November 29, 2022
8. Mid-Cycle communication	January 13, 2023 (Cancelled by Pfizer)
9. Late-Cycle meeting	April 6, 2023 (Cancelled by Pfizer)
10. Action Due Date	May 31, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Manufacturing Overview

ABRYSVO consists of the RSVpreF lyophilized antigen component and a sterile water diluent component which is used to reconstitute the RSVpreF lyophilized antigen component immediately prior to administration.

The RSVpreF A and RSVpreF B recombinant proteins are expressed in genetically engineered Chinese Hamster Ovary cell lines (CHO) grown in suspension culture using chemically-defined media without antibiotics or animal-derived components. The recombinant proteins are purified through a series of column chromatography and filtration steps followed by formulation with excipients, filling into vials, and lyophilization. The drug product (DP) is a sterile, lyophilized powder containing equal amounts of two conformationally stabilized drug substance (DS) antigens, (b) (4) (b) (4) The lyophilized DP is presented in a 2 mL clear glass vial, sealed with a stopper and an aluminum overseal with flip-off plastic cap.

RSVpreF vaccine (ABRYSVO) is a combination product consisting of a lyophilized DP vial, a fully assembled diluent (sterile water for injection) prefilled syringe, and a 13 mm vial adapter in a secondary package. A CBER device reviewer conducted the review of the pre-filled syringe. Based on the information provided in the application and cross-referenced master files, as well as additional information submitted subsequently, the device reviewer recommended approval from a device/combination product perspective.

RSVpreF Lyophilized Antigen Component of ABRYSVO

Composition

The composition of the RSVpreF antigen component and the function of the ingredients are provided in Table 2.

Table 2. Composition of RSVpreF Antigen Component (single dose)

Ingredient	**Quantity per 0.5 mL dose**	**Function**
RSVpreF antigen (RSV preF A+ RSV preF B)	120 mcg (60 mcg + 60 mcg)	Immunogen
Tromethamine Hydrochloride	1.04 mg	To achieve optimal pH as well as provide adequate buffering capacity
Tromethamine	0.11 mg	To achieve optimal pH as well as provide adequate buffering capacity
Polysorbate 80	0.08 mg	Surfactant prevents aggregation and prevents adsorption to glass vial.
Mannitol	22.5 mg	Bulking agent to enable an optimized lyophilization cycle
Sucrose	11.3 mg	Cryoprotectant stabilizer during DS storage and DP lyophilization
Sodium Chloride	1.1 mg	Provides ionic strength and stabilizes (b) (4)

Specifications and Methods

The tests and specifications applied for routine release of the RSVpreF antigen component are shown in Table 3.

Table 3. Drug Product Tests and Specifications

Quality attribute	Analytical procedure	Acceptance criteria
Appearance (before reconstitution)	Appearance before reconstitution (visual)	White cake essentially free from visible foreign particulates
Residual moisture	(b) (4)	(b) (4)
Reconstitution time	Reconstitution time	(b) (4)
Clarity	Appearance after reconstitution (clarity), (b) (4)	(b) (4)
Coloration	Appearance after reconstitution (coloration), (b) (4)	Not more intensely colored than (b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Protein concentration	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Uniformity of dosage units[a]	Content uniformity, (b) (4)	(b) (4)
PS80 concentration[a]	(b) (4)	(b) (4)
Identity[a]	(b) (4)	(b) (4)
(b) (4) (potency)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Endotoxin[c]	Endotoxin (b) (4) (b) (4)	(b) (4)
Sterility[d]	Sterility, (b) (4)	No growth detected
Container closure integrity[b]	(b) (4)	Pass

a. The test is not performed on stability samples
b. Test not performed at release; only performed annually on stability
c. Test performed at release and the end of shelf life. Release testing uses the (b) (4), and stability testing used the (b) (4)

d. Test performed at release and the end of shelf life. (b) (4) which is performed in accordance with the (b) (4) with the exception of (b) (4) and detection method, may also be used.

Abbreviations: (b) (4) EU = endotoxin units.

The potency of the DP is measured using three assays to characterize the vaccine antigen component, i) antigen content is determined by (b) (4), ii) relative potency is determined by the (b) (4) and iii) the (b) (4) conformation of RSVpreF protein is confirmed using (b) (4) (b) (4)

Stability of the DP

Stability studies were performed for DP stored under the long-term condition of 5 ± 3°C, the accelerated condition of (b) (4) The parameters tested throughout the stability evaluation of the RSVpreF antigen are appearance, residual moisture, reconstitution time, clarity, coloration, (b) (4) (b) (4) (b) (4)) (b) (4) and (b) (4) , (b) (4), protein concentration, (b) (4) (b) (4) (b) (4) (b) (4), endotoxin, sterility, (b) (4) antigen content by (b) (4) and container closure integrity test. The stability data provided in the application support a dating period of 18 months from the date of manufacture (i.e., filling date) when stored at 2°C to 8°C for the RSVpreF antigen lots filled in 2 mL glass vials.

Presentation and Packaging System

ABRYSVO is supplied in a kit that includes a vial of lyophilized antigen component, a pre-filled syringe containing sterile water for injection and a vial adapter. The lyophilized antigen component is reconstituted with the sterile water for injection to form a single dose of ABRYSVO. ABRYSVO is supplied in cartons of 1, 5, and 10 kits.

Stability of the vaccine after reconstitution

Pfizer conducted in-use stability studies to support the maximum temperature and time period that the reconstituted vaccine can retain its physicochemical properties. The critical quality attributes (CQAs) used to monitor the stability of the reconstituted vaccine are: appearance, (b) (4), (b) (4) in vitro relative potency (b) (4) (b) (4) by (b) (4) and (b) (4) by (b) (4) . Based on the data from these studies, ABRYSVO should be administered immediately after reconstitution or stored at 15°C to 30°C (59°F to 86°F) and used within 4 hours. The reconstituted vaccine should not be stored under refrigerated conditions (2°C to 8°C [36°F to 46°F]) and should not be frozen.

Comparability Protocols (CPs)

Pfizer submitted CPs for the replacement of reference standards, internal controls, and key reagents in the BLA:

- CP for (b) (4) used in the manufacture of (b) (4)
- CP for reprocessing of (b) (4) and (b) (4)
- CP for Introduction of Alternate Filters at (b) (4)

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. CBER reviewed these CPs and agreed with the reporting category of annual report for the changes listed above.

b. Clinical Assays

1) Reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) for the Detection of RSV-A and RSV-B using (b) (4) for Case Conformation:

   The Pfizer RT-qPCR test is designed to detect RSV in nasal swab samples and identify the infecting strain as subtype A and/or B. The RT-qPCR method is validated and suitable for its intended use as a limit test to identify nasal swab samples from the Phase 3 clinical study C3671013 as positive or negative for RSV-A and or RSV-B.

2) (b) (4) Assay for the Detection of Functional Antibodies to Respiratory Syncytial Virus in Test Serum

   The (b) (4) RSV-A and RSV-B (b) (4) assay is validated and suitable for use for detecting RSV neutralizing antibodies in immune adults' serum and is suitable for use in measuring anti-RSV neutralizing antibody responses elicited by ABRYSVO. The assay is linear and precise over the assay range of serum dilution of (b) (4) for RSV-A, and (b) (4) for RSV-B. The Limit of Detection for the test was set at a titer of (b) (4).

c. Testing Specifications

Analytical Chemistry
The analytical methods and their validations and/or qualifications reviewed for the ABRYSVO drug substance and drug product were found to be adequate for their intended use.

d. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

e. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ABRYSVO are listed in the table below. The activities performed and inspectional histories are noted in Table 4.

Table 4. Manufacturing Facilities Table for ABRYSVO (Respiratory Syncytial Virus Vaccine)

Name/Address	FEI number	DUNS number	Inspection /Waiver	Justification /Results
(b) (4) DS manufacturing	(b) (4)	(b) (4)	Waiver	CBER/DMPQ (b) (4) VAI
(b) (4) DP formulation, fill/finish, release testing, labeling, and packaging	(b) (4)	(b) (4)	Waiver	CBER/DMPQ (b) (4) NAI
(b) (4) Labeling and packaging	(b) (4)	(b) (4)	Waiver	CBER/DMPQ (b) (4) NAI
(b) (4) DP release testing	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI

CBER- Center for Biologics Evaluation and Research, DS – drug substance; DP – drug product; DMPQ – Division of Manufacturing and Product Quality; NAI – No Action Indicated; OBPO - Office of Biological Products Operations; ORA – Office of Regulatory Affairs; VAI – Voluntary Action Indicated.

CBER/DMPQ conducted a PLI at (b) (4) in (b) (4) and a Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

DMPQ conducted a PLI at (b) (4) in (b) (4) for the DP formulation, fill/finish, and labeling of the primary packaging. A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

DMPQ conducted a PLI at (b) (4) in (b) (4) for the labeling of the DP primary and secondary packaging. A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

ORA/OBPO performed a surveillance inspection of the (b) (4) (b) (4) manufacturing facility in (b) (4) A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

f. Container Closure System (CCS)

The RSVpreF vaccine combination product is provided as a kit including the lyophilized DP in a 2 mL glass vial, a 1 mL Type (b) (4) glass standard PFS containing sterile water diluent for reconstitution, and an individually packaged 13 mm vial adapter. The kit is defined as a co-packaged combination product under 21 CFR Part 3.2(e). The primary packaging components used for RSVpreF vaccine are described in Table-5. The primary components are sterilized before use. Pfizer conducted the container closure integrity testing (CCIT) employing (b) (4) method for the lyophilized product and diluent; all acceptance criteria were met.

Table 5. Container closure components and manufacturer

Component	Description	Manufacturer
Lyophilized drug product container	2 mL colorless glass vial with a high hydrolytic resistance	(b) (4)
Lyophilized drug product closure	13 mm Chlorobutyl rubber stopper, coated; (b) (4)	
Lyophilized drug product vial seal	13 mm aluminum vial seal with tamper-evident polypropylene flip off cap	
Diluent syringe	1 mL (b) (4) (b) (4) Borosilicate glass	
Diluent syringe plunger stopper	1-3 mL stopper gray (b) (4) elastomer	

Component	Description	Manufacturer
Vial adapter	13 mm Sterile, plastic fluid transfer device, in a blister package	(b) (4)

g. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not significantly alter the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

ABRYSVO has been evaluated in repeat-dose toxicity studies and in reproductive-developmental toxicity study in animals. Based on nonclinical toxicity assessments, there are no significant safety issues to report. ABRYSVO has not been evaluated for its carcinogenic or mutagenic potential or for impairment of fertility. Overall, based on the nonclinical toxicity assessments provided in the application, CBER concluded that there are no significant safety issues for the proposed indication in 60 years of age and older.

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral and cellular immune responses to ABRYSVO, were obtained in the clinical studies. The data demonstrated that ABRYSVO induces RSV-specific cell-mediated immune responses as well as RSV-specific humoral immunity. ABRYSVO induces an immune response against RSVpreF that protects against lower respiratory tract disease caused by RSV in older adults.

6. Clinical/Statistical

a. Clinical Program

The applicant included data from 6 clinical studies in the BLA to support the safety and effectiveness of ABRYSVO. The clinical studies described in this SBRA are shown in Table 6.

Table 6. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of ABRYSVO

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 mcg (final)
C3671014	Phase 3, Lot-to-Lot, Safety, Immunogenicity	N=993 n=745 Adults 18-49 years	RSVpreF 120 mcg (final)
C3671001	Phase 1/2 First-in-human, Dose-finding, Safety, Immunogenicity	N=1,235 n=186 Adults 18-85 years	RSVpreF 120 mcg (final), RSVpreF (60 mcg, 120 mcg, 240 mcg) 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 mcg, 120 mcg, 240 mcg) with $Al(OH)_3$ adjuvant, or with CpG/$Al(OH)_3$ adjuvant, or without adjuvant (240 mcg only). Subset with co-ad with SIIV
C3671004	Phase 2 Safety, Immunogenicity	N=713 n=282 Non-pregnant women 18-49 years	RSVpreF 120 mcg (final), RSVpreF (120 mcg, 240 mcg) 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 mcg (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 mcg without adjuvant)
*Only the active vaccine(s) is listed. Each of the studies also included a placebo group

Study C3671013 is an ongoing, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of RSVpreF in individuals 60 years of age and older. Participants were randomized 1:1

to receive a single intramuscular injection of RSVpreF or placebo, with randomization stratified by age group, 60-69 years (62%), 70-79 years (32%), and ≥80 years (6%). The study was initiated on August 31, 2021, and is planned to be conducted through 2 RSV seasons, with the primary efficacy analysis assessed during the first RSV season.

There were 240 clinical sites included in seven countries (the US, South Africa, Japan, Canada, Finland, the Netherlands, and Argentina) with a safety population of 34,284 participants. There were 158 US sites with a safety population of 20,501 US participants.

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

Exclusion Criteria
Individuals were excluded in the study if any one of the criteria met, i) immunocompromised individuals with known or suspected immunodeficiency, ii) individuals who receive chronic systemic treatment with immunosuppressive therapy, iii) receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration, iv) previous vaccination with any investigational RSV vaccine, v) serious chronic disorder, including metastatic malignancy, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, and, vi) bleeding diathesis or condition associated with prolonged bleeding.

Primary Efficacy Analyses

A total of 35,971 participants were enrolled in the study. 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 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 two primary efficacy endpoints, tested sequentially, were i) vaccine efficacy (VE) in preventing first-episode of LRTD-RSV with 2 or more symptoms with onset at least 14 days after vaccination and, ii) VE in preventing first-episode LRTD-RSV with 3 or more symptoms with onset at least 14 days after vaccination. A case of LRTD-RSV was defined as an RT-PCR confirmed RSV illness with two or more, or three or more, of the following respiratory symptoms within 7 days of symptom onset and lasting more than 1 day during the same illness: new or increased cough, wheezing, sputum production, shortness of breath, or tachypnea (≥25 breaths/min or 15% increase from resting baseline).

As of the data cutoff date of July 8, 2022, there were 44 cases of first-episode of LRTD-RSV with ≥2 symptoms occurring after Day 15 (14 days after vaccination), 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 of the lower limit of the multiplicity-adjusted CI being >20% (Table 6). As of the data cutoff date of July 8, 2022, there were 16 cases of first-episode LRTD-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 7).

Table 7. Vaccine Efficacy of RSVpreF Against First Episode of LRTI-RSV With ≥2 or ≥3 Symptoms Starting 14 Days After Vaccination, Evaluable Efficacy Population, Study C3671013

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 (0.07) 1.2	33 (0.2) 3.6	66.7 (28.8, 85.8)
First episode of LRTI-RSV with ≥3 symptoms	2 (0.01) 0.2	14 (0.09) 1.5	85.7 (32.0, 98.7)

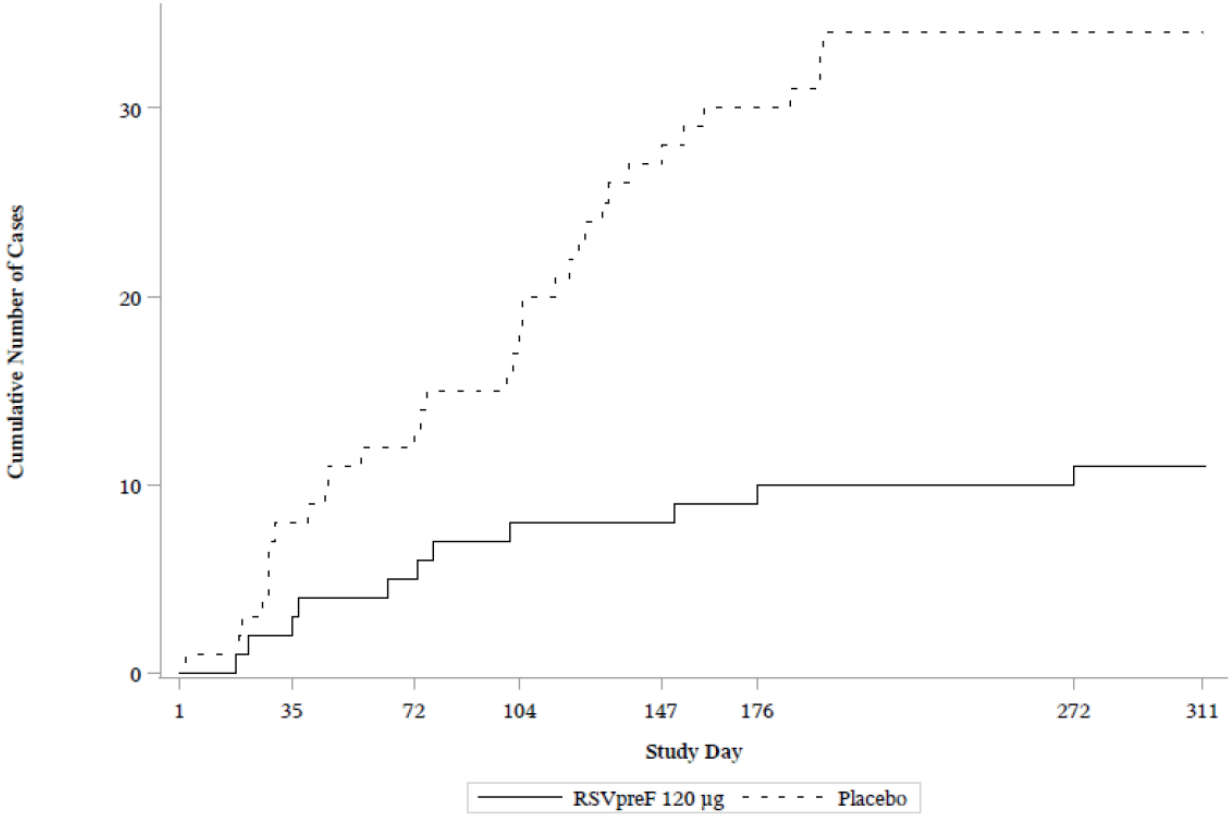
Source: Adapted from STN 125769/0 Study C3671013, Clinical Study Report, Table 10, Table 11.
Abbreviations: LRTI-RSV=lower respiratory tract illness associated with RSV; N=total number of participants in each vaccine group; n=number of participants meeting the efficacy endpoint case definition from Day 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.

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 C3671013



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 population who received multiple vaccinations due to multiple enrollments, the assigned “vaccine group (as randomized)” was based on the randomization group assigned to the first vaccination participant ID.

Secondary Efficacy Analyses

First Episode of ARI-RSV

ARI-RSV was defined as an illness involving 1 or more of the following respiratory illness symptoms, lasting more than 1 day: sore throat, cough, nasal congestion, nasal discharge, wheezing, sputum production, shortness of breath and laboratory-confirmed RSV infection within 7 days of ARI symptom onset.

As of the data cutoff date, there were 103 cases of first-episode of ARI-RSV reported occurring after Day 15, with 25 cases in the RSVpreF group compared to 78 in the

placebo group. In a descriptive analysis of vaccine efficacy, the VE for this endpoint was 67.9% (95% CI: 49.1, 80.4) (Table 8).

Table 8. Vaccine Efficacy of RSVpreF Against First Episode of ARI-RSV, Evaluable Efficacy Population, Study C3671013

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], % (95% CI)[e]
First episode of ARI-RSV	25 (0.15%) 2.71	78 (0.48%) 8.47	67.9% (49.1, 80.4)

Source: Adapted from STN 125769/43 Study C3671013, Response to 17 March 2023 Information Request, Table 40.19.
Abbreviation(s): ARI-RSV=acute respiratory illness associated with RSV; N = number of participants (at risk) in the specified vaccine group. These values are the denominators for the percentage calculations; n = Total number of cases of the specified endpoint; RSV=respiratory syncytial virus; VE=vaccine efficacy.
a. VE is defined as 1 - Risk Ratio and calculated as 1-(P/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases. Nominal 95% CI is obtained using the conditional exact test based on the binomial distribution of P.
b. IR (incidence rate) per 1000 PYO is defined as the number of cases / PYO * 1000. PYO is defined as the total ARI surveillance duration days across all participants at risk within each vaccine group, then divided by 365.25. ARI surveillance duration is from first vaccination date through death/discontinuation/surveillance cutoff date, 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. 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 LRTD-RSV (sLRTD-RSV)

A case of RSV-associated severe lower respiratory tract disease (sLRTD-RSV) was defined as a case meeting the RSV-LRTD criteria plus at least one of the following: hospitalization due to RSV-LRTD, new or increased oxygen supplementation, or mechanical ventilation including Continuous Positive Airway Pressure (CPAP). Because the pre-specified number of first-episode of sLRTD-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 sLRTD-RSV reported, both among placebo recipients; both participants were hospitalized and one required supplemental oxygen.

Exploratory and Post Hoc 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 9).

Table 9. 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 C3671013

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 (0.01) 0.1	9 (0.06) 1.0	88.9 (10.6, 99.8)
RSV Subgroup B	10 (0.06) 1.1	23 (0.14) 2.5	56.5 (-0.7, 82.8)
First episode of LRTI-RSV with ≥3 symptoms	--	--	--
RSV Subgroup A	1 (0.01) 0.1	3 (0.02) 0.3	66.7 (-393.7, 99.6)
RSV Subgroup B	1 (0.01) 0.1	10 (0.06) 1.1	90.0 (21.8, 99.8)
First episode of ARI-RSV	--	--	--
RSV Subgroup A	6 (0.04) 0.65	22 (0.13) 2.4	72.7 (30.6, 91.0)[c]
RSV Subgroup B	19 (0.11) 2.1	56 (0.34) 6.1	66.1 (42.0, 81.0)[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.
The evaluable efficacy population included all study participants who were eligible for the study; received study intervention to which they were randomized (RSVpreF or placebo); with a minimum follow-up through Day 15 after vaccination (Day 1 is the day of vaccination); and without major protocol violations before the symptom onset date of the confirmed ARI or LRTI case.
a. VE is defined as 1 - Risk Ratio and calculated as 1-(P/[1-P]), where P is the number of first episode of LRTI-RSV with ≥2 symptoms cases in RSVpreF group divided by the total number of first episode of LRTI-RSV with ≥2 symptoms cases. CI is obtained using the conditional exact test based on the binomial distribution of P, adjusted by Pocock error spending.
b. 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 there was no swab within 7 days of symptom onset for central lab testing available.

Demographics

Demographic characteristics among participants who received ABRYSVO and those who received placebo were generally similar with regard to age, gender, race, and ethnicity. The median age of participants in the Safety Population was 67 years, with 31.8% of participants between the ages of 70-79 years and 5.6% of participants ≥80 years of age at the time of study vaccination. Overall, most participants were White (78.3%), non-Hispanic/Latino (62.6%), and located in the US (59.8%).

Dose Selection

Study C3671001 was a first in human (FIH) dose-finding study that evaluated the safety, tolerability, and immunogenicity of RSVpreF with and without concomitant seasonal inactivated influenza vaccine (SIIV) administration in 1,235 nonpregnant female and male participants 18 to 85 years of age, divided into age subgroups of 18-49 and 50-85 years of age. In a subset of the participants, a second dose of RSVpreF was given alone or concomitantly with SIIV to assess the safety, tolerability, and immunogenicity of a second dose. Three dose levels of RSVpreF (60 mcg, 120 mcg, and 240 mcg) were evaluated in formulations with and without $Al(OH)_3$. In both age groups, RSVpreF elicited robust neutralizing responses against RSV subgroup A (RSV-A) and RSV subgroup B (RSV-B) 1 month after vaccination across all vaccine dose levels and formulations. These immune responses in RSVpreF vaccine recipients remained elevated compared to placebo recipients through 12 months after post-dose 1. The inclusion of $Al(OH)_3$ showed no benefit in enhancing immune responses at any dose level and the frequency and severity of local reactions trended higher in the groups receiving $Al(OH)_3$-containing formulations.

For those participants who were revaccinated with RSVpreF (240 mcg, with or without $Al(OH)_3$ adjuvant) 12 months after post-dose 1, RSV neutralizing titers increased at 1 month after revaccination, but the increase was lower than that observed after Dose 1. The RSV NT rate of decline was slower after revaccination compared to after Dose 1. All participants in the revaccination population received a higher dose level of RSVpreF for the initial vaccination and at 12 months after initial vaccination, compared to the 120 mcg dose level proposed for licensure. Thus, the data obtained from the revaccination portion of this study is of unclear relevance.

Reactogenicity trended higher in the younger age group and with adjuvanted vaccine formulations. There were no safety concerns identified in this study.

Study C3671002 was a Phase 1/2 dose- and formulation-finding study in participants 65-85 years of age. Seven RSVpreF formulations at 3 antigen dose levels of 60 mcg, 120 mcg, and 240 mcg of the prefusion F antigens formulated with $Al(OH)_3$ or $CpG/Al(OH)_3$, or RSVpreF with the prefusion F antigens alone at a single antigen dose level were administered concomitantly with SIIV in adults 65 through 85 years of age. A total of 313 participants were vaccinated in the study (252 active vaccine and 61 placebo). All RSVpreF doses and formulations elicited robust, persistent neutralizing responses when administered alone or concomitantly with SIIV. The inclusion of $CpG/Al(OH)_3$ showed no benefit in enhancing the immune response compared to RSVpreF formulations with $Al(OH)_3$ at any dose level or compared to

RSVpreF alone at the 240 mcg dose level. RSVpreF was safe and well tolerated when administered alone or concomitantly with SIIV, with no major differences observed across dose levels or formulations.

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

Coadministration with Tdap

Study C3671004 was a Phase 2b study that evaluated the safety, tolerability, and immunogenicity of the RSV vaccine when administered concomitantly with Tdap in healthy nonpregnant women 18 through 49 years of age. A total of 709 participants received: i) 120 mcg RSV vaccine antigen with concomitant Tdap, ii) 120 mcg RSV vaccine antigen with placebo, iii) 240 µg RSV vaccine antigen with $Al(OH)_3$ and concomitant Tdap, iv) 240 µg RSV vaccine antigen with $Al(OH)_3$ and placebo, or v) placebo and Tdap. Both formulations of RSVpreF were safe and well tolerated when administered alone or with Tdap.

Most reported local and systemic adverse reactions were mild or moderate in intensity, with generally higher rates of severe solicited systemic ARs in participants who received concomitant administration of RSVpreF and Tdap compared to those who received Tdap alone.

Human Challenge Study

Study WI257521 (Phase 2a) evaluated the safety, immunogenicity, and efficacy of a single dose of 120 mcg RSVpreF in an infectious virus challenge model in healthy adults 18–50 years of age. A total of 70 participants were randomized and received either study vaccine or placebo (35 participants in each group). Challenge virus RSV-A Memphis 37b (~4.5 Log_{10} plaque forming units) was administered intranasally. RSVpreF immunization was effective against symptomatic RSV infection and prevented shedding of infectious virus in healthy adults. VE against qRT-PCR confirmed symptomatic RSV infection by any 2 detectable qRT-PCR results over at least 2 consecutive days (primary endpoint) was 86.7% (95% CI: 53.8%–96.5%). Immunogenicity results showed that RSVpreF elicited large increases in neutralizing titers against RSV-A and RSV-B at 1 month after immunization. Overall, immunization with a single RSVpreF dose had a good safety profile and provided protection against symptomatic RSV infection in a viral challenge model.

Lot consistency

Study C3671014 was a Phase 3, multicenter, parallel-group, randomized, double-blind, placebo-controlled study that examined the immune response and the safety and tolerability profiles across 3 manufactured lots of RSVpreF when administered as a single 120 mcg dose level to healthy adults 18 through 49 years of age, to demonstrate lot equivalence in the manufacturing of RSVpreF. Across all vaccine

lots, 746 participants were vaccinated with RSVpreF 120 mcg, and 247 participants received the placebo.

The primary immunogenicity objective of the study was achieved. For both RSV-A and RSV-B, each pair of between-lot comparisons from the 3 vaccine lots met the predefined 1.5-fold equivalence criterion (2-sided 95% CI for each between lot geometric mean ratio (GMR) was contained in the interval 0.667 to 1.5) for the evaluable immunogenicity population. Subgroup analyses by sex showed similar results for females and males for both RSV-A and RSV-B. Overall, RSVpreF was safe and well tolerated, with safety profiles that were similar across the 3 RSVpreF vaccine lots and consistent with previous studies.

b. Bioresearch Monitoring (BiMo)

Bioresearch Monitoring inspections were issued for one domestic and two foreign clinical study sites that participated in the conduct of Study C3671013. The inspections did not reveal any issues that impact the data submitted in this original BLA.

c. Pediatrics

Safety and effectiveness of RSVpreF in individuals younger than 18 years of age have not been established. A presentation of Pfizer's Pediatric study plan was presented to the FDA Pediatric Review Committee (PeRC) on April 4, 2023. The committee agreed with the applicant's request for a deferral in pediatric subjects from birth to less than 18 years of age because the drug or biological product is ready for approval for use in adults before pediatric studies are complete.

7. Safety and Pharmacovigilance

Safety Analyses

The primary data to support the safety of RSVpreF in individuals 60 years of age and older are from Study C3671013, in which 34,284 participants received a dose of RSVpreF (n=17,215) or placebo (n=17,069).

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.

Solicited Local Adverse Reactions

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.

Solicited Systemic Adverse Reactions

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.

Subgroup Analyses

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

Unsolicited Adverse Events

The proportions of participants who reported unsolicited AEs within 1 month after vaccination were similar across groups (8.9% RSVpreF and 8.5% placebo). 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.

FDA conducted standardized Medical Dictionary for Regulatory Activities 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. Based on the FDA's review of available information, the SMQ for GBS identified 2 events in the RSVpreF group 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. The currently available information on atrial fibrillation is insufficient to determine a causal relationship to the vaccine.

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

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 system organ class Cardiac disorders for participants in both the RSVpreF (20 participants, 0.1%) and placebo (19 participants, 0.1%) groups. By preferred term, 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 agreed with the investigators' assessments of causality.

Serious Adverse Events

Through the data cutoff, SAEs were reported in 2.3% of participants in both the RSVpreF (n=396) and placebo (n=387) groups. SAEs were most frequently reported in the SOCs Cardiac disorders (RSVpreF 0.5%; placebo 0.5%) and infections and infestations (RSVpreF 0.5%; placebo 0.4%). There were three SAEs in the RSVpreF group that were assessed as related by the investigator and none in the placebo group: 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. Given the temporal association and biological plausibility, FDA agrees with the assessments of the investigators that these events were possibly related to study vaccine.

Across all studies, the safety data collected in the RSVpreF US clinical sites demonstrated an acceptable safety profile. RSVpreF was generally well tolerated. The reactogenicity and safety profile of RSVpreF in participants enrolled in the US was comparable to the reactogenicity and safety profile of RSVpreF in the overall population. Similarly, the reactogenicity and safety profile of RSVpreF in sub-groups of participants by sex, age, race, and ethnicity did not reveal any concerning differences. Two safety signals were identified: GBS and atrial fibrillation. These signals are to be further assessed in postmarketing safety studies.

Overall, the safety and effectiveness data provided in the application support the safety and effectiveness of RSVpreF for the proposed indication and usage.

Pharmacovigilance Plan (PVP)

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

8. Labeling

The proposed proprietary name, ABRYSVO, was reviewed and found acceptable by the Advertising and Promotional Labeling Branch (APLB) on December 8, 2022, and their recommendation was accepted by OVRR. CBER communicated the acceptability of the proprietary name to the applicant on December 19, 2022.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Package Insert (PI), Package and Container Labeling on May 11, 2023, and found them acceptable from a promotional and comprehension perspective.

The review team negotiated revisions to the PI. All labeling issues regarding the PI and the carton and container labels were resolved following communications with the Applicant.

9. Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was convened on February 28, 2023. A majority of the Committee members voted affirmatively (7 out of 12 votes) that the data supported the safety and effectiveness of ABRYSVO for prevention of LRTD caused by RSV in individuals 60 years of age and older. One committee member abstained from voting.

The committee members emphasized the need for postmarketing surveillance to continue to assess Guillain-Barré Syndrome (GBS), potential immune-mediated diseases (pIMDs) in general, and atrial fibrillation. Also, the Committee noted

limitations of the clinical development of ABRYSVO such as incomplete information on safety and effectiveness with repeat vaccination, concomitant use with other vaccines, the need for additional studies on the prevention of severe outcomes in at-risk populations, and the need for repeat vaccination. The Committee suggested that these issues should be addressed in the near future.

10. Other Relevant Regulatory Issues

The submission was granted priority review on November 29, 2022, based on the quality of safety and efficacy data from the Phase 3 study. ABRYSVO (RSVpreF vaccine) prevents a serious and life-threatening condition (RSV) in individuals 60 years of age or older, and if approved, would provide a significant improvement in safety and effectiveness because there were no vaccines licensed for the prevention of RSV disease in the US as of November 29, 2022, when the BLA was submitted.

The Applicant originally proposed an indication of prevention of acute respiratory disease and lower respiratory tract disease. However, after FDA review, it has been determined that the available data only support an indication of prevention of lower respiratory tract disease. This is due to the lack of data to support prevention of acute respiratory disease which is inclusive of upper respiratory tract disease.

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 LRTD cases. Additionally, 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. However, despite these limitations, due to the severity of RSV disease in older adults including those with chronic diseases, the benefits of reduction of morbidity and mortality due to RSV disease outweigh the risks at the current time.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in this original BLA submission, the Review Committee recommends approval of ABRYSVO for the labeled indication and usage.

b. Benefit/Risk Assessment

The Review Committee is in agreement that there are more benefits than risks associated with administering a single dose of ABRYSVO to individuals 60 years of age and older. However, there are still some uncertainties regarding the long-term immunogenicity and efficacy of ABRYSVO, its use in immunocompromised populations, co-administration with relevant vaccines (except the influenza vaccine), and the potential for immune-mediated diseases such as GBS and atrial fibrillation. A postmarketing safety study to evaluate GBS and other immune-mediated

demyelinating conditions associated with ABRYSVO is required. Also, Pfizer committed to conduct a study to assess the risk of atrial fibrillation. In addition, Pfizer plans to conduct, as a voluntary sponsor study, an active surveillance safety study among immunocompromised older adults aged ≥60 years after receiving ABRYSVO.

c. Requirements and Recommendation for Postmarketing Activities

Review of the available clinical trial data indicates that administration of RSVpreF may be associated with a risk of GBS and/or other immune-mediated demyelinating conditions, and/or a risk of atrial fibrillation and/or other supraventricular arrhythmias. Therefore, in addition to enhanced pharmacovigilance, postmarketing studies conducted as a Postmarketing Requirement (PMR) and a Postmarketing Commitment (PMC) are warranted to further assess these respective potential risks. In addition to these planned activities, Pfizer committed to conduct a safety study to assess the real-world safety of RSVpreF use in immunocompromised older adults (aged ≥60 years) who were excluded from the ongoing Phase 3 C3671013 study. Pfizer's PVP is acceptable. In addition, Pfizer agreed to complete their ongoing Phase 3 study C3671013 and submit a final study report, as a PMC.

Pfizer has committed to conduct the following postmarketing activities, which are specified in the approval letter.

PEDIATRIC REQUIREMENTS

The required studies are listed below.

1. Deferred pediatric study under PREA (Study C3671016), to evaluate safety and effectiveness in children and adolescents 2 to less than 18 years of age.

   Final Protocol Submission: September 30, 2023
   Study Completion: December 31, 2024
   Final Report Submission: June 30, 2025

2. Deferred pediatric study under PREA (Study C3671017), to evaluate safety and effectiveness in high-risk immunocompromised children 2 to <18 years of age.

   Final Protocol Submission: September 30, 2024
   Study Completion: December 31, 2025
   Final Report Submission: June 30, 2026

3. Deferred pediatric study under PREA (Study C3671018), to evaluate safety and effectiveness in seropositive, then seronegative infants <2 years of age.

   Final Protocol Submission: September 30, 2024
   Study Completion: December 31, 2027
   Final Report Submission: June 30, 2028

4. Deferred nonclinical program under PREA to evaluate vaccine-associated enhanced respiratory disease

   Final Protocol Submission: September 30, 2023
   Study Completion Date: August 31, 2024
   Final Report Submission: September 30, 2024

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

FDA has determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of GBS.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that Pfizer is required to conduct the following study:

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

   Final Protocol Submission: November 30, 2023
   Study Completion: May 31, 2029
   Final Report Submission: May 31, 2030

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

FDA acknowledged Pfizer's written commitment as described in their letter of April 14, 2023, and May 12, 2023 as outlined below:

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

   Final Protocol Submission: November 30, 2023
   Study Completion: February 28, 2027
   Final Report Submission: February 29, 2028

7. A Phase 3 study to Evaluate the Efficacy, Immunogenicity, and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Adults (Study C3671013) including sub-studies evaluating the safety and effectiveness of revaccination.

   Final protocol submission: Submitted

Study Completion Date: March 31, 2025
Final Report Submission: September 30, 2025

12. References

Branche AR, Saiman L, Walsh EE, et al. Incidence of respiratory syncytial virus infection among hospitalized adults, 2017-2020. Clin Infect Dis. 2022; 23;74(6):1004-11.

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

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

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

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

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

Johnson KM, Bloom HH, Mufson MA, and Chanock RM. (1962). Natural reinfection of adults by respiratory syncytial virus. Possible relation to mild upper respiratory disease.

Korsten K, Adriaenssens N, Coenen S, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. Eur Respir J. 2021;57(4).

McClure DL, Kieke BA, Sundaram ME, et al. Seasonal Incidence of Medically Attended Respiratory Syncytial Virus Infection in a Community Cohort of Adults ≥50 Years Old. PLoS One, 2014; Jul 15;9(7):e102586.

Murata Y, Falsey AR. Respiratory syncytial virus infection in adults. Antivir Ther. 2007;12(4 Pt B):659-70

Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289(2):179-86

Walsh EE, Peterson DR, Falsey AR. Risk factors for severe respiratory syncytial virus infection in elderly persons. J Infect Dis. 2004;189(2):233-8.