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Summary Basis for Regulatory Action

Date:	September 12, 2023
From:	Goutam Sen, Ph.D. Review Committee Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA STN:	125768/0
Applicant:	Pfizer Inc.
Submission Receipt Date:	December 21, 2022
Action Due Date:	August 21, 2023
Proper Name:	Respiratory Syncytial Virus Vaccine
Proprietary Name:	ABRYSVO
Indication:	Active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age.

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

Director, Product Office

Discipline Reviews	Reviewer / Consultant – Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • QC, Test Methods, Product Quality (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 Hector Carrero, OCBQ/DMPQ Zainab Mansaray-Storms, OCBQ/DMPQ Emnet Yitbarek, Ph.D., OCBQ/DBSQC Esmeralda Alvarado, OCBQ/DBSQC Hyesuk Kong, Ph.D., OCBQ/DBSQC Jing Lin, Ph.D., OCBQ/DBSQC George Kastanis, OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DPV) • BiMo	Yugenia Hong-Nguyen, M.D., OVRR/DVRPA Phillip Blanc, M.D., M.P.H., OBPV/DPV Haecin Chun, OCBQ/DIS/BMB
Statistical • Clinical data (OBPV/DB) • CMC data (OBPV/DB)	Rositsa Dimova, Ph.D., OBPV/DB Helen (Hairong) Shi, Ph.D., OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology • Animal pharmacology	Nabil Al-Humadi, Ph.D., OVRR/DVRPA Judy Beeler, M.D., OVRR/DVRPA
Labeling • Promotional (OCBQ/APLB) • Carton & Container	Oluchi Elekwachi, RPh., OCBQ/DCM/APLB Daphne Stewart, OVRR/DVRPA
Other Reviews not captured under above categories, for example: • Devices • Consults	Andrea Gray, Ph.D., CBER/ORO/DROP/RPB Brenda Baldwin, Ph.D., OVRR/DVRPA Harry Houghton, MS., OBPV/DB Melissa Lestini, MD., OC/OCPP/OPT/DPMH Carrie Ceresa, PharmD., OND/ORPURM/DPMH

• Regulatory Review	Nneka McNeal-Jackson, M.D., OND/ORPURM/DUOG Kristina Howard, DVM, Ph.D., DARS/CDER Sushanta Chakder, Ph.D.; Ilona Bebenek, PhD, DABT; David Klein, Ph.D., RDTS/CDER RPMs: Paul Keller, Ph.D., Vera Stupina, Ph.D. and Laura Montague
Advisory Committee Summary	Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was convened on May 18, 2023. Ten VRBPAC members voted "yes" and 4 voted "no" for safety and all VRBPAC members voted unanimously “yes” (n=14) for the effectiveness of ABRYSVO for prevention of LRTD caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals.

Table of Contents

GLOSSARY

AE	adverse event
AESI	adverse event of special interest
ARI	acute respiratory infection
BLA	Biologics License Application
BMI	body mass index
CI	confidence interval
EAC	Endpoint Adjudication Committee
(b) (4)	
GA	gestational age
GBS	Guillain-Barré Syndrome
GMR	geometric mean ratio
HBV	hepatitis B virus
HDP	hypertensive disorders of pregnancy
HIV	human immunodeficiency virus
LBW	low birth weight
LL	lower limit
LRTD	lower respiratory tract disease
mAb	monoclonal antibody
MA-LRTD	medically attended lower respiratory tract disease
MA-RTD	medically attended respiratory tract disease
MA-RTI	medically attended respiratory tract illness
mITT	modified intent-to-treat
NT	neutralizing titers
NTU	nephelometric turbidity unit
PAI	pre-approval inspection
PCR	polymerase chain reaction
PPROM	preterm premature rupture of membranes
preF	prefusion F protein
PLI	pre-license inspection
PROM	premature rupture of membranes
PT	pertussis toxin
PVP	pharmacovigilance plan
RhIG	Rho(D) immune globulin
RSV	respiratory syncytial virus
RSV MA-LRTD	RSV-confirmed medically attended lower respiratory tract disease
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RTI	respiratory tract illness
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SLE	systemic lupus erythematosus
SOC	System Organ Class
TT	tetanus toxoid
Tdap	Tetanus Toxoid, Diphtheria Toxoid and Acellular Pertussis Vaccine
VAI	Voluntary Action Indicated
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Introduction

Pfizer Inc. (Pfizer) submitted a new Biologics License Application (BLA) 125768 for licensure of their Respiratory Syncytial Virus (RSV) vaccine on December 21, 2022, for a new indication. The proprietary name of the vaccine is ABRYSVO. At the time of submission of STN 125768, ABRYSVO was under review under a separate BLA (STN 125769) for a different indication, under which it was subsequently approved for the indication of 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 on May 31, 2023. The new indication under STN 125768 is for active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age. Upon approval, BLA STN 125768 will be administratively closed, and future regulatory activity conducted under BLA STN 125769.

ABRYSVO consists of 120 mcg of lyophilized, recombinant antigen derived from the RSV fusion (F) surface glycoproteins of the two RSV subtypes, RSV-A (60 mcg) and RSV-B (60 mcg) stabilized in the pre-fusion trimeric conformation (RSVpreF). The vaccine 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 8°C. 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 and is the most frequent cause of lower respiratory tract illness in infants worldwide. High risk populations include infants and young children, elderly individuals, immunocompromised individuals (hematologic malignancies, hematopoietic stem cell transplant recipients, lung transplant recipients), and those with underlying cardiopulmonary conditions. In pregnant individuals, RSV infections

can lead to severe disease, requiring hospitalization for respiratory support, including supplemental oxygen, intubation, and/or mechanical ventilation.

Limited data are currently available on RSV disease burden in adults and women of childbearing age. Pregnancy is considered an immunologically attenuated state, and RSV infection in pregnancy has been associated with more severe disease and adverse outcomes (Gonik, 2019). Vertical transmission of RSV infection in pregnant women to their infants is possible and may be associated with adverse perinatal outcomes. Limited epidemiological studies suggest that RSV infection occurs in approximately 2% to 9% of pregnancies (Manti et al, 2022). A cross-sectional study of acute respiratory illness (ARI) in pregnancy found that 10% of ARI in pregnant women were due to RSV. However, severe RSV infection requiring hospitalization may be underreported due to infrequent testing (Hause et al., 2021).

The risk of primary infection in US infants less than 12 months of age ranges from 50 to 70%. The risk of RSV-associated LRTD is higher during the first year of life. RSV-associated hospitalization rates in infants under 1 year of age are 1 to 3%, with a peak in the first 3 months of life, and a 1 to 3% mortality in hospitalized infants. Risk factors for severe disease include prematurity, underlying chronic lung or heart disease, and immunodeficiency; however, healthy infants 0 to 6 months of age are also at significant risk for morbidity and mortality (Munoz et al, 2003).

RSV infection does not confer lasting immunity and re-infections occur throughout an individual's lifespan. 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. Although RSV disease represents a serious condition in infants less than one year of age, there is no specific RSV vaccine to protect infants from RSV disease. Nirsevimab, a prefusion F-specific mAb, was approved by the FDA for the prevention of RSV LRTD in neonates and infants born during or entering their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Two recombinant RSV vaccines, AREXVY and ABRYSVO, were recently approved by FDA for the 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	February 24, 2022
5. Request for comments and advice in lieu of Pre-BLA meeting	May 17, 2022 August 30, 2022
6. BLA 125768/0 submission	December 21, 2022
7. BLA filed	February 16, 2023
8. Mid-Cycle communication	April 19, 2023 (Cancelled by Pfizer)
9. Late-Cycle meeting	July 28, 2023
10. Action Due Date	August 21, 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) . 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 component. 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)
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)
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).

Stability of the DP

Stability studies were performed for DP stored under the long-term condition of storage at 5 ± 3°C, the accelerated condition of storage at (b) (4). The parameters tested throughout the stability evaluation of the RSVpreF antigen are appearance, residual moisture, reconstitution time, clarity, coloration, (b) (4) and (b) (4) protein concentration, (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 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) in vitro relative potency ((b) (4) (b) (4)) by (b) (4), and (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 (2°C to 8°C [36°F to 46°F]) or frozen conditions.

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 DS and DP 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.

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	ORA/OBPO (b) (4) CBER/DCM indicates this inspection will be classified as NAI
(b) (4) Labeling and packaging	(b) (4)	(b) (4)	Waiver	ORA/OPQO (b) (4) VAI

(b) (4) DP release testing	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) NAI

CBER- Center for Biologics Evaluation and Research; DCM- Division of Case Management; DS – drug substance; DP – drug product; DMPQ – Division of Manufacturing and Product Quality; NAI – No Action Indicated; OBPO - Office of Biological Products Operations; OPQO- Office of Pharmaceuticals Quality 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.

ORA/OBPO performed a surveillance inspection of the (b) (4) manufacturing facility in (b) (4). A Form FDA 483 list of observations was not issued, and CBER/Division of Case Management (DCM) indicates this inspection will be classified as NAI.

ORA/OPQO conducted a PAI at (b) (4) in (b) (4) and a Form FDA 483 with one item 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.

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 drug product (DP) in a 2 mL glass vial, a 1 mL Type (b) (4) glass standard prefilled syringe (PFS) containing sterile water diluent for reconstitution, and an individually packaged 13 mm vial adapter. The primary packaging components used for RSVpre F vaccine are described in the 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)

Component	Description	Manufacturer
Lyophilized drug product closure	13 mm Chlorobutyl rubber stopper, coated; (b) (4)	(b) (4)
Lyophilized drug product vial seal	13 mm aluminum vial seal with tamper-evident polypropylene flip off cap	(b) (4)
Diluent syringe	1 mL (b) (4) Borosilicate glass	(b) (4)
Diluent syringe plunger stopper	1-3 mL stopper gray (b) (4) elastomer	(b) (4)
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, the CBER Toxicology reviewer considered the nonclinical toxicology data to be adequate to support licensure.

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral and cellular immune responses to ABRYSVO, were obtained from 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. Antibodies to RSV antigens from individuals vaccinated in the third trimester of

pregnancy are transferred transplacentally to protect infants younger than 6 months of age against LRTD and severe LRTD caused by RSV.

6. Clinical/Statistical

a. Clinical Program

The applicant included data from 5 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)*
C3671008	Phase 3 Efficacy, Immunogenicity, Safety	N=7392, n=3682 (maternal) N=7128, n=3570 (infants) Pregnant women/ adolescents ≤49 years and their infants	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=187 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 year
C3671003	Phase 2 Safety, Immunogenicity	N=581 n=115 Pregnant women 18-49 years and their infants	RSVpreF 120 µg (final), RSVpreF (120 µg, 240 µg) with or without $Al(OH)_3$ adjuvant Subset: PCR assays for non-RSV respiratory pathogens in infants
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

Source: FDA-generated table
Abbreviations: $Al(OH)_3$=aluminum hydroxide; co-ad=concomitant administration; n=number of participants who received at least 1 dose of final RSVpreF; final=final formulation of RSVpreF (120 µg without adjuvant); SIIV=seasonal inactivated influenza vaccine
Notes: *Only the active vaccine(s) is listed. Each of the studies also included a placebo group

Study C3671008 is an ongoing, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of RSVpreF in infants born to women vaccinated during pregnancy, as well as the safety of RSVpreF in the pregnant women. Study-eligible pregnant individuals and adolescents ≤49 years of age were randomized in a 1:1 ratio to receive a single dose of RSVpreF or placebo. Maternal participants were followed from vaccination during pregnancy until 6 months after delivery. The study was initiated on June 17, 2020, is currently ongoing and being conducted at 216 sites in 18 countries (including the US). Eligible infant participants born to enrolled maternal participants during the first year of the study will participate from birth and will be followed for up to 24 months. All other infants born subsequently after the first year will participate from birth and for at least 12 months after birth. The primary efficacy endpoints were specified as RSV-associated, medically-attended lower respiratory tract disease (MA-LRTD) and severe RSV-associated MA-LRTD. RSV-associated MA-LRTD was defined as a medically-attended visit with a reverse transcription-polymerase chain reaction (RT-PCR) confirmed RSV illness with one or more of the following respiratory symptoms: tachypnea (respiratory rate ≥60 breaths/minute [<2 months of age], ≥50 breaths/minute [≥2 to 12 months of age], or ≥40 breaths/minute [≥12-24 months of age]); SpO2 measured in room air <95%; chest wall indrawing. RSV-associated severe LRTD was a subset defined as meeting the LRTD RSV criteria plus at least one of the following: tachypnea (respiratory rate ≥70 breaths/minute [<2 months of age], ≥60 breaths/minute [≥2 to 12 months of age], or ≥50 breaths/minute [≥12 to 24 months of age]); SpO2 measured in room air <93%; high-flow nasal cannula or mechanical ventilation (invasive or noninvasive), ICU admission for >4 hours and/or failure to respond/unconscious. Secondary efficacy endpoints included hospitalizations due to RSV. Study C3671008 was designed as an event-driven study with an original final analysis target of 124 adjudicated (primary endpoint) cases of MA-LRTD due to RSV at 90 days, and up to 2 interim analyses were planned. The second interim efficacy analysis was conducted on October 28, 2022, when 80 evaluable cases of MA-LRTD due to RSV within 90 days had accrued, including 39 evaluable cases of severe MA-LRTD due to RSV within 90 days. This was considered the final analysis for the primary efficacy objectives.

Inclusion Criteria

Individuals were eligible for inclusion in the study if they met all the following criteria: i) healthy women ≤49 years of age who are between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications or did not have a previous history of obstetric complications, ii) first-trimester data available, second-trimester data available, iii) receiving prenatal standard of care based on country requirements, iv) had a fetal anomaly ultrasound examination performed at ≥18 weeks of pregnancy with no significant fetal abnormalities observed, v) documented

negative HIV antibody, HBV surface antigen, and syphilis test during this pregnancy and prior to Visit 1 and, vi) pre-pregnancy body mass index (BMI) of <40 kg/m2.

Exclusion Criteria

Maternal participants are excluded from the study if any of the following criteria apply: i) pre-pregnancy BMI of >40 kg/m2, ii) bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection, iii) history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of vaccine, iv) current pregnancy resulting from in vitro fertilization, v) current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the study, including but not limited to the following: preeclampsia, eclampsia, or uncontrolled gestational hypertension, placental abnormality, polyhydramnios or oligohydramnios, significant bleeding or blood clotting disorder, endocrine disorders (including untreated hyperthyroidism or untreated hypothyroidism and diabetes mellitus type 1 or 2 prior to pregnancy or occurring during pregnancy if uncontrolled at the time of consent), any signs of premature labor with the current pregnancy or having ongoing medical/surgical intervention in the current pregnancy to prevent preterm birth, vi) prior pregnancy complications or abnormalities at the time of consent, based on the investigator's judgment, that will increase the risk associated with the participation in and completion of the study, including but not limited to the following: prior preterm delivery ≤34 weeks' gestation, prior stillbirth or neonatal death, previous infant with a known genetic disorder or significant congenital anomaly, vii) major illness of the maternal participant or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the maternal or infant participant's participation in, and completion of, the study or could preclude the evaluation of the maternal participant's response (includes positive serologic testing for regional endemic conditions assessed during routine maternal care, as per local standards of care and obstetric recommendations), viii) congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, within the year prior to enrollment, ix) participation in other studies involving investigational drug(s) within 28 days prior to consent and/or during study participation, x) receipt of monoclonal antibodies within the year prior to enrollment or the use of systemic corticosteroids for >14 days within 28 days prior to study enrollment, xi) current alcohol abuse or illicit drug use, and xii) receipt of blood or plasma products or immunoglobulin (Ig), from 60 days before IP administration, or planned receipt through delivery, with 1 exception, RhIG (e.g., RhoGAM), which can be given at any time.

Primary Efficacy Analyses

A total of 7392 maternal participants were randomized to receive RSVpreF (3695) or placebo (3697), 7358 (99.5%) completed vaccination, 7148 (96.7%) completed delivery, and 5683 (76.9%) completed the study. The primary efficacy endpoint for LRTD caused by RSV was evaluated only in the infant population. There were no pre-specified efficacy endpoints or collection of efficacy data pertaining to RSV

disease in pregnant individuals enrolled in the study. The infant evaluable efficacy population was the primary population for efficacy analyses. The analyses were also performed on the infant modified intent-to-treat (mITT) efficacy population. The vaccine efficacy (VE) results based on case accrual through the efficacy data cutoff date of September 30, 2022, met the statistical criterion for success (a CI lower bound >20%) for reducing severe MA-LRTD due to RSV, as confirmed by the Endpoint Adjudication Committee (EAC), at all timepoints starting at 90 days through 180 days.

The two primary efficacy endpoints, tested in parallel, were i) VE in preventing severe MA-LRTD due to RSV, within 90, 120, 150 and 180 days after birth, and ii) VE in preventing MA-LRTD due to RSV within 90, 120, 150 and 180 days after birth, where the testing over the specified time periods was conducted in a fixed sequence order for each of the two primary endpoints.

As of the data cutoff date of September 30, 2022, there were 6 cases of EAC-confirmed RSV-positive severe MA-LRTD cases in infants within 90 days after birth in the RSVpreF group and 33 in the placebo group, corresponding to a VE of 81.8% (99.5% CI: 40.6%, 96.3%). There were 19 cases of EAC-confirmed RSV-positive severe MA-LRTD cases in infants within 180 days after birth in the RSVpreF group and 62 in the placebo group, corresponding to a VE of 69.4% (97.58% CI: 44.3%, 84.1%) for RSVpreF, which met the pre-specified success criterion of all timepoints through 180 days after birth (Table 7). As of the data cutoff date of September 30, 2022, there were 24 cases of EAC-confirmed RSV-positive MA-LRTD cases in infants within 90 days after birth in the RSVpreF group and 56 in the placebo group, with a VE of 57.1% (99.5% CI: 14.7%, 79.8%) for RSVpreF. The VE results did not meet the statistical criterion for success within 90 days after birth for reducing MA-LRTD due to RSV as confirmed by the EAC, and therefore the results for this endpoint for the subsequent time periods after 90 days are considered descriptive. There were 57 cases of EAC-confirmed RSV-positive MA-LRTD cases in infants within 180 days after birth in the RSVpreF group and 117 in the placebo group, with a VE of 51.3% (97.58% CI: 29.4%, 66.8%) for RSVpreF with a lower bound of the 97.58% CI >20% (Table 8).

Table 7. Severe MA-LRTDs Due to RSV, Confirmed by the EAC, Occurring Within 90, 120, 150, 180 Days After Birth, Infant Participants, Evaluable Efficacy Population, Study C3671008

Time Interval	RSVpreF N=3495 n (%)	Placebo N=3480 n (%)	Vaccine Efficacy[a] (%) (CI)
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6, 96.3)[b]
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6, 88.8)[b]
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5, 85.9)[b]
180 Days after birth	19 (0.5)	62 (1.8)	69.4 (44.3, 84.1)[b]

Source: adapted from Pfizer CSR, Study C3671008
Abbreviations: EAC=Endpoint Adjudication Committee; MA-LRTD=medically attended lower respiratory tract disease
N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations; n=number of cases; RSV=respiratory syncytial virus.
a. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
b. Confidence intervals are 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).

Table 8. RSV-Positive MA-LRTDs, Confirmed by the EAC, Occurring Within 90, 120, 150, 180 Days After Birth, Infant Participants, Evaluable Efficacy Population, Study C3671008

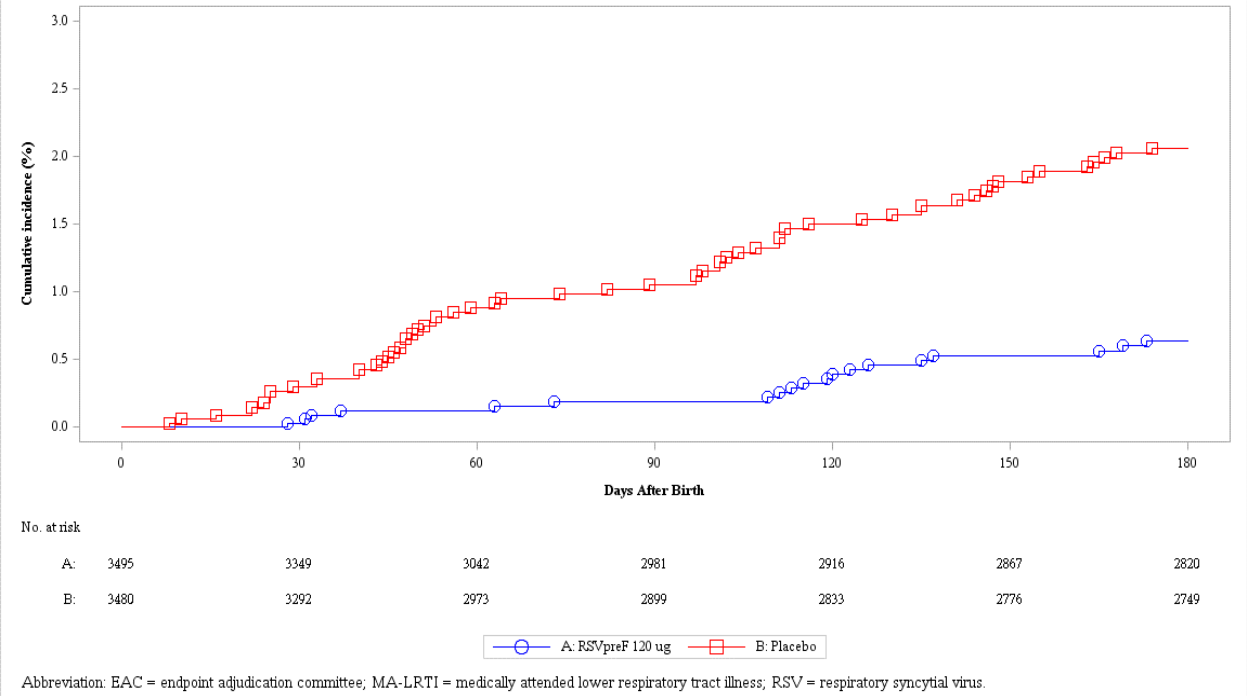
Time Interval	RSVpreF N=3495 n (%)	Placebo N=3480 n (%)	Vaccine Efficacy[a] (%) (CI)
90 days after birth	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)[b]
120 days after birth	35 (1.0)	81 (2.3)	56.8 (31.2, 73.5)[b]
150 days after birth	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9)[b]
180 days after birth	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)[b]

Source: adapted from Pfizer CSR, Study C3671008
Abbreviations: EAC=Endpoint Adjudication Committee; MA-LRTD=medically attended lower respiratory tract disease
N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations; n=number of cases; RSV=respiratory syncytial virus.
a. VE was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
b. Confidence intervals (CI) are 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).

Cumulative Case Accrual Curve

The cumulative case accrual curve for LRTD-RSV starting the day of vaccination, in the mITT Efficacy Population, is shown in Figure 1.

Figure 1. Kaplan-Meier Curves for Severe MA-LRTDs Due to RSV, Confirmed by the EAC, Occurring Within 180 Days After Birth, Infant Participants, Evaluable Efficacy Population, Study C3671008



Abbreviation: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.

Source: Pfizer Clinical Study Report, Study C3671008

Of 3568 infants in the RSVpreF group, 2 infants received palivizumab; of 3558 infants in the placebo group, 10 received palivizumab. No infant participants who received palivizumab had an EAC-confirmed RSV-positive MA-LRTD during the study.

Secondary Efficacy Analyses

Hospitalization Due to RSV Within 90, 120, 150, 180, and 360 Days After Birth

As of the cutoff date, there were 10 hospitalizations due to RSV confirmed by the EAC in infants within 90 days after birth in the RSVpreF group and 31 in the placebo group in the evaluable efficacy population, corresponding to a VE of 67.7% (99.17% CI: 15.9%, 89.5%) for RSVpreF. There were 19 hospitalizations due to EAC-confirmed RSV in infants within 180 days after birth in the RSVpreF group and 44 in the placebo group, corresponding to a VE of 56.8% (99.17% CI: 10.1%, 80.7%) for RSVpreF. These results met the statistical criterion for success (lower bound of the CI being >0%) for this endpoint at all timepoints within 180 days after birth. The statistical criterion for success was not met within 360 days after birth. Analysis of this secondary efficacy endpoint using the mITT population yielded similar results.

Table 9. Hospitalization Due to RSV, as Confirmed by the EAC, Within 90, 120, 150, 180, and 360 Days After Birth, Infant Participants, Evaluable Efficacy Population, Study C3671008

Time Interval	RSVpreF N=3495, n (%)	Placebo N=3480	Vaccine Efficacy[a] (%) (99.17% CI), n (%)
90 Days after birth	10 (0.3)	31 (0.9)	67.7 (15.9, 89.5)
120 Days after birth	15 (0.4)	37 (1.1)	59.5 (8.3, 83.7)

Time Interval	RSVpreF N=3495, n (%)	Placebo N=3480	Vaccine Efficacy[a] (%) (99.17% CI), n (%)
150 Days after birth	17 (0.5)	39 (1.1)	56.4 (5.2, 81.5)
180 Days after birth	19 (0.5)	44 (1.3)	56.8 (10.1, 80.7)
360 Days after birth	38 (1.1)	57 (1.6)	33.3 (-17.6, 62.9)

Source: adapted from Pfizer CSR, Study C3671008
Abbreviations: EAC=Endpoint Adjudication Committee; N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations; n=number of cases; RSV=respiratory syncytial virus.
a. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using Bonferroni procedure and accounting for the primary endpoints results.

MA-LRTD Due to RSV Within 210, 240, 270, and 360 Days After Birth

As of the cutoff date, there were 70 cases (2.0%) of investigator-reported RSV-positive MA-LRTD in infants within 210 days after birth in the RSVpreF group and 127 cases (3.6%) in the placebo group, corresponding to a VE of 44.9% (99.17% CI: 17.9%, 63.5%). Within 360 days after birth, there were 92 RSV-positive MA-LRTD cases (2.6%) in the RSVpreF group and 156 cases (4.5%) in the placebo group, corresponding to a VE of 41.0% (99.17% CI: 16.2%, 58.9%). Statistical success criterion was met (a CI lower bound >0%) at all timepoints within 210 to 360 days after birth for this secondary endpoint. However, it was noted that for the period from 181 to 360 days after birth, the number of RSV-confirmed MA-LRTD were similar in both treatment groups, with 35 new cases in the RSVpreF group, and 39 new cases in the placebo group.

Subpopulation Analyses

Study C3671008 was conducted in multiple regions and countries. Subgroup analyses for selected efficacy endpoints were performed on the following variables: maternal age at vaccination, GA at vaccination, country, country income level, duration of breastfeeding, exclusive breastfeeding, maternal smoking, number of household members, and racial/ethnic subgroups. In general, VE was consistent with those observed in the main analyses without clinically meaningful differences between subgroups observed; however, these subgroup analyses should be interpreted with caution due to low numbers of participants and cases in some subgroups.

Exploratory and Post Hoc Analyses

Efficacy analysis of the subgroup of infants born to pregnant individuals vaccinated at 32-36 weeks gestation

A potential risk of preterm birth was identified in this study. Thus, descriptive analyses of VE in the subgroup who received study vaccine at 32-36 weeks was undertaken to determine whether limiting vaccination to this GA group could mitigate this potential risk. These analyses were also performed by the Applicant and generated identical findings. See Table 10 and Table 11 for the subgroup analyses.

Table 10. Severe RSV MA-LRTD Subgroup Analysis by Gestational Age at Vaccination, Study C3671008

Time Period After Birth (Days)	GA (Weeks) at Vaccination	RSVpreF N	RSVpreF Cases n	Placebo N	Placebo Cases n	VE (%)	95% CI LL	95% CI UL
90	32-36	1572	1	1539	11	91.1	38.8	99.8
120	32-36	1572	3	1539	18	83.7	44.1	96.9
150	32-36	1572	4	1539	22	82.2	47.6	95.5
180	32-36	1572	6	1539	25	76.5	41.3	92.1

Source: FDA generated table. Adapted from Pfizer C3671008 CSR and VRBPAC May 18, 2023 FDA presentation
Abbreviations: GA=gestational age; VE=vaccine efficacy; CI=confidence interval; LL=lower limit; UL=upper limit

Table 11. RSV MA-LRTD Subgroup Analysis by GA at Vaccination, Study C3671008

Time Period After Birth (Days)	GA (Weeks) at Vaccination	RSVpreF N	RSVpreF Cases n	Placebo N	Placebo Cases n	VE (%)	95% CI LL	95% CI UL
90	32-36	1572	14	1539	21	34.7	-34.6	69.3
120	32-36	1572	18	1539	35	49.7	8.7	73.2
150	32-36	1572	20	1539	45	56.5	24.8	75.7
180	32-36	1572	24	1539	55	57.3	29.8	74.7

Source: FDA generated table. Adapted from Pfizer C3671008 CSR and VRBPAC May 18, 2023 FDA presentation
Abbreviations: GA=gestational age; VE=vaccine efficacy; CI=confidence interval; LL=lower limit; UL=upper limit

Demographic Characteristics, Maternal Participants

Maternal participants were 64.5% White, 19.6% Black or African American, 12.5% Asian, and 28.9% Hispanic/Latino. The median maternal age at the time of study vaccination was 29.0 years (range 14-47).

Demographic Characteristics, Infant participants

Demographic and baseline characteristics for the infant safety population were balanced across the 2 vaccine groups. Half of the infants were female. Most infants were White and non-Hispanic/non-Latino. Demographic and baseline characteristics by planned duration of follow-up were similar in Year 1 (infants followed for 24 months) and Year 2 (infants followed for 12 months) of the study.

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 subtypesA (RSV-A) and RSV subtypesB (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 (NT) 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 of RSVpreF for the initial vaccination and at 12 months after initial vaccination, compared to the 120 mcg dose proposed for licensure. Thus, the relevance of data obtained from the revaccination portion of this study is unclear.

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

Coadministration with Tdap

Study C3671004 was a Phase 2b study that evaluated the safety, tolerability, and immunogenicity of the RSVPreF vaccine when administered concomitantly with Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) in healthy nonpregnant women 18 through 49 years of age. A total of 713 non-pregnant women received: i) 120 mcg RSV vaccine antigen with concomitant Tdap, ii) 120 mcg RSV vaccine antigen with placebo, iii) 240 mcg RSV vaccine antigen with $Al(OH)_3$ and concomitant Tdap, iv) 240 mcg RSV vaccine antigen with $Al(OH)_3$ and placebo, or v) placebo and Tdap. The NI criteria for tetanus, diphtheria and RSV vaccine antigens were met. 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 adverse reactions (ARs) in participants who received concomitant administration of RSVpreF and Tdap compared to those who received Tdap alone.

Study C3671003

Study C3671003 was a Phase 2, multicenter, randomized, placebo-controlled, observer-blinded study to evaluate the safety, tolerability, and immunogenicity of RSV vaccine formulations in maternal participants and their infants. A total of 581 healthy pregnant individuals ≥18 and ≤49 years of age were randomized to receive 1 of 2 dose levels of bivalent RSV vaccine candidate at 120 mcg (60 mcg A and 60 mcg B) and 240 mcg (120 mcg A and 120 mcg B) of the prefusion RSV F antigen, formulated with or without aluminum hydroxide, or placebo. A total of 572 infants who were born to the vaccinated maternal participants were enrolled in the study and were included in the safety population; 522 infant participants were included in the evaluable immunogenicity population.

The safety, immunogenicity, and preliminary efficacy results from this Phase 2 study supported the selection of RSVpreF 120 mcg (without adjuvant) for Phase 3 development. Following vaccination, maternal-to-infant placental transfer ratios of RSV A- and RSV B-neutralizing antibody titers were >1 for all vaccine groups. When all vaccine groups were combined and compared to placebo, exploratory efficacy of maternal vaccination against RSV-associated MA-LRTD and severe MA-LRTD (within 6 months after birth) were 75% (95% CI: -11%, 97%) and 83% (95% CI: -48%, 99%), respectively. The most frequently reported local reaction was pain at the injection site and the most frequently reported systemic event was fatigue. A numerical imbalance in preterm births was observed in the RSVpreF vaccine groups compared with matched placebo controls. Preterm births occurred in 5.3% (6/114) of infants in the RSVpreF group and 2.6% (3/117) in the placebo group.

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)

BiMo inspection assignments were issued for three clinical investigator study sites that participated in the conduct of Protocol C3671008. The inspections did not reveal significant problems impacting the data submitted in support of this original BLA.

c. Pediatrics

Safety and effectiveness of RSVpreF in individuals younger than 10 years of age have not been established. A presentation of applicant's pediatric study plan was presented to the FDA Pediatric Review Committee (PeRC) on June 13, 2023. The committee agreed with the applicant's request for a partial waiver in children from birth to less than 10 years of age because ABRYSVO fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of children in this age group. Safety and effectiveness data from study C3671008 that specified enrollment eligibility of adolescent pregnant individuals and extrapolation of the data from older pregnant individuals to those 10 to <16 years of age fulfills the Pediatric Research Equity Act (PREA) requirement for the pediatric age group 10 to <17 years of age.

7. Safety and Pharmacovigilance

Safety Analyses

Safety Data for Maternal Participants

Safety data from Study C3671008 through the September 2, 2022, data cutoff included 7357 vaccinated pregnant participants (3682 RSVpreF vaccine recipients and 3675 placebo recipients), of whom 5683 participants (77.2%) had at least 6 months of follow-up post-delivery. Data were reported on solicited local and systemic adverse reactions within 7 days following vaccination. The most commonly reported solicited adverse reactions among RSVpreF recipients were fatigue (46.1% versus 43.8% in the placebo group), headache (31.0% versus 27.6% in the placebo group), muscle pain (26.5% versus 17.1% in the placebo group), and injection site pain (40.6% versus 10.1% in the placebo group). These were predominately mild and moderate, with 0.3% and 2.3% of local and systemic solicited adverse reactions, respectively, reported as grade 3 in severity. Most solicited adverse reactions, including the grade 3 local and systemic adverse reactions, resolved within 3-4 days post-vaccination. Fever was reported in 2.6% of participants in the RSVpreF group and 2.9% of participants in the placebo group. One (1) immediate adverse event (AE) of mild dizziness was reported in the RSVpreF vaccine group within 30 minutes of vaccination and resolved on the day of onset. This was considered by the study investigator and FDA to be related to vaccination.

The proportions of maternal participants with any AEs reported within 1 month after vaccination were 13.7% and 13.1% in the RSVpreF and placebo groups, respectively. AEs reported as severe or life-threatening within 1 month after vaccination occurred in 2.2% in the RSVpreF group and 1.5% in the placebo group and occurred most frequently in the System Organ Class (SOC) of Pregnancy, puerperium, and perinatal conditions (1.7% versus 1.0%). The frequencies of severe or life-threatening AEs occurring after vaccination but before delivery were reported in 3.0% versus 2.4% in the RSVpreF and placebo groups, respectively; and during the time between delivery and 1 month after delivery, were reported in 4.3% versus 4.1% in the RSVpreF and placebo groups, respectively.

The frequencies of serious adverse events (SAEs) in maternal participants to the data cutoff point were 16.2% and 15.2% in the vaccine and placebo groups, respectively. SAEs assessed as related by the investigator included 4 maternal participants in the RSVpreF group: 1 participant with severe pain in multiple extremities which started in the vaccinated extremity 2 days after vaccination; 1 episode of premature labor with onset 2 days after vaccination, which did not result in a preterm delivery; an episode of thrombocytopenia 6 days after vaccination with a subsequent diagnosis of systemic lupus erythematous (SLE) 5 months later; and 1 case of eclampsia with onset 15 days after vaccination.

An analysis of maternal outcomes of interest was performed for pregnancy-related conditions with the potential for associated premature delivery due to obstetric indications, e.g., hypertensive disorders of pregnancy (HDP), premature rupture of membranes (PROM), and preterm premature rupture of membranes (PPROM).

These pregnancy-related SAEs overall were reported in 152 (4.1%) vaccinated maternal participants versus 120 (3.3%) in the placebo group, including 68 (1.8%) cases of pre-eclampsia in the RSVpreF group and 53 (1.4%) cases of pre-eclampsia in the placebo group.

Premature delivery was reported as an adverse event of special interest (AESI) for maternal participants throughout the study in 5.6% (207/3682) versus 4.8% (175/3675) in the RSVpreF and placebo groups, respectively. The rate of premature deliveries in the general population is typically higher than 6% (CDC, 2022a; WHO, 2022), which is higher than the overall rate of premature deliveries observed in the clinical trial population. The numerical difference represents a potential safety signal.

Safety Data for Infant Participants

As of the data cutoff date of September 02, 2022, a numerical imbalance in preterm births was noted in the RSVpreF group (5.7%; 202/3568) compared with the placebo group (4.7%; 169/3558), in infants born to pregnant individuals vaccinated at 24-36 weeks of pregnancy.

Of all preterm infants in Study C3671008, approximately one-third were born to maternal participants who were vaccinated at 32-36 weeks. This subgroup (maternal participants vaccinated at 32-36 weeks gestation) represented approximately 45% of the clinical trial population. The safety data analyses from this subgroup reported preterm birth rates of 4.2% in all live births in the RSVpreF group and 3.7% in all live births in the placebo group. These subgroup analyses provided support for limiting the indication to active immunization of pregnant individuals at 32-36 weeks, eliminating the potential for increase in risk after vaccination with RSVpreF of both extremely preterm births (less than 28 weeks GA), where there is substantive morbidity and mortality, and very preterm births (28 to less than 32 weeks GA).

As of the data cutoff point, SAEs from birth to 24 months of age were reported in 17.5% in the RSVpreF group and 17.5% in the placebo group. SAEs within 1 month after birth were reported in 15.5% of infants in the RSVpreF group and 15.2% of infants in the placebo group. Congenital anomalies were reported in 5.0% of infants in the RSVpreF group and 6.2% in the placebo group.

The proportions of infant participants with any AE reported within 1 month after birth were 37.1% in the RSVpreF group and 34.5% in the placebo group. Low birth weight (LBW) was reported in 5.1% [95% CI: 4.4%, 5.8%] and 4.4% [95% CI: 3.7%, 5.0%] of infant participants in the RSVpreF and placebo groups, respectively. Neonatal jaundice occurred in 7.2% and 6.7% of infant participants in the RSVpreF and placebo groups, respectively. All other AEs among infant participants were reported with similar percentages between treatment groups and generally reflected rates of AEs that would be expected in neonatal and infant populations.

Deaths

There was 1 maternal death in the RSVpreF group due to postpartum hemorrhage and hypovolemic shock; FDA agreed with the investigator's assessment that this death was not related to vaccine administration.

There were 18 peripartum fetal deaths; 10 (0.3%) in the RSVpreF group, 8 (0.2%) in the placebo group. None of the intrauterine demises were assessed by the investigator as related to vaccination; FDA agrees that the fetal deaths reported in this study were unlikely to have been related to the IP based on review of available case narratives and evident lack of temporal relation of vaccination to the fetal loss events. Up to the data cutoff, a total of 17 infant deaths were reported: 5 (0.1%) in the RSVpreF group and 12 (0.3%) in the placebo group. No infant deaths were assessed by the investigator as related to maternal vaccination. Except for 1 of the infant deaths in the vaccine group, FDA agrees with the investigator's conclusions; for 1 death that resulted from prematurity-related complications, FDA was unable to exclude the possibility that the extreme prematurity and subsequent death was related to receipt of the investigational product. One infant in the placebo group died from RSV LRTD.

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)

Safety concerns for ABRYSVO include an important identified risk for preterm birth; important potential risks for Guillain-Barré syndrome (GBS), allergic reactions, supraventricular arrhythmias, and hypertensive disorders of pregnancy (HDP). There is missing information for use in immunocompromised pregnant women and use in immunocompromised older adults. The Applicant 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). The Applicant will conduct enhanced pharmacovigilance activities, including expedited reporting to Vaccine Adverse Event Reporting System (VAERS) (regardless of seriousness or label status) for 3 years post-approval and provide a summary and analysis in periodic safety reports for preterm birth and HDP. The Applicant will also perform enhanced pharmacovigilance activities for GBS and supraventricular arrhythmias, as indicated under the STN 125769/0 approval letter dated May 31, 2023.

The Applicant's pharmacovigilance plan includes four safety-related studies as postmarketing requirements (PMRs) to evaluate preterm birth and HDP following vaccination with RSVpreF (Note: the approval of BL 125769/0 for use of ABRYSVO in individuals 60 years of age and older also included a PMR study to assess GBS and a postmarketing commitment (PMC) study to assess atrial fibrillation). These studies will further assess the incidence of preterm births, HDP, and other potential risks in the postmarket setting.

8. Labeling

There was no new proposed proprietary name for Respiratory Syncytial Virus Vaccine under BLA 125768.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Package Insert, Package and Container Labeling on August 14, 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 VRBPAC meeting was convened on May 18, 2023. The committee discussed the balance between the convincing VE, including against severe LRTD, and AEs, particularly premature delivery/birth. The committee also discussed duration of vaccine protection, gestational age at time of vaccination, concomitant administration of other vaccines during pregnancy, and considerations for postmarketing studies. Ten VRBPAC members voted "yes" and 4 voted "no" for safety and all VRBPAC members voted unanimously “yes” (n=14) for the effectiveness of ABRYSVO for prevention of LRTD caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals. The Advisory Committee members expressed concern about preterm birth and stressed the importance of robust, timely postmarketing evaluation of preterm births.

10. Other Relevant Regulatory Issues

The submission was granted priority review on February 16, 2023, based on the quality of safety and efficacy data from the C36710080 Phase 3 study. ABRYSVO (RSVpreF vaccine) prevents a serious and life-threatening condition (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals, 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 U.S. as of December 21, 2022, when the BLA was submitted.

11. Recommendations and Benefit/Risk Assessment

d. 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 in pregnant individuals at 32-36 weeks gestational age.

e. Benefit/Risk Assessment

Given the available evidence, the review committee recognizes that the potential risks of preterm birth and HDP may outweigh the benefit of RSVpreF in pregnant individuals at 24-36 weeks of gestational age. Although the available data are insufficient to either establish or exclude a causal relationship between preterm birth and ABRYSVO, given the available evidence and the potential risks of HDP (that is a known risk factor for preterm birth), extremely preterm births, and very preterm births, the residual uncertainty and risks outweigh the demonstrated benefit of active immunization of pregnant individuals at 24-36 weeks evaluated in the Phase 3 development program. A more favorable balance of risks and benefit results from an indication limited to active immunization of pregnant individuals at 32-36 weeks, as doing so eliminates the potential for increase in risk of preterm delivery and births before 32 weeks of gestation after vaccination with ABRYSVO. The review committee is in agreement that the benefit of RSVpreF, specifically when administered between 32-36 weeks, outweighs the risks of vaccination including the potential risks of preterm birth and HDP. The Applicant will be required to conduct four PMR studies, which will further assess the incidence of preterm births, HDP, and other potential risks in the postmarket setting.

f. Requirements and Recommendation for Postmarketing Activities

Review of the available clinical trial data indicates that administration of RSVpreF at 24-36 weeks of gestational age may be associated with risks of preterm birth and hypertensive disorders of pregnancy. Therefore, in addition to enhanced pharmacovigilance, postmarketing studies conducted as Postmarketing Requirements (PMRs) are warranted to further assess these respective serious risks.

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

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

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 preterm birth, and to identify an unexpected serious risk of hypertensive disorders of pregnancy.

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

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

1. Study titled, “A Rapid Surveillance and Cohort Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy in the United States” (Protocol C3671027). This postmarketing database study will utilize Sentinel System claims data, including Medicaid claims data, to conduct near real-time monitoring and evaluate the serious risks of preterm birth and hypertensive disorders of pregnancy among approximately 80,000 pregnant women vaccinated with ABRYSVO in the United States compared to a cohort of pregnant women not exposed to ABRYSVO.

   We acknowledge the timetable you submitted on August 10, 2023, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: February 29, 2024

   Study Completion Date: August 31, 2028

   Final Report Submission: February 28, 2029

2. Study titled, “Post-Marketing Safety Study Using a Pregnancy Registry to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy” (Protocol C3671041).” This prospective, non-interventional pregnancy registry will evaluate the serious risks of preterm birth and hypertensive disorders of pregnancy in approximately 1,854 pregnant women (including 927 pregnant women exposed to ABRYSVO compared to a group of 927 pregnant women not exposed to ABRYSVO).

   We acknowledge the timetable you submitted on August 10, 2023, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: February 29, 2024

   Study Completion Date: September 30, 2030

   Final Report Submission: September 30, 2031

3. Study titled, “A Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy in an Integrated Healthcare System in the United States” (Protocol C3671042). This retrospective non-interventional cohort study using electronic healthcare data from a real-world healthcare system in the United States will evaluate the serious risks of preterm birth and hypertensive disorders of pregnancy in at least 4,712 ABRYSVO exposed pregnant women in comparison to a group of women not exposed to ABRYSVO.

   We acknowledge the timetable you submitted on August 10, 2023, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: February 29, 2024

Study Completion Date: February 28, 2029

Final Report Submission: August 31, 2030

4. Study titled, “Safety of respiratory syncytial virus stabilized prefusion F subunit vaccine (RSVpreF) in pregnant women and their offspring in a real world setting in Europe” (Protocol C3671026). This retrospective cohort study using electronic healthcare data from the Vaccine Monitoring Collaboration for Europe (VAC4EU) will evaluate the serious risks of preterm birth and hypertensive disorders of pregnancy in ABRYSVO-exposed pregnant women compared to pregnant women not exposed to ABRYSVO.

   We acknowledge the timetable you submitted on August 10, 2023, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: March 31, 2024

   Study Completion Date: March 31, 2029

   Final Report Submission: September 30, 2029

12. References

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