Vaccines and Related Biological Products Advisory Committee Meeting
May 18, 2023

FDA Briefing Document

Respiratory Syncytial Virus Vaccine
(Proposed Trade Name: Abrysvo)

Applicant:
Pfizer, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Vaccines and Related Biological Products Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought a Biologics License Application (BLA) submitted to the US Food and Drug Administration (FDA) to support licensure of RSVpreF (Abrysvo), with the proposed indication and use to "prevent lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals" to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AE	adverse event
AESI	adverse events of special interest
ARI	acute respiratory illness
BLA	Biologics License Application
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
dLIA	direct-binding Luminex immunoassay
EAC	endpoint adjudication committee
e-diary	electronic diary
E-DMC	external data monitoring committee
ERD	enhanced respiratory disease
FDA	US Food and Drug Administration
FI-RSV	formalin-inactivated RSV
HBV	hepatitis B virus
HCV	hepatitis C virus
HIC	high-income countries
HIV	human immunodeficiency virus
GMT	geometric mean titer
GMR	geometric mean ratio
LBW	low birth weight
LMIC	low- and middle-income countries
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract illness (*Note: The Applicant references LRTI in the clinical study report)*
LRTD-RSV	RSV-associated lower respiratory tract disease (*Note: RSV-positive illness or disease will be referred to as LRTD-RSV throughout this document, consistent with the proposed indication)*
LRTI-RSV	RSV-associated lower respiratory tract illness
MAE	a nonserious AE that results in evaluation at a medical facility
MA-LRTD	medically attended lower respiratory tract disease
MA-LRTI	medically attended lower respiratory tract illness
MA-LRTI-RSV	RSV confirmed medically attended lower respiratory tract illness
MA-RTI	medically attended respiratory tract illness
mITT	modified intent to treat
NAAT	nucleic acid amplification test
NDCMC	newly diagnosed chronic medical condition
PCR	polymerase chain reaction
preF	prefusion F protein
PT	MedDRA Preferred Term
PVP	pharmacovigilance plan
RSV	respiratory syncytial virus
RSVpreF	respiratory syncytial virus prefusion F protein vaccine
RTD	respiratory tract disease
RTI	respiratory tract illness
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event

sLRTI-RSV	severe RSV-associated lower respiratory tract illness
SOC	System Organ Class
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On December 21, 2022, Pfizer, Inc. (the Applicant) submitted a Biologics License Application (BLA) to the US Food and Drug Administration (FDA) to support licensure of RSVpreF (Abrysvo), with the proposed indication and use to "prevent lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals." RSVpreF is a bivalent recombinant protein subunit vaccine which consists of equal amounts of stabilized prefusion F (preF) antigens from the two major RSV subgroups: RSV A and RSV B. The proposed dosing regimen is a single intramuscular injection at the dose level of 120 µg. Data from 5 clinical studies were submitted in support of the BLA. The primary data to support the safety and efficacy of RSVpreF for use in pregnancy consist of data from an ongoing multinational Phase 3 randomized, double-blind and placebo-controlled trial (Study C3671008, referred to as Study 1008 throughout this document) in which 7392 participants were randomized to receive a single dose of RSVpreF (n=3695) or placebo (n=3697). The placebo consisted of excipients matched to those in the RSVpreF vaccine formulation, minus the active ingredients, with a similar appearance to the investigational product.

Submission of the BLA followed a successful protocol-specified interim analysis that evaluated primary efficacy endpoints of RSV-confirmed medically attended lower respiratory tract disease (MA-LRTD-RSV) occurring in infants within 90, 120, 150, and 180 days after birth. As of the September 30, 2022 data cutoff, the median duration of follow-up for efficacy was approximately 9 months.

Study 1008 was initiated on June 17, 2020, is currently ongoing, and is a global study being conducted in 18 countries, in the Northern and Southern hemispheres.

Vaccine Efficacy Data

Vaccine efficacy (VE) was assessed in preventing severe LRTD-RSV (RSV-associated lower respiratory tract disease), defined as an infant with an MA-RTD (RSV-associated respiratory tract disease) visit and respiratory rate ≥70 bpm for <2 months of age, ≥60 bpm for ≥2 months to <12 months of age, or ≥50 bpm for ≥12 months to 24 months of age; or SpO2 <93% or high-flow nasal cannula or mechanical ventilation; or ICU admission for >4 hours; or failure to respond/unconscious; and RSV-positive test result. VE for severe LRTD-RSV within 90 days after birth was 81.8% (99.5% confidence interval [CI]: 40.6, 96.3) with 6 cases in the vaccine group and 33 cases in the placebo group; and VE within 180 days after birth was 69.4% (97.6% CI: 44.3, 84.1) with 19 cases in the vaccine group and 62 cases in the placebo group.

Vaccine efficacy (VE) was also assessed in preventing LRTD-RSV, defined as infant with an MA-RTD visit and respiratory rate ≥60 bpm for <2 months of age, ≥50 bpm for ≥2 months to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age; or SpO2 <95% or chest wall indrawing and RSV-positive test result. VE within 90 days after birth was 57.1% (99.5% CI: 14.7, 79.8) with 24 cases in the vaccine group and 56 cases in the placebo group; and VE within 180 days after birth was 51.3% (97.58% CI: 29.4, 66.8) with 57 cases in the vaccine group and 117 cases in the placebo group.

Planned secondary endpoint analyses supported the results of the primary VE analyses. A planned secondary endpoint analysis of VE against RSV-associated hospitalization within 180

days after birth was 56.8% (99.17% CI: 10.1, 80.7). A secondary endpoint analysis of VE against RSV MA-LRTD occurring within 360 days after birth was 41.0% (99.17% CI: 16.2, 58.9).

Safety Data for Maternal Participants

Safety data from Study 1008 through the September 2, 2022 data cutoff for safety included 7357 pregnant participants (3681 RSVpreF vaccine recipients and 3676 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 AE (mild dizziness) was reported in the RSVpreF vaccine group within 30 minutes of vaccination which was considered by the study investigator and FDA to be related to vaccination. The AE resolved on the day of onset.

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. The number of 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 period of delivery to 1 month after delivery, were reported in 4.3% versus 4.1% in the RSVpreF and placebo groups, respectively.

The frequencies of non-fatal 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 5 months later; and 1 case of eclampsia with onset 15 days after vaccination.

Premature delivery was reported as an AESI for maternal participants throughout the study in 5.6% [95% CI: 4.9%, 6.4%] versus 4.7% [95% CI: 4.1%, 5.5%] in the RSVpreF and placebo groups, respectively. Although the rate of premature deliveries is higher in the general population (CDC, 2022; WHO, 2022) in comparison to the overall rate in this clinical trial population, a numerical difference was noted, although the 95% confidence intervals of the point estimates overlap.

There was 1 maternal death in the RSVpreF group due to postpartum hemorrhage and

hypovolemic shock; FDA agreed with the investigator's assessment as not related to vaccine administration.

Safety Data for Infant Participants

SAEs included the following the outcomes of ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomalies. The following adverse events of special interest (AESIs) are reported as SAEs: extremely preterm birth (<28 weeks) and extremely low birth weight (≤1000 g). 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. SAEs to the data cutoff included 17.5% in the RSVpreF group and 17.5% in the placebo group. Congenital anomalies were reported in 5.0% of infants in the RSVpreF group and 6.2% in the placebo group. For the SAE of extremely preterm birth (<28 weeks), there was 1 infant (<0.1%) in the RSVpreF group and 1 infant (<0.1%) in the placebo group. For the SAE of extremely low birth weight (≤1000 g), there was 1 infant (<0.1%) in the RSVpreF group and there were 2 infants (<0.1%) in the placebo group.

AESIs for infant participants included preterm birth (born at <37 weeks' gestation), low birth weight (1001 to 2500 g), and developmental delay. AESIs within 1 month after birth were reported at 8.4% in the RSVpreF group and 7.2% in the placebo group. As of the data cutoff, premature births were reported in 5.7% [95% CI: 4.9%, 6.5%] of infant participants in the RSVpreF group compared with 4.7% [95% CI: 4.1%, 5.5%] in the placebo group. A numerical imbalance, though not statistically significant, was observed.

Of infants born prematurely, 89.6% of preterm births (5.0% of all live births) in the RSVpreF group and 92.9% of preterm births (4.4% of all live births) in the placebo group were born in the gestational age (GA) range of ≥34 to <37 weeks.

The AESI of 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.

Unsolicited non-serious AEs within 30 days were reported in 28.4% and 26.2% in infants in the RSVpreF and placebo groups, respectively. 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. Severe or life-threatening AEs from birth to 1 month of age were reported in 5.1% versus 4.5% of the RSVpreF and placebo groups, respectively. No infant participants were withdrawn from the study due to an AE reported within 1 month after birth.

One (1) AE of premature birth in an infant participant in the RSVpreF group was assessed as related to maternal vaccination by the investigator. The infant's mother was briefly hospitalized on day 4 post-vaccination due to concern for possible decreased fetal movement. The infant was born at 36 weeks and 5 days gestation, on day 86 post-vaccination, with a normal birth outcome and no complications.

A total of 18 peripartum fetal deaths were reported for the study pregnancy; 10 (0.3%) in 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 investigational product based on review of available case narratives and evident lack of temporal relation of vaccination to the fetal loss events.

A total of 17 infant deaths were reported to the data cutoff: 5 (0.1%) in the RSVpreF group and 12 (0.3%) in the placebo group. For infant deaths in the RSVpreF group, the FDA agrees with the investigator's conclusions for 4 out of 5 of the infant deaths; however, for 1 case of extreme prematurity in an infant born to an 18-year-old mother at 10 days after vaccination who died from prematurity-related complications, FDA is unable to exclude the possibility of the extreme prematurity and subsequent death being related to receipt of the investigational product.

A total of 7 infant deaths were reported during the neonatal period (the first 28 days of life); 2 in the RSVpreF group (including the 1 infant with extreme prematurity) and 5 in the placebo group.

One event of infant death in the placebo group was adjudicated by the endpoint adjudication committee (EAC) with a cause of "acute respiratory illness due to RSV."

In its pharmacovigilance plan (PVP), the Applicant identifies use in immunocompromised pregnant women as information that was not included in the pre-approval evaluations. The Applicant did not include any Important Identified or Important Potential Risks in its PVP. The Applicant proposes to further evaluate the safety of Abrysvo in pregnant women using US electronic healthcare claims data to compare safety outcomes in RSVpreF-exposed and RSVpreF-unexposed pregnant women and their newborns.

FDA is convening this meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss and vote on whether available safety and efficacy data support the licensure of RSVpreF to prevent LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals. Key efficacy findings included successful vaccine efficacy for prevention of LRTD caused by RSV in infants and successful vaccine efficacy for prevention of severe LRTD caused by RSV in infants for these pre-specified analyses. The safety data appear generally favorable for vaccine administration, and we noted potential uncertainty based on the numerical imbalance in premature deliveries. FDA will be asking VRBPAC members to vote on whether the results of the vaccine efficacy trial demonstrate evidence of vaccine effectiveness and to vote on whether the safety data support a favorable risk analysis with VRBPAC discussion of the safety data, for example the numerical imbalance observed in premature deliveries.

Note: Our understanding is that the Applicant's development program enrolled cis-gendered women in the clinical trials and therefore this document uses "women" or "pregnant women" or "pregnant individuals" when referring to participants in the clinical trials. We note that the safety and efficacy findings in this development program would also be applicable to trans-male individuals who may be pregnant.

2. Background

2.1 General Product Information

Product name: Respiratory Syncytial Virus Vaccine

Proposed trade name: Abrysvo

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

The vaccine used in this development program is the identical vaccine and dose that was used in the Phase 3 evaluation of Abrysvo in the adult population 60 years of age and older, which was the subject of the February 28, 2023 meeting of the VRBPAC.

Proposed indication: (Pfizer proposal) - Abrysvo is a bivalent vaccine indicated for prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals.

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

2.2 Epidemiology

RSV is a highly contagious human pathogen that causes respiratory tract illness in individuals of all age groups and is the most frequent cause of lower respiratory tract illness in infants worldwide.

Limited data are available currently 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).

In a study by Chu et al., 2016, assessing pregnancy complications associated with RSV infection, RSV was detected in 14 (0.4%) of 3693 women. Of the 7 (50%) women who sought care due to acute RSV illness, 2 (29%) delivered prematurely. In an international study examining RSV infection in pregnant women from high-income countries who were hospitalized, 38% were diagnosed with pneumonia, and 48% had prolonged hospitalization. The majority of RSV cases were detected in the third trimester. Among women who did not deliver during that admission, there was an association between RSV positivity and subsequent preterm birth (29% in RSV-positive women, 15% in RSV-negative women) (Regan et al., 2018). In a meta-analysis study of 2942 documented cases of RTD, there were 62 RSV infections. Overall, 6.1% of RSV episodes developed maternal pneumonia. Complications in the infant were reported in approximately 1 out of 10 pregnancies; 9.1% of RSV pregnancies resulted in preterm delivery and/or in a low-birth-weight infant (Riccò et al., 2022). Studies to date have been limited by the small number of patients who underwent testing for RSV.

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

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

Following the implementation of nonpharmacologic interventions for the prevention of COVID-19 that began in March of 2020, the number of RSV infections in the US significantly decreased. Interactions between SARS-CoV-2 and other respiratory viruses may have had additional impact on RSV epidemiology. RSV activity in the US remained low through the 2020-2021 fall-winter season but began to increase in the spring of 2021, with variable numbers of cases throughout the US and continuing through the spring, summer and fall. This “interseasonal” activity was a change from the typical pre-pandemic RSV seasonal epidemiology (American Academy of Pediatrics, 2022).

2.3 Clinical Manifestations, Diagnosis, and Treatment

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

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

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

2.4 Vaccine-Associated Enhanced Respiratory Disease

Vaccine-associated ERD has been a theoretical risk and subject of a May 17, 2017 VRBPAC discussion. The concerns of ERD have been largely alleviated by results of recently conducted animal and human studies of RSV vaccine candidates, including reassuring safety results in this development program. See Appendix A for more details regarding the theoretical risk of ERD.

2.5 Safety and Efficacy of Pharmacologically Related Products

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

At the time this briefing document was prepared, FDA review of BLAs for RSV vaccines for use in adults 60 years of age and older are ongoing.

3. FDA Review of Clinical Safety and Efficacy Data

3.1 Overview of Clinical Studies

Data from five clinical studies with RSVpreF were submitted to support the current BLA, summarized in Table 1 below. Study C3671008 (referred to as Study 1008) is an ongoing Phase 3 study to evaluate efficacy, immunogenicity, and safety in infants born to pregnant individuals randomized to receive a single dose of 120 µg of RSVpreF or placebo, and is the focus of the BLA review to support substantial evidence of effectiveness and safety. Results from Study 1008 are discussed in detail in Section 3.2. Two additional Phase 2 studies will be discussed in this briefing document.

Study C3671003 (referred to as Study 1003 throughout this document) is a Phase 2b, multicenter, randomized, placebo-controlled, observer-blinded study in which up to 650 healthy pregnant women 18-49 years of age were randomized to receive 1 dose of investigational vaccine product (at a dose of 120 µg or 240 µg) formulated with or without aluminum hydroxide, or placebo. Assessments included descriptions of safety, tolerability, and immunogenicity in maternal participants as well as safety and characteristics of transplacentally transferred antibodies in their infants. Acute respiratory illness surveillance was conducted in infants for an exploratory analysis of efficacy against RSV-associated LRTD.

Study C3671004 (referred to as Study 1004 throughout this document) is a Phase 2b, multicenter, randomized, placebo-controlled, observer-blinded study in which 713 healthy nonpregnant women 18-49 years of age were randomized to 1 of 5 vaccine groups: RSVpreF 120 µg and placebo, RSVpreF 120 µg and Tdap, RSVpreF 140 µg with aluminum hydroxide and placebo, RSVpreF 240 µg with aluminum hydroxide and Tdap, or placebo and Tdap. Primary immunogenicity objectives included evaluation of noninferiority of antibody responses to vaccine antigens in Tdap when concomitantly administered with RSVpreF vaccine to Tdap alone.

The remaining two studies will not be discussed in this briefing document beyond this section.

Study C3671014 is a Phase 3 lot-to-lot immunogenicity study intended to support manufacturing consistency; this study met the predefined study success criteria for demonstration of similar

immune responses across 3 lots of 120-µg RSVpreF. The safety database included 745 healthy adults 18-49 years of age who received one dose of RSVpreF. There were no SAEs and no deaths reported during this study, and no concerning safety events were observed.

Study C3671001 was a Phase 1/2 dose-finding study evaluating 3 dose levels of RSVpreF, with and without aluminum hydroxide adjuvant, in adults 18-85 years of age. Safety and immunogenicity data from Study 1001 supported the selection of the 120-µg dose level of RSVpreF without adjuvant, as the final formulation to be tested in later phase studies, including Study 1008.

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

Study Number	Study Type	Total Randomized (N) Total Final RSVpreF (n) Age Group	Test Product(s)*
C3671008	Phase 3: Efficacy, Immunogenicity, Safety	N=7357, n=3681 (maternal) N=7128, n=3570 (infants) Pregnant women/ adolescents ≤49 years and their infants	RSVpreF 120 µg (final)
C3671004	Phase 2: Safety, Immunogenicity	N=713, n=282 Non-pregnant women 18-49 years	RSVpreF 120 ug (final), RSVpreF 240 µg with $Al(OH)_3$ adjuvant, or without adjuvant Subset: co-ad with Tdap
C3671014	Phase 3: Lot-to-Lot, Safety, Immunogenicity	N=993, n=745 Adults 18-49 years	RSVpreF 120 µg (final)
C3671003	Phase 2: Safety, Immunogenicity	N=581 N=116 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
C3671001	Phase 1/2: First-in-human, Dose-finding, Safety, Immunogenicity	N=1,235, n=186 Adults 18-85 years	RSV preF 120ug (final), RSVpreF (60 µg, 120 ug, 240 µg) with or without $Al(OH)_3$ adjuvant Subset: co-ad with SIIV; Subset: re-vaccination at 1 year

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)
Notes: *Only the active vaccine(s) is listed. Each of the studies also included a placebo group

3.2 Study 1008

Study Title: A Phase 3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of 120-µg RSVpreF vaccine in infants born to women who were vaccinated during pregnancy

3.2.1 Objectives, Endpoints, Statistical Criteria

Primary Efficacy Objectives

1. To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTD due to RSV.
   Endpoints: RSV-positive MA-LRTD occurring within 90, 120, 150, and 180 days after birth

2. To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTD due to RSV.
   Endpoints: severe MA-LRTD occurring within 90, 120, 150, and 180 days after birth

Statistical success criteria: The lower bound of the multiplicity-adjusted CI is >20% for either one of the 2 primary endpoints.

Secondary Efficacy Objectives

1. To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.
   Endpoints: hospitalizations due to RSV occurring within 90, 120, 150, 180, and 360 days after birth

2. To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTD.
   Endpoints: Any MA-LRTD occurring within 90, 120, 150, 180, and 360 days after birth

3. To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTD due to RSV.
   Endpoints: RSV-positive MA-LRTD occurring within 210, 240, 270, and 360 days after birth

Statistical success criteria for the Secondary Efficacy Endpoints: Upon success for one of the primary efficacy endpoints, the three secondary endpoints will be tested in parallel (with a fixed sequence testing for the different time points), with a success criterion met for the respective endpoint if the lower bound of the multiplicity-adjusted CI is >0.

Key Exploratory Objectives:

1. To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTD due to RSV A and RSV B.
   Endpoints: RSV subgroup A- and subgroup B-specific MA-LRTD.

2. To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTD due to RSV.
   Endpoints: RSV-positive MA-RTD occurring within 90, 120, 150, 180, and 181 to 730 days after birth.

3. To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTD due to RSV in infants after 12 months of age.
   Endpoints: MA-LRTD due to RSV occurring 361 to 730 days after birth.

Primary Safety Objectives

Maternal Participants

To describe the safety and tolerability of RSVpreF.

Endpoints

- prespecified local reactions within 7 days after vaccination.

- prespecified systemic events within 7 days after vaccination.
- AEs from the time of vaccination through 1 month after vaccination.
- SAEs throughout the study (Visit 1 through 6-month postdelivery study visit).

Infant Participants
To describe the safety of RSVpreF.

Endpoints:

- AEs from birth to 1 month of age.
- Specific birth outcomes: Congenital anomalies and AESIs (prematurity, LBW, developmental delay)
- SAEs and newly diagnosed chronic medical conditions (NDCMCs):
    - from birth to 6 months of age (first RSV season for all infant participants).
    - birth to 12 months of age (for all infant participants).
    - birth to 24 months of age (for infant participants born to maternal participants enrolled during the first year of the study).

3.2.2 Design

Study 1008 is a Phase 3, randomized, double-blinded, placebo-controlled multi-regional trial to evaluate the efficacy and safety of 120-µg RSVpreF vaccine in infants born to women who were vaccinated during pregnancy. The study was initiated on June 17, 2020, is currently ongoing and being conducted at 216 sites in 18 countries (including the US). Study-eligible pregnant women and adolescents ≤49 years of age were randomized in a 1:1 ratio to receive a single dose of RSVpreF or placebo. The dose of RSV prefusion F glycoproteins in RSVpreF was 120 µg (60 µg A and 60 µg B) without an adjuvant. Maternal participants were followed from vaccination during pregnancy until 6 months after delivery. 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. Infant participants born to maternal participants enrolled during the first year of the study (with an estimated due date on or before September 30, 2021) had 6 scheduled study visits, while all other infant participants had up to 4 scheduled study visits. For infant participants enrolled during the first year of the study, the extended study duration involves longer-term RTD surveillance to address safety and the possibility of conferred extended protection during a second RSV season.

For all infant participants, data were collected for any medically attended respiratory disease (MA-RTD) to assess for cases of LRTD and severe LRTD due to RSV (efficacy endpoints). Throughout the study, all respiratory illnesses, SAEs, and NDCMCs were assessed in this population. MA-RTDs are recorded as AEs or SAEs for the first 72 hours of life, but only recorded as such after this time point if assessed as related to maternal vaccination or resulting in death.

The following AESIs are to be reported as SAEs:

- Extremely preterm birth (<28 weeks)
- Extremely low birth weight (≤1000 g).

For maternal participants, the active collection period for nonserious AEs begins from the time of informed consent and continues through a minimum of 28 calendar days after vaccination. The active collection period for SAEs continues until the maternal participant completes the study.

The following AESI are reported for maternal participants:

- Preterm delivery
- Positive viral (PCR or antigen-based) testing for SARS-CoV-2, when not reported during a MA-RTD visit, should be reported as SARS-CoV-2 test positive

For maternal participants, RTD surveillance period starts from vaccination until the end of the study (6 months after delivery). MA-RTDs will be captured as exploratory endpoints, no nasal swab collection (self-reported events).

Monitors were responsible for reviewing adherence to the protocol; compliance with good clinical practice; data accuracy, completeness, and consistency. All MA-RTDs meeting the protocol definition for a potential study primary efficacy endpoint were adjudicated by an independent Endpoint Adjudication Committee (EAC). The EAC was blinded to the maternal participants' vaccine assignments. An external data monitoring committee (E-DMC) monitored for vaccine safety, efficacy, and potential study futility.

All maternal participants were randomly assigned to study intervention using an interactive response technology (IRT). The participant, study coordinator, and all site staff including laboratory testing personnel were blinded to study intervention allocation throughout the study. The E-DMC reviewed safety data at defined intervals as specified in the charter. An unblinded Pfizer clinician was present at the interim analysis closed sessions.

Population

Important Inclusion Criteria:
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.

Enrollment was monitored to help ensure distribution of vaccination with respect to maternal GA.

(See Appendix B) for further details of inclusion/exclusion criteria)

Temporary Vaccination Delay Criteria – Maternal Participants
The prevaccination blood draw and vaccination should take place on the same day. In the event that this is not possible, the prevaccination blood draw is also permissible within 7 days before the vaccination visit.
The following conditions are temporary or self-limiting and a maternal participant may be vaccinated once the condition(s) has/have resolved and if no other exclusion criteria are met:

- Current febrile illness (body temperature ≥38°C) or other acute illness within 48 hours before investigational product administration.
- Diagnosed malaria within the last 7 days prior to investigational product administration.
- Receipt of any inactivated vaccine (including licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary or emergency use) within 14 days or any live vaccine within 28 days before investigational product administration.
- If systemic corticosteroids (equivalent of ≥20 mg/day of prednisone) have been administered short term (≤14 days) for treatment of an acute illness, investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intra-bursal, or topical corticosteroids were permitted.

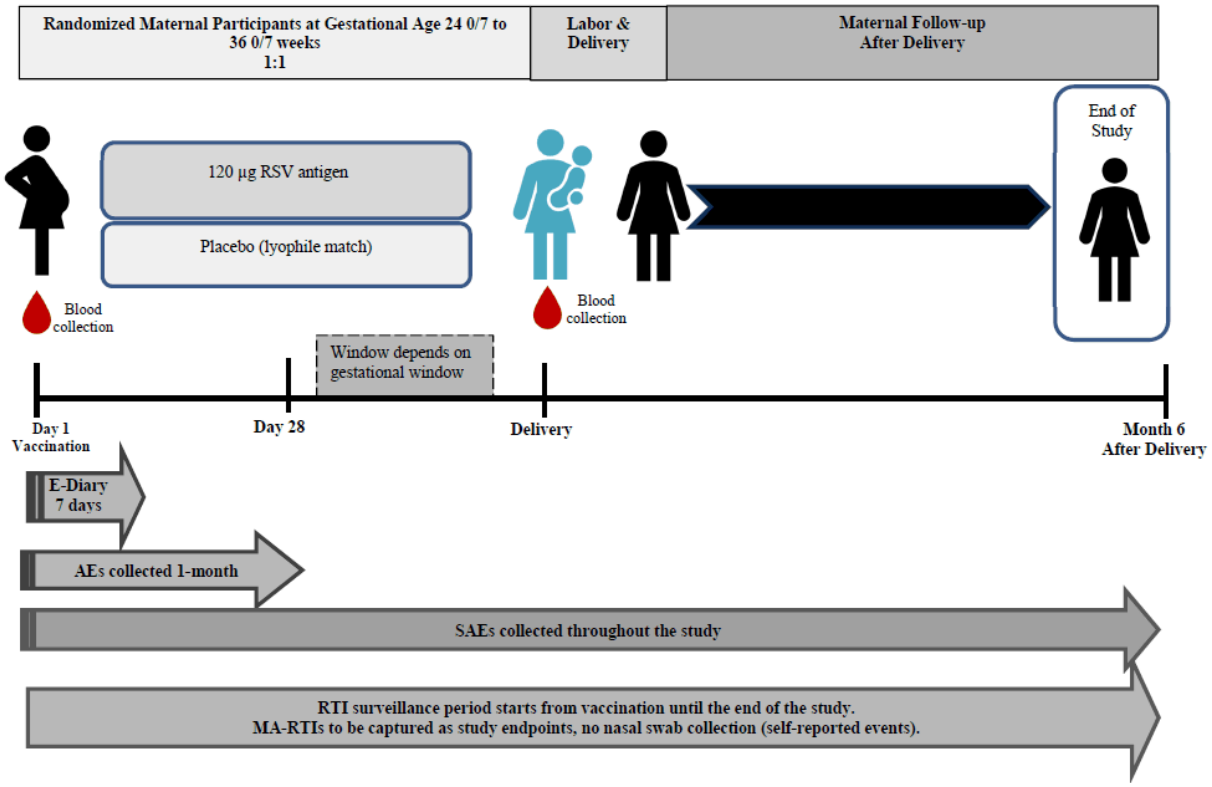
Schedule of Activities for Maternal Participants

Screening and vaccination (28 days prior to vaccination to Day 1): Vital signs, targeted physical/obstetric examination, record details of antenatal steroid treatment, monoclonal antibodies, blood products, or Rho(D) immune globulin, maternal participant's Guillain-Barré syndrome status, blood sampling within 7 days before vaccination visit, baseline assessment of prespecified systemic events.

Day 1: Vaccination

1 month follow-up (28 to 42 days after vaccination), delivery, 6-month postdelivery (180 to 210 days after delivery), clinic or telephone, maternity unit.

Figure 1. Study Design, Maternal Participants



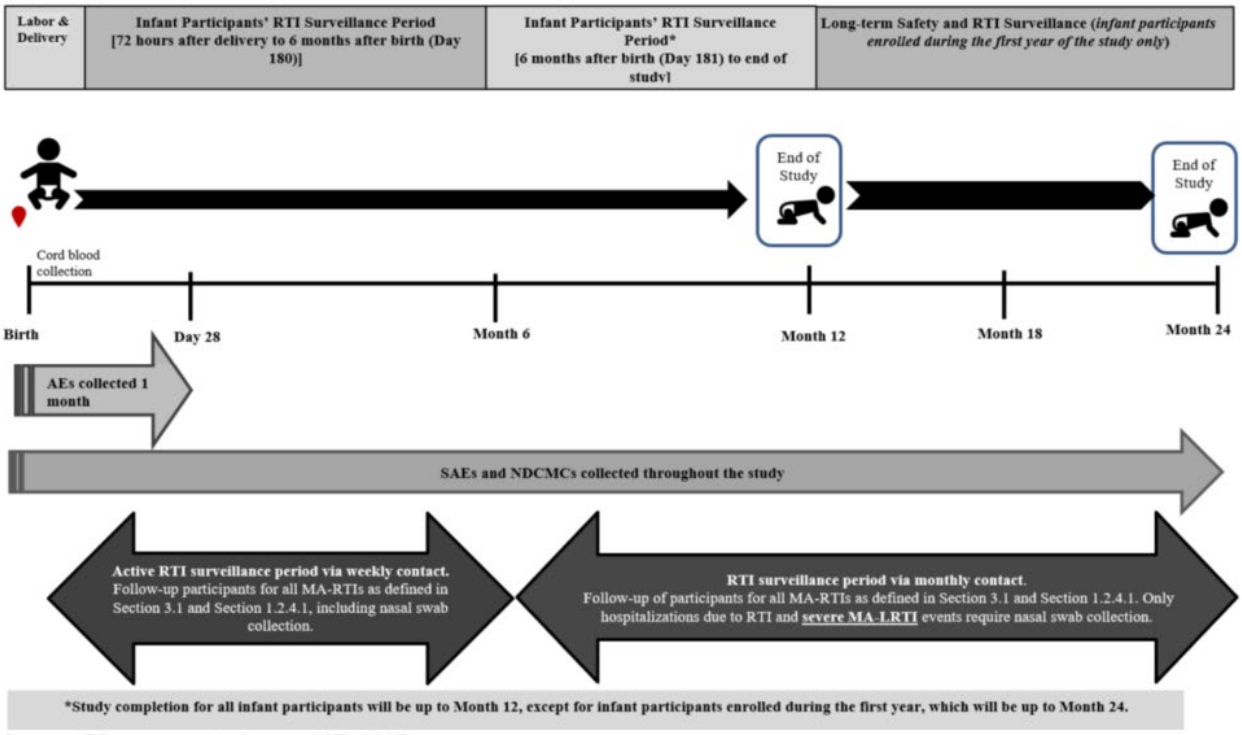
Source: Pfizer protocol, Study c3671008

Schedule of Activities for Infant Participants

Visit 1: birth to 7 days after birth; Visit 2: 1-month follow-up (28 to 48 days after birth); Visit 3: 6-month follow-up (180 to 210 days after birth); Visit 4: 12-month follow-up (350 to 378 days after birth). RTD study visits: Birth to 180 days after birth (as soon as possible after confirmed MA-RTD and preferably within 72 hours or up to 10 days); 181 days after birth to the end of the study (as soon as possible after confirmed MA-RTD and preferably within 72 hours or up to 10 days).

Long-term follow-up for infant participants enrolled in the first year of the study: Visit 5: 18-month follow-up (525 to 574 days after birth); Visit 6: 24-month follow-up (714 to 742 days after birth).

Figure 2. Study Design, Infant Participants



Source: Pfizer protocol, Study c3671008

Case Definitions

The case definitions for the efficacy endpoints are shown in Table 2.

Table 2. Primary and Secondary Endpoint Events and Definitions in Infant Participants

Study Endpoints / Assessments	Study Definitions
Medically attended visit	Infant participant has been taken to or seen by a healthcare provider (e.g., outpatient or inpatient visit, emergency room, urgent care, or home visit)
MA-RTD visit for infant participant	A medically attended visit AND 1 or more of the following RTD signs and symptoms: • Nasal discharge for 24 hours or more • Difficulty breathing, labored breathing, or rapid breathing for any duration • Cough • Inability to feed for any duration because of respiratory symptoms • Apnea • Any other respiratory symptom of concern
RSV-positive test[a]	RSV RT-PCR–positive test result by Pfizer central laboratory **OR** RSV-positive test result by certified laboratory with NAAT for RSV
MA-RTD due to RSV[b]	An MA-RTD visit **AND** RSV-positive test result
MA-LRTD due to any cause	Infant with an MA-RTD visit **AND** fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age], ≥50 bpm for ≥2 months to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** SpO_2 <95% **OR** Chest wall indrawing

Study Endpoints / Assessments	Study Definitions
MA-LRTD due to RSV[b]	Infant with an MA-RTD visit **AND** RSV-positive test result **AND** one or more of the following: fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age] or ≥50 bpm for ≥2 to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** SpO_2 <95% **OR** chest wall indrawing
Hospitalized RTD due to RSV[b]	An RTD due to RSV that results in hospitalization
Severe MA-LRTD due to RSV	Infant with an MA-RTD visit **AND** RSV-positive test result **AND** one or more of the following: fast breathing (RR ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for ≥2 months to <12 months of age, or ≥50 bpm for ≥12 months to 24 months of age) **OR** SpO_2 <93% **OR** High-flow nasal cannula or mechanical ventilation (i.e., invasive or noninvasive) **OR** ICU admission for >4 hours **OR** Failure to respond/unconscious
Protocol-defined primary endpoint	Any MA-LRTD or severe MA-LRTD due to RSV as determined by an EAC

Source: adapted from Pfizer CSR, Study 1008
Abbreviations: bpm=breaths per minute; EAC=endpoint adjudication committee; ICU=intensive care unit; MA LRTD=medically attended lower respiratory tract disease; MA-RTD=medically attended respiratory tract disease; NAAT=nucleic acid amplification technology; RR=respiratory rate; RSV=respiratory syncytial virus; RTD=respiratory tract disease; SpO2=oxygen saturation.
a. RSV-positive testing is defined as a positive RSV test conducted on a sample obtained during the medically attended visit or within 10 days (where Day 1 is the day of the MA-RTD visit).
b. The EAC will determine if the endpoint criteria have been met upon review of the site source documentation from the MA-RTD visit and RTD study visits, including all available RSV test results.

Efficacy Monitoring

MA-RTDs in the infant participant will be identified from 72 hours after birth until the end of the infant's participation in the study. If the infant participant meets any RTD criteria listed below that require a visit to an HCP (outpatient or inpatient visit, emergency room, urgent care, or scheduled home visit), an RTD study visit by the study staff will be required.

RTD criteria (if the infant experiences 1 or more of the following respiratory signs or symptoms): nasal discharge for 24 hours or more, difficulty breathing, labored breathing, or rapid breathing for any duration, cough, inability to feed for any duration due to respiratory symptoms, apnea, any other respiratory symptoms of concern.

RSV-positive test: RSV RT-PCR-positive test result by Pfizer central laboratory OR RSV-positive test result by certified laboratory with nucleic acid amplification test (NAAT) for RSV.

Evaluation of Immunogenicity

Because the study is ongoing, analyses of infant immunogenicity endpoints have not yet been conducted and were not included in the submission reviewed. The Applicant plans for immunogenicity analyses to be included in a future supplemental report.

Evaluation of Safety

Study oversight included Institutional Review Board or Independent Ethics Committee review and approval of the study protocol, amendments, the informed consent, and other relevant documents before the study was initiated. This study used an E-DMC, which used a reporting statistician who was independent of the Applicant and reviewed safety data at defined intervals. An unblinded Pfizer clinician was present at the interim analysis closed sessions. Per protocol, after the DMC declared study success of MA-LRTD cases at Day 90, the unblinded clinician communicated internally so that the study was unblinded to specific Applicant staff for this interim analysis.

Safety, Maternal

- For maternal participants, a physical exam was performed and a baseline assessment of systemic events was recorded in the e-diary within 7 days prior to vaccination.
- Solicited local reactions (pain, redness, swelling at injection site) and systemic events (fever, fatigue, headache, nausea, muscle pain, joint pain, vomiting, diarrhea) were reported by maternal participants via e-diary from the time of vaccination (Day 1) through 7 days after vaccination. AEs were collected through 1 month after vaccination.
- SAEs and AESIs (including premature delivery) were collected through the 6-month postdelivery study visit.
- Safety events associated with the fetus of a maternal participant (before/during birth until infant takes a live breath) were reported for the maternal participant.

Safety, Infants

- AEs and SAEs in infants are captured once the infant takes a live breath. MA-RTDs are recorded as AEs or SAEs for the first 72 hours of life, but only recorded as AEs or SAEs after this time point if assessed as related to maternal vaccination or resulting in death.
- For infant participants, all AEs were collected from birth through 1 month of age.
- SAEs, AESIs, and NDCMCs were collected through the infants' participation in the study (up to 12 or 24 months of age).
- AESIs for infant participants included preterm birth (born at <37 weeks' gestation), low birth weight (1001 to 2500 g), and developmental delay.
- SAEs included ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomalies. The following AESIs are to be reported as SAEs: extremely preterm birth (<28 weeks), extremely low birth weight (≤1000 g).

Analysis Populations

Populations used for the study analyses are displayed in Table 3 below. The infant evaluable efficacy population was the primary population for efficacy analyses. Analyses of reactogenicity were based on the maternal safety population. Analyses of AEs were based on the maternal and infant safety populations.

Table 3. Analysis Populations

Population	Description
Evaluable efficacy, infant	All infant participants who met the following criteria: • Were eligible for the study. • Were born to the maternal participants who received the investigational product to which they were randomized (RSVpreF or placebo) at least 14 days prior to delivery. • Did not receive palivizumab or another monoclonal antibody targeting RSV. • Had no major protocol violations. • Did not have transfusions of more than 20 mL/kg of any blood products at <180 days.
mITT efficacy, infant	All infant participants who were born to vaccinated maternal participants.
Safety, infant	All infant participants who were born to vaccinated maternal participants.
Safety, maternal	All randomized maternal participants who received investigational product.

Source: Section 9.3, c3671008 protocol
Abbreviations: mITT=modified intent to treat

3.2.3 Participant Disposition

Disposition of Maternal Participants

Table 4 below provides details of the disposition of maternal participants. The safety population of maternal participants included a total of 7357 participants: RSVpreF (N=3681); placebo (N=3676). A total of 34 maternal participants (14 RSVpreF, 21 placebo) were excluded from the safety population because they were not vaccinated. One (1) maternal/infant pair in the RSVpreF group was unblinded at the request of the Argentina National Administration of Drugs, Foods and Medical Devices (ANMAT) because the maternal participant was less than18 years of age at time of enrollment. The country age minimum for participation in this study was 18. The maternal and infant participant pair were excluded from all population analyses. One (1) maternal participant randomized to the placebo group received RSVpreF at vaccination and was included in the RSVpreF group for the safety analysis (the participant's infant was not included in the efficacy analysis because she was still pregnant at the September 2, 2022 data cutoff date).

Table 4. Disposition of Maternal Participants

Disposition	RSVpreF n (%)	Placebo n (%)	Total n (%)
Randomized[a]	3695	3697	7392
Participants excluded from safety population	14 (0.4)	21 (0.6)	35 (0.5)
Safety population	3681 (99.6)	3676 (99.4)	7357 (99.5)
Completed vaccination	3682 (99.6)	3676 (99.4)	7358 (99.5)
Completed 1 month after vaccination	3652 (98.8)	3642 (98.5)	7294 (98.7)
Withdrawn after vaccination but before 1 month after vaccination	9 (0.2)	7 (0.2)	16 (0.2)
Reason for w/d	--	--	--
Lost to follow-up	3 (<0.1)	1 (<0.1)	4 (<0.1)
Withdrawal by subject	6 (0.2)	6 (0.2)	12 (0.2)

Disposition	RSVpreF n (%)	Placebo n (%)	Total n (%)
Completed delivery	3578 (96.8)	3570 (96.6)	7148 (96.7)
Withdrawn after vaccination but before delivery	29 (0.8)	31 (0.8)	60 (0.8)
Reason for w/d:	--	--	--
Lost to follow-up	8 (0.2)	10 (0.3)	18 (0.2)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)
Withdrawal by subject	19 (0.5)	19 (0.5)	38 (0.5)
Completed month-24 follow-up for the study	2840 (76.9)	2843 (76.9)	5683 (76.9)
Withdrawn after delivery	146 (4.0)	136 (3.7)	282 (3.8)
Reason for w/d	--	--	--
Adverse event	0	1 (<0.1)	1 (<0.1)
Death	1 (<0.1)	0	1 (<0.1)
Lost to follow-up	82 (2.2)	68 (1.8)	150 (2.0)
No longer meets eligibility criteria	1 (<0.1)	0	1 (<0.1)
Other	10 (0.3)	7 (0.2)	17 (0.2)
Physician decision	1 (<0.1)	0	1 (<0.1)
Protocol deviation	0	1 (<0.1)	1 (<0.1)
Withdrawal by subject	51 (1.4)	59 (1.6)	110 (1.5)
Ongoing[b]	667 (18.1)	666 (18.0)	1333 (18.0)

Source: adapted from Pfizer CSR, Study 1008
n=Number of participants in the specified category.
a. This value is the denominator for the percentage calculations.
b. Ongoing refers to participants who were randomized and have not yet completed the 24-month follow-up and have not withdrawn.

Disposition of Infant Participants

The evaluable efficacy population included a total of 6975 infants (3495 RSVpreF, 3480 placebo). The modified intent-to-treat (mITT) efficacy population included a total of 7126 infant participants (3568 RSVpreF group, 3558 placebo). The most common reason for exclusion of infant participants from the evaluable efficacy population was due to the mother not being vaccinated at least 14 days prior to delivery. Two infant participants in RSVpreF group were excluded from all population analyses due to being unblinded during the study; one infant was unblinded and withdrawn from the study by request of the maternal participant after the infant experienced hypoxic ischemic encephalopathy (determined to be an AE at birth unrelated to vaccine administration) and one infant participant was unblinded and withdrawn due to a maternal protocol deviation as described above (in “Disposition of Maternal Participants”).

Table 5. Disposition of Infant Participants

Disposition	RSVpreF n (%)	Placebo n (%)	Total n (%)
Enrolled[a]	3570	3558	7128
Safety population	3568 (99.9)	3558 (100.0)	7126 (100.0)
Participants excluded:	--	--	--
Mother not vaccinated	0	0	0
Not eligible unblinded during study	2 (<0.1)	0	2 (<0.1)
mITT efficacy population	3568 (99.9)	3558 (100.0)	7126 (100.0)
Participants excluded from mITT efficacy population:	--	--	--
Mother not vaccinated	0	0	0
Not eligible unblinded during study	2 (<0.1)	0	2 (<0.1)
Evaluable efficacy population	3495 (97.9)	3480 (97.8)	6975 (97.9)
Participants excluded from evaluable efficacy population:	--	--	--

Disposition	RSVpreF n (%)	Placebo n (%)	Total n (%)
Not eligible unblinded during study	2 (<0.1)	0	2 (<0.1)
Infant not eligible for study	3 (<0.1)	4 (0.1)	7 (<0.1)
Mother not vaccinated as randomized	0	0	0
Mother had major protocol violations before delivery	27 (0.8)	19 (0.5)	46 (0.6)
Mother not vaccinated at least 14 days prior to delivery	44 (1.2)	56 (1.6)	100 (1.4)
Infant had major protocol violations	0	1 (<0.1)	1 (<0.1)
Completed 1 month follow-up	3423 (95.9)	3400 (95.6)	6823 (95.7)
Withdrawn before 1 month after birth	52 (1.5)	60 (1.7)	112 (1.6)
Reason for w/d:	--	--	--
Death	2 (<0.1)	6 (0.2)	8 (0.1)
Lost to follow-up	22 (0.6)	26 (0.7)	48 (0.7)
Other	3 (<0.1)	6 (0.2)	9 (0.1)
Withdrawal by parent/guardian	25 (0.7)	22 (0.6)	47 (0.7)
Completed 6 months follow-up	2830 (79.3)	2824 (79.4)	5654 (79.3)
Withdrawn after 1 month but before 6 months after birth	92 (2.6)	83 (2.3)	175 (2.5)
Reason for w/d:	--	--	--
Death	3 (<0.1)	5 (0.1)	8 (0.1)
Lost to follow-up	54 (1.5)	36 (1.0)	90 (1.3)
Other	8 (0.2)	10 (0.3)	18 (0.3)
Withdrawal by parent/guardian	27 (0.8)	32 (0.9)	59 (0.8)
Completed 12 months follow-up	1631 (45.7)	1616 (45.4)	3247 (45.6)
Withdrawn after 6 months but before 12 months after birth	41 (1.1)	52 (1.5)	93 (1.3)
Reason for w/d:	--	--	--
Death	0	1 (<0.1)	1 (<0.1)
Lost to follow-up	31 (0.9)	35 (1.0)	66 (0.9)
Other	1 (<0.1)	7 (0.2)	8 (0.1)
Withdrawal by parent/guardian	9 (0.3)	9 (0.3)	18 (0.3)

Source: adapted from Pfizer CSR, Study 1008
n=Number of participants in the specified category.
a. The values in this row are used as the denominators for the percentage calculations for vaccine groups for all rows.

As of the safety data cutoff date (September 2, 2022), 45.6% of infant participants (1,631 in the RSVpreF group and 1,616 infants in the placebo group) had completed the 12-month follow-up visit. Only 3 infants in each group (<0.1% of participants) had completed the 24-month follow-up visit. 93.4% of infant participants (3,343 infants in the RSVpreF group and 3,317 infants in the placebo group) were ongoing in the study. The Applicant plans to submit final data for these participants in a future report.

3.2.4 Demographics and Other Baseline Characteristics

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).

Table 6. Demographics and Other Baseline Characteristics, Maternal Participants, Safety Population, Study C3671008

Demographics and Other Baseline Characteristics	RSVpreF N=3682 n (%)	Placebo N=3675 n (%)	Total N=7357 n (%)
Sex	--	--	--
Female	3682 (100.0)	3675 (100.0)	7357 (100.0)
Male	NA	NA	NA
Median age at vaccination (years) (range)	29.0 (16-45)	29.0 (14-47)	29.0 (14-47)
Median GA at vaccination (weeks) (range)	31.30 (24.0-36.6)	31.30 (24.0-36.9)	31.30 (24.0-36.9)
GA at vaccination	--	--	--
≥24 wks to <28 wks	941 (25.6)	909 (24.7)	1850 (25.1)
≥28 wks to <32 wks	1085 (29.5)	1128 (30.7)	2213 (30.1)
≥32 wks to ≤36 wks	1653 (44.9)	1632 (44.4)	3285 (44.7)
>36 wks	3 (<0.1)	6 (0.2)	9 (0.1)
Race	--	--	--
White	2383 (64.7)	2365 (64.4)	4748 (64.5)
Asian	454 (12.3)	464 (12.6)	918 (12.5)
Black or African American	720 (19.6)	723 (19.7)	1443 (19.6)
American Indian or Alaskan Native	38 (1.0)	37 (1.0)	75 (1.0)
Native Hawaiian or Other Pacific Islander	9 (0.2)	12 (0.3)	21 (0.3)
Multiracial	30 (0.8)	21 (0.6)	51 (0.7)
Not reported or unknown	48 (1.3)	53 (1.4)	101 (1.4)
Ethnicity	--	--	--
Hispanic/Latino	1049 (28.5)	1075 (29.3)	2124 (28.9)
Not Hispanic/non-Latino	2603 (70.7)	2567 (69.9)	5170 (70.3)
Not reported or unknown	30 (0.8)	33 (0.9)	63 (0.9)

Source: adapted from Pfizer CSR, Study 1008
N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=Number of participants in the specified category; GA=Gestational age; NA=Not applicable.
Note: Participant 13081001 is counted under ≥24 weeks to <28 weeks however actual age was 23 weeks 6 days.

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.

3.2.5 Vaccine Efficacy

3.2.5.1 Analyses of Primary Endpoints

Infant Primary Efficacy Endpoints

Severe MA-LRTD Due to RSV Within 90, 120, 150, and 180 Days After Birth

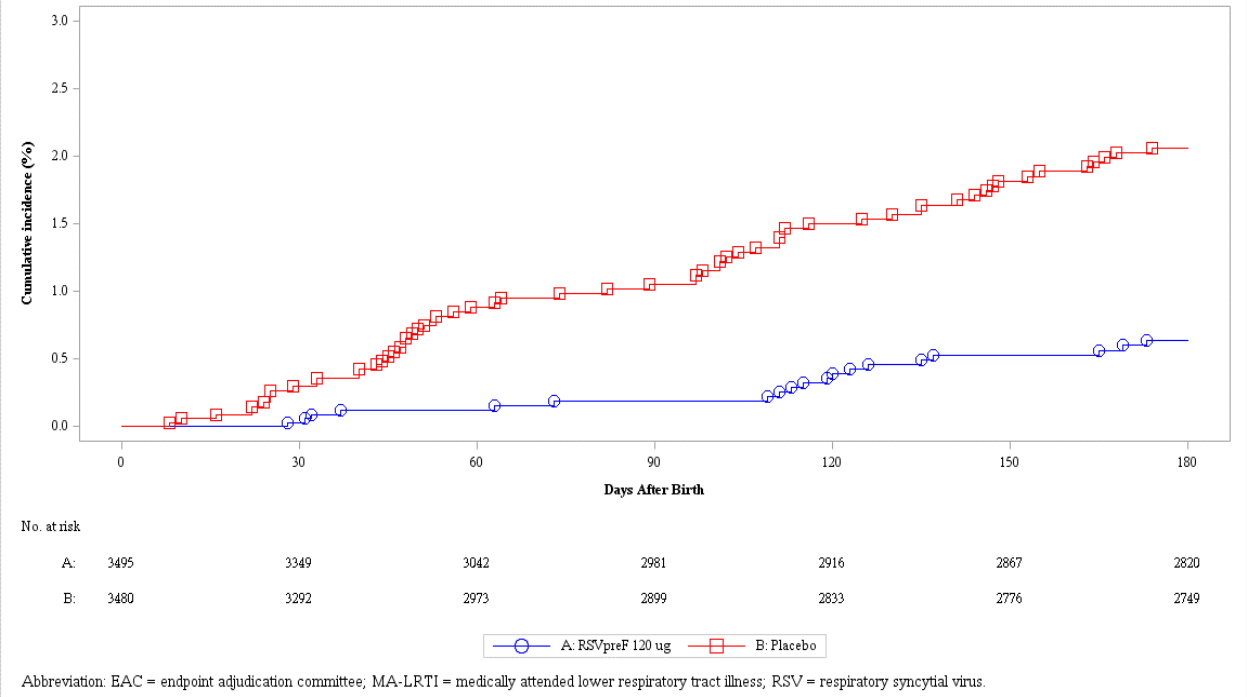
As of the efficacy data cutoff date (September 30, 2022), there were 6 cases of EAC-confirmed RSV-positive severe MA-LRTD cases in infants within 90 days after birth in the RSVpreF group and 33 in the placebo group, corresponding to a VE of 81.8% (99.5% CI: 40.6%, 96.3%) for RSVpreF. There were 19 cases 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. These results met the statistical criterion for success for this endpoint at all timepoints through 180 days after birth. Analysis of this primary endpoint using the mITT population yielded similar results. The mITT population had 2 additional cases (8 cases) of EAC-confirmed RSV-positive severe MA-LRTD cases in infants within 90 days after birth in the RSVpreF group (corresponding to VE of 75.8%) and 1 additional case of EAC-confirmed RSV-positive severe MA-LRTD cases in infants within 150 days after birth in the placebo group.

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

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 1008
Abbreviations: EAC=endpoint adjudication committee; MA-LRTD=medically attended lower respiratory tract illness
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).

Figure 3. 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



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

Source: Pfizer Clinical Study Report, Study c3671008

MA-LRTD Due to RSV Within 90, 120, 150, and 180 Days After Birth

As of the cutoff date, 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. However, the independent data monitoring committee (DMC), who evaluated these results as part of a pre-specified analysis following the “end” of the RSV season in the fall of 2022, recommended proceeding with a full evaluation of primary and secondary analyses because successful vaccine efficacy was demonstrated for the severe LRTDs due to RSV as noted in Table 7 above. The statistical analysis plan pre-specified the two analyses and criteria for success based on appropriate corrections for type I error.

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.

Analysis of this primary endpoint using the mITT population yielded similar results. The mITT population had 3 additional cases of EAC-confirmed RSV-positive MA-LRTD in infants within 90 days after birth in the RSVpreF group and 1 additional case of EAC-confirmed RSV-positive MA-LRTD in infants within 150 days after birth in the placebo group.

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

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 1008
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).

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.

3.2.5.2 Secondary Efficacy Analyses

Secondary Efficacy Endpoints

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 EAC-confirmed RSV 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 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

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)
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 1008
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 Day 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, rates 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.

All-Cause MA-LRTD Within 90, 120, 150, 180, and 360 Days After Birth

As of the cutoff date, there were 392 cases of investigator-reported all-cause MA-LRTD in infants within 180 days after birth in the RSVpreF group and 402 in the placebo group in the evaluable efficacy population, corresponding to a VE of 2.5% (99.17% CI: -17.9%, 19.4%) for RSVpreF. There were 504 cases of all-cause MA-LRTD in infants within 360 days after birth in the RSVpreF group and 531 in the placebo group, corresponding to a VE of 5.1% (99.17% CI: -12.1%, 19.6%) for RSVpreF. These results did not meet the statistical criterion for success for this endpoint at any measured timepoints through 360 days after birth.

3.2.5.3 Exploratory Analyses

VE was observed for the following exploratory efficacy endpoints: MA-RTD due to RSV within 180 days after birth as confirmed by the EAC, and severe MA-LRTDs and MA-LRTDs due to RSV subgroup B within 180 days after birth as confirmed by the EAC.

MA-RTD Due to RSV Within 730 Days After Birth

As of the data cutoff, the number of EAC-confirmed RSV-positive MA-RTD cases in infants within 180 days after birth was 157 in the RSVpreF group and 253 in the placebo group in the evaluable efficacy population, corresponding to a VE of 37.9% (95% CI: 24.0%, 49.5%). During the period within 181 to 360 days after birth, there were 130 (3.7%) investigator-reported RSV-positive MA-RTD cases in the RSVpreF group and 112 (3.2%) in the placebo group (VE of -16.1% [95% CI: -50.8, 10.5]). During the period of 361 to 730 days after birth, there were 21 (0.6%) investigator-reported RSV-positive MA-RTD cases in the RSVpreF group and 23 (0.7%) in the placebo group (VE of 8.7% [95% CI: -72.6%, 51.9%]).

MA-LRTD Due to RSV Within 361 to 730 Days After Birth

Limited data available as of the data cutoff for the period of 361 to 730 days after birth suggest that rates of MA-LRTD due to RSV remained similar in both treatment groups. Within 361 to 730 days after birth, there were 4 cases of RSV-positive MA-LRTD in infants in the RSVpreF group (0.1%) and 6 (0.2%) in the placebo group, corresponding to VE of 33.3% (95% CI: -181.1%, 86.2%).

Severe MA-LRTDs and MA-LRTDs Due to RSV A and RSV B Within 180 Days After Birth

The majority of EAC-confirmed RSV MA-LRTD cases in the study were due to RSV subgroup B. As of the data cutoff, the number of severe MA-LRTD cases due to RSV subgroup B in infants within 180 days after birth was 11 cases in the RSVpreF group, 44 cases in the placebo group, for a VE of 75.0% (95% CI: 50.8%, 88.4%). The number of severe MA-LRTD cases due to RSV subgroup A within 180 days after birth was 7 cases in the RSVpreF group, 14 cases in the placebo group, for a VE of 50.0% (95% CI: -32.4%, 82.9%). The number of MA-LRTD cases due to RSV subgroup B in infants within 180 days after birth was 38 cases in the RSVpreF group and 87 cases in the placebo group, with a VE of 56.3% (95% CI: 35.4%, 71.0%). The

number of cases due to RSV subgroup A within 180 days after birth was 19 cases in the RSVpreF group, 26 cases in the placebo group, for a VE of 26.9% (95% CI: -37.2%, 61.8%).

3.2.6 Safety

As of the safety data cutoff date (September 2, 2022), 7,392 maternal participants were randomized, 7,358 (99.5%) completed vaccination, 7,148 (96.7%) completed delivery, and 5,683 (76.9%) completed the study.

3.2.6.1 Safety Overview- Maternal Participants

Table 10 provides an overview of the rates of reported adverse events in the RSVpreF group compared to the placebo group during the study period.

Table 10. Overview of AEs, Maternal Participants, Study C3671008, Safety Population

Event	RSVpreF n/N (%)	Placebo n/N (%)
Immediate AEs within 30 minutes	1/3682 (<0.1)	1/3675 (<0.1)
Solicited injection site reactions within 7 days	1557/3663 (42.5)	378/3639 (10.4)
Solicited systemic adverse reactions within 7 days	2340/3663 (63.9)	2157/3640 (59.3)
Unsolicited non-serious AE within 30 days	412/3682 (11.2)	396/3675 (10.8)
SAEs	--	--
Within 30 days after vaccination	154/3682 (4.2)	137/3675 (3.7)
Day 1 through 6 months after delivery	598/3682 (16.2)	558/3675 (15.2)
From Day 1 to data lock point	598/3682 (16.2)	558/3675 (15.2)
Deaths to data lock point	1/3682 (<0.1)	0/3675
Withdrawal due to AE Day 1 through 6 months after delivery	0/3682	1/3675 (<0.1)
AESIs	--	--
Within 30 days after vaccination	99/3682 (2.7)	92/3675 (2.5)
Day 1 through 6 months after delivery	337/3682 (9.2)	280/3675 (7.6)
From Day 1 to data lock point	337/3682 (9.2)	280/3675 (7.6)

Source: adapted from Pfizer CSR and sCSR, Study 1008
Abbreviations: AESI=adverse events of special interest; SAE=serious adverse event.
N=number of participants in the specified vaccine group except solicited injection site and systemic adverse reactions. N=number of participants reporting "yes" or "no" for at least 1 day for solicited injection site and systemic adverse reactions. This value is the denominator for the percentage calculations; n=Number of participants in the specified category

3.2.6.2 Solicited Adverse Reactions

Local Reactions, Maternal Participants

The proportions of maternal participants with local reactions reported within 7 days after vaccination were higher in the RSVpreF group compared to the placebo. Most local reactions were mild or moderate in severity for both groups; severe local reactions were reported for 0.3% of maternal participants in the RSVpreF group. The most common local reaction was pain at the injection site, reported by 40.6% of participants in the RSVpreF group and 10.1% of participants in the placebo group. The median day of onset for any local reaction for the RSVpreF group was

Day 2. Median durations for local reactions in the RSVpreF were as follows: 3 days for redness, 2 days for swelling, 2 days for pain at the injection site.

Table 11. Local Reactions, by Maximum Severity, Within 7 Days After Vaccination, Maternal Participants, Safety Population

Local Reaction	RSVpreF N=3663 n (%)	Placebo N=3639 n (%)
Any redness[a]	265 (7.2)	8 (0.2)
Mild redness[a]	181 (4.9)	4 (0.1)
Moderate redness[a]	78 (2.1)	4 (0.1)
Severe redness[a]	6 (0.2)	0
Any swelling[a]	227 (6.2)	8 (0.2)
Mild swelling[a]	150 (4.1)	5 (0.1)
Moderate swelling[a]	73 (2.0)	3 (<0.1)
Severe swelling[a]	4 (0.1)	0
Any pain at injection site[b]	1488 (40.6)	369 (10.1)
Mild pain at injection site[b]	1319 (36.0)	337 (9.3)
Moderate pain at injection site[b]	165 (4.5)	32 (0.9)
Severe pain at injection site[b]	4 (0.1)	0
Any local reaction[c]	1557 (42.5)	378 (10.4)
Mild local reaction[c]	1296 (35.4)	343 (9.4)
Moderate local reaction[c]	250 (6.8)	35 (1.0)
Severe local reaction[c]	11 (0.3)	0

Source: adapted from Pfizer sCSR, Study 1008
N=number of participants reporting "yes" or "no" for the specified reaction for at least 1 day. This value is the denominator for the percentage calculations; n=Number of participants reporting a maximum severity of mild, moderate, or severe based on the severity scales with the specified characteristic.
a. Mild is >2.0 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10 cm.
b. Mild=does not interfere with activity, moderate=interferes with activity, severe=prevents daily activity.
c. Any local reaction=any pain at the injection site, any swelling, or any redness.

Systemic Events, Maternal Participants

The proportions of maternal participants who reported systemic events within 7 days after vaccination were similar in the RSVpreF and placebo groups and most events were mild or moderate in severity. The most frequently reported systemic event within 7 days after vaccination was fatigue (46.1% in the RSVpreF group, 43.8% in the placebo group). Muscle pain was more common in the RSVpreF group (26.5%) than the placebo group (17.1%). Headache incidence was higher in the RSVpreF group (31.0%) compared to the placebo group (27.6%). The incidence of fever was low and was similar between the RSVpreF and placebo groups (≤2.9%); most were low-grade. Severe systemic events within 7 days after vaccination were reported for 2.3% of maternal participants in both groups. The median day of onset for any systemic event for the RSVpreF group was Day 2. Median duration of each systemic reaction was as follows: 1 day for fever, 2 days for fatigue, 2 days for headache, 1 day for nausea, 2 days for muscle pain, 2 days for joint pain, 1 day for vomiting, and 1 day for diarrhea.

Table 12. Systemic Events by Maximum Severity Within 7 Days After Vaccination, Maternal Participants, Safety Population

Systemic Event	RSVpreF N=3663 n (%)	Placebo N=3638 to 3640* n (%)
Fever (≥38.0°C)	94 (2.6)	107 (2.9)
38.0°C to 38.4°C	61 (1.7)	55 (1.5)
38.5°C to 38.9°C	29 (0.8)	42 (1.2)
39.0°C to 40.0°C	1 (<0.1)	5 (0.1)
>40.0°C	3 (<0.1)	5 (0.1)
Any fatigue[a]	1688 (46.1)	1595 (43.8)
Mild	856 (23.4)	828 (22.7)
Moderate	782 (21.3)	715 (19.6)
Severe	50 (1.4)	52 (1.4)
Any headache[a]	1134 (31.0)	1004 (27.6)
Mild	739 (20.2)	651 (17.9)
Moderate	380 (10.4)	340 (9.3)
Severe	15 (0.4)	13 (0.4)
Any nausea[a]	732 (20.0)	701 (19.3)
Mild	527 (14.4)	501 (13.8)
Moderate	197 (5.4)	192 (5.3)
Severe	8 (0.2)	8 (0.2)
Any muscle pain[a]	972 (26.5)	623 (17.1)
Mild	643 (17.6)	363 (10.0)
Moderate	315 (8.6)	248 (6.8)
Severe	14 (0.4)	12 (0.3)
Any joint pain[a]	424 (11.6)	382 (10.5)
Mild	238 (6.5)	218 (6.0)
Moderate	180 (4.9)	161 (4.4)
Severe	6 (0.2)	3 (<0.1)
Any vomiting[b]	287 (7.8)	254 (7.0)
Mild	233 (6.4)	196 (5.4)
Moderate	46 (1.3)	56 (1.5)
Severe	8 (0.2)	2 (<0.1)
Any diarrhea[c]	412 (11.2)	417 (11.5)
Mild	335 (9.1)	343 (9.4)
Moderate	73 (2.0)	67 (1.8)
Severe	4 (0.1)	7 (0.2)
Any systemic event[d]	2340 (63.9)	2157 (59.3)

Source: adapted from Pfizer sCSR, Study 1008
*N=number of participants reporting "yes" or "no" for at least 1 day. This value is the denominator for the percentage calculations and only 3 participants had missing data for an individual solicited adverse event; the percentage was the same regardless of the actual denominator; n=Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.
a. Mild=does not interfere with activity, moderate=some interference with activity, severe = prevents daily routine activity.
b. Mild=1 to 2 times in 24 hours, moderate=>2 times in 24 hours, severe = requires intravenous hydration.
c. Mild=2 to 3 loose stools in 24 hours, moderate=4 to 5 loose stools in 24 hours, severe = 6 or more loose stools in 24 hours.
d. Any systemic event=any fatigue, any headache, any vomiting, any nausea, any diarrhea, any muscle pain or any joint pain.

3.2.6.3 Unsolicited AEs- Maternal Participants

Immediate AEs

Two immediate AEs were reported within 30 minutes of vaccine administration (1 in RSVpreF, 1 in placebo): 1 related immediate AE of dizziness occurred in the RSVpreF group, considered

mild in severity and resolved on the day of onset; and 1 unrelated immediate AE of COVID-19 occurred in the placebo group, considered moderate in severity and resolved 11 days later.

Unsolicited AEs Within 1 Month After Vaccination

The proportions of maternal participants with any AEs reported within 1 month after vaccination were similar in the RSVpreF group (13.7%) and placebo group (13.1%). Most AEs were mild or moderate in severity for both groups; severe AEs were reported in 1.7% and 1.3% of maternal participants in the RSVpreF and placebo groups, respectively. There were no participants with AEs leading to withdrawal reported within 1 month after vaccination.

AEs assessed as related to study intervention by the investigator were in ≤0.4% of maternal participants. All related AEs were reported after vaccination but before delivery, except for 2 related AEs reported from delivery to 1 month after delivery. AESIs within 1 month of vaccination were reported at a similar frequency for both groups; 2.7% in the RSVpreF group versus 2.5% in the placebo group. SAEs within 1 month after vaccination were reported in 4.2% in the RSVpreF group and 3.7% in the placebo group. Life-threatening AEs were reported in ≤0.5% of maternal participants for both groups. Immediate AEs were reported in <0.1% of maternal participants for both groups.

The most frequently reported AEs in maternal participants from vaccination through the 1-month follow-up visit for the RSVpreF and placebo groups were in the SOCs of *Pregnancy, puerperium and perinatal conditions* (7.0% versus 6.2%, respectively) and *Infections and infestations* (2.0% for both groups). While some of the AEs in the preferred term (PT) were characterized by the investigator as premature delivery, subsequently FDA describes the total number of premature deliveries observed in the study.

AEs from vaccination through the 1-month follow-up visit considered by the study investigator to be related to vaccination were infrequent (0.4% in the RSVpreF group and 0.1% in the placebo group) and occurred mostly in the SOC of *General disorders and administration site conditions*. Most related AEs occurred after vaccination but before delivery. Two AEs in the RSVpreF group from delivery to 1 month after delivery were considered to be possibly related to study vaccine by FDA, in agreement with the investigator's assessment: an event of eclampsia with onset 15 days after vaccination, and an episode of premature delivery (the maternal participant was hospitalized 4 days after vaccination due to concern for possible decreased fetal movement; the mother later delivered a live female infant with at 36 weeks, 5 days gestation, 86 days after vaccination with no complications aside from mild prematurity).

Adverse Events of Special Interest

Premature delivery was reported in 5.6% (95% CI: 4.9%, 6.4%) versus 4.7% (95% CI: 4.1%, 5.5%) in the RSVpreF and placebo groups, respectively, during the time period after vaccination to 6 months after delivery. A numerical imbalance between groups was noted.

Positive viral (PCR or antigen-based) testing for SARS-CoV-2, when not reported during a MA-RTI visit, were reported as SARS-CoV-2 test positive. Positive SARS-CoV-2 tests were reported in 3.9% of maternal participants in the RSVpreF group and 3.0% of maternal participants in the placebo groups after vaccination through 6 months after delivery.

Adverse Events Leading to Study Withdrawal

There were no participants with AEs leading to withdrawal reported within 1 month after vaccination. To the data cutoff, there were no cases of withdrawal due to AE in the RSVpreF group; there was 1 case of withdrawal due to AE in the placebo group.

Subgroup Analyses

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

3.2.6.4 Serious Adverse Events- Maternal Participants

Deaths

No maternal deaths or intrauterine demises were assessed by the investigator as related to vaccination, and FDA generally agrees with these assessments. There was 1 maternal death in the RSVpreF group due to postpartum hemorrhage and hypovolemic shock, which was reported from delivery to 1 month after delivery, and FDA agrees that this maternal death was not associated with vaccine administration.

Note: Intrauterine deaths were reported in Study 1008 under maternal safety outcomes, but are included in this report under infant safety outcomes (SAEs- Infant Participants).

Non-fatal SAEs

SAEs reported in maternal participants after vaccination to 6 months after delivery was 16.2% for the RSVpreF group and 15.2% for the placebo group. For both groups, most SAEs reported as of the data cutoff date occurred from delivery to 1 month after delivery (10.1% versus 10.0%) and after vaccination but before delivery (7.2% versus 6.1%). After vaccination to 6 months after delivery, SAEs were most frequently reported in the SOC of *Pregnancy, puerperium and perinatal conditions* in the RSVpreF group (12.1%) and placebo group (11.2%). The most frequently reported SAEs by PT in the RSVpreF group (≥1.0%) were pre-eclampsia (1.8%), fetal distress syndrome (1.8%), gestational hypertension (1.1%), nonreassuring fetal heart rate (1.0%), and arrested labor (1.0%); these event rates were generally similar in the placebo group (1.4%, 1.6%, 1.0%, 0.8%, and 1.1%, respectively).

To the data cutoff date, SAEs were assessed as related by the investigator in 4 maternal participants in the RSVpreF group and 1 maternal participant in the placebo group.

Based on review of the event narratives and temporal association of these events to vaccination, FDA agrees with the investigator's assessments that there was a reasonable possibility that these events were related to the study intervention.

RSVpreF group:

- Severe pain in multiple extremities, initially in the vaccinated extremity with onset 2 days after vaccination. This event resolved 6 days later.
- Premature labor, with onset 2 days after vaccination, resolved 1 day later, and the infant was delivered at full term.
- Systemic lupus erythematosus, with onset of thrombocytopenia noted 6 days after vaccination. The participant was diagnosed 5 months later with systemic lupus erythematosus (SLE) and the episode of thrombocytopenia was attributed to SLE.
- Eclampsia, with onset 15 days after vaccination, at 38 weeks gestation. The participant had onset of proteinuria and elevated blood pressure 7 days after vaccination, and had a seizure on day 15 after vaccination. During hospitalization, she was diagnosed with suspected posterior reversible encephalopathy syndrome (PRES) based on imaging findings. The event was considered resolved on day 127.

Placebo group:

- Premature separation of placenta, with onset 2 days after vaccination. This event resolved 48 days later.

3.2.6.5 Birth Outcomes

The AESI of premature birth was reported in 5.7% of infants (95% CI: 4.9%, 6.5%) in the RSVpreF group and in 4.7% (95% CI: 4.1%, 5.5%) in the placebo group. A numerical imbalance of 1% was noted between the two study groups with a higher number of preterm births occurring in the RSVpreF vaccine group. This difference did not appear to be statistically significant because the two-sided 95% CIs of the point estimates overlap.

Most preterm infants were near term; 5.0% of live births in the RSVpreF group and 4.4% of live births in the placebo group were in the GA range of ≥34 to <37 weeks at birth.

Low birth weight (LBW) was reported in 5.1% (95% CI: 4.4%, 5.8%) in the RSVpreF group and 4.4% (95% CI: 3.7%, 5.0%) of infant participants in the placebo group.

For the SAE of extremely preterm birth (<28 weeks), there was 1 infant (<0.1%) in the RSVpreF group and 1 infant (<0.1%) in the placebo group. For the SAE of extremely low birth weight (≤1000 g), there was 1 infant (<0.1%) in the RSVpreF group and 2 infants (<0.1%) in the placebo group.

No meaningful differences were detected with respect to Apgar scores recorded at birth.

A subgroup analysis of live birth outcomes by high-income countries /low- and middle-income countries (HIC/LMIC) did not demonstrate a trend towards increased incidence of preterm births in high-income countries or in low-income to lower middle-income countries. However, a difference was noted in the preterm birth rate between vaccine recipients (8.3%) and placebo recipients (4.0%) in South Africa (upper middle-income economy).

Table 13. Live Birth Outcomes by Subcategory of HIC, LMIC

Country / Gestational Age at Birth	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
High income	2494	2484
≥24 weeks to <28 weeks	0	1 (<0.1)
≥28 weeks to <34 weeks	13 (0.5)	7 (0.3)
≥34 weeks to <37 weeks	113 (4.5)	118 (4.8)
≥37 weeks to <42 weeks	2360 (94.6)	2351 (94.6)
≥42 weeks	6 (0.2)	5 (0.2)
Upper middle income	964	961
≥24 weeks to <28 weeks	1 (0.1)	0
≥28 weeks to <34 weeks	7 (0.7)	4 (0.4)
≥34 weeks to <37 weeks	64 (6.6)	35 (3.5)
≥37 weeks to <42 weeks	882 (91.5)	906 (94.3)
≥42 weeks	9 (0.9)	15 (1.6)

Country / Gestational Age at Birth	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
Lower middle income	32	34
≥24 weeks to <28 weeks	0	0
≥28 weeks to <34 weeks	0	0
≥34 weeks to <37 weeks	1 (3.1)	2 (5.9)
≥37 weeks to <42 weeks	30 (93.8)	32 (94.1)
≥42 weeks	1 (3.1)	0
Low income	78	79
≥24 weeks to <28 weeks	0	0
≥28 weeks to <34 weeks	0	0
≥34 weeks to <37 weeks	2 (2.6)	2 (2.5)
≥37 weeks to <42 weeks	71 (91.0)	67 (84.8)
≥42 weeks	5 (6.4)	10 (12.7)

Source: adapted from Pfizer study c3671008 CSR p. 903 - Table 14.98 – Live Birth Outcomes by Country Subcategories
Abbreviations: HIC=high-income countries; LMIC=low- and middle-income countries

Table 14. Live Birth Outcomes by Select Countries (US, South Africa)

Country	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
South Africa	**469**	**471**
≥24 weeks to <28 weeks	1 (0.2)	0
≥28 weeks to <34 weeks	4 (0.9)	3 (0.6)
≥34 weeks to <37 weeks	34 (7.2)	16 (3.4)
≥37 weeks to <42 weeks	420 (89.6)	439 (93.2)
≥42 weeks	9 (1.9)	12 (2.5)
United States	1654	1644
≥24 weeks to <28 weeks	0	1 (<0.1)
≥28 weeks to <34 weeks	11 (0.7)	5 (0.3)
≥34 weeks to <37 weeks	83 (5.0)	81 (4.9)
≥37 weeks to <42 weeks	1556 (94.1)	1553 (94.5)
≥42 weeks	2 (0.1)	2 (0.1)

Source: adapted from Pfizer CSR

The AESI of developmental delay was reported in 0.3% in each study group to the data cutoff.

Table 15. Live Birth Outcomes, Infant Participants, Safety Population

Participants	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
Gestational age at birth	--	--
≥24 weeks to <28 weeks	1 (<0.1)	1 (<0.1)
≥28 weeks to <34 weeks	20 (0.6)	11 (0.3)
≥34 weeks to <37 weeks	180 (5.0)	157 (4.4)
≥37 weeks to <42 weeks	3343 (93.7)	3356 (94.3)
≥42 weeks	21 (0.6)	30 (0.8)

Participants	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
Outcome	--	--
Normal	3172 (88.9)	3149 (88.5)
Congenital malformation/anomaly	174 (4.9)	203 (5.7)
Other neonatal problem	219 (6.1)	200 (5.6)
Low birth weight (≤ 2500 g)	181 (5.1)	155 (4.4)
Extremely low birth weight (≤ 1000 g)	1 (<0.1)	2 (<0.1)
Very low birth weight (> 1000 g to ≤ 1500 g)	3 (<0.1)	6 (0.2)
Low birth weight (> 1500 g to ≤ 2500 g)	177 (5.0)	147 (4.1)
Developmental delay[a]	12 (0.3)	10 (0.3)

Source: adapted from Pfizer CSR, Study 1008
N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=number of participants with the specified characteristic.
a. Developmental delay refers to an adverse event of special interest reported at any time after birth during the study period.

Table 16. Time From Vaccination to Birth Among Preterm and at Term Births, Infant Participants, Safety Population

Days from Vaccination to Birth	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)	Total N=7126 n (%)
Preterm deliveries[a]	201 (5.6)	169 (4.7)	370
≤7 days[a]	11 (5.5)	13 (7.7)	24 (6.5)
>7 days to ≤30 days[a]	69 (34.3)	58 (34.3)	127 (34.3)
>30 days[a]	121 (60.2)	98 (58.0)	219 (59.2)
At term deliveries	3364	3386	6750
≤7 days[a]	1 (<0.1)	2 (<0.1)	3 (<0.1)
>7 days to ≤30 days[a]	516 (15.3)	498 (14.7)	1014 (15.0)
>30 days[a]	2847 (84.6)	2886 (85.2)	5733 (84.9)

Source: adapted from Pfizer CSR, Study 1008
N=number of participants having birth date in the specified vaccine group. This value is the denominator for the percentage calculations; n=Number of participants in the specified category.
Note: Six participants have missing gestational age at birth in database, so are not included in counts above. Preterm/at term deliveries are determined based on gestational age at birth. Preterm=gestational age at birth less than 37 weeks. At term=gestational age at birth of 37 weeks or more. Number of days between vaccination and birth is calculated as birth date - vaccination date. Percentages for this row are based on the number of preterm/at term deliveries, respectively.
a. N=201 and N=169 are derived from the Applicant datasets; FDA noted up to 9 additional premature deliveries, but this does not change the overall findings of an approximately 1% difference between treatment groups in premature deliveries.

3.2.6.6 Safety Overview- Infant Participants

Table 17. Overview of AEs, Infant Participants, Study 1008, Up To 24 Months Follow-Up

Adverse Event Category	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
Any AE	1473 (41.3)	1403 (39.4)
Unsolicited non-serious AEs within 30 days	1012 (28.4)	931 (26.2)
SAEs	--	--
Within 30 days after birth	553 (15.5)	541 (15.2)
Up to 6 months after birth	595 (16.7)	585 (16.4)
Up to 12 months after birth	619 (17.3)	611 (17.2)
Up to data lock point	625 (17.5)	623 (17.5)
Deaths to data lock point	5 (0.1)	12 (0.3)
Congenital anomalies	180 (5.0)	220 (6.2)

Adverse Event Category	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
NDCMCs	--	--
Within 30 days after birth	6 (0.2)	6 (0.2)
Up to 6 months after birth	45 (1.3)	57 (1.6)
Up to 12 months after birth	75 (2.1)	83 (2.3)
Up to data lock point	87 (2.4)	99 (2.8)
AESIs	--	--
Within 30 days after birth	298 (8.4)	257 (7.2)
Up to 6 months after birth	334 (9.4)	282 (7.9)
Up to 12 months after birth	366 (10.3)	324 (9.1)
Up to data lock point	386 (10.8)	344 (9.7)
Premature births	202 (5.7)	169 (4.7)
Withdrawals due to AE up to data lock point	0	0

Source: adapted from Pfizer CSR, Study 1008
Abbreviations: NDCMC: Newly Diagnosed Chronic Medical Condition; SAE=serious adverse event.
N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=Number of participants in the specified category. Infant safety data cut-off date: September 2, 2022.

3.2.6.7 Unsolicited AEs- Infant Participants

Adverse Events Reported Within 1 Month After Birth

The proportions of infant participants with any AE reported within 1 month after birth were similar for the RSVpreF and placebo groups (37.1% in the RSVpreF group, 34.5% in the placebo group). Most AEs were mild or moderate in severity across both groups; severe or life-threatening AEs were reported in 5.1% versus 4.5% of infant participants in the RSVpreF group versus placebo group, respectively. There were no infant participants with AEs leading to withdrawal reported within 1 month after birth.

One AE of prematurity in the RSVpreF group (born at GA 36 weeks and 5 days, Day 86 post-vaccination) was assessed by the study investigator as related to maternal vaccination. The maternal participant was hospitalized 4 days post-vaccination with report of possible decreased fetal movement. Fetal movement was determined to be present on evaluation and she was discharged home the same day. She later delivered a live female infant with no complications and a normal birth outcome aside from mild prematurity. The investigator's rationale was that another cause for the premature delivery was not found; therefore, "the event will be handled as related to" the investigational product. Given the temporal association of the hospitalization for concern for possible decreased fetal movement, FDA agrees with the investigator's assessment that premature delivery was possibly related to the investigational product.

Adverse Events Reported Up to 24 Months of Age

The proportions of infant participants with any AE reported from birth to 24 months of age were 41.3% in the RSVpreF group and 39.4% in the placebo group. The most frequently reported AEs in infant participants from birth to 24 months of age were in the SOCs of *Pregnancy, puerperium and perinatal conditions* (16.8% versus 15.6%), *Congenital, familial and genetic disorders* (8.0% versus 8.3%), and *Respiratory, thoracic and mediastinal disorders* (7.7% versus 7.3%). By PT, the most frequently reported AE in the RSVpreF group from birth to 24 months of age was jaundice neonatal (7.2%) which was reported in 6.8% of the placebo group.

Newly Diagnosed Chronic Medical Conditions

A newly diagnosed chronic medical condition (NDCMC) is protocol-defined as "a disease or

medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects (e.g., asthma)." NDCMCs reported within 1 month after birth were balanced, with 0.2% of infant participants in each group. NDCMCs to the data cutoff point were reported in 2.4% versus 2.8% of infant participants in the RSVpreF and placebo groups, respectively. Asthma-related diagnoses reported either during MA-RTD visits or reported as AEs occurred in 2.7% in the RSVpreF group and 3.1% in the placebo group. No infant participants were withdrawn from the study due to an NDCMC.

Adverse Events of Special Interest

AESIs within 1 month after birth were reported in 8.4% in the RSVpreF group and 7.2% in the placebo group. AESIs through the data cutoff date were reported in 10.8% in the RSVpreF group and 9.7% in the placebo group.

SAEs- Infant Participants

Fetal Deaths

A total of 18 intrauterine deaths were reported for the index pregnancy; 10 intrauterine deaths in the RSVpreF group (0.3%) and 8 intrauterine deaths in the placebo group (0.2%). These included fetal demises, fetal deaths and stillbirths; these terms were used indistinctively during the study. The intrauterine deaths represented various clinical conditions and presentations resulting in fetal demise without clear evidence of a common pathophysiology. None of the intrauterine demises were assessed by the investigator as related to vaccination; FDA agrees with this conclusion based on review of available case narratives and evident lack of temporal relation of vaccination to the fetal loss events.

In addition, 3 spontaneous abortions were reported from 1 to 6 months of follow-up of study participants in subsequent pregnancies; 1 in the RSVpreF group and 2 in the placebo group.

Infant Deaths

A total of 17 infant deaths were reported from birth to 24 months of age: 5 (0.1%) in the RSVpreF group and 12 (0.3%) in the placebo group. Of infant deaths in the RSVpreF vaccine group, 1 neonate had meconium aspiration syndrome with hypoxic ischemic encephalopathy, aortic and tricuspid valve incompetence, subarachnoid hemorrhage and possible adrenal insufficiency and died on day of life 6; 1 infant with Down syndrome and congenital heart defect had possible pneumonia and died on day of life 132; 1 infant had acute enterovirus/rhinovirus infection with interstitial lung disease and suffered a cardiopulmonary arrest at home on day of life 61; 1 infant with extreme prematurity was born at 27 weeks, 3 days gestation and had respiratory distress, acute kidney injury, and electrolyte abnormalities and died on day of life 4; 1 infant died at 52 days of life following suspected acute gastroenteritis with likely severe dehydration. No infant deaths were assessed by the investigator as related to maternal vaccination. FDA agrees with the investigator's conclusions for 4 out of 5 of the infant deaths in the vaccine group; however, for the one infant with extreme prematurity and prematurity-related complications leading to death, FDA is unable to exclude the possibility of the extreme prematurity and subsequent death being related to receipt of the investigational product.

Most infant deaths occurred in South Africa. There were 10 infant deaths in South Africa, 1 in Gambia, 1 in Brazil, 3 in U.S., 1 in Japan, and 1 in the Philippines.

A premature birth was reported as a primary cause of death for 1 infant in the placebo group; the infant also had bacterial meningitis with sepsis. Another infant in the placebo group was born prematurely but this was not determined to be a cause of death.

For the 1 infant in the RSVpreF group with extreme prematurity at 27 weeks and 3 days gestation who died on day of life 4, the investigator determined that the death was not related to the investigational product. The FDA is unable to draw definitive conclusions regarding potential relation of this case of extreme prematurity to the investigational product.

There were 2 deaths in the RSVpreF group and 5 in the placebo group that occurred during the neonatal period (within the first 28 days of life).

Of the infants who died, one infant in each group had a congenital anomaly; 1 infant in the RSVpreF vaccine group was diagnosed with Trisomy 21 and congenital heart defects and 1 infant in the placebo group had left ventricular hypoplasia. Both infants were born full-term. Although an overall imbalance was noted in the rate of congenital abnormalities with a higher number of cases of congenital anomalies occurring in the placebo group, this was not associated with an imbalance in neonatal deaths.

During the time interval from 1 month to 6 months of age, in the placebo group, 1 event with a study investigator-reported event term of “death” was adjudicated by the EAC with a cause of “acute respiratory illness due to RSV.” The narrative for this event is described below:

> *This was a full-term infant with normal birth outcome, who presented with nasal discharge and cough at 114 days after birth. The infant was hospitalized and RSV PCR was positive. The infant was later noted to have feeding problems following the acute respiratory illness and died at 120 days after birth. Cause of death was reported by the investigator as unknown.*

Non-Fatal SAEs

Congenital Anomalies

Congenital anomalies reported as SAEs occurred at a similar frequency in the RSVpreF and placebo groups (5.0% and 6.2%).

Table 18. Serious Adverse Events of Congenital Anomalies by System Organ Class and Preferred Term, Infant Participants, Safety Population

System Organ Class Preferred Term	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
Any event	180 (5.0)	220 (6.2)
Cardiac defects[a]	44 (1.2)	54 (1.5)
Atrial septal defect	31 (0.9)	40 (1.1)
Bicuspid aortic valve	3 (<0.1)	0
Coarctation of the aorta	2 (<0.1)	2 (<0.1)
Congenital aortic anomaly	0	1 (<0.1)

System Organ Class Preferred Term	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
Heart disease congenital	1 (<0.1)	1 (<0.1)
Hypoplastic left heart syndrome	0	1 (<0.1)
Left-to-right cardiac shunt	1 (<0.1)	1 (<0.1)
Pulmonary artery stenosis congenital	0	1 (<0.1)
Pulmonary valve stenosis	6 (0.2)	6 (0.2)
Ventricular septal defect	15 (0.4)	20 (0.6)
Other Congenital, familial, and genetic disorders[b]	4 (0.1)	6 (0.2)
Cleft lip and palate	0	1 (<0.1)
Cleft palate	0	2 (<0.1)
Congenital central nervous system anomaly	1 (<0.1)	0
Spina bifida occulta	0	1 (<0.1)
Trisomy 21	3 (<0.1)	2 (<0.1)

Source: adapted from Pfizer CSR, Study 1008
N=number of participants in the vaccine group. This value is the denominator for the percentage calculations; n=Number of participants reporting at least 1 occurrence of the specified adverse event. For "any event", n=number of participants reporting at least 1 occurrence of any adverse event.
a. Cardiac defects" includes only the specified Congenital Anomaly SAE terms. These were coded under the MedDRA SOC of 'Congenital, familial and genetic disorders', except for pulmonary valve stenosis which is coded under the MedDRA SOC of 'Cardiac disorders'.
b. Other congenital, familial and genetic disorders" includes only the specified Congenital Anomaly SAE terms, all of which were coded under the MedDRA SOC of congenital, familial and genetic disorders.

Other Non-fatal SAEs

Most SAEs occurred from birth to 1 month of age. SAEs were reported in 15.5% in the RSVpreF group and 15.2% in the placebo group. 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. No SAEs in infant participants were considered related to maternal vaccination.

Table 19. Other Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term, Infant Participants, Safety Population, 24 Months of Follow-up or Data Cut-off

System Organ Class	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
Any event	625 (17.5)	623 (17.5)
Respiratory, thoracic and mediastinal disorders	163 (4.6)	149 (4.2)
Pregnancy, puerperium and perinatal conditions	140 (3.9)	126 (3.5)
Infections and infestations	108 (3.0)	90 (2.5)
Preferred Term		
Jaundice neonatal	75 (2.1)	66 (1.9)
Hyperbilirubinemia neonatal	49 (1.4)	40 (1.1)
Respiratory distress	47 (1.3)	43 (1.2)

Source: adapted from Pfizer CSR, Study 1008

3.3 Study 1003

Title: “A Phase 2b, Randomized, Placebo-Controlled, Observer-Blinded Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine in Pregnant Women 18 Through 49 Years of Age and Their Infants”

This Phase 2 study is designed to describe the safety, tolerability, and immunogenicity of RSV vaccine formulations in maternal participants and their infants.

3.3.1 Study Design

Study 1003 was a Phase 2b, multicenter, randomized, placebo-controlled, observer-blinded study in which up to 650 healthy pregnant women ≥18 and ≤49 years of age were randomized to receive 1 of 2 dose levels of bivalent RSV vaccine candidate at 120 µg (60 µg A and 60 µg B) and 240 µg (120 µg A and 120 µg B) of the prefusion RSV F antigen, formulated with or without aluminum hydroxide, or placebo (1:1:1:1:1 randomization). Assessments included descriptions of safety, tolerability, and immunogenicity in maternal participants as well as safety and characteristics of transplacentally transferred antibodies in their infants. Acute respiratory illness surveillance was conducted in infants for an exploratory analysis of efficacy against RSV-associated LRTD. Vaccination of mothers occurred at a time of year such that the infant was likely to be exposed to RSV during the first 6 months of life.

Study 1003 was initiated just prior to a typical pre-pandemic RSV season in 2019. Northern hemisphere vaccination of maternal participants took place from August 14, 2019 to November 6, 2019 with births from September 12, 2019 to February 24, 2020. Southern hemisphere vaccination ran from January 29 to March 19, 2020 (Argentina and Chile) and March 21 to July 2, 2020 (South Africa) with births from March 2, 2020 to June 14, 2020 (Argentina and Chile) and June 7, 2020 to October 10, 2020 (South Africa).

Pregnant women participated in the study from enrollment during their pregnancy to approximately 12 months after delivery of their infants. The total duration was up to approximately 17 months depending on GA at the time of vaccination. Infants participated from the time of birth to approximately 12 months of age. Study period: August 7, 2019 (first participant enrolled in the trial) to September 30, 2021 (last participant completed the trial). Serology completion date: January 5, 2022.

Schedule of Activities for Maternal Participants

- Visit 0 (Day -14 to Day -2 prior to vaccination): screening and baseline laboratory assessments Day 1 (Vaccination): blood draw for serologic assessment, review of baseline laboratory results
- 2-week follow-up visit (14-17 days after vaccination): vital signs, obstetric examination, safety laboratory blood draw
- Additional visits at 1-month follow-up visit (28 to 42 days after vaccination), delivery, 1-month postdelivery visit (28-35 days after delivery), 6-month postdelivery visit (168 to 210 days after delivery), 12-month postdelivery visit (350 to 378 days after delivery)

The overall design was similar to study 1008, with additional visits at 2 weeks post-vaccination, 1 month post-delivery, and 12 months post-delivery.

Schedule of Activities for Infant Participants

- Birth (birth to 7 days after birth): demography, birth outcome information (including Ballard score), vital signs, physical exam, non-study vaccine information, monoclonal antibodies or blood transfusions history recorded, eligibility reviewed, cord blood sample for serologic assessment, record concomitant medications to treat an AE
- Additional visits at 1 month follow-up (28-35 days after birth), 2-month follow-up (49-63 days after birth), 4-month follow-up (112 to 126 days after birth), 6-month follow-up (168 to 210 days after birth), and 12-month follow-up (350 to 378 days after birth)

The overall design was similar to study 1008, with additional visits at 2 months and 4 months after birth. The study was intended to identify a vaccine dose and formulation to bring forward in Phase 3 development.

Safety Assessments

The primary endpoint was the safety evaluation of maternal participants experiencing prespecified local and systemic reactions, unsolicited adverse events within 1 month following vaccination, and obstetric complications. Infants were assessed for birth outcomes and adverse events, including SAE and MAEs through 12 months of age.

Medical history, physical examination, and assessment of eligibility were performed on all maternal participants at randomization. Maternal participants were followed for local and systemic reactions immediately following vaccination and were asked to monitor and record local reactions and systemic events each evening in the e-diary for 7 days following vaccination (Day 1) through Day 7. A physical examination and measurement of vital signs will be performed on all infant participants at each visit. Significant medical history and observations from examination will be documented in the case report form (CRF). AEs, MAEs (a nonserious AE that results in evaluation at a medical facility), and SAEs will be reported.

3.3.2 Population

Enrolled in this study were healthy adult pregnant participants and their infants, once born. Enrollment was monitored to help ensure distribution of vaccination across the GA range of ≥24 0/7 and ≤36 0/7 weeks. Key exclusion criteria were individuals with chronic medical conditions (e.g., autoimmune disorders or chronic viral hepatitis), extreme obesity, immunocompromise, or history of pregnancy complications (e.g., prior pre-eclampsia).

3.3.3 Surveillance/Monitoring

Pregnant women participated in the study from enrollment during their pregnancy, and for approximately 12 months after delivery of their infants. The total duration was up to approximately 17 months depending on GA at the time of vaccination. Infants participated from the time of birth and for approximately 12 months after birth. The protocol, amendments, and other relevant documents were reviewed and approved by an Institutional Review Board/ Independent Ethics Committee prior to study initiation. An IRC and an E-DMC monitored safety in this study.

Efficacy Assessments

Immunogenicity assessments in the maternal-infant pairs were assessed as secondary endpoints. RSV-positive LRTD in infants was an exploratory objective. A midturbinate swab for RSV and other respiratory pathogen analysis will be collected from each infant participant during any unplanned acute respiratory tract illness visit.

Medically significant RSV-associated LRTD was defined based on clinical observation and RT-PCR confirmation. An episode must meet the following criteria to be considered an RSV LRTD case: One or more of the following signs of LRTD: nasal flaring, lower chest wall indrawing or subcostal retractions, rhonchi, grunting, wheezing, crackles/rales/crepitations, PLUS one of the following signs/symptoms of medically significant respiratory disease: Increased respiratory rate

(≥60 breaths/min [<2 months of age], ≥45 breaths/min [2 to 6 months of age]), use of mechanical ventilation (intubation or noninvasive positive pressure ventilation), difficulty feeding, signs of dehydration (sunken fontanelle, dry mucous membranes, tenting of skin), and proven RSV by positive RT-PCR.

Medically attended LRTD was defined as a medically attended visit and presence of 1 of the following signs of LRTD: tachypnea (respiratory rate ≥60 breaths/minute (<2 months of age) or ≥50 breaths/minute (≥2 to 12 months of age); SpO2 measured in room air <95%; chest wall indrawing.

Medically attended severe LRTD was defined as a medically attended visit and presence of 1 of the following signs of severe LRTD: tachypnea (respiratory rate ≥70 breaths per minute (<2 months of age) or ≥60 breaths per minute (≥2 to 12 months of age); SpO2 measured in room air <93%; high-flow nasal cannula or mechanical ventilation (invasive or noninvasive); ICU admission for >4 hours; unresponsive/unconscious.

Serum samples were obtained and assayed for RSV A- and RSV B-neutralizing antibody levels (neutralizing titer), anti-RSV prefusion F IgG/IgG1 levels, and Ig levels against nonvaccine RSV antigens. Testing was performed by a facility designated by Pfizer. All infants had cord blood sample collected at birth.

3.3.4 Demographics and Other Baseline Characteristics

Maternal Participants

Of the 579 maternal participants in the safety population, 579 completed vaccination, 574 delivered infants (5 withdrew from the study before delivery), and 521 completed the study. Demographic characteristics of maternal participants were similar across vaccine groups. The median age at vaccination was approximately 27 years, and the median GA at vaccination was approximately 30 weeks. Participants in the 24 to <27-week GA stratum were somewhat underrepresented. Most maternal participants were White and non-Hispanic/non-Latino.

Table 20. Demographic Characteristics, Maternal Participants, Safety Population

Demographic Characteristics	RSVpreF N=115 n (%)	Placebo N=117 n (%)
Sex: Female	115 (100.0)	117 (100.0)
Race	--	--
White	85 (73.9)	94 (80.3)
Black or African American	25 (21.7)	19 (16.2)
Asian	1 (0.9)	0
American Indian or Alaskan native	0	1 (0.9)
Native Hawaiian or other Pacific Islander	0	1 (0.9)
Multiracial	0	2 (1.7)
Not reported	4 (3.5)	0
Ethnicity		
Hispanic/Latino	32 (27.8)	33 (28.2)
Ethnicity: Non-Hispanic/non-Latino	83 (72.2)	84 (71.8)

Demographic Characteristics	RSVpreF N=115 n (%)	Placebo N=117 n (%)
Age at vaccination (years)	--	--
N	115	117
Mean (SD)	26.9 (4.6)	26.3 (5.0)
Median	28.0	26.0
Min, max	(18, 36)	(18, 40)
Gestational age at vaccination (weeks)	--	--
N	115	117
Mean (SD)	30.1 (3.6)	30.4 (3.5)
Median	30.0	30.7
Min, max	(24.0, 36.1)	(24.0, 36.0)
Gestational age at vaccination	--	--
24 to <27 Weeks	25 (21.7)	22 (18.8)
27 to <30 Weeks	31 (27.0)	29 (24.8)
30 to <33 Weeks	29 (25.2)	33 (28.2)
≥33 Weeks	30 (26.1)	33 (28.2)
Cohort		
Northern hemisphere	102 (88.7)	104 (88.9)
Southern hemisphere	13 (11.3)	13 (11.1)

Source: adapted from Pfizer CSR, Study 1008
N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=Number of participants in the specified category.

Infant Participants

Demographic characteristics of infant participants generally reflected those of their mothers. Half of the infants were female and the majority were White and non-Hispanic/non-Latino. Most infants were born at term; the median GA at birth was approximately 39 weeks.

Table 21. Demographic Characteristics, Infant Participants, Safety Population

Demographic Characteristics	RSVpreF 120 µg (N=114) n(%)	Placebo (N=116) n(%)
Sex	--	--
Male	52 (45.6)	63 (54.3)
Female	62 (54.4)	53 (45.7)
Gestational age at birth (weeks)	--	--
N	114	116
Mean (SD)	39.1 (1.1)	39.1 (1.2)
Median	39.1	39.1
Min, max	(35.4, 41.4)	(33.1, 41.7)

Source: adapted from Pfizer CSR, Study 1008
N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=Number of participants with the specified characteristic.

3.3.5 Maternal-Infant Placental Transfer

Maternal-to-infant placental transfer ratio of RSV neutralizing titers of RSV A and RSV B was assessed in a subgroup of approximately 200 maternal-infant pairs.

There appeared to be maternal-to-infant placental transfer of antibodies that achieved the pre-specified goal of geometric mean 50% neutralization titers that met a ratio of the infant to the

mother of >1, although it was noted that this was achieved for both the RSVpreF and placebo groups. The clinical significance of this finding is unknown.

3.3.6 Infant Exploratory Endpoints

Rates of RSV-positive LRTD

When all vaccine groups were combined and compared to placebo, efficacy of maternal vaccination against RSV-associated MA-LRTD and severe MA-LRTD were 75% and 83%, respectively. All 95% CIs for vaccine efficacy include zero.

Table 22. Efficacy of Maternal Vaccination Against RSV-Associated Lower Respiratory Tract Illness in Infants Through End of Study, Infant Participants, Safety Population

Endpoint Description	RSVpreF N=456 Number of Cases (%)	Placebo N=116 Number of Cases (%)	Vaccine Efficacy[a] (95% CI)[a]
Medically significant LRTD[b]	3(0.7)	3(2.6)	75% (-90%, 97%)
Medically attended LRTD[c]	5(1.1)	5(4.3)	75% (-11%, 94%)
Medically attended Severe LRTD[d]	2(0.4)	3(2.6)	83% (-48%, 99%)

Source: adapted from Pfizer CSR, Study 1008
Abbreviations: LRTD=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.
a. Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group.

3.3.7 Safety Primary Endpoint Analyses

Safety results were similar to findings in study 1008. The proportion of maternal participants reporting pain at the injection site was higher in participants who received RSVpreF formulated with Al(OH)3 compared with those who received non-Al(OH)3 formulations.

SAEs within 1 month after vaccination were reported in 1 maternal participant (0.9%) in the RSVpreF 120 µg group, 3 (2.6%) in the RSVpreF 120 µg/Al(OH)3 group, 2 (1.7%) in the RSVpreF 240 µg group, 4 (3.5%) in the RSVpreF 240 µg/Al(OH)3 group, and 3 (2.6%) in the placebo group. Serious adverse events appeared to be balanced overall between treatment groups and FDA is still evaluating safety information from this study.

No SAEs reported for infant participants were considered related, by the investigator or the FDA, to maternal vaccination. One infant participant in the placebo group was withdrawn following unrelated SAEs (diagnosed with hypoxia, neonatal respiratory distress syndrome, atrial septal defect, and patent ductus arteriosus) occurring shortly after birth.

For study 1003, as noted in the below table, there was a numerical imbalance in preterm births in the RSVpreF vaccine groups compared with matched placebo controls.

Table 23 below describes the observation of live and premature deliveries in this study.

Table 23. Birth Outcomes, Study 1003, Maternal Participants, Safety Population

Outcome	RSVpreF 120ug N=115 n (%)	RSVpreF 120ug + Al(OH)3 N=117 n (%)	RSVpreF 240ug N=116 n (%)	RSVpreF 240ug + Al(OH)3 N=114 n (%)	Placebo N=117 n (%)
Full term live delivery	108 (93.9)	113 (96.6)	106 (91.4)	108 (94.7)	113 (96.6)
Premature live delivery	6 (5.2)	4 (3.4)	8 (6.9)	4 (3.5)	3 (2.6)
Stillbirth	0	0	0	0	1 (0.9)

Source: Pfizer. Adapted from Table 14.75 in Study 1003 CSR. Pregnancy Outcomes – Maternal Participants – Safety Population.

No maternal or infant deaths were reported during Study 1003. One fetal death occurred in the placebo group.

3.4 Study 1004

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

3.4.1 Study Design

This was a Phase 2, multicenter, placebo-controlled, randomized, observer-blind study in healthy nonpregnant women, 18-49 years of age, randomized to evaluate concomitant administration of RSVpreF and Tdap.

Participants were randomized in a 1:1:1:1:1 ratio to receive 1 of 5 vaccine groups. Participants received 2 injections administered concomitantly. A 0.5 mL dose of study vaccine was administered intramuscularly as follows:

- RSVpreF 120 µg and Placebo (saline solution)
- RSVpreF 120 µg and Tdap
- RSVpreF 240 µg + Al(OH)3 and Placebo
- RSVpreF 240 µg + Al(OH)3 and Tdap
- Placebo and Tdap

RSV Vaccine Antibody Testing

Sera was collected and assayed for RSV A- and RSV B-neutralizing antibody levels, anti-RSV prefusion F immunoglobulin G (IgG) levels, and immunoglobulin (Ig) levels against nonvaccine RSV antigens. RSV A- and RSV B-neutralizing antibody levels were determined and reported as the neutralizing titer.

Tdap Antibody Testing

Sera was collected and assayed for IgG antibodies to Tdap antigens.

Study Vaccines

The investigational product(s) are RSV vaccine, Tdap, and placebo (saline control). RSVpreF investigational vaccine product was supplied as a lyophilized mixture of equal quantities of 2 stabilized prefusion RSV F antigens, one from each of the RSV subgroups A and B. The dose

level of 120 µg RSV antigen was reconstituted with sterile water for injection. The 240 µg dose was reconstituted with sterile $Al(OH)_3$. The placebo was presented as a sterile saline solution for injection (0.9% NaCl injection, in a 0.5 mL dose). US-licensed Tdap was provided by the Applicant. For each vaccine group (RSVpreF and saline placebo, RSVpreF and Tdap, or placebo and Tdap), a 0.5 mL volume of RSVpreF, placebo, or Tdap was administered intramuscularly by an unblinded site staff member. Participants received 2 injections at Visit 1 in accordance with the randomization schedule.

- RSVpreF: Investigational RSV vaccine. Diluent: sterile water for injection
- Boostrix (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed [Tdap]
- Placebo (0.9% sodium chloride)

3.4.2 Population

Key eligibility criteria were generally healthy adult females.

3.4.3 Immunogenicity Analyses

3.4.3.1 Analyses of Primary Endpoint(s)

Most subjects were non-Hispanic White females and most completed the study with very few lost to follow up or withdrawn from the study.

Anti-TTd and Anti-DTd Antibody Concentrations

The primary objective of demonstrating noninferiority was met for both anti-DTd and anti-TTd immune responses, per the predefined threshold for noninferiority of the immune response to TTd and DTd (the lower bound of the 2-sided 95% CI for the difference between combined RSVpreF/Tdap groups and placebo/Tdap group is >-10%). The percentage of participants with anti-DTd and anti-TTd antibody concentrations ≥0.1 IU/mL was similar for the combined RSVpreF/Tdap groups and the placebo/Tdap group prior to vaccination. The difference in the percentage of participants with anti-DTd antibody concentrations ≥0.1 IU/mL for the combined RSVpreF/Tdap groups and the placebo/Tdap group was -1.8% (95% CI: -4.6%, 1.7%) at 1 month after vaccination. All participants in the combined RSVpreF/Tdap groups and placebo/Tdap group achieved anti-TTd antibody concentrations ≥0.1 IU/mL at 1 month after vaccination; the difference for the combined RSVpreF/Tdap groups and the placebo/Tdap group was 0.0% (95% CI: -1.4%, 2.8%).

Anti-pertussis Antibody GMRs

The primary objective of demonstrating noninferiority was ***not*** met for anti-PT, anti-FHA, and anti-PRN immune responses, per the predefined threshold for noninferiority of the immune response to anti-pertussis components (the lower bound of the 2-sided 95% CI >0.67 for the GMC ratio of the combined RSVpreF/Tdap groups to the placebo/Tdap group). The GMCs for anti-PT, anti-FHA, and anti-PRN antibodies were similar for the combined RSVpreF/Tdap groups and the placebo/Tdap group prior to vaccination. The GMRs for anti-PT, anti-FHA, and anti-PRN antibodies for the combined RSVpreF/Tdap groups in comparison to the placebo/Tdap group were 0.80 (95% CI: 0.64, 1.00), 0.59 (95% CI: 0.50, 0.70), and 0.60 (95% CI: 0.48, 0.76), respectively, at 1 month after vaccination. At the time of the preparation of this document, FDA is evaluating the clinical significance of these findings and whether co-administration of Abrysvo and Tdap can be considered appropriate.

RSV Neutralizing Antibody Titer GMRs

The primary objective of demonstrating noninferiority for both RSV A and RSV B immune responses was met, per the predefined threshold for noninferiority of the immune response to RSV (the lower bound of the 2-sided 95% CI >0.5 [noninferiority margin of 2-fold] for the GMT ratio of combined RSVpreF/Tdap groups divided by combined RSVpreF/placebo groups for RSV A- and RSV B-neutralizing antibodies).

Observed RSV A and RSV B GMTs were similar for the combined RSVpreF/Tdap groups and the combined RSVpreF/placebo groups before vaccination. The RSV A and RSV B 50% neutralizing titer GMRs for the combined RSVpreF/Tdap groups and the combined RSVpreF/placebo groups were 0.97 and 0.96, respectively, at 1 month after vaccination. The lower bound values of the 2-sided 95% CIs for the RSV A and RSV B 50% neutralizing titer GMRs were 0.84 and 0.81, respectively.

3.4.3.2 Analyses of Secondary Endpoints

Since the primary objective for demonstrating noninferiority of RSV responses was met, the secondary objective of noninferiority of RSV responses was tested using a more stringent 1.5-fold margin. Per the predefined threshold for determining noninferiority of the immune response to RSV (the lower bound of the 2-sided 95% CI >0.67 for the GMT ratio of combined RSVpreF/Tdap groups divided by combined RSVpreF/placebo groups for RSV A- and RSV B-neutralizing antibodies), the secondary objective of demonstrating noninferiority of immune responses to RSV by a 1.5-fold margin was met for both RSV A and RSV B immune responses (lower bound 2-sided 95% CI value range = 0.78 to 0.84 at 1 month after vaccination).

3.4.4 Safety Analyses

Overview of Adverse Events

A total of 709 participants were vaccinated; 282 participants received the final formulation of RSVpreF. Table 24, which pertains to participants who received the final formulation, provides an overview of the rates of adverse events in the vaccine co-administration groups compared to the control group during the study period.

Solicited local and systemic adverse events did not differ substantially among vaccine treatment groups and were generally similar to study subjects in Study 1008 who received RSVpreF 120 µg. The rates of solicited local reactions were higher in participants receiving the RSVpreF vaccine. The rates of solicited systemic reactions were similar across study groups. The rates of unsolicited adverse reactions were comparable between groups. There were no serious, immediate or life-threatening AEs reported within 1 month of vaccination and no AEs that lead to withdrawal. No participants died during the study.

Table 24. Overview of Adverse Events, Study C3671004, Safety Population

Event	RSVpreF 120µg/ Placebo N=141 n/N (%)	RSVpreF 120 µg/ Tdap N=141 n/N (%)	Placebo/ Tdap N=141 n/N (%)
Immediate unsolicited AE within 30 minutes after vaccination	0/141	0/141	0/141
Solicited injection site reaction within 7 days[a]	59/141 (41.8)	64/141 (45.4)	36/139 (25.9)
Solicited systemic adverse reactions within 7 days	94/141 (66.7)	109/141 (77.3)	96/139 (69.1)
Unsolicited non-serious AE within 30 days	8/141 (5.7)	11/141 (7.8)	13/141 (9.2)
SAEs within 30 days	0/141	0/141	0/141
Deaths	0/141	0/141	0/141
Withdrawal due to AE within 30 days	0/141	0/141	0/141
AESIs within 30 days	NA	NA	NA

Source: adapted from Pfizer CSR
Abbreviations: NA=not applicable; n=number of participants in the specified category
N=number of participants in the vaccine group. These values were used as the denominators for the percentage calculations.
Solicited local reactions were assessed at the RSVpreF injection site in the study groups receiving RSVpreF 120 µg and saline placebo concomitantly or RSVpreF 120 µg and Tdap concomitantly. Solicited local reactions were assessed at the saline placebo injection site in the study group receiving placebo and Tdap concomitantly.

Solicited Local Adverse Reactions

Most local reactions were of mild or moderate intensity. The median durations of pain and redness at the injection site were the same in the RSVpreF 120 µg/placebo group and the RSVpreF 120 µg/Tdap group (2.00 days for pain or redness in both groups), with median duration of swelling 2.50 days and 2.00 days for the RSVpreF 120 µg/placebo and RSVpreF 120 µg/Tdap groups, respectively. The median duration of pain at the injection site, redness, and swelling in the placebo/Tdap group were 1, 2, and 1.50 days, respectively.

Non-serious Unsolicited Adverse Events with 30 days of Vaccination

Non-serious unsolicited AEs were balanced between groups. Unsolicited AEs were reported in 8 (5.7%) in RSVpreF/placebo group, 11 (7.8%) in RSVpreF/Tdap group, and 13 (9.2%) in the placebo/Tdap group.

3.4.4.1 Deaths

No participants died during this study.

3.4.4.2 Nonfatal Serious Adverse Events

There was 1 SAE of spontaneous abortion that occurred after Visit 2 (Day 42) and was reported by a participant in the RSVpreF 240 µg + Al(OH)3/placebo group. This SAE was not considered related to the vaccine per the investigator; FDA agrees with this assessment based on lack of temporal association. There were no SAEs in the other study groups.

3.5 Safety Review of Studies Submitted to the BLA

In the 5 supporting clinical studies submitted to the BLA, a total of 4,144 participants received any dose level and formulation of RSVpreF. Review of the safety data from these studies did not reveal any significant safety concerns. Local reactogenicity was reported more frequently in vaccine recipients compared with placebo recipients. The most common local reaction was pain at the injection site.

Across all 5 studies, SAEs assessed as related occurred in 4 maternal participants in the RSVpreF group (all in the 1008 study): an episode of severe diffuse extremity pain which resolved within one week of onset, an episode of premature labor which did not result in a premature infant, an episode of thrombocytopenia which was determined to be an early sign of autoimmune disease (SLE), and a case of eclampsia at 38 weeks gestation.

A numerical imbalance in the rate of preterm births was observed in the maternal/infant population (studies 1008 and 1003), with preterm births in 5.7% and 4.7% in the RSVpreF and placebo groups, respectively.

One case of preterm birth in an infant born at 36 weeks and 5 days gestation, day 86 post-vaccination, in the RSVpreF group, was considered related to receipt of the investigational product. The infant had a normal birth outcome and no complications.

4. Pharmacovigilance Plan (PVP)

In its PVP submitted to the BLA (version 0.1), the Applicant identifies use in immunocompromised pregnant women as Missing Information. The Applicant did not include any Important Identified or Important Potential Risks in its PVP. The Applicant proposes to further evaluate the safety of Abrysvo in pregnant women using US electronic healthcare claims data to compare safety outcomes in RSVpreF-exposed and RSVpreF-unexposed pregnant women and their newborns.

5. Summary of Efficacy and Safety

The effectiveness of RSVPreF immunization during pregnancy (at 24 to 36 weeks gestation) to prevent infant RSV MA-LRTD [51.3% (97.6% CI: 29.4%, 66.8%)] and severe RSV MA-LRTD [69.4% (97.6% CI: 44.3%, 84.1%)] within 180 days after birth was demonstrated, based on study 1008 results up to the data cutoff date (September 30, 2022).

For the time period from 181 to 360 days after birth, rates of RSV-confirmed MA-LRTD were similar in both treatment groups. Available data for the period of 361 to 730 days after birth suggest that rates of MA-LRTD due to RSV remained similar in both treatment groups.

Across all studies, the safety database included 3797 maternal participants (1773 maternal participants enrolled from US sites) who received 120 µg of RSVpreF vaccine. Severe local and systemic reactions following RSVpreF vaccination were uncommon (severe local reactions: 0.5% and 0.4% of female and maternal participants, respectively; severe systemic reactions: 2.8% and 2.7% of female and maternal participants, respectively). 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. There were no meaningful differences between treatment groups in the overall rates of unsolicited AEs within 1 month after vaccination. AEs and SAEs in infant participants were reported at a similar frequency across the RSVpreF and placebo groups.

There was an imbalance in the percentage of premature infants reported in study 1008, with more preterm births in the vaccine group (5.7% in the RSVpreF group vs. 4.7% in the placebo group). The difference in rates of preterm births was not statistically significant; overall, the rates were lower than the incidence of preterm births in the general population, which is approximately 10% (CDC, 2022; WHO, 2022). A similar difference in premature births of 0.9%

(between the vaccine group and the placebo group) was also observed in the Integrated Summary of Safety population, which included pregnancy outcomes from the Phase 2 and Phase 3 studies.

6. Topics for VRBPAC Discussion

The VRBPAC will convene on May 18, 2023, to discuss and vote on whether the available data support the safety and effectiveness of Abrysvo for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals.

Appendix A: Vaccine-Associated Enhanced Respiratory Disease

In the late 1960s, evaluation of a formalin-inactivated RSV vaccine (FI-RSV) in RSV-naïve infants was associated with enhanced respiratory disease (ERD) following subsequent natural RSV infection (Kim et al, 1969). Two vaccine recipients died following RSV infection. The mechanisms responsible for FI-RSV vaccine-associated ERD are still not fully understood; however, studies suggest that inadequate production of neutralizing antibody despite an increase in overall antibody titer and an exaggerated Th2 response after subsequent infection may be implicated (Chin et al, 1969; Kapikian et al, 1969; Fulginiti et al, 1969; Polack et al, 2002). The risk of ERD in older children and adults is low, due to priming by prior natural RSV infection (Acosta et al, 2016).

Studies of cell-mediated responses suggest that T-cell responses in infants may differ from that in adults. Data from studies in mice and humans indicate that distinct epigenetic profiles and processes may play a role in responses of T cells in infants. CD4+ T cell responses may develop more slowly in infants than adults after primary infection with certain viruses. Responses in infants to some vaccine antigens may reflect T_H2-predominant cytokine responses due to hypomethylation within the promoter region regulating expression of T_H2 type cytokines while the promoter region for T_H1 cytokines is hypermethylated, decreasing expression of IFNγ and other T_H1 cytokines. The robust IL-4 response that occurs in young infants following exposure to antigen is toxic to T_H1 type CD4+ T cells and induces apoptosis of these cells, further skewing the cytokine response (PrabhuDas et al, 2011).

Theoretical Risk of ERD If Infants Were To Be Actively Immunized

It has been hypothesized that pulmonary deposition of immune complexes and complement are associated with ERD. In a study by Polack et al, 2002, lungs of mice immunized with FI-RSV and challenged with RSV-stained hematoxylin and eosin (H&E) showed “a patchy mononuclear cell infiltration of the alveolar walls and a peribronchiolar and perivascular lymphomonocytic infiltration with a moderate number of interspersed neutrophils and eosinophils.” Lungs of placebo recipients and mice immunized with live RSV contained fewer mononuclear cells after RSV challenge. To confirm the role of complement in the pathophysiology of ERD, C3-deficient and wildtype mice were immunized with FI-RSV and then challenged with RSV infection. Both groups developed similar alveolar, peribronchiolar, and perivascular mononuclear cellular infiltration with neutrophils. While the histopathology findings for both groups were similar; differences were noted between the two groups on pulmonary function studies. FI-RSV-immunized, RSV-challenged wildtype mice had a significant increase in airway hyperresponsiveness as compared with C3-deficient mice, which demonstrated that complement is critical for bronchoconstriction in ERD. Additionally, an antibody against C4d (which is a sensitive marker of complement activation mediated by immune complexes using the classical pathway) was used to stain lung sections obtained from the two children who died of ERD confirming a role for immune complexes in vaccine-associated ERD in children immunized with FI-RSV.

Theoretical Risk of ERD in Infants Following Waning Passive Immunity

In a randomized, double-blind, placebo-controlled study evaluating safety and immunogenicity of the RSV purified fusion protein-2 (PFP-2) vaccine in 35 healthy women in the third trimester of pregnancy and their infants, there was no increase in the frequency of morbidity associated with respiratory tract illnesses in infants of vaccine recipients, and there was no evidence of

enhanced T-cell or cytokine activity in infants of vaccine recipients compared with infants of placebo recipients (Munoz, 2003). Two immunization and challenge studies in animals (mice and rats) demonstrated that passive transfer of antibodies to naïve pups through maternal vaccination with FI-RSV prior to challenge did not result in ERD upon subsequent live RSV challenge (Blanco et al; Kwon et al). These studies demonstrated that anti-FI-RSV IgG alone cannot predispose to ERD following challenge.

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

Appendix B: Inclusion/Exclusion Criteria for Study 1008

Inclusion Criteria:

- 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.
- GA must be based upon 1 of the following composite criteria based on timing and availability of data on the last menstrual period (LMP) and an ultrasound examination performed in the first or second trimester. The earliest ultrasound data available during the current pregnancy should be used. In countries where the routine practice is for the GA determination to be based upon the first trimester ultrasound examination alone, without the LMP, this routine practice will be accepted.
- First-trimester data available (data obtained at ≤13 6/7 weeks).
- Second-trimester data available (data obtained at 14 0/7 to 27 6/7 weeks).
- Receiving prenatal standard of care based on country requirements.
- Had a fetal anomaly ultrasound examination performed at ≥18 weeks of pregnancy with no significant fetal abnormalities observed.
- Documented negative HIV antibody, HBV surface antigen, and syphilis test during this pregnancy and prior to Visit 1.
- Pre-pregnancy body mass index (BMI) of <40 kg/m2.

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

- Pre-pregnancy body mass index (BMI) of >40 kg/m2.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the investigational product or any related vaccine.
- Current pregnancy resulting from in vitro fertilization. Participants known to have used clomiphene citrate and/or letrozole with or without intrauterine insemination (IUI) are permitted.
- 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.

- 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.
- 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).
- 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.
- Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.
- Participation in other studies involving investigational drug(s) within 28 days prior to consent and/or during study participation.
- 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. Permitted treatments include the receipt of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies, prednisone doses of <20 mg/day for ≤14 days and, inhaled/nebulized, intra-articular, intrabursal, or topical corticosteroids.
- Current alcohol abuse or illicit drug use.
- Receipt of blood or plasma products or immunoglobulin (Ig), from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (e.g., RhoGAM), which can be given at any time.

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