BLA Clinical Review Memorandum

Application Type	Biologics License Application (BLA)
STN	125768/0
CBER Received Date	December 21, 2022
PDUFA Goal Date	August 21, 2023
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Yugenia Hong-Nguyen, M.D. Medical Officer CRB1, DVRPA, OVRR, CBER
Review Completion Date / Stamped Date	August 21, 2023
Supervisory Concurrence	Lucia Lee, MD Medical Officer-Team Leader CRB1, DVRPA, OVRR, CBER Joseph Toerner, MD, MPH Acting Deputy Director DVRPA, OVRR, CBER
Applicant	Pfizer Inc.
Established Name	Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine
(Proposed) Trade Name	ABRYSVO
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	After reconstitution, each 0.5 mL dose contains a total of 120 µg of RSV prefusion F protein (60 µg RSV A and 60 µg RSV B)
Dosage Form(s) and Route(s) of Administration	Solution for intramuscular injection
Dosing Regimen	Single 0.5 mL dose
Applicant's Indication(s) and Intended Population(s)	Prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals.
Final Indication and Population	Active immunization of pregnant individuals at 32 through 36 weeks gestational age (GA) for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
ARI	acute respiratory infection
BLA	Biologics License Application
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
DMC	Data Monitoring Committee
DT	diphtheria toxoid
EAC	Endpoint Adjudication Committee
e-diary	electronic diary
E-DMC	external Data Monitoring Committee
ERD	enhanced respiratory disease
FDA	US Food and Drug Administration
FHA	filamentous hemagglutinin adhesin
FI-RSV	formalin-inactivated RSV
GA	gestational age
GBS	Guillain-Barré Syndrome
GMT	geometric mean titer
GMR	geometric mean ratio
H&E	hematoxylin and eosin
HBV	hepatitis B virus
HCV	hepatitis C virus
HDP	hypertensive disorders of pregnancy
HIC	high-income countries
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IP	investigational product
LBW	low birth weight
LL	lower limit
LMIC	low- and middle-income countries
LRTD	lower respiratory tract disease
mAb	monoclonal antibody
MAE	medically attended adverse event
MA-LRTD	medically attended lower respiratory tract disease
MA-RTD	medically attended respiratory tract disease
MA-RTI	medically attended respiratory tract illness
mITT	modified intent-to-treat
NAAT	nucleic acid amplification test
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
NT	neutralizing titers
PCR	polymerase chain reaction
PD	protocol deviation
PFP-2	purified fusion protein-2

PPROM	preterm premature rupture of membranes
preF	prefusion F protein
PRN	pertactin
PROM	premature rupture of membranes
PT	pertussis toxin
PVP	pharmacovigilance plan
RhIG	Rho(D) immune globulin
RSV	respiratory syncytial virus
RSV MA-LRTD	RSV-confirmed medically attended lower respiratory tract disease
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
RTI	respiratory tract illness
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SLE	systemic lupus erythematosus
SOC	System Organ Class
TT	tetanus toxoid
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 respiratory syncytial virus stabilized prefusion F subunit vaccine (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 subtypes, 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 proposed indication. 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 (IP).

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 (RSV MA-LRTD) 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 for the infants 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.

Efficacy Data

When individuals were immunized at 24 through 36 weeks gestational age (GA) of pregnancy (hereafter referred to as "24-36 weeks"), vaccine efficacy (VE) was assessed in preventing severe RSV-associated lower respiratory tract disease (RSV LRTD), defined as an infant with an RSV-associated medically attended respiratory tract disease (RSV MA-RTD) and respiratory rate ≥70 breaths per minute (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 RSV LRTD 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. VE was also assessed in preventing RSV LRTD, defined as infant with a medically attended respiratory disease (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.

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).

For the subgroup analyses of RSV MA-LRTD and severe RSV MA-LRTD by subgroup of GA at vaccination, decreased VE through 90 days after birth was noted in infants born to pregnant individuals who were vaccinated between 24 to <28 weeks gestation, whereas for infants whose mothers were vaccinated between 32 through 36 weeks gestation (hereafter referred to as "32-36 weeks"), VE against severe RSV MA-LRTD and VE against any RSV MA-LRTD appeared similar to the VEs in the overall population of infants whose mothers were vaccinated at 24-36 weeks gestation. These subgroup analyses were not controlled for multiple comparisons.

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 adverse event (AE) of mild dizziness was reported in the RSVpreF vaccine group within 30 minutes of vaccination and resolved on the day of onset. This was considered by the study investigator and FDA to be related to vaccination.

The proportions of maternal participants with any AEs reported within 1 month after vaccination were 13.7% and 13.1% in the RSVpreF and placebo groups, respectively. 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 between delivery and 1 month after delivery, were reported in 4.3% versus 4.1% in the RSVpreF and placebo groups, respectively.

The frequencies of 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 (SLE) 5 months later; and 1 case of eclampsia with onset 15 days after vaccination.

An analysis of maternal outcomes of interest was performed for pregnancy-related conditions with the potential for associated premature delivery due to obstetric indications, e.g., hypertensive disorders of pregnancy (HDP), premature rupture of membranes (PROM), and preterm premature rupture of membranes (PPROM). These pregnancy-related SAEs overall were reported in 152 (4.1%) vaccinated maternal participants versus 120 (3.3%) in the placebo

group, including 68 (1.8%) cases of preeclampsia in the RSVpreF group and 53 (1.4%) cases of preeclampsia in the placebo group.

Premature delivery was reported as an adverse event of special interest (AESI) for maternal participants throughout the study in 5.6% (207/3682) versus 4.8% (175/3675) in the RSVpreF and placebo groups, respectively. The rate of premature deliveries in the general population is typically higher than 6% (CDC, 2022a; WHO, 2022), which is higher than the overall rate of premature deliveries observed in the clinical trial population. The numerical difference represents a *potential* safety signal in part because the 95% CIs 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 that this death was not related to vaccine administration.

There were 18 peripartum fetal deaths; 10 (0.3%) in the RSVpreF group, 8 (0.2%) in the placebo group. None of the intrauterine demises were assessed by the investigator as related to vaccination; FDA agrees that the fetal deaths reported in this study were unlikely to have been related to the IP based on review of available case narratives and evident lack of temporal relation of vaccination to the fetal loss events.

Safety Data for Infant Participants

As of the data cutoff of September 2, 2022, in infants born to pregnant individuals vaccinated at 24-36 weeks of pregnancy, a numerical imbalance in preterm births was noted in the RSVpreF group (5.7%; 202/3568) compared with the placebo group (4.7%; 169/3558).

Of all preterm infants in Study 1008, approximately one-third were born to maternal participants who were vaccinated at 32-36 weeks. This subgroup (maternal participants vaccinated at 32-36 weeks gestation) represented approximately 45% of the clinical trial population. The safety data analyses from this subgroup reported preterm birth rates of 4.2% in all live births in the RSVpreF group and 3.7% in all live births in the placebo group. These subgroup analyses provided support for limiting the indication to active immunization of pregnant individuals at 32-36 weeks, eliminating the potential for increase in risk after vaccination with RSVpreF of both extremely preterm births (less than 28 weeks GA), where there is substantive morbidity and mortality, and very preterm births (28 to less than 32 weeks GA).

As of the data cutoff point, SAEs from birth to 24 months of age were reported in 17.5% in the RSVpreF group and 17.5% in the placebo group. SAEs within 1 month after birth were reported in 15.5% of infants in the RSVpreF group and 15.2% of infants in the placebo group. Congenital anomalies were reported in 5.0% of infants in the RSVpreF group and 6.2% in the placebo group. Up to the data cutoff, a total of 17 infant deaths were reported: 5 (0.1%) in the RSVpreF group and 12 (0.3%) in the placebo group. No infant deaths were assessed by the investigator as related to maternal vaccination. Except for 1 of the infant deaths in the vaccine group, FDA agrees with the investigator's conclusions; for 1 death that resulted from prematurity-related complications, FDA was unable to exclude the possibility that the extreme prematurity and subsequent death was related to receipt of the investigational product. One infant in the placebo group died from RSV LRTD.

The proportions of infant participants with any AE reported within 1 month after birth were 37.1% in the RSVpreF group and 34.5% in the placebo group. Low birth weight (LBW) was reported in 5.1% [95% CI: 4.4%, 5.8%] and 4.4% [95% CI: 3.7%, 5.0%] of infant participants in

the RSVpreF and placebo groups, respectively. Neonatal jaundice occurred in 7.2% and 6.7% of infant participants in the RSVpreF and placebo groups, respectively. All other AEs among infant participants were reported with similar percentages between treatment groups and generally reflected rates of AEs that would be expected in neonatal and infant populations.

Pharmacovigilance

The Applicant will be required to conduct four postmarketing studies to assess the serious risks of preterm birth and HDP:

1. US retrospective claims database (Sentinel and Medicaid) study
2. US prospective registry study
3. EU database study using electronic health records (EHR) data
4. US retrospective cohort study using EHR data

The Applicant will also be required to conduct enhanced pharmacovigilance with expedited reporting for preterm birth and HDP.

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.

Advisory Committee Meeting

On May 18, 2023, FDA convened at a meeting of 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. The Committee discussed the balance between the convincing vaccine efficacy, including against severe LRTD, and AEs, particularly premature delivery/birth. The Committee also discussed duration of vaccine protection, gestational age at the time of vaccination, concomitant administration of other vaccines during pregnancy, and considerations for postmarketing studies. VRBPAC members voted unanimously "yes" (n=14) that the available data were adequate to support the effectiveness of immunization with ABRYSVO during the second or third trimester of pregnancy (24-36 weeks gestation) to prevent RSV LRTD and severe RSV LRTD in infants, from birth through 6 months of age. Ten VRBPAC members voted "yes" and 4 voted "no" on whether the available data were adequate to support the safety of immunization with ABRYSVO during the second or third trimester of pregnancy (24-36 weeks gestation) to prevent RSV LRTD and severe RSV LRTD in infants, from birth through 6 months of age. Safety concerns were primarily regarding the numerical imbalance in preterm births.

1.1 Demographic Information: Subgroup Demographics and Analysis

Efficacy

Study 1008 was conducted in multiple regions and countries. Subgroup analyses for selected efficacy endpoints were performed on the following variables: maternal age at vaccination, GA at vaccination, country, country income level, duration of breastfeeding, exclusive breastfeeding, maternal smoking, number of household members, and racial/ethnic subgroups.

VE by various subgroup analyses was generally consistent with those observed in the main analyses. An analysis of VE in individual countries showed somewhat lower VE in South Africa, Spain, and the Netherlands, but the two-sided 95% CIs were wide due to a fewer number of enrolled participants in those countries. VE in the US appeared to be consistent with VE overall in the study. Thus, *clinically* meaningful differences between subgroups were not observed; however, these subgroup analyses should be interpreted with caution due to low numbers of participants and observed RSV cases in some subgroups. For the subgroup analyses of RSV MA-LRTD and severe RSV MA-LRTD by subgroup of GA at vaccination, a consistent trend towards decreased VE was noted in infants born to pregnant individuals who were vaccinated between 24 to <28 weeks gestation compared with VE in the overall population of infants born to pregnant individuals vaccinated at 24-36 weeks gestation.

Safety

Subgroup analyses of AEs reported in maternal participants by race or maternal age at vaccination did not reveal any clinically meaningful differences across subgroups. Subgroup analyses of AEs reported in infant participants by race, sex or maternal age at vaccination did not show clinically meaningful differences between study groups. However, results by maternal age should be interpreted with caution due to the low number of maternal subjects less than 18 years old.

Subgroup analyses of live birth outcomes by country for the infant safety population showed a higher incidence of prematurity and LBW infants in South Africa and Argentina. In South Africa, preterm birth was reported in 8.3% (39/469) in the RSVpreF group and 4.0% (19/471) in placebo group, and LBW occurred in 10.4% (49/469) of infants in the RSVpreF group and 6.8% (32/471) in the placebo group. In Argentina, preterm birth was reported in 6.4% (27/423) in the RSVpreF group and 4.0% (17/416) in the placebo group, and LBW occurred in 2.6% (11/423) in the RSVpreF group and 1.2% (5/416) in placebo group. In the US, preterm birth was reported in 5.7% (94/1644) in the RSVpreF group versus 5.3% (87/1644) of infants in the placebo group, of which 11 infants (0.7%) in the RSVpreF group and 5 (0.3%) in the placebo group were born between 28 weeks to <34 weeks gestation. Also in the US subgroup, LBW was reported in 4.2% (70/1654) in the RSVpreF group and 4.0% (65/1644) in the placebo group.

1.2 Patient Experience Data

No patient experience data were submitted with the application

2. Clinical and Regulatory Background

2.1 Vaccine Composition

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 subtypes: RSV subtype A prefusion F (60 µg) and RSV subtype 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. ABRYSVO was approved on May 31, 2023 for the prevention of LRTD caused by RSV in individuals 60 years of age and older.

2.2 Epidemiology

RSV is a common cause of bronchiolitis and viral pneumonia in infants and is the leading cause of infant hospitalizations in the US (Suh et al., 2022). RSV hospitalization rates are highest within the first 3 months of life; RSV disease is associated with a mortality of 1-3% 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).

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 infection (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 individuals from high-income countries (HICs) 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 respiratory tract disease (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 LBW infant (Riccò et al., 2022). Studies to date have been limited by the small number of patients who underwent testing for RSV.

RSV infection does not confer lasting immunity and reinfections occur throughout individual lifespans. There is currently no immune marker or antibody 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).

2.3 Clinical Manifestations, Diagnosis, and Treatment

RSV 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 (RTI). Symptoms consistent with upper RTI 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.

2.4 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). Vaccine-associated ERD has been a theoretical risk for 21st century investigational RSV vaccine development, and was the 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 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Palivizumab (Synagis; MedImmune), is a monoclonal antibody (mAb) approved by the FDA for prevention of severe RSV disease in high-risk infants.

Nirsevimab (Beyfortus; AstraZeneca and Sanofi), a prefusion F-specific mAb, was approved by the FDA on July 17, 2023, for the prevention of RSV LRTD in neonates and infants born during or entering their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

2.6 Safety and Efficacy of Pharmacologically Related Products

Two RSV vaccines, AREXVY (GlaxoSmithKline Biologicals) and ABRYSVO (RSVpreF; Pfizer, Inc.) were approved by the FDA (on May 3, 2023 and May 31, 2023, respectively) for the prevention of LRTD caused by RSV in individuals 60 years of age and older. Clinical data to support the safety and effectiveness and indication and use in individuals 60 years and older are described in the US prescribing information (Abrysvo, 2023; Arexvy, 2023).

Currently, there is no vaccine available for the prevention of RSV disease in infants.

2.7 Previous Human Experience with the Product (Including Foreign Experience)

No postmarketing data are available at this time.

2.8 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

- Fast Track Designation Granted: September 11, 2018
- End of Phase 2 Meeting: January 31, 2020
- Breakthrough Therapy Designation Granted: February 24, 2022
- Pre-BLA meeting: November 18, 2022
- VRBPAC meeting: May 18, 2023 (see Section 5.4.1 for details)
- Updated PVP to include four postmarketing pregnancy safety studies (August 2023)

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

This BLA contains safety and efficacy data from 5 studies, which were conducted in accordance with Good Clinical Practice and International Committee on Harmonization guidelines. The informed consent form for each study contained all the essential elements as stated in 21 CFR

50.25. In accordance with 21 CFR 312.120, the Applicant provided the required elements to ensure that each study conformed with Good Clinical Practice.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Studies C3671001, -1003, -1004, -1014, and -1008
Was a list of clinical investigators provided? ☒ Yes ☐ No
Total number of investigators identified: 2,642
Number of investigators who are sponsor employees (including both full-time and part-time employees): 2
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Total of 15 (the study investigator provided a disclosure form for each study that they participated in; 10 investigators participated in a single study, 1 investigator participated in 2 studies, and another investigator participated in 3 studies).
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 10 (1 investigator participated in 2 studies) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 5 (1 investigator participated in 3 studies) Is an attachment provided with details of the disclosable financial interests/arrangements? ☒Yes ☐ No Is a description of the steps taken to minimize potential bias provided? ☒Yes ☐ No
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1 Is an attachment provided with the reason? ☒ Yes ☐ No Yes, an attachment was provided (see Section 1.3.4 in the original BLA) The Applicant made additional attempts to contact the Clinical Investigator to obtain disclosable financial information in order to meet the recommendations in the FDA's Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators for certifying Due Diligence.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing were reviewed and determined to support licensure. Facility information was reviewed by the Center for Biologics Evaluation and Research (CBER) reviewers in Division of Biological Standards and Quality Control (DBSQC) and found to be sufficient and acceptable.

4.2 Assay Validation

The CMC reviewers and biostatisticians concluded that the clinical assays to confirm RSV diagnosis (Study 1008 and 1003) and serological assays to assess antibody responses of concomitantly administered Tdap and RSVpreF were adequate to support the intended use.

4.3 Nonclinical Pharmacology/Toxicology

The CBER Toxicology reviewer considered the nonclinical toxicology data to be adequate to support licensure.

4.4 Statistics

The CBER statistical reviewer confirmed the key statistical analyses for safety and efficacy and found no major statistical issues that would impact the interpretation of the data and conclusions. Please refer to the review document from the statistics team.

4.5 Pharmacovigilance

The Applicant's pharmacovigilance plan (PVP) includes serious risks such as preterm birth and HDP, in addition to other risks (i.e., Guillain-Barré syndrome [GBS] and other immune-mediated demyelinating conditions, allergic reactions, and supraventricular arrhythmias) and missing information (i.e., use in immunocompromised older adults and use in immunocompromised pregnant individuals). For the above serious risks, the Applicant will conduct enhanced pharmacovigilance activities, including expedited reporting to VAERS (regardless of seriousness or label status) for 3 years post-approval and a summary and analysis in periodic safety reports. Four planned postmarketing pregnancy safety studies to evaluate the serious risks of preterm birth and HDP include:

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

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

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

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

Please refer to the Office of Biostatistics and Pharmacovigilance, Division of Pharmacovigilance review memorandum for further details on the PVP and postmarketing safety studies, including study milestone dates.

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

5.1 Review Strategy

This BLA included clinical data from 5 studies. The clinical, labeling, and financial disclosure information sections of the application were reviewed with detailed analyses of the main trials’ study reports and pertinent line listings, case report forms (CRFs), and datasets.

5.2 BLA Documents That Serve as the Basis for the Clinical Review

The following amendments were reviewed in support of this application (listed by modules):

- Amendment 0: Modules 1 and 5
- Amendment 1: Modules 1, 2, and 5
- Amendment 2: Modules 1 and 5
- Amendment 5: Modules 1 and 5
- Amendment 6: Module 1
- Amendment 7: Modules 1 and 5
- Amendment 9: Modules 1 and 5
- Amendment 10: Module 1
- Amendment 12: Modules 1 and 5
- Amendment 13: Module 1
- Amendment 14: Modules 1 and 5
- Amendment 15: Modules 1 and 5
- Amendment 16: Modules 1 and 5
- Amendment 17: Module 1
- Amendment 18: Module 1
- Amendment 19: Modules 1 and 5
- Amendment 20: Modules 1 and 5
- Amendment 21: Module 1
- Amendment 22: Module 1
- Amendment 23: Module 1
- Amendment 24: Module 1
- Amendment 25: Module 1
- Amendment 26: Module 1
- Amendment 27: Module 1
- Amendment 28: Module 1
- Amendment 29: Module 1
- Amendment 31: Module 1
- Amendment 32: Modules 1 and 5

- Amendment 33: Module 1
- Amendment 34: Modules 1 and 5
- Amendment 36: Module 1
- Amendment 38: Modules 1 and 5
- Amendment 39: Modules 1 and 5
- Amendment 40: Modules 1 and 5
- Amendment 41: Modules 1 and 5
- Amendment 42: Modules 1 and 5
- Amendment 43: Module 1
- Amendment 44: Module 1
- Amendment 46: Module 1

5.3 Table of Studies/Clinical Trials

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=7358, n=3682 (maternal) N=7128, n=3570 (infants) Pregnant individuals/ adolescents ≤49 years and their infants	RSVpreF 120 µg (final)
C3671004	Phase 2: Safety, Immunogenicity	N=713, n=141 (co-ad), n=141 (RSVpreF alone) Non-pregnant women 18-49 years	RSVpreF 120 µg (final), RSVpreF 240 µg with $Al(OH)_3$ adjuvant, or without adjuvant Subsets: co-ad with Tdap, RSVpreF alone
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 (5 study groups) n=115 (RSVpreF 120 µg (final) group) Pregnant individuals 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=1235, n=186 Adults 18-85 years	RSVpreF 120 µg (final), RSVpreF (60 µg, 120 µg, 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; PCR=polymerase chain reaction; SIIV=seasonal inactivated influenza vaccine; 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

5.4 Consultations

5.4.1 Advisory Committee Meeting

On May 18, 2023, FDA convened at a meeting of 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. The Committee discussed the balance between the convincing VE, including against severe LRTD, and AEs, particularly premature delivery/birth. The Committee also discussed duration of vaccine protection, GA at the time of vaccination, concomitant administration of other vaccines during pregnancy, and considerations for postmarketing studies. VRBPAC members voted unanimously “yes” (n=14) that the available data were adequate to support the effectiveness of immunization with ABRYSVO during the second or third trimester of pregnancy (24-36 weeks gestation) to prevent RSV LRTD and severe RSV LRTD in infants, from birth through 6 months of age. Ten VRBPAC members voted "yes" and 4 voted "no" on whether the available data were adequate to support the safety of immunization with ABRYSVO during the second or third trimester of pregnancy (24-36 weeks gestation) to prevent RSV LRTD and severe RSV LRTD in infants, from birth through 6 months of age. Safety concerns were primarily regarding the numerical imbalance in preterm births.

5.4.2 External Consults/Collaborations

N/A

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C3671008

Title: “A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Infants Born to Women Vaccinated During Pregnancy” (NCT04424316)[1]

Study 1008 is an ongoing randomized, double-blinded, placebo-controlled Phase 3 study designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against RSV MA-LRTD and severe RSV MA-LRTD in infants.

[1] *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” or “maternal immunization” 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.*

The safety and efficacy data submitted to the BLA are based on a start date of June 17, 2020 through the data cutoff dates of September 2, 2022 and September 30, 2022, respectively. For maternal participants, the planned duration of follow-up is approximately 10 months, depending on GA at the time of vaccination and when the infant is born. For infant participants born to enrolled maternal participants during the first year of the study, the planned duration of RSV surveillance and safety follow-up is up to 24 months of age. Infants enrolled in the second year of the study will participate from the time of birth and for at least 12 months after birth.

The median safety follow-up time from the day of vaccination (Day 1) as of the safety data cutoff for the maternal safety population was 237 (range 1-679) days in the RSVpreF group and 237 (range 1-712) days in the placebo group. The median follow-up time for the infant safety population was 272 (range 1-725) days in the RSVpreF group and 267 (range 1-722) days in the placebo group.

Immunogenicity assessments for Study 1008 are not described in this memo.

6.1.1 Objectives

There were two pre-specified primary objectives: Efficacy of RSVpreF against RSV MA-LRTD and efficacy against severe RSV MA-LRTD. The study would be declared a success if the statistical criterion for *either* primary endpoint was met. The appropriate statistical controls for multiple comparisons were prespecified.

Two 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 subtype A- and subtype 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).

6.1.2 Design Overview

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 individuals 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 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. A medically attended visit refers to an evaluation for which the infant participant has been taken to or evaluated by a healthcare provider (e.g., outpatient or inpatient visit, emergency room, urgent care, or home visit).

> Reviewer Comment: *"MA-LRTD due to RSV" or "RSV MA-LRTD" and "LRTD due to RSV" or "RSV LRTD" are used interchangeably in this document and are not different outcome assessments. "LRTD due to RSV" is an outcome assessment that included a medically attended visit.*

The following AESIs are to be reported as SAEs:

- Extremely preterm birth (<28 weeks)
- Extremely LBW (≤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 AESIs are reported for maternal participants:

- Preterm delivery (delivery at <37 weeks gestation)
- Positive viral (PCR or antigen-based) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), when not reported during an 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.

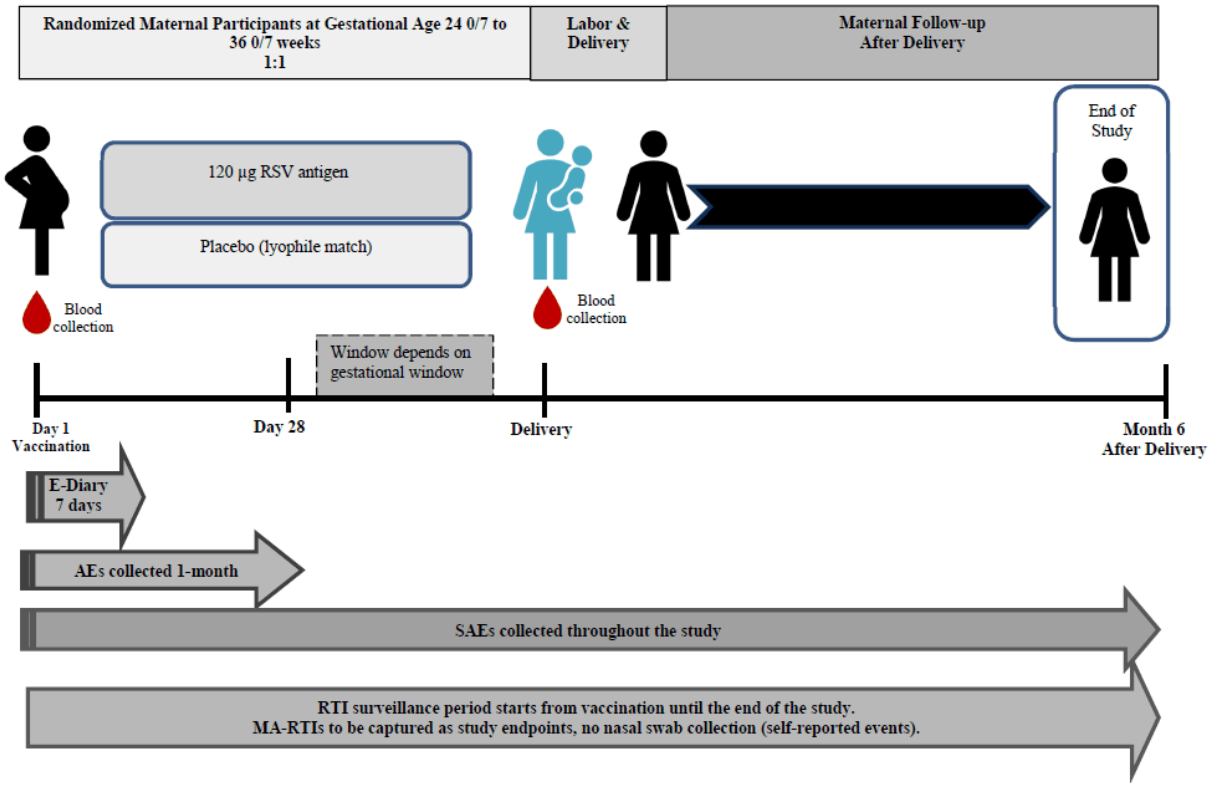
Schedule of Activities for Maternal Participants

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 (RhIG), maternal participant's GBS 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, Study 1008



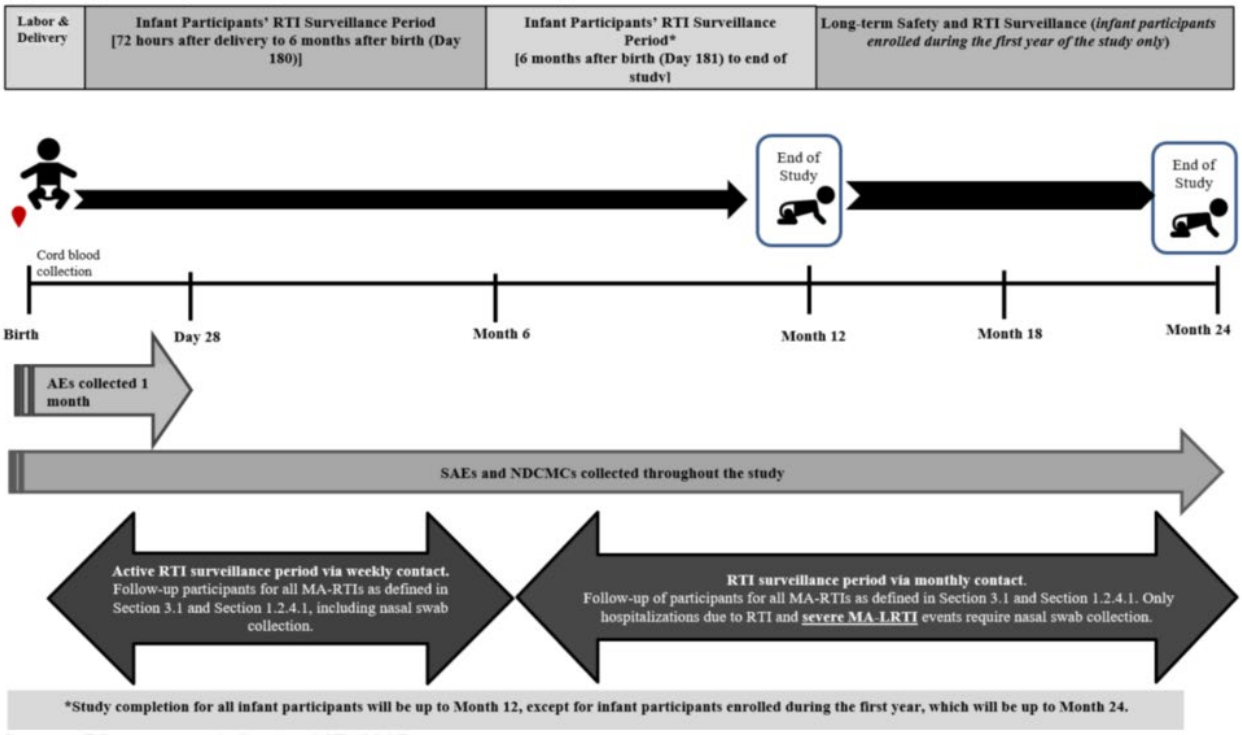
Source: Pfizer protocol, Study C3671008

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, Study 1008



Source: Pfizer protocol, Study C3671008

6.1.3 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 IP administration.
- Diagnosed malaria within the last 7 days prior to IP 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 IP administration.
- If systemic corticosteroids (equivalent of ≥20 mg/day of prednisone) have been administered short term (≤14 days) for treatment of an acute illness, IP 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.

6.1.4 Study Treatments or Agents Mandated by the Protocol RSVpreF: Investigational RSV Vaccine

- Dose and route of administration: 0.5 mL single dose intramuscular
- Formulation: 2 stabilized RSV prefusion F antigens, in equal amounts from RSV subtypes A and B. The total dose of the RSV drug product was 120 µg of the RSV prefusion F antigen (60 mcg of each stabilized RSV prefusion F antigens, A and B).
- Presentation: The antigen component was supplied as a lyophilized white cake in a glass vial. The diluent (sterile water for injection) was supplied in a pre-filled syringe (PFS).
- Lots: AT3605Z (19-001847), DX2987 (20-003765)

Placebo: Lyophile match, containing excipients matched to those in the RSVpreF vaccine formulation, without the active ingredients. The physical appearance of the reconstituted RSVpreF and placebo are similar. Lots: DC8153 (19-005013), DE0469 (19-005014).

6.1.5 Directions for Use

RSVpreF was supplied as a lyophilized antigen component (a sterile white powder) in a glass vial. For reconstitution, a pre-filled syringe (PFS) containing a sterile water diluent component and a vial adapter were used in preparing the vaccine. Detailed instructions for reconstituting the vaccine are described in Section 2.2 of the ABRYSVO package insert.

6.1.6 Sites and Centers

There were 216 sites in 18 countries: Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, and the US. A total of 7392 maternal participants were randomized to one of two study groups, with 3353 maternal participants in the US. The US, South Africa, and Argentina had the highest enrollment.

6.1.7 Surveillance/Monitoring

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.

Efficacy Monitoring

Midturbinate nasal swabs were collected from infant participants following any medically attended respiratory tract illness (MA-RTI) visit during the RSV surveillance period from birth until Visit 3, and for all hospitalizations due to RTI and severe cases of MA-LRTD during the RTI surveillance period from Visit 3 until the end of the study.

MA-RTDs in the infant participant were identified from 72 hours after birth until the end of the infant's participation in the study. If the infant participant met any RTD criteria listed below that required 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 was required.

RTD criteria were met if the infant experienced 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.

An RSV-positive test was an RSV reverse transcriptase polymerase chain reaction (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.

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 1008

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
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

Study Endpoints / Assessments	**Study Definitions**
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 test; 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.

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.

Evaluation of Safety

Safety, Maternal

- For maternal participants, a physical exam was performed, and a baseline assessment of systemic events was recorded in the electronic diary (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 (live birth at <37 weeks' gestation), LBW (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 LBW (≤1000 g).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1

6.1.9 Statistical Considerations & Statistical Analysis Plan

This study was event-driven. Planned enrollment of approximately 6900 mother-infant pairs was anticipated to result in 124 evaluable cases of RSV MA-LRTD up to 90 days after birth, assuming that the true VE was 60%. The incidence rate of RSV MA-LRTD due to RSV was estimated to be approximately 1.75% in the US and approximately 3.90% in the other geographic regions.

The following hypotheses were tested for the primary and secondary efficacy endpoints, where H_0 and H_a represented the null and alternative hypotheses, respectively:

1. Primary efficacy endpoints: H_0: VE ≤20% versus H_a: VE >20% against RSV MA-LRTD or severe RSV MA-LRTD (defined as the percentage relative risk reduction in the incidence of MA-LRTD or severe MA-LRTD due to RSV in the RSV vaccine group, relative to the placebo group).
2. Secondary efficacy endpoints: H_0: VE ≤0% versus H_a: VE >0% against hospitalization due to RSV, MA-LRTD due to RSV through 360 days, or all-cause MA-LRTD (defined as the percentage relative risk reduction in the incidence of hospitalization due to RSV, MA-LRTD due to RSV through 360 days after birth, or all-cause MA-LRTD in the RSV vaccine group, relative to the placebo group).

Statistical success for the two primary endpoints, RSV MA-LRTD and severe RSV MA-LRTD, would be declared if the lower bound of the multiplicity-adjusted CI was >20% for either of the primary endpoints. Hypothesis testing of the primary endpoints evaluated at 120, 150 and 180 days was conditional on rejection of the null hypotheses for the earlier time intervals. Hypothesis testing of the secondary endpoints was conditional upon rejection of the null hypothesis for at least 1 of the primary endpoints. The overall power was >90%.

Interim analyses

- A first interim analysis was conducted in April 2022 when 56 evaluable cases of RSV MA-LRTD up to 90 days after birth had accrued. The efficacy criterion was met for cases up to 90 days after birth but not 150 days. The E-DMC recommended continuation of the study.

- A second interim analysis was conducted on October 28, 2022 following the predicted end of the fourth RSV season in the study (efficacy data cutoff: September 30, 2022). Eighty evaluable cases of RSV MA-LRTD up to 90 days after birth had accrued, including 39 evaluable cases of severe RSV MA-LRTD. The E-DMC recommended to stop the study for efficacy because the pre-specified success criterion for VE was met

for 1 of the 2 primary efficacy endpoints, thereby triggering the final analysis for all efficacy endpoints.

6.1.10 Study Population and Disposition

This section provides an overview of the demographics and disposition of study participants. Of the 7392 maternal participants randomized to receive RSVpreF (3695) or placebo (3697), 7358 (99.5%) completed vaccination, 7148 (96.7%) completed delivery, and 5683 (76.9%) completed the study. Most withdrawals by maternal participants occurred following delivery; the most frequent reason for withdrawal was “lost to follow-up.” See Table 5 for additional details on disposition.

6.1.10.1 Populations Enrolled/Analyzed

Analysis Populations

Populations used for the study efficacy and safety analyses are displayed in Table 3 below. Note that the primary efficacy endpoint for LRTD cause by RSV was evaluated only in the infant population. There were no pre-specified efficacy endpoints or collection of efficacy data pertaining to RSV disease in pregnant individuals enrolled in the trial. The infant evaluable efficacy population was the primary population for efficacy analyses. The analyses were also performed on the infant modified intent-to-treat (mITT) efficacy population. 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, Study 1008

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 IP to which they were randomized (RSVpreF or placebo) at least 14 days prior to delivery. • Did not receive palivizumab or another mAb 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 IP.

Source: Section 9.3, C3671008 protocol
Abbreviations: mITT=modified intent-to-treat; IP=investigational product; mAb=monoclonal antibody

6.1.10.1.1 Demographics

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 4. Demographics and Other Baseline Characteristics, Maternal Participants, Safety Population, Study 1008

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[a]	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: a. Participant (b) (6) 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.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline characteristics of the maternal population including general medical and obstetric history were similar between groups. Important characteristics of the pregnant individuals enrolled in the study include:

- The majority of maternal participants were in the GA stratum of 32-36 weeks at the time of vaccination (44.7%).
- The median maternal age at the time of study vaccination was 29.0 years (range 16-45 years in the RSVpreF group).
- Most maternal participants had a history of 0 or 1 pregnancies prior to the study pregnancy.

Participant Compliance

Transmission of e-diary data was similar for both groups on each day (ranging from 89.2% to 94.6%). A total of 64.8% and 62.1% of maternal participants in the RSVpreF and placebo groups transmitted e-diary data on all 7 days, respectively.

6.1.10.1.3 Subject Disposition

Disposition of Maternal Participants

Table 5 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).

Of the 7392 maternal participants randomized to receive RSVpreF (3695) or placebo (3697), 7358 (99.5%) completed vaccination, 7148 (96.7%) completed delivery, and 5683 (76.9%) completed the study. Most withdrawals by maternal participants occurred following delivery; the most frequent reason for withdrawal was "lost to follow-up." See Table 5 for details of disposition. One (1) maternal participant in the placebo group withdrew from the study due to the AE of premature delivery.

Table 5. Disposition of Maternal Participants, Study 1008

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)
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)

Disposition	RSVpreF n (%)	Placebo n (%)	Total n (%)
Completed 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
Notes: 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 mITT efficacy population included a total of 7126 infant participants (3568 RSVpreF, 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 (PD) as described above (in “Disposition of Maternal Participants”).

Table 6. Disposition of Infant Participants, Study 1008

Disposition	RSVpreF n (%)	Placebo n (%)	Total n (%)
Enrolled[a]	3570	3558	7128
Planned 12 months follow-up	1599 (44.8)	1591 (44.7)	3190 (44.8)
Planned 24 months follow-up	1971 (55.2)	1967 (55.3)	3938 (55.2)
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	--	--	--
Not eligible unblinded during study	2 (<0.1)	0	2 (<0.1)

Disposition	RSVpreF n (%)	Placebo n (%)	Total n (%)
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)
Withdrawn after 12 months but before 18 months after birth	29 (1.5)	28 (1.4)	57 (1.4)
Completed 18 months follow-up	720 (36.5)	687 (34.9)	1407 (35.7)
Completed 24 months follow-up	3 (0.2)	3 (0.2)	6 (0.2)
Ongoing[b]	3343 (93.6)	3317 (93.2)	6660 (93.4)

Source: adapted from Pfizer CSR, Study 1008
Abbreviations: mITT=modified intent-to-treat; w/d=withdrawal
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.
b. Ongoing refers to participants who were enrolled and have not yet completed or withdrawn.

As of the safety data cutoff date (September 2, 2022), 45.6% of infant participants (1631 in the RSVpreF group and 1616 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 (3343 infants in the RSVpreF group and 3317 infants in the placebo group) were ongoing in the study. The Applicant plans to submit final data for these participants in a future report.

Reviewer Comment: *Note the discrepancy in the total number of pregnant individuals enrolled in the trial versus the total number of infants. This difference accounts for pregnant individuals who were enrolled in the study but had not yet delivered by the time of the data cutoff.*

6.1.11 Efficacy Analyses

The VE results based on case accrual through the efficacy data cutoff date of September 30, 2022 met the statistical criterion for success (a CI lower bound >20%) for reducing severe MA-LRTD due to RSV, as confirmed by the EAC, at all timepoints starting at 90 days through 180 days.

The first interim efficacy analysis for the study was conducted in April 2022 when 56 evaluable cases of MA-LRTD due to RSV within 90 days after birth had accrued in infant participants. The efficacy criterion was met for cases within 90 days after birth but not within 150 days, and the recommendation of the E-DMC was to continue the study. The double-blind was maintained after the first interim analysis. The second interim efficacy analysis was conducted on October 28, 2022, following the predicted end of the fourth RSV season in the study (two RSV seasons in each hemisphere). At this time, 80 evaluable cases of MA-LRTD due to RSV within 90 days had accrued, including 39 evaluable cases of severe MA-LRTD due to RSV within 90 days. The recommendation of the E-DMC was to stop the study for efficacy because the success criterion for VE were met for one of the two primary efficacy endpoints. This second interim analysis was considered the final analysis of the study primary efficacy objectives. For this analysis, 174 evaluable cases of RSV-positive MA-LRTD within 180 days after birth were submitted for adjudication through September 30, 2022 and included in the data cutoff.

Enrollment for maternal participants was completed on October 3, 2022. Ongoing study participants continue to remain in blinded follow-up.

6.1.11.1 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.

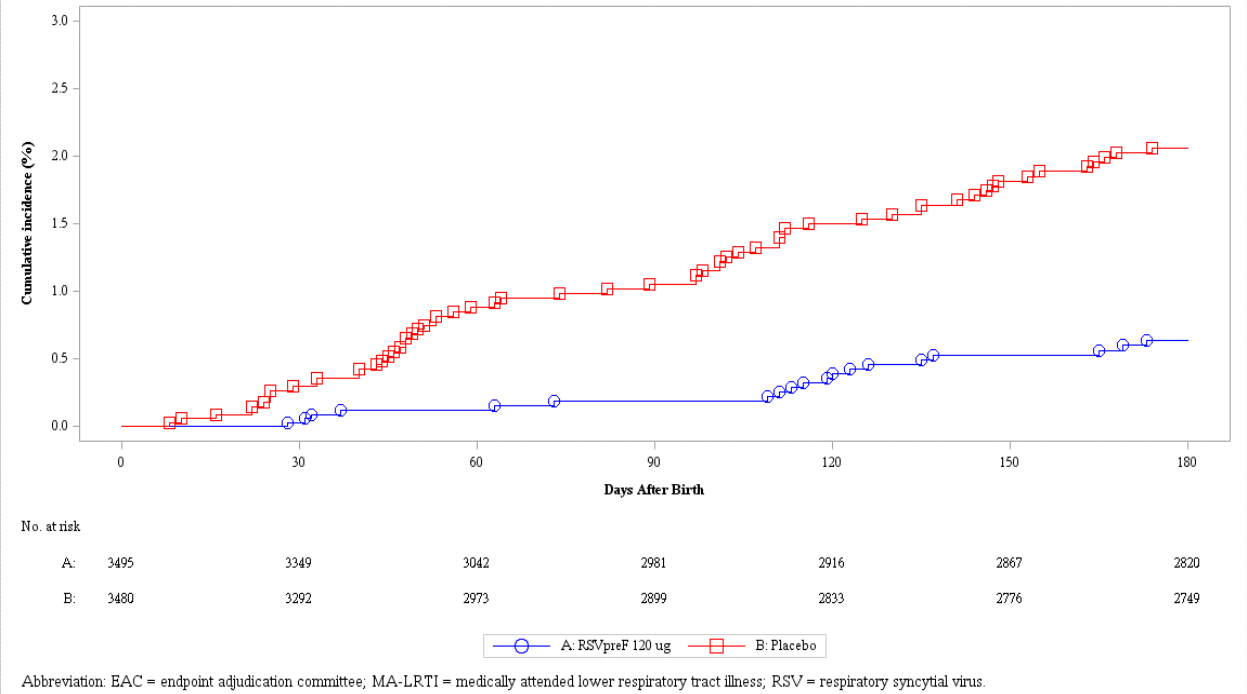
Analysis of this primary endpoint using the mITT population yielded similar results. The mITT population had 2 additional cases (8 cases) of EAC-confirmed RSV-positive severe MA-LRTD cases in infants within 90 days after birth in the RSVpreF group (corresponding to VE of 75.8%) and 1 additional case 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, Study 1008

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 disease N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations; n=number of cases; RSV=respiratory syncytial virus.
a. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
b. Confidence intervals are 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).

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, Study 1008



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 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 VE was demonstrated for severe LRTD 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, Study 1008

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.

6.1.11.2 Analyses of Secondary Endpoints

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, Study 1008

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 Days After Birth

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

6.1.11.3 Subpopulation Analyses

Study 1008 was conducted in multiple regions and countries. Subgroup analyses for selected efficacy endpoints were performed on the following variables: maternal age at vaccination, GA at vaccination, country, country income level, duration of breastfeeding, exclusive breastfeeding, maternal smoking, number of household members, and racial/ethnic subgroups. In general, VE was consistent with those observed in the main analyses without clinically meaningful differences between subgroups observed; however, these subgroup analyses should be interpreted with caution due to low numbers of participants and cases in some subgroups.

For the subgroup analyses of RSV MA-LRTD and severe RSV MA-LRTD by subgroup of GA at vaccination, a consistent trend suggestive of lower VE was noted in infants of pregnant individuals who were vaccinated between 24 to <28 weeks gestation.

6.1.11.4 Dropouts and/or Discontinuations

Few maternal participants withdrew after vaccination but before 1 month after vaccination (0.2%) or after vaccination but before delivery (0.8%). Most withdrawals by maternal participants occurred after delivery; the most frequent reason for withdrawal by maternal participants after delivery was “lost to follow-up” (2.0%). One participant in the placebo group withdrew due to an AE of premature delivery. “Lost to follow up” was also the main reason noted for withdrawal of infant participants. The number of infant participants withdrawn for other reasons were few and were comparable between the two groups. No infant participants were withdrawn due to an AE.

6.1.11.5 Exploratory and Post Hoc Analyses

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

A descriptive analysis of the subgroup who received study vaccine at 32-36 weeks was undertaken because of the safety findings in this study: the potential risk of preterm births. In a risk mitigation effort to limit vaccination to this GA group, these analyses help to describe VE in this subgroup. These analyses were also performed by the Applicant and generated identical findings. See Table 10 and Table 11 for the subgroup analysis.

Table 10. Severe RSV MA-LRTD Subgroup Analysis by Gestational Age at Vaccination, Study 1008

Time Period After Birth (Days)	GA (Weeks) at Vaccination	RSVpreF N	RSVpreF Cases n	Placebo N	Placebo Cases n	VE (%)	95% CI LL	95% CI UL
90	32-36	1572	1	1539	11	91.1	38.7	99.8
120	32-36	1572	3	1539	18	83.7	44.1	96.9
150	32-36	1572	4	1539	22	82.2	47.6	95.5
180	32-36	1572	6	1539	25	76.5	41.3	92.1

Source: FDA generated table. Adapted from Pfizer 1008 CSR and VRBPAC May 18, 2023 FDA presentation
Abbreviations: GA=gestational age; VE=vaccine efficacy; CI=confidence interval; LL=lower limit; UL=upper limit

Table 11. RSV MA-LRTD Subgroup Analysis by GA at Vaccination, Study 1008

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

Source: FDA generated table. Adapted from Pfizer 1008 CSR and VRBPAC May 18, 2023 FDA presentation
Abbreviations: GA=gestational age; VE=vaccine efficacy; CI=confidence interval; LL=lower limit; UL=upper limit

Reviewer Comment: *Subgroup analyses of RSV MA-LRTD and severe RSV MA-LRTD by subgroup of GA at vaccination suggest that VE generally remains consistent with the primary analyses when the minimum GA at vaccination is restricted to 32 weeks. For infants whose mothers were vaccinated between 32-36 weeks gestation, VE against any RSV MA-LRTD appeared lower within 90 days after birth (consistent with the study's overall finding that did not meet a prespecified statistical success criterion) but was more favorable within 180 days. For prevention of severe RSV MA-LRTD, VE in this subgroup was similar to the overall population. A trend towards lower efficacy was noted in infants of mothers who were vaccinated between 24 to <28 weeks gestation, particularly within 180 days after birth. The results should be interpreted with caution because these analyses were post-hoc and were not controlled for multiple comparisons.*

6.1.11.6 Efficacy Analysis RSV-LRTD Due to RSV A and RSV B

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 subtype B. As of the data cutoff, the number of severe MA-LRTD cases due to RSV subtype 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 subtype 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 subtype 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 subtype 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%).

6.1.12 Safety Analyses

As of the safety data cutoff date (September 2, 2022), 7392 maternal participants were randomized, 7358 (99.5%) completed vaccination, 7148 (96.7%) completed delivery, and 5,683 (76.9%) completed the study.

6.1.12.1 Methods

Prompted reactogenicity (local reactions and systemic events) was captured by maternal participants via an e-diary. A baseline assessment of systemic events within 7 days prior to vaccination was obtained. Safety events that were associated with the fetus of a maternal participant (before/during birth until an infant takes a live breath) were reported for the maternal participant. AEs and SAEs in infants are captured once the infant takes a live breath. MA-RTIs 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 through 1 month after birth. SAEs (including congenital anomalies), AESIs, and NDCMCs were collected through the infants' participation in the study (up to 12 or 24 months of age).

6.1.12.2 Overview of Adverse Events

Safety Overview- Maternal Participants

Table 12 provides an overview of the rates of AEs reported in maternal participants in the RSVpreF group compared to the placebo group during the study period.

Table 12. Overview of AEs, Maternal Participants, Safety Population, Study 1008

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 cutoff	598/3682 (16.2)	558/3675 (15.2)
Deaths to data cutoff	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 cutoff	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

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 13. Local Reactions, by Maximum Severity, Within 7 Days After Vaccination, Maternal Participants, Safety Population, Study 1008

Local Reaction	RSVpreF N=3663 n (%)	Placebo N=3639 n (%)
Any redness[a]	264 (7.2)	8 (0.2)
Mild redness[a]	182 (5.0)	4 (0.1)
Moderate redness[a]	77 (2.1)	4 (0.1)
Severe redness[a]	5 (0.1)	0
Any swelling[a]	227 (6.2)	8 (0.2)
Mild swelling[a]	150 (4.1)	5 (0.1)
Moderate swelling[a]	74 (2.0)	3 (<0.1)
Severe swelling[a]	3 (<0.1)	0
Any pain at injection site[b]	1488 (40.6)	369 (10.1)
Mild pain at injection site[b]	1321 (36.1)	337 (9.3)
Moderate pain at injection site[b]	163 (4.4)	32 (0.9)
Severe pain at injection site[b]	4 (0.1)	0
Any local reaction[c]	1556 (42.5)	378 (10.4)
Mild local reaction[c]	1297 (35.4)	343 (9.4)
Moderate local reaction[c]	249 (6.8)	35 (1.0)
Severe local reaction[c]	10 (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 14. Systemic Events by Maximum Severity Within 7 Days After Vaccination, Maternal Participants, Safety Population, Study 1008

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)	1594 (43.8)
Mild	856 (23.4)	828 (22.8)
Moderate	783 (21.4)	714 (19.6)
Severe	49 (1.3)	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)	700 (19.2)
Mild	527 (14.4)	502 (13.8)
Moderate	197 (5.4)	190 (5.2)
Severe	8 (0.2)	8 (0.2)
Any muscle pain[a]	972 (26.5)	623 (17.1)
Mild	644 (17.6)	363 (10.0)
Moderate	314 (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	47 (1.3)	56 (1.5)
Severe	7 (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)	68 (1.9)
Severe	4 (0.1)	6 (0.2)
Any systemic event[d]	2340 (63.9)	2156 (59.2)
Mild	1193 (32.6)	1087 (29.9)
Moderate	1064 (29.0)	987 (27.1)
Severe	83 (2.3)	82 (2.3)

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.

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%). The proportions of maternal participants with unsolicited non-serious AEs reported within 1 month after vaccination were 11.2% in the RSVpreF group and 10.8% in the placebo group.

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).

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 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% (207/3682 [95% CI: 4.9%, 6.4%]) versus 4.8% (175/3675 [95% CI: 4.1%, 5.5%]) in the RSVpreF and placebo groups, respectively. A numerical imbalance between groups was noted that is generally reflective of the infant 'preterm birth' safety data.

> Reviewer Comment: *In the CSR and original datasets for Study 1008, premature delivery was reported in 5.6% (206/3682) in the RSVpreF group and 4.7% (174/3675) in the placebo*

group. Discrepancies were noted by the FDA in the reports of "Premature delivery" AEs for 3 maternal subjects and "Premature baby" for their infants. The Applicant resolved these discrepancies as follows:

- *Stillbirths (6 preterm stillbirths in the RSVpreF group and 5 preterm stillbirths in the placebo group) largely accounted for the difference between AESI terms of premature delivery in maternal participants and premature birth in infant participants; while these events were reported as premature delivery, there was no associated live infant birth.*
- *Three preterm births (2 in the RSVpreF group and 1 in the placebo group) occurred in infant participants whose mothers were not initially reported as having preterm deliveries.*
- *One "premature delivery" was reported in a maternal participant in the RSVpreF group who had delivered at term.*

Following resolution of these discrepancies, the corrected rates for premature delivery as a "maternal adverse event" included 207/3682 (5.6%) in the RSVpreF group and 175/3675 (4.8%) in the placebo group.

Note: The rates of "preterm birth" as an AE for the safety sections of the package insert will reflect the rates of live preterm births among the infants observed in Study 1008: 5.7% and 4.7%, for RSVpreF and placebo groups, respectively.

Positive viral (PCR or antigen-based) testing for SARS-CoV-2, when not reported during an 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.

Subpopulation Analyses

Analyses of unsolicited AEs reported in maternal participants by demographic subgroup, including race or maternal age at vaccination, did not reveal any clinically meaningful differences across subgroups; however, small sample sizes limit the interpretability of some analyses.

Safety Overview- Infant Participants

The table below provides an overview of the rates of reported AEs in the RSVpreF group compared to the placebo group during the study period.

Table 15. Overview of AEs, Up To 24 Months Follow-Up, Infant Participants, Study 1008

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)

Adverse Event Category	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
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 cutoff	625 (17.5)	623 (17.5)
Deaths to data cutoff	5 (0.1)	12 (0.3)
Congenital anomalies	180 (5.0)	220 (6.2)
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 cutoff	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 cutoff	386 (10.8)	344 (9.7)
Premature births	202 (5.7)	169 (4.7)
Withdrawals due to AE up to data cutoff	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.

Unsolicited AEs- Infant Participants

Birth Outcomes

Approximately 94.7% of the infants were born at term, i.e., ≥37 weeks gestation. The following will describe an overview of preterm births and/or preterm deliveries, described for the maternal-infant pairs. Note that we also describe preterm deliveries, which are recorded as maternal AEs in the study. Preterm births are recorded as infant AEs.

> Reviewer Comment: *Few discrepancies between the rates of preterm deliveries and preterm births were identified on our review of these outcomes.*
>
> *Note that in Studies 1008 and 1003, "premature delivery" or "preterm delivery" were reported as maternal safety outcomes and were not limited to live births. "Premature birth," "preterm birth," or "premature baby" refer to live infant births before 37 weeks gestation*[2] *and were reported under infant safety outcomes* (CDC, 2022a; WHO, 2022).

[2] The following definitions are used throughout:
"Preterm": birth at less than 37 weeks gestation (**N.B.** "Preterm" and "premature" are synonymous in the context of a delivery/birth occurring before 37 weeks gestation) [Preterm Birth | Maternal and Infant Health | Reproductive Health | CDC; https://www.marchofdimes.org/complications/premature-babies.aspx]
"Very preterm": birth at 28 to less than 32 weeks gestation [*WHO definition:* Preterm birth (who.int)]
"Extremely preterm": birth at less than 28 weeks gestation [*WHO definition:* Preterm birth (who.int)]

Overview of Preterm Births

Table 16. Overview of Preterm Deliveries, Study 1008

Preterm Deliveries by GA at Delivery	GA at Vaccination, Maternal Subjects 32-36 Weeks RSVpreF N=69	GA at Vaccination, Maternal Subjects 32-36 Weeks Placebo N=60	GA at Vaccination, Maternal Subjects 24-36 Weeks RSVpreF N=207	GA at Vaccination, Maternal Subjects 24-36 Weeks Placebo N=175
27 to <34 weeks	2 (2.9%)	2 (3.3%)	24 (11.6%)	15 (8.6%)
27 to <32 weeks	-	-	9 (4.3%)	9 (5.1%)
32 to <34 weeks	2 (2.9%)	2 (3.3%)	15 (7.2%)	6 (3.4%)
34 to <37 weeks	67 (97.1%)	58 (96.7%)	183 (88.4%)	160 (91.4%)

Source: FDA generated table adapted from Study 1008.
Abbreviations: GA=gestational age
Notes: N=Preterm Delivery

Table 16 shows the observed numbers of preterm deliveries by GA for the subset of maternal participants who were vaccinated between 32-36 weeks and for maternal participants who were vaccinated between 24-36 weeks.

> Reviewer Comment: *Of infants born to mothers who were vaccinated prior to 32 weeks gestation, 22 infants in the RSVpreF group and 13 infants in the placebo group were delivered before 34 weeks gestation, and represent an almost 2-fold increase in the risk of preterm births. By limiting the timing of vaccination to 32-36 weeks GA, the risk of extremely preterm and very preterm births (as sub-categorized by the World Health Organization [WHO, 2022]) is eliminated. The number of births characterized as "moderate" preterm births, between 32-34 weeks GA, was observed in 2 versus 2 in the RSVpreF and placebo subgroups, respectively, of pregnant individuals vaccinated at 32-36 weeks GA.*

The AESI of premature birth was reported in 5.7% of infants (202/3568, 95% CI: 4.9%, 6.5%) in the RSVpreF group and in 4.7% (169/3558, 95% CI: 4.1%, 5.5%) in the placebo group; the difference in rates for this AESI was 0.91% (95% CI: -0.12%, 1.95%). Although the 95% CI crosses zero and therefore was not of statistical significance, we note that the study was not powered for formal hypothesis testing for safety. Nevertheless, this numerical imbalance raises safety concerns. 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 (Table 19).

Of infants born to pregnant individuals who were vaccinated between 32-36 weeks gestation, 4.2% (68/1631) in the RSVpreF group and 3.7% (59/1610) in the placebo group were born preterm. Of all preterm infants in Study 1008, approximately one-third were born to maternal participants vaccinated between 32-36 weeks. The subgroup of infants born to maternal participants vaccinated between 32-36 weeks represents approximately 45% of the clinical trial population. The majority of preterm infants were born to maternal participants who were vaccinated before 32 weeks.

An imbalance in the percentage of LBW babies was observed in the study, with 5.1% (95% CI: 4.4%, 5.8%) in the RSVpreF group and 4.4% (95% CI: 3.7%, 5.0%) in the placebo group.

Despite an imbalance in LBW infants, the rates of small for gestational age (SGA) infants were balanced between groups, with 0.9% (32/3568) in the RSVpreF group and 1.1% (38/3558) in the placebo group reported as “small for dates.”

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 LBW (≤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.

As shown in the table below, 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).

In the US, although the overall rates of preterm births were balanced, a numerical imbalance was noted in the GA range at birth of 28 to <34 weeks (see Table 18).

Table 17. Live Birth Outcomes by Subcategory of HIC, LMIC, Study 1008

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)
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 18. Live Birth Outcomes by Select Countries (US, South Africa), Study 1008

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, Study 1008

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

Table 19. Live Birth Outcomes, Infant Participants, Safety Population, Study 1008

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)
Outcome	--	--
Normal	3172 (88.9)	3149 (88.5)
Congenital malformation/anomaly[a]	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[b]	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. Numbers are lower than the numbers reported later for “Congenital Anomalies" because these events were recorded at the timing of the birth and there were a few additional anomalies noted after birth and before the data cutoff.
b. Developmental delay refers to an adverse event of special interest reported at any time after birth during the study period.

Table 20. Time From Vaccination to Delivery Among Preterm and at Term Deliveries, Maternal Participants, Safety Population, Study 1008

Days from Vaccination to Delivery	RSVpreF N=3682 n (%)	Placebo N=3675 n (%)	Total N=7357 n (%)
Live Preterm deliveries[a]	201	169	370
≤7 days	11 (5.5)	13 (7.7)	24 (6.5)
>7 days to ≤30 days	69 (34.3)	58 (34.3)	127 (34.3)
>30 days	121 (60.2)	98 (58.0)	219 (59.2)
At term deliveries[b]	3364	3386	6750
≤7 days	1 (<0.1)	2 (<0.1)	3 (<0.1)
>7 days to ≤30 days	516 (15.3)	498 (14.7)	1014 (15.0)
>30 days	2847 (84.6)	2886 (85.2)	5733 (84.9)

Source: adapted from Pfizer CSR, Study 1008
N=number of maternal participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=Number of participants in the specified category.
Note: Preterm/at term deliveries are determined based on gestational age at delivery. Preterm=gestational age at delivery less than 37 weeks. At term=gestational age at delivery of 37 weeks or more. Number of days between vaccination and delivery is calculated as birth date minus vaccination date. Percentages for this row are based on the number of preterm/at term deliveries, respectively.
a. These are the denominators for the percentages for live preterm deliveries at the time of the data cutoff of September 02, 2022.
b. These are the denominators for the percentages for live term deliveries at the time of the data cutoff of September 02, 2022. Note that one "live delivery" was a set of twins.

As shown in the table above, prematurity overall did not appear to be temporally associated with vaccination, with the majority of participants delivering outside of the 30-day AE reporting period.

Table 21. Time From Vaccination to Delivery for Preterm Live Births by Gestational Age at Vaccination, Study 1008

Gestational Age At Vaccination (Weeks)	Preterm Live Births RSVpreF N=202[a]	Preterm Live Births Placebo N=169
All (≥24)	--	--
Number of Births	202	169
Days from vaccination to birth - Mean (SD)	40.4 (23.4)	41.6 (24.94)
Days from vaccination to birth -Median (Min, Max)	37.5 (3, 88)	40 (2, 91)
24 to <28	--	--
Number of Births	63	59
Days from vaccination to birth - Mean (SD)	66 (15.20)	67.8 (13.75)
Days from vaccination to birth -Median (Min, Max)	68 (10, 88)	70 (20, 91)
28 to <32	--	--
Number of Births	71	51
Days from vaccination to birth - Mean (SD)	40 (13.64)	40.6 (14.24)
Days from vaccination to birth -Median (Min, Max)	41 (5, 63)	40 (12, 63)
32 to <34	--	--
Number of Births	40	32
Days from vaccination to birth - Mean (SD)	22.2 (7.19)	21.2 (7.74)

Gestational Age At Vaccination (Weeks)	Preterm Live Births RSVpreF N=202[a]	Preterm Live Births Placebo N=169
Days from vaccination to birth -Median (Min, Max)	23 (8, 34)	20 (4, 34)
≥34	--	--
Number of Births	28	27
Days from vaccination to birth - Mean (SD)	10 (4.27)	10.1 (5.26)
Days from vaccination to birth -Median (Min, Max)	10 (3, 19)	10 (2, 20)

Source: Adapted from datasets and CSR, Study 1008.
Notes: N=subset of infants born preterm out of the entire study population.
a. There were 201 live preterm deliveries in the RSVpreF group resulting in 202 live births, as 1 pregnancy was a twin pregnancy.

As shown in the table above, an analysis of the time from vaccination to the time of preterm delivery did not show a difference between the RSVpreF group and the placebo group and the median time from vaccination to preterm birth delivery was approximately 40 days. While an underlying pathophysiologic mechanism for the vaccine increasing the risk of preterm birth has not been determined, vaccination with RSVpreF was not shown to be associated with a "prompt" delivery.

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). The proportions of infant participants with unsolicited non-serious AEs within 1 month after birth were 28.4% in RSVpreF group and 26.2% in 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.

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 preferred term, 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.

In general, most AEs in infant participants were commonly occurring events during the neonatal period, e.g., neonatal jaundice (7.2% versus 6.8%), neonatal hyperbilirubinemia (3.0% versus 2.9%), respiratory distress (1.9% versus 1.8%), and neonatal respiratory distress (0.5% versus 0.6%). There were no trends observed to suggest these events were attributable to vaccination of maternal participants, with the exception of the imbalance in preterm births.

Newly Diagnosed Chronic Medical Conditions

An 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.

6.1.12.3 Deaths

Maternal 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 hypovolemic shock secondary to postpartum hemorrhage following a home birth. FDA agrees that this maternal death was not associated with vaccine administration.

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, terms that 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. No 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 IP.

Most infant deaths occurred in South Africa. There were 10 infant deaths in South Africa, 1 in Gambia, 1 in Brazil, 3 in US, 1 in Japan, and 1 in the Philippines. 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 IP. The FDA is unable to draw definitive conclusions regarding potential relation of this case of extreme prematurity to the IP.

There were 2 deaths in the RSVpreF group and 5 in the placebo group that occurred during the neonatal period (<1 month 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 at 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, there was 1 infant in the placebo group who died with an adjudicated diagnosis of “acute respiratory illness due to RSV.”

Infant deaths and preterm births subsequent to the data cutoff

Subsequent to the data cutoff of September 2, 2022, there were 7 additional preterm births (4 in the RSVpreF and 3 in the placebo group) and 8 additional LBW infants (5 in the RSVpreF group and 3 in the placebo group) since the primary analysis. There were 5 additional deaths (3 in the RSVpreF and 2 in the placebo group).

6.1.12.4 Nonfatal Serious Adverse Events

Serious Adverse Events- Maternal Participants

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 preferred term in the RSVpreF group (≥1.0%) were preeclampsia (1.8%), fetal distress syndrome (1.8%), gestational hypertension (1.1%), non-reassuring 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. This event resolved 1 day later, and the infant was delivered at term.
- SLE with thrombocytopenia noted 6 days after vaccination. The participant was diagnosed 5 months later with SLE and the episode of thrombocytopenia was attributed to SLE.
- Eclampsia diagnosed 15 days after vaccination, at 38 weeks gestation. The participant developed 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.

Reviewer Comment: *Pain was observed with greater frequency among vaccinated individuals, and the resolution of severe pain in the extremities has potential to represent a safety concern and will be included in safety labeling of local and systemic adverse reactions. Preterm births and HDPs are potential safety risks and will be under active postmarketing surveillance with several required studies to evaluate these safety signals. FDA agrees with the subsequent ascertainment that the one SAE of thrombocytopenia is likely related to an underlying SLE disorder and likely not attributable to study vaccination.*

Placebo group:

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

An analysis of maternal SAEs of interest was performed, specifically for pregnancy-related conditions most likely to result in delivery for obstetric indications; e.g., HDP, PROM, and PPROM. HDP and PROM could warrant prompt delivery for maternal or fetal indications; e.g., are associated with an increased risk of preterm delivery. Overall, these pregnancy related SAEs of interest were reported in 152 (4.1%) vaccinated maternal participants and 120 (3.3%) placebo recipients, with the following frequencies: preeclampsia in 68 (1.8%) versus 53 (1.4%), hypertension in 13 (0.4%) versus 6 (0.2%), gestational hypertension in 41 (1.1%) versus 38 (1.0%), and PPROM in 15 (0.4%) versus 10 (0.3%) maternal participants who received RSVpreF versus placebo, respectively. See Table 22 below.

Table 22. Pregnancy-Related SAEs, Maternal Safety Population, Study 1008

Preferred Term	RSVpreF 120 µg (N=3682) n (%)	Placebo (N=3675) n (%)	RD (%) 95% CI	RR 95% CI
Select pregnancy-related SAE[a]	**152 (4.1)**	**120 (3.3)**	**0.9 (0.0, 1.7)**	**1.3 (1.0, 1.6)**
Eclampsia	3 (0.1)	2 (0.1)	0.0 (-0.1, 0.1)	1.5 (0.3, 9.0)
Gestational hypertension	**41 (1.1)**	**38 (1.0)**	0.1 (-0.4, 0.6)	1.1 (0.7, 1.7)
HELLP syndrome	2 (0.1)	3 (0.1)	-0.0 (-0.1, 0.1)	0.7 (0.1, 4.0)
Hypertension	**13 (0.4)**	**6 (0.2)**	0.2 (-0.0, 0.4)	2.2 (0.8, 5.7)

Preferred Term	RSVpreF 120 µg (N=3682) n (%)	Placebo (N=3675) n (%)	RD (%) 95% CI	RR 95% CI
Preeclampsia	**68 (1.8)**	**53 (1.4)**	0.4 (-0.2, 1.0)	1.3 (0.9, 1.8)
Premature rupture of membranes	15 (0.4)	16 (0.4)	-0.0 (-0.3, 0.3)	0.9 (0.5, 1.9)
Preterm premature rupture of membranes	**15 (0.4)**	**10 (0.3)**	0.1 (-0.1, 0.4)	1.5 (0.7, 3.3)
Superimposed preeclampsia	0 (0.0)	2 (0.1)	-0.1 (-0.1, 0.0)	N/A

Source: Adapted from CSR Study C3671008
Abbreviations: SAE=serious adverse event; RD=risk difference; RR=relative risk
Notes: Subjects filtered for safety population. Events filtered to treatment-emergent events. Percentages calculated with premature delivery subgroup totals as denominator. All counts represent unique subjects within each subgroup. Analysis in table includes after vaccination to 6 months after delivery.
a. Conditions do not make up all pregnancy-related SAEs for maternal subjects, only the following select pregnancy-related conditions of interest potentially associated with preterm delivery are reported here: eclampsia, gestational hypertension, HELLP syndrome, hypertension, pre-eclampsia, premature rupture of membranes, preterm premature rupture of membranes, superimposed pre-eclampsia.

Reviewer Comment: *The estimated background prevalence of HDP in the general population is approximately 14.6% (*Ford, 2022*). The rate of hypertensive disorders of pregnancy in this trial was considerably lower than 14.6%, likely because participants enrolled in the trial represented a "healthier" pregnant population. Nevertheless, postmarketing safety requirements will be evaluating the potential risk of HDP.*
The extent of long-term sequelae on maternal health following a diagnosis of HDP is not fully established.

*"Years after a pregnancy complicated by preeclampsia, women are at increased risk of chronic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, kidney disease, thromboembolism, hypothyroidism, and even impaired memory… A vulnerability to future cardiovascular disease after a preeclamptic pregnancy has been recognized… After preeclampsia, but before the clinical onset of cardiovascular and renovascular disease, there may be evidence of subclinical pathology recognized as components of the metabolic syndrome. This includes obesity, endothelial dysfunction, sympathetic overactivity, increased peripheral vascular and renovascular resistance, insulin resistance, and hyperlipidemia. This is followed by often-silent conditions that include hypertension, diabetes, and renal impairment, which appear more likely to develop after a preeclamptic pregnancy. This often will lead to premature coronary artery disease, overt renal disease, and a reduced life expectancy" (*Williams, 2011*).*

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 23. Serious Adverse Events of Congenital Anomalies by System Organ Class Preferred Term, Infant Participants, Safety Population, Study 1008

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)
Ventricular septal defect	15 (0.4)	20 (0.6)
Pulmonary valve stenosis	6 (0.2)	6 (0.2)
Bicuspid aortic valve	3 (<0.1)	0
Coarctation of the aorta	2 (<0.1)	2 (<0.1)
Heart disease congenital	1 (<0.1)	1 (<0.1)
Left-to-right cardiac shunt	1 (<0.1)	1 (<0.1)
Hypoplastic left heart syndrome	0	1 (<0.1)
Pulmonary artery stenosis congenital	0	1 (<0.1)
Congenital aortic anomaly	0	1 (<0.1)
Other Congenital, familial, and genetic disorders[b]	4 (0.1)	6 (0.2)
Trisomy 21	3 (<0.1)	2 (<0.1)
Cleft palate	0	2 (<0.1)
Congenital central nervous system anomaly	1 (<0.1)	0
Cleft lip and palate	0	1 (<0.1)
Spina bifida occulta	0	1 (<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 24. 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, Study 1008

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

6.1.12.5 Subpopulation Analyses

Subgroup analyses of AEs reported in infant participants by race, sex, or maternal age at vaccination did not show clinically meaningful differences between study groups. Results by maternal age should be interpreted with caution due to the low number of maternal subjects less than 18 years of age.

Subgroup analyses of live birth outcomes (LBW) by country for the infant safety population showed a higher incidence of prematurity and LBW infants in South Africa and Argentina. In South Africa, prematurity was reported in 8.3% (39/469) in the RSVpreF group and 4.0% (19/471) in placebo group and was noted to be a statistically significant difference (though these safety analyses were descriptive and the study was not powered for formal hypothesis testing for safety); LBW occurred in 10.4% (49/469) of infants in the RSVpreF group and 6.8% (32/471) in the placebo group. In Argentina, prematurity was reported in 6.4% (27/423) in the RSVpreF group and 4.0% (17/416) in the placebo group; LBW occurred in 2.6% (11/423) in the RSVpreF group and 1.2% (5/416) in the placebo group. In the US, prematurity was reported in 5.7% (94/1644) in the RSVpreF group versus 5.3% (87/1644) infants, of which 11 infants (0.7%) in the RSVpreF group and 5 (0.3%) in the placebo group were born during between 28 weeks to <34 weeks gestation; 4.2% (70/1654) in the RSVpreF group and 4.0% (65/1644) in the placebo group were LBW.

> Reviewer Comment: *Although the overall rates of preterm birth in the US were similar between the RSVpreF group and placebo, a numerical imbalance was observed for the GA range at birth of 28 to <34 weeks, with twice as many preterm births occurring in the vaccine group compared to the placebo group* (Table 18)*, similar to the imbalance in preterm births observed in the entire trial population.*

6.1.12.6 Dropouts and/or Discontinuations

One maternal participant in the placebo group withdrew from the study due to the AE of premature delivery. No infant participants were withdrawn from the study due to an AE.

6.1.13 Study Summary and Conclusions

Efficacy Summary/Conclusions

The statistical criterion for success was met for the primary efficacy endpoint of severe MA-LRTD due to RSV in infants, at all timepoints from 90 days through 180 days after birth. Maternal vaccination with RSVpreF was 81.8% (99.5% CI: 40.6%, 96.3%) efficacious in preventing incidence of severe MA-LRTD due to RSV in infant participants within 90 days after birth, and 69.4% (97.58% CI: 44.3%, 84.1%) efficacious in preventing incidence of severe MA-LRTD due to RSV in infant participants within 180 days after birth.

The statistical criterion for success was not met for the primary efficacy endpoint of MA-LRTD due to RSV in infants; however, clinically meaningful efficacy was observed at all timepoints from 90 days through 180 days after birth. Maternal vaccination with RSVpreF was 57.1% (99.5% CI: 14.7%, 79.8%) efficacious in preventing incidence of MA-LRTD due to RSV in infant participants within 90 days after birth, and 51.3% (97.58% CI: 29.4%, 66.8%) efficacious in preventing incidence of MA-LRTD due to RSV in infant participants within 180 days after birth.

RSVpreF demonstrated efficacy in prevention of RSV-associated hospitalizations through 180 days after birth. Maternal vaccination with RSVpreF was 67.7% efficacious in preventing incidence of infant hospitalization (secondary objective met) within 90 days after birth due to

RSV (99.17% CI: 15.9, 89.5) and 56.8% efficacious in preventing incidence of infant hospitalization within 180 days after birth due to RSV (99.17% CI: 10.1, 80.7).

For infants whose mothers were vaccinated between 32 through 36 weeks gestation, VE was consistent with the VE findings in the overall study population. For example, just as VE against severe RSV MA-LRTD met a success criterion for VE in the overall study population within 90 days to 180 days after birth, the subgroup at 32 through 36 weeks gestational age showed similarly robust VE findings at all time points within 90 days to 180 days after birth. Also similar between the overall study population and the subgroup at 32 through 36 weeks gestational age were the VE findings against any RSV MA-LRTD, in which a success criterion was not met within 90 days after birth but showed strong evidence of VE within 180 days after birth. A trend towards lower efficacy was noted in the subgroup analysis of infants of mothers who were vaccinated between 24 to <28 weeks gestation, particularly within 180 days after birth.

Safety Summary/Conclusions

Administration of RSVpreF showed local reactions that were more common in the RSVpreF group and were generally mild to moderate in severity, with a median duration of 2.0 days. The most common local reaction for RSVpreF recipients was pain at the injection site (40.6%). Severe local reactions were reported for 0.3% of RSVpreF recipients.

Systemic events were reported at a similar frequency for both groups and were generally mild to moderate in severity, with a median duration of 1.0 to 3.0 days. The most common systemic event for RSVpreF recipients was fatigue (46.1%); muscle pain (26.5%), and headache (31.0%). Severe systemic events were reported for 2.3% of RSVpreF recipients. The incidence of fever was low and was similar for RSVpreF and placebo groups (≤2.9%); most were low-grade. Most solicited adverse reactions resolved within 3-4 days post-vaccination.

A numerical imbalance was noted in HDP. Overall, pregnancy related SAEs (HDP, PROM, and PPROM) were reported in 152 amongst vaccinated maternal participants versus 120 in the placebo group, with 68 cases of preeclampsia in maternal participants who were vaccinated with RSVpreF and 53 cases in those who received placebo. This finding is considered a potential risk and will be evaluated in 4 separate postmarketing requirement (PMR) studies.

Premature delivery was reported as an AESI for maternal participants in 5.6% [95% CI: 4.9%, 6.4%] versus 4.8% [95% CI: 4.1%, 5.5%] in the RSVpreF and placebo groups, respectively; and preterm births (as an AE for infants) occurred in 5.7% [95% CI: 4.9%, 6.5%] and 4.7% [95% CI: 4.1%, 5.5%] in the RSVpreF and placebo groups, respectively. Note that preterm birth (an *infant* adverse reaction) rates were consistent with the maternal premature delivery rates. We note the numerical difference between the study arms as a *potential for* risk signal which will be evaluated in PMR studies.

Restricting the indication for vaccination to 32-36 weeks appears to provide a more favorable balance of risk and benefit.

6.2 Study C3671004

NCT04071158
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."

Participants were randomized to 1 of 5 vaccine groups, and received 2 injections administered concomitantly:

- RSVpreF 120 µg and Placebo (saline)
- RSVpreF 120 µg and Tdap
- RSVpreF 240 µg + $Al(OH)_3$ and Placebo
- RSVpreF 240 µg + $Al(OH)_3$ and Tdap
- Placebo and Tdap

6.2.1 Objectives

Primary Immunogenicity Objectives

The objectives of Study 1004 were to evaluate the safety and immunogenicity of Tdap when concomitantly administered with RSVpreF.

1. To demonstrate that the immune responses induced by Tdap when administered concomitantly with RSVpreF are noninferior to immune responses induced by Tdap alone. The endpoints were the percentage of participants with tetanus toxoid (TT) immunoglobulin G (IgG) antibody concentrations ≥0.1 IU/mL, the percentage of participants with diphtheria toxoid (DT) IgG antibody concentrations ≥0.1 IU/mL, and geometric mean concentration (GMC) ratios for each of the pertussis antigens (pertussis toxin [PT], filamentous hemagglutinin adhesin [FHA], pertactin [PRN]). Timepoint: 1 month after vaccination.

   Noninferiority (NI) would be demonstrated if the lower limit (LL) of the 2-sided 95% CI for the
   - difference (combined RSVpreF $_{(120µg, 240µg)}$ /Tdap groups minus Tdap group) in the percentage of participants with anti-TT concentrations ≥0.1 IU/mL was > -10%
   - difference (combined RSVpreF $_{(120µg, 240µg)}$ /Tdap groups minus Tdap group) in the percentage of participants with anti-DT concentrations ≥0.1 IU/mL was > -10%
   - GMC ratio (combined RSVpreF $_{(120µg, 240µg)}$ /Tdap groups divided by Tdap group) was >0.67 for each pertussis antigen (PT, FHA, and PRN).

2. To demonstrate that the immune responses induced by RSVpreF when administered concomitantly with Tdap are noninferior to the immune responses induced by RSVpreF alone.
   The endpoints were the geometric mean titer (GMT) ratios for RSV A- and RSV B-neutralizing antibody titers. Timepoint: 1 month after vaccination.

   NI would be demonstrated if the LL of the 2-sided 95% CI for the GMT ratio (combined RSVpreF $_{(120\ µg, 240\ µg)}$ /Tdap groups divided by combined RSVpreF $_{(120\ µg, 240\ µg)}$ groups) was >0.5.

6.2.2 Design Overview

This study was a Phase 2, placebo-controlled, randomized, observer-blind study. A total of 713 non-pregnant women, 18 through 49 years of age (hereafter abbreviated 18-49 years of age), were randomized in a 1:1:1:1:1 ratio to 1 of 5 vaccine groups. Since the physical appearance of the RSV vaccine, Tdap, and placebo differed, personnel administering the study products were unblinded to the vaccine assignment. Safety information was collected by other study staff.

Safety parameters were assessed through 1 month after the vaccination visit. Antibody responses to the antigens contained in RSVpreF and Tdap were measured 1 month after vaccination.

6.2.3 Population

The study population consisted of women 18-49 years of age. Individuals with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before study enrollment, were eligible to participate in the study.

Key exclusion criteria were as follows:

- Pregnant or breastfeeding.
- Vaccination within 5 years with DTs and TTs and acellular pertussis vaccine adsorbed (DTaP) or tetanus and diphtheria toxoids adsorbed (Td) vaccine before IP administration, per the Boostrix package insert.
- Previous vaccination with any licensed or investigational RSV vaccine, or planned receipt of non-study RSV vaccine throughout the study.
- History of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, GBS, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin dependent Type 1 diabetes mellitus.
- Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction/anaphylaxis to any component of vaccines being administered in the study.
- Immunocompromised participants with known or suspected immunodeficiency.
- Treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

- RSVpreF: supplied as a lyophilized mixture of equal quantities of 2 stabilized prefusion RSV F antigens, one from each of the RSV subtypes A and B.

- The dose level of 120 µg RSV antigen (Lot# AT3605Z) was reconstituted with sterile water for injection (Lot# 6016778). The 240 µg dose was reconstituted with sterile $Al(OH)_3$. After reconstitution, each dose was approximately 0.5 mL.

- Tdap [Boostrix]: each 0.5 mL dose contains 5 Lf (limits of flocculation) of TT, 2.5 Lf of DT, acellular pertussis antigens (8 µg of inactivated pertussis toxin [PT], 8 µg of filamentous hemagglutinin [FHA], and 2.5 µg of pertactin [PRN]). Lot# 2Y74B.

- Placebo: 0.9% sodium chloride. Lot# 18-000719.

6.2.5 Directions for Use

See Section 6.2.4 (diluents for reconstitution of lyophilized RSVpreF). Please refer to the ABRYSVO package insert for more detailed directions.

6.2.6 Sites and Centers

A total of 713 subjects were randomized at 16 sites in the US.

6.2.7 Surveillance/Monitoring

Solicited local reactions (redness, swelling, pain at the injection site) and systemic events (fatigue, headache, vomiting, nausea, diarrhea, muscle pain, joint pain) were collected daily on Day 1 (day of vaccination) through Day 7 and recorded in an e-diary. For study groups receiving RSVpreF concomitantly with placebo (saline) or Tdap, local reactions were assessed at the RSVpreF injection site. For the study group receiving placebo (saline) and Tdap concomitantly, local reactions were assessed at the saline injection site. AEs, medically attended adverse events (MAEs), and SAEs were assessed through 1 month after vaccination(s). An E-DMC reviewed unblinded data during closed meeting sessions.

6.2.8 Endpoints and Criteria for Study Success

See Section 6.2.1

6.2.9 Statistical Considerations & Statistical Analysis Plan

Please see Section 6.2.1 for objectives, endpoints, and statistical criteria.

Planned enrollment of 710 participants would result in 128 evaluable participants per study group, assuming a non-evaluable rate of 10%. The overall power to demonstrate NI on all 7 primary endpoints is 92.1%.

Main changes to the planned analyses for the study were made and documented in Protocol Amendment 1 (dated September 17, 2019) and SAP Amendment 1 (dated November 8, 2019). Per CBER recommendations, a key secondary immunogenicity objective was added to evaluate NI based on 1.5-fold differences in RSV GMT ratios, for RSV-A and RSV-B antigens, and the study sample size was increased from approximately 680 participants to approximately 710 participants.

6.2.10 Study Population and Disposition

The disposition and demographic characteristics only for the final formulation of RSVpreF (120 µg) and the comparator group (placebo/Tdap) are presented in this section.

6.2.10.1 Populations Enrolled/Analyzed

- Safety: defined as randomized participants who received at least 1 dose of the IP.
- Evaluable: defined as participants who receive all doses of the IPs to which they were randomized, had blood drawn for assay testing within the specified time frame, had at least 1 valid and determinate assay result at the 1-month post-vaccination visit, and had no major protocol violations.

6.2.10.1.1 Demographics

The study population consisted of female participants aged 18 to 49 years, with a mean age of 35.6 years (median 37, range 18-49). Demographic characteristics were similar across vaccine groups.

Table 25. Demographic Characteristics, Safety Population, Study 1004

Demographic Characteristics	RSVpreF 120 µg / Placebo N=141 n (%)	RSVpreF 120 µg / Tdap N=141 n (%)	Placebo/Tdap N=141 n (%)
Sex: Female	141 (100.0)	141 (100.0)	141 (100.0)
Race	--	--	--
White	100 (70.9)	98 (69.5)	97 (68.8)
Black or African American	29 (20.6)	28 (19.9)	38 (27.0)
Asian	12 (8.5)	9 (6.4)	5 (3.5)
American Indian or Alaska Native	0	2 (1.4)	1 (0.7)
Native Hawaiian or Other Pacific Islander	0	1 (0.7)	0
Multiracial	0	2 (1.4)	0
Not reported	0	1 (0.7)	0
Ethnicity:	--	--	--
Hispanic or Latino	23 (16.3)	16 (11.3)	16 (11.3)
Non-Hispanic/non-Latino	116 (82.3)	125 (88.7)	125 (88.7)
Not reported	2 (1.4)	0	0
Age at vaccination (years): Mean (SD)	35.6 (9.2)	35.7 (8.7)	34.4 (9.2)
Age at vaccination (years): Median (min, max)	39.0 (19, 49)	38.0 (18, 49)	35.0 (18, 49)

Source: Table 5, adapted from Pfizer CSR, Study 1004
Abbreviations: N=number of participants in the specified vaccine group. These values were used as the denominators for the percentage calculations; n=number of participants in the specified category.

6.2.10.1.2 Subject Disposition

Table 26. Participant Disposition (RSVpreF 120 µg groups, Placebo/Tdap group), Study 1004

Disposition	RSVpreF 120 µg/ Placebo N=143 n (%)	RSVpreF 120 µg/ Tdap N=143 n (%)	Placebo/ Tdap N=141 n (%)	Total N=427 n (%)
Randomized	143 (100.0)	143 (100.0)	141 (100.0)	427 (100.0)
Safety population	141 (98.6)	141 (98.6)	141 (100.0)	423 (99.1)
Evaluable immunogenicity population	135 (94.4)	135 (94.4)	134 (95.0)	404 (94.6)
Completed 1-month post-vaccination visit	140 (97.9)	139 (97.2)	136 (96.5)	415 (97.2)

Source: C3561004 report.pdf, Table 3 and Table 4.
Abbreviation: N=number of randomized participants in the vaccine group. These values were used as the denominators for the percentage calculations; n=number of participants in the specified category.

Of the 423 participants in the safety population for study groups who received RSVpreF 120 µg/Tdap, RSVpreF 120 µg/placebo, or Placebo/Tdap, 404 (94.6%) participants were included in the evaluable population. The most common reason for exclusion from the evaluable populations was that participants did not have at least 1 valid and determinate assay result. Lost to follow-up was the most common reason for withdrawal before the 1-month post-vaccination visit.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoints

Percentages of Participants with Anti-DT and Anti-TT IgG Antibody Concentrations ≥0.1 IU/mL

The NI criteria were met for both anti-DT and anti-TT immune responses; at 1-month post-vaccination, the LL of the 2-sided 95% CI for the difference (combined RSVpreF/Tdap groups minus placebo/Tdap group) in the percentages of participants was >-10% for anti-DT and anti-TT (-4.6% and -1.4%, respectively). The percentages of participants with anti-DT and anti-TT antibody concentrations ≥0.1 IU/mL prior to vaccination were similar for the combined RSVpreF/Tdap groups and the placebo/Tdap group.

Pertussis Antibody GMC Ratios

At 1 month after vaccination, the LL of the 2-sided 95% CI of the GMC ratio ($GMC_{\text{combined RSVpreF (120µg, 240µg)}}$ /GMC_{Tdap}) was 0.64 for PT, 0.50 for FHA, and 0.48 for PRN, which did not meet the non-inferiority criterion (lower limit of the 95% CI for the GMC ratio was >0.67).

RSV Neutralizing Antibody GMT Ratios

The NI criterion for RSV A and RSV B immune responses was met; the LL of the 2-sided 95% CI was >0.5 for the GMT ratio (combined RSVpreF/Tdap groups divided by combined RSVpreF/placebo groups) for RSV A- and RSV B-neutralizing GMT. The RSV A and RSV B 50% neutralizing titer geometric mean ratios (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 LL of the 2-sided 95% CIs for RSV A and RSV B 50% neutralizing titer GMT ratios were 0.84 and 0.81, respectively.

6.2.11.2 Analyses of Secondary Endpoints

Since the primary objective for demonstrating NI of RSV responses was met, the secondary objective of NI of RSV responses was tested using a more stringent 1.5-fold margin. Per the predefined threshold for determining NI 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 NI 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 = 0.84 and 0.81 at 1 month after vaccination).

6.2.11.3 Subpopulation Analyses

The sample sizes of approximately 140 in each of the groups were too small in this Phase 2 study to draw meaningful conclusions from subpopulation analyses

6.2.11.4 Exploratory Analysis

Reduced GMCs to all pertussis antigens were still observed among participants who received RSV 120 µg/Tdap versus Tdap only.

Table 27. Ratio of Pertussis Antibody GMCs at 1 Month After Tdap Administered Concomitantly With RSVpreF (120µg), Evaluable Immunogenicity Population, Study 1004

Pertussis Antigen	RSVpreF 120µg/Tdap GMC N=135	Placebo/Tdap GMC N=134	GMC ratio (RSVpreF 120 µg/Tdap divided by Tdap) (95% CI)
PT	40.5	45.9	0.88 (0.68, 1.14)
FHA	119.5	191.3	0.62 (0.52, 0.76)

Pertussis Antigen	RSVpreF 120µg/Tdap GMC N=135	Placebo/Tdap GMC N=134	GMC ratio (RSVpreF 120 µg/Tdap divided by Tdap) (95% CI)
PRN	148.3	257.1	0.58 (0.45, 0.74)

Source: C3671004 report.pdf, adapted from Table 14.
Abbreviations: GMC=geometric mean concentration; GMR=geometric mean ratios; LLOQ=lower limit of quantitation; PT=pertussis toxin; FHA=filamentous hemagglutinin; PRN=pertactin.
Note: The LLOQ values for each antibody were: Anti-PT=0.9 EU/mL, Anti-FHA=2.9 EU/mL, and Anti-PRN=3.0 EU/mL. Assay results below the LLOQ were set to 0.5 × LLOQ.
N=evaluable immunogenicity population, defined as participants who receive all doses of the investigational products to which they were randomized, had blood drawn for assay testing within the specified time frame, had at least 1 valid and determinate assay result at the 1 month post-vaccination visit, and had no major protocol violations.

6.2.12 Safety Analyses

6.2.12.1 Methods

See Section 6.1.7 of Study 1008. The methods of safety data collection and analyses were identical between these studies.

6.2.12.2 Overview of Adverse Events

Of 709 vaccinated participants, 282 received the final formulation of RSVpreF (120 µg). Table 28, which pertains to participants who received the final formulation, provides an overview of the rates of AEs in the concomitant administration groups compared to the control group. Solicited local and systemic AEs 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 RSVpreF and Tdap concomitantly compared to local reactions in participants receiving RSVpreF or Tdap alone. 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 28. Overview of Adverse Events, Safety Population, Study 1004

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, Study C3671004
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.
a. 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.

6.2.12.3 Deaths

No maternal or infant participants died during the study.
One (1) SAE of spontaneous abortion (fetal death) was reported by a participant in the RSVpreF 240 µg + $Al(OH)_3$/placebo group after Visit 2 (Day 42), which was not considered by FDA to be related to study vaccination.

6.2.12.4 Nonfatal Serious Adverse Events

There were no SAEs reported in the other study groups.

6.2.12.5 Dropouts and/or Discontinuations

No participants were withdrawn during the study for safety-related reasons.

6.2.13 Study Summary and Conclusions

The NI criteria for tetanus, diphtheria and RSV vaccine antigens were met. Lower GMCs to the acellular pertussis antigens (PT, FHA, and PRN) when RSVpreF (120 µg or 240 µg+Alum) was administered concomitantly with Tdap compared to pertussis GMCs when Tdap was administered alone; the LL of the 2-sided 95% CI of the GMC ratio ($GMC_{RSVpreF/Tdap}/GMC_{Tdap}$) was 0.64 for PT, 0.50 for FHA, and 0.48 for PRN, which did not meet the pre-specified non-inferiority criterion (lower limit of the 95% CI for the GMC ratio was >0.67). Similar results were observed when pertussis GMCs were analyzed by RSV formulation (exploratory analysis). Because there are no established serological correlates of protection for pertussis, the clinical implications of the lowered responses to pertussis antigens are unknown. Likewise, whether similar results observed when Tdap and RSVpreF are concomitantly administered to mothers during the third trimester of pregnancy would result in diminished effectiveness against pertussis in the mother is unknown.
There were no safety signals observed in this study.

6.3 Study C3671003

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” (NCT 04032093)

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

6.3.1 Objectives (Primary, Secondary)

Primary Safety Objective: Maternal Participants

To describe the safety and tolerability of an RSV vaccine in women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.
Endpoints: The percentage of maternal participants reporting:

- 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
- Obstetric complications, MAEs, and SAEs throughout the study

Primary Safety Objective: Infant Participants

To assess the safety of maternal immunization in infants born to women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.
Endpoints: The percentage of infant participants born to maternal participants receiving 1 dose of IP with:

- Specific birth outcomes
- AEs from birth to 1 month of age
- SAEs, AESIs (congenital anomalies, developmental delay), and MAEs through 12 months of age

Secondary Immunogenicity Objective: Maternal Participants

To describe the immune responses elicited by an RSV vaccine in women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.
Endpoints:

- GMT, geometric mean fold rise (GMFR), GMR for RSV A- and RSV B-neutralizing antibody titers of the RSV vaccine group and the placebo group measured:
    - Before vaccination
    - 2 weeks after vaccination
    - 1 month after vaccination
    - At delivery

Secondary Immunogenicity Objective: Infant Participants

To describe RSV antibody levels in infants born to women ≥18 through 49 years of age who were vaccinated with 1 dose of RSV vaccine during pregnancy.
Endpoints:

- GMT, GMR for RSV A- and RSV B-neutralizing antibody titers measured at:
- Birth
    - 1 month
    - 2 months
    - 4 months
    - 6 months

Infant participants were randomly assigned to 1 of 2 blood sampling schedules.

Key Exploratory Objectives:

1) To describe rates of RSV-positive LRTD in the study population (determined by RT-PCR)
   Endpoint: All LRTD caused by RSV determined by RT-PCR.

2) To describe the distribution of other pathogens causing acute RTI in the study population.
   Endpoint: PCR-based assay positivity for non-RSV respiratory pathogens in midturbinate swabs obtained at unplanned acute RTI visits.

6.3.2 Study Design

Study 1003 was a Phase 2b, multicenter, randomized, placebo-controlled, observer-blinded study in which up to 650 healthy pregnant individuals ≥18 and ≤49 years of age were randomized to receive 1 of 2 dose levels of bivalent RSV vaccine candidate at 120 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 transplacental 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 individuals 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. The study period was from August 7, 2019 (first participant enrolled in the trial) to September 30, 2021 (last participant completed the trial). Serology completion date was on 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): demographics, 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 AEs within 1 month following vaccination, and obstetric complications. Infants were assessed for birth outcomes and AEs, including SAEs

and MAEs through 12 months of age. Congenital anomalies and developmental delay were reported as an AESI.

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 was performed on all infant participants at each visit. Significant medical history and observations from examination were documented in the CRF. AEs, MAEs (a nonserious AE that results in evaluation at a medical facility), and SAEs were reported.

6.3.3 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), severe obesity, immunocompromise, or history of pregnancy complications (e.g., prior preeclampsia).

6.3.4 Study Treatments or Agents Mandated by the Protocol

Investigational Product Lot Numbers

Lots: RSVpreF: AT3605Z (19-001847) for 120-µg dose, AT3609Z (19-001849) for 240-µg dose

- Dose and route of administration: 0.5 mL intramuscular
- Formulation: 2 stabilized prefusion RSV F glycoproteins (RSV A and RSV B). The total dose of RSV drug product was 120 µg or 240 µg
- Presentation: Lyophilized cake in a vial, reconstituted by diluent of either sterile water or a sterile suspension of $Al(OH)_3$ in water
- The fill volume of the IP vial and diluent vial were designed such that the intended vaccine dose was delivered in a 0.5-mL injection volume
- Diluent lot for RSVpreF (sterile water): 911001 (19-001256)
- Diluent/adjuvant lot (aluminum hydroxide adjuvant): AY3454 (19-001853)
- Placebo: A sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose): 18-000719

6.3.5 Directions for Use

RSVpreF was supplied as a lyophilized antigen component (a sterile powder) in a glass vial. For individuals randomized to the arm of the study for RSVpreF without adjuvant, the diluent for reconstitution was sterile water for injection. For individuals randomized to the arm of the study for RSVpreF with adjuvant, the diluent for reconstitution was a sterile suspension of $Al(OH)_3$. The investigational vaccines in this study were administered by intramuscular injection. Please refer to the ABRYSVO package insert for more detailed directions.

6.3.6 Sites and Centers

This study was planned to be conducted at a total of 66 sites in 6 countries (Argentina [4], Australia [3], Chile [6], New Zealand [2], South Africa [1], and the US [50]); however, only sites in 4 countries (Argentina, Chile, South Africa, and the US) randomized participants. The total

number of subjects screened was 1350; the total number of subjects randomized was 1153, with the majority (1024) being in US sites.

6.3.7 Surveillance/Monitoring

Pregnant individuals 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 was collected from each infant participant during any unplanned acute RTI 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.

MA-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.

Severe MA-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.

6.3.8 Endpoints and Criteria for Study Success

Please refer to Section 6.3.1

6.3.9 Statistical Considerations & Statistical Analysis Plan

Up to 650 healthy pregnant individuals ≥18 and ≤49 years of age were planned to be randomized. No formal statistical hypothesis testing was performed in this study. All analyses for immunogenicity and safety data were descriptive in nature. An estimation approach was used to assess the safety and immunogenicity objectives. Statistical decision rules were not utilized in this study. An analysis was performed when the delivery-visit RSV-neutralizing antibody titer data from all maternal and infant participants AND the 1-month-after-birth visit data for infant participants were available. A further analysis was performed when all data were available from the infant participants' 6-month visit. The final analysis will be performed after all participants have completed the study and when all data are available. GMT and associated 2-sided 95% CI will be calculated at each available time point for each vaccine group; 95% CI will be calculated by back transformation of the 95% CI for the mean of the logarithmically transformed assay results computed using Student's t-distribution. Descriptive summary statistics were used.

6.3.10 Study Population and Disposition

This study planned to enroll up to 650 healthy pregnant women to be randomized in a 1:1:1:1:1 ratio to receive a single dose of 1 of 2 RSV dose levels (120 µg or 240 µg) formulated with or without $Al(OH)_3$ or placebo.

6.3.10.1 Populations Enrolled/Analyzed

Populations Analyzed - Maternal Participants

A total of 778 maternal participants were screened and 581 maternal participants were randomized to receive the following: RSVpreF 120 µg (116 participants), RSVpreF 120 µg + $Al(OH)_3$ (117 participants), RSVpreF 240 µg (116 participants), RSVpreF 240 µg + $Al(OH)_3$ (115 participants), and placebo (117 participants). All maternal participants who were vaccinated were included in the safety population (579 participants), 574 delivered infants (5 withdrew from the study before delivery), and 521 completed the study.

Infant Participants

A total of 572 infant participants entered the study and were included in the safety population and 522 infant participants were included in the evaluable immunogenicity population. The most frequent reason for exclusion of maternal participants from the evaluable immunogenicity population was a major PD.

No participants were excluded from the safety population. The most frequent reasons for exclusion of infant participants from the evaluable immunogenicity population were lack of a valid and determinate assay result at birth and mother had a major PD.

6.3.10.1.1 Demographics

Overall, characteristics of the maternal and infant participants in Study 1003 were similar to participants in Study 1008, with some differences in demographics, e.g., due to fewer participating countries in Study 1003, a greater percentage of Asian participants were enrolled in Study 1008 than in Study 1003 (12.5% versus 1% of maternal participants, respectively).

Maternal Participants

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 29. Demographic Characteristics, Maternal Participants, Safety Population of Two Selected Groups, Study 1003

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)
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 1003
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.

Reviewer Comment: *Only the final formulation of the RSVpreF vaccine group and the placebo group are shown in the above table.*

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.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical/behavioral characteristics were similar between study groups and were generally consistent with those in Study 1008.

6.3.10.1.3 Subject Disposition

Disposition of Participants

Maternal Participants - All 579 maternal participants who were vaccinated were included in the safety population, 574 completed delivery, and 521 completed the study. Most randomized participants (99.7%) completed vaccination; 2 participants were randomized in error, were not vaccinated, and were withdrawn from the study. Almost all (98.8%) of maternal participants completed delivery of their infants in the study. Of 115 maternal participants in the final formulation (RSVpreF 120 µg) group, 114 completed delivery. One maternal participant was withdrawn after vaccination but before delivery.

Maternal participants who delivered within 1 month of vaccination were not eligible to complete the 1 month after vaccination visit. The most frequent reason for withdrawal during the study was lost to follow-up. Two participants were withdrawn after randomization but before vaccination (randomized in error and listed as withdrawn due to “other”). A single participant listed as withdrawn due to “other” was withdrawn after delivery but before completing the study due to relocating out of the study area. The most frequent PD in the category of inclusion/exclusion criteria was a history of or known current pregnancy complications or abnormalities that would increase the risk associated with the participant’s participation in and completion of the study (8 participants) and laboratory test results at the screening visit outside the normal reference value for pregnant individuals according to their trimester in pregnancy (7 participants).

Infant Participants - Of the 572 infant participants in the safety population, 557 completed the 1-month visit, 540 completed the 6-month visit, and 519 completed the study. Most infant participants completed the 1-month and 6-month visit. The most frequent reason for withdrawal during the study was lost to follow-up. One infant participant (in the placebo group) was withdrawn due to AEs (atrial septal defect, patent ductus arteriosus, hypoxia, lung disorder, and neonatal respiratory distress syndrome) following birth. One participant was withdrawn due to relocation out of study area.

6.3.11 Secondary / Immunogenicity Analyses

Maternal-Infant Placental Transfer

One of the secondary endpoints in this study assessed maternal-to-infant placental transfer ratios of RSV A- and RSV B-neutralizing antibody titers in a subgroup of approximately 200 maternal-infant pairs. The maternal-to-infant placental transfer of antibodies achieved the pre-specified goal of geometric mean 50% neutralization titers; maternal-to-infant placental transfer ratios of RSV neutralizing titers (NTs) of RSV A, RSV B, and combined RSV A and RSV B were

>1 for all vaccine groups. However, it was noted that this was achieved for both the RSVpreF and placebo groups; the clinical significance of this finding is unknown.

6.3.11.1 Dropouts and/or Discontinuations

One maternal participant in the RSVpreF 120 µg group withdrew from the study after vaccination but prior to delivery, due to "withdrawal by subject." No maternal participants were discontinued from the study due to AEs. One infant participant whose mother received placebo was discontinued from the study due to severe AEs of atrial septal defect, patent ductus arteriosus, and lung disorder, and life-threatening events of hypoxia and neonatal respiratory distress syndrome. None of these events were related to maternal vaccination.

6.3.11.2 Exploratory and Post Hoc Analyses

Exploratory Endpoints:

Infant Exploratory Efficacy 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 VE include zero.

Table 30. Efficacy of Maternal Vaccination Against RSV-Associated Lower Respiratory Tract Disease in Infants Through End of Study, Infant Participants, Safety Population, Study 1003

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

Source: adapted from Pfizer CSR, Study 1003
Abbreviations: LRTD=lower respiratory tract disease
a. N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations.
b. 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.
c. Defined as presence of one or more of the following physical examination signs: nasal flaring, lower chest wall indrawing or subcostal retractions, rhonchi, grunting, wheezing, crackles/rales/crepitations; plus 1 of the following: tachypnea (respiratory rate =60 breaths per minute (<2 months [<60 days] of age) or =45 breaths per minute (2 to 6 months [=60 days to =180 days] of age)), use of mechanical ventilation (intubation or noninvasive positive pressure ventilation), difficulty feeding, signs of dehydration: sunken fontanelle, dry/sticky mucous membranes, tenting of skin.
d. Defined as a medically attended visit and presence of 1 of the following signs of lower respiratory tract illness: tachypnea (respiratory rate =60 breaths per minute (<2 months [60 days] of age) or =50 breaths per minute (=2 to 12 months of age)); peripheral capillary oxygen saturation (SpO2) measured in room air <95%; chest wall indrawing.
e. Defined as a medically attended visit and presence of 1 of the following signs of severe lower respiratory tract illness: tachypnea (respiratory rate =70 breaths per minute (<2 months [60 days] 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.

Copathogens

In total, 16 non-RSV pathogens were detected in infant midturbinate swabs at unplanned infant visits by RT-PCR-based assay positivity. The distribution of non-RSV respiratory pathogens was not meaningfully different between maternal RSVpreF and placebo groups.
Rhinovirus was the most common non-RSV respiratory pathogen identified in both groups (16.1% and 23.7% in RSVpreF and placebo groups, respectively).
SARS-CoV-2 detection was rare with 4 cases occurring between June 2020 and September 2020.

Subgroup analysis by geographical cohort revealed no clinically meaningful trends.

6.3.12 Safety 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.

6.3.12.1 Methods

Methods of the collection of AEs/reactions were similar to Study 1008. Please refer to Section 6.1.12.1.

6.3.12.2 Overview of Adverse Events

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 AEs appeared to be balanced overall between treatment groups. 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. There were no safety signals observed in this study.

In Study 1003, a numerical imbalance in preterm births was observed in the RSVpreF vaccine groups compared with matched placebo controls. Preterm births occurred in 5.3% (6/114) of infants in the RSVpreF group and 2.6% (3/117) in the placebo group.

> Reviewer Comment: *Note that 114 out of the 115 maternal participants who received the formulation (RSVpreF 120 µg) group completed delivery (1 maternal participant withdrew from the study prior to delivery). In the RSVpreF group, 5.2% (6/115) of maternal participants delivered preterm and 5.3% (6/114) of infants were born preterm.*

Table 31 below describes the observation of live and premature deliveries for the maternal safety population in Study 1003.

Table 31. Birth Outcomes, Maternal Participants, Safety Population, Study 1003

Outcome	RSVpreF 120 µg N=115 n (%)	RSVpreF 120 µg + Al(OH)3 N=117 n (%)	RSVpreF 240 µg N=116 n (%)	RSVpreF 240 µg + Al(OH)3 N=114 n (%)	Placebo N=117 n (%)
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.

> Reviewer Comment: *FDA finds the comparative safety data from Study 1008, particularly the imbalance in preterm births, to be most relevant for this BLA review. This study also provides supportive mechanistic data for vaccine effectiveness, the placental transfer of maternal antibodies following vaccination.*

6.3.12.3 Deaths

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

6.3.12.4 Nonfatal Serious Adverse Events

Maternal Participants - SAEs were reported similarly among all groups of maternal participants and were mostly associated with pregnancy-related conditions. No SAEs were considered related to vaccination.

Infant Participants - SAEs across RSVpreF groups were reported by 35 (31.0%) to 44 (39.3%) infant participants, and 38 (32.8%) participants who received placebo. No SAEs were considered related to maternal vaccination with IP.

6.3.12.5 Adverse Events of Special Interest (AESIs)

No AESI of developmental delay were reported during the study. Most AESIs of congenital anomalies were mild, and those of at least moderate severity were reported in a similar frequency across all groups. None of these events were considered related to maternal vaccination with IP. In Study 1003, preterm births and preterm deliveries were not reported as AESIs.

6.3.12.6 Dropouts and/or Discontinuations

No maternal participants withdrew from the study due to AEs. One infant participant whose mother received placebo was discontinued from the study due to severe AEs of atrial septal defect, patent ductus arteriosus, lung disorder, and life-threatening events of hypoxia and neonatal respiratory distress syndrome. None of these events were related to maternal vaccination with IP.

6.3.13 Study Summary and Conclusions

The safety, immunogenicity, and preliminary efficacy results from this Phase 2 study supported the selection of RSVpreF 120 µg (without adjuvant) for Phase 3 development.

Following vaccination, maternal-to-infant placental transfer ratios of RSV A- and RSV B-neutralizing antibody titers were >1 for all vaccine groups.

When all vaccine groups were combined and compared to placebo, exploratory efficacy of maternal vaccination against RSV-associated MA-LRTD and severe MA-LRTD were 75% and 83%, respectively.

The most frequently reported local reaction was pain at the injection site and the most frequently reported systemic event was fatigue.

In Study 1003, a numerical imbalance in preterm births was observed in the RSVpreF vaccine group compared with matched placebo controls, with 5.3% (6/114) of infants in the RSVpreF group and 2.6% (3/117) of infants in the placebo group born prematurely. This imbalance was noted to be similar to the imbalance seen in preterm births in Study 1008.

6.4 Study C3671014

Title: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of 3 Lots of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine in Healthy Adults. (NCT05096208)

Study 1014 was designed as a lot-to-lot consistency, immunogenicity, and safety study in healthy males or nonpregnant females ages of 18 and ≤49 years. Participants received 1 dose of 1 of 3 lots of RSVpreF or placebo and were followed for 1 month after vaccination.

The primary immunogenicity endpoint of lot consistency was demonstrated for both RSV A and RSV B, with the resultant 2-sided 95% Cis for GMRs at 1 month after vaccination for each pair of individual vaccine lots (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) contained within the prespecified interval (0.667, 1.5).

Safety data from Study 1014 are available from 745 RSVpreF recipients and 238 placebo recipients, of which 970 participants (97.7%) completed the total study duration of 1-month post-vaccination. Solicited local and systemic ARs were mostly mild to moderate and of short duration. There were no meaningful imbalances in the overall rates of unsolicited AEs within 1 month following vaccination between vaccine and placebo recipients. There were no deaths or SAEs reported in the study.

Please see clinical memo for STN 125769.0 for a detailed description of the study design and results.

6.5 Study C3671001

Title "A Phase ½, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding, First-In-Human Study to Describe the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine in Healthy Adults" (NCT03529773)

In the context of this review, Study C3671001 was a Phase 1/Phase 2 placebo-controlled, randomized and observer blind dose-finding study designed to assess the safety and immunogenicity of different doses of RSVpreF with and without adjuvant in healthy male and non-pregnant female participants 18-85 years of age. Participants were enrolled into two age subgroups (18-49 years and 50-85 years) and were randomized to receive RSVpreF at 3 escalating dose levels of 60 µg, 120 µg, and 240 µg, with or without aluminum hydroxide ($Al[OH]_3$) or placebo (Vaccination 1). The study design and results are described in the clinical memo for STN 125769.0.

The results from this study supported the Applicant's selection of 120 µg RSVpreF for evaluation in pregnant individuals in Phase 3 development.

6.6 Internal FDA Consultations

DVRPA formally consulted the Office of Pediatric Therapeutics, the Division of Pediatrics and Maternal Health (who subsequently involved the Division of Urology, Obstetrics, and Gynecology and CDER's Office of Surveillance and Epidemiology in the consultation), and CDER's Reproductive and Developmental Toxicology working group. The following section provides succinct summary conclusions of their consultant documents and are filed in this BLA.

Office of Pediatric Therapeutics (OPT)

(b) (5)

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) - Division of Pediatrics and Maternal Health (DPMH) and Division of Urology, Obstetrics and Gynecology (DUOG)

(b) (5)

Division of Applied Regulatory Science (DARS)

(b) (5)

Reproductive and Developmental Toxicology Subcommittee (RDTS)

(b) (5)

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication for Active Immunization of Pregnant Individuals

Because the Applicant submitted one Phase 3 adequate and well-controlled trial, a substantive integrated overview of efficacy was not performed for this BLA review. We found the Applicant's data from this study fulfilled the Agency's requirement to demonstrate substantial evidence of effectiveness. In this BLA, study results met a pre-specified successful efficacy finding for the entire study population for the prevention of severe RSV LRTD. The reason for conducting a descriptive post-hoc efficacy evaluation in the subgroup vaccinated at 32-36 weeks was for a safety concern of risk of preterm birth. VE was similar in this subgroup analysis; therefore, limiting an indication to immunization at 32-36 weeks does not impact the efficacy findings. The effectiveness standard is based on the following description in FDA's guidance document on establishing effectiveness: *One adequate and well-controlled clinical investigation supported by data that provide strong mechanistic support.* The trial design and endpoints for this indication provided for a robust finding of VE. The strong mechanistic support includes the favorable efficacy findings in the population of adults over 60 years of age in the prevention of RSV LRTD. There were Phase 2 study results that showed placental transfer of antibodies directed against RSV to the infants of pregnant individuals who were vaccinated. Finally, favorable point-estimate VE was demonstrated in a Phase 2 study, although the sample size was smaller and not adequately powered for a statistically significant finding of VE. FDA finds that this vaccine has met the Agency's effectiveness standard.

> Reviewer Comment: *Effectiveness of the two approved RSV monoclonal antibody (mAb) products provides mechanistic support for the effectiveness of passive "immunization" of infants, which results from active immunization with RSVpreF during pregnancy. It is important to note that there may be significant mechanistic differences between RSVpreF and RSV mAbs, including that RSVpreF vaccine efficacy derives from a polyclonal response in humans, while the efficacy of mAbs derives from genetic engineering of mAbs. The effectiveness data for RSV mAbs were not included in this application.*

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Of the 5 studies submitted in this BLA, 2 studies evaluated RSVpreF vaccine (ABRYSVO) in which the populations of pregnant individuals and their infants were followed for AEs/reactions.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

In the 5 supporting clinical studies submitted to the BLA, a total of 4144 participants received any dose level and formulation of RSVpreF.

We integrated the safety findings from 2 studies: Study 1008 (the Phase 3 study) and Study 1003 (the Phase 2 study in pregnant individuals that evaluated perinatal outcomes). The safety database included 3797 maternal participants (1773 maternal participants enrolled from US sites) who received the final formulation of the RSVpreF vaccine (RSVpreF 120 µg dose without $Al(OH)_3$).

Table 32. Number and Percentage of Maternal/Female Participants at Safety Analysis Time Points, Safety Population, Studies 1008 and 1003

Study	RSVpreF at 1 Month Post-Vaccination n/N (%)	Placebo at 1 Month Post-Vaccination n/N (%)	RSVpreF at 6 Months After Delivery n/N (%)	Placebo at 6 Months After Delivery n/N (%)	RSVpreF at Data Cutoff[a] n/N (%)	Placebo at Data Cutoff[a] n/N (%)
1008	3651/3682 (99.2)	3642/3675 (99.1)	2840/3682 (77.1)	2843/3675 (77.4)	2840/3682 (77.1)	2843/3675 (77.4)
1003[b]	417/462 (90.3)	101/117 (86.3)	422/462 (91.3)	99/117 (84.6)	422/462 (91.3)	99/117 (84.6)

Source: Pfizer CSR, Study C3671008
Abbreviations: 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
Notes:
a. Number of maternal subjects completing last scheduled study visit at data cutoff. (=6 months post-delivery for C3671003 and C3671008)
b. Numbers for Study 1003 include participants who received other formulations (not only final formulation) of RSVpreF.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In terms of solicited local and systemic reactions in the days following vaccination, all studies submitted to this BLA showed generally similar local and systemic reactions. Thus, the results from the largest clinical trial, Study 1008 that enrolled over 7000 pregnant individuals, are the best representation of reactogenicity of RSVpreF. Study 1008 was also conducted in 18 countries across multiple continents in a wide variety of racial and ethnic groups, and the demographics of all pregnant individuals enrolled in the development program are generally reflective of the diverse patient population in the US.

8.2.3 Categorization of Adverse Events

AEs were categorized by SAEs and infant outcomes (preterm births).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

There are always limitations when pooling data across studies. When considering the sizes of the safety databases among the studies in this clinical development program, Study 1008 has by far the largest sample size evaluated for safety. While pooling data can result in helpful analyses, the safety data from Study 1008 is most reflective of the safety of RSVpreF vaccine.

8.4 Safety Results

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. Local reactogenicity was reported more frequently in vaccine recipients compared with placebo recipients. The most common local reaction was pain at the injection site.

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.

An imbalance in the rate of preterm births was observed in both maternal studies (Studies 1008 and 1003). In Study 1008, prematurity was reported in 5.7% of infants in the RSVpreF group and 4.7% in the placebo group. A similar trend was noted in Study 1003, with prematurity reported in 5.3% of infants in the RSVpreF group and 2.6% in the placebo group. 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.

In addition, a numerical imbalance in pregnancy-related SAEs of interest (HDP, PROM, and PPROM) was observed in Study 1008, with 4.1% (152/3682) occurring in vaccinated maternal participants versus 3.3% (120/3675) in placebo recipients. Three (3) cases of preeclampsia were reported in Study 1003, all in the *placebo* arm. As a result, 3 additional cases of preeclampsia are reported in the total cases of preeclampsia for the combined Studies 1008 and 1003. No additional cases of these pregnancy-related SAEs accrued in Study 1003.

Table 33. Pregnancy-related SAEs, Maternal Safety Population, Combined Studies 1003 and 1008

Preferred Term	RSVpreF 120 µg n (%) N=3797	Placebo n (%) N=3792	RD % (95% CI)	RR (95% CI)
Pregnancy-related SAEs[a]	**152 (4.0)**	**123 (3.2)**	**0.8 (-0.1, 1.6)**	**1.2 (1.0, 1.6)**
Eclampsia	3 (0.1)	2 (0.1)	0.0 (-0.1, 0.1)	1.5 (0.3, 9.0)
Gestational hypertension	41 (1.1)	38 (1.0)	0.1 (-0.4, 0.5)	1.1 (0.7, 1.7)
HELLP syndrome	2 (0.1)	3 (0.1)	-0.0 (-0.1, 0.1)	0.7 (0.1, 4.0)
Hypertension	13 (0.3)	6 (0.2)	0.2 (-0.0, 0.4)	2.2 (0.8, 5.7)
Preeclampsia	68 (1.8)	56 (1.5)	0.3 (-0.3, 0.9)	1.2 (0.9, 1.7)
Premature rupture of membranes	15 (0.4)	16 (0.4)	-0.0 (-0.3, 0.3)	0.9 (0.5, 1.9)
Preterm premature rupture of membranes	15 (0.4)	10 (0.3)	0.1 (-0.1, 0.4)	1.5 (0.7, 3.3)
Superimposed preeclampsia	0 (0.0)	2 (0.1)	-0.1 (-0.1, 0.0)	N/A

Source: Adapted from CSR Study C3671008
Abbreviations: SAE=serious adverse event; RD=risk difference; RR=relative risk
Notes: Subjects filtered for safety population. Events filtered to treatment-emergent events. Percentages calculated with premature delivery subgroup totals as denominator. All counts represent unique subjects within each subgroup. Analysis in table includes after vaccination to 6 months after delivery.
a. Conditions do not make up all SAEs for maternal subjects, only select pregnancy-related conditions of interest associated with preterm delivery.

8.4.1 Deaths

There was 1 death in a maternal participant and 1 additional death of a non-pregnant individual in the pooled safety database; neither were directly attributable to RSVpreF vaccination.

8.4.2 Nonfatal Serious Adverse Events

Across both studies conducted in pregnant individuals (Studies 1008 and 1003) who received the final formulation of RSVpreF (120 µg dose), the overall rates of any SAEs were reported in

15.9% (605/3797) and 15.1% (572/3792) of RSVpreF and placebo recipients, respectively. SAEs observed at higher percentages in maternal participants included preeclampsia (RSVpreF 1.8% [68/3797] versus placebo 1.5% [56/3792]) and gestational hypertension (RSVpreF 1.1% [41/3797] versus placebo 1.0% [38/3792]).

Across both studies, the rates of any SAEs in infant participants were 18.1% (666/3682) and 18.0% (661/3674) in the RSVpreF and placebo groups, respectively. SAEs in infant participants included hyperbilirubinemia neonatal (RSVpreF 1.3% [49/3682] and placebo 1.1% [40/3674]), jaundice neonatal (RSVpreF 2.1% [76/3682] and placebo 1.8% [66/3674], premature baby (RSVpreF 1.4% [51/3682] and placebo 1.2% [44/3674]), and respiratory distress (RSVpreF 1.3% [47/3682] and placebo 1.2% [44/3674]).

8.4.3 Adverse Events of Special Interest

In Study 1008, a numerical imbalance was observed in preterm births and preterm deliveries which were reported as AESIs. A similar trend was observed in Study 1003. Note that preterm births and preterm deliveries were not reported as AESIs in Study 1003.

8.5 Safety Conclusions

A numerical imbalance in preterm births observed in both the Phase 3 and Phase 2 studies (Studies 1008 and 1003) suggests that preterm births may be associated with RSVpreF vaccination. In addition, in Study 1008 a numerical imbalance was observed in pregnancy-related events (e.g., HDP) that may be associated with preterm delivery.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Studies conducted in pregnant individuals are described in Section 6.1 (Study 1008) and Section 6.3 (Study 1003).

9.1.2 Use During Lactation

It is not known whether RSVpreF is excreted in human milk. Data are not available to assess the effects of RSVpreF on the breastfed infant or on milk production/excretion.

9.1.3 Pediatric Use and PREA Considerations

The Applicant requested a partial waiver of studies in individuals younger than 10 years of age for the proposed indication. Safety and effectiveness data from Study 1008 that specified enrollment eligibility of adolescent pregnant individuals and extrapolation of the data from older pregnant individuals to those 10 to <16 years of age fulfills PREA for the pediatric age group 10 to <17 years of age.

In Study 1008, the safety population included 9 maternal participants in the RSV group and 8 maternal participants in the placebo group who were younger than 18 years of age. The youngest maternal participant to receive RSVpreF was 16 years old and the youngest maternal participant to receive placebo was 14 years old.

9.1.4 Immunocompromised Patients

The safety and effectiveness of RSVpreF was not evaluated in immunocompromised individuals.

9.1.5 Geriatric Use

RSVpreF is approved for use in individuals 60 years of age and older. For this indication for active immunization of pregnant individuals, geriatric use is not relevant.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

The clinical reviewers recommend approval for immunization of pregnant individuals at 32-36 weeks and the benefit of VE outweighs the potential risks. Although the available data are insufficient to either establish or exclude a causal relationship between preterm birth and ABRYSVO, given the available evidence and the potential risks of HDP (that is a known risk factor for preterm birth), extremely preterm births, and very preterm births, the residual uncertainty and risks outweigh the demonstrated benefit of active immunization of pregnant individuals at 24-36 weeks evaluated in the Phase 3 development program. A more favorable balance of risks and benefit results from an indication limited to active immunization of pregnant individuals at 32-36 weeks, as doing so eliminates the risk of preterm delivery and births before 32 weeks of gestation.

Active immunization of pregnant individuals limited to 32-36 weeks has the potential to mitigate risks that can be readily incorporated into the package insert for a clear description of safety for the healthcare provider and the pregnant individual.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Consideration of a potential indication for immunization of pregnant individuals at 24-36 weeks:

Given the available evidence, the potential risks of preterm birth and HDP outweigh the benefit of VE in this population. This point of view on safety with regard to the imbalance in preterm births was clearly expressed by 4 members of VRBPAC during the May 18, 2023 discussion and vote of “no” for vaccine safety. Based on the available evidence, the clinical reviewers agree that the potential risks outweigh the benefit for the broader population of pregnant individuals at 24 through 36 weeks gestation, considering the following:

- Preterm birth at earlier GAs, for example preterm births before 32 weeks, has substantive and well-documented morbidity and mortality associations.
- HDP occurring at earlier GAs has substantive associations with maternal morbidity and mortality, and clearly poses a risk of preterm birth.
- An excess number of very preterm births at 28 to less than 32 weeks gestational age or extremely preterm births less than 28 weeks gestational age would overshadow a VE finding for prevention of RSV disease (CDC, 2022a; WHO, 2022).
- The imbalance of preterm birth of RSVpreF vaccine compared to placebo was noted in a Phase 2 clinical trial; thus, two controlled trials show the same finding of the imbalance in preterm births.

- A vaccine related to RSVpreF, in a different development program, was halted for an imbalance in very preterm births with higher numbers, including neonatal deaths attributable to extreme preterm births, among pregnant individuals receiving the investigational vaccine.
- Nirsevimab is FDA-approved for prevention of RSV disease, thus altering the balance of both risk and benefit because its use in infants would not pose "maternal" risks of preterm births or HDP.

Consideration of an indication for immunization of pregnant individuals at 32-36 weeks:

The clinical review team finds that the benefit of VE outweighs the potential risks of preterm births and HDP. The clinical reviewers' analyses that benefit outweighs risks is based on the following considerations:

- From a pragmatic approach, active immunization of pregnant individuals at 32-36 weeks "eliminates" the risk of both extremely preterm births, where there is substantive morbidity and mortality, and very preterm births.
- There was a successful finding of VE in Study 1008 overall and the subgroup analysis of efficacy in the subgroup who received vaccination at 32-36 weeks showed a similar point estimate of VE.
- The subgroup analysis of efficacy in the subgroup of the earliest GAs of 24-28 weeks showed a lower point estimate of VE; although these subgroup analyses are post-hoc and not controlled for multiple comparisons, these analyses provide additional support for a finding of VE in the subgroup 32-36 weeks. That is, VE does not appear to be "driven" by subgroups below 32 weeks, and these post-hoc analyses are hypothesis-generating for the potential of a more favorable VE in 32-36 weeks.
- An analysis of the timing of vaccine administration to the time of preterm birth did not differ between the RSVpreF group and the placebo group and the median time from vaccination to preterm birth delivery was approximately 40 days. Although a mechanism for why preterm births might be associated with RSVpreF is unknown, a temporal association between vaccine administration and preterm birth was not observed.
- Safety analyses of preterm births show that a greater proportion of the preterm births occurred among pregnant individuals vaccinated earlier than 32 weeks.
- Safety analyses of preterm births show a difference of 0.5%, instead of overall 1.0%, in the subgroup of pregnant individuals who received vaccine at 32-36 weeks.
- One infant died of RSV disease in the placebo group; one death due to RSV in the placebo group represents a death during a time period in which there were far fewer cases of RSV, as this study was conducted during the years of physical distancing during the COVID-19 pandemic with a stark reduction in RSV cases.
- Nirsevimab's efficacy findings appeared to be very similar to RSVpreF's efficacy findings, in terms of the proportions of potential "breakthrough" cases of RSV among a "treated" infant population.
- It is acknowledged that nirsevimab would not pose any risks to a pregnant individual, and the premarketing safety database of nirsevimab appears very favorable in infants and children; a large postmarketing safety evaluation of nirsevimab in infants and children after more widespread use is not available at this time.
- Because ABRYSVO is FDA-approved and licensed for use (in a population 60 years of age and older), substantive "off-label" use in a pregnant population of any GA may occur in part based on vaccine administration at sites outside of traditional health care settings. Furthermore, the results of Study 1008 have been published in a major scientific journal and this publication did not highlight the safety information and potential risks that would

appear in the package insert, if approved. As a result, the healthcare practitioner or pregnant individual would not be made fully aware of any warnings and precautions and safety information based on this publication alone.
- In contrast to not approving ABRYSVO for this indication, approval will allow for the relevant information on efficacy and safety from this product's development program to be clearly described in the package insert, including warnings and precautions and relevant safety information.
- Availability of an RSV vaccine indicated for active immunization of pregnant individuals at 32-36 weeks would provide an additional option for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age that would be expected to enhance public health and would probably increase health equity.

Thus, the clinical reviewers in DVRPA favor approval of ABRYSVO for an indication for the active immunization of pregnant individuals at 32-36 weeks for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.

Table 34. Table of the Summary of Risk and Benefit

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• RSV is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups and is a common cause of bronchiolitis and viral pneumonia in infants. • Among infants, RSV hospitalization rates are highest in the first 3 months of life, with mortality between 1% to 3%. • RSV infection does not confer lasting immunity and re-infections occur throughout individual lifespans.	• LRTD due to RSV infection in infants is a serious and life-threatening condition and can be associated with significant morbidity and mortality.
Unmet Medical Need	• Treatment for RSV infection is limited to supportive care. • There is currently no vaccine available for prevention of RSV disease in infants. • During the BLA review for RSVpreF for the maternal vaccination indication for protection of infants, an mAb (nirsevimab) was approved by the FDA for the prevention of RSV LRTD in neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.	• Currently there are two licensed vaccines for the prevention of LRTD caused by RSV with an indication in older adults. • This product (RSVpreF) was in development for maternal immunization for prevention of RSV in the infant.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• Effectiveness of RSVpreF immunization during pregnancy was demonstrated to prevent severe infant RSV MA-LRTD within 180 days • VE 81.8% (99.5% CI: 40.6%, 96.3%) within 90 days • VE 69.4% (97.6% CI: 44.3%, 84.1%) within 180 days • Supportive evidence that RSVpreF immunization during pregnancy is effective in preventing RSV MA-LRTD in infants • VE 57.1% (99.5% CI: 14.7%, 79.8%) within 90 days • VE 51.3% (97.6% CI: 29.4%, 66.8%) within 180 days • Subgroup analysis of vaccination at 32-36 weeks gestation: • VE 91.1% (95% CI: 38.7, 99.8%) for prevention of severe RSV MA-LRTD within 90 days after birth; VE 76.5% (95% CI: 41.3, 92.1%) for prevention of severe RSV MA-LRTD within 180 days after birth • VE 34.7% (95% CI: -34.6%, 69.3%) for prevention of RSV MA-LRTD within 90 days after birth; VE 57.3% (95% CI: 29.8%, 74.7%) for prevention of RSV MA-LRTD within 180 days after birth • Secondary endpoint of hospitalization due to RSV--Prevention of hospitalization due to RSV: • VE 67.7% (99.17% CI: 15.9, 89.5) within 90 days after birth • VE 56.8% (99.17% CI: 10.1, 80.7) within 180 days after birth	• VE was established on the basis of prevention of severe LRTD caused by RSV at all timepoints within 180 days • Clinically meaningful benefit was observed for prevention of any LRTD caused by RSV despite not meeting prespecified success criterion at the 90-day timepoint; VE was shown at all subsequent time points (prespecified lower bound of 2-sided 95% CI was above 20%) • The subgroup 32-36 weeks showed similar VE compared to the overall population • A secondary prespecified analysis showed benefit in prevention of hospitalization due to RSV disease • Benefit outweighs risk for the population of pregnant individuals 32-36 weeks
Risk	• An imbalance of preterm births was observed in two clinical studies of ABRYSVO (Phase 2 and Phase 3 studies) • Subgroup analysis in the subgroup of 32-36 weeks at vaccination showed a 0.5% difference in preterm births as compared with a 1% difference overall for the full 24-36 week window for vaccination • An imbalance of the serious adverse reactions of HDP showed a greater proportion among RSVpreF-vaccinated pregnant individuals • Available data are insufficient to either establish or exclude a causal relationship between preterm birth and ABRYSVO.	• Observation of the imbalance of preterm births in two studies, as well as observations in another “similar” vaccine, suggest that the risk of preterm births might be a true risk • HDP represents a potential risk • There has been no demonstration of a direct benefit to pregnant individuals • The potential risks of preterm birth and HDP outweigh the benefit for the full GA window of 24-36 weeks that was evaluated in this development program

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Precluding the potential risk of extreme preterm births and very preterm births by not vaccinating pregnant individuals before 32 weeks • Limiting the potential risk of moderate preterm births (between 32 and 34 weeks) in the population of pregnant individuals 32-36 weeks	• Labeling for an indication of use in pregnant individuals at 32-36 weeks • Warnings and Precautions for the potential risk of preterm births

11.2 Risk-Benefit Summary and Assessment

11.3 Discussion of Regulatory Options

FDA is approving ABRYSVO for active immunization of pregnant individuals at 32-36 weeks for the prevention of LRTD and severe LRTD caused by RSV. This is a traditional approval because efficacy was based on a clinical endpoint to prevent RSV disease and represents how a "patient feels, functions, or survives." There were no other regulatory options.

On the relationship to "regulatory options," we note that this product and indication has "breakthrough therapy designation." Two important outcomes of this designation in terms of DVRPA's regulatory actions included:

- A rolling review submission with the final portion of the BLA submission on December 21, 2022, a considerably tight time frame from the completion of the "final" efficacy analyses in October 2022, thus resulting of DVRPA prioritization of this review;
- Substantive safety discussions that occurred in light of the May 18, 2023, VRBPAC discussion and additional analyses submitted by the Applicant; these analyses were not considered in the framework of "a major amendment" and the original action goal date was maintained.

11.4 Recommendations on Regulatory Actions

FDA finds that the benefit of VE, specifically when the RSVpreF vaccine is administered between 32-36 weeks, outweighs risks of vaccination including the potential risk of preterm birth and HDP.

11.5 Labeling Review and Recommendations

The proprietary name ABRYSVO was reviewed by the Advertising and Promotional Labeling Branch and found acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.

11.5.1 Indication

"Active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age."

11.5.2 Warnings and Precautions

Potential Risk of Preterm Birth

The location of this will be "5.1", or "first" in the list of all Warnings and Precautions because it represents the most significant risk for healthcare practitioners to be aware of and the mitigation

to an approved indication for use in “pregnant individuals at 32 through 36 weeks gestational age.”

Drug Interactions included information regarding coadministration of ABRYSVO and Tdap.

Pregnancy was updated to include summary of safety information.

11.6 Recommendations on Postmarketing Actions

The Applicant will be required to conduct four postmarketing studies as PMRs under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the serious risks of preterm birth and HDP.

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 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, complement 3 (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

According to the "Guidelines on the quality, safety, and efficacy of respiratory syncytial virus vaccines" (WHO, 2020), a "safety and immunogenicity trial should be conducted in RSV-experienced subjects before considering a trial in RSV-naïve subjects… Such investigations may not be needed for live-attenuated RSV vaccines based on existing experience... Post-immunization surveillance of 175 very young infants given intranasal live-attenuated RSV vaccines did not identify a significant increase in risk of vaccine-associated ERD…." Additionally, testing for ERD is "not required for RSV vaccines indicated for use in RSV-experienced/non-naïve individuals."

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 RTIs 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., 2017; Kwon et al., 2014). These studies demonstrated that passively acquired anti-FI-RSV IgG alone did not predispose to ERD following challenge; these data support the current thinking that passively acquired anti-RSV IgG cannot prime infants for ERD in the absence of CD4+ T cells primed for overexuberant Th2-type cytokine responses.

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 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 IP 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 IP 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 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 IP administration, or planned receipt through delivery, with 1 exception, RhIG (e.g., RhoGAM), which can be given at any time.