RESPIRATORY SYNCYTIAL VIRUS STABILIZED BIVALENT PREFUSION F SUBUNIT VACCINE (RSVPREF / ABRYSVO)

BRIEFING DOCUMENT FOR VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE MEETING 18 MAY 2023

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LIST OF ABBREVIATIONS

Abbreviations	Term
ADR	adverse drug reaction
AEs	adverse events
AESI	adverse events of special interest
$Al(OH)_3$	aluminum hydroxide
BLA	Biologics License Application
bpm	breaths per minute
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
DS-Cav1	incompletely stabilized RSV F
DTd	diphtheria toxoid
EAC	Endpoint Adjudication Committee
E-DMC	External Data Monitoring Committee
EU	European Union
FDA	Food and Drug Administration
FIH	first in human
FI-RSV	formalin inactivated RSV vaccine
GA	gestational age
GLP	Good Laboratory Practices
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
HCP	healthcare provider
ICU	intensive care unit
IM	intramuscular
LBW	low birth weight
LLOQ	lower limit of quantification
LRTI	lower respiratory tract illness
mAb	monoclonal antibody
MAE	medically attended adverse event
MA-LRTI	medically attended lower respiratory tract illness
MA-RTI	medically attended respiratory tract illness
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
N/A	not applicable
NAAT	nucleic acid amplification test
NC	not calculated
NDCMC	newly diagnosed chronic medical condition
NIH	National Institutes of Health
OTC	over the counter
PCR	polymerase chain reaction
PDUFA	Prescription Drug User Fee Act
PT	Preferred Term
QoL	quality of life
RR	respiratory rate
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A

Abbreviations	Term
RSV B	respiratory syncytial virus subgroup B
RSV F	respiratory syncytial virus fusion (F) glycoprotein
RSVpreF	respiratory syncytial virus bivalent stabilized prefusion F subunit vaccine
RTI	respiratory tract illness
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
sLRTI-RSV	severe respiratory syncytial virus associated lower respiratory tract illness
SOC	System Organ Class
SpO_2	oxygen saturation
T4	bacteriophage T4
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed
Tris	tris(hydroxymethyl)aminomethane
TTd	tetanus toxoid
UR	uncertainty range
US	United States
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1. EXECUTIVE SUMMARY

This document summarizes the favorable benefit-risk profile for Pfizer's RSVpreF (Abrysvo), a bivalent respiratory syncytial virus (RSV) stabilized prefusion F subunit vaccine (RSVpreF) for the proposed indication for prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through 6 months of age, by active immunization of pregnant individuals.

The Biologics License Application (BLA) was submitted on 21 December 2022 to the Center for Biologics Evaluation and Research (CBER) and was granted Priority Review Designation on 16 February 2023. The Prescription Drug User Fee Act (PDUFA) action date for the BLA is 21 August 2023.

RSVpreF is a bivalent recombinant protein subunit vaccine which consists of equal amounts of stabilized prefusion F antigens from the two major RSV subgroups: RSV A and RSV B. The proposed dosing regimen is a single 0.5 mL intramuscular injection at the dose level of 120 µg to pregnant women in the late second through third trimester of pregnancy.

The RSVpreF vaccine is given to pregnant women to boost preexisting RSV-neutralizing antibody titers in the mother. Maternal antibodies are transferred transplacentally to the fetus and thus protect infants for the first months of life, when they are most vulnerable to severe RSV disease and hospitalization.[1] Maternal immunization is anticipated to overcome barriers to direct infant immunization or antibody prophylaxis. Firstly, the peak of hospitalization due to RSV disease occurs very early at 1 to 2 months after birth[2], thereby affording little time for a neonatal vaccine to elicit a protective immune response. Secondly, the immaturity of the neonatal immune system may limit immune responses induced by neonatal vaccination.[3,4] Finally, in contrast to passively administered monoclonal antibodies, maternal immunization induces a polyclonal antibody response reducing the likelihood of applying selective pressure against circulating viruses and reducing susceptibility of immune escape due to potential spontaneous F mutations.[5]

Pfizer has submitted data from 5 clinical studies to the BLA in support of the proposed maternal indication. In total, 4144 maternal participants have received any dose/formulation of RSVpreF in the clinical program, and 3682 maternal participants received the final RSVpreF 120 µg dose (see Table 1 for details). Pfizer also has an older adult program with its RSVpreF vaccine; data from this program supporting an indication for active immunization of individuals 60 years and older was submitted as a separate BLA on 30 September 2022 and discussed at a 28 February 2023 VRBPAC, with a PDUFA action date of 31 May 2023. To that extent, a total of approximately 25,017 participants 18-85 years of age, including male and female nonpregnant/pregnant participants across the maternal and older adult immunization clinical programs have received the RSVpreF 120 µg dose.

The primary pivotal data to support the safety and efficacy of RSVpreF in infants from birth through 6 months of age consist of data from an ongoing multi-national Phase 3, double-blind and placebo-controlled trial (Study C3671008) in 7392 maternal participants were randomized to receive RSVpreF (3695) or placebo (3697). Of those, 7357 pregnant women were included in the safety analysis (RSVpreF [n=3682] or placebo [n=3675]) at a median gestational age (GA) of 31.3 weeks (range: 24.0 to 36.9). Submission of the BLA followed a

successful protocol-specified interim analysis (considered the primary analysis as agreed with CBER and the basis for licensure for the proposed indication) that evaluated primary efficacy endpoints of laboratory-confirmed RSV-associated severe medically-attended lower respiratory tract illness (severe MA-LRTI) and MA-LRTI in infants. The statistical success criterion for VE was a lower bound of confidence interval (CI) >20%. As of the 30 September 2022 data cutoff, the median duration of follow-up for efficacy was approximately 9 months. The data for the primary analysis of maternal vaccination with RSVpreF 120 µg, as agreed upon with the FDA for consideration of licensure to support the proposed indication, are presented in this briefing document. While the study remains ongoing for long term safety, enrollment has concluded and additional data generated will be descriptive and are not the basis for licensure.

Vaccine efficacy (VE) of preventing laboratory-confirmed severe MA-LRTI in infants was 81.8% (99.5% CI: 40.6%, 96.3%) and 69.4% (97.58% CI: 44.3%, 84.1%) through 90 and 180 days after birth, respectively. VE preventing laboratory-confirmed MA-LRTI in infants was 57.1% (99.5% CI: 14.7%, 79.8%) through 90 days after birth. Though clinically meaningful efficacy was observed, this primary endpoint was not met as the CI lower bound was <20%. Clinically meaningful descriptive efficacy against laboratory-confirmed MA-LRTI was observed through 180 days after birth (VE of 51.3% [97.58% CI: 29.4%, 66.8%]).

Pre-specified analyses of secondary endpoints of VE (statistical success criteria of CI lower bound >0%) against RSV-associated MA-LRTI in infants were 44.9% (99.17% CI: 17.9%, 63.5%) and 41.0% [99.17% CI: 16.2%, 58.9%]) through 210 and 360 days after birth respectively.

Another planned analysis of a secondary endpoint of VE against RSV-associated hospitalization demonstrated VE of 67.7% (99.17% CI: 15.9%, 89.5%) and 56.8% (99.17% CI: 10.1%, 80.7%) through 90 and 180 days after birth respectively, but VE did not persist through 360 days after birth. Finally, RSVpreF did not reduce the incidence of infant MA-LRTI due to any cause within 90 days after birth (VE = 2.5%; 99.17% CI: -17.9%, 19.4%) or at any other time point. Of note, a pre-specified analysis of an exploratory endpoint of VE against RSV-associated medically attended respiratory tract illness (MA-RTI) showed a VE of 37.9% (95% CI: 24.0%, 49.5%) through 180 days after birth.
Safety data from Study C3671008 through the 02 September 2022 data cutoff for safety included 7357 pregnant women vaccinated participants (3682 RSVpreF recipients and 3675 placebo recipients). In maternal participants:

- Solicited local and systemic adverse reactions within 7 days following vaccination were mild to moderate.

- Unsolicited adverse events (AEs) were followed in the Safety Population through 1 month following vaccination with no meaningful imbalances in the overall rates between vaccine and placebo recipients.

- Non-fatal serious adverse events (SAEs) and AEs of special interest (AESIs; preterm delivery, positive severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test) were reported in maternal participants from vaccination to 6 months after delivery and were balanced between study groups.

- AEs and SAEs in maternal participants were most often related to complications of pregnancy, labor, delivery, and the immediate postpartum period.

- There was only 1 maternal death in the trial, in RSVpreF group (due to postpartum hemorrhage and hypovolemic shock), considered unrelated to the study intervention.

- Stillbirths/fetal deaths were rare and reported in 10 (0.3%) RSVpreF recipients and 8 (0.2%) placebo recipients, none of which were considered related to study intervention.

Safety data from 3568 infant participants who were born to mothers who received RSVpreF demonstrated that the vaccine is safe and well tolerated.

- The incidence of overall AEs was 37.1% in the RSVpreF group and 34.5% in the placebo group; AEs within 1 month of birth assessed by the investigator as related to study intervention were similar in the RSVpreF group and placebo group.

- The incidences of SAEs, severe AEs, and life-threatening AEs were similar in the RSVpreF group and placebo group.

- The incidence of the AESI of preterm birth (<37 weeks; RSVpreF [5.6%; 95% CI: 4.9, 6.4] versus placebo [4.7%; 95% CI: 4.1, 5.5]) was numerically higher in the RSVpreF group, but the difference was not statistically meaningful. Additional AESIs of low birth weight (LBW, ≤2500g; RSVpreF [5.1%; 95% CI: 4.4, 5.8] versus placebo [4.3%; 95% CI: 3.7, 5.0]), developmental delay, positive SARS-CoV-2 test and newly diagnosed chronic medical conditions (NDCMCs) were similar in the RSVpreF and placebo groups.

- As of the safety data cutoff date of 02 September 2022, AEs leading to death were reported in 5 (0.1%) RSVpreF recipients and 12 (0.3%) placebo recipients, none of which were considered related to study intervention.

Benefit/Risk Conclusions

RSV is the leading cause of bronchiolitis and viral pneumonia in infants worldwide. Among infants <6 months of age, RSV is associated with around 1.4 million hospital admissions, and around 13,000 in-hospital deaths globally each year.[6] In the US, RSV is the leading cause of infant hospitalization, with approximately 1% to 3% of all children in the first 12 months of life hospitalized due to RSV lower respiratory tract disease.[7] A single 120 μg dose of the unadjuvanted RSVpreF administered to pregnant women has shown to be efficacious against RSV-associated severe MA-LRTI, MA-LRTI and hospitalization through 90 and 180 days after birth. The vaccine is safe and well tolerated in mothers with no meaningful imbalances between RSVpreF and placebo recipients. Among infants, there were fewer deaths in the RSVpreF group (5) than the placebo group (12); none were related to study intervention. No

major safety concerns have been identified in infants passively immunized with RSVpreF. A pharmacovigilance plan has been developed to determine the long-term safety profile of RSVpreF.

The RSVpreF maternal clinical program provides robust evidence that RSVpreF 120 µg is an efficacious and well tolerated vaccine in mothers, with no safety concerns in their infants. Collectively, these data support a favorable benefit/risk profile of RSVpreF and the proposed indication for the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals. Based on the results of the pivotal trial, the RSVpreF 120 µg vaccine has the potential to have an impact on reducing global infant mortality due to RSV.

Table 1. Studies in the RSVpreF Clinical Development Program Intended to Support the Maternal Indication

Study / Status	Brief Description	Participant Age Group	Female Participants ≤49 Years of Age Receiving Indicated Dose	
			Any RSVpreF Dose/ Formulation[a]	RSVpreF 120 µg[b]
Studies in Nonpregnant Participants				
C3671001 / completed (Section 5.2.1)	Phase 1/2 first in human in healthy participants • Dose ranging • RSVpreF formulated with/without $Al(OH)_3$ • Administration with or without SIIV • Revaccination	18-85 years	382	64
C3671004 / completed (Section 5.2.2)	Phase 2b coadministration study with Tdap in healthy nonpregnant women • Two dose levels, administered with or without Tdap	18-49 years	568	282
C3671014 / completed (Section 5.2.3)	Phase 3 lot consistency study in healthy participants • Final dose and formulation	18-49 years	453	453
Studies in Pregnant Participants				
C3671003 / completed (Section 5.3.1)	Phase 2b study in pregnant participants • Two dose levels, administered with or without $Al(OH)_3$	18-49 years	462	115
C3671008 / Primary analysis for all endpoints (safety and efficacy) complete; long term safety follow-up ongoing (Section 5.4)	Phase 3 pivotal safety and efficacy study in pregnant participants	≤49 years	3682	3682

a. Includes participants who received 60 µg, 120 µg or 240 µg of RSVpreF, with or without $Al(OH)_3$.
b. RSVpreF 120 µg without $Al(OH)_3$; final dose and formulation.
Abbreviations: $Al(OH)_3$=aluminum hydroxide; Tdap=tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; SIIV=seasonal inactivated influenza vaccine.
Note: Studies in the RSVpreF clinical development program to support the older adult indication are not included.

2. BACKGROUND INFORMATION

2.1. RSV Disease in Infants

RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in very young infants, in infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems.[7] Risk factors for RSV infection and disease include prematurity, cohousing with young siblings, day-care center attendance, and low levels of maternal neutralizing antibodies.[9] RSV infection is essentially universal by 2 years of age.[10]

Globally, in children <5 years of age, there are an estimated 33 million episodes of RSV-associated acute lower respiratory infection annually, resulting in an estimated 3.6 million hospitalizations and an estimated 26,300 (uncertainty range [UR] 15,100 – 49,100) in-hospital deaths.[6] A recent global metanalysis attempted to quantify additional RSV deaths occurring outside the hospital setting, resulting in an estimated 101,400 (UR 84,500-125,200) total RSV attributable deaths among children <5 years of age each year (eg, RSV-attributable deaths in the hospital and in the community).[6,11] The burden of severe RSV among children <5 years of age is concentrated in infancy; globally, 39% of all RSV-associated hospitalizations among children <5 years occur in the first 6 months of life, and within the first 6 months of life, 60% of RSV-associated hospitalizations occur among infants 0-3 months old.[12] Among infants <6 months of age, RSV is associated with 1.4 million (UR 1.0-2.0) hospital admissions, and 13,000 (UR 6,800 – 28,100) in-hospital deaths globally each year.[6] Overall, among infants <6 months of age, RSV-attributable deaths in both the hospital and the community are estimated to be 45,700 (UR 38,400 – 55,900). More than 97% of RSV-attributable deaths occur in low- and middle-income countries.[6]

In the US, RSV is the leading cause of infant hospitalization, with approximately 1% to 3% of all children in the first 12 months of life hospitalized due to RSV lower respiratory tract disease.[7] RSV leads to 2.1 million outpatient visits and 58,000 hospitalizations among children younger than 5 years old.[13,14] As with the global estimates, hospitalization is concentrated in younger life. A recent study of US hospitalization rates estimated that 50,400 (87%) of hospitalization in children <5 occur in those <2 years old[14], but the burden among those <2 years is even further focused in early infancy. A separate study focusing on hospitalization rates by age estimated that 50% of the hospitalizations among infants <1 year old occurred during the first three months of life, while 75-80% occurred during the first 6 months, and demonstrated that hospitalization rates peaked at 2 months of age.[2] Among infants, RSV-associated hospitalization rates are substantially higher than influenza-associated hospitalization rates.[15]

Several studies have demonstrated links between RSV LRTI (especially if the illness required hospitalization) and subsequent or recurrent non-RSV LRTI in the first two years of life.[16,17] Increased risk of bacterial pneumonia (including pneumococcal pneumonia) and acute otitis media have also been documented.[18-23] There is also evidence of a possible association between severe RSV disease in infancy and subsequent wheezing and asthma in later childhood.[16,24,25] RSV LRTI in the first few months of life increases the risk of asthma not only within the first decade of life but also possibly into adolescence and adulthood.[26,27]

RSV illness in children can also have adverse effects on quality of life (QoL). Among infants, symptoms of the acute illness (eg, cough, difficulty feeding and discomfort) can reduce QoL, and hospitalization can lead to both short- and long-term impacts on the child's emotional and physical wellbeing.[28-31] Parents and caregivers of infants with RSV may also experience difficulties related to their child's illness, including emotional distress, loss of sleep, missed work, and inability to adequately care for other family members.[29] More research is needed to quantify these impacts (both acute and longer term, including those associated with recurrent wheeze and asthma, etc), but assessing QoL in infants directly is challenging, as few validated tools (both for the age group and for RSV specifically) exist.[28] Furthermore, of the few available studies, most focus on inpatient disease and primarily on preterm infants, yet the burden of outpatient medically attended RSV is substantial, and while preterm infants are at increased risk of severe outcomes, most RSV occurs among those born healthy and full term.[13,28]

Prior to the coronavirus disease 2019 (COVID-19) pandemic, RSV was historically seasonal in the US, with annual peaks during the winter and spring[32], and predictable sub-national patterns. RSV transmission was disrupted by COVID-19 in recent years; very little RSV was seen in the winter of 2020-2021, but large out of season outbreaks occurred later in 2021 and 2022.[33] RSV transmission during the winter of 2022-2023 has been substantial[34,35], with hospitals and intensive care units (ICUs) overwhelmed with cases, straining capacity. Modeling studies suggest that RSV epidemics may continue to be unpredictable.[36]

2.2. Proposed Indication

The proposed indication for RSVpreF 120 µg is:

Prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals.

2.3. General Product Information

Pfizer's bivalent RSVpreF is comprised of equal quantities of 2 recombinant RSV F antigens representing the 2 major subgroups A and B, each structurally engineered for enhanced stability in the prefusion conformation. The total dose of the RSV drug product is 120 µg of the RSV prefusion F antigen (60 µg subgroup A, 60 µg subgroup B). The unadjuvanted formulation was selected based on the safety and immunogenicity data from the C3671003 maternal immunization study and the FIH C3671001 study.

The RSVpreF drug product is presented as a sterile lyophilized powder at the target strength of 240 mg/mL upon reconstitution and is filled in a 2 mL glass vial. Each vial of the lyophilized vaccine is reconstituted with 0.65 mL of sterile water diluent provided in a pre-filled syringe.

The bulk drug product formulation contains 20 mM Tris (tromethamine), 50 mM sodium chloride, 0.2 mg/mL polysorbate 80, 30 mg/mL sucrose and 60 mg/mL mannitol.

RSVpreF is administered intramuscularly, as a single 0.5-mL injection.

3. UNMET MEDICAL NEED

3.1. Current Strategies to Prevent or Treat RSV Disease

Currently, there is no licensed vaccine to prevent RSV disease. Treatment of RSV disease consists primarily of supportive care (eg, nutrition/hydration for infants who cannot maintain hydration, and supplemental oxygen).[37,38] The benefit of antiviral therapy (eg, ribavirin) for RSV is unclear, and therefore, it is rarely used to treat RSV, except in the context of severe immunosuppression[37], because of inconvenient administration, questionable benefit in immunocompetent patients, teratogenicity concerns based on nonhuman animal data, and high cost.[39-41] Acetaminophen and over the counter (OTC) cold medications may be used to relieve milder symptoms.[8]

Humanized monoclonal antibodies (mAbs) against the RSV F glycoprotein have demonstrated clinical efficacy. Palivizumab (Synagis®) binds antigenic site II - a site shared between prefusion and postfusion conformations of F. The mAb has demonstrated safety and efficacy against severe disease in high-risk infants and is currently authorized as immunoprophylaxis therapy for certain high-risk infants. In the US, this includes those with congenital heart disease, premature infants <29 weeks' gestational age, and high-risk-preterm infants born at <32 weeks' gestational age with chronic lung disease; such infants represent <3% of the birth cohort[42-45] In the European Union (EU), palivizumab is used in children <6 months of age who were born at 35 weeks gestational age or less, children <2 years of age who have been treated for bronchopulmonary dysplasia within the last 6 months, and children <2 years of age who were born with a serious heart condition.[46]

Limitations of palivizumab use include its high cost[42] and requirement for multiple monthly injections[47,48], making it impractical for broad use in infants, or use outside of high resource settings. However, its effectiveness highlights the importance of neutralizing antibodies in protection against RSV disease.[49,50] Improved mAbs directed at the RSV F glycoprotein have been evaluated in clinical studies since the licensure of palivizumab.[51] Motavizumab was effective at reducing hospitalization due to RSV[50], but further clinical development of this mAb was not pursued. Nirsevimab, a next-generation single dose, extended half-life prefusion F-specific mAb targeting antigenic site Ø, demonstrated efficacy against RSV LRTI in Phase 3 studies; nirsevimab has received marketing authorization in the EU in October 2022 and United Kingdom in November 2022 and is intended for broader use in all neonates and infants during their first RSV season.[49,52,53] These strategies rely on direct infant dosing which may present logistical challenges, including fitting a dose into an already complex infant immunization schedule and/or having to schedule a visit for administration to children born outside of the RSV season.

3.2. Scientific Rationale for RSVpreF Vaccine

The trimeric RSV F surface glycoprotein is the primary target of neutralizing antibodies and is the basis for the engineered antigens in Pfizer's vaccine candidate. During RSV entry into cells, F rearranges from a prefusion to a postfusion conformation. As it rearranges, F fuses the viral and host cell membranes. Structural data show that the postfusion F conformation used in many prior failed vaccine approaches is very different from the predominant prefusion conformation that is present on virions. The structural difference between conformations results in antigenic differences. In contrast to postfusion F, prefusion F is in an inherently unstable conformation that needs to be stabilized to be useful as an improved vaccine antigen.[54,55] Based on this new understanding, Pfizer has developed 2 structurally engineered, stabilized prefusion F vaccine antigens, one for each RSV subgroup. The Pfizer RSV vaccine program is based on the premise that prefusion F antigens will elicit higher neutralizing antibody titers and better protection than the postfusion F antigens in previous vaccine candidates.[56-58]

In 2013, the breakthrough determination of the crystal structure of prefusion RSV F in complex with an antibody fragment that prevented rearrangement from the prefusion to the postfusion conformation enabled a National Institutes of Health (NIH) laboratory to engineer a partially stabilized RSV F, termed DS-Cav1. This construct elicited approximately 10-fold higher neutralizing antibody titers than postfusion F in laboratory animals.[54,59] Building on the prefusion F crystal structure, Pfizer engineered RSV F constructs stabilized in the prefusion conformation. The constructs are RSV F ectodomains "locked" in the prefusion conformation by C-terminal bacteriophage T4 (T4) fibritin foldon trimerization domains and internal stabilizing mutations. The stabilized prefusion F subunit construct, on which the antigens in Pfizer's vaccine candidate are based, elicits >50-fold higher neutralizing titers than a postfusion F antigen in rhesus macaques.[60]

RSV F has approximately 90% amino acid identity between the 2 subgroups. Unlike types of polioviruses or types and subtypes of influenza, RSV subgroups are not serotypes, and some cross-neutralization occurs between RSV subgroups A and B. However, there are antigenic differences between the subgroups that could lead to differences in protective efficacy. Most of the sequence differences between the mature F glycoproteins of the subgroups are concentrated in the prefusion-specific epitopes that elicit the most potent RSV-neutralizing and protective antibody responses.[61,62] Therefore to cover current RSV diversity optimally, the Pfizer RSV vaccine candidate is based on recently circulating strains rather than a standard laboratory strain, and it is bivalent, with 1 F antigen (genotype Ontario) from subgroup A (preF A) and another (genotype Buenos Aires) from subgroup B (preF B). The prefusion F stabilizing mutations were introduced into each of these background F sequences. In cotton rats, immunization with the bivalent mixture elicited higher overall neutralizing titers than the constituent monovalent components.

3.3. Rationale for Maternal Immunization to Prevent RSV Disease in Infants

Maternal immunization is a powerful public health approach that has been used across the globe for decades to safely and successfully prevent neonatal tetanus, pertussis in early infancy, influenza in pregnant individuals and young infants, and more recently, COVID-19.[63-65] Platforms for vaccine delivery in antenatal care are well-established in many countries, and rates of uptake for vaccines routinely recommended in pregnancy are comparable to and often exceed coverage levels of other vaccines recommended for adults.[63-68] In addition to prevention of illness in infants, additional benefits to the pregnant person, the pregnancy and the fetus have been observed when vaccines are administered in pregnancy, including prevention of severe disease in the vaccinated individual and improved birth outcomes.[63-65] Vaccination in pregnancy also has the potential to provide the infant with an ongoing supply of vaccine-induced maternal antibodies via breastmilk after birth.[63,64]

Maternal immunization to protect infants against RSV disease is anticipated to overcome potential barriers to direct (eg, active) infant immunization. One barrier is the very early peak of RSV disease, occurring approximately 1 to 2 months after birth, which affords little time for a neonatal vaccine to elicit a protective immune response.[69] Other barriers include the immaturity of the neonatal immune system and potential suppression of active RSV antibody responses by maternal antibodies.[70] Maternal immunization also provides potential advantages over prophylactic administration of mAb to infants. In addition to those described previously (eg, not needing to rely on direct infant dosing which may present logistical challenges, including fitting a dose into an already complex infant immunization schedule and/or having to schedule a visit for administration to children born outside of the RSV season), maternal immunization can provide protection from the first day of life, induces a polyclonal antibody response and therefore has a low likelihood of applying selective pressure against circulating viruses, and may also provide additional benefit via antibodies in breastmilk.

Perhaps the greatest barrier to direct infant immunization is the history of vaccine-mediated RSV disease enhancement following immunization of RSV-naive infants with a formalin inactivated RSV vaccine (FI-RSV).[71] FI-RSV elicited a predominantly non-neutralizing antibody response and a Th2-biased cell-mediated response, both of which are considered potential contributing factors to disease enhancement.[72] Current understanding of the immunological mechanisms underlying this enhanced disease suggest that it is limited to immunization of RSV naïve individuals.[73] Because pregnant women are universally RSV experienced, it is not expected that they would be at risk of a disease-enhancing immune response to the vaccine that could exacerbate infection in themselves or their infants. A previous study of maternal immunization with an investigational RSV F vaccine not stabilized in the prefusion form showed an acceptable safety profile despite eliciting a relatively weak RSV-neutralizing antibody response and a higher non-neutralizing RSV-binding antibody response in pregnant women.[74] In addition, in a standard cotton rat infectious RSV challenge model, the Pfizer subunit vaccine candidate showed no sign of causing pulmonary disease enhancement.

The goal of maternal immunization is to boost preexisting RSV-neutralizing antibody titers in the mother. Maternal antibodies are transferred transplacentally to the fetus and thus protect infants for the first months of life, when they are most vulnerable to severe RSV disease.[1] Vaccination with the prefusion RSV F antigens elicits a higher ratio of neutralizing to non-neutralizing antibodies[75,76], more closely matching the profile in naturally exposed individuals.

Maternal antibodies are effective in preventing many diseases.[77-80] Naturally acquired maternal and cord-blood RSV-neutralizing antibody titers correlate with the duration of passive infant protection from RSV and reduction in infant hospitalization due to RSV disease.[9,57,81] The goal of maternal immunization is to increase maternal neutralizing antibodies in infants, such that RSV serum neutralization titers will remain above a protective threshold through the period of greatest risk, including the time of greatest immunologic and pulmonary immaturity.

Maternal immunization with RSVpreF is designed to protect infants through their first 6 months of life when the risk of RSV hospitalization is highest (50% and 75%-80% of hospitalizations during the first year of life occur in the first 3 months and 6 months of life, respectively[2]). Importantly, this approach can confer protection that is present at birth, without the logistical challenges that might be involved with direct infant immunization or prophylactic mAb administration, such as adding an additional product into a complex infant immunization schedule and ensuring vaccine administration prior to any opportunities for RSV exposure, the latter of which could require an additional and potentially unanticipated well-child visit if RSV seasonality remains difficult to predict. Maternal immunization also circumvents the issue of suboptimal immune responses to active immunization in very early infancy that can necessitate administering multiple vaccine doses over several months, leaving the infant unprotected or sub optimally protected in the meantime. Maternal immunization also induces a polyclonal antibody response, and therefore has a low likelihood of applying selective pressure against circulating viruses.

4. SUMMARY OF KEY NONCLINICAL STUDIES

Nonclinical studies in mice, cotton rats, and rhesus macaques supported selection of the RSV subgroup A and subgroup B stabilized prefusion F antigens for RSVpreF. The in vivo data demonstrated, in RSV-naïve experimental animals, that immunization with stabilized prefusion F elicits much higher neutralizing titers than immunization with postfusion F.

To support the clinical development, RSVpreF in representative clinical formulations were tested in a Good Laboratory Practice (GLP)-compliant repeat-dose toxicity study in rats and a GLP-compliant combined fertility and pre- and postnatal developmental toxicity study in pregnant and lactating rabbits.

In both studies, RSVpreF was administered at 120 µg preF A and 120 µg of preF B (240 µg total antigen per dose), or 2 times the recommended clinical dose by intramuscular (IM) injections. Repeat-dose administrations of RSVpreF (1 dose every 3 or 2 weeks for a total of 3 doses) to Wistar Han rats were tolerated without evidence of systemic toxicity, and produced a functional antibody response and anticipated, nonadverse, local inflammatory reactions. No indications of maternal systemic toxicity or effects on mating performance,

female fertility, or embryo-fetal or postnatal survival, growth, or development in the F1 offspring were observed in the combined fertility and developmental toxicity study in rabbits following the administration of RSVpreF for a total of 4 doses (twice premating and twice during gestation).

5. OVERVIEW OF CLINICAL STUDIES IN MATERNAL IMMUNIZATION CLINICAL DEVELOPMENT PLAN

The maternal immunization clinical development plan for RSVpreF comprises 5 studies summarized in Table 12 and described briefly below. Among the 5 studies in the clinical development plan, 2 were conducted in maternal participants:

- **C3671008** is the pivotal Phase 3 study investigating the efficacy, safety, and immunogenicity of a single 120 µg dose level of RSVpreF administered to pregnant women ≤49 years of age including adolescents to protect infants against RSV disease. C3671008 is the only study in the maternal clinical development plan that was designed to evaluate the efficacy of RSVpreF 120 µg in protecting infants against RSV, and the efficacy results from this study provide the basis for the VE of RSVpreF 120 µg.

- **C3671003** investigated the safety, tolerability, and immunogenicity of 2 dose levels (120 µg and 240 µg) of RSVpreF, formulated with or without $Al(OH)_3$, in pregnant women 18-49 years of age. Study C3671003 also evaluated the efficacy of RSVpreF in preventing LRTI in infants caused by RSV as an exploratory endpoint.

The other 3 studies were conducted in nonpregnant participants, and these studies are included in the BLA to provide additional safety and coadministration data on RSVpreF:

- **C3671001** investigated the safety, tolerability, and immunogenicity of various dose levels (60 µg, 120 µg and 240 µg) and formulations (with or without $Al(OH)_3$) of RSVpreF when administered alone or coadministered with SIIV in healthy participants 18-85 years of age.

- **C3671004** investigated the safety, tolerability, and immunogenicity of various dose levels (120 µg and 240 µg) and formulations (with or without $Al(OH)_3$) of RSVpreF when administered alone or coadministered with Tdap in healthy nonpregnant women 18-49 years of age.

- **C3671014** was a lot consistency study which investigated the immunogenicity, safety, and tolerability of 3 lots of the dose and formulation (120 µg without $Al(OH)_3$) used in the pivotal study in healthy participants 18-49 years of age.

The dose and formulation of RSVpreF selected for pivotal study C3671008 (120 µg without $Al(OH)_3$) was based on the safety and immunogenicity data from the C3671003 maternal immunization study and the FIH study C3671001. At the 120 µg and 240 µg dose levels, administered with or without $Al(OH)_3$, RSVpreF elicited robust immune responses in healthy participants 18-85 years of age (C3671001) and in pregnant women 18-49 years of age (C3671003). In study C3671003, no substantial dose-dependent increase in infant neutralizing titers was observed at the 240 µg dose level compared to the 120 µg dose level, or with inclusion of $Al(OH)_3$. Also, maternal-to-infant placental transfer ratios were >1 for all vaccine groups and maternal vaccination with RSVpreF elicited RSV-neutralizing GMTs in infants that were higher than placebo at birth through 6 months after delivery.

5.1. Key Licensure Agreements with the FDA

Throughout the development of RSVpreF, Pfizer sought input from CBER on the clinical development plan for the maternal indication, and on the design of the pivotal Phase 3 C3671008 study endpoints that would support licensure. The key agreements from these interactions are summarized below.

In February 2020, CBER agreed that for the Phase 3 C3671008 study, a VE in either one of the parallel primary endpoints of MA-LRTI or severe MA-LRTI with a lower bound of >20% for the CI would be sufficient to support licensure. CBER also accepted Pfizer's proposal that 3000 mother-infant pairs exposed to the final formulation with a safety follow-up of at least 6 months after birth at the time of filing with either interim or final efficacy analysis would support licensure. Subsequently, on 08 March 2022, in a written response to a Type C Meeting Request, CBER also agreed that an interim analysis could be conducted when at least 43 cases had accrued at ≤90 days and that this interim analysis would be sufficient to support licensure if the VE met an alpha-adjusted lower bound of >20%.

In April 2022, an E-DMC reviewed results of the first interim analysis when 56 MA-LRTI cases had accrued through 90 days and recommended continuation of the study since not all timepoints met the statistical success criterion. No safety concerns were observed. In August 2022, CBER agreed to Pfizer's proposal to conduct the second interim analysis after accrual of at least 62 cases through 90 days in accordance with the overall study analysis plan for final analysis, whereby success of a primary endpoint at 90 days after birth would be sufficient to stop the study for efficacy and declare success (or futility) of the study overall. Specifically, if vaccine efficacy at 90 days met the success criterion (lower bound of CI>20%) using the appropriate multiplicity adjusted alpha level for the second interim analysis, Pfizer proposed that the trial would be concluded and all subsequent and pre-specified timepoints (120, 150, 180 days after birth) would be tested utilizing the alpha reserved for the primary analysis, applying the multiplicity adjustments defined in the statistical analysis plan. CBER also agreed that the second interim analysis could be conducted at the predicted end of the fourth RSV season (two in the northern hemisphere and two in the southern hemisphere) and that these data could be submitted in a BLA as the basis for licensure for the proposed indication.

5.2. Supportive Studies in Nonpregnant Participants

- In healthy participants 18-85 years of age, RSVpreF elicited robust immune responses that remained elevated through 12 months after vaccination, and were consistent between age groups, across dose levels, and for formulations with or without $Al(OH)_3$.

- In healthy nonpregnant women 18-49 years of age, concomitant administration of RSVpreF with Tdap compared to RSVpreF or Tdap alone demonstrated non-inferiority in immune responses to RSV A and RSV B, as well as to DTd and TTd. Immune responses to pertussis components were lower, but the clinical significance of this is unknown.

- In healthy participants 18-49 years of age, 3 lots of RSVpreF corresponding to the final formulation elicited neutralizing titers that were within the predefined 1.5-fold equivalence criterion and thus lot-to-lot consistency was demonstrated.

- All dose levels and formulations of RSVpreF studied in the 3 supportive studies were safe and well-tolerated.

5.2.1. Phase 1/2 Study C3671001 – First in Human

The completed first in human (FIH) dose and formulation-finding Study C3671001 (Table 12) evaluated the safety, tolerability, and immunogenicity of RSVpreF with and without concomitant seasonal inactivated influenza vaccine (SIIV) administration in 1235 nonpregnant female and male participants 18 to 85 years of age, divided into age subgroups of 18-49 and 50-85 years of age to support the maternal and the older adult indications. Three dose levels of RSVpreF (60 µg, 120 µg, and 240 µg) were evaluated in formulations with and without $Al(OH)_3$. Analyses were performed for participants 18-49 or 50-85 years of age as specified in Table 12.

Of the 1235 participants randomized, 1233 were vaccinated and 1135 (91.9%) completed the 12 month follow up visit. In the Sentinel Cohort, 84 participants were vaccinated in the 18-49 year age group and 84 were vaccinated in the 50-85 year age group. In the Expanded Cohort, 533 participants were vaccinated in the 18-49 year age group and 532 were vaccinated in the 65-85 year age group.

In both age groups, RSVpreF elicited robust neutralizing responses against RSV subgroup A (RSV A) and RSV subgroup B (RSV B) 1 month after vaccination across all vaccine dose levels and formulations. The inclusion of $Al(OH)_3$ showed no benefit in enhancing immune responses at any dose level and the frequency and severity of local reactions trended higher in the groups receiving $Al(OH)_3$ containing formulations, noticeably in the younger (18-49 year) age group. Immune responses trended higher in the younger age group than the older age group and in females than males. RSV A– and RSV B–neutralizing titer geometric mean fold rises (GMFRs) remained 4- to 5-fold higher at 12 months after vaccination compared to before vaccination, indicating antibody persistence.

Coadministration of RSVpreF with SIIV was evaluated descriptively early in RSVpreF clinical development. At each dose level and formulation RSV neutralizing titers were similar with or without SIIV coadministration with RSVpreF. Immune responses to SIIV as measured by hemagglutination inhibition assay (HAI) GMTs trended lower when RSVpreF was coadministered with SIIV compared with SIIV alone. A study (C3671006) to evaluate the noninferiority of responses to RSVpreF co-administered with SIIV versus responses to either vaccine administered alone is clinically complete, and data from this study will be available in Quarter 2 of 2023 and are planned to be submitted to regulatory agencies.

Analyses of local reaction, systemic event, and AEs endpoints (listed in Table 12) in both cohorts demonstrated that RSVpreF was safe and well tolerated when administered alone or with SIIV.

At approximately 12 months after the first RSVpreF vaccination, the RSVpreF 240 µg groups were randomized to receive initial vaccination or revaccination with placebo or the same RSVpreF dose level/formulation as Dose 1 (RSVpreF 240 µg with or without $Al(OH)_3$) and with or without SIIV. The RSVpreF 240 µg groups were chosen for the revaccination phase prior to final dose level and formulation selection. Revaccination after 12 months increased RSV neutralizing titer levels, but increases were slightly lower than increases observed after Vaccination 1. Similar to the initial RSVpreF dose, titers at 12 months after revaccination (Dose 2) remained above baseline (pre-revaccination).

5.2.2. Phase 2b Study C3671004 – Coadministration with Tdap

Study C3671004 was a Phase 2b, placebo controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of the RSV vaccine when administered concomitantly with Tdap in healthy nonpregnant women 18 through 49 years of age. Participants were randomized in a 1:1:1:1:1 ratio to receive one of the following 5 schedules: 120 µg RSV vaccine antigen with concomitant Tdap, 120 µg RSV vaccine antigen with placebo, 240 µg RSV vaccine antigen with $Al(OH)_3$ and concomitant Tdap, 240 µg RSV vaccine antigen with $Al(OH)_3$ and placebo, or placebo and Tdap.

Of 709 participants vaccinated, 695 (97.5%) completed the 1 month post-vaccination visit.

The primary objective of demonstrating noninferiority was met for both anti-DTd and anti-TTd immune responses, per the predefined threshold for determining noninferiority of the immune response to TTd and DTd (the lower bound of the 2-sided 95% CI for the difference between combined RSVpreF/Tdap groups and placebo/Tdap group is >-10%) (Figure 9A). The primary objective of demonstrating noninferiority was not met for anti-PT, anti-FHA, and anti-PRN immune responses, per the predefined threshold for determining noninferiority of the immune response to antipertussis components (the lower bound of the 2-sided 95% CI for the GMC ratio of the combined RSVpreF/Tdap groups to the placebo/Tdap group is > 0.67) (Figure 9B).

The primary objective of demonstrating noninferiority for both RSV A and RSV B immune responses was met, per the predefined threshold for determining noninferiority of the immune response to RSV (the lower bound of the 2-sided 95% CI for the GMT ratio for combined RSVpreF/Tdap groups divided by combined RSVpreF/placebo groups are >0.5 [noninferiority margin of 2-fold] for RSV A– and RSV B–neutralizing antibodies) (Figure 9B).

Per the predefined threshold for determining noninferiority of the immune response to RSV (the lower bound of the 2-sided 95% CI for the GMT ratio for combined RSVpreF/Tdap groups divided by combined RSVpreF/placebo groups are >0.67 [noninferiority margin of 1.5-fold] for RSV A– and RSV B–neutralizing antibodies), the secondary objective of demonstrating noninferiority of immune responses to RSV by a 1.5-fold margin was met for both RSV A and RSV B immune responses (lower bound 2-sided 95% CI value range = 0.78 to 0.84 at 1 month after vaccination) (Figure 9B).

Both formulations of RSVpreF were safe and well tolerated when administered alone or with Tdap. Most reported local reactions or systemic events were mild or moderate in intensity. The observed incidence of systemic events of severe intensity ranged from 2.8% to 6.4% for participants who received RSVpreF alone, 4.2% to 4.3% for participants who received either RSVpreF formulation with Tdap, and 0.7% for participants who received Tdap alone.

The frequency of AEs reported within 1 month after vaccination ranged from 5.6% to 10.4% of participants across vaccine groups (Table 13). There were 7 medically attended AEs (MAEs) reported during the study that were mostly reported by single participants, and none were serious, immediate, or related to study treatment. There were no SAEs, immediate AEs, or life-threatening AEs reported within 1 month of vaccination in this study. One (1) participant reported the SAE of spontaneous abortion at 42 days post-vaccination, but this event was considered to be unrelated to study treatment.

The results of this study confirm that the 2 RSVpreF formulations when administered with and without the $Al(OH)_3$ adjuvant were safe and well tolerated when administered alone or concomitantly with Tdap in healthy non-pregnant women 18 through 49 years of age. Immunogenicity data indicated non-inferiority in immune response to the diphtheria and tetanus components. Immune response to the pertussis component of Tdap was lower when RSVpreF and Tdap were administered concomitantly as compared to Tdap administered alone, but the clinical relevance of this observation is unknown.

5.2.3. Phase 3 Study C3671014 – Lot Consistency

The completed Phase 3, multicenter, parallel-group, randomized, double-blind, placebo-controlled Study C3671014 (Table 12) examined the immune response and the safety and tolerability profiles across 3 manufactured lots of RSVpreF when administered as a single 120 μg dose level to healthy adults 18 through 49 years of age, to demonstrate lot equivalence in the manufacturing of RSVpreF.

Across all vaccine lots, 745 participants were randomized and vaccinated with RSVpreF 120 μg, and 247 participants were randomized and vaccinated with placebo. In total, 97.7% of participants completed the study.

Non-inferiority was met for both RSV A and RSV B neutralizing titers, with each pair of between-lot comparisons from the 3 vaccine lots meeting the predefined 1.5-fold equivalence criterion (2 sided 95% CI for each between lot comparison based on the geometric mean ratio (GMR) was contained in the interval 0.667 to 1.5) for the evaluable immunogenicity population (Table 14). Subgroup analyses by sex showed similar results for females and males for both RSV A and RSV B.

Overall, RSVpreF was safe and well tolerated, with safety profiles that were similar across the 3 RSVpreF vaccine lots and consistent with previous studies.

5.3. Supportive Study in Pregnant Participants

- In healthy pregnant participants 18-49 years of age, all dose levels and formulations of RSVpreF elicited robust neutralizing titers which persisted above baseline through 6 months after delivery.

- Maternal to infant placental transfer ratios of neutralizing antibodies were >1 for all vaccine groups.

- RSV neutralizing titers in infants born to vaccinated mothers remained high through 6 months after birth.

- Higher neutralizing titers in maternal participants vaccinated with $Al(OH)_3$ containing formulations did not translate to higher neutralizing titers in their infants.

- All dose levels and formulations of RSVpreF were safe and well-tolerated.

- The results of this study provided support for advancement of the RSVpreF 120 µg unadjuvanted formulation into a large, global Phase 3 safety and efficacy study.

5.3.1. Phase 2b Study C3671003

Study C3671003 was a Phase 2b, multicenter, randomized, placebo-controlled study that assessed the safety, tolerability, and immunogenicity in maternal participants as well as safety and characteristics of transplacentally transferred antibodies in their infants.

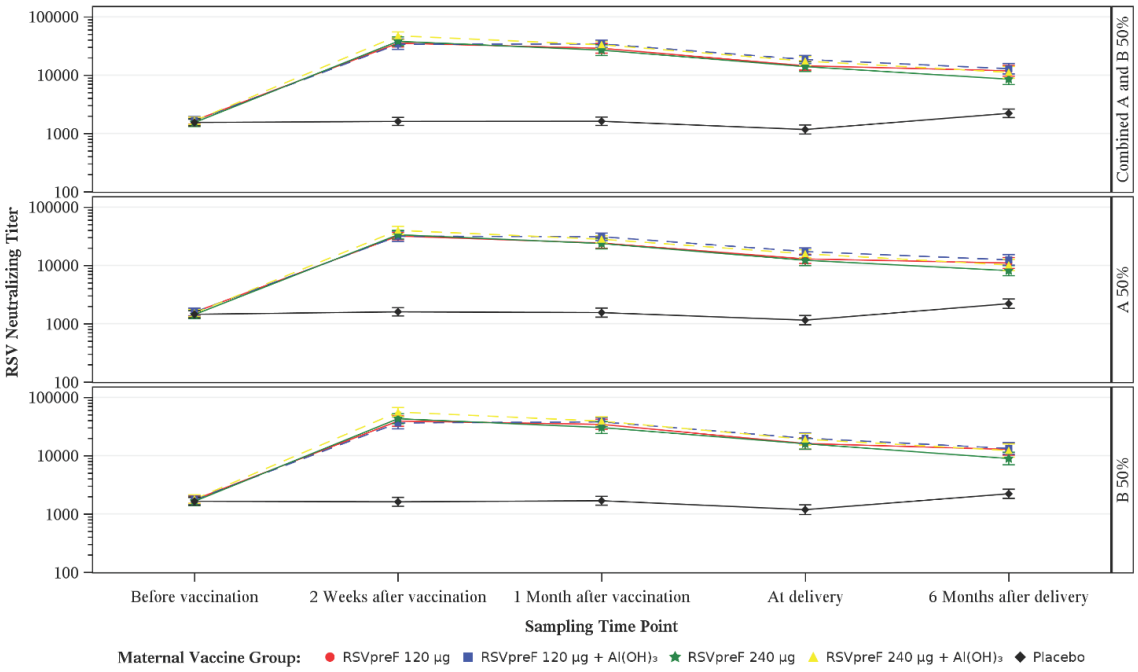
Healthy pregnant women 18 through 49 years of age were randomized to receive a single intramuscular injection of one of 2 dose levels of RSVpreF at 120 µg (60 µg A and 60 µg B) or 240 µg (120 µg A and 120 µg B) of the prefusion RSV F antigen, formulated with or without $Al(OH)_3$, or placebo (1:1:1:1:1 randomization), with planned vaccination between 24-0/7 and 36-0/7 weeks. This completed study included 579 vaccinated maternal participants in 4 countries (US, Argentina, Chile, and South Africa).

Across groups, the median age at vaccination was approximately 27 years, and the median gestational age at vaccination was approximately 30 weeks. A lower proportion of participants (19.7%) were enrolled in the 24 to <27-week gestational age stratum compared to other gestational age strata (26.3% to 27.1%). Most maternal participants were White (75.8%) or Black or African American (20.6%), and non-Hispanic/non-Latino (72.2%).

The study included 572 infants born to vaccinated maternal participants. Demographic characteristics of infant participants generally reflect those of their mothers. Half of the infants were female and the majority of infants were White (73.4%) or Black or African American (20.6%), and non-Hispanic/non-Latino (70.6%). Most infants were born at term; the median gestational age at birth was approximately 39 weeks.

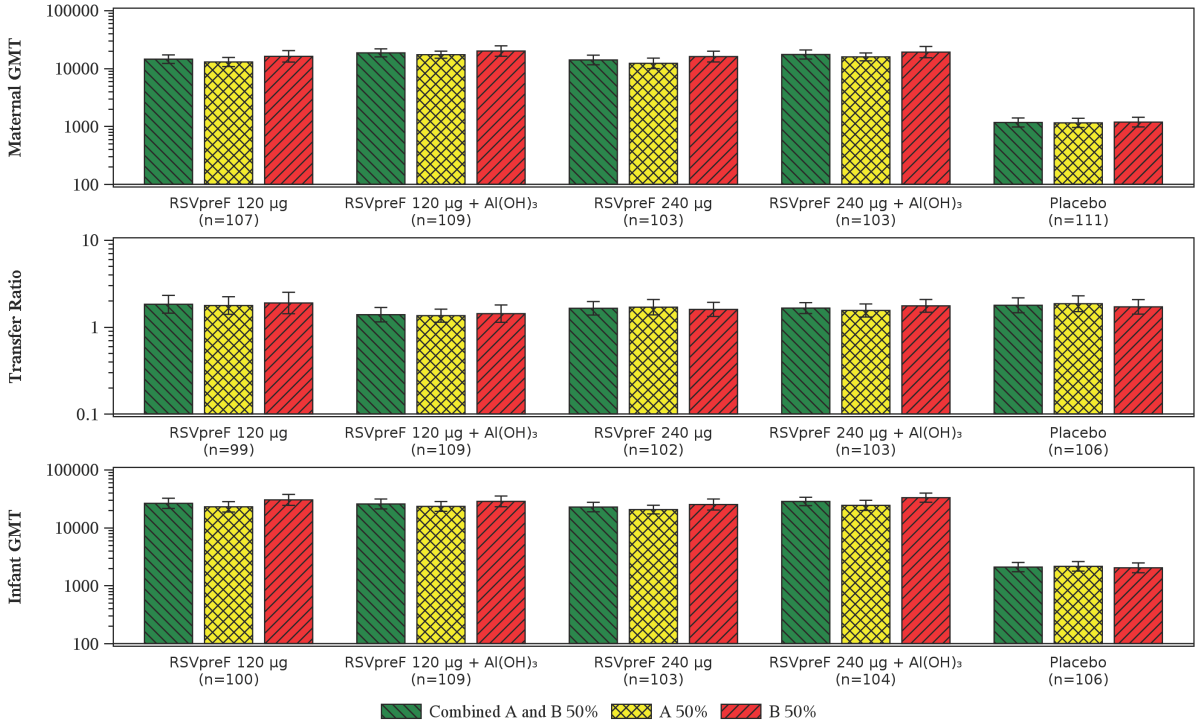
RSVpreF at all dose levels and formulations elicited robust neutralizing titers in maternal participants 2 weeks after vaccination (GMFRs ranging from 20.8 to 27.7) that persisted above baseline (GMFRs ranging from 5.6 to 7.7) through 6 months after delivery (Figure 1). RSVpreF GMTs also remained above levels observed in placebo participants through 6 months after delivery. Maternal-to-infant placental transfer ratios were >1 for all groups (Figure 2) demonstrating that maternal antibodies are efficiently transferred to infant participants. RSV neutralizing GMTs in infants through 6 months of life remained higher in those born to vaccinated mothers (943 to 1569) than infants born to mothers who received placebo (232) (Figure 3). RSV neutralizing GMTs in maternal participants were higher after vaccination with RSVpreF formulated with $Al(OH)_3$ than without $Al(OH)_3$; however, this did not result in higher RSV neutralizing titer GMTs in their infants.

Figure 1. Line Plot for RSV 50% Neutralizing Titers – Maternal Participants – Evaluable Immunogenicity Population



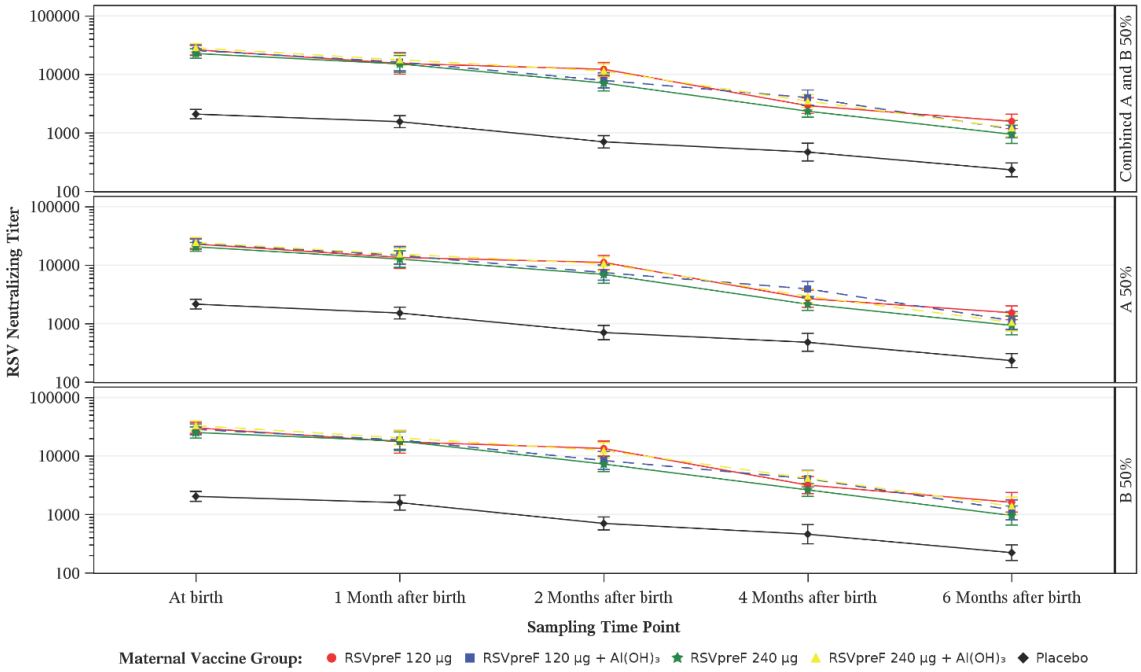
Abbreviation: RSV = respiratory syncytial virus.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2022 (00:56) Source Data: adva Table Generation: 01MAR2022 (21:31) (Cutoff Date: 16DEC2021, Snapshot Date: 16DEC2021) Output File: ./nda1/C3671003_CSR/adva_f002

Figure 2. Maternal and Infant RSV 50% Neutralizing Titer GMTs to Demonstrate Transfer Ratios - Evaluable Immunogenicity Population



Abbreviation: RSV = respiratory syncytial virus.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2022 (00:56) Source Data: adva Table Generation: 23FEB2022 (07:34) (Cutoff Date: 16DEC2021, Snapshot Date: 16DEC2021) Output File: ./nda1/C3671003_CSR/adva_f004_ratio

Figure 3. Line Plot for RSV 50% Neutralizing Titers - Infant Participants - Evaluable Immunogenicity Population



Abbreviation: RSV = respiratory syncytial virus.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2022 (00:56) Source Data: adva Table Generation: 01MAR2022 (21:31) (Cutoff Date: 16DEC2021, Snapshot Date: 16DEC2021) Output File: ./nda1/C3671003_CSR/adva_f002b

In an exploratory efficacy analysis, when all vaccine groups were combined and compared to placebo, efficacy of maternal vaccination through the data cutoff date against RSV-associated medically significant infant LRTI, medically attended LRTI, and medically attended severe LRTI were 75% (95% CI: -90%, 97%), 75% (95% CI: -11%, 94%), and 83% (95% CI: -48%, 99%), respectively. When analyzed through 180 days after birth, the corresponding VEs were 83.0%, 84.7%, and 91.5% (Table 2). When the analysis was limited to northern hemisphere infants, the efficacy estimates were 75% (95% CI: -251%, 98%), 85% (95% CI: 22%, 98%), and 92% (95% CI: -6%, 100%) for medically significant, medically attended, and medically attended severe RSV-associated LRTI, respectively.

Table 2. Efficacy of Maternal Vaccination Against RSV-Associated Lower Respiratory Tract Illness in Infants Through 180 Days - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)		
	RSVpreF (N[a]=456)	Placebo (N[a]=116)	
Endpoint Description	**Number of Cases (%)**	**Number of Cases (%)**	**Vaccine Efficacy[b] (95% CI)[b]**
Medically significant LRTI[c]	2(0.4)	3(2.6)	83.0% (-48.0%, 98.6%)
Medically attended LRTI[d]	3(0.7)	5(4.3)	84.7% (21.5%, 97.6%)
Medically attended Severe LRTI[e]	1(0.2)	3(2.6)	91.5% (-5.6%, 99.8%)

Abbreviation: LRTI = lower respiratory tract illness.
Medically attended visit = infant participant has been taken to or seen by a healthcare provider (eg, outpatient or inpatient visit, emergency room, urgent care, or home visit).
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.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2022 (01:49) Source Data: adli Table Generation: 05MAY2022 (21:33)
(Data cutoff date : 16DEC2021 Database snapshot date : 16DEC2021) Output File: ./nda1/C3671003 CSR ADHOC/adli s002 ve 180

5.3.1.1. Safety in Maternal Participants

Local reactions were reported more frequently by maternal participants who received RSVpreF compared with the placebo group. The most common local reaction in maternal participants across all RSVpreF vaccine groups and placebo was pain at the injection site. Most local reactions were mild or moderate and few local reactions of redness or swelling were reported. Severe local reaction (pain at the injection site) was reported by 1 participant who received 240 µg RSVpreF. In addition, 2 participants who received 120 µg RSVpreF + $Al(OH)_3$ formulation that did not progress also reported severe local reactions (pain at the injection site).

In general, systemic events were reported similarly among all maternal participants (RSVpreF and placebo groups). Most systemic events were mild or moderate. The most frequently reported severe systemic event across all groups was fatigue. Few fevers were reported, and most were mild or moderate. One participant who received 120 µg RSVpreF + $Al(OH)_3$ reported a Grade 4 fever.

AEs in maternal participants within 1 month after vaccination were reported in a similar frequency across all vaccine groups with no clear association with dose level or formulation (Table 15). No immediate AEs or AEs leading to withdrawal were reported. Within 1 month after vaccination, SAEs, severe AEs, and MAEs were reported in a similar frequency across all groups. One participant who received RSVpreF 120 µg reported a related AE of dizziness that began on Day 1 with a severity of mild that resolved the same day. AEs reported in at least 4 or more maternal participants in any group within 1 month after vaccination were abdominal pain, nausea, and premature delivery. There were no dose- or formulation-related trends in these most frequently reported AEs.

There were no deaths of maternal participants reported during the study. SAEs were reported similarly among all groups of maternal participants and were mostly associated with pregnancy-related conditions. One stillbirth occurred in a maternal participant who received placebo.

Most maternal participants in this study had uncomplicated pregnancies and delivered via the vaginal route at term.

5.3.1.2. Safety in Infant Participants

AEs in infant participants within 1 month of age were reported in a similar frequency across all vaccine groups with no clear association with dose level or formulation (Table 16). SAEs, severe AEs, and MAEs in infant participants within 1 month of age were reported in a similar frequency across all vaccine groups with no clear association with dose level or formulation. There were no related AEs reported in infant participants throughout the study. One infant participant who received placebo was withdrawn 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. Across all vaccine groups AEs reported in at least 4 or more infant participants in any group were hyperbilirubinemia (range of 2 to 11 participants) and jaundice (range of 5 to 12 participants). None of these most frequently

reported AEs in any vaccine group had incidences that were significantly different from placebo.

There were no deaths of infant participants reported during the study. 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 reported for infant participants were considered related to maternal vaccination with investigational product.

There were no AESI of developmental delay reported throughout the study. Most AESI of congenital anomalies were mild and those of at least moderate severity were reported in a similar frequency across all groups. Note that all congenital anomalies were to be reported as SAEs in the protocol for C3671003, regardless of severity. The congenital anomalies in Study C3671003 were investigator-determined based on guidance from the World Health Organization (WHO)[82], which had included many physical findings that are often considered not clinically significant or are normal variants (eg, umbilical hernia, mongolian spot, etc). The WHO guidance was updated in 2020 to exclude these conditions.[83] None of these events were considered related to maternal vaccination with investigational product.

Most infants were born at term and had uncomplicated transitions after delivery (Table 17). Specific birth complications were reported with similar frequency across study groups.

5.4. Pivotal Phase 3 Efficacy Study C3671008 in Pregnant Participants

- Maternal vaccination with RSVpreF 120 µg was 81.8% efficacious at preventing severe MA-LRTI due to RSV in infant participants within 90 days after birth and 69.4% efficacious at preventing severe MA-LRTI due to RSV in infant participants within 180 days after birth.

- RSVpreF also demonstrated a significant reduction in RSV-positive MA-LRTIs through 360 days after birth, and RSV-associated hospitalizations through 180 days after birth.

- RSVpreF 120 µg was safe and well tolerated by maternal participants. AEs and SAEs in maternal participants were reported with similar frequency across the RSVpreF and placebo groups, and were most often related to complications of pregnancy, labor, delivery, and the immediate postpartum period. Pregnancy outcomes were similar across both groups.

- No safety signals were detected in infant participants through up to 24 months after birth. Birth outcomes for infant participants were similar for the RSVpreF and placebo groups. No meaningful differences were detected with respect to prematurity, Apgar scores, or low birthweight.

5.4.1. Study C3671008 Background

C3671008 Study Design and Methodology

C3671008 is the Phase 3, multicenter, randomized, double-blinded, placebo-controlled study designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against MA-LRTI and severe LRTI caused by RSV in infants. Healthy women ≤49 years of age including adolescents who were between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination were evaluated for eligibility. Maternal participants were randomized in a 1:1 ratio to either RSVpreF 120 µg (unadjuvanted) or placebo. Vaccination of maternal participants was planned at a time of year such that the infant was likely to be exposed to seasonal RSV during the first 6 months of life. It was originally anticipated that approximately 6900 mother-infant pairs would be needed to accumulate the 124 per-protocol cases prior to the global COVID-19 pandemic. Nonpharmaceutical interventions associated with the COVID-19 pandemic led to the reduced transmission of RSV and shifts of typical RSV seasonality in many geographies.[84] It resulted in lower-than-expected endpoint accrual, particularly for infants born during 2020. With the variable RSV season, the sample size could be increased up to 10,000 maternal participants based on the number of cases of RSV.

This is an event-driven study with an original final analysis target of 124 adjudicated (primary endpoint) cases of MA-LRTI due to RSV; up to 2 interim analyses were to be performed after at least 43 cases within 90 days had occurred. Assessments include parameters to allow descriptions of safety, tolerability, and immunogenicity of the vaccine in maternal participants and in their infants. For all infant participants, data were collected for any medically attended respiratory illness to assess for cases of lower respiratory tract illness due to RSV (efficacy endpoint). Additionally, throughout the study, all respiratory illnesses, SAEs, and NDCMCs reported were assessed in this population. For infant participants enrolled during the first year of the study, the extended 24-month study duration involves longer-term respiratory tract illness surveillance and safety oversight to address safety and the possibility of conferred enhanced protection (antibody persistence) during a second RSV season. For infant participants enrolled during the second year of the study, follow up is 12 months.

All medically attended respiratory tract illnesses (MA-RTIs) meeting the protocol definition for a potential study primary endpoint were adjudicated by an independent adjudication committee. In addition, this study utilized an external data monitoring committee (E-DMC) to monitor vaccine safety, efficacy, and potential study futility.

Included in this briefing document are the results of all infant primary and secondary efficacy endpoints and the key exploratory endpoint results as agreed to by CBER (Section 5.1). Data for the exploratory immunogenicity analyses for this ongoing study are not available at this time; immunogenicity data will be available in Quarter 1 of 2024 and are planned to be submitted to regulatory agencies.

5.4.1.1. Efficacy Assessments

MA-RTIs in infant participants were identified from 72 hours after the infant's delivery until the end of the infant's participation in the study. If the infant participant met any RTI criteria listed below (Table 3) that required a visit by or a visit to an healthcare provider (HCP) (outpatient or inpatient visit, emergency room, urgent care, or scheduled home visit), an RTI study visit by the study staff was required (for all infants <180 days after birth; for infants >180 days after birth, only those with severe symptoms or who were hospitalized).

Evaluation of these MA-RTI events were based on predefined clinical signs and symptoms and testing criteria (Table 3) obtained at the medically attended visit with the HCP and/or the study visit. These events were assessed and confirmed to be contributing to the study endpoints by an independent Endpoint Adjudication Committee (EAC) as per the protocol.

Table 3. Study Endpoint Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
Medically attended visit	Infant participant has been taken to or seen by a healthcare provider (eg, outpatient or inpatient visit, emergency room, urgent care, or home visit)
MA-RTI visit for infant participant	A medically attended visit AND 1 or more of the following RTI 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[b] laboratory with NAAT for RSV
MA-RTI due to RSV[a]	• An MA-RTI visit **AND** • RSV-positive test result
MA-LRTI due to any cause	• Infant with an MA-RTI 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-LRTI due to RSV[a]	• Infant with an MA-RTI visit **AND** • 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 AND • RSV-positive test result
Hospitalized RTI due to RSV[a]	An RTI due to RSV that results in hospitalization

Table 3. Study Endpoint Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
Severe MA-LRTI due to RSV[a]	• Infant with an MA-RTI visit AND • 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 (ie, invasive or noninvasive) **OR** • ICU admission for >4 hours **OR** • Failure to respond/unconscious AND • RSV-positive test result
Protocol-defined primary endpoint	• Any MA-LRTI or severe MA-LRTI due to RSV as determined by an EAC[c]

Abbreviations: bpm=breaths per minute; EAC=Endpoint Adjudication Committee; ICU=intensive care unit; MA-LRTI =medically attended lower respiratory tract illness; MA-RTI=medically attended respiratory tract illness; NAAT=nucleic acid amplification technology; RR=respiratory rate; RSV=respiratory syncytial virus; RT-PCR=reverse transcriptase polymerase chain reaction; RTI=respiratory tract illness; SpO_2=oxygen saturation.

a. The EAC will determine if the endpoint criteria have been met upon review of the site source documentation from the MA-RTI and RTI study visits, including all available RSV test results.

b. See the EAC charter for more details regarding the certified laboratory.

c. Severe MA-LRTI cases that are adjudicated by the EAC will always be MA-LRTI cases (severe MA-LRTIs are a subset of the MA-LRTIs).

The EAC remained blinded to the maternal participants' vaccine assignments, and the EAC's assessment of these events represented the final confirmed endpoint classification of the event. The efficacy-related events for adjudication included all RSV-associated MA-RTI events.

The EAC was responsible for adjudicating whether MA-RTI events fulfill the protocol-defined clinical criteria as a primary endpoint, including if the event was due to RSV based on confirmatory testing, and the severity of the RSV illness (eg, MA-RTI, MA-LRTI, severe MA-LRTI, and/or hospitalizations). The EAC adjudicated all cases through the active follow-up period including all primary cases occurring up to 180 days after birth. The EAC also reviewed all MA-LRTI cases due to any pathogen when related to deaths.

5.4.1.2. Efficacy Endpoints

5.4.1.2.1. Primary Efficacy Endpoints – Infant Participants

- RSV-positive MA-LRTI (as confirmed by the EAC) occurring within 90 days, 120 days, 150 days, and 180 days after birth (see Section 5.4.1.5 for sequence of testing across time points).

- Severe MA-LRTI due to RSV (as confirmed by the EAC) occurring within 90 days, 120 days, 150 days, and 180 days after birth (see Section 5.4.1.5 for sequence of testing across time points).

5.4.1.2.2. Secondary Efficacy Endpoints – Infant Participants

- Hospitalization due to RSV (as confirmed by the EAC) occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth.

- MA-LRTI due to any cause with protocol-defined criteria occurring within 90 days, 120 days, 150 days, 180 days, and 360 days after birth.

- RSV-positive MA-LRTI occurring within 210 days, 240 days, 270 days, and 360 days after birth.

5.4.1.3. Interim Efficacy Analysis

A first interim analysis was conducted in April 2022 when 56 evaluable cases of MA-LRTI 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 (Table 18), and the E-DMC reviewing the results recommended continuation of the study. The double-blind was maintained after the first interim analysis.

A second interim analysis was conducted on 28 October 2022 following the predicted end of the fourth RSV season in the study (efficacy data cutoff: 30 September 2022). At this time point, 80 evaluable cases of MA-LRTI due to RSV within 90 days had accrued, including 39 evaluable cases of severe MA-LRTI due to RSV within 90 days. The recommendation of the E-DMC was to stop the study for efficacy because the pre-specified success criterion for VE was met for 1 of the 2 primary efficacy endpoints (Section 5.4.2.1.1), thereby triggering the final analysis for all endpoints.

Enrollment for maternal participants was completed on 03 October 2022. Ongoing study participants continue to remain in blinded follow-up after the primary analyses to evaluate long term safety.

5.4.1.4. Statistical Analyses

For the efficacy and safety analyses presented in this briefing document:

- The infant evaluable efficacy population was the primary population for efficacy analyses. The analyses were also conducted 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.

The following analyses were also performed:

- Subgroup analyses for selected efficacy endpoints were performed on the following variables: maternal GA at vaccination, country, country income level, exclusive breastfeeding, duration of breastfeeding, maternal smoking, number of household members, and maternal age at vaccination.

5.4.1.5. Hypotheses and Decision Rules

The null hypothesis was that VE for both primary endpoints was less than or equal to 20%, against the alternative that VE for at least one of the primary endpoints was greater than 20%. For each secondary endpoint the null hypothesis was that VE was less than or equal to 0%, against the alternative that VE was greater than 0%. Hypothesis testing of the secondary endpoints was conditional upon rejection of the null hypothesis for at least 1 of the primary endpoints.

The 2 primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV were tested in parallel using a Bonferroni multiplicity adjustment procedure, whereby half the available alpha was used on each of the 2 endpoints. Success of the trial required rejection of the null hypothesis (ie, a CI lower bound >20%) for either of the 2 primary endpoints.

Testing of the 2 primary endpoints across the time intervals followed a fixed sequence with a gatekeeping strategy.

Up to 2 interim analyses could be performed to assess efficacy and safety after at least 43 cases of MA-LRTI due to RSV within 90 days had occurred. Based on the fraction of cases included in an interim analysis, an alpha level was derived based on a Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. Consideration was given to stopping the study for efficacy if the analysis of either primary endpoint through 90 days met the statistical success criterion.

5.4.2. Study C3671008 Efficacy Results (Infant Participants)

Demographics of the Study Population

As of the safety data cutoff date (02 September 2022), 7392 maternal participants were randomized to receive RSVpreF (3695) or placebo (3697). Most randomized participants (99.5%) completed vaccination. Demographic and baseline characteristics for the maternal safety population were similar across the 2 vaccine groups. The largest representation of maternal participants (44.7%) was in the gestational age ≥32 weeks to ≤36 weeks stratum at the time of vaccination (Table 4). 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. Most maternal participants had a history of 0 or 1 pregnancies prior to the study pregnancy.

Table 4. Selected Demographic Characteristics - Maternal Participants - Safety Population

	Vaccine Group (as Administered)		
	RSVpreF 120 µg (N[a]=3682) n[b] (%)	Placebo (N[a]=3675) n[b] (%)	Total (N[a]=7357) n[b] (%)
Age at vaccination (years)			
N	3682	3675	7357
Mean (SD)	29.1 (5.64)	29.0 (5.74)	29.0 (5.69)
Median (Range)	29.0 (16- 45)	29.0 (14- 47)	29.0 (14- 47)
Gestational Age (GA) at vaccination (weeks)			
N	3682	3675	7357
Mean (SD)	30.83 (3.538)	30.82 (3.550)	30.83 (3.544)
Median (Range)	31.30 (24.0- 36.6)	31.30 (24.0- 36.9)	31.30 (24.0- 36.9)
Gestational Age (GA) at vaccination			
≥24 weeks to <28 weeks	941 (25.6)	909 (24.7)	1850 (25.1)
≥28 weeks to <32 weeks	1085 (29.5)	1128 (30.7)	2213 (30.1)
≥32 weeks to ≤36 weeks	1653 (44.9)	1632 (44.4)	3285 (44.7)
>36 weeks	3 (<0.1)	6 (0.2)	9 (0.1)

Note: Participant (b) (6) is counted under ≥24 weeks to <28 weeks however actual age was 23 weeks 6 days.
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants in the specified category.

As of the safety data cutoff date (02 September 2022), 7128 infant participants were born to mothers randomized to RSVpreF (3570) or placebo (3558) and were enrolled in the study. Of these, 95.7% and 79.3% of infant participants had completed the follow-up visits at 1 month and 6 months after birth, respectively. Demographic and baseline characteristics for the infant safety population were balanced across the 2 vaccine groups. Half of the infants were female, and, reflective of the enrolled population, the majority of infants were white and non-Hispanic/non-Latino. Most infants were born at term (≥93.7% born at ≥37 weeks to <42 weeks); refer to Section 5.4.5.1.10.1 for details regarding birth outcomes during the study.

5.4.2.1. Infant Primary Efficacy Endpoints

5.4.2.1.1. Severe MA-LRTI Due to RSV, Occurring Within 90, 120, 150, and 180 Days After Birth, as Confirmed by the EAC

The VE results based on case accrual through the efficacy data cutoff date met the statistical criterion for success (a CI lower bound >20%) for reducing severe MA-LRTI due to RSV as confirmed by the EAC, at all timepoints through 180 days (Table 5 and Figure 4).

In the evaluable efficacy population:

- There were 39 cases of EAC-confirmed RSV-positive severe MA-LRTI cases in infants within 90 days after birth, including 6 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 81 cases of EAC-confirmed RSV-positive severe MA-LRTI cases in infants within 180 days after birth, including 19 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.

Analysis of this primary endpoint using the mITT population yielded similar results. In the mITT population, additional cases of EAC-confirmed RSV-positive severe MA-LRTI cases in infants included: 2 in the RSVpreF group occurring within 90 days after birth in the RSVpreF group; 1 in the placebo group occurring within 150 days after birth.

Table 5. Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

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

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
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-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
c. 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).
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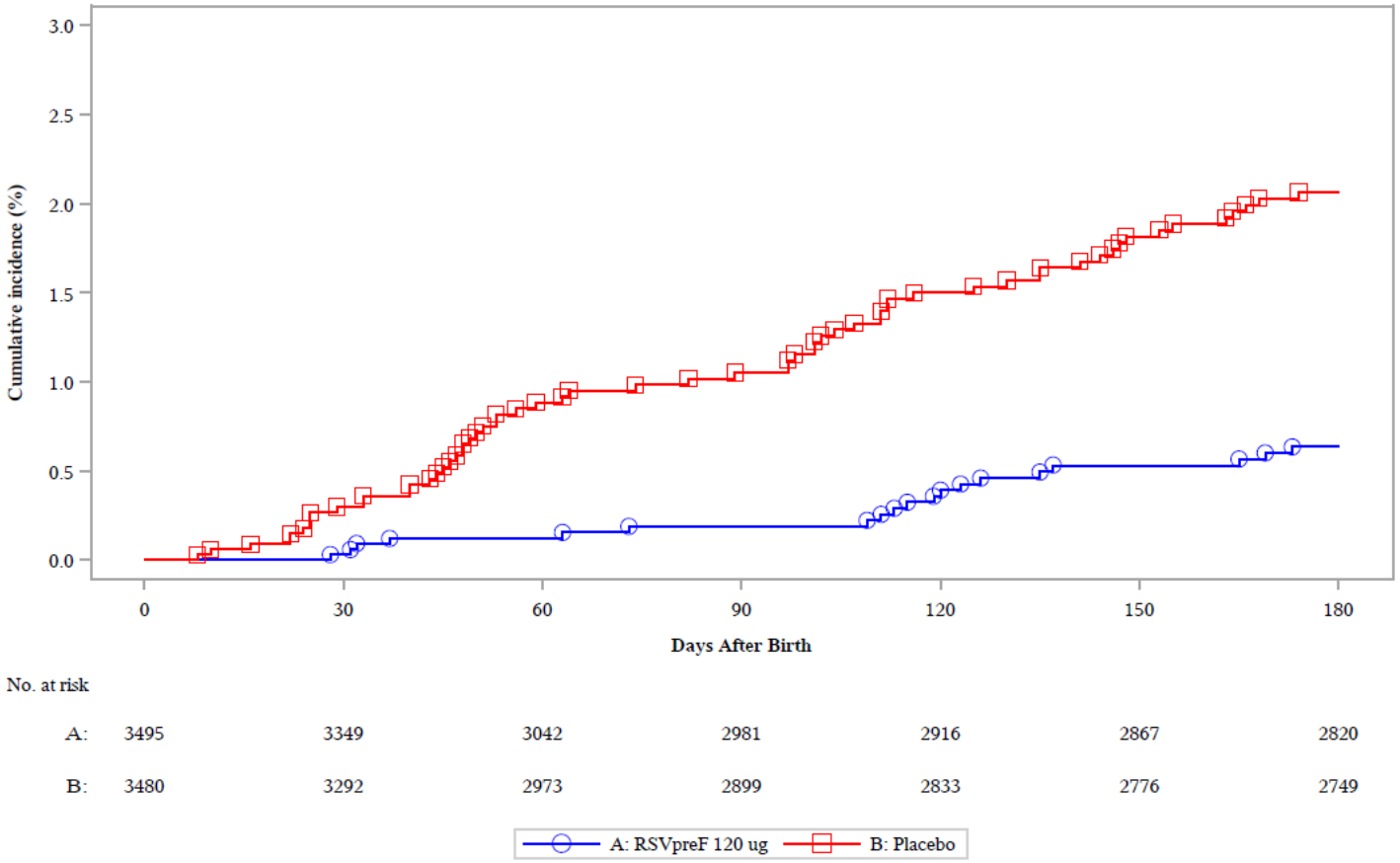
(Database snapshot date : 14OCT2022) Output File: ./mat 1008/C3671008 REX/adprim s001b rsvsev

Figure 4. Kaplan-Meier Curves for Severe MA-LRTIs Due to RSV Confirmed by EAC Within 180 Days After Birth - Infant Participants - Evaluable Efficacy Population



Abbreviation: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
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(Database snapshot date : 14OCT2022) Output File: ./mat_1008/C3671008_REX/adprim_f001_rsvsev_d180

5.4.2.1.2. MA-LRTI Due to RSV, Occurring Within 90, 120, 150 and 180 Days After Birth, as Confirmed by the EAC

The VE results based on case accrual through the efficacy data cutoff date did not meet the statistical criterion for success (a CI lower bound >20%) for reducing MA-LRTI due to RSV as confirmed by the EAC (Table 6 and Figure 5).

In the evaluable efficacy population:

- There were 80 cases of EAC-confirmed RSV-positive MA-LRTI cases in infants within 90 days after birth, including 24 in the RSVpreF group and 56 in the placebo group, corresponding to a VE of 57.1% (99.5% CI: 14.7%, 79.8%) for RSVpreF.

- There were 174 cases of EAC-confirmed RSV-positive MA-LRTI cases in infants within 180 days after birth, including 57 in the RSVpreF group and 117 in the placebo group, corresponding to a VE of 51.3% (97.58% CI: 29.4%, 66.8%) for RSVpreF.

Despite not meeting the statistical success criterion at 90 days as a consequence of the stringent alpha level applied at the second IA, the estimate of VE is consistent with those seen at later timepoints where a higher alpha level is used for these descriptive summaries and the lower bounds of the CIs are consistently >20% through 180 days. Although these results cannot be considered statistically significant based on the pre-specified multiplicity strategy, nominal unadjusted 1-sided p-values at each analysis timepoint, provided in Table 6 as an additional post-hoc summary, indicate that the results for this endpoint at all timepoints are consistent with a true VE of more than 20%, are clinically meaningful and support the proposed indication.

Analysis of this primary endpoint using the mITT population yielded similar results. In the mITT population, additional cases of EAC-confirmed RSV-positive MA-LRTI in infants included: 3 in the RSVpreF group occurring within 90 days after birth; 1 in the placebo group occurring within 150 days after birth.

Table 6. RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)			
	RSVpreF 120 µg (N[a] =3495)	Placebo (N[a]=3480)		
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (CI)	Nominal P-value[d]
90 Days after birth[c]	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)	0.0058
120 Days after birth[c]	35 (1.0)	81 (2.3)	56.8 (31.2, 73.5)	0.0012
150 Days after birth[c]	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9)	0.0017
180 Days after birth[c]	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)	0.0011

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

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-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.

c. 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).

d. Unadjusted 1-sided nominal p-value for the null hypothesis that vaccine efficacy ≤20%. Statistical significance cannot be claimed for these analyses due to the planned testing strategy and the failure to meet the statistical success criterion at 90 days for this endpoint.

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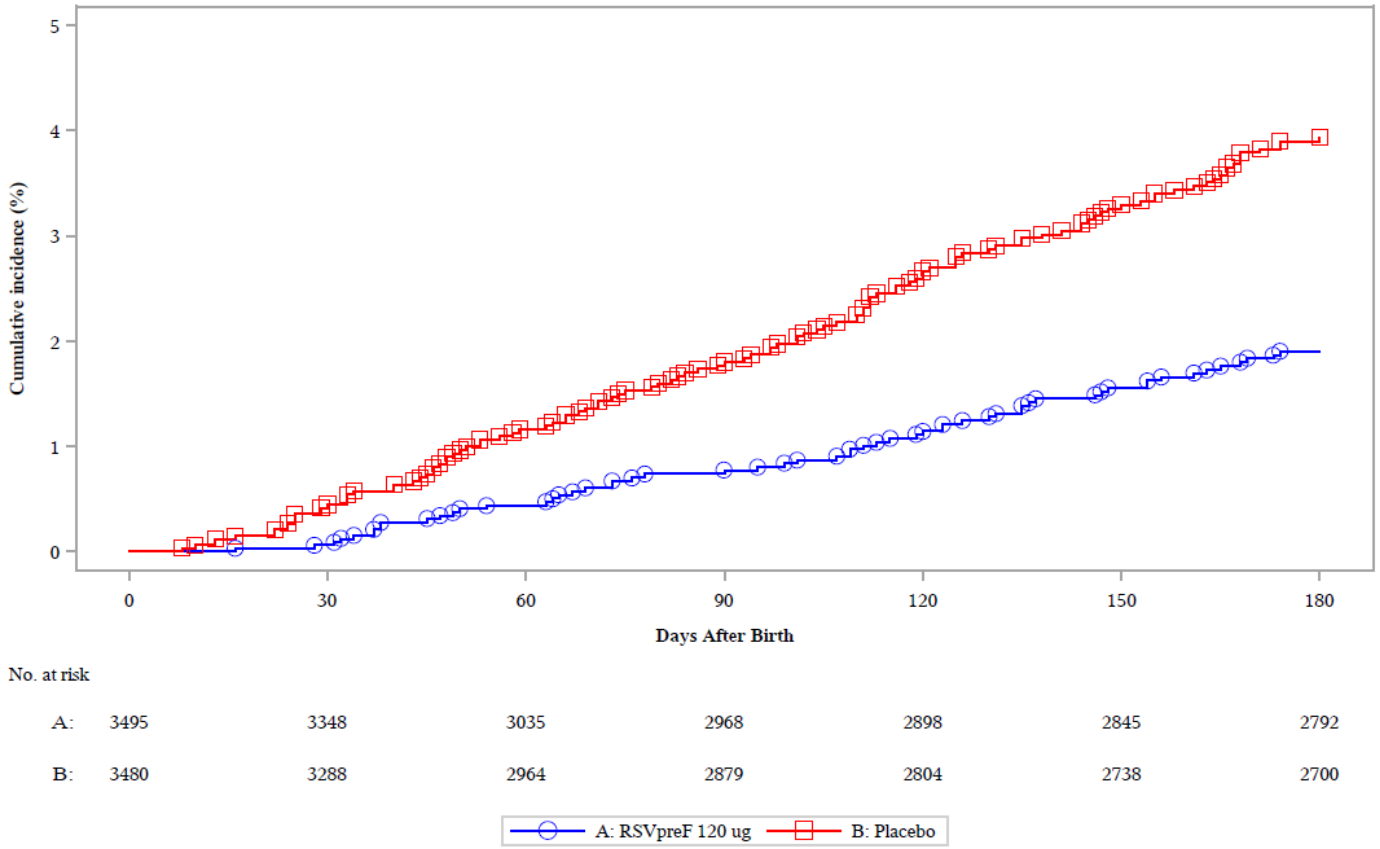
(Database snapshot date : 14OCT2022) Output File: ./mat 1008/C3671008 REX/adprim s001b rsvpos

Figure 5. Kaplan-Meier Curves for RSV-Positive MA-LRTIs Confirmed by EAC Within 180 Days After Birth - Infant Participants - Evaluable Efficacy Population



Abbreviation: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
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(Database snapshot date : 14OCT2022) Output File: ./mat_1008/C3671008_REX/adprim_f001_rsvpos_d180

5.4.2.2. Infant Secondary Efficacy Endpoints

5.4.2.2.1. MA-LRTI Due to RSV, Occurring Within 210, 240, 270, and 360 Days After Birth, as Reported by Investigators

The VE results based on case accrual through the efficacy data cutoff date met the statistical criterion for success (a CI lower bound >0%) for investigator-reported RSV-positive MA-LRTI in infants, at all timepoints within 210 to 360 days after birth (Figure 6).

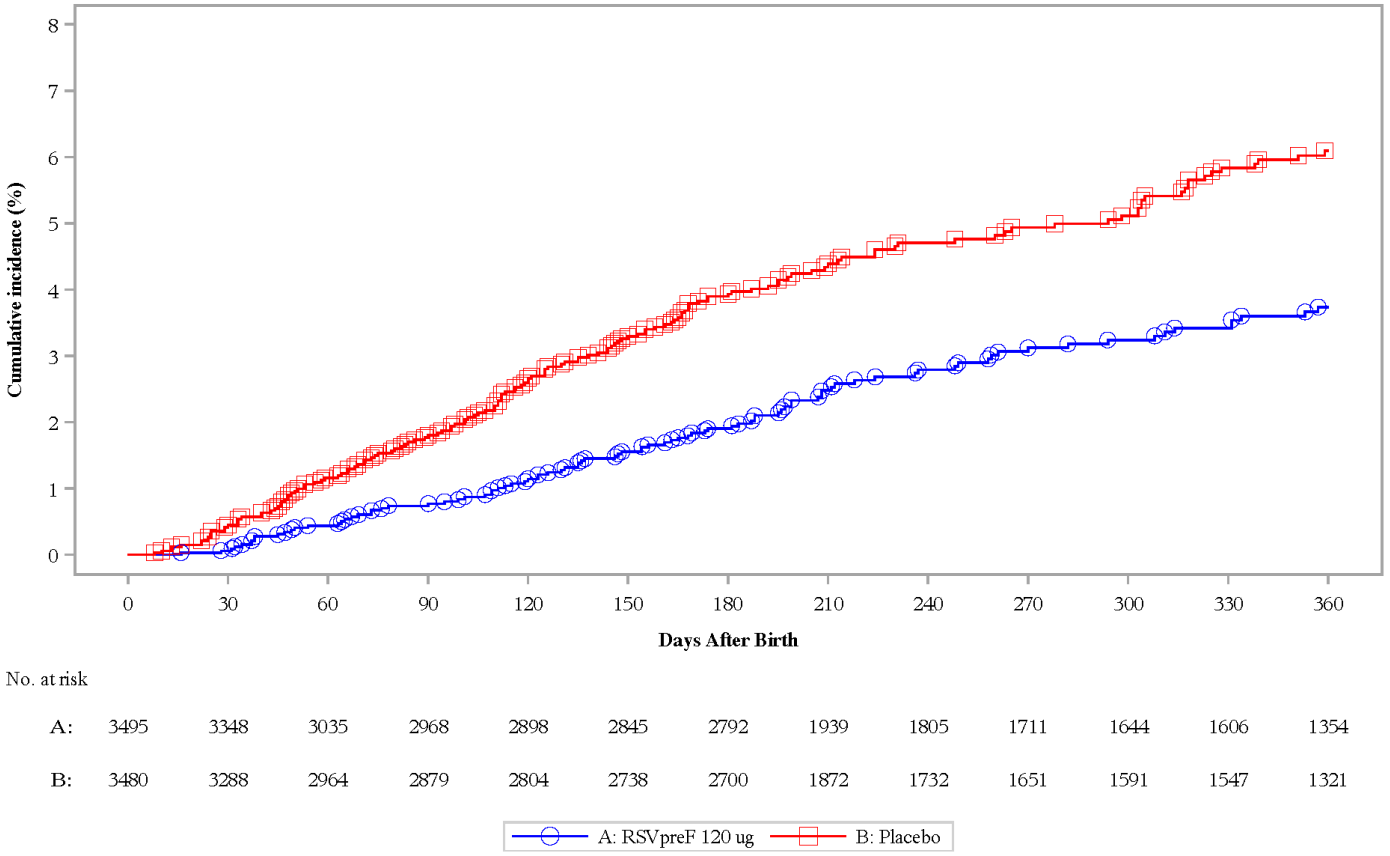
In the evaluable efficacy population:

- There were 197 cumulative cases of investigator-reported RSV-positive MA-LRTI in infants within 210 days after birth, including 70 in the RSVpreF group and 127 cases in the placebo group, corresponding to a VE of 44.9% (99.17% CI: 17.9%, 63.5%) for RSVpreF.

- There were 248 cumulative cases of investigator-reported RSV-positive MA-LRTI in infants within 360 days after birth, including 92 in the RSVpreF group and 156 cases in the placebo group, corresponding to a VE of 41.0% (99.17% CI: 16.2%, 58.9%) for RSVpreF.

Analysis of this secondary endpoint using the mITT population yielded similar results.

Figure 6. Kaplan-Meier Curves for RSV-Positive MA-LRTIs Occurring Within 360 Days After Birth - Evaluable Efficacy Population



Abbreviation: MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
PFIZER CONFIDENTIAL SDTM Creation: 18OCT2022 (21:24) Source Data: adrsvef Table Generation: 08NOV2022 (23:24)
(Database snapshot date : 14OCT2022) Output File: ./mat_1008/C3671008_REX/adprim_f001_rsvposd_d360

5.4.2.2.2. Hospitalization Due to RSV, Occurring Within 90, 120, 150, 180 and 360 Days After Birth, as Confirmed by the EAC

The VE results based on case accrual through the efficacy data cutoff date met the statistical criterion for success (a CI lower bound >0%) for reducing hospitalizations due to EAC-confirmed RSV in infants, at all timepoints through 180 days. The statistical criterion for success was not met at 360 days.

In the evaluable efficacy population:

- There were 41 hospitalizations due to EAC-confirmed RSV in infants within 90 days after birth, including 10 in the RSVpreF group and 31 in the placebo group, corresponding to a VE of 67.7% (99.17% CI: 15.9%, 89.5%) for RSVpreF.

- There were 63 hospitalizations due to EAC-confirmed RSV in infants within 180 days after birth, including 19 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.

Analysis of this secondary efficacy endpoint using the mITT population yielded similar results.

5.4.2.2.3. MA-LRTI Due to Any Cause, Occurring Within 90, 120, 150, 180 and 360 Days After Birth, as Reported by Investigators

The VE results in the evaluable efficacy population based on case accrual through the efficacy data cutoff date did not meet the statistical criterion for success (a CI lower bound >0%) for reducing investigator-reported all-cause MA-LRTI in infants at any of the measured timepoints through 360 days after birth. Of note, in this study conducted during the COVID-19 pandemic, MA-LRTI due to RSV within 180 days of birth constituted 22% of MA-LRTI due to any cause in the same period (174 out of 794 cases), an atypically low proportion that was probably related to the pandemic.[85] Pre-pandemic studies of LRTI identified RSV as the most common individual pathogen in settings where pneumococcal conjugate vaccines are in use, responsible for 50-80% of bronchiolitis and 40% of pneumonia among children <1 year.[86,87]

Analysis of this secondary endpoint using the mITT population yielded similar results.

5.4.2.2.4. Subgroup Analyses of Primary and Secondary Efficacy Endpoints

Subgroup analyses for the primary and secondary efficacy endpoints summarized in the preceding sections were performed according to maternal GA at vaccination, country, country subcategories, exclusive breastfeeding, duration of breastfeeding, maternal smoking, number of household members, and maternal age at vaccination. Overall, VEs were generally similar to those observed in the main analyses above and did not identify any clinically meaningful differences between subgroups. However, these results should be interpreted with caution as several subgroups (eg, by country) included a limited number of cases and participants, which contributed to wide CIs around the point estimates. In this study, a total of 12 infant participants received palivizumab, 2 in the RSVpreF group and 10 in the placebo

group. None of the infants who received palivizumab reported an RSV-associated MA-LRTI during the study.

VEs of RSVpreF against severe MA-LRTI and MA-LRTI caused by RSV within 180 days of birth in US participants are provided in Table 19 and Table 20, respectively.

5.4.2.3. Infant Exploratory Endpoint

Included in this briefing document are the key exploratory endpoint results in infants.

5.4.2.3.1. MA-RTI Due to RSV, Occurring Within 90, 120, 150, and 180 Days After Birth, as Confirmed by the EAC

VE was observed based on case accrual through the efficacy data cutoff date for EAC-confirmed RSV-positive MA-RTI in infants, at all timepoints through 180 days after birth.

In the evaluable efficacy population:

- There were 177 EAC-confirmed RSV-positive MA-RTI cases in infants within 90 days after birth, including 67 in the RSVpreF group and 110 in the placebo group, corresponding to a VE of 39.1% (95% CI: 16.7%, 55.7%) for RSVpreF.

- There were 410 EAC-confirmed RSV-positive MA-RTI cases in infants within 180 days after birth, including 157 in the RSVpreF group and 253 in the placebo group, corresponding to a VE of 37.9% (95% CI: 24.0%, 49.5%) for RSVpreF.

5.4.3. Study C3671008 Safety Assessments

Safety data in the ongoing maternal studies, including the C3671008 study are reviewed by the investigator, the sponsor, and an E-DMC. The E-DMC conducts unblinded reviews on a regular basis throughout the trial, including in the period after the primary analysis. The E-DMC has continued to recommend that the study continue as planned in support of a favorable benefit risk profile for both maternal and infant participants.

5.4.4. Study C3671008 Safety Results (Maternal Participants)

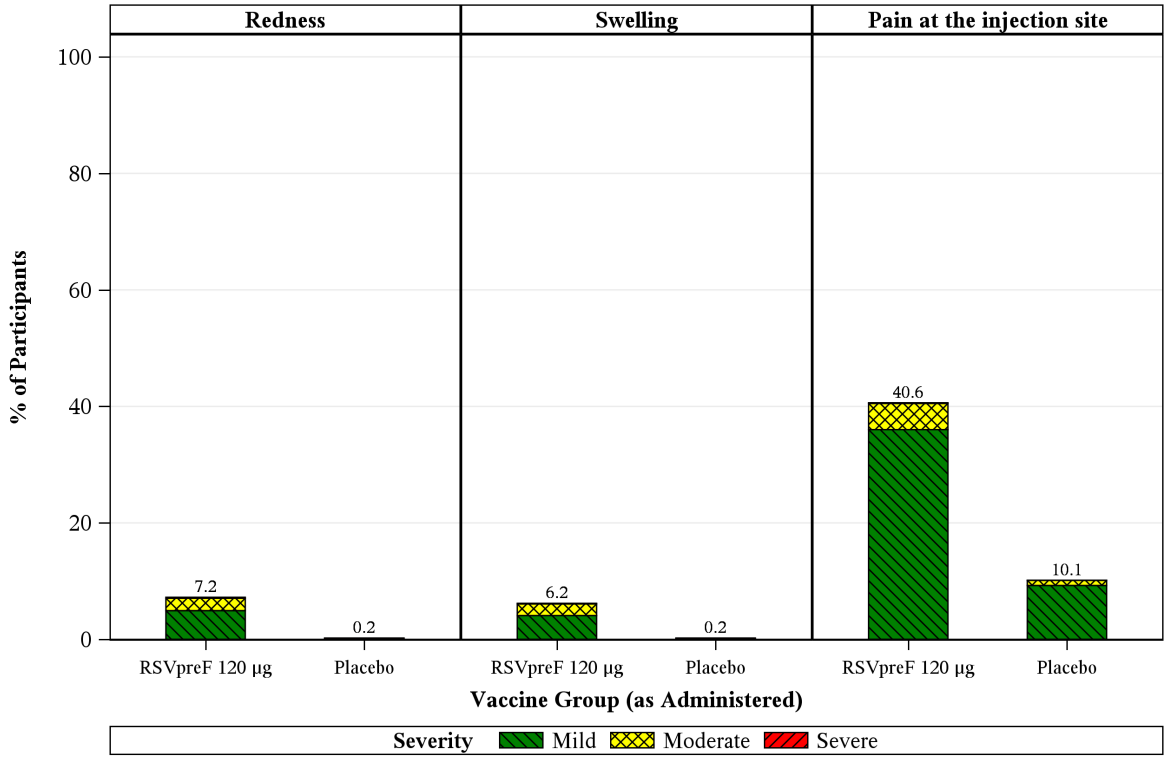
5.4.4.1. Reactogenicity

5.4.4.1.1. Local Reactions

The proportions of maternal participants with local reactions reported within 7 days after vaccination were higher in the RSVpreF group compared to the placebo group (Figure 7 and Table 21). 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 and 0% in the placebo 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 with a median duration of 2.0 to 3.0 days.

Figure 7 Participants Reporting Local Reactions by Maximum Severity Within 7 Days After Vaccination – Maternal Participants – Safety Population



Note: Number above each bar denotes percentage of participants reporting the reaction with any severity.
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5.4.4.1.2. Systemic Events

A baseline assessment of systemic events within 7 days prior to vaccination was recorded. Prevaccination and post-vaccination systemic events reported in maternal participants are presented in Figure 8 and Table 22.

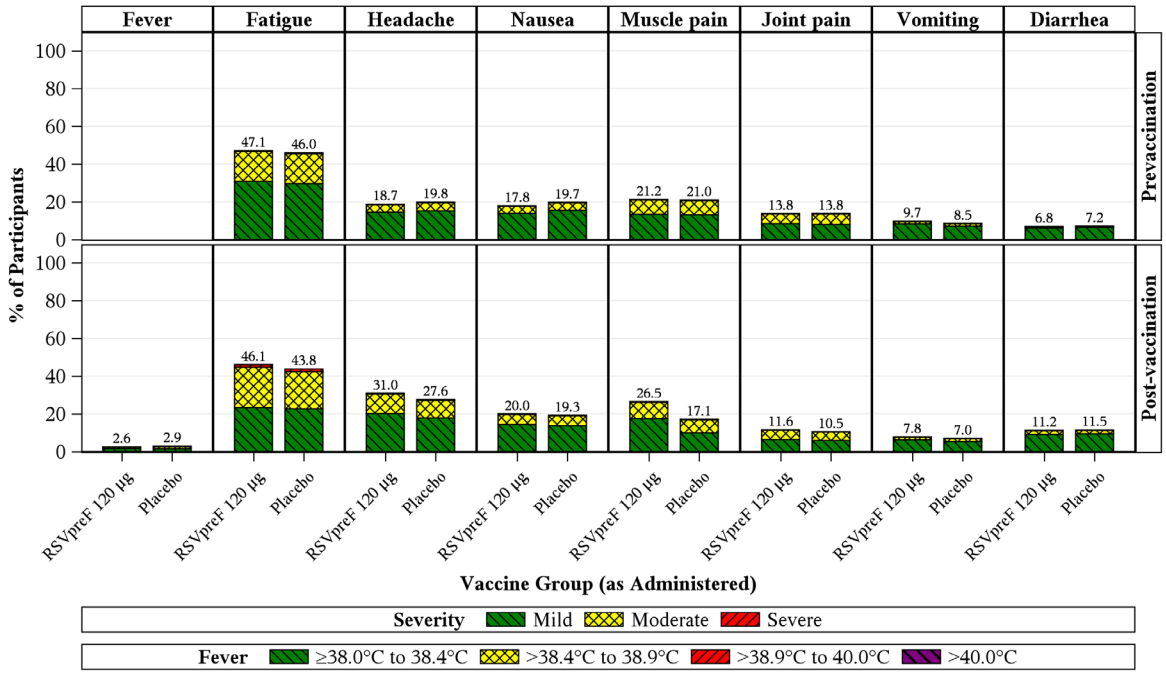
The proportions of maternal participants who reported systemic events within 7 days prior to vaccination were similar in the RSVpreF and placebo groups, and most events were mild or moderate in severity for both groups (Figure 8 and Table 22). The most frequently reported systemic event within 7 days prior to vaccination was fatigue, reported by 47.1% of participants in the RSVpreF group and 46.0% of participants in the placebo group, highlighting a common feature of pregnancy independent of vaccination.

The proportions of maternal participants who reported systemic events within 7 days after vaccination were generally similar in the RSVpreF and placebo groups, and most events were mild or moderate in severity for both groups (Figure 8 and Table 22). Severe systemic events within 7 days after vaccination were reported for 2.3% of maternal participants in both groups. The most frequently reported systemic event from vaccination to 7 days after vaccination was fatigue, reported by 46.1% of participants in the RSVpreF group and 43.8%

of participants in the placebo group, thus generally similar as reported within 7 days prior to vaccination. The incidence of fever was low and was similar for RSVpreF and placebo groups (≤2.9%), and most were ≤38.9 °C. Muscle pain was reported more frequently in the RSVpreF group (26.5%) compared to the placebo group (17.1%). Headache incidence was slightly higher in the RSVpreF group (31.0%) compared to the placebo group (27.6%) (Figure 8 and Table 22).

The median day of onset for any systemic event for the RSVpreF group was day 2 with a median duration of 1.0 to 3.0 days.

Figure 8 Participants Reporting Systemic Events by Maximum Severity - Maternal Participants - Safety Population



Note: Number above each bar denotes percentage of participants reporting the event with any severity.
PFIZER CONFIDENTIAL SDTM Creation: 21NOV2022 (00:37) Source Data: adfacevd Table Generation: 21NOV2022 (22:42) (Snapshot Date: 14OCT2022) Output File: ./mat_1008/C3671008_REX_REACTO_SUPP/adce_f001_se_max

5.4.4.2. Adverse Events

5.4.4.2.1. Overview of Adverse Events by Category

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. For maternal participants, all AEs were collected through 1 month after vaccination (noting maternal participants could have delivered their infants during this time interval); SAEs and AESIs were collected through the 6 months postdelivery visit.

Overall, for each category of AE reported within 1 month after vaccination, proportions were similar for maternal participants in the RSVpreF and placebo groups (Table 7). The proportions of participants with any AEs reported within 1 month after vaccination were similar in the RSVpreF group (13.7%) and placebo group (13.1%). Most AEs were mild or moderate in severity for both groups; severe AEs were reported in ≤1.7% of maternal participants. 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 reported in ≤0.4% of maternal participants (Table 7). All related AEs were reported after vaccination but before delivery, with the exception of 2 related AEs reported from delivery to 1 month after delivery.

AESI within 1 month of vaccination were reported at a similar frequency for both groups (≤2.7%). AESI were collected for maternal participants through 6 months after delivery.

SAEs within 1 month after vaccination were reported at a similar frequency for both groups (≤4.2%). SAEs were collected for maternal participants through 6 months after delivery. 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.

Table 7. Number (%) of Participants Reporting Adverse Events by Category Within 1 Month After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=3682)		Placebo (N[a]=3675)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Any event	506 (13.7)	(12.6, 14.9)	482 (13.1)	(12.0, 14.3)
Serious	154 (4.2)	(3.6, 4.9)	137 (3.7)	(3.1, 4.4)
Immediate[d]	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
Severe	63 (1.7)	(1.3, 2.2)	48 (1.3)	(1.0, 1.7)
Life-threatening	19 (0.5)	(0.3, 0.8)	11 (0.3)	(0.1, 0.5)
Related	14 (0.4)	(0.2, 0.6)	5 (0.1)	(0.0, 0.3)
AESIs	99 (2.7)	(2.2, 3.3)	92 (2.5)	(2.0, 3.1)
AE leading to withdrawal	0	(0.0, 0.1)	0	(0.0, 0.1)

Table 7. Number (%) of Participants Reporting Adverse Events by Category Within 1 Month After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=3682)		Placebo (N[a]=3675)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]

Abbreviation: AESIs = adverse events of special interest.
Note: MedDRA (v25.0) coding dictionary applied.
Note: The severity of the event is in the determination of the investigator.
Note: Per statistical analysis plan, 1 month after vaccination reflects a 30-day period. However, as per protocol, non-serious adverse events were only solicited through 28 days after vaccination. AESIs and SAEs were solicited throughout the study for maternal participants.
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. 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.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product for maternal participants.
PFIZER CONFIDENTIAL SDTM Creation: 03JAN2023 (21:19) Source Data: adae Table Generation: 03JAN2023 (22:30)
(Data cutoff date : 02SEP2022 Database snapshot date : 14OCT2022) Output File:
./mat 1008/C3671008 REX CBER/adae s151a in1

5.4.4.2.2. Adverse Events by System Organ Class and Preferred Term

The proportions of participants with any unsolicited AEs reported within 1 month after vaccination were similar in the RSVpreF group (13.7%) and placebo group (13.1%). 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%) and Infections and infestations (2.0% for both groups). By PT, the most frequently reported AE in both groups was premature delivery which was solicited as an AESI (2.1% in the RSVpreF group versus 1.9% in the placebo group).

AEs in maternal participants reported at delivery to 1 month after delivery were similar in the RSVpreF group (16.0%) and in the placebo group (15.5%). AEs were reported in ≤2.3% of maternal participants between 1 month after delivery to 6 months after delivery.

Among AEs reported in at least 1% of participants in either group, pre-eclampsia occurred at a similar frequency for both vaccine groups within 1 month after vaccination (1.0% versus 0.9% for the RSVpreF and placebo groups, respectively. The AE of premature delivery was solicited as an AESI throughout the study (refer to Section 5.4.4.2.9 for additional details) and occurred at a similar frequency in both the RSVpreF and placebo groups within 1 month after vaccination (2.1% versus 1.9%, respectively; risk difference 0.24% [95% CI: -0.41%,

0.89%]). Among AEs reported in <1% in either group, the incidences of selected severe or life-threatening AEs in the RSVpreF and placebo groups, respectively, were: pre-eclampsia (0.5% versus 0.2%); premature delivery (0.2% versus 0.1%); and premature labor (0.1% versus 0%).

5.4.4.2.2.1. Subgroup Analyses by Race or Maternal Age at Vaccination

Subgroup analyses of AEs reported in maternal participants within 1 month after vaccination by race or maternal age at vaccination in both the RSVpreF and placebo groups suggested no clinically meaningful differences across subgroups. However, results by maternal age should be interpreted with caution due to the low number of subjects less than 18 years old.

5.4.4.2.3. Related Adverse Events

AEs from vaccination through the 1-month follow-up visit that were considered related to vaccination were infrequent (0.4% in the RSVpreF group and 0.1% in the placebo group) and occurred most commonly in the SOC of General disorders and administration site conditions.

Most related AEs occurred after vaccination but before delivery. Of these related AEs, 5 were assessed as SAEs by the investigator: 4 maternal participants in the RSVpreF group and 1 maternal participant in the placebo group. Refer to Section 5.4.4.2.7 for additional details.

5.4.4.2.4. Immediate Adverse Events

Two (2) immediate AEs reported within 30 minutes of vaccine administration (Table 7):

- 1 related immediate AE of dizziness occurred in the RSVpreF group. This event was mild in severity and resolved on the day of onset.

- 1 unrelated immediate AE of COVID-19 occurred in the placebo group. This event was moderate in severity and resolved 11 days later.

5.4.4.2.5. Severe or Life-Threatening Adverse Events

The number of AEs reported as severe or life-threatening within 1 month after vaccination were balanced across the RSVpreF and placebo groups (2.2% versus 1.5%) and occurred most frequently within the SOC of Pregnancy, puerperium and perinatal conditions (1.7% versus 1.0%). Those assessed as related included 1 severe AE (SAE of pain in extremity in the RSVpreF group) and 2 life-threatening AEs (SAE of premature labor and SAE of eclampsia in the RSVpreF group). Refer to Section 5.4.4.2.7 for further details for related SAEs.

AESIs and SAEs that were severe or life-threatening were recorded through 6 months after delivery. The frequencies of severe or life-threatening AEs by time interval were balanced across the RSVpreF and placebo groups, with most severe or life-threatening AEs occurring after vaccination but before delivery (3.0% versus 2.4%) or from delivery to 1 month after delivery (4.3% versus 4.1%).

5.4.4.2.6. Deaths

Deaths reported in maternal participants included events of intrauterine demises as they are associated with the fetus; those reported as of the data cutoff date are presented in Table 8. No maternal deaths or intrauterine demises were assessed by the investigator as related to vaccination.

There was 1 maternal death in the RSVpreF group due to postpartum hemorrhage and hypovolemic shock, which was reported on D58 following vaccination.

A total of 21 intrauterine demises were reported in maternal participants after vaccination to 6 months after delivery, and frequencies were similar for the RSVpreF group (11 participants [0.3%]) and placebo group (10 participants [0.3%]). This included fetal demises (the terms fetal death and stillbirth were used interchangeably during the study) reported for the index pregnancy, as well as spontaneous abortions reported for subsequent pregnancies in the time interval from 1 month after vaccination to 6 months after delivery.

- In 18 participants, fetal demises (fetal deaths or stillbirths) were reported: 10 in the RSVpreF group and 8 in the placebo group. For most of the cases, there was no abnormality on gross inspection and for the few that had pathology performed, abnormalities of the placenta or cord were noted but did not appear to follow any pattern. No fetal abnormalities were described in any case.

- In 3 participants, spontaneous abortions (for subsequent pregnancies) were reported: 1 in the RSVpreF group and 2 in the placebo group.

Table 8. Summary of Intrauterine Demises - Maternal Participants - Safety Population

		Vaccine Group (as Administered)			
		RSVpreF 120 µg (N[a]=3682)		Placebo (N[a]=3675)	
Event Type	Preferred Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Any Intrauterine Demise in Index Pregnancy	Any event	10 (0.3)	(0.1, 0.5)	8 (0.2)	(0.1, 0.4)
Any Intrauterine Demise in the Subsequent Pregnancy (after delivery to 6 months after delivery)	Any event	1 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)

a. N = number of participants in the vaccine group. This value is the denominator for the percentage calculations.
b. n = number of participants reporting at least 1 occurrence of any adverse event or death term.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.

5.4.4.2.7. Serious Adverse Events

SAEs were reported in maternal participants from vaccination to 6 months after delivery. Overall, the proportions of maternal participants with any SAEs reported after vaccination to 6 months after delivery were similar in the RSVpreF group (16.2%) and placebo group (15.2%). For both groups, most SAEs reported as of the data cutoff date occurred in the intervals from delivery to 1 month after delivery (10.1% versus 10.0%) and after vaccination but before delivery (7.2% versus 6.1%).

After vaccination to 6 months after delivery, SAEs were most frequently reported in the SOC of Pregnancy, puerperium and perinatal conditions in the RSVpreF group (12.1%) and placebo group (11.2%). The most frequently reported SAEs by PT in the RSVpreF group (≥1.0%) were pre-eclampsia (1.8%), fetal distress syndrome (1.8%), gestational hypertension (1.1%), nonreassuring fetal heart rate (1.0%), and arrested labor (1.0%); these events were reported similarly 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. These events are briefly noted below.

In the RSVpreF group:

- Pain in extremity (severe; Section 5.4.4.2.5) with onset 2 days after vaccination. This event resolved 6 days later.
- Premature labor (life-threatening; Section 5.4.4.2.5) with onset 2 days after vaccination that resolved 1 day later. The participant subsequently delivered an infant at term.
- Systemic lupus erythematosus (moderate severity) with onset 6 days after vaccination. This event resolved 21 days later.
- Eclampsia (life-threatening; Section 5.4.4.2.5) with onset 15 days after vaccination. This event resolved 113 days later.

In the placebo group:

- Premature separation of placenta (moderate severity) with onset 2 days after vaccination. This event resolved 48 days later.

5.4.4.2.8. Discontinuations from Study Due to Adverse Events

One (1) maternal participant in the placebo group withdrew from the study due to the AE of premature delivery.

5.4.4.2.9. Adverse Events of Special Interest

The AESI of premature delivery was reported at a similar frequency for the RSVpreF and placebo groups (5.6% [95% CI: 4.9, 6.4] versus 4.7% [95% CI: 4.1, 5.5], respectively) after vaccination to 6 months after delivery.

Positive SARS-CoV-2 tests were reported at a similar frequency for the RSVpreF and placebo groups after vaccination through 6 months after delivery (3.9% versus 3.0%).

5.4.4.2.10. Other Safety Evaluations

5.4.4.2.10.1. Pregnancy Outcomes

Most maternal participants (70.4%) delivered via vaginal delivery and the median GA at delivery was 39.14 weeks for both groups. The median days between vaccination and delivery were similar for both groups (54.0 days versus 55.0 days).

5.4.4.2.11. Adverse Drug Reactions

This section contains adverse drug reactions (ADRs) which are adverse events for which there is a reason to conclude that the drug caused the event(s). The Sponsor determines ADRs following a thorough assessment of available evidence from non-clinical, clinical, and post-marketing information. Factors considered in the determination of ADRs may include (but not be limited to) temporal relationship, frequency of occurrence, drug mechanism of action, biological plausibility, dose response, drug class effects, lack of confounding factors, dechallenge and rechallenge information, and an investigator's assessment of relatedness. ADRs in this section may be non-serious or serious.

ADRs identified for maternal participants in Study C3671008 included vaccination site pain (very common; ≥10%), headache (very common; ≥10%), myalgia (very common; ≥10%), vaccination site redness (common; ≥1% and <10%), and vaccination site swelling (common; ≥1% and <10%) (Table 9).

Table 9. Adverse Drug Reactions (ADRs) by System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to <1/10
General disorders and administration site conditions	Vaccination site pain	Vaccination site redness, Vaccination site swelling
Musculoskeletal and connective tissue disorders	Myalgia	
Nervous system disorders	Headache	

PFIZER CONFIDENTIAL Source Data: adfacevd and adae Output File: ./mat_1008_bl_eff/C3671008_ADR/adr_ns020 Date of Generation: 05DEC2022 (21:14)

5.4.5. Study C3671008 Safety Results (Infant Participants)

5.4.5.1. Adverse Events

5.4.5.1.1. Overview of Adverse Events by Category

AEs and SAEs in infants were captured once the infant took a live breath. MA-RTIs were 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).

Overall, for each category of AE reported within 1 month after birth, proportions were similar for infant participants in the RSVpreF and placebo groups (Table 10). The proportions of participants with any AE reported within 1 month after birth were 37.1% in the RSVpreF group and 34.5% in the placebo group. Most AEs were mild or moderate in severity across both groups; severe AEs were reported in ≤4.5% of infant participants. There were no infant participants with AEs leading to withdrawal reported within 1 month after birth.

One (1) AE of premature baby in an infant participant in the RSVpreF group was assessed as related to maternal vaccination by the investigator.

AESIs within 1 month after birth were reported at a similar frequency for both groups (≤8.4%). AESIs in infant participants were collected up to 24 months after birth.

SAEs within 1 month after birth were reported at a similar frequency for both groups (≤15.5%). SAEs in infant participants were collected up to 24 months after birth.

NDCMCs within 1 month after birth were reported in 0.2% of infant participants in both the RSVpreF and placebo groups. NDCMCs in infant participants were collected up to 24 months after birth.

Table 10. Number (%) of Participants Reporting Adverse Events by Category Within 1 Month After Birth - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Any event	1324 (37.1)	(35.5, 38.7)	1229 (34.5)	(33.0, 36.1)
Serious	553 (15.5)	(14.3, 16.7)	541 (15.2)	(14.0, 16.4)
Severe	161 (4.5)	(3.9, 5.2)	134 (3.8)	(3.2, 4.4)
Life-threatening	34 (1.0)	(0.7, 1.3)	34 (1.0)	(0.7, 1.3)

Table 10. Number (%) of Participants Reporting Adverse Events by Category Within 1 Month After Birth - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Related	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
AESIs	298 (8.4)	(7.5, 9.3)	257 (7.2)	(6.4, 8.1)
Congenital Anomalies	172 (4.8)	(4.1, 5.6)	210 (5.9)	(5.2, 6.7)
NDCMCs	6 (0.2)	(0.1, 0.4)	6 (0.2)	(0.1, 0.4)
AE leading to withdrawal	0	(0.0, 0.1)	0	(0.0, 0.1)

Abbreviations: AESIs = adverse events of special interest; NDCMCs = newly diagnosed chronic medical conditions.
Note: MedDRA (v25.0) coding dictionary applied.
Note: The severity of the event is in the determination of the investigator.
Note: Per statistical analysis plan, 1 month after birth reflects a 30-day period. However, as per protocol, non-serious adverse events were only solicited through 28 days after birth. AESIs, SAEs and NDCMCs were solicited throughout the study for infant participants.
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. 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.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 18OCT2022 (22:24) Source Data: adae Table Generation: 02NOV2022 (22:19)
(Data cutoff date : 02SEP2022 Database snapshot date : 14OCT2022) Output File: ./mat_1008/C3671008_REX/adae_s151b_in1

5.4.5.1.2. Adverse Events by System Organ Class and Preferred Term

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

AEs reported in at least 1% of infant participants in either group occurred at a similar frequency for both groups within 1 month of birth. The most frequently reported of these PTs for the RSVpreF and placebo groups included the related terms of jaundice neonatal (7.2% versus 6.7%) and hyperbilirubinemia neonatal (3.0% versus 2.9%).

The PTs of premature baby and low birth weight baby were recorded as AESIs throughout the study (refer to Section 5.4.5.1.9 for additional details on AESIs reported during the

study). Premature baby occurred at a similar frequency in both the RSVpreF and placebo groups (5.7% versus 4.7%, respectively; risk difference 0.91% [95% CI: -0.12%, 1.95%]).

Low birth weight baby also occurred at a similar frequency in both the RSVpreF and placebo groups (5.1% versus 4.4%, respectively; risk difference 0.72% [95% CI: -0.27%, 1.71%]).

5.4.5.1.2.1. Subgroup Analyses by Race, Gender, or Maternal Age at Vaccination Relative to Chronological Age

Subgroup analyses of AEs reported in infant participants by race, gender, or maternal age at vaccination by time intervals relative to chronological age suggested that AEs were reported more commonly in races other than white and were similar in the RSVpreF and placebo groups. Results by maternal age should be interpreted with caution due to the low number of maternal subjects less than 18 years old.

5.4.5.1.3. Related Adverse Events

One (1) AE of premature baby (mild in severity; GA 36 weeks and 5 days[1]) in the RSVpreF group (relative day 86 to maternal vaccination and relative day 1 to infant birth) was assessed by the investigator as related to maternal vaccination. The frequencies of reports of SAEs of premature baby were similar for the RSVpreF and placebo groups (1.4% versus 1.2%; refer to Section 5.4.5.1.7 for details).

5.4.5.1.4. Severe or Life-Threatening Adverse Events

The frequencies of severe or life-threatening AEs by time interval were balanced across the RSVpreF and placebo groups, with most occurring at birth to 1 month of age (5.1% versus 4.5%). Severe or life-threatening AEs occurred most frequently within the SOC of Respiratory, thoracic, and mediastinal disorders (2.5% versus 1.9%).

No severe or life-threatening AEs in infant participants were related to maternal vaccination.

5.4.5.1.5. Newly Diagnosed Chronic Medical Conditions

As of the data cutoff, NDCMCs were reported at a similar frequency for infant participants in the RSVpreF and placebo groups through 6, 12, and 24 months after birth (2.4% versus 2.8%).

Asthma-related diagnoses reported either during MA-RTI visits or reported as AEs occurred at a similar frequency for the RSVpreF and placebo groups (2.7% versus 3.1%). No infant participants were withdrawn from the study due to an NDCMC.

[1]Infant GA at birth is entered by the study site into the Case Report Form at birth.

5.4.5.1.6. Deaths

Infant deaths reported as of the data cutoff date are presented by time interval in Table 11, starting with those reported across all time intervals (birth to 24 months of age). No infant deaths were assessed by the investigator as related to maternal vaccination.

In total, 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 (relative risk RSVpreF:placebo = 0.42; 95% CI [0.15, 1.18]). In the RSVpreF group, each death event term was reported for 1 infant.

During the time interval from 1 month to 6 months of age, in the placebo group one event with an investigator reported event term of "death" was adjudicated by the EAC with a cause of "acute respiratory illness due to RSV." Briefly, a Japanese female infant, born at 40 weeks and 1 day with a normal birth outcome, presented with nasal discharge and cough at 114 days after birth. Two days later the infant was examined at the hospital: RSV test was PCR positive, and SARS-CoV-2 was negative by local testing. No medications were prescribed, and the infant was not hospitalized. A follow-up visit the day after confirmed that the infant was in good general condition. Two days later the maternal participant noticed feeding problems; the following day the maternal participant reported that the infant died, 120 days after birth. The cause of death was reported by the investigator as unknown. The investigator assessed the event as not related to study intervention.

Table 11. Summary of Deaths - Infant Participants - Safety Population

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Time Interval	Death Details Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Birth to 24 months of age	Any death event	5 (0.1)	(0.0, 0.3)	12 (0.3)	(0.2, 0.6)
	Death	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Enterovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Gastroenteritis	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Ill-defined disorder	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Interstitial lung disease	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Low birth weight baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Meconium aspiration syndrome	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Meningitis	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Multiple organ dysfunction syndrome	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Neonatal asphyxia	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Neonatal respiratory distress	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)

Table 11. Summary of Deaths - Infant Participants - Safety Population

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N^a=3568)		Placebo (N^a=3558)	
Time Interval	Death Details Term	n^b (%)	(95% CI)[c]	n^b (%)	(95% CI)[c]
	Pneumonia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Premature baby	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Pulmonary hypertension	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Rhinovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Sepsis neonatal	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Small for dates baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sudden infant death syndrome	0	(0.0, 0.1)	3 (<0.1)	(0.0, 0.2)
	Ventricular hypoplasia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Birth to 1 month of age	Any death event	2 (<0.1)	(0.0, 0.2)	5 (0.1)	(0.0, 0.3)
	Meconium aspiration syndrome	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Multiple organ dysfunction syndrome	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Neonatal asphyxia	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Premature baby	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Pulmonary hypertension	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sepsis neonatal	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Ventricular hypoplasia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
1 Month to 6 months of age	Any death event	3 (<0.1)	(0.0, 0.2)	6 (0.2)	(0.1, 0.4)
	Death	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Enterovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Gastroenteritis	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Ill-defined disorder	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Interstitial lung disease	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Low birth weight baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Meningitis	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Neonatal respiratory distress	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Pneumonia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Premature baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Rhinovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Small for dates baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sudden infant death syndrome	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)

Table 11. Summary of Deaths - Infant Participants - Safety Population

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Time Interval	Death Details Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
6 Months to 12 months of age	Any death event	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sudden infant death syndrome	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)

Note: Both primary and secondary causes of death are listed for each event.
a. N = number of participants in the vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified death term. For "any death event", n = number of participants reporting at least 1 occurrence of any death term.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 15OCT2022 (02:45) Source Data: addd Table Generation: 08NOV2022 (21:05)
(Database snapshot date : 14OCT2022) Output File: ./mat 1008/C3671008 REX/adae s150b dth

5.4.5.1.7. Serious Adverse Events

Overall, the proportions of infant participants with any SAEs reported from birth to 24 months of age were similar in the RSVpreF group (17.5%) and placebo group (17.5%). For both groups, most SAEs reported as of the data cutoff date occurred from birth to 1 month of age (≤15.5%). No SAEs in infant participants were considered related to maternal vaccination.

From birth to 24 months of age, SAEs were most frequently reported in the SOCs of Respiratory, thoracic and mediastinal disorders, Pregnancy, puerperium and perinatal conditions, and Infections and infestations (4.6%, 3.9%, and 3.0%, respectively) in the RSVpreF group; results by SOC were similar in the placebo group (4.2%, 3.5%, and 2.5%, respectively). The most frequently reported SAEs by PT in the RSVpreF group (≥1.0%) were jaundice neonatal (2.1%), hyperbilirubinemia neonatal (1.4%), premature baby (1.4%), and respiratory distress (1.3%); these events were reported similarly in the placebo group (1.9%, 1.1%, 1.2%, and 1.2%, respectively).

Congenital anomalies reported as SAEs occurred at a similar frequency in the RSVpreF and placebo groups (5.0% and 6.2%). Note that all congenital anomalies were to be reported as SAEs in the protocol for C3671008, regardless of severity. The congenital anomalies in Study C3671008 were prespecified and based on the Metropolitan Atlanta Congenital Defects Program[88] and normal variants were not included.

5.4.5.1.8. Discontinuations from Study Due to Adverse Events

No infant participants were withdrawn from the study due to an AE.

5.4.5.1.9. Adverse Events of Special Interest

AESIs in this study included low birth weight (LBW) birth (defined as birthweight ≤2500g), preterm birth (defined as GA <37 weeks), developmental delay, and positive testing for SARS-CoV-2 (when not reported during a MA-RTI visit) and were reported at a similar frequency for the RSVpreF and placebo groups (Table 23).

Based on the study design and inclusion/exclusion criteria, the overall incidence of preterm births was lower than the background rates in all countries where the study was conducted.[89] There were no statistically meaningful imbalances between RSVpreF and placebo recipients in the overall rates of preterm birth (5.7% [95% CI: 4.9, 6.5] versus 4.7% [95% CI: 4.1, 5.5], respectively) (Table 23). However, a numerical imbalance was observed in upper-middle income countries between RSVpreF and placebo recipients: there were 72 preterm births (GA <37 weeks) among 964 births in the RSVpreF group (7.5% [95% CI: 5.9, 9.3]) and 39 preterm births (GA <37 weeks) among 961 births in the placebo group (4.1% [95% CI: 2.9, 5.5]) (Table 24). No such imbalances were observed in either high income countries, which includes the United States (126/2494 births, 5.1% versus 126/2484 births, 5.1%, respectively), or low/low-middle income countries (3/110 births, 2.7% versus 4/113 births, 3.5%, respectively). The clinical significance of the observed imbalance between treatment groups in upper-middle income countries is unknown, particularly given that the imbalance was not observed in high income countries, despite there being a 2.5 times higher number of births in the latter. No observed adverse effect, including no increase in mortality, was seen in preterm births. No differences were observed between the RSVpreF and placebo groups with respect to time from vaccination to birth among preterm as well as at term infants (Table 25).

There were no statistically meaningful imbalances between RSVpreF and placebo recipients in the overall AESI rates of LBW (5.1% [95% CI: 4.4, 5.8] versus 4.3% [95% CI: 3.7, 5.0], respectively) (Table 23). A numerical imbalance was observed in upper-middle income countries between RSVpreF and placebo recipients: 66 LBW births in the RSVpreF group (6.8% [95% CI: 5.3, 8.6]) and 42 LBW births in the placebo group (4.4% [95% CI: 3.2, 5.9]) (Table 24). This numerical imbalance between treatment groups with regard to LBW, a potentially more objective outcome which does not have the variability introduced by GA dating methods that define prematurity, was lesser than that observed for the preterm birth outcome (Table 24). No imbalances were observed between RSVpreF and placebo groups in either high income countries, which includes the Unites States (108 LBW births [4.3%] versus 102 LBW births [4.1%]), and low/low-middle income countries (7 LBW births [6.4%] versus 11 LBW births [9.7%]). The clinical significance of the observed imbalance between treatment groups in upper-middle income countries is unknown, particularly given that the imbalance was not observed in high income countries, despite there being a 2.5 times higher number of births in the latter. No observed adverse effect, including no increase in mortality, was seen in LBW infants.

The AESI of developmental delay using the Preferred Term “developmental delay” or more specific terms that investigators deemed consistent with developmental delay were reported at a similar frequency for the RSVpreF and placebo groups (Table 23).

5.4.5.1.10. Other Safety Evaluations

5.4.5.1.10.1. Birth Outcomes

Birth outcomes for infant participants were similar for the RSVpreF and placebo groups. No meaningful differences were detected with respect to GA at birth, Apgar scores, or birthweight. Most infants were born at term (≥93.7%; ≥37 weeks to < 42 weeks GA). Most of the pre-term infants were near-term (≥4.4% were ≥34 to <37 weeks).

5.4.5.1.11. Adverse Drug Reactions

No ADRs were identified in infant participants born to vaccinated mothers.

5.5. Summary of Integrated Safety Analyses

In addition to the safety analyses performed for each study, safety analyses were also conducted on a pooled safety database of 9651 participants from the 5 studies in the maternal clinical development plan. Among the maternal participants from studies C3671008 and C3671003 in this pooled database, there were a total of 4144 participants who received any dose/formulation of RSVpreF (Table 26), 3797 participants who received the 120 µg final dose and formulation, and 3792 participants who received placebo. Safety analyses were also performed on a pooled safety database of 7698 infant participants from studies C3671008 and C3671003, of which 4024 participants were born to mothers who received any dose/formulation of RSVpreF, 3682 participants were born to mothers who received the 120 µg final dose and formulation, and 3674 participants were born to mothers who received placebo.

Note that regarding studies with male and nonpregnant female participants (Studies C3671001, C3671004 and C3671014), the pooled database only included female participants ≤49 years of age.

Note that all congenital anomalies in infants were reported as SAEs in studies C3671003 and C3671008. The congenital anomalies in Study C3671003 were investigator-determined based on guidance from the WHO[82], which had included many physical findings that are often considered not clinically significant or normal variants (eg, umbilical hernia, mongolian spot, etc). The WHO guidance was updated in 2020 to exclude these conditions.[83] The congenital anomalies in Study C3671008 were prespecified and based on the Metropolitan Atlanta Congenital Defects Program[88] and normal variants were not included.

All episodes of developmental delay for both maternal studies were defined as AESI to be collected throughout the study period. None were reported in the C3671003 study.

Because of differences in AESI definitions between Studies C3671003 (congenital anomalies and developmental delay for infant participants) and C3671008 (preterm birth, low birth weight, developmental delay, and a positive SARS-CoV-2 test for infant participants; preterm birth and a positive SARS-CoV-2 test for maternal participants), no integrated

analyses of AESI were performed on the pooled safety database. AESI are summarized by study in this briefing document and not included in the integrated safety summary below.

Because the RSVpreF vaccine is intended for use in pregnant individuals, the focus of this section is on the overall safety profile of RSVpreF at any dose/formulation in maternal and infant participants. The safety profile of RSVpreF 120 µg, both in the pooled analysis as well as in Study C3671008, was consistent with that observed for RSVpreF at any dose level/formulation and is briefly noted only in the reactogenicity and AE overview sections.

In the summaries below, the maternal safety population comprises all randomized pregnant participants from Studies C3671003 and C3671008 who received 1 dose of study intervention (either vaccine or placebo). The infant safety population comprises all infant participants born to these women. All populations were analyzed according to the actual vaccine administered; infants are analyzed according to the actual vaccine administered to their mothers.

5.5.1. Exposure to RSVpreF Across Studies C3671008 and C3671003 in the Maternal Clinical Development Program

Among maternal participants, 4144 participants received any dose level/formulation of RSVpreF. The median follow-up time after vaccination for these participants was 8.13 months (range: 0.0, 20.0), and ≥6 months follow-up safety data was available for 3637 (87.8%) of these participants. Of the total maternal participants, 3797 participants received RSVpreF 120 µg. The median follow-up time after vaccination for these participants was 7.97 months (range: 0.0, 18.8), and ≥6 months follow-up safety data was available for 3304 (87.0%) of these participants.

Among infant participants, 4024 participants were born to mothers who received any dose level/formulation of RSVpreF. The median follow-up time after birth for these participants was 11.97 months (range: 0.0, 24.3), and ≥6 months follow-up safety data was available for 3401 (84.5%) of these participants. Of the total infant participants, 3682 participants were born to mothers who received RSVpreF 120 µg. The median follow-up time after birth for these participants was 11.70 months (range: 0.0, 24.3), and ≥6 months follow-up safety data was available for 3069 (83.4%) of these participants.

5.5.2. Safety Profile of RSVpreF in Maternal Participants

Among maternal participants who received any dose level/formulation of RSVpreF, the proportions of participants reporting any AEs within 1 month after vaccination were similar in the pooled RSVpreF (15.0%) and the placebo (13.5%) groups (Table 27). AEs assessed as related by the investigator were reported in 0.4% of the pooled RSVpreF group and 0.2% of the placebo group. Most AEs were mild or moderate in severity; severe AEs were reported by similar proportion of participants in the RSVpreF (1.7%) and placebo (1.3%) groups. SAEs were reported in 4.0% of the pooled RSVpreF group and 3.7% of the placebo group. AEs leading to deaths, life-threatening AEs, AEs leading to withdrawal and immediate AEs were reported in ≤0.5% across both groups.

Among maternal participants who received RSVpreF 120 µg, the safety profile within 1 month after vaccination, both in the pooled analysis (Table 27) as well as in Study C3671008 (Table 7), was similar to that observed in maternal participants who received any dose level/formulation of RSVpreF (Table 27). In a subgroup analysis conducted on US participants only, the safety profile of RSVpreF in the US Safety Population was consistent with that observed in the overall analysis (Table 28).

Among maternal participants who received any dose level/formulation of RSVpreF, the proportions of participants reporting any AEs from vaccination through the data cutoff date were slightly higher in the pooled RSVpreF (30.7%) and the placebo (27.8%) groups (Table 29). AEs assessed as related by the investigator were reported in 0.4% of the pooled RSVpreF group and 0.2% of the placebo group. Most AEs were mild or moderate in severity; severe AEs were reported by similar proportion of participants in the RSVpreF (5.7%) and placebo (5.5%) groups. SAEs were reported in 15.8% of the pooled RSVpreF group and 15.1% of the placebo group. AEs leading to deaths, life-threatening AEs and AEs leading to withdrawal were reported in ≤1.6% in both groups.

5.5.3. Safety Profile of RSVpreF in Infant Participants

Among infant participants born to mothers who received any dose level/formulation of RSVpreF, the proportions of participants experiencing any AEs within 1 month after birth were 38.4% in the pooled RSVpreF group and 35.1% in the placebo group (Table 30). AEs assessed as related by the investigator were similar in the RSVpreF and placebo (<0.1%). Most AEs were mild or moderate in severity; severe AEs were reported by similar proportion of participants in the RSVpreF (4.6%) and placebo (3.9%) groups. SAEs were reported in 16.8% of the pooled RSVpreF group and 15.6% of the placebo group. AEs leading to deaths, life-threatening AEs, AEs leading to withdrawal were reported in ≤1.0% across both groups. Congenital anomalies were reported at a similar frequency in the RSVpreF and placebo groups (6.3%). Developmental delays were reported in <0.1% of the pooled RSVpreF group and 0% of the placebo group.

Among infant participants born to mothers who received RSVpreF 120 µg, the safety profile within 1 month after birth, both in the pooled analysis (Table 30) as well as in Study C3671008 (Table 10), was similar to that observed in infant participants born to maternal participants who received any dose level/formulation of RSVpreF (Table 30). In a subgroup analysis conducted on US participants only, the safety profile of RSVpreF in the US Safety Population was consistent with that observed in the overall analysis (Table 31).

Among infant participants born to mothers who received any dose level/formulation of RSVpreF, the proportions of participants experiencing any AEs from birth through the data cutoff date were 44.8% in the pooled RSVpreF and 40.7% in the placebo group (Table 32). AEs assessed as related by the investigator were similar in the RSVpreF and placebo groups (<0.1%). Most AEs were mild or moderate in severity; severe AEs were similar in the RSVpreF (5.5%) and placebo (4.6%) groups. SAEs were reported in 19.5% of the pooled RSVpreF group and 18.0% of the placebo group. AEs leading to deaths, life-threatening AEs, AEs leading to withdrawal were reported in ≤1.3% across both groups. Congenital anomalies were reported in ≤7.1% across both groups. Developmental delays were reported at a similar frequency in the RSVpreF and placebo groups (0.3%).

6. PHARMACOVIGILANCE

At this time, Pfizer has not identified any safety concerns from the clinical trial safety data and the vaccine reactogenicity profile is well tolerated in pregnant individuals and their infants. The safety profile of the product will be communicated appropriately in labelling documents.

Post-marketing safety surveillance will be conducted as part of Pfizer's routine pharmacovigilance activities. This includes the timely (1) collection, analysis, and review of safety data from all sources (including spontaneous case reports, literature, post-authorization safety study) for safety signal detection and (2) the subsequent assessment and evaluation of potential safety signals to determine whether there is a potential causal association between an event and the administration of the vaccine. Dependent on the characterization of the relevant safety risks, appropriate pharmacovigilance and risk mitigation actions are taken, in accordance with regulatory guidelines.

In addition, Pfizer will conduct a post-marketing safety study to continue to monitor the safety of RSVpreF in the general population of pregnant people, including individuals who are immunocompromised. Outcomes of interest will include the following pregnancy and neonatal safety outcomes: stillbirth, preterm birth, small for gestational age, and low birth weight.

7. BENEFIT/RISK ASSESSMENT

7.1. Benefits

RSVpreF is intended to prevent RSV disease in young infants, a potentially serious or life-threatening condition.

Maternal immunization with RSVpreF is designed to protect infants from birth through their first 6 months of life when the risk of RSV hospitalization is highest (50% and 75% of hospitalizations during the first year of life occur in the first 3 months and 6 months of life, respectively[2]). The potential for maternal immunization to protect the infant through their period of greatest risk of severe disease has many benefits. This approach alleviates logistical challenges of direct infant immunization or prophylactic mAb administration, which include adding an additional product into a complex infant immunization schedule and ensuring vaccine administration prior to any opportunities for RSV exposure. Immune responses to vaccines in very early infancy can also be suboptimal; multiple vaccine doses are often needed to elicit protective immunity in infants, which would further prolong the window of vulnerability between birth and when sufficient vaccine-induced protection from active immunization could be established. Maternal immunization also induces a polyclonal antibody response, and therefore has a low likelihood of applying selective pressure against circulating viruses.

The pivotal study C3671008 provides robust evidence that RSVpreF, when administered as a single 120 µg dose to pregnant mothers, confers protection against severe MA-LRTI due to RSV in infants which remains significant through 6 months after birth. Clinically meaningful efficacy against MA-LRTI due to RSV in infants through 180 days after birth was also observed, though the VE at 90 days after birth did not meet the statistical success criterion.

Maternal vaccination with RSVpreF was also efficacious in reducing the incidence of MA-LRTI due to RSV from 210 days through 360 days after birth. Cumulative efficacy for the secondary endpoint is primarily driven by efficacy at less than 180 days. However, with mothers vaccinated year-round in the trial this endpoint may approximate the real-world efficacy for infants born in and out of the RSV season but exposed within their first year. In infants born to RSVpreF vaccinated mothers, efficacy was also seen in reducing the incidence of infant hospitalization due to RSV within 180 days after birth. Taken together, the evidence from the Phase 3 study demonstrates that RSVpreF may protect against clinically significant RSV disease (or illness) and therefore have a substantial global public health impact.

In the pivotal C3671008 study, among infants 0 to 180 days old, RSVpreF demonstrated clinically significant vaccine effectiveness of 69.4% against severe RSV LRTI, 56.8% against hospitalization due to RSV, and 51.3% against medically attended RSV LRTI. Applying these measures of vaccine efficacy to the estimated 629,000 outpatient visits, and 27,000 hospitalizations in the United States due to RSV that occur each year in children <6 month old, RSVpreF has the potential to prevent more than 16,000 hospitalizations and 322,000 outpatient visits, if available for the 2023-2024 RSV season.

7.2. Risks

A total of 4144 maternal participants received any dose level/formulation of RSVpreF in the maternal immunization clinical program, including 3682 maternal participants who received RSVpreF 120 µg in the pivotal C3671008 study. In this study, local reactions and systemic events following administration of RSVpreF 120 µg were generally mild to moderate in severity. The incidences of AEs, SAEs, severe AEs, life-threatening AEs, and AEs assessed as related were similar between the RSVpreF and placebo groups within 1 month after vaccination. The only death in the study, in a RSVpreF recipient, was considered not related to study intervention. Intrauterine demises, including fetal demises, were balanced between the 2 groups and none were assessed as related to study intervention. There were no participants with AEs leading to withdrawal reported within 1 month after vaccination. AESIs were also balanced between the two groups. The majority of pregnancies resulted in live, term births. No important identified or potential risks were detected for RSVpreF 120 µg when administered as a single dose to pregnant women ≤49 years of age in Study C3671008. A similar overall safety profile was observed in the integrated safety analyses for the pooled RSVpreF 120 µg dose level and for the pooled any dose level/formulation of RSVpreF.

A total of 4024 infant participants were born to maternal participants who received any dose level/formulation of RSVpreF in the maternal immunization clinical program, including 3568 infants born to mothers who received RSVpreF 120 µg in the pivotal C3671008 study. In this study, the incidence of AEs was 37.1% in the RSVpreF group and 34.5% in the placebo group within 1 month after birth; SAEs, severe AEs, life-threatening AEs, and AEs assessed as related were similar between the RSVpreF and placebo groups. The incidence of infant participant deaths was similar between the 2 groups, and none of the deaths were considered related to study intervention. AESIs were reported at similar frequencies in both groups, including developmental delays. The clinical significance of numerical imbalances in certain

events in select regions (eg, numerical imbalances preterm birth and low birth weight in upper middle-income countries) is unknown, given that it was limited to select subgroups and there was no difference in overall incidence of preterm birth or low birth weight. The incidence of NDCMCs was also similar in the 2 groups. Birth outcomes were similar in the RSVpreF and placebo groups, and no meaningful differences were detected between the 2 groups with respect to prematurity, Apgar scores, or low birthweight. A similar overall safety profile was observed in the integrated safety analyses for the pooled RSVpreF 120 µg dose level and for the pooled any dose level/formulation of RSVpreF.

Overall, RSVpreF was well tolerated in pregnant women receiving the vaccine and their infants.

7.3. Benefit/Risk Assessment

RSV is the leading cause of bronchiolitis and viral pneumonia in infants worldwide. Among infants <6 months of age, RSV is associated with around 1.4 million hospital admissions, and around 13,000 in-hospital deaths globally each year.[6] In the US, RSV is the leading cause of infant hospitalization, with approximately 1% to 3% of all children in the first 12 months of life hospitalized due to RSV lower respiratory tract disease.[7] A single 120 µg dose of the unadjuvanted RSVpreF administered to pregnant women has shown to be efficacious against RSV-associated severe MA-LRTI, MA-LRTI and hospitalization through 90 and 180 days after birth. The vaccine is safe and well tolerated in mothers with no meaningful imbalances between RSVpreF and placebo recipients. Among infants, there were fewer deaths in the RSVpreF group (5) than the placebo group (12); none were related to study intervention. No major safety concerns have been identified in infants passively immunized with RSVpreF. A pharmacovigilance plan has been developed to determine the long-term safety profile of RSVpreF.

The RSVpreF maternal clinical program provides robust evidence that RSVpreF 120 µg is an efficacious and well tolerated vaccine in mothers, with no safety concerns in their infants. Collectively, these data support a favorable benefit/risk profile of RSVpreF and the proposed indication for the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals. Based on the results of the pivotal trial, the RSVpreF 120 µg vaccine has the potential to have an impact on reducing global infant mortality due to RSV.

8. APPENDICES

8.1. Studies in the RSVpreF Clinical Development Program for the Maternal Indication

Table 12. Summary of Studies in the RSVpreF Maternal Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 3 **Study C3671008** (Primary analysis for all endpoints [safety and efficacy] complete; long term safety follow-up ongoing) 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	This study is assessing the efficacy, safety, and immunogenicity of maternal immunisation with RSVpreF in healthy pregnant women and their infants. Study-eligible pregnant women were enrolled and randomized 1:1 to receive either a single dose of RSVpreF or placebo. This was a multicentre study, including sites in both the northern and southern hemispheres, and will span multiple RSV seasons. (Global Study)	A single dose of 120 µg (60 µg A and 60 µg B) RSVpreF was selected for use in this study. Approximately 6900 healthy pregnant women ≤49 years of age will be randomly assigned to investigational product. Therefore, approximately 6900 mother-infant pairs will participate in the study. However, with the variable RSV season, sample size may need to increase, and enrolment could go up to 10,000 maternal participants based on the number of cases of RSV.	**Infant Participants:** **Efficacy:** RSV-positive MA-LRTI and/or severe MA-LRTI as confirmed by the endpoint adjudication committee: occurring within 90, 120, 150, and 180 days after birth **Safety:** Specific birth outcomes AEs from birth to 1 month of age SAEs and NDCMCs from birth through 6, 12, and 24 months of age **Maternal Participants:** **Safety:** The incidence of: Prespecified local reactions and systemic events within 7 days after vaccination AEs from the time of vaccination through 1 month after vaccination SAEs throughout the study	**Infant Participants:** **Efficacy:** Hospitalization due to RSV as confirmed by the EAC occurring within 90, 120, 150, 180, and 360 days after birth MA-LRTI due to any cause occurring within 90, 120, 150, 180, and 360 days after birth RSV-positive MA-LRTI occurring within 210, 240, 270, and 360 days after birth

Table 12. Summary of Studies in the RSVpreF Maternal Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 1/2 **Study C3671001** **(Completed)** Title: A Phase 1/2, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding, First in human Study to Describe the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus Vaccine (RSV Vaccine) in Healthy Adults	The study assessed the safety, tolerability, and immunogenicity of 6 RSVpreF bivalent formulations (RSV A and B) at 3 escalating dose levels of 60 µg (30 µg A and 30 µg B), 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, with or without $Al(OH)_3$, when administered alone or concomitantly with SIIV. (US Study)	This study utilized a sentinel cohort (Phase 1) and an expanded cohort (Phase 2). One thousand two hundred thirty-five nonpregnant female and male participants 18 to 85 years of age were randomized. **Participants in the Phase 1**: Male and female participants 18 to 49 years of age. Male and female participants 50 to 85 years of age. **Participants in the Phase 2:** Male and female participants 18 to 49 years of age. Male and female participants 65 to 85 years of age. The age groups were run in parallel.	**Sentinel and expanded cohorts:** Local reactions within 14 days after Vaccination 1. Systemic events within 14 days after Vaccination 1. AEs within 1 month after Vaccination 1. Medically attended AEs and SAEs through 12 months after Vaccination 1. **Expanded cohort:** AEs within 1 month after Vaccination 2.	**Sentinel cohort:** RSV A– and RSV B–neutralizing titers measured before Vaccination 1, and 2 weeks and 1, 2, 3, and 6 months after Vaccination 1. **Expanded cohort:** RSV A and RSV B antibody titers measured before Vaccination 1, and 1, 2, 3, and 6 months after Vaccination 1. **Expanded cohort:** HAI titers for all strains and neutralization titers for the H3N2 strain in the SIIV measured before and 1 month after SIIV administration.

Table 12. Summary of Studies in the RSVpreF Maternal Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 2b Study C3671003 (Completed) 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.	The study assessed the safety, tolerability, and immunogenicity in maternal participants as well as the safety and characteristics of transplacentally transferred antibodies in their infants. Healthy pregnant women were randomized to receive one of 2 dose levels of bivalent (RSV A and B) RSV vaccine, specifically 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 $Al(OH)_3$, or placebo. This was a multicentre study, including sites in both the northern and southern hemispheres. (Global Study)	Healthy pregnant women ≥ 18 and ≤ 49 years of age were enrolled during their late 2nd or 3rd trimester (24 to 36 weeks) Five hundred seventy-nine healthy maternal participants were followed for safety for 12 months after delivery. Infants were enrolled at birth and actively followed for safety and respiratory illness for 12 months after birth.	**Maternal Participants:** 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 up to 12 months. **Infant Participants:** Specific birth outcomes AEs from birth to 1 month of age SAEs, AEs of special interest (congenital anomalies, developmental delay), and MAEs through 12 months of age Congenital anomalies	**Maternal Participants:** RSV A and RSV B neutralizing antibody titers measured before vaccination, 2 weeks, 1 month after vaccination, and at delivery. **Infant Participants:** RSV A and RSV B neutralizing antibody titers measured at birth and at 1, 2, 4, and 6 months after birth.

Table 12. Summary of Studies in the RSVpreF Maternal Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 2b **Study C3671004** **(Completed)** 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	The study assessed safety, tolerability, and any impact on immune responses to either vaccine when the RSV vaccine and Tdap were given concomitantly in healthy nonpregnant women. Participants were randomized in a 1:1:1:1:1 ratio to receive one of the following 5 schedules: 120 µg RSV vaccine antigen (60 µg A and 60 µg B) with concomitant Tdap, 120 µg RSV vaccine antigen with placebo, 240 µg RSV vaccine antigen (120 µg A and 120 µg B) with $Al(OH)_3$ and concomitant Tdap, 240 µg RSV vaccine antigen with $Al(OH)_3$ and placebo, or placebo and Tdap. (US Study)	Seven hundred thirteen healthy nonpregnant women, 18 through 49 years of age, were randomized to evaluate concomitant administration of the RSV vaccine and a US-licensed Tdap.	**Immunogenicity:** Anti-TTd and anti-DTd antibodies and anti-pertussis components (anti-PT, anti-FHA, and anti-PRN) measured 1 month after vaccination. RSV A and RSV B neutralizing antibody titers measured 1 month after vaccination. **Safety:** Prespecified local reactions within 7 days after vaccination. Prespecified systemic events within 7 days after vaccination. AEs within 1 month after vaccination. MAEs and SAEs throughout the study.	**Immunogenicity:** RSV A– and RSV B–neutralizing antibody titers measured 1 month after vaccination.

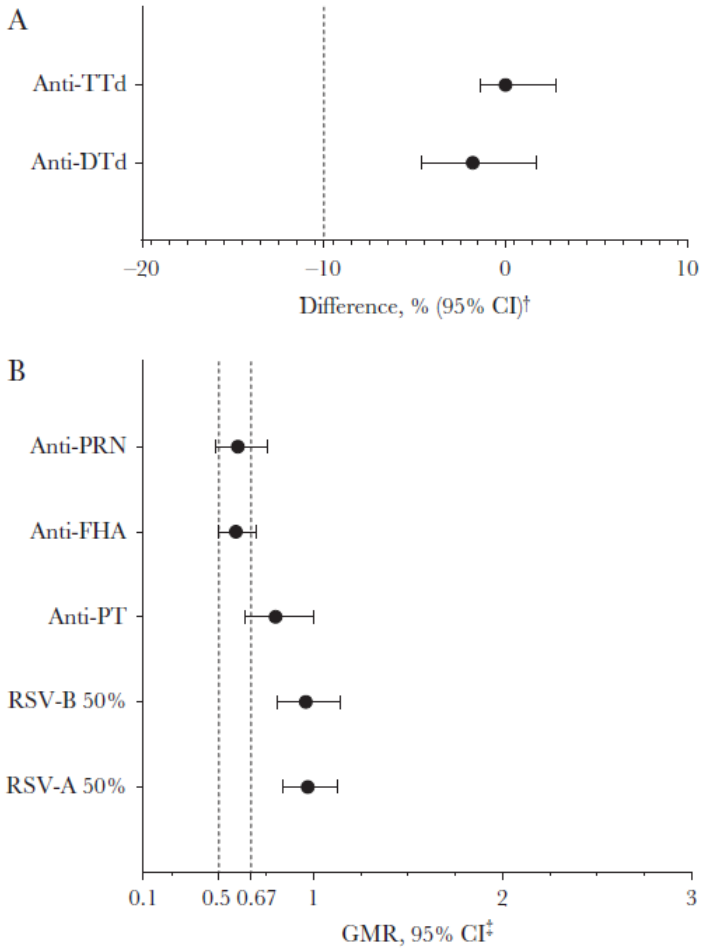
Table 12. Summary of Studies in the RSVpreF Maternal Clinical Development Program

Study	Description (Location)	Population/Groups	Primary Endpoints	Secondary Endpoints
Phase 3 **Study C3671014** **(Completed)** 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	The study assessed the safety, tolerability, and immunogenicity across 3 manufactured lots of RSVpreF when administered to healthy adults to demonstrate lot equivalence in manufacturing of RSVpreF. Participants were randomized in a 1:1:1:1 ratio to receive 1 of 3 lots of RSVpreF or placebo. (US Study)	Nine hundred ninety three healthy participants, 18 through ≤49 years of age, were randomized to receive 1 of 3 lots of RSVpreF or placebo.	**Immunogenicity:** RSV A and RSV B NTs **Safety:** Local reactions for 7 days after vaccination Systemic events for 7 days after vaccination AEs through study completion SAEs through study completion	N/A

8.2. Additional Data from Supportive Studies in the RSVpreF Clinical Development Program

8.2.1. Study C3671004

Figure 9. Immunogenicity Endpoints, Coadministration of RSVpreF with Tdap - Evaluable Immunogenicity Population



†Difference in the percentage of participants achieving anti-TTd or anti-DTd antibody concentrations ≥0.1 IU/mL between the combined RSVpreF/Tdap groups and placebo/Tdap group (RSVpreF/Tdap – placebo/Tdap).
‡Geometric mean ratios (GMRs) were calculated as the group mean differences of logarithmically transformed antibody levels and back-transformed to the original units. Anti-pertussis component antibody GMRs were calculated using combined RSVpreF/Tdap geometric mean concentrations (GMCs) as numerators and placebo/Tdap GMCs as denominators, and RSV neutralizing titer GMRs were calculated using combined RSVpreF/Tdap geometric mean titers (GMTs) as numerators and combined RSVpreF/placebo GMTs as denominators. Noninferiority for anti-pertussis toxin, anti-pertactin, and anti-filamentous hemagglutinin required the lower 95% confidence limit to be >0.67. Noninferiority for RSV-A– and RSV-B– neutralizing titers required the lower 95% confidence limit to be >0.5 for the primary objective and >0.67 for the secondary objective.
Source: Peterson et al[90]

Table 13. All Adverse Events by Category – Reported Within 1 Month After Vaccination – Safety Population

	Vaccine Group (as Administered)				
	RSVpreF 120 µg/ Placebo (N[a]=141)	**RSVpreF 120 µg/ Tdap (N[a]=141)**	**RSVpreF 240 µg + Al(OH)3/Placebo (N[a]=142)**	**RSVpreF 240 µg + Al(OH)3/Tdap (N[a]=144)**	**Placebo/Tdap (N[a]=141)**
Adverse Event Category	**n[b] (%) (95% CI)[c]**	**n[b] (%) (95% CI)[c]**	**n[b] (%) (95% CI)[c]**	**n[b] (%) (95% CI)[c]**	**n[b] (%) (95% CI)[c]**
Any event	8 (5.7) (2.5, 10.9)	11 (7.8) (4.0, 13.5)	8 (5.6) (2.5, 10.8)	15 (10.4) (5.9, 16.6)	13 (9.2) (5.0, 15.3)
Serious	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.5)	0 (0.0, 2.6)
Immediate[d]	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.5)	0 (0.0, 2.6)
Severe	2 (1.4) (0.2, 5.0)	1 (0.7) (0.0, 3.9)	1 (0.7) (0.0, 3.9)	0 (0.0, 2.5)	0 (0.0, 2.6)
Life-threatening	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.5)	0 (0.0, 2.6)
Related	1 (0.7) (0.0, 3.9)	1 (0.7) (0.0, 3.9)	1 (0.7) (0.0, 3.9)	3 (2.1) (0.4, 6.0)	0 (0.0, 2.6)
Medically attended[e]	2 (1.4) (0.2, 5.0)	0 (0.0, 2.6)	0 (0.0, 2.6)	2 (1.4) (0.2, 4.9)	3 (2.1) (0.4, 6.1)
AEs leading to withdrawal	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.6)	0 (0.0, 2.5)	0 (0.0, 2.6)

Note: The classification of adverse events is based on MedDRA (Version 22.1).
a. N = number of subjects in the vaccine group. These values were used as the denominators for the percentage calculations.
b. n = Number of subjects reporting at least 1 event of the type specified.
c. Exact 2-sided CI calculated using the Clopper and Pearson method.
d. An immediate AE is any AE that occurred within the first 30 minutes after administration of the investigational product.
e. Refers to non-serious AEs.
PFIZER CONFIDENTIAL SDTM Creation: 10APR2020 (02:24) Source Data: adae Output File: ./nda1/C3671004/adae s015 Date of Generation: 02JUL2020 (23:38)

8.2.2. Study C3671014

Table 14. Ratio of 50% Neutralizing Geometric Mean Titers Between Individual RSVpreF Lots at 1 Month After Vaccination – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)								
	Group 1 RSVpreF Lot 1		Group 2 RSVpreF Lot 2		Group 3 RSVpreF Lot 3		Comparison GMR[a] (95% CI[a])		
RSV Subgroup	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	n[b]	GMT[c] (95% CI[c])	Group 1 RSVpreF Lot 1 / Group 2 RSVpreF Lot 2	Group 1 RSVpreF Lot 1 / Group 3 RSVpreF Lot 3	Group 2 RSVpreF Lot 2 / Group 3 RSVpreF Lot 3
A	236	25238.1 (22867.7, 27854.2)	236	25207.5 (22360.8, 28416.6)	238	24130.9 (21536.3, 27038.1)	1.00 (0.858, 1.169)	1.05 (0.900, 1.215)	1.04 (0.886, 1.232)
B	236	21701.9 (19433.1, 24235.6)	236	20317.3 (17944.4, 23003.9)	238	19238.1 (16920.0, 21873.9)	1.07 (0.905, 1.261)	1.13 (0.953, 1.336)	1.06 (0.884, 1.262)

Abbreviations: GMT = geometric mean titer; GMR = geometric mean ratio; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
a. GMRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the difference in LS means and corresponding CIs based on analysis of logarithmically transformed assay results using a linear regression model.
b. n = Number of participants with valid and determinate assay results for the specified assay at the given sampling timepoint.
c. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 18MAY2022 (11:31) Table Generation: 18MAY2022 (11:31)
(Database snapshot date : 05May2022) Output File: ./nda oa/C3671014 CSR/adva s007 gmr evimm

8.2.3. Study C3671003

Table 15. Number (%) of Participants Reporting Adverse Events, by Category, Within 1 Month After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)				
	RSVpreF 120 µg (N^a=115)	RSVpreF 120 µg + $Al(OH)_3$ (N^a=117)	RSVpreF 240 µg (N^a=116)	RSVpreF 240 µg + $Al(OH)_3$ (N^a=114)	Placebo (N^a=117)
Adverse Event Category	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]
Any event	26 (22.6) (15.3, 31.3)	28 (23.9) (16.5, 32.7)	35 (30.2) (22.0, 39.4)	26 (22.8) (15.5, 31.6)	29 (24.8) (17.3, 33.6)
Serious	1 (0.9) (0.0, 4.7)	3 (2.6) (0.5, 7.3)	2 (1.7) (0.2, 6.1)	4 (3.5) (1.0, 8.7)	3 (2.6) (0.5, 7.3)
Immediate[d]	0 (0.0, 3.2)	0 (0.0, 3.1)	0 (0.0, 3.1)	0 (0.0, 3.2)	0 (0.0, 3.1)
Severe	2 (1.7) (0.2, 6.1)	3 (2.6) (0.5, 7.3)	1 (0.9) (0.0, 4.7)	2 (1.8) (0.2, 6.2)	2 (1.7) (0.2, 6.0)
Life-Threatening	1 (0.9) (0.0, 4.7)	0 (0.0, 3.1)	1 (0.9) (0.0, 4.7)	0 (0.0, 3.2)	0 (0.0, 3.1)
Related	1 (0.9) (0.0, 4.7)	0 (0.0, 3.1)	0 (0.0, 3.1)	0 (0.0, 3.2)	0 (0.0, 3.1)
Medically attended[e]	5 (4.3) (1.4, 9.9)	7 (6.0) (2.4, 11.9)	6 (5.2) (1.9, 10.9)	10 (8.8) (4.3, 15.5)	6 (5.1) (1.9, 10.8)
AE leading to withdrawal	0 (0.0, 3.2)	0 (0.0, 3.1)	0 (0.0, 3.1)	0 (0.0, 3.2)	0 (0.0, 3.1)

Note: MedDRA (v24.1) coding dictionary applied.
Note: Adverse events that occurred prior to vaccination are not included in this summary.
Note: The severity of the event is in the determination of the investigator.
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. 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.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product for maternal participants.
e. Refers to nonserious AEs and excludes SAEs.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2022 (00:50) Source Data: adae Table Generation: 27JAN2022 (20:30)
(Data cutoff date : 16DEC2021 Database snapshot date : 16DEC2021) Output File: ./nda1/C3671003 CSR/adae s151 in1

Table 16. Number (%) of Participants Reporting Adverse Events, by Category, Within 1 Month of Age - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)				
	RSVpreF 120 µg (N^a=114)	RSVpreF 120 µg + $Al(OH)_3$ (N^a=117)	RSVpreF 240 µg (N^a=113)	RSVpreF 240 µg + $Al(OH)_3$ (N^a=112)	Placebo (N^a=116)
Adverse Event Category	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]	n^b (%) (95% CI)[c]
Any event	58 (50.9) (41.3, 60.4)	55 (47.0) (37.7, 56.5)	53 (46.9) (37.5, 56.5)	55 (49.1) (39.5, 58.7)	59 (50.9) (41.4, 60.3)
Serious	31 (27.2) (19.3, 36.3)	33 (28.2) (20.3, 37.3)	28 (24.8) (17.1, 33.8)	33 (29.5) (21.2, 38.8)	31 (26.7) (18.9, 35.7)
Severe	4 (3.5) (1.0, 8.7)	9 (7.7) (3.6, 14.1)	5 (4.4) (1.5, 10.0)	5 (4.5) (1.5, 10.1)	8 (6.9) (3.0, 13.1)
Life-Threatening	1 (0.9) (0.0, 4.8)	4 (3.4) (0.9, 8.5)	2 (1.8) (0.2, 6.2)	0 (0.0, 3.2)	1 (0.9) (0.0, 4.7)
Related	0 (0.0, 3.2)	0 (0.0, 3.1)	0 (0.0, 3.2)	0 (0.0, 3.2)	0 (0.0, 3.1)
Medically attended[d]	4 (3.5) (1.0, 8.7)	7 (6.0) (2.4, 11.9)	9 (8.0) (3.7, 14.6)	7 (6.3) (2.5, 12.5)	7 (6.0) (2.5, 12.0)
AE leading to withdrawal	0 (0.0, 3.2)	0 (0.0, 3.1)	0 (0.0, 3.2)	0 (0.0, 3.2)	1 (0.9) (0.0, 4.7)

Note: MedDRA (v24.1) coding dictionary applied.
Note: The severity of the event is in the determination of the investigator.
a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. 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.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. Refers to non-serious AEs and excludes SAEs.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2022 (00:50) Source Data: adae Table Generation: 27JAN2022 (20:30)
(Data cutoff date : 16DEC2021 Database snapshot date : 16DEC2021) Output File: ./nda1/C3671003 CSR/adae s151b in1

Table 17. Birth Outcomes - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)				
	RSVpreF 120 µg (N^a=114)	**RSVpreF 120 µg + $Al(OH)_3$ (N^a=117)**	**RSVpreF 240 µg (N^a=113)**	**RSVpreF 240 µg + $Al(OH)_3$ (N^a=112)**	**Placebo (N^a=116)**
	n^b (%)	**n^b (%)**	**n^b (%)**	**n^b (%)**	**n^b (%)**
Gestational age (weeks)					
n	114	117	113	112	116
Mean (SD)	39.06 (1.092)	38.96 (1.279)	38.86 (1.523)	39.07 (1.089)	39.08 (1.165)
Median	39.14	39.00	39.00	39.29	39.14
Min, max	(35.4, 41.4)	(31.4, 41.0)	(31.3, 41.6)	(34.7, 41.4)	(33.1, 41.7)
Apgar score - 1 minute					
n	111	116	112	111	114
Median	8.0	8.0	8.0	9.0	8.0
Min, max	(2, 9)	(5, 9)	(3, 10)	(0, 9)	(1, 9)
Apgar score - 5 minute					
n	111	116	112	111	114
Median	9.0	9.0	9.0	9.0	9.0
Min, max	(7, 10)	(5, 10)	(6, 10)	(1, 10)	(4, 10)
Apgar score - 10 minute					
n	11	11	11	8	13
Median	9.0	9.0	9.0	9.0	9.0
Min, max	(9, 10)	(8, 10)	(6, 10)	(5, 10)	(5, 10)
Ballard score					
n	49	40	46	48	35
Median	39.0	38.0	38.0	39.0	38.0
Min, max	(20, 45)	(19, 43)	(0, 43)	(17, 45)	(19, 44)
Did the infant cry immediately after delivery					
Yes	108 (94.7)	109 (93.2)	104 (92.0)	102 (91.1)	108 (93.1)
No	4 (3.5)	3 (2.6)	5 (4.4)	5 (4.5)	6 (5.2)
Not reported	2 (1.8)	5 (4.3)	4 (3.5)	5 (4.5)	2 (1.7)
Did the infant suckle shortly after delivery					
Yes	105 (92.1)	106 (90.6)	101 (89.4)	96 (85.7)	106 (91.4)
No	7 (6.1)	6 (5.1)	6 (5.3)	8 (7.1)	8 (6.9)
Not reported	2 (1.8)	5 (4.3)	6 (5.3)	8 (7.1)	2 (1.7)
Congenital malformation/anomaly[c]					
Yes	19 (16.7)	14 (12.0)	16 (14.2)	22 (19.6)	16 (13.8)
No	95 (83.3)	103 (88.0)	96 (85.0)	90 (80.4)	99 (85.3)
Not reported	0	0	1 (0.9)	0	1 (0.9)

Table 17. Birth Outcomes - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)				
	RSVpreF 120 µg (N^a=114)	RSVpreF 120 µg + $Al(OH)_3$ (N^a=117)	RSVpreF 240 µg (N^a=113)	RSVpreF 240 µg + $Al(OH)_3$ (N^a=112)	Placebo (N^a=116)
	n^b (%)	n^b (%)	n^b (%)	n^b (%)	n^b (%)

a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. As documented in response to this question in the CRF.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2022 (00:50) Source Data: adfaio Table Generation: 14FEB2022 (21:35)
(Data cutoff date : 16DEC2021 Database snapshot date : 16DEC2021) Output File: ./nda1/C3671003 CSR/adfa s001

8.3. Additional Data from Pivotal Phase 3 Study C3671008

Table 18. RSV-Positive MA-LRTIs Confirmed by EAC Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg	Placebo	
Time Interval	Number of Cases	Number of Cases	Vaccine Efficacy[a] (%) (99.83% CI)
90 Days after birth	13	43	69.8 (20.3, 90.5)
120 Days after birth	20	58	65.5 (23.1, 86.2)
150 Days after birth	26	66	60.6 (18.9, 82.3)
180 Days after birth	33	81	NC*
Conditional power[b]	99.8%		

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; NC = not calculated; 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 based on the available alpha at the interim analysis using the O'Brien-Fleming alpha spending function.
b. Conditional power is the probability to demonstrate success at the final analysis with 124 cases, conditional upon the cases observed so far and assuming VE = 60% following the futility check.
PFIZER CONFIDENTIAL SDTM Creation: 14APR2022 (02:50) Source Data: adrsvef Table Generation: 20APR2022 (11:21)
(Database snapshot date : 13APR2022) Output File: N:\Pfizer C3671008\Analysis - 20220419\adprim s001b rsvpos

*Vaccine efficacy at 180 Days after birth was not displayed at the time of the interim analysis, however VE of 59.3% (99.83% CI: 22.4%, 79.8%) was calculated.

Table 19. Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth by Subgroups - Infant Participants - Evaluable Efficacy Population

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N^a =3495)		Placebo (N^a=3480)		
Time Interval	Subgroup Variable	Subgroup	n^b	Number of Cases (%)	n^b	Number of Cases (%)	Vaccine Efficacy[c] (%) (95% CI)
90 Days after birth	Country	United States	1619	1 (<0.1)	1597	10 (0.6)	90.1 (30.7, 99.8)
120 Days after birth	Country	United States	1619	4 (0.2)	1597	14 (0.9)	71.8 (10.3, 93.2)
150 Days after birth	Country	United States	1619	7 (0.4)	1597	17 (1.1)	59.4 (-3.1, 85.8)
180 Days after birth	Country	United States	1619	9 (0.6)	1597	23 (1.4)	61.4 (13.4, 84.3)

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

a. N = number of participants (at risk) in the specified group.

b. n = number of participants (at risk) in the specified group for the specified characteristic. These values are used as the denominators for the percentage calculations.

c. Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of cases in the RSVpreF group 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.

Table 20. RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth by Subgroups - Infant Participants - Evaluable Efficacy Population

			Maternal Vaccine Group (as Randomized)				
			RSVpreF 120 µg (N[a] =3495)		Placebo (N[a]=3480)		
Time Interval	Subgroup Variable	Subgroup	n[b]	Number of Cases (%)	n[b]	Number of Cases (%)	Vaccine Efficacy[c] (%) (95% CI)
90 Days after birth	Country	United States	1619	2 (0.1)	1597	15 (0.9)	86.8 (43.4, 98.5)
120 Days after birth	Country	United States	1619	7 (0.4)	1597	22 (1.4)	68.6 (23.9, 88.7)
150 Days after birth	Country	United States	1619	12 (0.7)	1597	30 (1.9)	60.5 (20.6, 81.6)
180 Days after birth	Country	United States	1619	17 (1.1)	1597	40 (2.5)	58.1 (24.4, 77.7)

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
a. N = number of participants (at risk) in the specified group.
b. n = number of participants (at risk) in the specified group for the specified characteristic. These values are used as the denominators for the percentage calculations.
c. Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of cases in the RSVpreF group 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.

Table 21. Local Reactions, by Maximum Severity, Within 7 Days After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)					
	RSVpreF 120 µg			Placebo		
Local Reaction	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]
Redness[d]						
Any	3663	265 (7.2)	(6.4, 8.1)	3639	8 (0.2)	(0.1, 0.4)
Mild	3663	181 (4.9)	(4.3, 5.7)	3639	4 (0.1)	(0.0, 0.3)
Moderate	3663	78 (2.1)	(1.7, 2.7)	3639	4 (0.1)	(0.0, 0.3)
Severe	3663	6 (0.2)	(0.1, 0.4)	3639	0	(0.0, 0.1)
Swelling[d]						
Any	3663	227 (6.2)	(5.4, 7.0)	3639	8 (0.2)	(0.1, 0.4)
Mild	3663	150 (4.1)	(3.5, 4.8)	3639	5 (0.1)	(0.0, 0.3)
Moderate	3663	73 (2.0)	(1.6, 2.5)	3639	3 (<0.1)	(0.0, 0.2)
Severe	3663	4 (0.1)	(0.0, 0.3)	3639	0	(0.0, 0.1)
Pain at injection site[e]						
Any	3663	1488 (40.6)	(39.0, 42.2)	3639	369 (10.1)	(9.2, 11.2)
Mild	3663	1319 (36.0)	(34.5, 37.6)	3639	337 (9.3)	(8.3, 10.2)
Moderate	3663	165 (4.5)	(3.9, 5.2)	3639	32 (0.9)	(0.6, 1.2)
Severe	3663	4 (0.1)	(0.0, 0.3)	3639	0	(0.0, 0.1)
Any local reaction[f]						
Any	3663	1557 (42.5)	(40.9, 44.1)	3639	378 (10.4)	(9.4, 11.4)
Mild	3663	1296 (35.4)	(33.8, 37.0)	3639	343 (9.4)	(8.5, 10.4)
Moderate	3663	250 (6.8)	(6.0, 7.7)	3639	35 (1.0)	(0.7, 1.3)
Severe	3663	11 (0.3)	(0.2, 0.5)	3639	0	(0.0, 0.1)

a. 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.
b. n = Number of participants reporting a maximum severity of mild, moderate, or severe based on the severity scales with the specified characteristic.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. Mild is >2.0 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10 cm.
e. Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
f. Any local reaction = any pain at the injection site, any swelling, or any redness.
PFIZER CONFIDENTIAL SDTM Creation: 21NOV2022 (00:37) Source Data: adfacevd Table Generation: 21NOV2022 (22:42)
(Data cutoff date : 02SEP2022 Database snapshot date : 14OCT2022) Output File:
./mat 1008/C3671008 REX REACTO SUPP/adce s010

Table 22. Systemic Events, by Maximum Severity Within 7 Days Before and Within 7 Days After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)											
	RSVpreF 120 µg						Placebo					
	Within 7 Days Before Vaccination			Within 7 Days After Vaccination			Within 7 Days Before Vaccination			Within 7 Days After Vaccination		
Systemic Event	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]
Fever(≥38.0ºC)												
≥38.0°C	N/A			3663	94 (2.6)	(2.1, 3.1)	N/A			3638	107 (2.9)	(2.4, 3.5)
38.0°C to 38.4°C	N/A			3663	61 (1.7)	(1.3, 2.1)	N/A			3638	55 (1.5)	(1.1, 2.0)
38.5°C to 38.9°C	N/A			3663	29 (0.8)	(0.5, 1.1)	N/A			3638	42 (1.2)	(0.8, 1.6)
39.0°C to 40.0°C	N/A			3663	1 (<0.1)	(0.0, 0.2)	N/A			3638	5 (0.1)	(0.0, 0.3)
>40.0°C	N/A			3663	3 (<0.1)	(0.0, 0.2)	N/A			3638	5 (0.1)	(0.0, 0.3)
Fatigue[d]												
Any	3637	1712 (47.1)	(45.4, 48.7)	3663	1688 (46.1)	(44.5, 47.7)	3621	1664 (46.0)	(44.3, 47.6)	3640	1595 (43.8)	(42.2, 45.4)
Mild	3637	1123 (30.9)	(29.4, 32.4)	3663	856 (23.4)	(22.0, 24.8)	3621	1075 (29.7)	(28.2, 31.2)	3640	828 (22.7)	(21.4, 24.1)
Moderate	3637	577 (15.9)	(14.7, 17.1)	3663	782 (21.3)	(20.0, 22.7)	3621	569 (15.7)	(14.5, 16.9)	3640	715 (19.6)	(18.4, 21.0)
Severe	3637	12 (0.3)	(0.2, 0.6)	3663	50 (1.4)	(1.0, 1.8)	3621	20 (0.6)	(0.3, 0.9)	3640	52 (1.4)	(1.1, 1.9)
Headache[d]												
Any	3637	680 (18.7)	(17.4, 20.0)	3663	1134 (31.0)	(29.5, 32.5)	3621	717 (19.8)	(18.5, 21.1)	3639	1004 (27.6)	(26.1, 29.1)
Mild	3637	530 (14.6)	(13.4, 15.8)	3663	739 (20.2)	(18.9, 21.5)	3621	553 (15.3)	(14.1, 16.5)	3639	651 (17.9)	(16.7, 19.2)
Moderate	3637	143 (3.9)	(3.3, 4.6)	3663	380 (10.4)	(9.4, 11.4)	3621	157 (4.3)	(3.7, 5.1)	3639	340 (9.3)	(8.4, 10.3)
Severe	3637	7 (0.2)	(0.1, 0.4)	3663	15 (0.4)	(0.2, 0.7)	3621	7 (0.2)	(0.1, 0.4)	3639	13 (0.4)	(0.2, 0.6)
Nausea[d]												
Any	3637	648 (17.8)	(16.6, 19.1)	3663	732 (20.0)	(18.7, 21.3)	3621	715 (19.7)	(18.5, 21.1)	3640	701 (19.3)	(18.0, 20.6)
Mild	3637	508 (14.0)	(12.9, 15.1)	3663	527 (14.4)	(13.3, 15.6)	3621	562 (15.5)	(14.4, 16.7)	3640	501 (13.8)	(12.7, 14.9)
Moderate	3637	137 (3.8)	(3.2, 4.4)	3663	197 (5.4)	(4.7, 6.2)	3621	147 (4.1)	(3.4, 4.8)	3640	192 (5.3)	(4.6, 6.1)
Severe	3637	3 (<0.1)	(0.0, 0.2)	3663	8 (0.2)	(0.1, 0.4)	3621	6 (0.2)	(0.1, 0.4)	3640	8 (0.2)	(0.1, 0.4)
Muscle pain[d]												
Any	3637	772 (21.2)	(19.9, 22.6)	3663	972 (26.5)	(25.1, 28.0)	3621	760 (21.0)	(19.7, 22.4)	3639	623 (17.1)	(15.9, 18.4)

Table 22. Systemic Events, by Maximum Severity Within 7 Days Before and Within 7 Days After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)											
	RSVpreF 120 µg						Placebo					
	Within 7 Days Before Vaccination			Within 7 Days After Vaccination			Within 7 Days Before Vaccination			Within 7 Days After Vaccination		
Systemic Event	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]
Mild	3637	489 (13.4)	(12.4, 14.6)	3663	643 (17.6)	(16.3, 18.8)	3621	477 (13.2)	(12.1, 14.3)	3639	363 (10.0)	(9.0, 11.0)
Moderate	3637	275 (7.6)	(6.7, 8.5)	3663	315 (8.6)	(7.7, 9.6)	3621	271 (7.5)	(6.6, 8.4)	3639	248 (6.8)	(6.0, 7.7)
Severe	3637	8 (0.2)	(0.1, 0.4)	3663	14 (0.4)	(0.2, 0.6)	3621	12 (0.3)	(0.2, 0.6)	3639	12 (0.3)	(0.2, 0.6)
Joint pain[d]												
Any	3637	501 (13.8)	(12.7, 14.9)	3663	424 (11.6)	(10.6, 12.7)	3621	501 (13.8)	(12.7, 15.0)	3639	382 (10.5)	(9.5, 11.5)
Mild	3637	309 (8.5)	(7.6, 9.4)	3663	238 (6.5)	(5.7, 7.3)	3621	290 (8.0)	(7.1, 8.9)	3639	218 (6.0)	(5.2, 6.8)
Moderate	3637	186 (5.1)	(4.4, 5.9)	3663	180 (4.9)	(4.2, 5.7)	3621	202 (5.6)	(4.9, 6.4)	3639	161 (4.4)	(3.8, 5.1)
Severe	3637	6 (0.2)	(0.1, 0.4)	3663	6 (0.2)	(0.1, 0.4)	3621	9 (0.2)	(0.1, 0.5)	3639	3 (<0.1)	(0.0, 0.2)
Vomiting[e]												
Any	3637	352 (9.7)	(8.7, 10.7)	3663	287 (7.8)	(7.0, 8.8)	3621	309 (8.5)	(7.6, 9.5)	3639	254 (7.0)	(6.2, 7.9)
Mild	3637	307 (8.4)	(7.6, 9.4)	3663	233 (6.4)	(5.6, 7.2)	3621	259 (7.2)	(6.3, 8.0)	3639	196 (5.4)	(4.7, 6.2)
Moderate	3637	45 (1.2)	(0.9, 1.7)	3663	46 (1.3)	(0.9, 1.7)	3621	48 (1.3)	(1.0, 1.8)	3639	56 (1.5)	(1.2, 2.0)
Severe	3637	0	(0.0, 0.1)	3663	8 (0.2)	(0.1, 0.4)	3621	2 (<0.1)	(0.0, 0.2)	3639	2 (<0.1)	(0.0, 0.2)
Diarrhea[f]												
Any	3637	249 (6.8)	(6.0, 7.7)	3663	412 (11.2)	(10.2, 12.3)	3621	260 (7.2)	(6.4, 8.1)	3639	417 (11.5)	(10.4, 12.5)
Mild	3637	224 (6.2)	(5.4, 7.0)	3663	335 (9.1)	(8.2, 10.1)	3621	236 (6.5)	(5.7, 7.4)	3639	343 (9.4)	(8.5, 10.4)
Moderate	3637	21 (0.6)	(0.4, 0.9)	3663	73 (2.0)	(1.6, 2.5)	3621	23 (0.6)	(0.4, 1.0)	3639	67 (1.8)	(1.4, 2.3)
Severe	3637	4 (0.1)	(0.0, 0.3)	3663	4 (0.1)	(0.0, 0.3)	3621	1 (<0.1)	(0.0, 0.2)	3639	7 (0.2)	(0.1, 0.4)
Any systemic event[g]												
Any	3637	2264 (62.2)	(60.7, 63.8)	3663	2340 (63.9)	(62.3, 65.4)	3621	2286 (63.1)	(61.5, 64.7)	3640	2157 (59.3)	(57.6, 60.9)
Mild	3637	1359 (37.4)	(35.8, 39.0)	3663	1193 (32.6)	(31.1, 34.1)	3621	1367 (37.8)	(36.2, 39.4)	3640	1087 (29.9)	(28.4, 31.4)
Moderate	3637	866 (23.8)	(22.4, 25.2)	3663	1064 (29.0)	(27.6, 30.5)	3621	872 (24.1)	(22.7, 25.5)	3640	987 (27.1)	(25.7, 28.6)

Table 22. Systemic Events, by Maximum Severity Within 7 Days Before and Within 7 Days After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)											
	RSVpreF 120 µg						Placebo					
	Within 7 Days Before Vaccination			Within 7 Days After Vaccination			Within 7 Days Before Vaccination			Within 7 Days After Vaccination		
Systemic Event	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]	N[a]	n[b](%)	(95% CI)[c]
Severe	3637	39 (1.1)	(0.8, 1.5)	3663	83 (2.3)	(1.8, 2.8)	3621	47 (1.3)	(1.0, 1.7)	3640	83 (2.3)	(1.8, 2.8)

Abbreviation: N/A = not applicable.
a. N = number of subjects reporting "yes" or "no" for at least 1 day. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting maximum severity of mild, moderate, or severe based on the severity scales.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. Mild = does not interfere with activity, moderate = some interference with activity, severe = prevents daily routine activity.
e. Mild = 1 to 2 times in 24 hours, moderate = >2 times in 24 hours, severe = requires intravenous hydration.
f. 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.
g. Any systemic event = any fatigue, any headache, any vomiting, any nausea, any diarrhea, any muscle pain or any joint pain.
PFIZER CONFIDENTIAL SDTM Creation: 21NOV2022 (00:37) Source Data: adfacevd Table Generation: 21NOV2022 (22:42)
(Data cutoff date : 02SEP2022 Database snapshot date : 14OCT2022) Output File:
./mat 1008/C3671008 REX REACTO SUPP/adce s020

Table 23. Adverse Events of Special Interest Reported, by Time Intervals, System Organ Class and Preferred Term - Infant Participants - Safety Population

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Time Interval	System Organ Class Preferred Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Birth to 24 months of age	Any Event	386 (10.8)	(9.8, 11.9)	344 (9.7)	(8.7, 10.7)
	General disorders and administration site conditions	2 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)
	Developmental delay	2 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)
	Investigations	87 (2.4)	(2.0, 3.0)	88 (2.5)	(2.0, 3.0)
	Head lag abnormal	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	SARS-CoV-2 test positive	87 (2.4)	(2.0, 3.0)	87 (2.4)	(2.0, 3.0)
	Nervous system disorders	10 (0.3)	(0.1, 0.5)	8 (0.2)	(0.1, 0.4)
	Fine motor delay	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Gross motor delay	1 (<0.1)	(0.0, 0.2)	4 (0.1)	(0.0, 0.3)
	Hypotonia	1 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)
	Language disorder	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Motor developmental delay	2 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Motor dysfunction	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sensory disturbance	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Speech disorder	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Speech disorder developmental	4 (0.1)	(0.0, 0.3)	1 (<0.1)	(0.0, 0.2)
	Pregnancy, puerperium and perinatal conditions	297 (8.3)	(7.4, 9.3)	253 (7.1)	(6.3, 8.0)
	Low birth weight baby	181 (5.1)	(4.4, 5.8)	154 (4.3)	(3.7, 5.0)
	Premature baby	202 (5.7)	(4.9, 6.5)	169 (4.7)	(4.1, 5.5)
Birth to 1 month of age	Any Event	298 (8.4)	(7.5, 9.3)	257 (7.2)	(6.4, 8.1)
	Investigations	2 (<0.1)	(0.0, 0.2)	5 (0.1)	(0.0, 0.3)
	SARS-CoV-2 test positive	2 (<0.1)	(0.0, 0.2)	5 (0.1)	(0.0, 0.3)
	Nervous system disorders	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Hypotonia	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Pregnancy, puerperium and perinatal conditions	297 (8.3)	(7.4, 9.3)	253 (7.1)	(6.3, 8.0)
	Low birth weight baby	181 (5.1)	(4.4, 5.8)	154 (4.3)	(3.7, 5.0)
	Premature baby	202 (5.7)	(4.9, 6.5)	169 (4.7)	(4.1, 5.5)
1 Month to 6 months of age	Any Event	37 (1.0)	(0.7, 1.4)	26 (0.7)	(0.5, 1.1)
	Investigations	37 (1.0)	(0.7, 1.4)	24 (0.7)	(0.4, 1.0)
	Head lag abnormal	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)

Table 23. Adverse Events of Special Interest Reported, by Time Intervals, System Organ Class and Preferred Term - Infant Participants - Safety Population

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Time Interval	System Organ Class Preferred Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
	SARS-CoV-2 test positive	37 (1.0)	(0.7, 1.4)	23 (0.6)	(0.4, 1.0)
	Nervous system disorders	0	(0.0, 0.1)	3 (<0.1)	(0.0, 0.2)
	Gross motor delay	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Hypotonia	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
6 Months to 12 months of age	Any Event	36 (1.0)	(0.7, 1.4)	45 (1.3)	(0.9, 1.7)
	General disorders and administration site conditions	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Developmental delay	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Investigations	32 (0.9)	(0.6, 1.3)	40 (1.1)	(0.8, 1.5)
	SARS-CoV-2 test positive	32 (0.9)	(0.6, 1.3)	40 (1.1)	(0.8, 1.5)
	Nervous system disorders	3 (<0.1)	(0.0, 0.2)	4 (0.1)	(0.0, 0.3)
	Gross motor delay	1 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)
	Motor developmental delay	2 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Motor dysfunction	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sensory disturbance	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
12 Months to 24 months of age	Any Event	25 (0.7)	(0.5, 1.0)	21 (0.6)	(0.4, 0.9)
	General disorders and administration site conditions	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Developmental delay	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Investigations	18 (0.5)	(0.3, 0.8)	19 (0.5)	(0.3, 0.8)
	SARS-CoV-2 test positive	18 (0.5)	(0.3, 0.8)	19 (0.5)	(0.3, 0.8)
	Nervous system disorders	6 (0.2)	(0.1, 0.4)	1 (<0.1)	(0.0, 0.2)
	Fine motor delay	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Language disorder	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Speech disorder	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Speech disorder developmental	4 (0.1)	(0.0, 0.3)	1 (<0.1)	(0.0, 0.2)

Table 23. Adverse Events of Special Interest Reported, by Time Intervals, System Organ Class and Preferred Term - Infant Participants - Safety Population

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N[a]=3568)		Placebo (N[a]=3558)	
Time Interval	System Organ Class Preferred Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]

Note: MedDRA (v25.0) coding dictionary applied.
Note: Per statistical analysis plan, 1 month after birth reflects a 30-day period. However, as per protocol, non-serious adverse events were only solicited through 28 days after birth. AESIs were solicited throughout the study for infant participants.
a. N = number of participants in the vaccine group. This value is the denominator for the percentage calculations.
b. 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.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 18OCT2022 (21:24) Source Data: adae Table Generation: 08NOV2022 (21:05)
(Data cutoff date : 02SEP2022 Database snapshot date : 14OCT2022) Output File:
./mat 1008/C3671008 REX/adae s150b aesi

Table 24. Live Birth Outcomes by Country Subcategories - Infant Participants - Safety Population

Country Subcategories		Maternal Vaccine Group (as Administered) RSVpreF 120 µg (N[a]=3568) n[b] (%)	Maternal Vaccine Group (as Administered) Placebo (N[a]=3558) n[b] (%)
High income	Infants born to maternal participants vaccinated[c]	2494	2484
	Gestational age at birth		
	≥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)
	Extremely low birth weight (≤ 1000 g)	0	0
	Very low birth weight (> 1000 g to ≤ 1500 g)	2 (<0.1)	5 (0.2)
	Low birth weight (> 1500 g to ≤ 2500 g)	106 (4.3)	97 (3.9)
Upper middle income	Infants born to maternal participants vaccinated[c]	964	961
	Gestational age at birth		
	≥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 (3.6)
	≥37 weeks to <42 weeks	882 (91.5)	906 (94.3)
	≥42 weeks	9 (0.9)	15 (1.6)
	Extremely low birth weight (≤ 1000 g)	1 (0.1)	2 (0.2)
	Very low birth weight (> 1000 g to ≤ 1500 g)	1 (0.1)	1 (0.1)
	Low birth weight (> 1500 g to ≤ 2500 g)	64 (6.6)	39 (4.1)
Lower middle income	Infants born to maternal participants vaccinated[c]	32	34
	Gestational age at birth		
	≥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
	Extremely low birth weight (≤ 1000 g)	0	0
	Very low birth weight (> 1000 g to ≤ 1500 g)	0	0
	Low birth weight (> 1500 g to ≤ 2500 g)	3 (9.4)	3 (8.8)
Low income	Infants born to maternal participants vaccinated[c]	78	79
	Gestational age at birth		
	≥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)

Table 24. Live Birth Outcomes by Country Subcategories - Infant Participants - Safety Population

Country Subcategories	Maternal Vaccine Group (as Administered) RSVpreF 120 µg (N[a]=3568) n[b] (%)	Maternal Vaccine Group (as Administered) Placebo (N[a]=3558) n[b] (%)
≥37 weeks to <42 weeks	71 (91.0)	67 (84.8)
≥42 weeks	5 (6.4)	10 (12.7)
Extremely low birth weight (≤ 1000 g)	0	0
Very low birth weight (> 1000 g to ≤ 1500 g)	0	0
Low birth weight (> 1500 g to ≤ 2500 g)	4 (5.1)	8 (10.1)

Note: The World Bank Group. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed: 19 May 2021.
a. N = number of participants in the specified vaccine group.
b. n = Number of participants with the specified characteristic.
c. This value is the denominator for the percentage calculations except Apgar scores.

Table 25. Time from Vaccination to Birth Among Preterm and At Term Births - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)		
	RSVpreF 120 µg (N[a]=3568)	Placebo (N[a]=3558)	Total (N[a]=7126)
Days from Vaccination to Birth	**n[b] (%)**	**n[b] (%)**	**n[b] (%)**
Preterm deliveries	201	169	370
≤7 days[c]	11 (5.5)	13 (7.7)	24 (6.5)
>7 days to ≤30 days[c]	69 (34.3)	58 (34.3)	127 (34.3)
>30 days[c]	121 (60.2)	98 (58.0)	219 (59.2)
At term deliveries	3364	3386	6750
≤7 days[c]	1 (<0.1)	2 (<0.1)	3 (<0.1)
>7 days to ≤30 days[c]	516 (15.3)	498 (14.7)	1014 (15.0)
>30 days[c]	2847 (84.6)	2886 (85.2)	5733 (84.9)

Note: Six participants have missing gestational age at birth in database, so are not included in counts above.
Note: Preterm/at term deliveries are determined based on gestational age at birth. Preterm = gestational age at birth less than 37 weeks. At term = gestational age at birth of 37 weeks or more.
Note: Number of days between vaccination and birth is calculated as birth date - vaccination date.
a. N = number of participants having birth date in the specified vaccine group. This value is the denominator for the percentage calculations;
b. n = Number of participants in the specified category.
c. Percentages for this row are based on the number of preterm/at term deliveries, respectively.
PFIZER CONFIDENTIAL SDTM Creation: 19OCT2022 (10:52) Source Data: adsl Table Generation: 15MAR2023 (22:19)
(Data cutoff date : 02SEP2022 Database snapshot date : 14OCT2022) Output File: ./mat_1008/C3671008_ACIP/adsl_s005

8.4. Additional Data from Integrated Safety Analyses

Table 26. Pooled Safety Database of Female Participants ≤49 Years of Age

Study	Brief Description	Sex	Age (Years)	RSVpreF Dose(s)/ Formulation(s)	Safety Sample Size (Females ≤49 Years of Age): Any RSVpreF Dose/ Formulation[a]	Safety Sample Size (Females ≤49 Years of Age): RSVpreF 120 µg[b]
Studies in Maternal Participants						
C3671003	Phase 2b, maternal	Pregnant women	18-49	120 µg, 240 µg, with/without $Al(OH)_3$	462	115
C3671008[c]	Phase 3, maternal efficacy	Pregnant women	≤49	120 µg, without $Al(OH)_3$	3682	3682
Total Maternal Participants					**4144**	**3797**
Studies in Nonpregnant Participants						
C3671001[d]	FIH, dose/formulation	Male/ female	18-49; 50-85	60 µg, 120 µg, 240 µg, with/without $Al(OH)_3$	382	64
C3671004	Phase 2b, Tdap coadministration	Female	18-49	120 µg, 240 µg, with/without $Al(OH)_3$	568	282
C3671014	Phase 3, lot consistency	Male/ female	18-49	120 µg, without $Al(OH)_3$	453	453
Total Participants					**5547**	**4596**

a. Includes participants who received 60 µg, 120 µg or 240 µg of RSVpreF, with or without $Al(OH)_3$.
b. RSVpreF 120 µg without $Al(OH)_3$; final dose and formulation.
c. Ongoing study.
d. Only the data after the first vaccination in Study C3671001 was included in the pooled safety database.

Table 27. Adverse Events by Category Reported Within 1 Month After Vaccination - All Maternal and All Female Participants - Safety Population

	All Maternal Participants			All Female Participants		
	Pooled RSVpreF[a] (N[b]=4144)	RSVpreF 120 µg (N[b]=3797)	Placebo (N[b]=3792)	Pooled RSVpreF[a] (N[b]=5547)	RSVpreF 120 µg (N[b]=4596)	Placebo (N[b]=4104)
Adverse Event Category	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**
Any event	622 (15.0) (13.9, 16.1)	533 (14.0) (12.9, 15.2)	512 (13.5) (12.4, 14.6)	754 (13.6) (12.7, 14.5)	591 (12.9) (11.9, 13.9)	537 (13.1) (12.1, 14.2)
Serious	164 (4.0) (3.4, 4.6)	155 (4.1) (3.5, 4.8)	140 (3.7) (3.1, 4.3)	165 (3.0) (2.5, 3.5)	155 (3.4) (2.9, 3.9)	140 (3.4) (2.9, 4.0)
Immediate[e]	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	2 (<0.1) (0.0, 0.1)	2 (<0.1) (0.0, 0.2)	1 (<0.1) (0.0, 0.1)
Severe	71 (1.7) (1.3, 2.2)	65 (1.7) (1.3, 2.2)	50 (1.3) (1.0, 1.7)	83 (1.5) (1.2, 1.9)	72 (1.6) (1.2, 2.0)	51 (1.2) (0.9, 1.6)
Life-threatening	22 (0.5) (0.3, 0.8)	21 (0.6) (0.3, 0.8)	11 (0.3) (0.1, 0.5)	22 (0.4) (0.2, 0.6)	21 (0.5) (0.3, 0.7)	11 (0.3) (0.1, 0.5)
Related	16 (0.4) (0.2, 0.6)	16 (0.4) (0.2, 0.7)	6 (0.2) (0.1, 0.3)	32 (0.6) (0.4, 0.8)	25 (0.5) (0.4, 0.8)	6 (0.1) (0.1, 0.3)
AE leading to withdrawal	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)
Death[f]	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)

Note: Maternal participants from studies C3671003 and C3671008 are pooled in the "all maternal participants" category.
Note: Female participants ≤ 49 years from studies C3671001 (Dose 1 only), C3671003, C3671004, C3671008, C3671014 are pooled in the "all female participants" category.
Note: MedDRA (v25.0) coding dictionary applied.
Note: Revaccination data of C3671001 is not included and only the data after the first vaccination of C3671001 is included.
a. "Pooled RSVpreF" includes participants who received any dose and formulation of RSVpreF across different studies.
b. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
c. 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.
d. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
e. An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product.
f. Refers to AEs leading to deaths.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./mat_1008_bl_eff/RSV_maternal/adae_s151a_in1 Date of Generation: 22NOV2022 (04:10)

Table 28. Adverse Events by Category Reported Within 1 Month After Vaccination - All Maternal and All Female Participants - US Safety Population

	All Maternal Participants			All Female Participants		
	Pooled RSVpreF[a] (N[b]=2081)	RSVpreF 120 µg (N[b]=1773)	Placebo (N[b]=1770)	Pooled RSVpreF[a] (N[b]=3484)	RSVpreF 120 µg (N[b]=2572)	Placebo (N[b]=2082)
Adverse Event Category	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**	**n[c] (%) (95% CI)[d]**
Any event	329 (15.8) (14.3, 17.4)	247 (13.9) (12.4, 15.6)	239 (13.5) (11.9, 15.2)	461 (13.2) (12.1, 14.4)	305 (11.9) (10.6, 13.2)	264 (12.7) (11.3, 14.2)
Serious	74 (3.6) (2.8, 4.4)	65 (3.7) (2.8, 4.6)	51 (2.9) (2.2, 3.8)	75 (2.2) (1.7, 2.7)	65 (2.5) (2.0, 3.2)	51 (2.4) (1.8, 3.2)
Immediate[e]	0 (0.0, 0.2)	0 (0.0, 0.2)	0 (0.0, 0.2)	1 (<0.1) (0.0, 0.2)	1 (<0.1) (0.0, 0.2)	0 (0.0, 0.2)
Severe	36 (1.7) (1.2, 2.4)	31 (1.7) (1.2, 2.5)	18 (1.0) (0.6, 1.6)	48 (1.4) (1.0, 1.8)	38 (1.5) (1.0, 2.0)	19 (0.9) (0.6, 1.4)
Life-threatening	14 (0.7) (0.4, 1.1)	13 (0.7) (0.4, 1.3)	6 (0.3) (0.1, 0.7)	14 (0.4) (0.2, 0.7)	13 (0.5) (0.3, 0.9)	6 (0.3) (0.1, 0.6)
Related	9 (0.4) (0.2, 0.8)	9 (0.5) (0.2, 1.0)	3 (0.2) (0.0, 0.5)	25 (0.7) (0.5, 1.1)	18 (0.7) (0.4, 1.1)	3 (0.1) (0.0, 0.4)
AE leading to withdrawal	0 (0.0, 0.2)	0 (0.0, 0.2)	0 (0.0, 0.2)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.2)
Death[f]	0 (0.0, 0.2)	0 (0.0, 0.2)	0 (0.0, 0.2)	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.2)

Note: Maternal participants from studies C3671003 and C3671008 are pooled in the "all maternal participants" category.
Note: Female participants ≤ 49 years from studies C3671001 (Dose 1 only), C3671003, C3671004, C3671008, C3671014 are pooled in the "all female participants" category.
Note: MedDRA (v25.0) coding dictionary applied.
Note: Revaccination data of C3671001 is not included and only the data after the first vaccination of C3671001 is included.
a. "Pooled RSVpreF" includes participants who received any dose and formulation of RSVpreF across different studies.
b. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
c. 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.
d. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
e. An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product.
f. Refers to AEs leading to deaths.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./mat_1008_bl_eff/RSV_maternal/adae_s151a_in2 Date of Generation: 22NOV2022 (04:10)

Table 29. Adverse Events by Category Reported Throughout Study After Vaccination - All Maternal and All Female Participants - Safety Population

	All Maternal Participants			All Female Participants		
	Pooled RSVpreF[a] (N[b]=4144)	RSVpreF 120 µg (N[b]=3797)	Placebo (N[b]=3792)	Pooled RSVpreF[a] (N[b]=5547)	RSVpreF 120 µg (N[b]=4596)	Placebo (N[b]=4104)
Adverse Event Category	n[c] (%) (95% CI)[d]	n[c] (%) (95% CI)[d]	n[c] (%) (95% CI)[d]	n[c] (%) (95% CI)[d]	n[c] (%) (95% CI)[d]	n[c] (%) (95% CI)[d]
Any event	1274 (30.7) (29.3, 32.2)	1111 (29.3) (27.8, 30.7)	1056 (27.8) (26.4, 29.3)	1546 (27.9) (26.7, 29.1)	1191 (25.9) (24.7, 27.2)	1098 (26.8) (25.4, 28.1)
Serious	654 (15.8) (14.7, 16.9)	605 (15.9) (14.8, 17.1)	572 (15.1) (14.0, 16.3)	665 (12.0) (11.1, 12.9)	607 (13.2) (12.2, 14.2)	572 (13.9) (12.9, 15.0)
Severe	237 (5.7) (5.0, 6.5)	207 (5.5) (4.8, 6.2)	207 (5.5) (4.8, 6.2)	264 (4.8) (4.2, 5.4)	216 (4.7) (4.1, 5.4)	209 (5.1) (4.4, 5.8)
Life-threatening	67 (1.6) (1.3, 2.0)	63 (1.7) (1.3, 2.1)	43 (1.1) (0.8, 1.5)	68 (1.2) (1.0, 1.6)	64 (1.4) (1.1, 1.8)	43 (1.0) (0.8, 1.4)
Related	17 (0.4) (0.2, 0.7)	17 (0.4) (0.3, 0.7)	6 (0.2) (0.1, 0.3)	34 (0.6) (0.4, 0.9)	27 (0.6) (0.4, 0.9)	6 (0.1) (0.1, 0.3)
AE leading to withdrawal	0 (0.0, 0.1)	0 (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)
Death[e]	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.1)	0 (0.0, 0.1)	2 (<0.1) (0.0, 0.1)	2 (<0.1) (0.0, 0.2)	0 (0.0, 0.1)

Note: Maternal participants from studies C3671003 and C3671008 are pooled in the "all maternal participants" category.
Note: Female participants ≤ 49 years from studies C3671001 (Dose 1 only), C3671003, C3671004, C3671008, C3671014 are pooled in the "all female participants" category.
Note: MedDRA (v25.0) coding dictionary applied.
Note: Revaccination data of C3671001 is not included and only the data after the first vaccination of C3671001 is included.
a. "Pooled RSVpreF" includes participants who received any dose and formulation of RSVpreF across different studies.
b. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
c. 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.
d. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
e. Refers to AEs leading to deaths.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./mat_1008_bl_eff/RSV_maternal/adae_s151a_in3 Date of Generation: 22NOV2022 (04:10)

Table 30. Adverse Events by Category Reported Within 1 Month After Birth - Infant Participants - Safety Population

Adverse Event Category	Pooled RSVpreF[a] (N[b]=4024) n[c] (%) (95% CI)[d]	RSVpreF 120 µg (N[b]=3682) n[c] (%) (95% CI)[d]	Placebo (N[b]=3674) n[c] (%) (95% CI)[d]
Any event	1545 (38.4) (36.9, 39.9)	1382 (37.5) (36.0, 39.1)	1288 (35.1) (33.5, 36.6)
Serious	678 (16.8) (15.7, 18.0)	584 (15.9) (14.7, 17.1)	572 (15.6) (14.4, 16.8)
Congenital anomaly	254 (6.3) (5.6, 7.1)	197 (5.4) (4.6, 6.1)	230 (6.3) (5.5, 7.1)
Severe	184 (4.6) (3.9, 5.3)	165 (4.5) (3.8, 5.2)	142 (3.9) (3.3, 4.5)
Life-threatening	41 (1.0) (0.7, 1.4)	35 (1.0) (0.7, 1.3)	35 (1.0) (0.7, 1.3)
Related	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.2)	0 (0.0, 0.1)
AE leading to withdrawal	0 (0.0, 0.1)	0 (0.0, 0.1)	1 (<0.1) (0.0, 0.2)
Developmental delay	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.2)	0 (0.0, 0.1)
Death[e]	2 (<0.1) (0.0, 0.2)	2 (<0.1) (0.0, 0.2)	6 (0.2) (0.1, 0.4)

Note: Infants are presented according to their mother's vaccine group.
Note: Infant participants from studies C3671003 and C3671008 are included.
Note: MedDRA (v25.0) coding dictionary applied.
a. "Pooled RSVpreF" includes participants who received any dose and formulation of RSVpreF across different studies.
b. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
c. 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.
d. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
e. Refers to AEs leading to infant deaths after a live birth.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./mat 1008 bl eff/RSV maternal/adae s151b in1 Date of Generation: 22NOV2022 (04:10)

Table 31. Adverse Events by Category Reported Within 1 Month After Birth - Infant Participants - US Safety Population

Adverse Event Category	Pooled RSVpreF[a] (N[b]=2059) n[c] (%) (95% CI)[d]	RSVpreF 120 µg (N[b]=1756) n[c] (%) (95% CI)[d]	Placebo (N[b]=1747) n[c] (%) (95% CI)[d]
Any event	835 (40.6) (38.4, 42.7)	689 (39.2) (36.9, 41.6)	677 (38.8) (36.5, 41.1)
Serious	326 (15.8) (14.3, 17.5)	245 (14.0) (12.4, 15.7)	269 (15.4) (13.7, 17.2)
Congenital anomaly	164 (8.0) (6.8, 9.2)	110 (6.3) (5.2, 7.5)	126 (7.2) (6.0, 8.5)
Severe	82 (4.0) (3.2, 4.9)	67 (3.8) (3.0, 4.8)	73 (4.2) (3.3, 5.2)
Life-threatening	17 (0.8) (0.5, 1.3)	11 (0.6) (0.3, 1.1)	16 (0.9) (0.5, 1.5)
Related	1 (<0.1) (0.0, 0.3)	1 (<0.1) (0.0, 0.3)	0 (0.0, 0.2)
AE leading to withdrawal	0 (0.0, 0.2)	0 (0.0, 0.2)	1 (<0.1) (0.0, 0.3)
Developmental delay	1 (<0.1) (0.0, 0.3)	1 (<0.1) (0.0, 0.3)	0 (0.0, 0.2)
Death[e]	0 (0.0, 0.2)	0 (0.0, 0.2)	0 (0.0, 0.2)

Note: Infants are presented according to their mother's vaccine group.
Note: Infant participants from studies C3671003 and C3671008 are included.
Note: MedDRA (v25.0) coding dictionary applied.
a. "Pooled RSVpreF" includes participants who received any dose and formulation of RSVpreF across different studies.
b. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
c. 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.
d. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
e. Refers to AEs leading to infant deaths after a live birth.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./mat 1008 bl eff/RSV maternal/adae s151b in2 Date of Generation: 22NOV2022 (04:10)

Table 32. Adverse Events by Category Reported After Birth - Infant Participants - Safety Population

Adverse Event Category	Pooled RSVpreF[a] (N[b]=4024) n[c] (%) (95% CI)[d]	RSVpreF 120 µg (N[b]=3682) n[c] (%) (95% CI)[d]	Placebo (N[b]=3674) n[c] (%) (95% CI)[d]
Any event	1802 (44.8) (43.2, 46.3)	1557 (42.3) (40.7, 43.9)	1495 (40.7) (39.1, 42.3)
Serious	784 (19.5) (18.3, 20.7)	666 (18.1) (16.9, 19.4)	661 (18.0) (16.8, 19.3)
Congenital anomaly	286 (7.1) (6.3, 7.9)	213 (5.8) (5.1, 6.6)	244 (6.6) (5.9, 7.5)
Severe	222 (5.5) (4.8, 6.3)	193 (5.2) (4.5, 6.0)	169 (4.6) (3.9, 5.3)
Life-threatening	47 (1.2) (0.9, 1.6)	41 (1.1) (0.8, 1.5)	48 (1.3) (1.0, 1.7)
Related	1 (<0.1) (0.0, 0.1)	1 (<0.1) (0.0, 0.2)	0 (0.0, 0.1)
AE leading to withdrawal	0 (0.0, 0.1)	0 (0.0, 0.1)	1 (<0.1) (0.0, 0.2)
Developmental delay	12 (0.3) (0.2, 0.5)	12 (0.3) (0.2, 0.6)	10 (0.3) (0.1, 0.5)
Death[e]	5 (0.1) (0.0, 0.3)	5 (0.1) (0.0, 0.3)	12 (0.3) (0.2, 0.6)

Note: Infants are presented according to their mother's vaccine group.
Note: Infant participants from studies C3671003 and C3671008 are included.
Note: MedDRA (v25.0) coding dictionary applied.
a. "Pooled RSVpreF" includes participants who received any dose and formulation of RSVpreF across different studies.
b. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
c. 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.
d. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
e. Refers to AEs leading to infant deaths after a live birth.
PFIZER CONFIDENTIAL Source Data: adae Output File: ./mat 1008 bl eff/RSV maternal/adae s151b in3 Date of Generation: 22NOV2022 (04:10)

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