

Application Type	Original BLA
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CBER Received Date	December 21, 2022
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Division / Office	DVRPA/OVRR
Clinical Reviewer(s)	Yugenia Hong-Nguyen, MD
Project Manager	Goutam Sen, PhD Paul Keller, PhD Laura Montague Vera Stupina, PhD
Priority Review	Yes
Reviewer Name(s)	Rositsa B Dimova, PhD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Ye Yang, PhD Team Lead, VEB/DB/OBPV
	Tsai-Lien Lin, PhD Branch Chief, VEB/DB/OBPV
	John Scott, PhD Director, DB/OBPV
Applicant	Pfizer Inc.
Established Name	Respiratory Syncytial Virus (RSV) Bivalent Stabilized Prefusion F Subunit Vaccine
(Proposed) Trade Name	ABRYSVO
Pharmacologic Class	Respiratory Syncytial Virus (RSV) vaccine
Formulation(s), including Adjuvants, etc	120 micrograms (mcg) of RSV stabilized prefusion F protein (60 mcg A and 60 mcg B antigens)
Dosage Form(s) and Route(s) of Administration	0.5 mL dose administered intramuscularly
Dosing Regimen	A single 0.5 mL dose
Indication(s) and Intended Population(s)	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.



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## GLOSSARY

AE	Adverse Event
AESI	Adverse Event of Special Interest
BLA	Biologics License Application
CBER	Center for Biologics Evaluation, Research and Review
CDER	Center for Drugs Evaluation, Research and Review
CI	Confidence Interval
CSR	Clinical Study Report
EAC	Endpoint Adjudication Committee
E-DMC	External Data Monitoring Committee
FDA	Food and Drug Administration
GA	Gestational Age
IR	Information Request
LMIC	Lower- And Middle-Income Country
LRTD	Lower respiratory tract disease
LRTI	Lower respiratory tract illness
MA-LRTI	Medically Attended Lower Respiratory Tract Illness
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
PCR	Polymerase Chain Reaction
PT	Preferred Term
RCT	Randomized Controlled Trial
RD	Risk Difference
RSV	Respiratory Syncytial Virus
RSVpreF	Respiratory Syncytial Virus Prefusion F Subunit Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class
UK	United Kingdom
US	United States
VE	Vaccine Efficacy

### 1. Executive Summary

Pfizer, Inc. submitted an original Biologics License Application (BLA) on December 21, 2022 (STN 125768/0) for their Respiratory Syncytial Virus (RSV) stabilized prefusion F subunit vaccine ABRYSV0 (also referred to as RSVpreF in this review memo) for the indication of 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 pivotal phase 3 study C3671008 entitled “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” serves as the primary evidence of effectiveness and safety for the sought

indication. The primary efficacy objectives of the study are to evaluate the efficacy of RSVpreF in reducing the incidence of medically attended lower respiratory tract illness (MA-LRTI) due to RSV and of severe MA-LRTI due to RSV. The primary safety objectives are to describe the safety profile of RSVpreF in maternal participants who were vaccinated during pregnancy and in their infants. The data and analyses submitted in this application were based on a data cutoff date of September 30, 2022 for efficacy endpoints, and a data cutoff date of September 2, 2022 for safety endpoints.

Study C3671008 was designed as an event-driven study with an original final analysis target of 124 adjudicated (primary-endpoint) cases of MA-LRTI due to RSV at 90 days. There was no specific case target for the additional primary endpoint of severe MA-LRTI. Up to 2 interim analyses of the primary endpoint (MA-LRTI due to RSV) were planned in the protocol 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, the alpha level was planned to be derived using the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. The exact number of cases at each interim analysis was not fixed, however, no fewer than 43 cases were planned to be included in the first interim analysis and no fewer than 62 cases were to be included in the second interim analysis.

The study was designed to assess the efficacy, safety, and immunogenicity of RSVpreF vaccine (120 µg [60 µg RSV A and 60 µg RSV B]) compared to placebo (1:1 randomization) in infants born to healthy women and adolescents ( $\leq 49$  years of age) vaccinated with a single dose during pregnancy between 24 and 36 weeks gestational age, as well as the safety and immunogenicity in the pregnant women. The study is global, and is being conducted in 18 countries (Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, United States). It spans over multiple RSV seasons.

The second and final interim analysis was conducted in October 2022 when there were a total of 80 evaluable cases of MA-LRTI due to RSV within 90 days from birth confirmed by the endpoint adjudication committee (EAC) and 39 cases of severe MA-LRTI due to RSV within 90 days from birth confirmed by EAC.

A total of 7392 participants were randomized to receive RSVpreF (n=3695) or placebo (n=3697). Of these, 3682 maternal participants received RSVpreF and 3675 maternal participants received placebo. As of the data cut-off date, there were 3568 infants born to maternal participants who received RSVpreF and 3558 infants born to maternal participants who received placebo. Vaccine efficacy (VE) for severe MA-LRTI due to RSV within 90 days from birth confirmed by EAC was 81.8%, 99.5% CI (40.6%, 96.3%), and within 180 days, VE was 69.4%, 97.58% CI (44.3%, 84.1%). As the lower bound of the adjusted CI was  $>20\%$ , the statistical criterion for this endpoint was met for all time periods through 180 days after birth. VE for MA-LRTI due to RSV within 90 days from birth confirmed by EAC was 57.1%, 99.5% CI (14.7%, 79.8%), and within 180 days VE was 51.3%, 97.58% CI (29.4%, 66.8%). As the lower bound of the O'Brien-

Fleming type I error-adjusted 99.5% CI for VE for the 90-day period was <20%, based on the prespecified fixed sequence testing rule, formal hypothesis testing for VE in the subsequent time intervals stops, and the respective results for this endpoint are considered descriptive. For the subsequent time intervals (120 to 180 days after birth), 97.58% CIs were used, and the respective lower bounds were >20%. For the MA-LRTIs due to RSV within 90 days, the 97.58% CI for VE would be (24.8%, 76.5%). Taking this into consideration and that the lower bounds of the CIs were >20% for VE for the time periods of 120 to 180 days after birth, the data suggest that the RSVpre F vaccine is efficacious within 180 days after birth for the prevention of MA-LRTI due to RSV.

For maternal participants, 506 (13.7%, 95% CI [12.6%, 14.9%]) RSVpreF recipients and 481 (13.1%, 95% CI [12.0%, 14.2%]) placebo recipients experienced at least one adverse event (AE) within 1 month after vaccination. Of these, there were 154 (4.2%, 95% CI [3.6%, 4.9%]) participants in the RSVpreF group and 137 (3.7%, 95% CI [3.1%, 4.4%]) in the placebo group who reported a serious adverse event (SAE). From vaccination through 6 months after delivery, SAEs were reported by 598 (16.2%) maternal subjects in the RSVpreF group and by 558 (15.2%) maternal subjects in the placebo group. By preferred term (PT), the most frequently reported SAEs were pre-eclampsia (1.8% vs 1.4%), fetal distress syndrome (1.8% vs. 1.6%), gestational hypertension (1.1% vs. 1.0%), nonreassuring fetal heart rate (1.0% vs. 0.8%), and arrested labor (1.0% vs. 1.1%). SAE of premature delivery was reported in 28 (0.8%, 95% CI [0.5%, 1.1%]) subjects in the RSVpreF group and in 23 (0.6%, 95% CI [0.4%, 0.9%]) subjects in the placebo group.

The Adverse Event of Special Interest (AESI) of premature delivery was reported among 207 (5.6%, 95% CI [4.9%, 6.4%]) maternal participants in the RSVpreF group and among 175 (4.8%, 95% CI [4.1%, 5.5%]) maternal participants in the placebo group after vaccination. The risk difference (RD) was 0.86%, 95% CI (-0.15%, 1.88%). The safety analyses were descriptive in nature and the study was not powered for formal hypothesis testing between the study arms with regard to safety. While the lower bound of the 95% CI was <0, I defer to the clinical reviewer whether the observed numerical imbalance in premature deliveries between the study arms is of clinical concern and whether a restriction on the indication with regard to the vaccination window should be recommended. Most of the preterm deliveries occurred between 34 and <37 weeks gestation. Among those who were vaccinated between 24 and <32 weeks gestation, there were 9 (0.4%) in the RSVpreF arm and 9 (0.4%) in the placebo arm with a premature delivery between 27 weeks and prior to 32 weeks gestation, and there were 13 (0.6%) subjects in the RSVpreF arm and 4 (0.2%) in the placebo arm with a premature delivery between 32 weeks and prior to 34 weeks gestation. Among those who were vaccinated between 32 and <37 weeks gestation, there were 2 (0.1%) in the RSVpreF arm and 2 (0.1%) in the placebo arm with a premature delivery between 32 weeks and prior to 34 weeks gestation.

For maternal participants, local reactions were reported by 42.5% of participants in the RSVpreF group and by 10.4% of participants in the placebo group, with pain at the injection site being the most commonly-reported reaction (40.6% versus 10.1%,

respectively). At least one systemic event was reported by 63.9% of participants in the RSVpreF group and by 59.3% of participants in the placebo group. The most commonly reported systemic events after the RSVpreF vaccination were fatigue (46.1%) and headache (31.0%). Please refer to the review by the clinical reviewer (Dr. Yugenya Hong-Nguyen) for details on the safety analyses.

For infant participants, within 1 month after birth, 1324 (37.1%, 95% CI [35.5%, 38.7%]) in the RSVpreF group and 1229 (34.5%, 95% CI [33.0%, 36.1%]) in the placebo group experienced at least one AE. Of these, there were 553 (15.5%, 95% CI [14.3%, 16.7%]) infant participants in the RSVpreF group and 541 (15.2%, 95% CI [14.0%, 16.4%]) in the placebo group who experienced an SAE. From birth through the data cutoff date, SAEs were reported for 625 (17.5%, 95% CI [16.3%, 18.8%]) infants in the RSVpreF group and for 623 (17.5%, 95% CI [16.3%, 18.8%]) infants in the placebo group. None of the SAEs in infant participants were considered related to maternal vaccination by the investigator. By PT, the most frequently reported SAEs were jaundice neonatal (2.1% vs 1.9%), hyperbilirubinemia neonatal (1.4% vs 1.1%), premature baby (1.4% vs 1.2%), and respiratory distress (1.3% vs 1.2%; RSVpreF group vs. placebo group). Congenital anomalies reported as SAEs were reported for 5.0% of the infants in the RSVpreF group and for 6.2% of the infants in the placebo group. For infants, AESIs included low birth weight baby and premature baby. Low birth weight baby was reported for 181 (5.1%, 95% CI [4.4%, 5.8%]) infants in the RSVpreF group and for 154 (4.3%, 95% CI [3.7%, 5.0%]) infants in the placebo group, with RD=0.72%, 95% CI (-0.27%, 1.71%). Premature baby events for the infants corresponded to those premature maternal deliveries that resulted in live births. Accordingly, premature baby AE was reported for 202 (5.7%, 9.5% CI [4.9%, 6.5%]) infants in the RSVpreF group and for 169 (4.7%, 95% CI [4.1%, 5.5%]) infants in the placebo group, with RD=0.91%, 95% CI (-0.12%, 1.95%).

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss Pfizer's application was held on May 18, 2023. In particular, there was a discussion among the committee members on the safety of the vaccine due to the observed imbalance of the adverse event of premature delivery for the mothers (respectively premature baby for the infants) between the RSVpreF and placebo groups. The two questions posed to the committee for voting were: (1) "Are the available data adequate to support the effectiveness of immunization with ABRYSSVO during the second or third trimester of pregnancy (24-36 weeks gestational age) to prevent RSV lower respiratory tract disease (LRTD) and severe RSV LRTD in infants, from birth through 6 months of age?" and (2) "Are the available data adequate to support the safety of immunization with ABRYSSVO during the second or third trimester of pregnancy (24-36 weeks gestational age) to prevent RSV LRTD and severe RSV LRTD in infants, from birth through 6 months of age?". There were a total of 14 voting committee members. On question (1), 14 out of 14 voting committee members voted "Yes". On question (2), 10 out of 14 voting committee members voted "Yes", and 4 out of 14 voting committee members voted "No".

The applicant's statistical analyses were appropriate and consistent with those prespecified in the study protocol and Statistical Analysis Plan (SAP). I verified the key results presented in this application.

In conclusion, the submitted data suggest that RSVpreF is efficacious in preventing severe MA-LRTI due to RSV and MA-LRTI due to RSV through 180 days from birth in the infants born to vaccinated pregnant individuals. The applicant described the safety profile of the vaccine for the safety follow-up period as of the data cut-off date. Conclusions on the clinical interpretation of the observed numerical imbalance in preterm births between the study arms and potential restrictions on the vaccination window are deferred to the clinical reviewer.

## **2. Clinical and Regulatory Background**

Respiratory Syncytial Virus (RSV) may cause a substantial disease burden and mortality in young infants, especially in those <6 months of age. The RSV seasonality in the United States (US) lasts approximately 6 months with a peak during the winter months.

Pfizer Inc.'s RSVpreF vaccine (ABRYSVO) was approved in the United States on May 31, 2023 (STN 125769/0) for use in adults, ages 60 years old and above, for the prevention of lower respiratory tract disease (LRTD) due to RSV (LRTD-RSV). Currently, there is no licensed vaccine for the prevention of RSV disease in infants.

Pfizer, Inc. submitted an original BLA on December 21, 2022 (STN 125768/0) for RSVpreF for the indication of prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals. The dose/formulation in this application is the same as ABRYSVO, which is indicated for adults 60 years of age and older.

RSV bivalent stabilized prefusion F subunit vaccine (RSVpreF) consists of 60 micrograms of RSV subgroup A stabilized prefusion F protein, and 60 micrograms of RSV subgroup B stabilized prefusion F protein.

The pivotal phase 3 study C3671008 entitled "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" serves as the primary evidence of effectiveness and safety for the sought indication. Additionally, the submission includes the Clinical Study Report (CSR) and datasets for the lot consistency study C3671014, as well as for the early phase studies C3671001, C3671003, and C3671004, which are intended to serve as supportive evidence for RSVpreF (Table 1, Section 5.3). An integrated summary of safety based on these studies was included as well.

A meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss this application was held on May 18, 2023 (see Section 5.4).



## 2.1 Disease or Health-Related Condition(s) Studied

RSV causes respiratory tract infections in individuals of all age groups. RSV may cause bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress. It is a leading cause of hospitalization among infants (Hall et al. 2013). It has been estimated that globally, in 2019, there were approximately 1.4 million RSV-associated acute lower respiratory infection hospital admissions, and approximately 45,700 RSV-attributable overall deaths in infants aged 0 to 6 months. The majority of the RSV-attributable deaths were in low-income and middle-income countries (LMICs; Li et al. 2022).

### References:

Hall, C.B., Weinberg, G.A., Blumkin, A.K., Edwards, K.M., Staat, M.A., Schultz, A.F., Poehling, K.A., Szilagyi, P.G., Griffin, M.R., Williams, J.V., Zhu, Y., Grijalva, C.G., Prill, M.M., Iwane, M.K. (2013). Respiratory Syncytial Virus–Associated Hospitalizations Among Children Less than 24 Months of Age. *Pediatrics*, **132** (2): e341–e348.

Li, Y., Wang, X., Blau, D.M. et al. (2022). Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *The Lancet*, **399**, 2047–2064.

## 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Please refer to the review by the clinical reviewer.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

Deficiencies related to the data standards format in the initial submission of the datasets were identified by the data standards reviewer. In response to CBER request, the applicant submitted updated datasets on May 16, 2023 to STN 125768/0/20. A follow-up Information Request (IR) was sent to the applicant on June 13, 2023. The issues were subsequently resolved with the submission of updated datasets on June 27, 2023 (STN 125768/0/32).

Additionally, discrepancies in the reports of “Premature delivery” adverse events (AE) for 3 maternal subjects and the reports of “Premature baby” for their infants, and on the timing of “Premature delivery” events for 2 other maternal subjects were identified. The applicant also reported that a maternal subject for whom there was a “Premature delivery” report had actually delivered in term. These discrepancies were subsequently resolved by the applicant in their responses.

The final submission quality is acceptable.

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

Please refer to the reviews by the corresponding discipline reviewers.

## **5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW**

### **5.1 Review Strategy**

This review focuses primarily on the efficacy and safety data from the pivotal phase 3 study C3671008 with data cutoff dates of September 2, 2022 (safety) and September 30, 2022 (efficacy). Integrated analyses of safety based on studies C3671001, C3671003, C3671004, C3671008, C3671014 are discussed as well.

### **5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review**

The applicant submitted the Clinical Study Report (CSR) and data in Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) formats from the pivotal phase 3 study C3671008 to STN 125768/0/1 on December 21, 2022. A supplemental Clinical Study Report (CSR) was submitted to STN 125768/0/2 on January 23, 2023. This supplemental CSR includes the results of revised maternal reactogenicity and safety analyses as per CBER request to integrate any local reactions and systemic events that were reported as AEs (and not reported in the e-diary) into the local reaction and systemic event analyses. As discussed above, subsequent updates to the datasets were submitted on May 16, 2023 to STN 125768/0/20. These were requested in IR#13 to address deficiencies in the data standards format. Additionally, a clarification regarding identified discrepancies in the reports of “Premature delivery” adverse events (AE) for 3 maternal subjects and the reports of “Premature baby” for the infants, was submitted to STN 125768/0/28 on June 16, 2023. Another update to the datasets for study C3671008, to address identified deficiencies with the data standards format, was submitted on June 27, 2023 to STN 125768/0/32, and the affected datasets were the following: SDTM - AE, SUPPAE, CE, SUPPCE, CO, VS, SUPPVS, FACE, SUPPFACE, RELREC; ADaM - ADAE, ADCEVD, ADFACEVD.

The datasets and CSR for the phase 2 study C3671003 were submitted to STN 125768/0/1 on December 21, 2022. The datasets and CSRs for studies C3671001 (phase 1), C3671004 (phase 2) and C3671014 (phase 3 lot consistency) were submitted to STN 125768/0/0 on November 30, 2022, and subsequently revised datasets were submitted to STN 125768/0/7 on March 10, 2023 to address identified deficiencies with the data standards format.

### **5.3 Table of Studies/Clinical Trials**

Studies conducted to support the licensure of RSVpreF are summarized in Table 1. Study C3671008 serves as the primary evidence of safety and effectiveness of RSVpreF for the proposed indication. The rest of the studies are considered supportive.

Table 1. Clinical Studies Included in the Biologics License Application.

Study (Country)  Study Start/Status	Study Design	Study Population	Treatment Groups / No. of Randomized Participants
<b>C3671008</b>  (Global study: Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, US)  June 17, 2020  Ongoing	A Phase 3 study to evaluate the efficacy, immunogenicity, and safety of RSVpreF vaccine in infants born to women vaccinated during pregnancy	Healthy pregnant Women ≤49 years of age, between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination	<b>Maternal Participants:</b> <u>Placebo</u> N= 3697  <u>RSVpreF 120 µg</u> N= 3695  <b>Infant Participants (born to vaccinated maternal participants):</b> <u>Placebo</u> N= 3558  <u>RSVpreF 120 µg</u> N= 3570
<b>C3671001</b> (US study)  April 18, 2018 Completed: November 20, 2019 Expanded Cohort (Revaccination): April 18, 2018 Completed: December 28, 2020	A Phase 1/2, placebo-controlled, randomized, observer-blind, dose-finding, first-in-human study to describe the safety, tolerability, and immunogenicity of RSVpreF vaccine in healthy adults	Healthy male and female participants 18-85 years of age	<b>Sentinel Cohort Age 18 through 49</b> RSVpreF 60 µg: N=12 RSVpreF 60 µg + Al(OH) <sub>3</sub> : N=12 RSVpreF 120 µg: N=12 RSVpreF 120 µg + Al(OH) <sub>3</sub> : N=12 RSVpreF 240 µg: N=12 RSVpreF 240 µg + Al(OH) <sub>3</sub> : N=12 Placebo: N=12  <b>Expanded Cohort Age 18 through 49</b> RSVpreF 60 µg+ SIIV: N=41 RSVpreF 60 µg+ Placebo: N=42 RSVpreF 60 µg + Al(OH) <sub>3</sub> + SIIV: N=41 RSVpreF 60 µg + Al(OH) <sub>3</sub> +Placebo: N=41 RSVpreF 120 µg+ SIIV: N=41 RSVpreF 120 µg+ Placebo: N=41 RSVpreF 120 µg + Al(OH) <sub>3</sub> + SIIV: N=41 RSVpreF 120 µg + Al(OH) <sub>3</sub> +Placebo: N=41 RSVpreF 240 µg+ SIIV: N=41 RSVpreF 240 µg+ Placebo: N=42 RSVpreF 240 µg + Al(OH) <sub>3</sub> + SIIV: N=41 RSVpreF 240 µg + Al(OH) <sub>3</sub> +Placebo: N=41 Placebo+Placebo: N=41
<b>C3671003</b> (Global study: Argentina, Chile, South Africa, US)  August 7, 2019	A Phase 2b, randomized, placebo controlled, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of an RSV vaccine in	Healthy pregnant women 18 through 49 years of age, between 24 0/7 and 36 0/7 weeks of gestation on the	<b>Maternal Participants</b> RSVpreF 120 µg: N=116 RSVpreF 120 µg + Al(OH) <sub>3</sub> : N=117 RSVpreF 240 µg: N=116 RSVpreF 240 µg + Al(OH) <sub>3</sub> : N=115 Placebo: N=117

Study (Country)  Study Start/Status	Study Design	Study Population	Treatment Groups / No. of Randomized Participants
Completed September 30, 2021	pregnant women 18 through 49 years of age and their infants	day of planned vaccination	<b>Infant Participants (born to vaccinated maternal participants)</b> RSVpreF 120 µg: N=114 RSVpreF 120 µg + Al(OH) <sub>3</sub> : N=117 RSVpreF 240 µg: N=113 RSVpreF 240 µg + Al(OH) <sub>3</sub> : N=112 Placebo: N=116
<b>C3671004</b> (US study)  October 1, 2019  Completed December 11, 2019	A Phase 2b, placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of RSVpreF vaccine when administered concomitantly with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy nonpregnant women 18 through 49 years of age	Healthy nonpregnant female participants 18-49 years of age	RSVpreF 120 µg + Placebo: N=143 RSVpreF 120 µg + Tdap: N=143 RSVpreF 240 µg + Al(OH) <sub>3</sub> + Placebo: N=143 RSVpreF 240 µg + Al(OH) <sub>3</sub> + Tdap: N=143 Placebo + Tdap: N=141
<b>C3671014</b> (US study)  October 21, 2021  Completed April 4, 2022	A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of 3 lots of RSVpreF vaccine in healthy adults	Healthy male and female participants 18 49 years of age	Placebo: N=247 RSVpreF 120 µg Lot 1: N=249 RSVpreF 120 µg Lot 2: N=247 RSVpreF 120 µg Lot 3: N=250

Abbreviations: M = Male; F = Female; W/B/O = White/Black/Other; Min/max = Minimum/maximum; Al(OH)<sub>3</sub> = Aluminum hydroxide; SIIV = Seasonal Inactivated Influenza Vaccine.  
Source: Adapted from Tabular Listing of Clinical Studies Included in STN 125760/0/1.

## 5.4 Consultations

### 5.4.1 Advisory Committee Meeting

A VRBPAC meeting to discuss Pfizer's application was held on May 18, 2023. In particular, there was a discussion among the committee members on the safety of the vaccine due to the observed imbalance of the adverse event of premature delivery for the mothers (respectively premature baby for the infants) between the RSVpreF and placebo groups. The two questions posed to the committee for voting were: (1) "Are the available data adequate to support the effectiveness of immunization with ABRYSSVO during the second or third trimester of pregnancy (24-36 weeks gestational age) to prevent RSV lower respiratory tract disease (LRTD) and severe RSV LRTD in infants, from birth through 6 months of age?" and (2) "Are the available data adequate to support the safety

of immunization with ABRYSSVO during the second or third trimester of pregnancy (24-36 weeks gestational age) to prevent RSV LRTD and severe RSV LRTD in infants, from birth through 6 months of age?”. There were a total of 14 voting committee members. On question (1), 14 out of 14 voting committee members voted “Yes”. On question (2), 10 out of 14 voting committee members voted “Yes”, and 4 out of 14 voting committee members voted “No”.

#### 5.4.2 External Consults/Collaborations

The clinical review team consulted CDER on the reported safety events in this BLA application. Please refer to the review by the clinical reviewer for details on their requested consults.

### 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

#### 6.1 Study C3671008

C3671008 is an ongoing randomized, double-blinded, placebo-controlled phase 3 study designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against medically attended LRTI (MA-LRTI) due to RSV and medically attended severe LRTI due to RSV in infants. The submitted BLA includes a completed analysis of the primary and secondary efficacy endpoints and of safety endpoints, based on an enrollment start date of June 17, 2020 through the data cutoff dates of September 2, 2022 (for safety) and September 30, 2022 (for efficacy). The applicant stated that exploratory serology data for infant and maternal participants and supplemental safety and efficacy data for participants ongoing in the study will be submitted in a future report.

##### 6.1.1 Objectives

#### Infant Participants

Table 2. Study Objectives, Endpoints, and Population-level Summaries – Infant Participants.

Objectives	Population-level Summaries	Endpoints
Primary Efficacy:	Primary Efficacy:	Primary Efficacy:
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluative participants).	RSV-positive MA-LRTI as confirmed by the endpoint adjudication committee (EAC): <ul style="list-style-type: none"> <li>occurring within 90 days after birth.</li> <li>occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria.</li> <li>occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria.</li> <li>occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.</li> </ul>

Objectives	Population-level Summaries	Endpoints
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluative participants).	Severe MA-LRTIs due to RSV as confirmed by the EAC: <ul style="list-style-type: none"> <li>• occurring within 90 days after birth.</li> <li>• occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria.</li> <li>• occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria.</li> <li>• occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.</li> </ul>
<b>Primary Safety:</b>	<b>Primary Safety:</b>	<b>Primary Safety:</b>
To describe the safety of RSVpreF.	In infant participants born to maternal participants receiving 1 dose of investigational product, the percentage of participants with each safety endpoint in each vaccine group.	<ul style="list-style-type: none"> <li>• Specific birth outcomes.</li> <li>• AEs from birth to 1 month of age.</li> <li>• SAEs and NDCMCs: <ul style="list-style-type: none"> <li>- from birth through 6 months of age (first RSV season for all infant participants).</li> <li>- from birth through 12 months of age (for all infant participants).</li> <li>- from birth through 24 months of age (for infant participants born to maternal participants enrolled during the first year of the study).</li> </ul> </li> </ul>
<b>Secondary Efficacy:</b>	<b>Secondary Efficacy:</b>	<b>Secondary Efficacy:</b>
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluative participants).	Hospitalization due to RSV: <ul style="list-style-type: none"> <li>• occurring within 90 days after birth.</li> <li>• occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria.</li> <li>• occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria.</li> <li>• occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.</li> <li>• occurring within 360 days after birth, if the analysis at 180 days meets efficacy criteria.</li> </ul>

Objectives	Population-level Summaries	Endpoints
To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI.	VE, defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluative participants).	MA-LRTI due to any cause with protocol-defined criteria: <ul style="list-style-type: none"> <li>• occurring within 90 days after birth.</li> <li>• occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria.</li> <li>• occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria.</li> <li>• occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.</li> <li>• occurring within 360 days after birth, if the analysis at 180 days meets efficacy criteria.</li> </ul>
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV.	Vaccine efficacy (VE), defined as the relative risk reduction of the endpoint in the RSV vaccine group compared to the placebo group, for infant participants born to maternal participants receiving 1 dose of investigational product and in compliance with the key protocol criteria (evaluative participants).	RSV-positive MA-LRTI: <ul style="list-style-type: none"> <li>• occurring within 210 days after birth.</li> <li>• occurring within 240 days after birth, if the analysis at 210 days meets efficacy criteria.</li> <li>• occurring within 270 days after birth, if the analysis at 210 days meets efficacy criteria.</li> <li>• occurring within 360 days after birth, if the analysis at 270 days meets efficacy criteria.</li> </ul>
<b>Exploratory:</b>	<b>Exploratory:</b>	<b>Exploratory:</b>
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI due to RSV.	-	RSV-positive MA-RTI: <ul style="list-style-type: none"> <li>• occurring within 90 days after birth.</li> <li>• occurring within 120 days after birth.</li> <li>• occurring within 150 days after birth.</li> <li>• occurring within 180 days after birth.</li> <li>• occurring 181 to 730 days after birth.</li> </ul>
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-RTI.	-	The incidence of all-cause MA-RTIs from vaccination up to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTI due to RSV in infants after 12 months of age.	-	MA-LRTIs due to RSV occurring 361 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of severe MA-LRTI due to RSV in infants after 6 months of age.	-	Severe MA-LRTIs due to RSV occurring 181 to 730 days after birth.

Objectives	Population-level Summaries	Endpoints
To evaluate the efficacy of RSVpreF in reducing the incidence of hospitalization due to RSV in infants after 6 months of age.	-	Hospitalization due to RSV occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of all-cause MA-LRTI in infants after 6 months of age.	-	MA-LRTIs due to any cause occurring 181 to 730 days after birth.
To evaluate the efficacy of RSVpreF in reducing the incidence of MA-LRTIs due to RSV A and the incidence of MA-LRTIs due to RSV B.	-	RSV subgroup A– and subgroup B–specific MA-LRTI.
To describe the non-RSV infectious etiology of MA-RTI in the study population.	-	Positivity for non-RSV respiratory pathogens obtained at unplanned MA-RTI visits.
To evaluate RSV serum neutralizing titers elicited by RSVpreF and transferred transplacentally. <sup>a</sup>	-	RSV A and RSV B serum neutralizing titers measured at birth.
To assess the impact of RSVpreF on RSV illness based on socioeconomic factors.	-	Primary and secondary efficacy by select demographic risk factors (eg, breastfeeding, maternal smoking, number of household members).
To assess the effect of RSVpreF on healthcare utilization.	-	Univariate summaries of healthcare utilization variables, which may include the following: number and type of medical visits, length of hospital stay, requirement for mechanical ventilation, requirement for respiratory diagnostic procedures, requirement for IV fluids, requirement for prescriptions, and antibiotic use.
To describe the efficacy of RSVpreF in reducing the incidence of MA-RTI, MA-LRTI, and severe MA-LRTI in premature infants <37 weeks of age.	-	MA-RTI, MA-LRTI, and severe MA-LRTI due to RSV occurring 0 to 730 days after birth.

<sup>a</sup> To be reported at a later time.

Source: C3671008 Study Protocol, Amendment 7, dated August 8, 2022, p. 40-43.



## **Maternal Participants**

Table 3. Study Objectives, Endpoints, and Population-level Summaries – Maternal Participants.

<b>Objectives</b>	<b>Population-level Summaries</b>	<b>Endpoints</b>
<b>Primary Safety:</b>	<b>Primary Safety:</b>	<b>Primary Safety:</b>
To describe the safety and tolerability of RSVpreF.	In maternal participants receiving 1 dose of investigational product, the percentage of maternal participants with each safety endpoint in each vaccine group.	The incidence of: <ul style="list-style-type: none"> <li>• prespecified local reactions within 7 days after vaccination.</li> <li>• prespecified systemic events within 7 days after vaccination.</li> <li>• AEs from the time of vaccination through 1 month after vaccination.</li> <li>• SAEs throughout the study (Visit 1 through the 6-month-postdelivery study visit).</li> </ul>
<b>Exploratory:</b>	<b>Exploratory</b>	<b>Exploratory:</b>
To describe MA-RTI in this study population.	-	The incidence of all-cause MA-RTIs from vaccination up to 180 days after delivery.
To evaluate the immune responses elicited by RSVpreF. <sup>a</sup>	-	<ul style="list-style-type: none"> <li>• RSV A and RSV B serum neutralizing titers and prefusion F IgG titers measured: <ul style="list-style-type: none"> <li>• before vaccination.</li> <li>• at delivery.</li> </ul> </li> </ul>

<sup>a</sup> To be reported at a later time.

Source: C3671008 Study Protocol, Amendment 7, dated August 8, 2022, p. 44.

## **Endpoints Definitions**

Table 4. Study Endpoints Definitions.

<b>Study Endpoints/Assessments</b>	<b>Definitions</b>
Medically attended visit	Infant participant has been taken to or seen by a healthcare provider (e.g., outpatient or inpatient visit, emergency room, urgent care, or home visit)
MA-RTI visit for infant participant	A medically attended visit AND 1 or more of the following RTI signs and symptoms: <ul style="list-style-type: none"> <li>• Nasal discharge for 24 hours or more</li> <li>• Difficulty breathing, labored breathing, or rapid breathing for any duration</li> <li>• Cough</li> <li>• Inability to feed for any duration because of respiratory symptoms</li> <li>• Apnea</li> <li>• Any other respiratory symptom of concern</li> </ul>
RSV-positive test <sup>a</sup>	<ul style="list-style-type: none"> <li>• RSV RT-PCR–positive test result by Pfizer central laboratory</li> </ul> <b>OR</b> <ul style="list-style-type: none"> <li>• RSV-positive test result by certified laboratory with NAAT for RSV</li> </ul>

Study Endpoints/Assessments	Definitions
MA-RTI due to RSV <sup>b</sup>	<ul style="list-style-type: none"> <li>An MA-RTI visit</li> <li><b>AND</b></li> <li>RSV-positive test result</li> </ul>
MA-LRTI due to any cause	<ul style="list-style-type: none"> <li>Infant with an MA-RTI visit</li> <li><b>AND</b></li> <li>Fast breathing (RR <math>\geq</math>60 bpm for &lt;2 months of age [&lt;60 days of age], <math>\geq</math>50 bpm for <math>\geq</math>2 months to &lt;12 months of age, or <math>\geq</math>40 bpm for <math>\geq</math>12 months to 24 months of age) <b>OR</b></li> <li>SpO<sub>2</sub> &lt;95% <b>OR</b></li> <li>Chest wall indrawing</li> </ul>
MA-LRTI due to RSV <sup>b</sup>	<ul style="list-style-type: none"> <li>Infant with an MA-RTI visit</li> <li><b>AND</b></li> <li>Fast breathing (RR <math>\geq</math>60 bpm for &lt;2 months of age [&lt;60 days of age] or <math>\geq</math>50 bpm for <math>\geq</math>2 to &lt;12 months of age, or <math>\geq</math>40 bpm for <math>\geq</math>12 months to 24 months of age) <b>OR</b></li> <li>SpO<sub>2</sub> &lt;95% <b>OR</b></li> <li>Chest wall indrawing</li> <li><b>AND</b></li> <li>RSV-positive test result</li> </ul>
Hospitalized RTI due to RSV <sup>b</sup>	An RTI due to RSV that results in hospitalization
Severe MA-LRTI due to RSV <sup>b</sup>	<ul style="list-style-type: none"> <li>Infant with an MA-RTI visit</li> <li><b>AND</b></li> <li>Fast breathing (RR <math>\geq</math>70 bpm for &lt;2 months of age [&lt;60 days of age], <math>\geq</math>60 bpm for <math>\geq</math>2 months to &lt;12 months of age, or <math>\geq</math>50 bpm for <math>\geq</math>12 months to 24 months of age) <b>OR</b></li> <li>SpO<sub>2</sub> &lt;93% <b>OR</b></li> <li>High-flow nasal cannula or mechanical ventilation (ie, invasive or noninvasive) <b>OR</b></li> <li>ICU admission for &gt;4 hours <b>OR</b></li> <li>Failure to respond/unconscious</li> <li><b>AND</b></li> <li>RSV-positive test result</li> </ul>
Protocol-defined primary endpoint	<ul style="list-style-type: none"> <li>Any MA-LRTI or severe MA-LRTI due to RSV as determined by an EAC</li> </ul>

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; RTI = respiratory tract illness; SpO<sub>2</sub> = oxygen saturation.

a. RSV-positive testing is defined as a positive RSV test conducted on a sample obtained during the medically attended visit or within 10 days (where Day 1 is the day of the MA-RTI visit).

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

Source: C3671008 Study Protocol, Amendment 7, dated August 8, 2022, p. 38-39.

### 6.1.2 Design Overview

Study C3671008 was designed as an event-driven study with an original final analysis target of 124 adjudicated (primary-endpoint) cases of MA-LRTI due to RSV at 90 days. There was no specific case target for the additional primary endpoint of severe MA-LRTI. Up to 2 interim analyses of the primary endpoint (MA-LRTI due to RSV) were

planned in the protocol after at least 43 cases of MA-LRTI due to RSV within 90 days had occurred.

The study was designed to assess the efficacy, safety, and immunogenicity of RSVpreF vaccine (120 µg [60 µg RSV A and 60 µg RSV B]) compared to placebo (1:1 randomization) in infants born to healthy women and adolescents ( $\leq 49$  years of age) vaccinated with a single dose during pregnancy between 24 and 36 weeks gestational age, as well as the safety and immunogenicity in the pregnant women. The study is global, and is being conducted in 18 countries (Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, United States). It spans over multiple RSV seasons.

The first interim efficacy analysis was conducted in April 2022 when 56 evaluable cases of MA-LRTI due to RSV within 90 days after birth had accrued. According to the applicant, the efficacy criterion was met for MA-LRTI due to RSV within 90 days after birth but not within 150 days, and the recommendation of the E-DMC was to continue the study. The blinding in the study was maintained after the first interim analysis. The second interim efficacy analysis was conducted on October 28, 2022, following the presumed end of the fourth RSV season in the study. At that time, 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 applicant reported that the recommendation of the E-DMC was to stop the study for efficacy since the success criterion for VE was met for one of the two primary efficacy endpoints. This second interim analysis is considered the final analysis of the study primary efficacy objectives, according to the criteria specified in the study protocol.

This CSR includes analyses of the efficacy endpoints in infants through the data cutoff date of September 30, 2022 and of the safety endpoints through the data cutoff date of September 2, 2022. Enrolment for maternal participants was completed on October 3, 2022. Ongoing study participants continue follow-up in a blinded fashion.

### **6.1.3 Population**

The maternal participants population included healthy pregnant women and adolescents  $\leq 49$  years of age, who were between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, and who were at no known increased risk for complications. The infant participants population included the infants born to the maternal participants upon provision of informed consent by the infants' parent(s)/legal guardian(s).

### **6.1.4 Study Treatments or Agents Mandated by the Protocol**

The study intervention includes a single intramuscular injection into the deltoid muscle of RSVpreF vaccine (120 µg) or placebo (matching the physical appearance of the vaccine).

### 6.1.6 Sites and Centers

This study was conducted at 216 sites in: the United States (129), Argentina (8), Australia (4), Brazil (4), Canada (3), Chile (7), Denmark (4), Finland (7), Gambia (1), Japan (12), Republic of Korea (5), Mexico (5), Netherlands (3), New Zealand (4), Philippines (1), South Africa (8), Spain (6), and Taiwan (5).

### 6.1.8 Hypotheses and Criteria for Study Success

For the infant primary efficacy objectives and secondary efficacy objectives, RSVpreF would be compared to placebo, testing the following hypotheses:

1. Primary efficacy objectives:  $H_0$ :  $VE \leq 20\%$  vs  $H_a$ :  $VE > 20\%$  against MA-LRTI or severe MA-LRTI due to RSV (defined as the percentage relative risk reduction in the incidence of MA-LRTI or severe MA-LRTI due to RSV in the RSV vaccine group, relative to the placebo group). The incidence of MA-LRTI due to RSV and of severe MA-LRTI due to RSV in infant participants were to be evaluated in time periods of up to 90 days, 120 days, 150 days, and 180 days after birth and compared between the two arms in a fixed sequence order.
2. Secondary efficacy objectives:  $H_0$ :  $VE \leq 0\%$  vs  $H_a$ :  $VE > 0\%$  against hospitalization due to RSV, MA-LRTI due to RSV through 360 days, or all-cause MA-LRTI (defined as the percentage risk reduction in the incidence of hospitalization due to RSV, MA-LRTI due to RSV through 360 days after birth, or all-cause MA-LRTI in the RSV vaccine group, relative to the placebo group). Hypothesis testing of the secondary endpoints is conditional upon rejection of the null hypothesis for at least 1 of the primary endpoints. Testing of the secondary endpoints over the respective time periods was to be conducted in a fixed sequence order.

$H_0$  and  $H_a$  represent the null and alternative hypotheses, respectively. VE was defined as  $VE = 100 \times (1 - \text{risk ratio})$ . Risk ratio was calculated as the ratio of the case count in the RSVpreF group to the corresponding case count in the placebo group. The overall type I error was set at 2.5% (one-sided).

The two primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV were to be tested in parallel using the Bonferroni multiplicity adjustment procedure, i.e., half the available alpha (based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function) was used for each of the two primary endpoints. Success of the trial was to be claimed upon rejection of the null hypothesis (i.e., a CI lower bound  $> 20\%$ ) for either one of the two primary endpoints. Testing of the two primary endpoints across the time intervals was planned to follow a fixed sequence with a gatekeeping strategy. For each of the two primary endpoints, testing with regard to the incidence within 90 days after birth was to be conducted first at the multiplicity-adjusted alpha level. If the respective null hypothesis was rejected, testing proceeded with regard to the incidence within 120 days after birth for that endpoint, otherwise, the testing stops. Testing would proceed to the endpoints evaluated at 150 days and 180 days, conditional on rejection of the null hypotheses for all earlier time intervals.

Hypothesis testing for the secondary endpoints was conditional upon demonstrating success through 180 days for at least one of the two primary efficacy endpoints. The secondary endpoints would be tested in parallel at an overall type I error across primary and secondary endpoint families at the available alpha level at no more than 2.5% one-sided. The alpha level available for the secondary endpoints would be dependent upon the results of the primary endpoints. If both primary endpoints were successful through 180 days, the full alpha would be available for the secondary endpoints. If only 1 of the 2 primary endpoints was successful through 180 days, half the alpha would be available. A Bonferroni multiplicity adjustment would be used for the hypothesis testing for the three secondary endpoints. VE would be evaluated sequentially at the respective time periods. The same fixed-sequence testing and gatekeeping strategy used for the primary endpoints would be employed.

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for study C3671008 (version 6, dated September 2, 2022) was pre-specified and was submitted with the application in STN 125768/0. A brief overview of the SAP is presented below.

**Analysis populations:** The definitions of the study Analysis Populations are shown in Table 5. The primary population for efficacy analyses was the Evaluable Efficacy Population. Supplementary analyses were planned using the modified Intent-to-Treat (mITT) Efficacy Population.

Table 5. Analysis Populations.

Population	Description
Enrolled	All participants who signed the informed consent document.
Randomly assigned to investigational product	All maternal participants who were assigned a randomization number in the IRT system.
Evaluable efficacy – infant (per-protocol)	All infant participants who were born to maternal participants who did not have major protocol deviations prior to the delivery and who received the investigational product to which they were randomized at least 14 days prior to delivery, are eligible, and had no major protocol deviations.
mITT efficacy – infant	All infant participants who were born to vaccinated maternal participants.
Safety – infant	All infant participants who were born to vaccinated maternal participants.
Safety – maternal	All randomized maternal participants who received investigational product.

Source: C3671008 Statistical Analysis Plan, version 6, dated September 2, 2022, p. 34.

## **Analyses for the Primary Efficacy Endpoints and the Secondary Efficacy Endpoints:**

### **Primary Analyses**

The primary population for the efficacy analyses was the Evaluable Efficacy Population. VE for the primary analyses was estimated based on the case count ratio. This method assumes that the cases follow a Poisson distribution and assumes equal person-time of follow-up.

$$VE = 1 - C_v/C_p = 1 - P/(1 - P)$$

where:

$C_v$  = number of cases in the RSVpreF group

$C_p$  = number of cases in the placebo group

$P$  = number of cases in the RSVpreF group divided by the total number of cases (combined RSVpreF and placebo)

The CIs for VE were derived from the conditional exact test based on the binomial distribution of  $P$  (the number of cases in the RSVpreF group, given the total number of cases in both groups).

The 95% CI for proportions were constructed based on the Clopper-Pearson method, and the 95% CI for differences in the proportions were constructed using the Miettinen and Nurminen method.

**Sensitivity/supportive Analyses:** Sensitivity analyses of the primary endpoints were conducted under various assumptions about the missing swab results for cases that qualify as MA-LRTI events based on clinical signs and symptoms but do not have a valid RSV swab result. In each scenario, cases with imputed positive RSV results were added to the confirmed RSV-positive cases and vaccine efficacy in the augmented set of cases were analyzed. Multiple imputation was performed to randomly assign missing swab results. Additional sensitivity analyses in the mITT Efficacy Analysis Population were also conducted.

**Subgroup analysis:** For the primary efficacy endpoints, subgroup analyses were pre-specified for the following variables: GA at the time of vaccination ( $\geq 24$  to  $< 28$  weeks,  $\geq 28$  to  $< 32$  weeks,  $\geq 32$  to  $\leq 36$  weeks), country, country subcategories (level of income), age at vaccination ( $< 18$  years,  $\geq 18$  years), breastfeeding, maternal smoking, number of household members, and infants who received palivizumab.

### **Analyses for the Primary Safety Endpoints:**

Participants were summarized by vaccine group according to the study intervention they actually received (Safety Population). The proportion of participants reporting each event and the respective 95% CI based on the Clopper-Pearson method were reported. The 95% CI for the difference in the proportions (between study intervention group) were computed using the Miettinen and Nurminen method.

**Interim Analyses (IA):** This is an event-driven study with a target of 124 adjudicated (primary-endpoint) cases of MA-LRTI due to RSV at 90 days. There was no specific case

target for the second primary endpoint of severe MA-LRTI. Up to two interim analyses were planned when at least 43 cases of MA-LRTI-due-to-RSV within 90 days have occurred. Based on the fraction of cases included in an interim analysis, the alpha level was planned to be derived using the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. The exact number of cases at each interim analysis was not fixed, however, no fewer than 43 cases were planned to be included in the first interim analysis and no fewer than 62 cases were to be included in the second interim analysis. It was planned that the study may be stopped early for efficacy if the analysis of either primary endpoint through 90 days indicates statistically significant efficacy. Hypothesis testing for the secondary endpoints was conditional upon demonstrating success through 180 days for at least one of the two primary efficacy endpoints. Futility was also to be assessed at the interim analyses using conditional power. Specifically, it was specified that the study may be stopped for futility if the conditional power falls below 20%.

The first interim analysis was conducted when 56 evaluable cases of MA-LRTI due to RSV within 90 days after birth had accrued. For the endpoints inspected at the interim analysis (MA-LRTI and severe MA-LRTI at 90 days), the O'Brien-Fleming alpha spending function determined the alpha to be used and was split between the endpoints using the Bonferroni correction. Since MA-LRTI through 180 days was inspected at the first interim analysis with a 2-sided alpha of 0.0017, the analysis of the primary endpoints at 120 days and later after a successful second interim analysis at 90 days would use a 2-sided alpha of  $0.05 - 0.0017 = 0.0483$ , to be split between the endpoints using the Bonferroni correction.

## 6.1.10 Study Population and Disposition

### 6.1.10.1 Populations Enrolled/Analyzed

In the study, as of the safety data cutoff date of September 2, 2022, 7392 maternal participants were randomized to receive RSVpreF (3695) or placebo (3697) (Table 6). Of the randomized participants, 7358 (99.5%) received the study vaccine. As of the data cutoff date, 7294 (98.7%) completed the 1-month safety follow-up visit, 7148 (96.7%) completed delivery and 5683 (76.9%) completed the study. Most withdrawals occurred after delivery, with 146 (4%) in the RSVpreF arm and 136 (3.7%) in the placebo arm.

Table 6. Disposition of Maternal Participants (as randomized).

Population	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
Randomized	3695	3697	7392
Vaccinated	3682 (99.6)	3676 (99.4)	7358 (99.5)
Completed 1 month after vaccination	3652 (98.8)	3642 (98.5)	7294 (98.7)
Withdrawn after vaccination but before 1 month after vaccination	9 (0.2)	7 (0.2)	16 (0.2)
Reason for withdrawal:	-	-	-

Population	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
Lost to follow-up	3 (<0.1)	1 (<0.1)	4 (<0.1)
Withdrawal by subject	6 (0.2)	6 (0.2)	12 (0.2)
Completed delivery	3578 (96.8)	3570 (96.6)	7148 (96.7)
Withdrawn after vaccination but before delivery	29 (0.8)	31 (0.8)	60 (0.8)
Reason for withdrawal:	-	-	-
Lost to follow-up	8 (0.2)	10 (0.3)	18 (0.2)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)
Withdrawal by subject	19 (0.5)	19 (0.5)	38 (0.5)
Completed study	2840 (76.9)	2843 (76.9)	5683 (76.9)
Withdrawn after delivery	146 (4.0)	136 (3.7)	282 (3.8)
Reason for withdrawal:	-	-	-
Adverse event	0	1 (<0.1)	1 (<0.1)
Death	1 (<0.1)	0	1 (<0.1)
Lost to follow-up	82 (2.2)	68 (1.8)	150 (2.0)
No longer meets eligibility criteria	1 (<0.1)	0	1 (<0.1)
Other	10 (0.3)	7 (0.2)	17 (0.2)
Physician decision	1 (<0.1)	0	1 (<0.1)
Protocol deviation	0	1 (<0.1)	1 (<0.1)
Withdrawal by subject	51 (1.4)	59 (1.6)	110 (1.5)
Ongoing	667 (18.1)	666 (18.0)	1333 (18.0)

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 7, p. 40-41.

Table 7 shows the disposition of the infant participants as of the safety data cutoff date. There were 7128 infant participants born to mothers who were randomized to receive RSVpreF or placebo, of whom 3423 (95.9%) infants whose mothers were randomized to receive RSVpreF and 3400 (95.6%) infants whose mothers were randomized to receive placebo have completed the 1-month follow-up visit. Respectively, 2830 (79.3%) and 2824 (79.4%) infants have completed the 6-month follow-up visit. The 12-month follow-up visit was completed by 1631 (45.7%) and 1616 (45.4%) infants, respectively. Since follow-up for the majority of the infant subjects were ongoing by the time of the data cutoff date, the applicant stated that they will provide final data for these participants in a future report.

Table 7. Disposition of Infant Participants (maternal vaccine group as randomized).

Population	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
Enrolled <sup>a</sup>	3570	3558	7128
Planned 12 months follow-up	1599 (44.8)	1591 (44.7)	3190 (44.8)
Planned 24 months follow-up <sup>b</sup>	1971 (55.2)	1967 (55.3)	3938 (55.2)
Completed 1 month follow-up	3423 (95.9)	3400 (95.6)	6823 (95.7)
Withdrawn before 1 month after birth	52 (1.5)	60 (1.7)	112 (1.6)



Population	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
Reason for withdrawal:	-	-	-
Death	2 (<0.1)	6 (0.2)	8 (0.1)
Lost to follow-up	22 (0.6)	26 (0.7)	48 (0.7)
Other	3 (<0.1)	6 (0.2)	9 (0.1)
Withdrawal by parent/guardian	25 (0.7)	22 (0.6)	47 (0.7)
Completed 6 months follow- up	2830 (79.3)	2824 (79.4)	5654 (79.3)
Withdrawn after 1 month but before 6 months after birth	92 (2.6)	83 (2.3)	175 (2.5)
Reason for withdrawal:	-	-	-
Death	3 (<0.1)	5 (0.1)	8 (0.1)
Lost to follow-up	54 (1.5)	36 (1.0)	90 (1.3)
Other	8 (0.2)	10 (0.3)	18 (0.3)
Withdrawal by parent/guardian	27 (0.8)	32 (0.9)	59 (0.8)
Completed 12 months follow- up	1631 (45.7)	1616 (45.4)	3247 (45.6)
Withdrawn after 6 months but before 12 months after birth	41 (1.1)	52 (1.5)	93 (1.3)
Reason for withdrawal:	-	-	-
Death	0	1 (<0.1)	1 (<0.1)
Lost to follow-up	31 (0.9)	35 (1.0)	66 (0.9)
Other	1 (<0.1)	7 (0.2)	8 (0.1)
Withdrawal by parent/guardian	9 (0.3)	9 (0.3)	18 (0.3)
Completed 24 months follow- up	3 (<0.1)	3 (<0.1)	6 (<0.1)
Withdrawn after 12 months but before 24 months after birth	36 (1.0)	34 (1.0)	70 (1.0)
Reason for withdrawal:	-	-	-
Lost to follow-up	30 (0.8)	25 (0.7)	55 (0.8)
Other	3 (<0.1)	3 (<0.1)	6 (<0.1)
Withdrawal by parent/guardian	3 (<0.1)	6 (0.2)	9 (0.1)
Completed the study as planned	6 (0.2)	12 (0.3)	18 (0.3)
Ongoing	3343 (93.6)	3317 (93.2)	6660 (93.4)

a. The values in this row are used as the denominators for the percentage calculations for vaccine groups for all rows except otherwise specified in footnote b.

b. The values in this row are used as the denominators for the percentage calculations for vaccine groups for rows related to 24 months completion/withdrawal.

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 8, p. 42-43.

The maternal participant analysis populations are shown in Table 8 according to the vaccine group to which they were randomized. A total of 34 (0.5%) maternal participants were randomized but not vaccinated. There was 1 maternal participant who was

randomized to placebo, however received RSVpreF at vaccination, and was respectively included in the RSVpreF group for the safety analyses. As of the data cutoff date, this participant had not delivered.

Table 8. Maternal Participants Analysis Populations (vaccine group as randomized)

Analysis Populations	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
<b>Randomized</b>	3695	3697	7392
<b>Safety Population</b>	3681 (99.6)	3676 (99.4)	7357 (99.5)
Participants excluded from safety population:	-	-	-
Not vaccinated	13 (0.4)	21 (0.6)	34 (0.5)
Participant not eligible - unblinded during study	1 (<0.1)	0	1 (<0.1)

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 9, p. 45.

Table 9 shows the analysis populations for the infant participants. The Safety Population included a total of 3568 infant participants whose mothers received RSVpreF and 3558 infant participants whose mothers received placebo. There were 2 infants, whose mothers received RSVpreF, and were excluded from the Safety, mITT, and Evaluable Efficacy populations. The applicant stated that one of these infants was unblinded and withdrawn from the study as requested by the infant's mother after the infant experienced an unrelated AE at birth (hypoxic ischemic encephalopathy). For the second infant that was excluded, the applicant stated that the maternal/infant pair was unblinded as requested by the Argentina National Administration of Drugs, Foods and Medical Devices, as the maternal participant was <18 years of age at the time of enrollment, while the country's minimum age for participation in this study was 18. The Evaluable Efficacy Population included a total of 3495 (97.9%) infant participants whose mothers received RSVpreF and 3480 (97.8%) infant participants whose mothers received placebo. The most frequent reason for exclusion from the Evaluable Efficacy Population was that the mother was vaccinated less than 14 days prior to delivery.

Table 9. Infant Participants Analysis Populations (maternal vaccine group as randomized)

Analysis Populations	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
<b>Enrolled</b>	3570	3558	7128
<b>Safety Population</b>	3568 (99.9)	3558 (100.0)	7126 (100.0)
Participants excluded from safety population:	-	-	-
Mother not vaccinated	0	0	0
Participant not eligible - unblinded during study	2 (<0.1)	0	2 (<0.1)
<b>mITT efficacy population</b>	3568 (99.9)	3558 (100.0)	7126 (100.0)
Participants excluded from mITT efficacy population:	-	-	-
Mother not vaccinated	0	0	0

Analysis Populations	RSVpreF 120 µg n (%)	Placebo n (%)	Total n (%)
Participant not eligible - unblinded during study	2 (<0.1)	0	2 (<0.1)
<b>Evaluable efficacy population</b>	3495 (97.9)	3480 (97.8)	6975 (97.9)
Participants excluded from evaluable efficacy population:	-	-	-
Participant not eligible - unblinded during study	2 (<0.1)	0	2 (<0.1)
Infant not eligible for study	3 (<0.1)	4 (0.1)	7 (<0.1)
Mother not vaccinated as randomized	0	0	0
Mother had major protocol violations before delivery	27 (0.8)	19 (0.5)	46 (0.6)
Mother not vaccinated at least 14 days prior to delivery	44 (1.2)	56 (1.6)	100 (1.4)
Infant had major protocol violations	0	1 (<0.1)	1 (<0.1)

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 10, p. 46.

#### 6.1.10.1.1 Demographics

Table 10 shows the demographic and baseline characteristics by study group for the maternal participants Safety Population. The characteristics were comparable between the study groups.

Table 10. Demographic and Baseline Characteristics of the Maternal Participants (Safety Population).

Characteristics	RSVpreF 120 µg (N=3682) n (%)	Placebo (N=3675) n (%)	Total (N=7357) n (%)
Race	-	-	-
White	2383 (64.7)	2365 (64.4)	4748 (64.5)
Black or African American	720 (19.6)	723 (19.7)	1443 (19.6)
Asian	454 (12.3)	464 (12.6)	918 (12.5)
American Indian or Alaskan Native	38 (1.0)	37 (1.0)	75 (1.0)
Native Hawaiian or other Pacific Islander	9 (0.2)	12 (0.3)	21 (0.3)
Multiracial	30 (0.8)	21 (0.6)	51 (0.7)
Not reported	41 (1.1)	45 (1.2)	86 (1.2)
Unknown	7 (0.2)	8 (0.2)	15 (0.2)
Ethnicity	-	-	-
Hispanic/Latino	1049 (28.5)	1075 (29.3)	2124 (28.9)
Non-Hispanic/non-Latino	2603 (70.7)	2567 (69.9)	5170 (70.3)
Not reported	28 (0.8)	33 (0.9)	61 (0.8)
Unknown	2 (<0.1)	0	2 (<0.1)
Age at vaccination (years)	-	-	-
Mean (SD)	29.1 (5.64)	29.0 (5.74)	29.0 (5.69)

Characteristics	RSVpreF 120 µg (N=3682) n (%)	Placebo (N=3675) n (%)	Total (N=7357) n (%)
Median (Range)	29.0 (16- 45)	29.0 (14- 47)	29.0 (14- 47)
Gestational Age (GA) at vaccination (weeks)	-	-	-
Mean (SD)	30.83 (3.54)	30.82 (3.55)	30.83 (3.54)
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)
Country	-	-	-
Argentina	455 (12.4)	455 (12.4)	910 (12.4)
Australia	11 (0.3)	13 (0.4)	24 (0.3)
Brazil	36 (1.0)	37 (1.0)	73 (1.0)
Canada	27 (0.7)	28 (0.8)	55 (0.7)
Chile	86 (2.3)	85 (2.3)	171 (2.3)
Denmark	31 (0.8)	31 (0.8)	62 (0.8)
Finland	75 (2.0)	73 (2.0)	148 (2.0)
Gambia	98 (2.7)	98 (2.7)	196 (2.7)
Japan	230 (6.2)	232 (6.3)	462 (6.3)
Korea	7 (0.2)	5 (0.1)	12 (0.2)
Mexico	38 (1.0)	37 (1.0)	75 (1.0)
Netherlands	97 (2.6)	95 (2.6)	192 (2.6)
New Zealand	50 (1.4)	49 (1.3)	99 (1.3)
Philippines	40 (1.1)	39 (1.1)	79 (1.1)
South Africa	482 (13.1)	478 (13.0)	960 (13.0)
Spain	118 (3.2)	124 (3.4)	242 (3.3)
Taiwan	130 (3.5)	130 (3.5)	260 (3.5)
USA	1671 (45.4)	1666 (45.3)	3337 (45.4)

Source: Adapted from C3671008 Clinical Study Report, dated December 6, 2022, Table 11, p. 47-48.

Table 11 shows the demographic characteristics by study group for the infant Safety Population. The characteristics were comparable between the study groups.

Table 11. Demographic Characteristics of the Infant Participants (Safety Population, Maternal Vaccine Group as Administered).

Characteristics	RSVpreF 120 µg (N=3568) n (%)	Placebo (N=3558) n (%)	Total (N=7126) n (%)
Sex	-	-	-
Male	1816 (50.9)	1793 (50.4)	3609 (50.6)
Female	1752 (49.1)	1765 (49.6)	3517 (49.4)

Characteristics	RSVpreF 120 µg (N=3568) n (%)	Placebo (N=3558) n (%)	Total (N=7126) n (%)
Race	-	-	-
White	2294 (64.3)	2284 (64.2)	4578 (64.2)
Black or African American	687 (19.3)	688 (19.3)	1375 (19.3)
Asian	420 (11.8)	430 (12.1)	850 (11.9)
American Indian or Alaskan Native	42 (1.2)	36 (1.0)	78 (1.1)
Native Hawaiian or other Pacific Islander	13 (0.4)	11 (0.3)	24 (0.3)
Multiracial	65 (1.8)	59 (1.7)	124 (1.7)
Not reported	37 (1.0)	40 (1.1)	77 (1.1)
Unknown	10 (0.3)	10 (0.3)	20 (0.3)
Ethnicity	-	-	-
Hispanic/Latino	1033 (29.0)	1039 (29.2)	2072 (29.1)
Non-Hispanic/non-Latino	2484 (69.6)	2473 (69.5)	4957 (69.6)
Not reported	49 (1.4)	44 (1.2)	93 (1.3)
Unknown	2 (<0.1)	2 (<0.1)	4 (<0.1)
Country	-	-	-
Argentina	423 (11.9)	416 (11.7)	839 (11.8)
Australia	11 (0.3)	13 (0.4)	24 (0.3)
Brazil	35 (1)	37 (1)	72 (1)
Canada	27 (0.8)	28 (0.8)	55 (0.8)
Chile	86 (2.4)	85 (2.4)	171 (2.4)
Denmark	30 (0.8)	31 (0.9)	61 (0.9)
Finland	75 (2.1)	73 (2.1)	148 (2.1)
Gambia	78 (2.2)	79 (2.2)	157 (2.2)
Japan	218 (6.1)	216 (6.1)	434 (6.1)
Korea	7 (0.2)	4 (0.1)	11 (0.2)
Mexico	37 (1)	37 (1)	74 (1)
Netherlands	97 (2.7)	95 (2.7)	192 (2.7)
New Zealand	49 (1.4)	47 (1.3)	96 (1.3)
Philippines	32 (0.9)	34 (1)	66 (0.9)
South Africa	469 (13.1)	471 (13.2)	940 (13.2)
Spain	117 (3.3)	123 (3.5)	240 (3.4)
Taiwan	123 (3.4)	125 (3.5)	248 (3.5)
USA	1654 (46.4)	1644 (46.2)	3298 (46.3)

Source: Adapted from C3671008 Clinical Study Report, dated December 6, 2022, Table 12, p. 49.

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The study eligibility criteria required that healthy women  $\leq 49$  years of age who were between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, and who were at no known increased risk for complications be enrolled. However, there was one participant with a twin pregnancy. Most maternal participants had a history of 0 (n=1220 [33.1%]) in the RSVpreF arm and

n=1221 [33.2%] in the placebo arm) or 1 (n=1151 [31.3%] in the RSVpreF arm and n=1110 [30.2%] in the placebo arm) pregnancies prior to the study pregnancy. History of pregnancy, puerperium and perinatal conditions was reported by 266 (7.2%) subjects in the RSVpreF arm and by 249 (6.8%) subjects in the placebo arm. Previous preterm deliveries were reported by 57 (1.5%) subjects in the RSVpreF arm and 61 (1.6%) in the placebo arm. History of pre-eclampsia was reported by 18 (0.5%) subjects in the RSVpreF arm and 11 (0.3%) subjects in the placebo arm. Please refer to the review by the clinical reviewer for details on the medical characterization of the enrolled population.

### 6.1.11 Efficacy Analyses

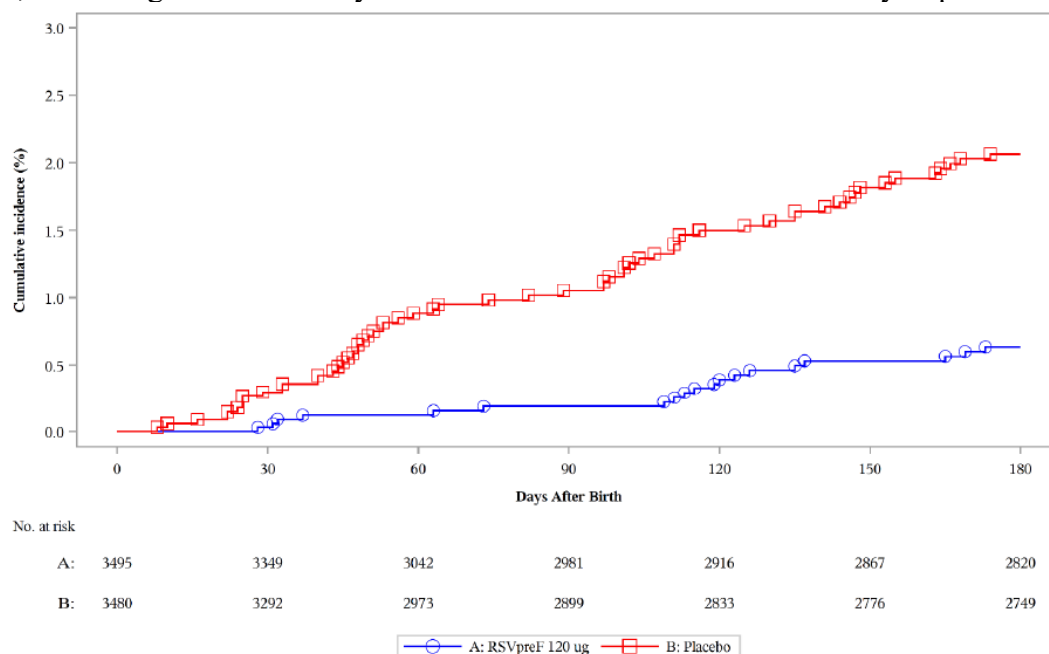
The application included data and results from the prespecified second interim analysis with a data cutoff date of September 30, 2022. As discussed above, the second interim efficacy analysis was conducted on October 28, 2022, following the presumed end of the fourth RSV season in the study. At that time, 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 applicant reported that the recommendation of the E-DMC was to stop the study for efficacy since the success criterion for VE was met for one of the two primary efficacy endpoints. This second interim analysis is considered the final analysis of the study primary efficacy objectives, according to the criteria specified in the study protocol.

#### 6.1.11.1 Analyses of Primary Endpoints

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

In the Evaluable Efficacy Population, there were a total of 39 infants with a case of severe MA-LRTI due to RSV confirmed by the EAC within 90 days from birth (Figure 1). Of these, 6 occurred in the RSVpreF group and 33 were in the placebo group, corresponding to a VE of 81.8%, 99.5% CI (40.6%, 96.3%), as shown in Table 12. As the lower bound of the CI was >20%, based on the prespecified fixed sequence testing rule, VE was assessed for the subsequent time interval of 120 days. Respectively, VE of 73.9%, 97.58% CI (45.6%, 88.8%) was estimated within 120 days after birth. Similarly, within 150 days after birth VE was estimated as 70.9%, 97.58% CI (44.5%, 85.9%), and within 180 days after birth VE was estimated as 69.4%, 97.58% CI (44.3%, 84.1%). As the lower bound of the CIs through 180 days after birth were >20%, the statistical criterion for success for this endpoint was met at all timepoints through 180 days.

Figure 1. Cumulative Case Accrual of Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring within 180 Days after Birth – Infants Evaluable Efficacy Population



Source: C3671008 Clinical Study Report, dated December 6, 2022, Figure 1, p. 53.

Table 12. Vaccine Efficacy of RSVpreF – 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)

Efficacy Endpoint Time Interval	RSVpreF N = 3495 Number of Cases (%)	Placebo N = 3480 Number of Cases (%)	Vaccine Efficacy <sup>a</sup> % (CI <sup>b</sup> )
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6, 96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6, 88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5, 85.9)
180 Days after birth	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.

- 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.
- Confidence intervals are 99.5% CI at 90 days (based on the alpha spending function and Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 13, p. 52.

*Reviewer's comment:* As discussed above (section 6.1.9), severe MA-LRTI due to RSV within 90 days after birth and MA-LRTI due to RSV within 90 days after birth were tested each at a 2-sided alpha of 0.005 derived using the O'Brien-Fleming alpha spending function with 80 cases of MA-LRTI due to RSV within 90 days out of the planned 124 cases. Because MA-LRTI through 180 days was inspected at the first interim analysis with a 2-sided alpha of 0.0017, the analysis of the primary endpoints at 120 days and

*later were tested using a 2-sided alpha of 0.05 -  $0.0017 = 0.0483$  split between the 2 primary endpoints using the Bonferroni correction.*

The applicant additionally conducted sensitivity analyses using the mITT Efficacy Population, which yielded VE of 66.7%, 97.58% CI (40.7%, 82.2%) within 180 days after birth for this endpoint. Additional sensitivity analyses to assess the effect of missing or invalid swab results, and of the severe MA-LRTI cases with positive RSV results (not restricted to adjudicated cases only) were conducted as well.

*Reviewer's comment: The results of the sensitivity analyses were consistent with that of the primary analysis for this endpoint.*

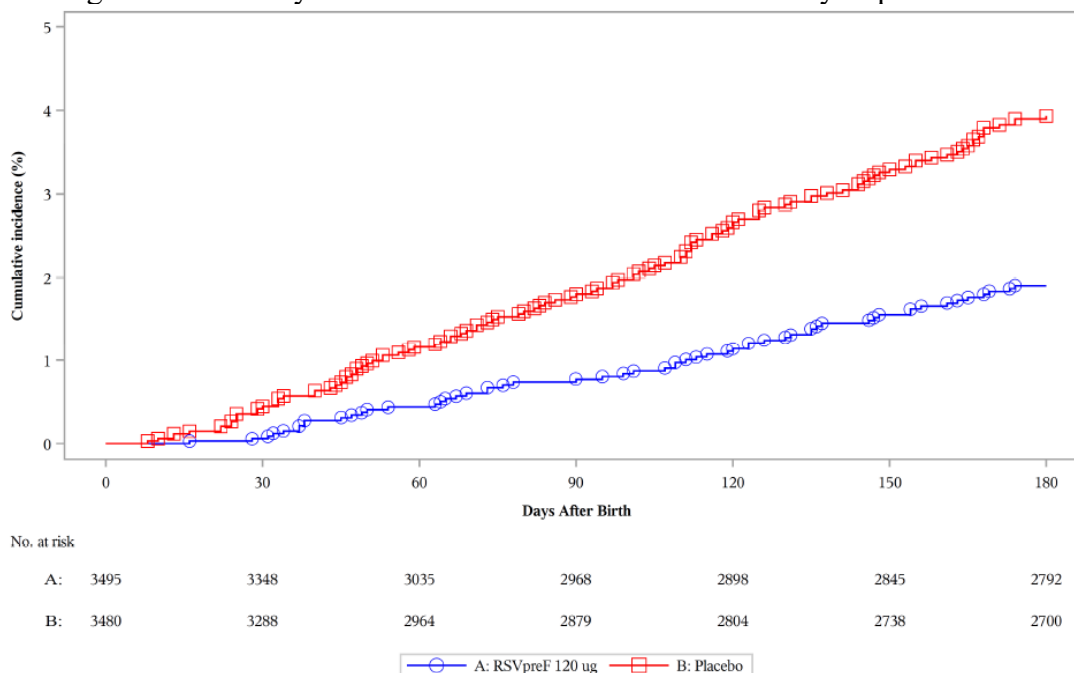
MA-LRTI Due to RSV Within 90, 120, 150, and 180 Days After Birth as Confirmed by the EAC

In the Evaluable Efficacy Population, there were a total of 80 infants with a case of MA-LRTI due to RSV confirmed by the EAC within 90 days from birth (Figure 2). Of these, 24 occurred in the RSVpreF group and 56 were in the placebo group, corresponding to a VE of 57.1%, 99.5% CI (14.7%, 79.8%), as shown in Table 13. As the lower bound of the CI was <20%, based on the prespecified fixed sequence testing rule, formal hypothesis testing for VE in the subsequent time intervals stops, and the respective results for this endpoint are considered descriptive. Respectively, within the time interval of 120 days after birth, VE was estimated as 56.8%, 97.58% CI (31.2%, 73.5%), within 150 days after birth VE was estimated as 52.5%, 97.58% CI (28.7%, 68.9%), and within 180 days after birth VE was estimated as 51.3%, 97.58% CI (29.4%, 66.8%).

*Reviewer's comment: The statistical criterion for success for this endpoint within 90 days was not met based on the O'Brien-Fleming type I error-adjusted 99.5% CI for VE, as the lower bound was 14.7%. For the subsequent time intervals (120 to 180 days after birth), as explained above, 97.58% CIs were used, and the respective lower bounds were >20%. For the MA-LRTIs due to RSV within 90 days, the 97.58% CI for VE would be (24.8%, 76.5%). Taking this into consideration and that the lower bounds of the CIs were >20% for VE for the time periods of 120 to 180 days after birth, the data suggest that the RSVpre F vaccine is efficacious within 180 days after birth for the prevention of MA-LRTI due to RSV.*



Figure 2. Cumulative Case Accrual of MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring within 180 Days after Birth – Infants Evaluable Efficacy Population



Source: C3671008 Clinical Study Report, dated December 6, 2022, Figure 2, p. 57.

Table 13. Vaccine Efficacy of RSVpreF –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)

Efficacy Endpoint Time Interval	RSVpreF N = 3495 Number of Cases (%)	Placebo N = 3480 Number of Cases (%)	Vaccine Efficacy <sup>a</sup> % (CI <sup>b</sup> )
90 Days after birth	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)
120 Days after birth	35 (1.0)	81 (2.3)	56.8 (31.2, 73.5)
150 Days after birth	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9)
180 Days after birth	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)

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

- 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.
- Confidence intervals are 99.5% CI at 90 days (based on the alpha spending function and Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 14, p. 56.

The applicant additionally conducted sensitivity analyses using the mITT Efficacy Population, which yielded VE of 49.2%, 97.58% CI (26.8%, 65.1%) within 180 days after birth for this endpoint. Additional sensitivity analyses to assess the effect of missing or invalid swab results, and of the MA-LRTI cases with positive RSV results (not restricted to adjudicated cases only) were conducted as well.

*Reviewer's comment: The results of the sensitivity analyses were consistent with that of the primary analysis for this endpoint.*

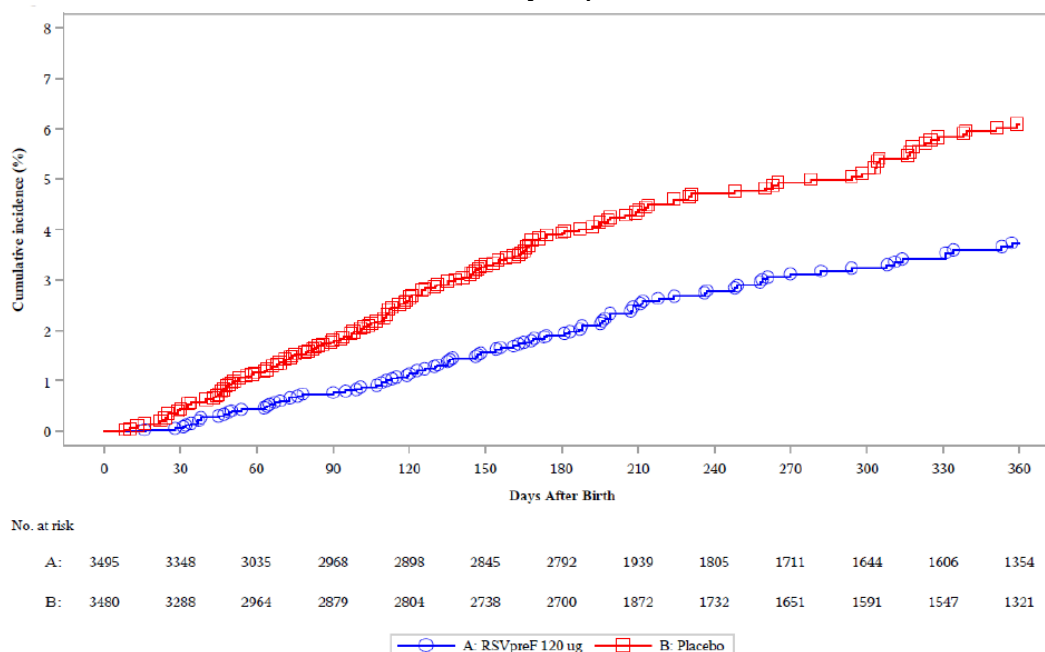
### 6.1.11.2 Analyses of Secondary Endpoints

There were 3 secondary efficacy endpoints in this study. Since the study success criterion was met only for one of the two primary endpoints through 180 days, the 3 secondary endpoints were analyzed using a two-sided alpha of  $0.025/3 = 0.0083$ , i.e., 99.17% CIs.

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

As of the cutoff date, there were 70 cases of investigator-reported RSV-positive MA-LRTI in infants within 210 days after birth in the RSVpreF group and 127 cases in the placebo group in the Evaluable Efficacy population, corresponding to a VE of 44.9% (99.17% CI: 17.9, 63.5) for RSVpreF (Figure 3, Table 14). The estimated VE within 240, 270, and 360 days after birth were respectively 42.9%, 99.17% CI (16.1%, 61.6%), 40.1%, 99.17% CI (13.0%, 59.2%), and 41.0%, 99.17% CI (16.2%, 58.9%). It is seen from the figure and the table that the accrual rates after 180 days, through 360 days after birth, were similar between the two arms, and that the VE estimates were primarily driven by the observed accrual prior to 180 days after birth.

Figure 3. Cumulative Case Accrual of RSV-Positive MA-LRTIs Occurring Within 360 Days After Birth – Infants Evaluable Efficacy Population



Source: C3671008 Clinical Study Report, dated December 6, 2022, Figure 14.3, p. 923.

Table 14. Vaccine Efficacy of RSVpreF – RSV-Positive MA-LRTIs Occurring Within 210, 240, 270, and 360 Days After Birth - Infant Participants - Evaluable Efficacy Population (maternal vaccine group as randomized)

Efficacy Endpoint Time Interval	RSVpreF N = 3495 Number of Cases (%)	Placebo N = 3480 Number of Cases (%)	Vaccine Efficacy <sup>a</sup> % (99.17% CI)
210 Days after birth	70 (2.0)	127 (3.6)	44.9 (17.9, 63.5)
240 Days after birth	76 (2.2)	133 (3.8)	42.9 (16.1, 61.6)
270 Days after birth	82 (2.3)	137 (3.9)	40.1 (13.0, 59.2)
360 Days after birth	92 (2.6)	156 (4.5)	41.0 (16.2, 58.9)

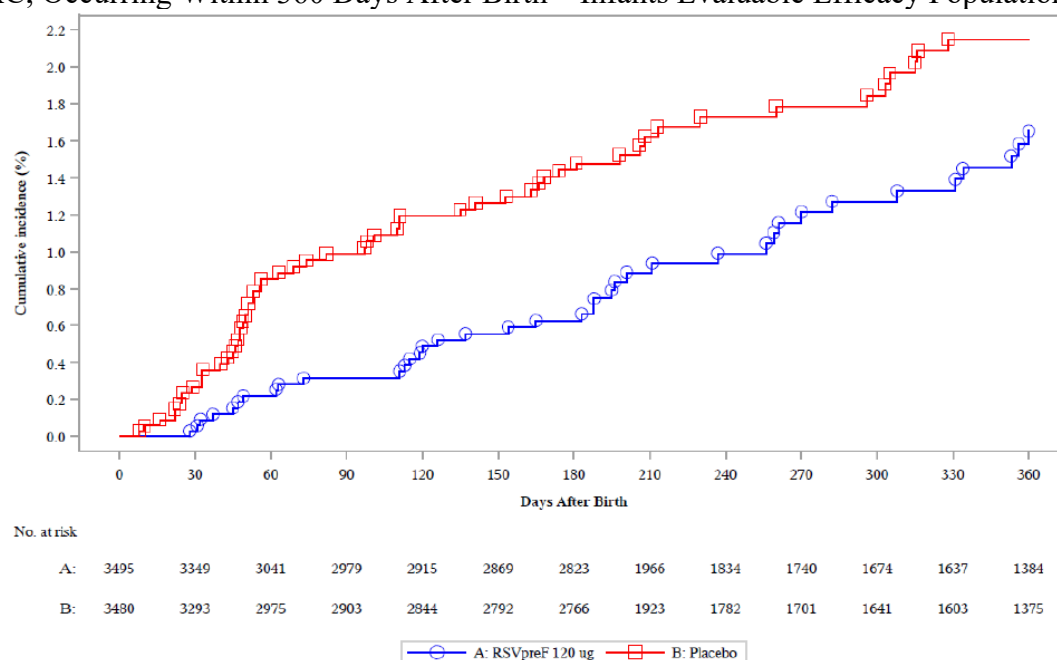
a. Vaccine efficacy was calculated as  $1 - (P/[1-P])$ , where P is the number of cases in the RSVpreF group divided by the total number of cases.

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 15, p. 59.

### Hospitalization Due to RSV Within 90, 120, 150, 180, and 360 Days as Confirmed by the EAC

As of the cutoff date, there were 10 hospitalizations due to RSV confirmed by the EAC in infants within 90 days after birth in the RSVpreF group and 31 in the placebo group in the Evaluable Efficacy population, corresponding to a VE of 67.7%, 99.17% CI (15.9%, 89.5%) for RSVpreF (Figure 4, Table 15). VE for hospitalizations due to RSV confirmed by the EAC within 120 days after birth was 59.5%, 99.17% CI (8.3%, 83.7%). The statistical criterion for success for this endpoint was met for the time periods through 180 days after birth. However, as it is seen, the case accrual rates beyond 120 days were similar between the two arms.

Figure 4. Cumulative Case Accrual of Hospitalizations Due to RSV, Confirmed by the EAC, Occurring Within 360 Days After Birth – Infants Evaluable Efficacy Population



Source: C3671008 Clinical Study Report, dated December 6, 2022, Figure 14.5, p. 925.

Table 15. Vaccine Efficacy of RSVpreF – Hospitalizations Due to RSV, Confirmed by the EAC, Occurring Within 90, 120, 150, 180, and 360 Days After Birth - Infant Participants - Evaluable Efficacy Population (maternal vaccine group as randomized)

Efficacy Endpoint Time Interval	RSVpreF N = 3495 Number of Cases (%)	Placebo N = 3480 Number of Cases (%)	Vaccine Efficacy <sup>a</sup> % (99.17 % CI)
90 Days after birth	10 (0.3)	31 (0.9)	67.7 (15.9, 89.5)
120 Days after birth	15 (0.4)	37 (1.1)	59.5 (8.3, 83.7)
150 Days after birth	17 (0.5)	39 (1.1)	56.4 (5.2, 81.5)
180 Days after birth	19 (0.5)	44 (1.3)	56.8 (10.1, 80.7)
360 Days after birth	38 (1.1)	57 (1.6)	33.3 (-17.6, 62.9)

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.

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 16, p. 60.

#### All-Cause MA-LRTI Within 90, 120, 150, 180, and 360 Days as Reported by Investigators

As of the cutoff date, there were 186 cases of investigator-reported all-cause MA-LRTI in infants within 90 days after birth in the RSVpreF group and 200 in the placebo group in the Evaluable Efficacy population, corresponding to a VE of 7.0%, 99.17% CI (-22.3%, 29.3%), as shown in Table 16. The statistical criterion for success for this endpoint was not met for any of the time periods through 360 days after birth.

Table 16. Vaccine Efficacy of RSVpreF – MA-LRTIs Due to Any Cause With Protocol Defined Criteria, Per Investigator, Occurring Within 90, 120, 150, 180, and 360 Days After Birth - Infant Participants - Evaluable Efficacy Population (maternal vaccine group as randomized)

Efficacy Endpoint Time Interval	RSVpreF N = 3495 Number of Cases (%)	Placebo N = 3480 Number of Cases (%)	Vaccine Efficacy <sup>a</sup> % (99.17 % CI)
90 Days after birth	186 (5.3)	200 (5.7)	7.0 (-22.3, 29.3)
120 Days after birth	261 (7.5)	278 (8.0)	6.1 (-18.3, 25.5)
150 Days after birth	331 (9.5)	349 (10.0)	5.2 (-16.5, 22.8)
180 Days after birth	392 (11.2)	402 (11.6)	2.5 (-17.9, 19.4)
360 Days after birth	504 (14.4)	531 (15.3)	5.1 (-12.1, 19.6)

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.

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 17, p. 62.

#### 6.1.11.3 Subpopulation Analyses

Descriptive subgroup analyses are presented in Tables 17 and 18 for VE against severe MA-LRTIs due to RSV and MA-LRTIs due to RSV, respectively.

Table 17. Exploratory Subgroup Analyses of VE Against Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 90 and 180 Days After Birth by Subgroups - Infant Participants - Evaluable Efficacy Population (maternal vaccine group as randomized)

Time period	Characteristics	RSVpreF n	RSVpreF Cases (%)	Placebo n	Placebo Cases (%)	VE % <sup>a</sup> (95% CI)
90 Days after birth	Maternal gestational age at vaccination	-	-	-	-	-
-	≥24 to <28 weeks	890	4 (0.4)	866	11 (1.3)	64.6 (-19.4, 91.8)
-	≥28 to <32 weeks	1030	1 (<0.1)	1070	11 (1.0)	90.6 (35.0, 99.8)
-	≥32 to ≤36 weeks	1572	1 (<0.1)	1539	11 (0.7)	91.1 (38.8, 99.8)
-	>36	3	0	5	0	NC
-	Maternal Age at Vaccination	-	-	-	-	-
-	<18 Years	8	0	7	0	NC
-	≥18 Years	3487	6 (0.2)	3473	33 (1.0)	81.9 (56.2, 93.8)
-	Country <sup>b</sup>	-	-	-	-	-
-	USA	1619	1 (<0.1)	1597	10 (0.6)	90.1 (30.7, 99.8)
-	Argentina	412	2 (0.5)	406	13 (3.2)	84.8 (33.0, 98.3)
-	Canada	26	0	28	1 (3.6)	100.0 (-4100.0, 100.0)
-	Chile	83	0	83	1 (1.2)	100.0 (-3800.0, 100.0)
-	Spain	114	1 (0.9)	122	1 (0.8)	-7.0 (-8300.5, 98.6)
-	Finland	75	0	71	1 (1.4)	100.0 (-3592.0, 100.0)
-	Japan	214	0	213	3 (1.4)	100.0 (-140.9, 100.0)
-	South Africa	461	2 (0.4)	468	3 (0.6)	32.3 (-490.8, 94.3)
-	Exclusive breastfeeding	-	-	-	-	-
-	Yes	936	3 (0.3)	931	7 (0.8)	57.4 (-86.7, 92.9)
-	No	2435	3 (0.1)	2403	25 (1.0)	88.2 (61.2, 97.7)
-	Maternal smoking	-	-	-	-	-
-	Smoker	104	0	78	0	NC
-	Nonsmoker	3391	6 (0.2)	3401	33 (1.0)	81.8 (55.9, 93.8)
-	Number of household members	-	-	-	-	-
-	0	1	0	1	0	NC
-	1	54	0	73	0	NC
-	2	829	2 (0.2)	878	5 (0.6)	57.6 (-158.8, 96.0)
-	3	1076	3 (0.3)	1031	10 (1.0)	71.3 (-11.6, 94.9)
-	4	675	1 (0.1)	650	3 (0.5)	67.9 (-299.8, 99.4)
-	≥5	844	0	827	14 (1.7)	100.0 (70.5, 100.0)
180 Days after birth	Maternal gestational age at vaccination	-	-	-	-	-
-	≥24 to <28 weeks	890	11 (1.2)	866	19 (2.2)	43.7 (-24.6, 75.8)
-	≥28 to <32 weeks	1030	2 (0.2)	1070	18 (1.7)	88.5 (51.8, 98.7)
-	≥32 to ≤36 weeks	1572	6 (0.4)	1539	25 (1.6)	76.5 (41.3, 92.1)
-	>36	3	0	5	0	NC

Time period	Characteristics	RSVpreF n	RSVpreF Cases (%)	Placebo n	Placebo Cases (%)	VE % <sup>a</sup> (95% CI)
-	Maternal Age at Vaccination	-	-	-	-	-
-	<18 Years	8	0	7	0	NC
-	≥18 Years	3487	19 (0.5)	3473	62 (1.8)	69.5 (48.3, 82.8)
-	Country <sup>b</sup>	-	-	-	-	-
-	USA	1619	9 (0.6)	1597	23 (1.4)	61.4 (13.4, 84.3)
-	Argentina	412	3 (0.7)	406	16 (3.9)	81.5 (35.5, 96.5)
-	Australia	11	0	13	1 (7.7)	100.0 (-4509.1, 100.0)
-	Brazil	35	1 (2.9)	35	0	NC
-	Canada	26	0	28	1 (3.6)	100.0 (-4100.0, 100.0)
-	Chile	83	0	83	2 (2.4)	100.0 (-432.5, 100)
-	Spain	114	1 (0.9)	122	2 (1.6)	46.5 (-927.9, 99.1)
-	Finland	75	0	71	1 (1.4)	100.0 (-3592.0, 100.0)
-	Japan	214	1 (0.5)	213	4 (1.9)	75.1 (-151.5, 99.5)
-	Netherlands	96	2 (2.1)	94	2 (2.1)	2.1 (-1250.9, 92.9)
-	South Africa	461	2 (0.4)	468	10 (2.1)	79.7 (4.7, 97.8)
-	Exclusive breastfeeding	-	-	-	-	-
-	Yes	936	5 (0.5)	931	13 (1.4)	61.7 (-14.3, 89.3)
-	No	2435	14 (0.6)	2403	48 (2.0)	71.2 (46.9, 85.3)
-	Maternal smoking	-	-	-	-	-
-	Smoker	104	2 (1.9)	78	2 (2.6)	25.0 (-934.7, 94.6)
-	Nonsmoker	3391	17 (0.5)	3401	60 (1.8)	71.6 (50.6, 84.5)
-	Number of household members	-	-	-	-	-
-	0	1	0	1	0	NC
-	1	54	1 (1.9)	73	0	NC
-	2	829	2 (0.2)	878	9 (1.0)	76.5 (-13.7, 97.5)
-	3	1076	8 (0.7)	1031	20 (1.9)	61.7 (9.2, 85.4)
-	4	675	2 (0.3)	650	12 (1.8)	84.0 (27.9, 98.3)
-	≥5	844	6 (0.7)	827	20 (2.4)	70.6 (24.1, 90.3)

Abbreviations: NC = not calculated.

- a. 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.

- b. Only countries with at least 1 endpoint case are shown.

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 14.21, p. 202-209.

Table 18. Exploratory Subgroup Analyses of VE Against MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 90 and 180 Days After Birth by Subgroups - Infant Participants - Evaluable Efficacy Population (maternal vaccine group as randomized)

Time period	Characteristics	RSVpreF n	RSVpreF Cases (%)	Placebo n	Placebo Cases (%)	VE % <sup>a</sup> (95% CI)
90 Days after birth	Maternal gestational age at vaccination	-	-	-	-	-
-	≥24 to <28 weeks	890	6 (0.7)	866	13 (1.5)	55.1 (-26.6, 86.0)
-	≥28 to <32 weeks	1030	4 (0.4)	1070	22 (2.1)	81.1 (44.4, 95.3)
-	≥32 to ≤36 weeks	1572	14 (0.9)	1539	21 (1.4)	34.7 (-34.6, 69.3)
-	>36	3	0	5	0	NC
-	Maternal Age at Vaccination	-	-	-	-	-
-	<18 Years	8	0	7	0	NC
-	≥18 Years	3487	24 (0.7)	3473	56 (1.6)	57.3 (30.0, 74.7)
-	Country <sup>b</sup>	-	-	-	-	-
-	USA	1619	2 (0.1)	1597	15 (0.9)	86.8 (43.4, 98.5)
-	Argentina	412	7 (1.7)	406	20 (4.9)	65.5 (15.1, 87.7)
-	Canada	26	1 (3.8)	28	1 (3.6)	-7.7 (-8353.5, 98.6)
-	Chile	83	2 (2.4)	83	2 (2.4)	0.0 (-1279.6, 92.8)
-	Denmark	30	0	29	1 (3.4)	100.0 (-3670.0, 100.0)
-	Spain	114	1 (0.9)	122	1 (0.8)	-7.0 (-8300.5, 98.6)
-	Finland	75	0	71	1 (1.4)	100.0 (-3592.0, 100.0)
-	Gambia	78	3 (3.8)	79	2 (2.5)	-51.9 (-1718.9, 82.6)
-	Japan	214	0	213	7 (3.3)	100.0 (30.9, 100.0)
-	South Africa	461	8 (1.7)	468	6 (1.3)	-35.4 (-373.3, 58.8)
-	Exclusive breastfeeding	-	-	-	-	-
-	Yes	936	10 (1.1)	931	13 (1.4)	23.5 (-88.9, 70.0)
-	No	2435	14 (0.6)	2403	42 (1.7)	67.1 (38.6, 83.4)
-	Maternal smoking	-	-	-	-	-
-	Smoker	104	0	78	0	NC
-	Nonsmoker	3391	24 (0.7)	3401	56 (1.6)	57.0 (29.5, 74.5)
-	Number of household members	-	-	-	-	-
-	0	1	0	1	0	NC
-	1	54	0	73	0	NC
-	2	829	3 (0.4)	878	9 (1.0)	64.7 (-41.5, 93.9)
-	3	1076	9 (0.8)	1031	18 (1.7)	52.1 (-12.3, 81.0)
-	4	675	7 (1.0)	650	9 (1.4)	25.1 (-126.0, 76.3)
-	≥5	844	5 (0.6)	827	19 (2.3)	74.2 (28.6, 92.5)
180 Days after birth	Maternal gestational age at vaccination	-	-	-	-	-
-	≥24 to <28 weeks	890	22 (2.5)	866	27 (3.1)	20.7 (-44.6, 57.0)
-	≥28 to <32 weeks	1030	11 (1.1)	1070	35 (3.3)	67.4 (34.2, 85.0)

Time period	Characteristics	RSVpreF n	RSVpreF Cases (%)	Placebo n	Placebo Cases (%)	VE % <sup>a</sup> (95% CI)
-	≥32 to ≤36 weeks	1572	24 (1.5)	1539	55 (3.6)	57.3 (29.8, 74.7)
-	>36	3	0	5	0	NC
-	Maternal Age at Vaccination	-	-	-	-	-
-	<18 Years	8	0	7	0	NC
-	≥18 Years	3487	57 (1.6)	3473	117 (3.4)	51.5 (32.9, 65.3)
-	Country <sup>b</sup>	-	-	-	-	-
-	USA	1619	17 (1.1)	1597	40 (2.5)	58.1 (24.4, 77.7)
-	Argentina	412	10 (2.4)	406	28 (6.9)	64.8 (25.4, 84.7)
-	Australia	11	0	13	1 (7.7)	100.0 (-4509.1, 100.0)
-	Brazil	35	1 (2.9)	35	1 (2.9)	0.0 (-7749.7, 98.7)
-	Canada	26	1 (3.8)	28	1 (3.6)	-7.7 (-8353.5, 98.6)
-	Chile	83	3 (3.6)	83	4 (4.8)	25.0 (-343.3, 89.0)
-	Denmark	30	0	29	1 (3.4)	100.0 (-3670.0, 100.)
-	Spain	114	2 (1.8)	122	6 (4.9)	64.3 (-99.5, 96.5)
-	Finland	75	0	71	1 (1.4)	100.0 (-3592.0, 100)
-	Gambia	78	3 (3.8)	79	4 (5.1)	24.0 (-349.0, 88.9)
-	Japan	214	1 (0.5)	213	8 (3.8)	87.6 (7.2, 99.7)
-	Netherlands	96	4 (4.2)	94	3 (3.2)	-30.6 (-791.3, 77.9)
-	Philippines	32	0	34	1 (2.9)	100.0 (-4043.8, 100.0)
-	Taiwan	120	1 (0.8)	124	0	NC
-	South Africa	461	14 (3.0)	468	18 (3.8)	21.0 (-68.0, 63.7)
-	Exclusive breastfeeding	-	-	-	-	-
-	Yes	936	16 (1.7)	931	31 (3.3)	48.7 (3.2, 73.8)
-	No	2435	41 (1.7)	2403	85 (3.5)	52.4 (30.1, 68.0)
-	Maternal smoking	-	-	-	-	-
-	Smoker	104	2 (1.9)	78	4 (5.1)	62.5 (-161.7, 96.6)
-	Nonsmoker	3391	55 (1.6)	3401	113 (3.3)	51.2 (32.0, 65.3)
-	Number of household members	-	-	-	-	-
-	0	1	0	1	0	NC
-	1	54	1 (1.9)	73	0	NC
-	2	829	4 (0.5)	878	15 (1.7)	71.8 (11.3, 93.2)
-	3	1076	18 (1.7)	1031	44 (4.3)	60.8 (30.8, 78.7)
-	4	675	11 (1.6)	650	22 (3.4)	51.9 (-3.6, 78.9)
-	≥5	844	23 (2.7)	827	35 (4.2)	35.6 (-12.1, 63.7)

Abbreviations: NC = not calculated.

- 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.
- Only countries with at least 1 endpoint case are shown.

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 14.27, p. 216-223.



*Reviewer's comment: The VE analyses by subgroups are of limited value in many of the subgroups due to the small numbers of cases accrued. Therefore, these results should be considered descriptive and should be interpreted with caution.*

#### 6.1.11.4 Dropouts and/or Discontinuations

The study is ongoing. Table 7 shows the study discontinuation rates for the infants and the reasons as of the data cutoff date. The rates were balanced between the two groups, with 1.5% in the RSVpreF group and 1.7% in the placebo group withdrawn before 1 month after birth. Approximately 95.9% of the infants in the RSVpreF group and 95.6% in the placebo group had completed 1 month follow-up. Six months of follow-up were completed by approximately 79.3% in the RSVpreF group and 79.4% in the placebo group. Approximately 2.6% of the infants in the RSVpreF group and 2.3% in the placebo group were withdrawn after 1 month but before 6 months after birth. Twelve months of follow-up were completed by approximately 45.7% in the RSVpreF group and 45.5% in the placebo group.

#### 6.1.12 Safety Analyses

This section summarizes the main safety analysis results. The data cut-off date for the safety assessments was September 2, 2022. The safety analyses were descriptive in nature, and no formal hypothesis testing was planned. For a more detailed discussion of the safety analyses, please refer to Dr. Yugenia Hong-Nguyen's clinical review memo.

#### Maternal Participants

The rates of unsolicited AEs by category for maternal participants are shown in Table 19. All AEs were collected through 1 month after vaccination. Overall, 506 (13.7%, 95% CI [12.6%, 14.9%]) RSVpreF recipients and 481 (13.1%, 95% CI [12.0%, 14.2%]) placebo recipients experienced at least one AE within 1 month after vaccination. Of these, 14 (0.4%, 95% CI [0.2%, 0.6%]) RSVpreF recipients and 4 (0.1%, 95% CI [0.0%, 0.3%]) placebo recipients reported events that were assessed as related to study intervention by the investigator. Within 1 month after vaccination, there were 154 (4.2%, 95% CI [3.6%, 4.9%]) participants in the RSVpreF group and 137 (3.7%, 95% CI [3.1%, 4.4%]) in the placebo group who reported an SAE.

Table 19. Adverse Events by Category from Vaccination through 1 Month after vaccination – Maternal Participants – Safety Population.

-	RSVpreF (N=3682)	RSVpreF (N=3682)	Placebo (N=3675)	Placebo (N=3675)
Adverse Event Category	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>
Any Event	506 (13.7)	(12.6, 14.9)	481 (13.1)	(12.0, 14.2)
Serious	154 (4.2)	(3.6, 4.9)	137 (3.7)	(3.1, 4.4)
Immediate <sup>c</sup>	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)	4 (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)

a. Number of participants reporting at least 1 occurrence of the specified adverse event category.

- b. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.  
c. Immediate AE refers to an AE reported in the 30-minute post vaccination observation period.  
Source: Study C3671008, created by the reviewer based on datasets in STN125768/0.

Through 1-month after vaccination, the most frequently reported AEs in maternal participants were in the System Organ Classes (SOCs) of Pregnancy, puerperium and perinatal conditions (7.0% in the RSVpreF group versus 6.2% in the placebo group) and Infections and infestations (2.0% for both groups). By Preferred Term (PT), the most frequently reported AE was premature delivery (which was solicited as an AESI), respectively at 2.1% in the RSVpreF group and at 1.9% in the placebo group.

SAEs and AESIs were collected through 6 months after delivery. From vaccination to 6 months after delivery, SAEs were reported by 598 (16.2%) maternal subjects in the RSVpreF group and by 558 (15.2%) maternal subjects in the placebo group. The most frequently reported SAEs were in the SOC of Pregnancy, puerperium and perinatal conditions in the RSVpreF group (n=446, 12.1%) and placebo group (n=411, 11.2%). By PT, the most frequently reported SAEs were pre-eclampsia (1.8% vs 1.4%), fetal distress syndrome (1.8% vs. 1.6%), gestational hypertension (1.1% vs. 1.0%), nonreassuring fetal heart rate (1.0% vs. 0.8%), and arrested labor (1.0% vs. 1.1%). SAE of premature delivery was reported in 28 (0.8%, 95% CI [0.5%, 1.1%]) subjects in the RSVpreF group and in 23 (0.6%, 95% CI [0.4%, 0.9%]) subjects in the placebo group.

There was 1 maternal death in the RSVpreF group due to postpartum hemorrhage and hypovolemic shock, which was reported from delivery to 1 month after delivery. Intrauterine demises were reported in 11 participants (0.3%) in the RSVpreF group and in 10 participants (0.3%) in the placebo group. The applicant stated that no maternal deaths or intrauterine demises were assessed by the investigator as related to vaccination. Please refer to the review by the clinical reviewer.

#### AESI of premature delivery

The AESI of premature delivery was reported among 207 (5.6%, 95% CI [4.9%, 6.4%]) maternal participants in the RSVpreF group and among 175 (4.8%, 95% CI [4.1%, 5.5%]) maternal participants in the placebo group after vaccination. The risk difference (RD) was 0.86%, 95% CI (-0.15%, 1.88%), and the relative risk (RR) was 1.18, 95% CI (0.97, 1.44), p-value=0.10. The distribution of the premature delivery AE by country is shown in Table 20. The lower bound of the 95% CI for the RR was greater than 1 only for South Africa. The Mantel-Haenszel estimate of the common RR (adjusted for country) was RR=1.18, 95% CI (0.97, 1.43).

Table 20. Premature Delivery Events by Country – Maternal Participants – Safety Population.

Country	RSVpreF N <sup>a</sup>	RSVpreF n (%) <sup>b</sup>	RSVpreF 95% CI (%) <sup>c</sup>	Placebo N <sup>a</sup>	Placebo n (%) <sup>b</sup>	Placebo 95% CI (%)	RR <sup>d</sup>	RR 95% CI <sup>e</sup>
USA	1671	95 (5.7)	(4.6, 6.9)	1666	92 (5.5)	(4.5, 6.7)	1.03	(0.78, 1.36)
Canada	27	0 (0.0)	(0.0, 0.0)	28	1 (3.6)	(0.1, 18.3)	0.00	-
Chile	86	7 (8.1)	(3.3, 16.1)	85	6 (7.1)	(2.6, 14.7)	1.15	(0.42, 3.17)

Country	RSVpreF N <sup>a</sup>	RSVpreF n (%) <sup>b</sup>	RSVpreF 95% CI (%) <sup>c</sup>	Placebo N <sup>a</sup>	Placebo n (%) <sup>b</sup>	Placebo 95% CI (%)	RR <sup>d</sup>	RR 95% CI <sup>e</sup>
South Africa	482	42 (8.7)	(6.4, 11.6)	478	19 (4.0)	(2.4, 6.1)	2.19	(1.30, 3.70)
Spain	118	4 (3.4)	(0.9, 8.5)	124	3 (2.4)	(0.5, 6.9)	1.40	(0.36, 5.52)
Finland	75	2 (2.7)	(0.3, 9.3)	73	1 (1.4)	(0.03, 7.4)	1.95	(0.26, 14.77)
Gambia	98	3 (3.1)	(0.6, 8.7)	98	2 (2.0)	(0.2, 7.2)	1.50	(0.30, 7.42)
Denmark	31	1 (3.2)	(0.1, 16.7)	31	0 (0.0)	(0.0, 0.0)	Undef	-
Taiwan	130	6 (4.6)	(1.7, 9.8)	130	7 (5.4)	(2.2, 10.8)	0.86	(0.31, 2.38)
New Zealand	50	2 (4.0)	(0.5, 13.7)	49	3 (6.1)	(1.3, 16.9)	0.65	(0.13, 3.17)
Mexico	38	3 (7.9)	(1.7, 21.4)	37	2 (5.4)	(0.7, 18.2)	1.46	(0.30, 7.10)
Argentina	455	27 (5.9)	(3.9, 8.5)	455	18 (4.0)	(2.4, 6.2)	1.50	(0.85, 2.67)
Australia	11	0 (0.0)	(0.0, 0.0)	13	1 (7.7)	(0.2, 36.0)	0.00	-
Netherlands	97	3 (3.1)	(0.6, 8.8)	95	3 (3.2)	(0.7, 9.0)	0.98	(0.23, 4.17)
Brazil	36	4 (11.1)	(3.1, 26.1)	37	1 (2.7)	(0.1, 14.2)	4.11	(0.65, 27.01)
Korea	7	0 (0.0)	(0.0, 0.0)	5	1 (20.0)	(0.5, 71.6)	0.00	-
Japan	230	7 (3.0)	(1.2, 6.2)	232	13 (5.6)	(3.0, 9.4)	0.54	(0.23, 1.30)
Philippines	40	1 (2.5)	(0.1, 13.2)	39	2 (5.1)	(0.6, 17.3)	0.49	(0.06, 3.63)

- Number (%) of maternal participants in the vaccine group. This number is the denominator for the percentage calculations.
- Number (%) of maternal participants reporting the AE of premature delivery as of the data cutoff date.
- Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
- Relative Risk (RSVpreF vaccine/Placebo).
- CI calculated using the Score method.

Source: Study C3671008, created by the reviewer based on datasets in STN125768/0.

The frequencies of deliveries by gestational age at vaccination for each arm for the maternal participants are given in Table 21. Most of the preterm deliveries occurred between 34 and <37 weeks gestation. Among those who were vaccinated between 24 and <32 weeks gestation, there were 9 (0.4%) in the RSVpreF arm and 9 (0.4%) in the placebo arm with a premature delivery between 27 weeks and prior to 32 weeks gestation. Among those who were vaccinated between 24 and <32 weeks gestation, there were 13 (0.6%) subjects in the RSVpreF arm and 4 (0.2%) in the placebo arm with a premature delivery between 32 weeks and prior to 34 weeks gestation. Among those who were vaccinated between 32 and <37 weeks gestation, there were 2 (0.1%) in the RSVpreF arm and 2 (0.1%) in the placebo arm with a premature delivery between 32 weeks and prior to 34 weeks gestation.

Table 21. Frequencies of Deliveries by Gestational Age at Vaccination – Maternal Participants – Safety Population.

Gestational Age at Vaccination	Gestational Age at Delivery	RSVpreF N <sup>a</sup>	RSVpreF n (%) <sup>b</sup>	RSVpreF 95% CI (%) <sup>c</sup>	Placebo N <sup>a</sup>	Placebo n (%) <sup>b</sup>	Placebo 95% CI (%) <sup>c</sup>
24 to <32 weeks	27 to <32	2026	9 (0.4)	(0.2, 0.8)	2037	9 (0.4)	(0.2, 0.8)
-	32 to <34	2026	13 (0.6)	(0.3, 1.1)	2037	4 (0.2)	(0.1, 0.5)
-	34 to <37	2026	116 (5.7)	(4.8, 6.8)	2037	102 (5.0)	(4.1, 6.0)
-	≥37	2026	1801 (88.9)	(87.4, 90.2)	2037	1836 (90.1)	(88.8, 91.4)
32 to <37 weeks	32 to <34	1656	2 (0.1)	(0.0, 0.4)	1638	2 (0.1)	(0.0, 0.4)
-	34 to <37	1656	67 (4.0)	(3.1, 5.1)	1638	58 (3.5)	(2.7, 4.6)
-	≥37	1656	1563 (94.4)	(93.2, 95.4)	1638	1550 (94.6)	(93.4, 95.7)

- a. Number (%) of maternal participants in the vaccine group. This number is the denominator for the percentage calculations.  
b. Number (%) of maternal participants with a reported delivery date as of the data cutoff date.  
c. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.

Source: Study C3671008, created by the reviewer based on datasets in STN125768/0.

*Reviewer's comment: The conducted safety analyses were descriptive in nature and the study was not powered for formal hypothesis testing between the study arms with regard to safety. The risk difference (RD) between the arms in premature delivery AEs was 0.86%, 95% CI (-0.15%, 1.88%). While the lower bound of the 95% CI was <0, I defer to the clinical reviewer whether the observed numerical imbalance in premature deliveries between the study arms is of clinical concern.*

#### Solicited Reactogenicity Events

Solicited local (pain at the injection site, redness, and swelling) and systemic (fever, nausea, diarrhea, vomiting, headache, fatigue, muscle pain, and joint pain) reactions were collected for 7 days after vaccination from maternal participants. Tables 22 and 23 show the rates of reported solicited adverse reactions by maximum severity. Local reactions were reported by 42.5% of the participants in the RSVpreF group and by 10.4% of the participants in the placebo group, with pain at the injection site being the most commonly reported reaction (40.6% versus 10.1%, respectively). At least one systemic event was reported by 63.9% of the participants in the RSVpreF group and by 59.3% of the participants in the placebo group. The most commonly reported systemic events after the RSVpreF vaccination were fatigue (46.1%) and headache (31.0%).

Table 22. Solicited Local Reactions by Maximum Severity within 7 Days after Vaccination – Maternal Participants – Safety Population

Local Reactions	RSVpreF N <sup>a</sup>	RSVpreF n <sup>b</sup> (%)	RSVpreF (95% CI) <sup>c</sup>	Placebo N <sup>a</sup>	Placebo n <sup>b</sup> (%)	Placebo (95% CI) <sup>c</sup>
Redness <sup>d</sup>	-	-	-	-	-	-
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 <sup>d</sup>	-	-	-	-	-	-
Any	3663	227 (6.2)	(5.4, 7.0)	3639	8 (0.2)	(0.1, 0.4)

Local Reactions	RSVpreF N <sup>a</sup>	RSVpreF n <sup>b</sup> (%)	RSVpreF (95% CI <sup>c</sup> )	Placebo N <sup>a</sup>	Placebo n <sup>b</sup> (%)	Placebo (95% CI <sup>c</sup> )
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 <sup>e</sup>	-	-	-	-	-	-
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 <sup>f</sup>	-	-	-	-	-	-
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. Number of participants reporting "yes" or "no" for the specified reaction for at least 1 day.

b. 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), based on 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, redness, or swelling.

Source: C3671008 Supplemental Clinical Study Report, Table 14.2, p. 22.

Table 23. Solicited Systemic Reactions by Maximum Severity within 7 Days after Vaccination – Maternal Participants - Safety Population

Systemic Reactions	RSVpreF N <sup>a</sup>	RSVpreF n <sup>b</sup> (%)	RSVpreF (95% CI <sup>c</sup> )	Placebo N <sup>a</sup>	Placebo n <sup>b</sup> (%)	Placebo (95% CI <sup>c</sup> )
Fever	-	-	-	-	-	-
≥38.0°C	3663	94 (2.6)	(2.1, 3.1)	3638	107 (2.9)	(2.4, 3.5)
38.0°C to 38.4°C	3663	61 (1.7)	(1.3, 2.1)	3638	55 (1.5)	(1.1, 2.0)
38.5°C to 38.9°C	3663	29 (0.8)	(0.5, 1.1)	3638	42 (1.2)	(0.8, 1.6)
39.0°C to 40.0°C	3663	1 (<0.1)	(0.0, 0.2)	3638	5 (0.1)	(0.0, 0.3)
>40.0°C	3663	3 (<0.1)	(0.0, 0.2)	3638	5 (0.1)	(0.0, 0.3)
Fatigue <sup>d</sup>	-	-	-	-	-	-
Any	3663	1688 (46.1)	(44.5, 47.7)	3640	1595 (43.8)	(42.2, 45.4)
Mild	3663	856 (23.4)	(22.0, 24.8)	3640	828 (22.7)	(21.4, 24.1)
Moderate	3663	782 (21.3)	(20.0, 22.7)	3640	715 (19.6)	(18.4, 21.0)
Severe	3663	50 (1.4)	(1.0, 1.8)	3640	52 (1.4)	(1.1, 1.9)
Headache <sup>d</sup>	-	-	-	-	-	-
Any	3663	1134 (31.0)	(29.5, 32.5)	3639	1004 (27.6)	(26.1, 29.1)
Mild	3663	739 (20.2)	(18.9, 21.5)	3639	651 (17.9)	(16.7, 19.2)
Moderate	3663	380 (10.4)	(9.4, 11.4)	3639	340 (9.3)	(8.4, 10.3)
Severe	3663	15 (0.4)	(0.2, 0.7)	3639	13 (0.4)	(0.2, 0.6)
Nausea <sup>d</sup>	-	-	-	-	-	-
Any	3663	732 (20.0)	(18.7, 21.3)	3640	701 (19.3)	(18.0, 20.6)
Mild	3663	527 (14.4)	(13.3, 15.6)	3640	501 (13.8)	(12.7, 14.9)
Moderate	3663	197 (5.4)	(4.7, 6.2)	3640	192 (5.3)	(4.6, 6.1)
Severe	3663	8 (0.2)	(0.1, 0.4)	3640	8 (0.2)	(0.1, 0.4)
Muscle pain <sup>d</sup>	-	-	-	-	-	-
Any	3663	972 (26.5)	(25.1, 28.0)	3639	623 (17.1)	(15.9, 18.4)
Mild	3663	643 (17.6)	(16.3, 18.8)	3639	363 (10.0)	(9.0, 11.0)

Systemic Reactions	RSVpreF N <sup>a</sup>	RSVpreF n <sup>b</sup> (%)	RSVpreF (95% CI) <sup>c</sup>	Placebo N <sup>a</sup>	Placebo n <sup>b</sup> (%)	Placebo (95% CI) <sup>c</sup>
Moderate	3663	315 (8.6)	(7.7, 9.6)	3639	248 (6.8)	(6.0, 7.7)
Severe	3663	14 (0.4)	(0.2, 0.6)	3639	12 (0.3)	(0.2, 0.6)
Joint pain <sup>d</sup>	-	-	-	-	-	-
Any	3663	424 (11.6)	(10.6, 12.7)	3639	382 (10.5)	(9.5, 11.5)
Mild	3663	238 (6.5)	(5.7, 7.3)	3639	218 (6.0)	(5.2, 6.8)
Moderate	3663	180 (4.9)	(4.2, 5.7)	3639	161 (4.4)	(3.8, 5.1)
Severe	3663	6 (0.2)	(0.1, 0.4)	3639	3 (<0.1)	(0.0, 0.2)
Vomiting <sup>e</sup>	-	-	-	-	-	-
Any	3663	287 (7.8)	(7.0, 8.8)	3639	254 (7.0)	(6.2, 7.9)
Mild	3663	233 (6.4)	(5.6, 7.2)	3639	196 (5.4)	(4.7, 6.2)
Moderate	3663	46 (1.3)	(0.9, 1.7)	3639	56 (1.5)	(1.2, 2.0)
Severe	3663	8 (0.2)	(0.1, 0.4)	3639	2 (<0.1)	(0.0, 0.2)
Diarrhea <sup>f</sup>	-	-	-	-	-	-
Any	3663	412 (11.2)	(10.2, 12.3)	3639	417 (11.5)	(10.4, 12.5)
Mild	3663	335 (9.1)	(8.2, 10.1)	3639	343 (9.4)	(8.5, 10.4)
Moderate	3663	73 (2.0)	(1.6, 2.5)	3639	67 (1.8)	(1.4, 2.3)
Severe	3663	4 (0.1)	(0.0, 0.3)	3639	7 (0.2)	(0.1, 0.4)
Any systemic event <sup>g</sup>	-	-	-	-	-	-
Any	3663	2340 (63.9)	(62.3, 65.4)	3640	2157 (59.3)	(24.3, 27.2)
Mild	3663	1359 (37.4)	(31.1, 34.1)	3640	1087 (29.9)	(14.0, 16.4)
Moderate	3663	866 (23.8)	(27.6, 30.5)	3640	987 (27.1)	(9.0, 11.0)
Severe	3663	83 (2.3)	(1.8, 2.8)	3640	83 (2.3)	(1.8, 2.8)

a. Number of subjects reporting "yes" or "no" for at least 1 day.

b. Number of subjects reporting maximum severity of mild, moderate, or severe based on the severity scales.

c. Exact 2-sided confidence interval (CI), based on 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.

Source: C3671008 Supplemental Clinical Study Report, Table 14.6, p. 26-28.

### **Infant Participants**

The rates of unsolicited AEs by category for infant participants are shown in Table 24. All AEs were collected through 1 month after birth. Overall, 1324 (37.1%, 95% CI [35.5%, 38.7%]) infants in the RSVpreF group and 1229 (34.5%, 95% CI [33.0%, 36.1%]) placebo recipients experienced at least one AE within 1 month after birth. Of these, 1 (<0.1%) infant in the RSVpreF group had an event that was assessed as related to study intervention by the investigator. Congenital Anomalies within 1 month after birth were reported for 172 (4.8%, 95% CI [4.1%, 5.6%]) infants in the RSVpreF group and for 210 (5.9%, 95% CI [5.2%, 6.7%]) infants in the placebo group. Within 1 month after birth, there were 553 (15.5%, 95% CI [14.3%, 16.7%]) infant participants in the RSVpreF group and 541 (15.2%, 95% CI [14.0%, 16.4%]) in the placebo group who experienced an SAE.

Table 24. Adverse Events by Category from Birth through 1 Month after Birth – Infant Participants – Safety Population (maternal vaccine group as administered).

-	RSVpreF (N=3568)	RSVpreF (N=3568)	Placebo (N=3558)	Placebo (N=3558)
Adverse Event Category	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>
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)
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)

a. Number of participants reporting at least 1 occurrence of the specified adverse event category.

b. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.

Source: C3671008 Clinical Study Report, dated December 6, 2022, Table 19, p. 71.

As of the data cutoff date, any AEs were reported for 1473 (41.3%, 95% CI [39.7%, 42.9%]) infants in the RSVpreF group and for 1403 (39.4%, 95% CI [37.8%, 41.1%]) infants in the placebo group. The most frequently reported AEs were in the SOC of Pregnancy, puerperium and perinatal conditions: respectively in n=600 (16.8%, 95% CI [15.6%, 18.1%]) and in n=556 (15.6%, 95% CI [14.4%, 16.9%]); Congenital, familial and genetic disorders: respectively in n=248 (8.0%, 95% CI [7.1%, 8.9%]) and in n=294 (8.3%, 95% CI [7.4%, 9.2%]); Respiratory, thoracic and mediastinal disorders: respectively in n=273 (7.7%, 95% CI [6.8%, 8.6%]) and in n=259 (7.3%, 95% CI [6.4%, 8.2%]). By PT, the most frequently reported AE was jaundice neonatal – in 257 (7.2%, 95% CI [6.4%, 8.1%]) infants in the RSVpreF group and in 241 (6.8%, 95% CI [6.0%, 7.6%]) infants in the placebo group.

For infants, AESIs included low birth weight baby and premature baby. Low birth weight baby was reported for 181 (5.1%, 95% CI [4.4%, 5.8%]) infants in the RSVpreF group and for 154 (4.3%, 95% CI [3.7%, 5.0%]) infants in the placebo group, with RD=0.72%, 95% CI (-0.27%, 1.71%). Premature baby event for the infants corresponded to those premature maternal deliveries that resulted in live births. Respectively, premature baby AE was reported for 202 (5.7%, 9.5% CI [4.9%, 6.5%]) infants in the RSVpreF group and for 169 (4.7%, 95% CI [4.1%, 5.5%]) infants in the placebo group, with RD=0.91%, 95% CI (-0.12%, 1.95%). Of note, among the 202 premature babies in the RSVpreF group were a set of twins. As of the data cutoff date, the AESI of developmental delay was reported for 2 infant participants (<0.1%) each in the RSVpreF and placebo groups. AESIs under the SOC of Nervous system disorders were reported for 10 (0.3%, 95% CI [0.1%, 0.5%]) infants in the RSVpreF group and for 8 (0.2%, 95% CI [0.1%, 0.4%]) infants in the placebo group.

*Reviewer's comment: The premature baby AEs for the infants corresponded to those premature maternal deliveries that resulted in live births.*

As of the data cutoff date, SAEs were reported for 625 (17.5%, 95% CI [16.3%, 18.8%]) infants in the RSVpreF group and for 623 (17.5%, 95% CI [16.3%, 18.8%]) infants in the placebo group. None of the SAEs in infant participants were considered related to maternal vaccination by the investigator. The most frequently reported events were in the SOC of Respiratory, thoracic and mediastinal disorders, Pregnancy, puerperium and perinatal conditions, and Infections and infestations, respectively at 4.6% vs 4.2%, 3.9% vs 3.5%, and 3.0% vs 2.5% (RSVpreF group vs. placebo group). The most frequently reported SAEs by PT in the RSVpreF group ( $\geq 1.0\%$ ) were jaundice neonatal (2.1% vs 1.9%), hyperbilirubinemia neonatal (1.4% vs 1.1%), premature baby (1.4% vs 1.2%), and respiratory distress (1.3% vs 1.2%; RSVpreF group vs. placebo group). Congenital anomalies reported as SAEs were reported for 5.0% of the infants in the RSVpreF group and for 6.2% of the infants in the placebo group.

As of the data cutoff date, there were 5 (0.1%) infant deaths reported among participants in the RSVpreF group and 12 (0.3%) among participants in the placebo group.

*Reviewer's comment: Please refer to the review by the clinical reviewer for details on the reported safety events and for conclusions on the clinical significance of these events.*

## 7. INTEGRATED OVERVIEW OF EFFICACY

There was no integrated analysis of efficacy in this application.

## 8. INTEGRATED OVERVIEW OF SAFETY

The applicant provided integrated summary of safety. Here we provide an overview of the safety assessments of the final formulation of RSVpreF (120 µg) in maternal participants and their infants. Data from maternal participants and their infants are available from the pivotal study C3671008 and from the phase 2 study C3671003.

### 8.1 Safety Assessment Methods

The safety assessment methods are discussed in section 6.1.9.

### 8.2 Safety Database

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The available database of maternal participants who received the final formulation of RSVpreF and their infants and the respective placebo recipients in the included studies is shown in Table 25.

Table 25. Safety Database – Studies in Maternal Participants and their Infants - Safety Population.

Participants Category	Studies	RSVpreF 120 µg n (%) <sup>a</sup>	Placebo n (%) <sup>a</sup>
Maternal Participants:	Total	3797	3792
-	Study C3671008	3682 (97.0)	3675 (96.9)
-	Study C3671003	115 (3.0)	117 (3.1)



Participants Category	Studies	RSVpreF 120 µg n (%) <sup>a</sup>	Placebo n (%) <sup>a</sup>
Infant Participants:	Total	3682	3674
-	Study C3671008	3568 (97.0)	3558 (96.9)
-	Study C3671003	114 (3.0)	116 (3.1)

Source: Created by the reviewer based on the data submitted to STN125768/0.

## 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

As Study C3671003 contributes only 3% to the safety database of the final formulation of RSVpreF in maternal participants and their infants, the demographic characteristics of the pooled dataset are similar to those from Study C3671008. Please refer to section 6.1.10.1.1, Tables 10 and 11.

## 8.4 Safety Results

### Maternal Participants

The rates of unsolicited AEs by category after vaccination throughout the studies for maternal participants are shown in Table 26. Overall, 1111 (29.3%, 95% CI [27.8%, 30.7%]) RSVpreF recipients and 1056 (27.8%, 95% CI [26.4%, 29.3%]) placebo recipients experienced at least one AE after vaccination. Of these, 17 (0.4%, 95% CI [0.3%, 0.7%]) RSVpreF recipients and 6 (0.2%, 95% CI [0.1%, 0.3%]) placebo recipients reported events that were assessed as related to study intervention by the investigator. Throughout the studies, there were 605 (15.9%, 95% CI [14.8%, 17.1%]) participants in the RSVpreF group and 572 (15.1%, 95% CI [14.0%, 16.3%]) in the placebo group who reported an SAE.

Table 26. Adverse Events by Category throughout Study after Vaccination – all Maternal Participants – Safety Population.

	RSVpreF (N=3797)	RSVpreF (N=3797)	Placebo (N=3792)	Placebo (N=3792)
Adverse Event Category	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>
Any Event	1111 (29.3)	(27.8, 30.7)	1056 (27.8)	(26.4, 29.3)
Serious	605 (15.9)	(14.8, 17.1)	572 (15.1)	(14.0, 16.3)
Severe	207 (5.5)	(4.8, 6.2)	207 (5.5)	(4.8, 6.2)
Life-threatening	63 (1.7)	(1.3, 2.1)	43 (1.1)	(0.8, 1.5)
Related	17 (0.4)	(0.3, 0.7)	6 (0.2)	(0.1, 0.3)
AE leading to withdrawal	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.1)
Death	1 (<0.1)	(0.0, 0.1)	0	(0.0, 0.1)

a. Number of participants reporting at least 1 occurrence of the specified adverse event category.

b. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.

Source: Adapted from the Integrated Summary of Safety submitted to STN125768/0, Table 1, p. 6.

Through 1-month after vaccination, the most frequently reported AEs in maternal participants were in the SOCs of Pregnancy, puerperium and perinatal conditions (6.8% in the RSVpreF group versus 6.2% in the placebo group) and Infections and infestations (2.1% for the RSVpreF group and 2.2% for the placebo group). By Preferred Term (PT), the most frequently reported AE was premature delivery, respectively at 2.1% in the RSVpreF group and at 1.9% in the placebo group.

SAEs and AESIs were collected through 6 months after delivery. After vaccination to 6 months after delivery, SAEs were reported by 605 (15.9%) maternal subjects in the RSVpreF group and by 572 (15.1%) maternal subjects in the placebo group. The most frequently reported SAEs were in the SOC of Pregnancy, puerperium and perinatal conditions in the RSVpreF group (n=450, 11.9%) and placebo group (421, 11.1%). By PT, the most frequently reported SAEs were pre-eclampsia (1.8% vs 1.5%), fetal distress syndrome (1.7% vs. 1.6%), gestational hypertension (1.1% vs. 1.0%), nonreassuring fetal heart rate (1.0% vs. 0.8%), and arrested labor (1.0% vs. 1.2%). SAE of premature delivery was reported in 28 (0.7%, 95% CI [0.5%, 1.1%]) subjects in the RSVpreF group and in 24 (0.6%, 95% CI [0.4%, 0.9%]) subjects in the placebo group.

### Infant Participants

The rates of unsolicited AEs by category after birth for infant participants are shown in Table 27. Overall, 1557 (42.3%, 95% CI [40.7%, 43.9%]) infants in the RSVpreF group and 1495 (40.7%, 95% CI [39.1, 42.3%]) infants in the placebo group experienced at least one AE after birth. Of these, 1 (<0.1%) infant in the RSVpreF had an event reported that was assessed as related to study intervention by the investigator. A total of 666 (18.1%, 95% CI [16.9%, 19.4%]) infants in the RSVpreF group and 661 (18.0%, 95% CI [16.8%, 19.3%]) in the placebo group had events reported as SAEs.

Table 27. Adverse Events by Category Reported after Birth – Infant Participants – Safety Population.

-	RSVpreF (N=3682)	RSVpreF (N=3682)	Placebo (N=3674)	Placebo (N=3674)
Adverse Event Category	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>	n (%) <sup>a</sup>	(95% CI) <sup>b</sup>
Any Event	1557 (42.3)	(40.7, 43.9)	1495 (40.7)	(39.1, 42.3)
Serious	666 (18.1)	(16.9, 19.4)	661 (18.0)	(16.8, 19.3)
Congenital anomaly	213 (5.8)	(5.1, 6.6)	244 (6.6)	(5.9, 7.5)
Severe	193 (5.2)	(4.5, 6.0)	169 (4.6)	(3.9, 5.3)
Life-threatening	41 (1.1)	(0.8, 1.5)	48 (1.3)	(1.0, 1.7)
Related	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
AE leading to withdrawal	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Developmental delay	12 (0.3)	(0.2, 0.6)	10 (0.3)	(0.1, 0.5)
Death	5 (0.1)	(0.0, 0.3)	12 (0.3)	(0.2, 0.6)

a. Number of participants reporting at least 1 occurrence of the specified adverse event category.

b. Exact 2-sided confidence interval (CI), based on the Clopper and Pearson method.

Source: Adapted from the Integrated Summary of Safety submitted to STN125768/0, Table 2, p. 7.

For the infants, through 1-month after birth, any AEs were reported for 1382 (37.5%, 95% CI [36.0%, 39.1%]) infants in the RSVpreF group and for 1288 (35.1%, 95% CI [33.5%, 36.6%]) infants in the placebo group. The most frequently reported AEs were in the SOCs of Pregnancy, puerperium and perinatal conditions: respectively in n=609 (16.5%, 95% CI [15.4%, 17.8%]) and in n=564 (15.4%, 95% CI [14.2%, 16.6%]); Congenital, familial and genetic disorders: respectively in n=300 (8.1%, 95% CI [7.3%, 9.1%]) and in n=302 (8.2%, 95% CI [7.4%, 9.2%]); Respiratory, thoracic and mediastinal disorders: respectively in n=273 (7.7%, 95% CI [6.8%, 8.6%]) and in n=259 (7.3%, 95% CI [6.4%, 8.2%]). By PT, the most frequently reported AE was jaundice neonatal – in

259 (7.0%, 95% CI [6.2%, 7.9%]) infants in the RSVpreF group and in 242 (6.6%, 95% CI [5.8%, 7.4%]) infants in the placebo group.

For infants, the most frequently reported SAEs were in the SOC of Congenital, familial and genetic disorders (4.9% vs. 5.7%), Respiratory, thoracic and mediastinal disorders (4.6% vs 4.2%), Pregnancy, puerperium and perinatal conditions (3.9% vs 3.5%), and Infections and infestations (3.0% vs 2.5%), in the RSVpreF group vs. placebo group. The most frequently reported SAEs by PT in the RSVpreF group ( $\geq 1.0\%$ ) were jaundice neonatal (2.1% vs 1.8%), hyperbilirubinemia neonatal (1.3% vs 1.1%), premature baby (1.4% vs 1.2%), and respiratory distress (1.3% vs 1.2%; RSVpreF group vs. placebo group).

Premature baby AE was reported for 208 (5.6%, 95% CI [4.9%, 6.4]) infants in the RSVpreF group and for 172 (4.7%, 95% CI [4.0%, 5.4%]) infants in the placebo group.

## 8.6 Safety Conclusions

The integrated analysis of safety was descriptive in nature and showed similar patterns as observed in the pivotal study C3671008. There was a numerical imbalance in reported premature births between the RSVpreF group and the placebo group. Please refer to the clinical review memo for details of the safety results and on the clinical significance of these.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

Results of the ongoing pivotal phase 3 study C3671008, entitled “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,” are summarized as follows:

- A total of 7392 participants were randomized to receive RSVpreF (n=3695) or placebo (n=3697). Of these, 3682 maternal participants received RSVpreF and 3675 maternal participants received placebo. As of the data cut-off date, there were 3568 infants born to maternal participants who received RSVpreF and 3558 infants born to maternal participants who received placebo.
- The study was designed as an event driven study with a final analysis target of 124 adjudicated (primary-endpoint) cases of MA-LRTI due to RSV at 90 days. The applicant conducted 2 interim analyses. The second and final interim analysis was conducted in October 2022 when there were a total of 80 evaluable cases of MA-LRTI due to RSV within 90 days from birth confirmed by EAC (24 in the RSVpreF group and 56 in the placebo group) and 39 cases of severe MA-LRTI due to RSV within 90 days from birth confirmed by EAC (6 in the RSVpreF group and 33 in the placebo group).

- VE for severe MA-LRTI due to RSV within 90 days from birth confirmed by EAC was 81.8%, 99.5% CI (40.6%, 96.3%), and within 180 days, VE was 69.4%, 97.58% CI (44.3%, 84.1%). As the lower bound of the adjusted CI was >20%, the statistical criterion for this endpoint was met for all time periods through 180 days after birth.
- VE for MA-LRTI due to RSV within 90 days from birth confirmed by EAC was 57.1%, 99.5% CI (14.7%, 79.8%), and within 180 days VE was 51.3%, 97.58% CI (29.4%, 66.8%). As the lower bound of the O'Brien-Fleming type I error-adjusted 99.5% CI for VE for the 90-day period was <20%, based on the prespecified fixed sequence testing rule, formal hypothesis testing for VE in the subsequent time intervals stops, and the respective results for this endpoint are considered descriptive. For the subsequent time intervals (120 to 180 days after birth), 97.58% CIs were used, and the respective lower bounds were >20%. For the MA-LRTIs due to RSV within 90 days, the 97.58% CI for VE would be (24.8%, 76.5%). Taking this into consideration and that the lower bounds of the CIs were >20% for VE for the time periods of 120 to 180 days after birth, the data suggest that the RSVpre F vaccine is efficacious within 180 days after birth for the prevention of MA-LRTI due to RSV.
- For the maternal participants, 506 (13.7%, 95% CI [12.6%, 14.9%]) RSVpreF recipients and 481 (13.1%, 95% CI [12.0%, 14.2%]) placebo recipients experienced at least one AE within 1 month after vaccination. Of these, there were 154 (4.2%, 95% CI [3.6%, 4.9%]) participants in the RSVpreF group and 137 (3.7%, 95% CI [3.1%, 4.4%]) in the placebo group who reported an SAE. From vaccination through 6 months after delivery, SAEs were reported by 598 (16.2%) maternal subjects in the RSVpreF group and by 558 (15.2%) maternal subjects in the placebo group. By PT, the most frequently reported SAEs were pre-eclampsia (1.8% vs 1.4%), fetal distress syndrome (1.8% vs. 1.6%), gestational hypertension (1.1% vs. 1.0%), nonreassuring fetal heart rate (1.0% vs. 0.8%), and arrested labor (1.0% vs. 1.1%). SAE of premature delivery was reported in 28 (0.8%, 95% CI [0.5%, 1.1%]) subjects in the RSVpreF group and in 23 (0.6%, 95% CI [0.4%, 0.9%]) subjects in the placebo group.
- The AESI of premature delivery was reported among 207 (5.6%, 95% CI [4.9%, 6.4%]) maternal participants in the RSVpreF group and among 175 (4.8%, 95% CI [4.1%, 5.5%]) maternal participants in the placebo group after vaccination. The risk difference (RD) was 0.86%, 95% CI (-0.15%, 1.88%). The conducted safety analyses were descriptive in nature, and the study was not powered for formal hypothesis testing between the study arms with regard to safety. While the lower bound of the 95% CI for RD was <0, I defer to the clinical reviewer whether the observed numerical imbalance in premature deliveries between the study arms is of clinical concern and whether a restriction on the indication with regard to the vaccination window should be recommended. Most of the preterm deliveries occurred between 34 and <37 weeks gestation. Among those who were vaccinated between 24 and <32 weeks gestation, there were 9 (0.4%) in the

- RSVpreF arm and 9 (0.4%) in the placebo arm with a premature delivery between 27 weeks and prior to 32 weeks gestation, and there were 13 (0.6%) subjects in the RSVpreF arm and 4 (0.2%) in the placebo arm with a premature delivery between 32 weeks and prior to 34 weeks gestation. Among those who were vaccinated between 32 and <37 weeks gestation, there were 2 (0.1%) in the RSVpreF arm and 2 (0.1%) in the placebo arm with a premature delivery between 32 weeks and prior to 34 weeks gestation.
- For maternal participants, local reactions were reported by 42.5% of participants in the RSVpreF group and by 10.4% of participants in the placebo group, with pain at the injection site being the most commonly reported reaction (40.6% versus 10.1%, respectively). At least one systemic event was reported by 63.9% of participants in the RSVpreF group and by 59.3% of participants in the placebo group. The most commonly reported systemic events after the RSVpreF vaccination were fatigue (46.1%) and headache (31.0%). Please refer to the review by the clinical reviewer (Dr. Yugenia Hong-Nguyen) for details on the safety analyses.
  - For infant participants, within 1 month after birth, 1324 (37.1%, 95% CI [35.5%, 38.7%]) in the RSVpreF group and 1229 (34.5%, 95% CI [33.0%, 36.1%]) in the placebo group experienced at least one AE. Of these, there were 553 (15.5%, 95% CI [14.3%, 16.7%]) infant participants in the RSVpreF group and 541 (15.2%, 95% CI [14.0%, 16.4%]) in the placebo group who experienced an SAE. From birth through the data cutoff date, SAEs were reported for 625 (17.5%, 95% CI [16.3%, 18.8%]) infants in the RSVpreF group and for 623 (17.5%, 95% CI [16.3%, 18.8%]) infants in the placebo group. None of the SAEs in infant participants were considered related to maternal vaccination by the investigator. By PT, the most frequently reported SAEs were jaundice neonatal (2.1% vs 1.9%), hyperbilirubinemia neonatal (1.4% vs 1.1%), premature baby (1.4% vs 1.2%), and respiratory distress (1.3% vs 1.2%; RSVpreF group vs. placebo group). Congenital anomalies reported as SAEs were reported for 5.0% of the infants in the RSVpreF group and for 6.2% of the infants in the placebo group. For infants, AESIs included low birth weight baby and premature baby. Low birth weight baby was reported for 181 (5.1%, 95% CI [4.4%, 5.8%]) infants in the RSVpreF group and for 154 (4.3%, 95% CI [3.7%, 5.0%]) infants in the placebo group, with RD=0.72%, 95% CI (-0.27%, 1.71%). Premature baby events for the infants corresponded to those premature maternal deliveries that resulted in live births. Respectively, premature baby AE was reported for 202 (5.7%, 9.5% CI [4.9%, 6.5%]) infants in the RSVpreF group and for 169 (4.7%, 95% CI [4.1%, 5.5%]) infants in the placebo group, with RD=0.91%, 95% CI (-0.12%, 1.95%).
  - The statistical methods used by the applicant were appropriate and corresponded to those prespecified in the study protocol and in the SAP. The results were verified based on data submitted in the SDTM format.

## 10.2 Conclusions and Recommendations

In conclusion, the primary efficacy objective of the study was met and the safety profile of the RSVpreF vaccine as of the data cutoff date for both maternal and infant participants was described. There was a numerical imbalance in premature deliveries (and respectively premature births) between the study arms. The conducted safety analyses were descriptive in nature and the study was not powered for formal hypothesis testing between the study arms with regard to safety. I defer to the clinical reviewer whether the observed numerical imbalance in premature deliveries between the study arms is of clinical significance and whether a restriction on the indication with regard to the vaccination window should be recommended. The study demonstrated that the RSVpreF vaccine is efficacious in preventing severe MA-LRTI due to RSV and MA-LRTI due to RSV through 180 days from birth in the infants born to vaccinated pregnant individuals.