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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Abrysvo

Respiratory syncytial virus vaccine (bivalent, recombinant)

Procedure no: EMEA/H/C/006027/P46/005

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	Start of procedure	27 May 2024	27 May 2024
☐	CHMP Rapporteur Assessment Report	1 July 2024	1 July 2024
☐	CHMP members comments	15 July 2024	15 July 2024
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	18 July 2024
☒	CHMP adoption of conclusions:	25 July 2024	25 July 2024

Table of contents

1. Introduction

On 30 April 2024, the MAH submitted a completed paediatric study C3671008, including the final analysis for Abrysvo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development programme

The MAH stated that C3671008, a Phase 3, randomised, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of RSVpreF vaccine in infants born to women vaccinated during pregnancy, is a standalone study. This was the single pivotal Phase 3 study to support the current indication for use of Abrysvo during pregnancy to protect infants of vaccinated mothers from RSV LRTI in the first 6 months of life.

In the initial MAA, the MAH provided the results in a CSR of 6 December 2022.

- In accordance with the protocol and SAP, the first interim efficacy analysis was conducted in April 2022, at which time 56 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth had accrued. The E-DMC reviewed the results and recommended continuation of the study.

- The second interim efficacy analysis was conducted on 28 October 2022 following the predicted end of the fourth RSV season (efficacy data cut-off: 30 September 2022; safety data cut-off: 02 September 2022). The analysis included 80 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth, of which 39 were severe MA-LRTI. The E-DMC recommended stopping the study because the success criterion for VE was met for one of the two primary efficacy endpoints.

- The initial application dossier reported all cases of RSV LRTI that had been documented up to the data cut-off date, thus providing information on cases that had occurred up to and beyond 180 days after birth as well as cases accrued with onset at up to 730 days after birth. These preliminary data suggested that the benefit of vaccination declined after day 180 post-natal.

- To provide more data about the safety profile of the vaccine, the MAH updated the safety data available from the study during the initial assessment procedure.

The MAH now provides the final CSR, dated 24 April 2024. This reports all data up to LPLV, which occurred on 27 October 2023.

2.2. Information on the pharmaceutical formulation used in the study

Prior to C3671008, the MAH conducted a dose-finding study in pregnant women using RSVpreF 120 and 240 µg per dose, with and without aluminium hydroxide (C3671003). This study included a descriptive analysis of infant RSV cases.

The results led to use of the final formulation with 120 µg per dose without aluminium hydroxide in the Phase 3 study C3671008.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for C3671008. This was a Phase 3, randomised, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of RSVpreF vaccine in infants born to women vaccinated during pregnancy.

The final CSR is dated 24 April 2024 and the data cut-off date (LPLV) is 27 October 2023.

2.3.2. Clinical study C3671008

Description

This was a Phase 3, randomised, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of RSVpreF vaccine in infants born to women vaccinated during pregnancy.

Methods

- *Study participants*

Pregnant women were eligible as follows:

1. Estimated at 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination based on LMP and the earliest U/S performed in the first or second trimester
2. Uncomplicated singleton pregnancy with no known increased risk for complications
3. Receiving prenatal standard of care based on country requirements
4. No significant abnormalities on U/S at ≥18 weeks
5. Negative HIV antibody test, syphilis test and HbsAg
6. Planned delivery at a participating hospital or birthing facility

Exclusions included the following:

1. Pre-pregnancy BMI >40 kg/m^2
2. Bleeding diathesis or condition associated with prolonged bleeding
3. History of severe adverse reaction associated with a vaccine and/or IMP component
4. Current pregnancy resulting from IVF
5. Prior preterm delivery at ≤34 weeks of gestation, prior stillbirth, prior neonatal death or infant with a known genetic disorder or significant congenital anomaly
6. Major illness and/or immunodeficiency or rheumatologic disorder requiring chronic treatment with immunosuppression within the year prior to study
7. Receipt of monoclonal antibodies within one year prior or systemic corticosteroids for >14 days within 28 days
8. Receipt of blood or plasma products or immunoglobulin within 60 days or expectation of receipt except for Rho(D) immune globulin

Vaccination was delayed in case of i) a febrile illness (body temperature ≥38°C); ii) other acute illness within 48 hours; iii) malaria within the last 7 days; or iv) receipt of inactivated vaccine within 14 days or live vaccine within 28 days.

Immunosuppressive therapy was prohibited during the course of the study. Non-study vaccines were not given concomitantly with study assignment or within 7 days and there was a 14-day window applied to pertussis-containing vaccines such as Tdap.

- *Treatments*

Pregnant women were randomised to receive RSVpreF containing 120 µg (60 µg of each of RSV A and B preF) or a matching placebo consisting of vaccine excipients. IM injections were into the non-dominant deltoid muscle.

- *Objectives*

See the table below for the primary efficacy and safety objectives in infants. The primary objective in pregnant women was safety.

There were multiple secondary efficacy and exploratory objectives in infants related to hospitalisation rates and disease rates determined within defined intervals timed from birth.

Study Objectives – Infant Participants

Primary Efficacy Objectives – Infant Participants	Estimands	Primary Efficacy Endpoints – Infant Participants
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 (evaluable participants).	RSV-positive MA-LRTI as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.
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 (evaluable participants).	Severe MA-LRTIs due to RSV as confirmed by the EAC: • occurring within 90 days after birth. • occurring within 120 days after birth, if the analysis at 90 days meets efficacy criteria. • occurring within 150 days after birth, if the analysis at 120 days meets efficacy criteria. • occurring within 180 days after birth, if the analysis at 150 days meets efficacy criteria.

Primary Safety Objective – Infant Participants	Estimand	Primary Safety Endpoints – Infant Participants
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.	• Specific birth outcomes. • AEs from birth to 1 month of age. • SAEs and NDCMCs: o from birth through 6 months of age *(first RSV season for all infant participants).* o from birth through 12 months of age *(for all infant participants).* o from birth through 24 months of age *(for infant participants born to maternal participants enrolled during the first year of the study).*

- *Outcomes/endpoints*

Infants

The definitions applied to infant efficacy endpoints are shown in the table. There was active surveillance in infants from 72 h after birth through 6 months after delivery (Visit 3). Study staff were to contact the infant's parent(s)/legal guardian(s) approximately every week (7 to 10 days) from birth until Visit 3 (6-month follow-up visit) to remind them to contact the investigational site promptly if the infant met the criteria for an MA-RTI event. Weekly contact was via the e-diary device or study-related mobile application, text, email, phone call or face-to-face. If the parent(s)/legal guardian(s) reported that the infant experienced an event requiring a visit to a healthcare provider, the site staff were to determine if the event met criteria for an MA-RTI. These criteria required:

- Nasal discharge for 24 hours or more
- Difficulty breathing, laboured breathing, or rapid breathing for any duration
- Cough
- Inability to feed for any duration due to respiratory symptoms
- Apnoea
- Any other respiratory symptom of concern

When the infant MA-RTI criterion was met or confirmed, the site/field worker was to obtain records from the medically attended visit and record the healthcare information. The infant was to be seen as soon as possible and optimally within 72 hours or up to 10 days for an RTI study visit. This visit could occur at home, at the study site (if discharged) or at an inpatient or other medical facility. Details of clinical signs and symptoms were recorded and a mid-turbinate nasal swab was collected (the aim was within 72 h) for testing at the central laboratory. Samples were analysed for RSV A, RSV B and other respiratory pathogens by PCR-based assays at Pfizer's central laboratory. Any RSV testing performed locally was considered valid if conducted in CLIA-certified central laboratories using FDA-cleared nucleic acid amplification technology (NAAT)-based test for RSV. Rapid antigen-based test results were not considered for endpoint assessment.

The active surveillance period was followed by long-term surveillance for infants from 6 months after delivery (Visit 3; 180-210 days after birth) until the last study visit (which was at a maximum of 24 months after birth).

During this period, study staff contacted the parent(s)/legal guardian(s) approximately every month (28 to 35 days) from Visit 3. At any other time in the first year after birth, the care-givers were to contact study staff if the infant developed the requisite signs/symptoms for a MA-RTI visit.

Table 1. Primary and Secondary Endpoint Events and Definitions in Infant Participants

Study Endpoints/Assessments	Study Definitions
Medically attended visit	Infant participant has been taken to or seen by a healthcare provider (eg, outpatient or inpatient visit, emergency room, urgent care, or home visit)
MA-RTI visit for infant participant	A medically attended visit AND 1 or more of the following RTI signs and symptoms: • Nasal discharge for 24 hours or more • Difficulty breathing, labored breathing, or rapid breathing for any duration • Cough • Inability to feed for any duration because of respiratory symptoms • Apnea • Any other respiratory symptom of concern
RSV-positive test[a]	• RSV RT-PCR–positive test result by Pfizer central laboratory **OR** • RSV-positive test result by certified laboratory with NAAT for RSV
MA-RTI due to RSV[b]	• An MA-RTI visit **AND** • RSV-positive test result as described in Section 8.1.1.1
MA-LRTI due to any cause	• Infant with an MA-RTI visit **AND** • Fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age], ≥50 bpm for ≥2 months to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <95% **OR** • Chest wall indrawing
MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age] or ≥50 bpm for ≥2 to <12 months of age, or ≥40 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <95% **OR** • Chest wall indrawing AND • RSV-positive test result as described in Section 8.1.1.1
Hospitalized RTI due to RSV[b]	An RTI due to RSV that results in hospitalization
Severe MA-LRTI due to RSV[b]	• Infant with an MA-RTI visit AND • Fast breathing (RR ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for ≥2 months to <12 months of age, or ≥50 bpm for ≥12 months to 24 months of age) **OR** • SpO_2 <93% **OR** • High-flow nasal cannula or mechanical ventilation (ie, invasive or noninvasive) **OR** • ICU admission for >4 hours **OR** • Failure to respond/unconscious AND • RSV-positive test result as described in Section 8.1.1.1
Protocol-defined primary endpoint	• Any MA-LRTI or severe MA-LRTI due to RSV as determined by an EAC

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_2 = oxygen saturation.

a. RSV-positive testing is defined as a positive RSV test (see Section 8.1.1.1) 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) as detailed in Section 8.11.7.

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.

There was an EAC appointed to adjudicate all efficacy endpoints that was blinded to vaccine assignment. The EAC's decision was regarded as the final confirmed endpoint classification of the event. All MA-RTI events were referred to the EAC for adjudication. As indicated above, identification of an MA-RTI was made by the investigational site and communicated to Pfizer or its designee. MA-RTI events could also be identified by Pfizer or its designee during the review of clinical data listings or by site monitors during routine monitoring of infant study records.

The EAC was responsible for adjudicating whether MA-RTI events fulfilled the protocol-defined criteria for a primary endpoint, whether the event was due to RSV based on confirmatory testing and the severity of the illness (MA-RTI, MA-LRTI or severe MA-LRTI). The EAC adjudicated all RSV-positive MA-RTI cases through the active follow-up period up to 180 days after birth as well as all RSV-associated cases of hospitalization and severe MA-LRTI. The Pfizer study team could also request that additional cases of interest be reported to the committee, including cases in which RSV testing was indeterminate or otherwise unclear. Cases that were determined to be RSV positive using non–NAAT-based clinical testing could also be adjudicated, explored and summarized descriptively.

A blood sample was to be collected from cord blood after the umbilical cord had been clamped and cut. If cord blood was unavailable, a blood sample was collected from the infant preferably within 24 hours but up to 7 days after birth. Full details of the infant condition at birth were collected as well as administration of any intervention, including palivizumab.

Pregnant and post-partum women

Starting from time of vaccination (Day) until the end of the study, all women were monitored for MA-RTIs. They were to notify the site and/field worker of the occurrence of any MA-RTI immediately but no later than the next study visit by any means allowed (as for infant contacts).

Pregnant women recorded solicited local reactions and systemic events (including temperature with digital thermometers) for 7 days after vaccination in an electronic diary (e-diary). Fever was defined as an oral temperature of ≥38.0°C and the highest temperature for each day was recorded in the e-diary. In the event of a fever on the last day the diary was completed, temperature was measured daily until fever resolved (1 day of less than 38.0°C) to collect a stop date in the CRF. In case of fever >38.9°C, the subject was to contact the investigator.

- *Sample size*

This was an event-driven study such that the sample size was determined as the number of subjects that needed to be randomised to accrue the required number of endpoint cases in the evaluable population.

There were two primary efficacy endpoints and the study could be declared a success based on one or both of these endpoints. The power for the study overall was therefore at least as high as the power for either primary endpoint individually. In order for the study to have at least 90% power to reject the null hypothesis for MA-LRTI due to RSV when true VE is 60%, a total of 124 cases of MA-LRTI due to RSV within 90 days of birth were required in the evaluable population. This also accounted for potential use of an alpha of 1.25% 1-sided within the multiplicity adjustment. There was no explicit case target for the endpoint of severe MA-LRTI due to RSV. Depending on the assumed true VE, power for that individual hypothesis may be lower, but the power for the primary endpoint family was to be at least 90%.

Hypotheses about VE may be restated as hypotheses about the proportion of cases in the RSV vaccine group, conditional upon a fixed total number of cases. If this proportion is p, the null hypothesis H0: VE ≤20% is equivalent to H0: $p \geq 0.444$; the assumption of VE = 60% corresponds to $p = 0.286$. Power was evaluated by the exact binomial test and the case target established as that number k for which power is guaranteed to be at least 90% for all $k^* \geq k$. The calculation accounted for the study design (1:1 randomisation vaccine:placebo), planned interim analyses of efficacy and an overall type 1 error of 2.5% 1-sided across the two primary endpoints.

The incidence of the primary endpoints was expected to vary by region, with an assumed rate for MA-LRTI due to RSV through 90 days in low-incidence countries of ~1.75% and ~3.9% in other regions. With these assumptions, and also allowing for 60% VE and 10% of subjects being non-evaluable, it was planned to enrol ~6900 pregnant women.

- *Randomisation*

Randomisation of pregnant women to vaccine groups occurred via an interactive response technology (IRT) system (interactive Web-based response [IWR]). There was no stratification at randomisation. The infants born to these women were manually assigned an infant participant number at birth.

- *Blinding (masking)*

This study was double-blind as the physical appearance of RSVpreF and placebo were matched. The pregnant women, parent(s)/legal guardian (if a minor), investigator, study coordinator and all site staff will be blinded. The sponsor study team members and the laboratory staff were blinded throughout the study to the vaccine assignments.

- *Statistical methods*

The null hypothesis to be tested concerns VE for the two primary endpoints. The RSV vaccine was compared to placebo testing the hypotheses H0: VE ≤20% vs. Ha: VE >20%. For all secondary efficacy endpoints, the RSV vaccine was compared to placebo testing the hypotheses H0: VE ≤0% vs Ha: VE >0%. Hypothesis testing of the secondary endpoints was conditional upon rejection of the null hypothesis for at least one of the primary endpoints.

The success criterion for each primary endpoint was not clearly stated in the protocol or statistical analysis plan. It was unclear if meeting the success criterion at 90 days alone is sufficient or if the success criterion must be met at each of 90, 120, 150 and 180 days.

For purposes of analysis, the populations were defined as shown in the table.

Population	Description
Enrolled	All maternal participants who sign the ICD.
Randomly assigned to investigational product	All maternal participants who are assigned a randomization number in the IRT system.
Evaluable efficacy – infant **(per-protocol)**	All infant participants who are eligible, are born to the maternal participants who received the investigational product to which they were randomized at least 14 days prior to delivery, did not receive palivizumab or another monoclonal antibody targeting RSV, have no major protocol violations, and did not have transfusions of more than 20 mL/kg of any blood products at <180 days.
Modified intent-to-treat (mITT) efficacy – infant	All infant participants who are born to vaccinated maternal participants.
Evaluable immunogenicity – infant	All infant participants who are eligible, are born to the maternal participants who received the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
Evaluable immunogenicity – maternal	All maternal participants who are eligible, receive the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations.
mITT immunogenicity – infant	All infant participants who are born to vaccinated maternal participants and have at least 1 valid and determinate assay result for the proposed analysis.
mITT immunogenicity – maternal	All randomized maternal participants who receive investigational product and have at least 1 valid and determinate assay result for the proposed analysis.
Safety – infant	All infant participants who are born to vaccinated maternal participants.
Safety – maternal	All randomized maternal participants who receive investigational product.

The estimands for efficacy in infants born to women who received assigned investigational product and were evaluable were:

☐ VE defined as the percentage relative risk reduction in the incidence of MA-LRTI due to RSV in the RSV vaccine group relative to the placebo group;

☐ VE defined as the percentage relative risk reduction in the incidence of severe MA-LRTI due to RSV in the RSV vaccine group relative to the placebo group;

☐ VE defined as the percentage relative risk reduction in the incidence of hospitalisation due to RSV in the RSV vaccine group relative to the placebo group;

☐ VE defined as the percentage relative risk reduction in the incidence of all-cause MA-LRTI in the RSV vaccine group relative to the placebo group.

For participants who discontinued from the study or had major protocol violations, all observations made after discontinuation or violation were censored.

The SAP (V 6.0) was dated 2 September 2022. It was developed and finalised before database lock for the first planned analysis. The table summarises the methods applied to the primary endpoints. See further below on the planned interim analyses mentioned in the table.

VE was to be analysed using a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups.

The two primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV were tested in parallel using a Bonferroni multiplicity adjustment procedure, whereby alpha = 0.0125 (one-sided) was allocated to each endpoint.

For intercurrent events and missing data: All post-discontinuation or post-violation observations were censored (e.g. infants given palivizumab or another monoclonal antibody targeting RSV or a transfusion of more than 20 mL/kg of any blood products at ≤180 days of age).

For each group, the number, percentage and 95% CI of EAC-confirmed RSV-positive MA-LRTI cases occurring within 90, 120, 150 and 180 days after birth were to be presented for each group. Severe MA-LRTI cases were regarded as a subset of all MA-LRTI cases.

VE was compared to placebo along with the corresponding 100(1- alpha)% CI (adjusted for the interim). This was based on raw numbers of cases with an adjustment for any differences in follow-up time. Kaplan-Meier curves showing accrual of cases over 180 days were to be presented.

Endpoint	Statistical Analysis Methods
Primary	• The analysis of efficacy will use a conditional exact test based on the binomial distribution of the number of disease cases in the RSV vaccine group, given the total number of cases in both groups. The incidence of MA-LRTI due to RSV and severe MA-LRTI due to RSV in infant participants will be evaluated in both groups up to 90 days, 120 days, 150 days, and 180 days after birth. • The infant evaluable efficacy population will be the primary population for efficacy analyses. The analysis will be repeated on the infant mITT efficacy population. • The 2 primary endpoints of MA-LRTI due to RSV and severe MA-LRTI due to RSV will be tested in parallel using a multiplicity adjustment procedure. Success of the trial requires rejection of the null hypothesis (ie, a CI lower bound >20%) for either one of the 2 primary endpoints. • The primary endpoint of severe MA-LRTI due to RSV may be demoted to a secondary endpoint if there are insufficient cases for an adequately powered analysis. During the trial, blinded accrual of cases will be monitored and prior to any unblinding, a decision rule for this change will be established based on the total number of cases of severe MA-LRTI due to RSV. • Testing of the 2 primary endpoints across the time intervals will follow a fixed sequence with a gatekeeping strategy. First, the hypothesis
	pertaining to the incidence of the 2 primary endpoints within 90 days after birth will be tested, at the full multiplicity-adjusted alpha level, using a multiplicity adjustment for the 2 endpoints. If that null hypothesis cannot be rejected, testing ends. Otherwise, testing proceeds to the incidence within 120 days after birth. Only primary endpoint(s) that are successful at all earlier time intervals will be considered at subsequent intervals. Testing will proceed to the endpoints evaluated at 150 days and 180 days, conditional on rejection of the null hypotheses for all earlier time intervals. Refer to the SAP for full details of the testing sequence and multiplicity correction strategy.

Endpoint	Statistical Analysis Methods
	• There may be up to 2 interim analyses of the MA-LRTI-due-to-RSV endpoint when there is an adequate number of cases (at least 43 cases within 90 days). Based on the fraction of cases included in an interim analysis, an alpha level will be derived based on a Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. For example, if there are 2 interim analyses at 43 cases and 62 cases, the appropriate 1-sided significance levels are 0.00014 at the first interim analysis, 0.0015 at the second interim analysis, and 0.0245 at the final analysis. Implementation of these 1-sided significance levels ensures the overall type 1 error for the primary endpoint will be no more than 0.025. See Section 9.5 for more details. • At the interim analyses there will also be an assessment for futility, based on conditional power for the MA-LRTI-due-to-RSV endpoint. If the probability of success at the end of the trial is low, given the interim analysis results and the initially assumed VE is applied to the remaining data, consideration will be given to stopping the study for futility. • CIs for VE will be calculated using the appropriate multiplicity-adjusted alpha level α. If the lower 100(1 - α)% confidence limit for VE exceeds 20%, the null hypothesis for that endpoint will be rejected. • At the end of the trial, the RSV vaccine may be deemed efficacious if there are 42 or fewer cases of MA-LRTI due to RSV in the RSV vaccine group out of the 124 total endpoint cases. This corresponds to an estimated VE = 49%, with a 97.6% CI = (21%, 68%). For severe MA-LRTI, assuming a total of 50 cases occur, the vaccine may be deemed efficacious if there are 13 or fewer cases in the RSV vaccine group. This corresponds to an estimated VE = 65%, with a 97.6% CI = (26%, 85%). For both of these examples, it is assumed a 1-sided alpha of 0.01225 applies to the endpoint in question.
	• Kaplan-Meier curves showing accrual of endpoint cases over 180 days will be presented. • There will be a sensitivity analysis of the primary endpoints to examine the impact of missing RSV swab results. Details are provided in the SAP.

The main analysis was also performed based on the mITT efficacy infant population. A supportive analysis of the primary endpoint was to be performed to address the potential intercurrent event of palivizumab administration via a composite estimand strategy in the mITT efficacy infant set. The endpoint was the occurrence of either MA-LRTI due to RSV (as defined for the main analysis) or receipt of palivizumab. VE was estimated in the same way as for the main analysis.

Where MA-LRTI and severe MA-LRTI visits had no accompanying valid central or local NAAT test results, positive or negative results were imputed. Based on a blinded review of swab results at the end of February 2022, approximately 22% of all swabs from MA-LRTI events with valid central lab results cases proved to be RSV-positive. Thus, a minority of the missing results were expected to be truly RSV-positive and imputation scenarios included:
☐ Missing swab results were assumed to be positive in the same proportion (by vaccine group) as the non-missing swab results in MA-LRTI events (missing-at-random assumption).

☐ For the vaccine group, missing swab results were assumed to be positive in higher proportions than the non-missing swab results in MA-LRTI events. In the placebo group missing swab results were assumed to be positive in the same proportion as the non-missing swab results in MA-LRTI events (missing-not-at-random assumption). A range of higher vaccine group positivity rates was assumed.

Multiple imputations were performed to randomly assign missing swab results. SAS PROC MI was used to generate 500 imputed data sets for each scenario. Mean and median VE across imputations, and the proportion of imputations with VE lower bound >20% were to be reported. If any such events were adjudicated, only those that were confirmed by the EAC as MA-LRTI or severe MA-LRTI were to undergo imputation. The imputed RSV-positive cases will be added to the per-protocol cases and VE estimated in the same way as for the main analysis.

In a further sensitivity analysis, where some evidence of RSV positivity existed from MA-LRTI and severe MA-LRTI visit swabs, any test indicating positivity for RSV was to be accepted and used to define MA-LRTI cases whenever the clinical symptoms qualify. Examples of positive swab results that did not count for the primary endpoint definition but were counted in this analysis were local non-NAAT tests, central laboratory PCR tests from samples taken outside the protocol-specified window and centrally-tested swabs that exceeded the documented stability testing duration but were positive. Where events were adjudicated, the EAC's decision on the event as MA-LRTI or severe MA-LRTI was Used. If not adjudicated, the event was assessed according to the protocol criteria for each event. VE including these additional RSV-positive cases was estimated in the same way as for the main analysis.

The applicant planned a combined analysis of the Phase 2b/Phase 3 efficacy data in infants using the Phase 3 endpoint definitions. This was described in the SAP. Cases in the four RSVpreF groups in Phase 2 were to be combined and VE was to be estimated by simple pooling without stratification/weighting using data available when all infants in both studies reached 180 days of age.

Interim analyses

The original final analysis target was 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.

The study was planned such that up to two interim analyses could be performed to assess efficacy and safety after at least 43 cases of MA-LRTI due to RSV within 90 days of birth had accrued. Because of the relatively low number of cases of severe MA-LRTI due to RSV expected, it was proposed that the interim analyses might not consider this endpoint. Interim analysis results could be used for internal business decisions regarding study planning, stopping for futility or stopping for early success.

The order of cases included in the interim analysis was determined by the EAC as those first confirmed as meeting the protocol-defined criteria. Only cases that had been fully adjudicated prior to taking a data snapshot were to be included in an interim analysis.

The analysis of efficacy was to use an O'Brien-Fleming alpha spending rule based on the fraction of cases of MA-LRTI due to RSV within 90 days available. The exact number of cases at each interim analysis was not fixed and could be decided based on operational reasons. However, no fewer than 43 cases were to be included in the first interim analysis and no fewer than 62 cases in the second interim analysis.

To control the overall type 1 error for the two primary endpoints at 2.5% 1-sided, a first interim analysis at43 cases would use a 1-sided significance level of 0.014%. If a second interim analysis were performed at 62 cases, it would use a 1-sided significance level of 0.15%. The final analysis at the target number of cases would use a 1-sided significance level of 2.45%. In each case, this alpha would be split between the two endpoints using the Bonferroni correction. The alpha levels used at interim and final analyses depended on the exact fraction of cases available at the interim analysis. Testing of the primary endpoints at the interim analysis was to follow the sequence of interval-specific tests. Secondary endpoints were not tested at the interim analysis.

Futility was to be assessed using conditional power. For example, if there were 62 cases available for the interim analysis, the table shows the case splits for which stopping the study was to be considered. The actual number of cases available could be slightly higher or lower than 62, and the decision rules amended accordingly.

Table 7. Example of Estimated Vaccine Efficacy and Confidence Intervals at an Interim Analysis

Total Cases	RSV Vaccine Group Cases	Placebo Group Cases	VE (CI)[a]	Notes
43 (First interim)	24	19	-26% (-145%, 34%)	Conditional power <20%,[b] possible futility declaration
43 (First interim)	6	37	84% (27%, 98%)	Maximum number of vaccine group cases permitted to declare VE >20%
62 (Second interim)	29	33	12% (-49%, 49%)	Conditional power <20%,[b] possible futility declaration
62 (Second interim)	14	48	71% (25%, 91%)	Maximum number of vaccine group cases permitted to declare VE >20%

Abbreviation: VE = vaccine efficacy.

a. Confidence level for efficacy declaration based on half the available alpha at each interim, assuming both MA-LRTI and severe MA-LRTI endpoints were inspected; 95% confidence level for futility.

b. Other conditional power levels may be considered as a trigger for a futility decision.

Final CSR

There was a secondary endpoint related to RSV LRTI cases with onset up to 360 days after birth. The number of cases accrued over time is updated in the final CSR.

There was no hypothesis testing conducted for the final, post-LPLV analysis.

The following additional analyses were performed:
☐ The main analysis was repeated based on the mITT efficacy infant population.
☐ Supportive analyses of the primary endpoints were performed to address the potential intercurrent event of palivizumab administration using the mITT efficacy infant population.
☐ Subgroup analyses for selected efficacy endpoints were performed on the following variables: maternal gestational age (GA) at vaccination, country, country income level, exclusive breastfeeding, duration of breastfeeding, maternal smoking, number of household members, and maternal age at vaccination.

C3671008 - Results Efficacy

In the initial MAA, the CSR was dated 6 December 2022. For convenience, the following includes some data from the main efficacy analysis as reported in the initial CSR along with the most pertinent results reported in the final CSR. For full details of the initial CSR, please consult prior assessment reports.

- *Participant flow*

The initial CSR reported data from 7392 pregnant women (3682 RSVpreF and 3675 placebo) while the infant safety population comprised 3568 and 3558 in respective groups. The final CSR reports on 7420 pregnant women randomised to RSVpreF (3711) or placebo (3709) before enrolment was terminated as well as 7307 infants (3660 RSVpreF and 3647 placebo).

The median follow-up time for all infants was 398 days (range: 1 – 939 days) in the RSVpreF group and 392 days (range: 1 – 1004 days) in the placebo group. Follow-up time for some infants exceeded 742 days (2 years) because they did not return within the designated time windows of the study.

Table 7. Disposition of All Participants - Maternal Participants

	Vaccine Group (as Randomized)		
	RSVpreF 120 µg	Placebo	Total
	n[a] (%)	n[a] (%)	n[a] (%)
Screened[b]			8075
Randomized[c]	3711	3709	7420
Completed vaccination	3698 (99.6)	3688 (99.4)	7386 (99.5)
Completed 1 month after vaccination	3689 (99.4)	3679 (99.2)	7368 (99.3)
Withdrawn after vaccination but before 1 month after vaccination	9 (0.2)	7 (0.2)	16 (0.2)
Reason for withdrawal			
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	3669 (98.9)	3658 (98.6)	7327 (98.7)
Withdrawn after vaccination but before delivery	29 (0.8)	30 (0.8)	59 (0.8)
Reason for withdrawal			
Lost to follow-up	8 (0.2)	10 (0.3)	18 (0.2)
Other	3 (<0.1)	2 (<0.1)	5 (<0.1)
Withdrawal by subject	18 (0.5)	18 (0.5)	36 (0.5)
Completed study	3515 (94.7)	3510 (94.6)	7025 (94.7)
Withdrawn after delivery	154 (4.1)	148 (4.0)	302 (4.1)
Reason for withdrawal			
Adverse event	0	1 (<0.1)	1 (<0.1)
Death	1 (<0.1)	0	1 (<0.1)
Lost to follow-up	85 (2.3)	78 (2.1)	163 (2.2)
No longer meets eligibility criteria	1 (<0.1)	0	1 (<0.1)
Other	13 (0.4)	9 (0.2)	22 (0.3)
Physician decision	1 (<0.1)	0	1 (<0.1)
Protocol deviation	0	1 (<0.1)	1 (<0.1)
Withdrawal by subject	53 (1.4)	59 (1.6)	112 (1.5)

a. n = Number of participants in the specified category.
b. A screened participant is a participant that signed informed consent.
c. This value is the denominator for the percentage calculations.

Table 8. Disposition of All Participants - Infant Participants

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Enrolled[b]	3660	3647	7307
Planned 12 months follow-up	1758 (48.0)	1746 (47.9)	3504 (48.0)
Planned 24 months follow-up[c]	1902 (52.0)	1901 (52.1)	3803 (52.0)
Completed 1 month follow-up	3585 (98.0)	3574 (98.0)	7159 (98.0)
Withdrawn before 1 month after birth	56 (1.5)	62 (1.7)	118 (1.6)
Reason for withdrawal			
Death	3 (<0.1)	6 (0.2)	9 (0.1)
Lost to follow-up	23 (0.6)	26 (0.7)	49 (0.7)
Other	4 (0.1)	6 (0.2)	10 (0.1)
Withdrawal by parent/guardian	26 (0.7)	24 (0.7)	50 (0.7)
Completed 6 months follow-up	3498 (95.6)	3479 (95.4)	6977 (95.5)
Withdrawn after 1 month but before 6 months after birth	99 (2.7)	98 (2.7)	197 (2.7)
Reason for withdrawal			
Death	3 (<0.1)	5 (0.1)	8 (0.1)
Lost to follow-up	59 (1.6)	46 (1.3)	105 (1.4)
Other	9 (0.2)	13 (0.4)	22 (0.3)
Withdrawal by parent/guardian	28 (0.8)	34 (0.9)	62 (0.8)
Completed 12 months follow-up	3422 (93.5)	3399 (93.2)	6821 (93.3)
Withdrawn after 6 months but before 12 months after birth	74 (2.0)	83 (2.3)	157 (2.1)
Reason for withdrawal			
Death	1 (<0.1)	3 (<0.1)	4 (<0.1)
Lost to follow-up	54 (1.5)	57 (1.6)	111 (1.5)
Other	5 (0.1)	12 (0.3)	17 (0.2)
Physician decision	1 (<0.1)	0	1 (<0.1)
Withdrawal by parent/guardian	13 (0.4)	11 (0.3)	24 (0.3)
Completed 18 months follow-up	1712 (90.0)	1681 (88.4)	3393 (89.2)
Withdrawn after 12 months but before 18 months after birth	53 (2.8)	67 (3.5)	120 (3.2)
Reason for withdrawal			
Lost to follow-up	40 (2.1)	45 (2.4)	85 (2.2)
Other	7 (0.4)	10 (0.5)	17 (0.4)
Physician decision	0	1 (<0.1)	1 (<0.1)
Withdrawal by parent/guardian	6 (0.3)	11 (0.6)	17 (0.4)
Completed 24 months follow-up	1656 (87.1)	1643 (86.4)	3299 (86.7)
Withdrawn after 18 months but before 24 months after birth	61 (3.2)	42 (2.2)	103 (2.7)
Reason for withdrawal			
Death	1 (<0.1)	0	1 (<0.1)
Lost to follow-up	48 (2.5)	37 (1.9)	85 (2.2)
Other	10 (0.5)	4 (0.2)	14 (0.4)
Withdrawal by parent/guardian	2 (0.1)	1 (<0.1)	3 (<0.1)
Completed the study as planned[d]	3317 (90.6)	3295 (90.3)	6612 (90.5)

Note: "Completed xxx months follow-up" means completed the respective visit.

a. n = Number of participants in the specified category.

b. 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 c.

c. The values in this row are used as the denominators for the percentage calculations for vaccine groups for rows related to 18 and 24 months completion/withdrawal.

d. Includes participants who completed the study as assigned to either 12 or 24 months after birth.

- *Baseline data*

The baseline characteristics of the pregnant women and infants was not substantially different from those reported in the initial CSR. Most pregnant women (44.9%) were in the gestational age range ≥32 weeks to ≤36 weeks at the time of vaccination. Most (64.6%) were White, while 19.6% were Black or African American, 12.5% were Asian and 29.1% were Hispanic/Latino. The median maternal age at the time of study vaccination was 29.0 years with a range from 14-47 years.

Half (49.4%) of the infants were female. The majority (63.9%) was white and non-Hispanic/non-Latino (69.1%). Most infants were born at term (≥93.6% born at ≥37 weeks to <42 weeks). Birth outcomes for infants were similar for the RSVpreF and placebo groups with no important differences with respect to GA at birth, Apgar scores or birthweight.

- *Numbers analysed*

The most common reason for exclusion of infants from the evaluable efficacy population was due to the mother not being vaccinated at least 14 days prior to delivery.

Table 10. Analysis Populations - Infant Participants

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a]=3660)	Placebo (N[a]=3647)	Total (N[a]=7307)
	n[b] (%)	n[b] (%)	n[b] (%)
Safety population	3658 (99.9)	3647 (100.0)	7305 (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)
mITT efficacy population	3658 (99.9)	3647 (100.0)	7305 (100.0)
Participants excluded from mITT efficacy population			
Mother not vaccinated	0	0	0
Participant not eligible - unblinded during study	2 (<0.1)	0	2 (<0.1)
Evaluable efficacy population	3585 (98.0)	3563 (97.7)	7148 (97.8)
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)	6 (0.2)	9 (0.1)
Mother not vaccinated as randomized	0	1 (<0.1)	1 (<0.1)
Mother had major protocol violations before delivery	27 (0.7)	21 (0.6)	48 (0.7)
Mother not vaccinated at least 14 days prior to delivery	44 (1.2)	58 (1.6)	102 (1.4)
Infant had major protocol violations	0	1 (<0.1)	1 (<0.1)

a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

- *Outcomes and estimation*

MA-LRTI within 90, 120, 150 and 180 days after birth confirmed by the EAC

First interim efficacy analysis (21 April 2022)
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 in infant participants. The efficacy criterion was met for cases within 90 days after birth but not within 150 days.

C3671008 INTERIM ANALYSIS 1, 21 APRIL 2022

EFFICACY TABLE REVIEWED BY DATA MONITORING COMMITTEE

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

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

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; NC = not calculated; RSV = respiratory syncytial virus.
a. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was based on the available alpha at the interim analysis using the O'Brien-Fleming alpha spending function.
b. Conditional power is the probability to demonstrate success at the final analysis with 124 cases, conditional upon the cases observed so far and assuming VE = 60% following the futility check.
PFIZER CONFIDENTIAL SDTM Creation: 14APR2022 (02:50) Source Data: adrsvef Table Generation: 20APR2022 (11:21)
(Database snapshot date : 13APR2022) Output File: N:\Pfizer C3671008\Analysis - 20220419\adprim_s001b_rsvpos

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

Second interim efficacy analysis (28 October 2022)
The point estimates for VE against MA-LRTI due to RSV based on all cases accrued through the data cut-off date were in the range 51-57%. The lower bounds of the CI were above the 20% pre-defined criterion for success except for cases occurring within the first 90 days after birth (lower bound 14.7%). The nominal unadjusted 1-sided p-values at each analysis time point, which indicate that the results for this endpoint are consistent with a true VE of more than 20%.

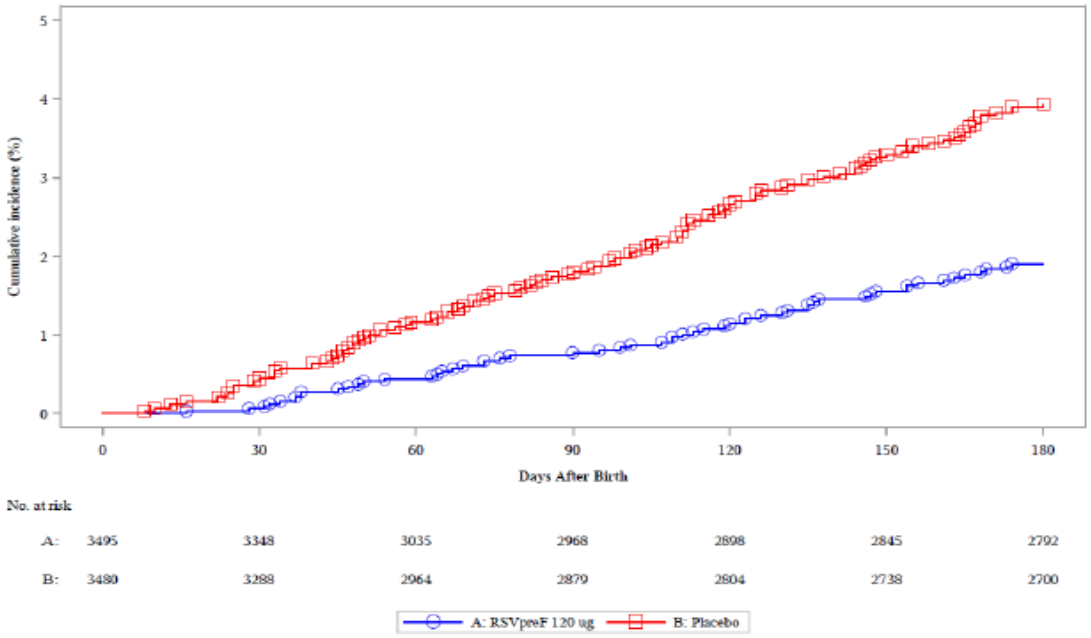
Results for the mITT population were similar with 3 additional cases in the vaccine group before day 90 and one in the placebo group before day 150. When all positive RSV tests were considered, including non-NAAT tests, the results were similar to the primary analysis.

Table 14. RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

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

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations.
b. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
c. Confidence intervals are 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).
d. Unadjusted 1-sided nominal p-value for the null hypothesis that vaccine efficacy ≤20%. Statistical significance cannot be claimed for these analyses due to the planned testing strategy and the failure to meet the statistical success criterion at 90 days for this endpoint.

Figure 2. Kaplan-Meier Curves for RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 180 Days After Birth - Infant Participants - Evaluable Efficacy Population



Final CSR based on LPLV

There was a small difference in case numbers with onset up to 180 days after birth. There were 25 cases of EAC-confirmed RSV-positive MA-LRTI within 90 days after birth in the RSVpreF group and 59 in the placebo group, corresponding to a VE of 57.6% (95% CI: 31.3, 74.6). There were 67 cases of EAC-confirmed RSV-positive MA-LRTI cases within 180 days after birth in the RSVpreF group and 132 in the placebo group, corresponding to a VE of 49.2% (95% CI: 31.4, 62.8). The mITT population had 3 additional cases of EAC-confirmed RSV-positive MA-LRTI in infants within 90 days after birth in the RSVpreF group and 1 additional case of EAC-confirmed RSV-positive MA-LRTI in infants within 150 days after birth in the placebo group.

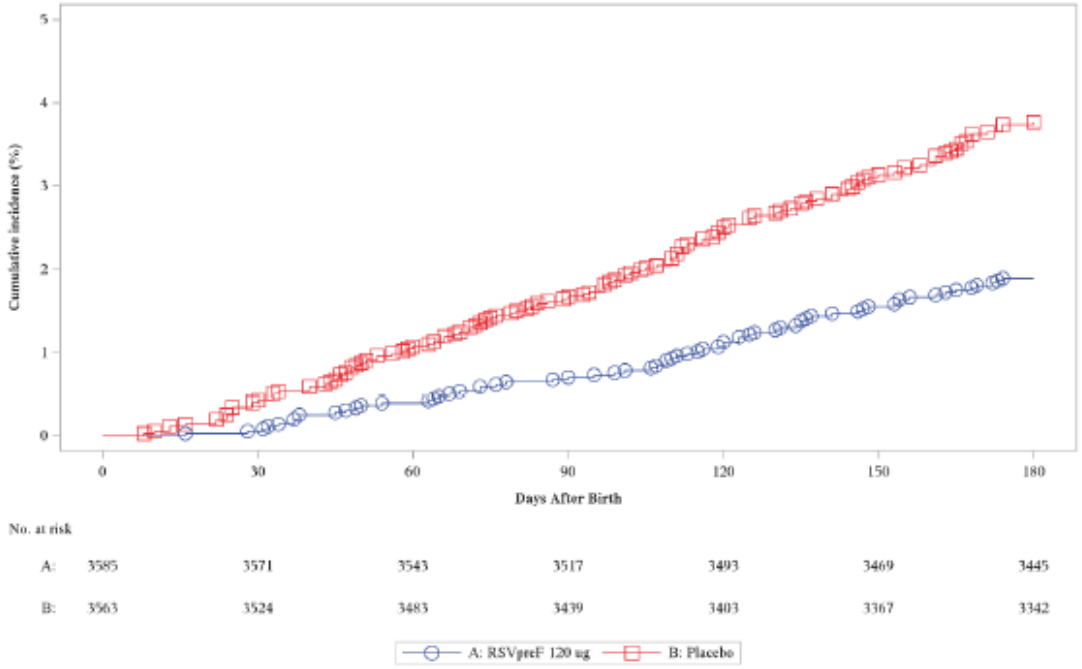
No infant participants who received palivizumab had an EAC-confirmed RSV-positive MA-LRTI during the study.

Table 14. RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a]=3585)	Placebo (N[a]=3563)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
90 Days after birth	25 (0.7)	59 (1.7)	57.6 (31.3, 74.6)
120 Days after birth	40 (1.1)	88 (2.5)	54.5 (33.2, 69.5)
150 Days after birth	55 (1.5)	110 (3.1)	50.0 (30.3, 64.5)
180 Days after birth	67 (1.9)	132 (3.7)	49.2 (31.4, 62.8)

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

Kaplan-Meier Curves for RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 180 Days After Birth - Infant Participants - Evaluable Efficacy Population



Severe MA-LRTI within 90, 120, 150 and 180 days after birth confirmed by the EAC

Second interim efficacy analysis (28 October 2022)

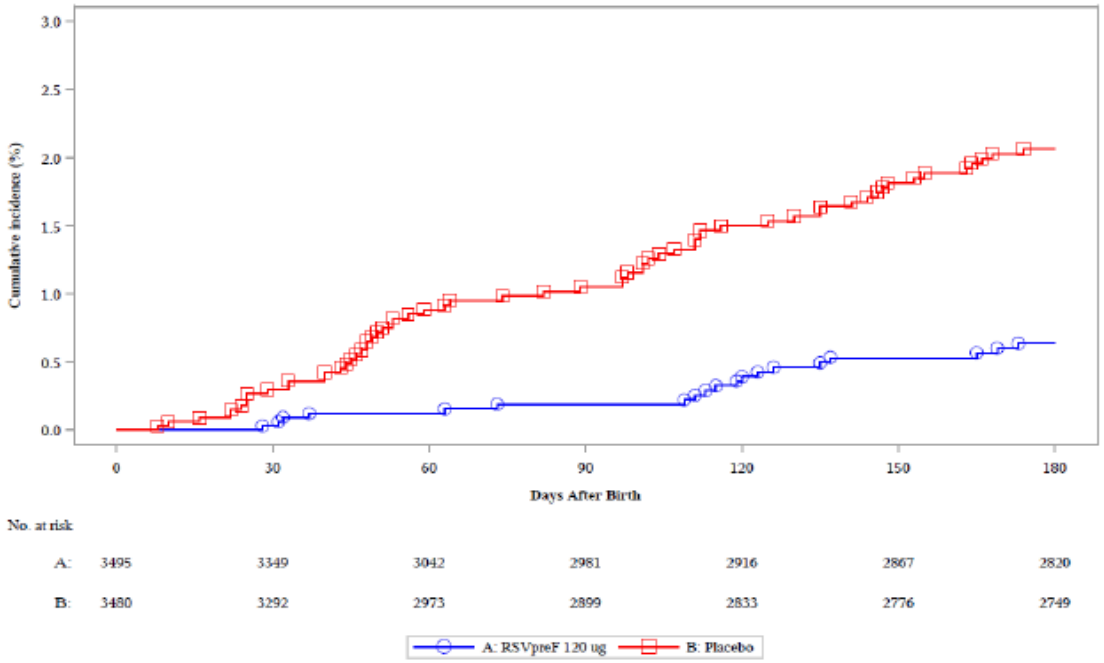
In the initial CSR, point estimates for VE against severe MA-LRTI due to RSV based on all cases accrued through the data cut-off date were in the range 69-82%. The lower bounds of the CI were all above 40%. At the data cut-off, there were 19 and 62 cases with onset up to 180 days after birth in respective groups, with VE of 69.4% (97.58% CI: 44.3%, 84.1

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

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

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

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



Final CSR based on LPLV

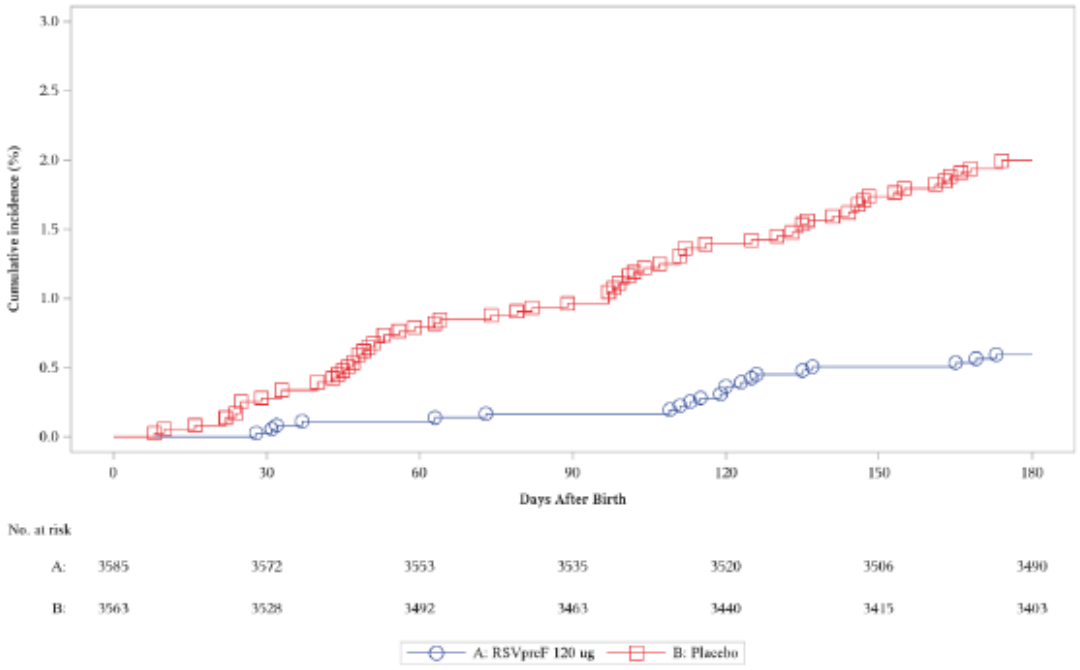
There were 6 cases of EAC-confirmed RSV-positive severe MA-LRTI within 90 days after birth in the RSVpreF group and 34 in the placebo group, corresponding to a VE of 82.4% (95% CI: 57.5, 93.9). There were 21 cases of EAC-confirmed RSV-positive severe MA-LRTI cases within 180 days after birth in the RSVpreF group and 70 in the placebo group, corresponding to a VE of 70.0% (95% CI: 50.6, 82.5). Analysis of this primary endpoint using the mITT population yielded similar results with only two additional cases within 90 days after birth in the RSVpreF group and 1 additional case within 150 days after birth in the placebo group.

Table 13. Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a]=3585)	Placebo (N[a]=3563)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
90 Days after birth	6 (0.2)	34 (1.0)	82.4 (57.5, 93.9)
120 Days after birth	13 (0.4)	49 (1.4)	73.5 (50.3, 86.8)
150 Days after birth	18 (0.5)	61 (1.7)	70.5 (49.4, 83.6)
180 Days after birth	21 (0.6)	70 (2.0)	70.0 (50.6, 82.5)

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

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



- *Ancillary analyses from the final CSR*

The EAC evaluated all events within 180 days after birth to determine if the event met criteria for the primary endpoints and evaluated hospitalized or severe MA-LRTIs up to 730 days after birth.

<u>MA-LRTI due to RSV within 210, 240, 270 and 360 days reported by investigators</u>

There were 81 cases of investigator-reported RSV-positive MA-LRTI within 210 days after birth in the RSVpreF group and 144 cases in the placebo group in the evaluable efficacy population, corresponding to a VE of 43.8% (95% CI: 25.6, 57.7). There were 122 and 182 cases in respective groups within 360

days after birth, corresponding to a VE of 33.0% (95% CI: 15.2, 47.1). Analysis of this secondary efficacy endpoint using the mITT population yielded similar results.

Table 15. RSV-Positive MA-LRTIs Occurring Within 210, 240, 270, and 360 Days After Birth - Infant Participants - Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a]=3585)	Placebo (N[a]=3563)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
210 Days after birth	81 (2.3)	144 (4.0)	43.8 (25.6, 57.7)
240 Days after birth	91 (2.5)	151 (4.2)	39.7 (21.3, 54.1)
270 Days after birth	102 (2.8)	157 (4.4)	35.0 (16.1, 49.9)
360 Days after birth	122 (3.4)	182 (5.1)	33.0 (15.2, 47.1)

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

Hospitalization due to RSV within 90, 120, 150, 180 and 360 Days confirmed by the EAC

There were 10 such hospitalizations within 90 days after birth in the RSVpreF group and 33 in the placebo group in the evaluable efficacy population, corresponding to a VE of 69.7% (95% CI: 37.1, 86.7) for RSVpreF. There were 21 and 47 instances in respective groups within 180 days after birth, corresponding to a VE of 55.3% (95% CI: 23.8, 74.6).

Table 16. 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)		
	RSVpreF 120 µg (N[a]=3585)	Placebo (N[a]=3563)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
90 Days after birth	10 (0.3)	33 (0.9)	69.7 (37.1, 86.7)
120 Days after birth	15 (0.4)	39 (1.1)	61.5 (28.6, 80.3)
150 Days after birth	18 (0.5)	42 (1.2)	57.1 (23.9, 76.8)
180 Days after birth	21 (0.6)	47 (1.3)	55.3 (23.8, 74.6)
360 Days after birth	50 (1.4)	66 (1.9)	24.2 (-11.1, 48.6)

Abbreviations: EAC = endpoint adjudication committee; RSV = respiratory syncytial virus.
a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations.
b. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.

A further 10 infants in the RSVpreF group and 12 in the placebo group were hospitalized due to EAC-confirmed RSV within 361 to 730 days after birth

All-Cause MA-LRTI within 90, 120, 150, 180 and 360 Days reported by investigators

There were 445 cases of investigator-reported all-cause MA-LRTI within 180 days after birth in the RSVpreF group and 464 in the placebo group in the evaluable efficacy population, corresponding to a VE point estimate of 4.1% (95% CI: -9.5, 16.0). There were 626 and 656 such cases within 360 days

after birth in respective groups, corresponding to a VE point estimate of 4.6% (95% CI: -6.6, 14.6). As previously concluded, vaccination was not efficacious in preventing all-cause MA-LRTI.

Other infant efficacy endpoints

Among 7148 in the infant evaluable efficacy population, 2547 (71.0) in the RSVpreF group and 2547 (71.5%) in the placebo group had at least 1 all-cause MA-RTI within 730 days after birth. There were 1591 and 1612 in respective groups who reported at least 1 all-cause MA-RTI event within 180 days after birth corresponding to a VE of 1.3% (95% CI: -5.8, 8.0%).

The number of EAC-confirmed RSV-positive MA-RTI cases within 180 days after birth was 187 in the RSVpreF group and 301 in the placebo group in the evaluable efficacy population, corresponding to a VE of 37.9% (95% CI: 25.2, 48.5%).

The number of investigator-reported RSV-positive MA-RTI cases in infants within 181 to 360 days after birth was 197 in the RSVpreF group and 172 in the placebo group (VE of -14.5% [95% CI: -41.7, 7.1%]). The numbers of RSV-positive MA-LRTI cases within 361 to 730 days after birth were 27 and 24 in respective groups (VE of -12.5% [95% CI: -103.7, 37.5%]). Similarly, there was no VE for severe cases within 181-360 and 361-720 days.

It remains the case that the majority of EAC-confirmed RSV MA-LRTI cases in the study were due to RSV-B. For EAC-confirmed MA-LRTI cases due to RSV subgroup B within 180 days after birth there were 43 cases in the RSVpreF group and 96 in the placebo group, corresponding to a VE of 55.2% (95% CI: 35.2, 69.5%). For EAC-confirmed severe MA-LRTI cases due to RSV subgroup B within 180 days after birth, there were 12 cases in the RSVpreF group and 49 cases in the placebo group, corresponding to VE of 75.5% (95% CI: 53.3, 88.1%).

For RSV-A, there were 24 and 32 EAC-confirmed MA-LRTI cases within 180 days of birth in respective groups, corresponding to a VE of 25.0% (95% CI: -31.4, 57.7%). For EAC-confirmed severe MA-LRTI cases due to RSV-A within 180 days after birth there were 8 and 17 cases in respective groups, corresponding to VE of 52.9% (95% CI: -15.1, 82.4%).

In premature infants (born <37 weeks gestation) there were 12 RSV-positive MA-RTI cases within 180 days after birth in the RSVpreF group and 15 in the placebo group, for a corresponding VE of 32.9% (95% CI: -53.4, 71.3%). For RSV-positive MA-LRTI there were 4 cases in the RSVpreF group and 6 in the placebo group, corresponding to a VE of 44.1% (95% CI: -135.6, 88.4%). For severe cases, there were 4 per group within 180 days after birth (VE of 16.2% [95% CI: -350.0, 84.4%]).

Immunogenicity

Data were obtained from a subset of maternal participants and their infants. This was not a randomised comparison.

In maternal participants, RSV A-, RSV B- and combined RSV A/B-neutralizing GMTs at delivery were higher in the RSVpreF group regardless of the time from vaccination to delivery. In the RSVpreF group, the GMTs and GMFRs were slightly higher in those who delivered <14 days or 14-29 days after vaccination compared to those who delivered >30 days after vaccination.

In infants, GMTs at birth were higher in the RSVpreF group compared to placebo, regardless of the time from maternal vaccination to delivery but lower in those born <14 days compared to those born 14-29 days or ≥30 days after maternal vaccination.

Table 18. RSV Neutralizing Titer GMTs by GA at Delivery – Maternal Participants – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)			
		<37 Weeks GA at Delivery		≥37 Weeks GA at Delivery	
		RSVpreF 120 µg	Placebo	RSVpreF 120 µg	Placebo
RSV Subgroup - TDV	Time Point[a]	GMT[b] (n[c]) (95% CI)[b]	GMT[b] (n[c]) (95% CI)[b]	GMT[b] (n[c]) (95% CI)[b]	GMT[b] (n[c]) (95% CI)[b]
A - 50%	Before vaccination	1457 (178) (1291.5, 1644.3)	1470 (148) (1278.9, 1689.0)	1412 (932) (1339.0, 1490.0)	1512 (970) (1437.5, 1591.3)
	At delivery	19565 (178) (16745.0, 22859.1)	1144 (148) (990.8, 1321.6)	16208 (936) (15336.6, 17129.2)	1362 (968) (1288.9, 1438.9)
B - 50%	Before vaccination	1769 (178) (1557.8, 2009.1)	1652 (148) (1450.0, 1882.2)	1618 (935) (1533.7, 1706.3)	1721 (970) (1631.2, 1815.4)
	At delivery	20672 (178) (17511.0, 24403.4)	1294 (148) (1122.8, 1492.2)	17654 (936) (16636.0, 18733.5)	1557 (968) (1471.3, 1646.7)
Combined A and B - 50%	Before vaccination	1606 (178) (1434.5, 1797.2)	1558 (148) (1371.5, 1770.3)	1512 (932) (1438.8, 1588.0)	1613 (970) (1536.9, 1693.5)
	At delivery	20111 (178) (17234.8, 23466.4)	1217 (148) (1064.5, 1391.4)	16915 (936) (16029.6, 17850.3)	1457 (966) (1383.4, 1535.1)

Abbreviations: GA = gestational age; GMT = geometric mean titer; LLOQ = lower limit of quantitation; RSV = respiratory syncytial virus; TDV = titer determining value.
Note: The LLOQ values for the neutralization titers are A - 50% = 242; B - 50% = 99.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. GMTs and 2-sided confidence intervals (CIs) were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (CIs based on the Student t distribution).
c. n = Number of participants with valid and determinate assay results for the specified subgroups at the given visit.

Table 19. RSV Neutralizing Titer GMTs by Maternal GA at Delivery – Infant Participants – Evaluable Immunogenicity Population

		Maternal Vaccine Group (as Randomized)			
		<37 Weeks GA at Birth		≥37 Weeks GA at Birth	
		RSVpreF 120 µg	Placebo	RSVpreF 120 µg	Placebo
RSV Subgroup - TDV	Time Point[a]	GMT[b] (n[c]) (95% CI)[b]	GMT[b] (n[c]) (95% CI)[b]	GMT[b] (n[c]) (95% CI)[b]	GMT[b] (n[c]) (95% CI)[b]
A - 50%	At birth	16555 (181) (14276.4, 19196.2)	1496 (150) (1291.0, 1734.7)	21503 (935) (20351.0, 22719.4)	1817 (972) (1715.9, 1923.3)
B - 50%	At birth	17874 (181) (15247.0, 20953.0)	1546 (151) (1351.0, 1769.6)	22608 (935) (21330.0, 23963.0)	1967 (975) (1853.4, 2088.2)
Combined A and B - 50%	At birth	17201 (181) (14842.8, 19935.0)	1522 (150) (1331.7, 1739.1)	22048 (935) (20921.6, 23236.1)	1892 (971) (1790.5, 1998.2)

Abbreviations: GA = gestational age; GMT = geometric mean titer; LLOQ = lower limit of quantitation; RSV = respiratory syncytial virus; TDV = titer determining value.
Note: The LLOQ values for the neutralization titers are A - 50% = 242; B - 50% = 99.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
a. Protocol-specified timing for blood sample collection.
b. GMTs and 2-sided confidence intervals (CIs) were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (CIs based on the Student t distribution).
c. n = Number of participants with valid and determinate assay results for the specified subgroups at the given visit.

In the RSVpreF group, maternal-to-infant placental transfer ratios were >1 in infants born ≥30 days after maternal vaccination but <1 in infants born <30 days after maternal vaccination.

Table 20. Maternal-to-Infant Placental Transfer Ratio of RSV A, RSV B, and Combined RSV A and B Neutralizing Titers by GA at Delivery – Evaluable Immunogenicity Population

	Maternal Vaccine Group (as Randomized)			
	<37 Weeks GA at Birth		≥37 Weeks GA at Birth	
	RSVpreF 120 µg	Placebo	RSVpreF 120 µg	Placebo
RSV Subgroup - TDV	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]	GM[a] (n[b]) (95% CI)[c]
A - 50%	0.87 (175) (0.76, 1.00)	1.31 (144) (1.18, 1.44)	1.33 (930) (1.26, 1.40)	1.33 (962) (1.28, 1.39)
B - 50%	0.88 (175) (0.77, 1.00)	1.20 (145) (1.10, 1.31)	1.28 (930) (1.22, 1.35)	1.27 (965) (1.21, 1.32)
Combined A and B - 50%	0.88 (175) (0.77, 1.00)	1.25 (144) (1.15, 1.36)	1.31 (930) (1.25, 1.37)	1.30 (959) (1.25, 1.35)

Abbreviations: GA = gestational age; GM = geometric mean; LLOQ = lower limit of quantitation; RSV = respiratory syncytial virus; TDV = titer determining value.
Note: The LLOQ values for the neutralization titers are A - 50% = 242; B - 50% = 99.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
a. GMs were calculated using all participants with available data for both maternal and infant participants.
b. n = Number of participants with valid and determinate assay results for both maternal and infant participants.
c. For each mother-infant dyad, the transfer ratio was calculated as the ratio of the infant's RSV neutralizing titer to the mother's. Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the ratios.

Among maternal participants in the RSVpreF group, the GMTs and GMFRs at delivery were lower in the EAC-confirmed infant cases group compared to the noncases group. The RSV A-, RSV B- and combined RSV A/B-neutralizing titre ratios of cases versus non-cases ranged from 0.71 to 0.74.

14.73. RSV Neutralizing Titer GMTs of Cases vs Non-Cases – Maternal Participants – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)			
		Cases		Non-Cases	
RSV Subgroup - TDV	Time Point[a]	RSVpreF 120 µg GMT[b] (n[c]) (95% CI)[b]	Placebo GMT[b] (n[c]) (95% CI)[b]	RSVpreF 120 µg GMT[b] (n[c]) (95% CI)[b]	Placebo GMT[b] (n[c]) (95% CI)[b]
A - 50%	Before vaccination	1693 (62) (1382.3, 2072.8)	1527 (125) (1332.2, 1749.6)	1411 (1016) (1341.3, 1485.0)	1508 (967) (1432.2, 1587.8)
	At delivery	13038 (62) (10089.5, 16849.0)	1236 (124) (1070.5, 1427.3)	16872 (1020) (16004.3, 17786.9)	1354 (966) (1280.5, 1431.2)
B - 50%	Before vaccination	1744 (62) (1413.2, 2151.5)	1748 (125) (1510.7, 2021.6)	1636 (1019) (1553.9, 1721.6)	1712 (967) (1623.4, 1805.9)
	At delivery	13341 (62) (10608.3, 16778.3)	1511 (124) (1309.3, 1742.7)	18360 (1020) (17345.3, 19433.1)	1529 (966) (1444.4, 1618.8)
Combined A and B - 50%	Before vaccination	1718 (62) (1414.3, 2086.9)	1633 (125) (1433.7, 1860.9)	1519 (1016) (1449.5, 1592.5)	1607 (967) (1530.3, 1687.3)
	At delivery	13189 (62) (10497.1, 16571.0)	1374 (123) (1207.5, 1564.0)	17600 (1020) (16715.9, 18531.1)	1439 (965) (1365.0, 1516.9)

Abbreviations: EAC = endpoint adjudication committee; GMT = geometric mean titer; LLOQ = lower limit of quantitation; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus; TDV = titer determining value.
Note: The LLOQ values for the neutralization titers are A - 50% = 242; B - 50% = 99.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: 'Cases' are infants with RSV-positive MA-LRTI within 180 days, confirmed by EAC.
a. Protocol-specified timing for blood sample collection.
b. GMTs and 2-sided confidence intervals (CIs) were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (CIs based on the Student t distribution).
c. n = Number of participants with valid and determinate assay results for the specified subgroups at the given visit.

Among infants in the RSVpreF group, RSV A-, RSV B- and combined RSV A/B-neutralizing GMTs at birth were slightly lower in the cases group compared to the noncases group.

14.76. RSV Neutralizing Titer GMTs of Cases vs Non-Cases – Infant Participants – Evaluable Immunogenicity Population

		Maternal Vaccine Group (as Randomized)			
		Cases		Non-Cases	
RSV Subgroup - TDV	Time Point[a]	RSVpreF 120 µg GMT[b] (n[c]) (95% CI)[b]	Placebo GMT[b] (n[c]) (95% CI)[b]	RSVpreF 120 µg GMT[b] (n[c]) (95% CI)[b]	Placebo GMT[b] (n[c]) (95% CI)[b]
A - 50%	At birth	20133 (64) (16240.6, 24958.7)	1868 (127) (1648.5, 2116.5)	21497 (1020) (20395.8, 22656.8)	1767 (968) (1666.1, 1874.3)
B - 50%	At birth	18768 (64) (15575.1, 22616.5)	2059 (128) (1777.5, 2385.4)	22816 (1020) (21571.7, 24132.5)	1899 (971) (1788.4, 2016.4)
Combined A and B - 50%	At birth	19439 (64) (16149.0, 23398.8)	1956 (127) (1724.5, 2219.0)	22147 (1020) (21054.9, 23294.8)	1834 (967) (1733.9, 1939.4)

Abbreviations: EAC = endpoint adjudication committee; GMT = geometric mean titer; LLOQ = lower limit of quantitation; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus; TDV = titer determining value.
Note: The LLOQ values for the neutralization titers are A - 50% = 242; B - 50% = 99.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: 'Cases' are infants with RSV-positive MA-LRTI within 180 days, confirmed by EAC.
a. Protocol-specified timing for blood sample collection.
b. GMTs and 2-sided confidence intervals (CIs) were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (CIs based on the Student t distribution).
c. n = Number of participants with valid and determinate assay results for the specified subgroups at the given visit.

14.77. RSV Neutralizing Titer GMTs for Cases vs Non-Cases in the RSVpreF Group – Infant Participants – Evaluable Immunogenicity Population

		Maternal Vaccine Group (as Randomized) RSVpreF 120 µg		
		Cases	Non-Cases	
RSV Subgroup - TDV	Time Point[a]	LS mean (95% CI)[b]	LS mean (95% CI)[b]	Ratio[c] (95% CI)[c]
A - 50%	At birth	24128.62 (16822.81, 34607.17)	27639.38 (20380.01, 37484.53)	0.87 (0.70, 1.08)
B - 50%	At birth	21684.14 (14785.72, 31801.08)	27543.67 (19931.14, 38063.73)	0.79 (0.63, 0.99)
Combined A and B - 50%	At birth	22873.75 (16214.01, 32268.90)	27591.48 (20631.11, 36900.09)	0.83 (0.67, 1.02)

Abbreviations: EAC = endpoint adjudication committee; GA = gestational age; GMT = geometric mean titer; LLOQ = lower limit of quantitation; LS = least squares; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus; TDV = titer determining value.
Note: The LLOQ values for the neutralization titers are A - 50% = 242; B - 50% = 99.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: 'Cases' are infants with RSV-positive MA-LRTI within 180 days, confirmed by EAC.
a. Protocol-specified timing for blood sample collection.
b. LS mean and 2-sided confidence intervals (CIs) were calculated by exponentiating the LS mean of logarithm of the titers and the corresponding CIs.
c. Ratios and 2-sided CIs were calculated by exponentiating the LS mean differences in the logarithms of the titers (cases participants - non-cases participants) and the corresponding CIs (CIs based on a GLM model and adjusting for race, country, GA at vaccination, GA at birth and maternal vaccination - delivery interval).

Maternal-to-infant placental transfer ratios were >1 for both the RSVpreF and placebo groups and did not differ appreciably between cases versus non-cases within the RSVpreF group.

C3671008 - Results Safety

All of the initial reactogenicity data following maternal vaccination and all other safety data from pregnant women and their infants up to the initial CSR safety cut-off date were previously reported, described and discussed. In the prior submission, the MAH also pooled the safety data from the Phase 2b and Phase 3 studies (C3671003 and C3671008) to provide a comprehensive description of safety in maternal participants and their infants.

In addition to the plans outlined in the protocol, the sponsor conducted programmatic changes on the safety and reactogenicity datasets to align with an updated dataset guidance request from FDA. Briefly, the guidance was to integrate any of the protocol defined 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. Infant safety data were not changed as a result of this guidance. The final CSR presents reactogenicity data using this guidance and a comparison to the data based on e-diary alone.

Following the initial unblinding of the study, Tier 1 AEs were identified (occurring within 1 month of vaccination or birth). Tier 1 AEs were preterm delivery and hypertensive disorders of pregnancy (pre-eclampsia, eclampsia, gestational hypertension, HELLP syndrome and superimposed pre-eclampsia in maternal participants and prematurity in infant participants. The final CSR summarises these and reports the difference in proportions and 2-sided 95% CI plus a p-value.

The following sections reflect the updated dataset used to develop the final CSR.

Patient exposure

For numbers of pregnant women exposed to vaccine (total 7386; 7025 completed) and total live infants born to these mothers (7307; 6612 completed a visit at 12 or 24 months) in C3671008 please see Tables 7 and 8 above. The median follow-up time after birth was 392 (placebo group) to 398 (vaccine group) days (range 1-1004 days).

Adverse events

<u>AEs in vaccinees</u>

The proportion of pregnant women who had any local reaction(s) within 7 days of study drug administration was higher in the RSVpreF group on each reporting day and overall (see below). Most local reactions were mild or moderate in severity; severe AEs were reported by 0.3% in the RSVpreF group. The most common local reaction was pain (40.7% vs. 10.2%). The median day of onset was day 2 and the median duration of reactions was 2-3 days.

In contrast, similar proportions in each group reported systemic reactions, of which most were mild or moderate in severity and the most common was fatigue. The incidence of fever was low (<3%) in both groups although muscle pai was reported more frequently in the vaccine group (26.6% vs. 17.1%).

14.82. Any Local Reactions Reported on Each Day After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)					
	RSVpreF 120 µg			Placebo		
Day	N[a]	n[b] (%)	(95% CI)[c]	N[a]	n[b] (%)	(95% CI)[c]
1	3359	313 (9.3)	(8.4, 10.4)	3341	250 (7.5)	(6.6, 8.4)
2	3541	958 (27.1)	(25.6, 28.6)	3444	125 (3.6)	(3.0, 4.3)
3	3447	994 (28.8)	(27.3, 30.4)	3357	43 (1.3)	(0.9, 1.7)
4	3418	676 (19.8)	(18.5, 21.2)	3340	28 (0.8)	(0.6, 1.2)
5	3361	365 (10.9)	(9.8, 12.0)	3312	27 (0.8)	(0.5, 1.2)
6	3310	188 (5.7)	(4.9, 6.5)	3290	23 (0.7)	(0.4, 1.0)
7	3319	91 (2.7)	(2.2, 3.4)	3298	18 (0.5)	(0.3, 0.9)
Any day[d]	3678	1565 (42.6)	(40.9, 44.2)	3651	380 (10.4)	(9.4, 11.4)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 through Day 7 after vaccination. Reactogenicity reported in the CRF during the e-diary collection period are included.
Note: Any local reaction: any redness, swelling or pain at the injection site of at least mild severity.
a. N = number of participants reporting yes or no for any local reaction on the specified day. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting any local reaction on the specified day.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. Any day includes Day 1 to Day 7. n = Number of participants reporting yes for any day. N = number of participants

Figure 3 Participants Reporting Local Reactions by Maximum Severity Within 7 Days After Vaccination – Maternal Participants – Safety Population

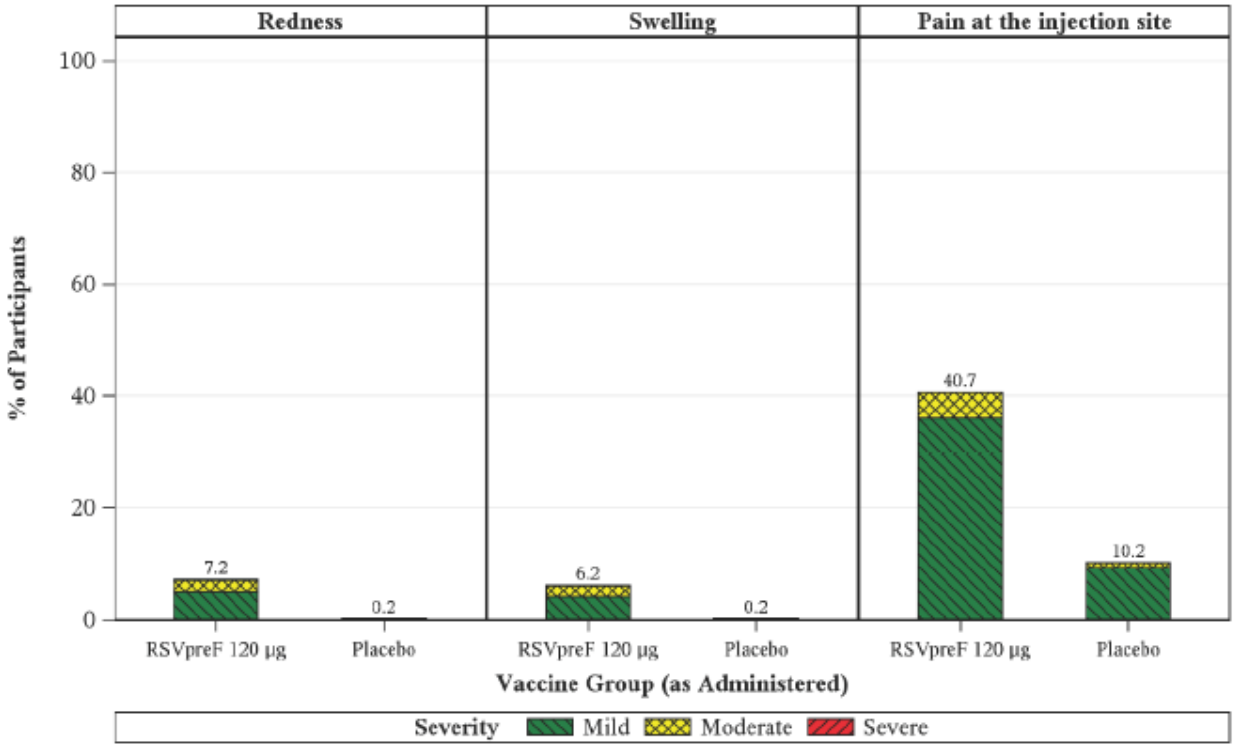
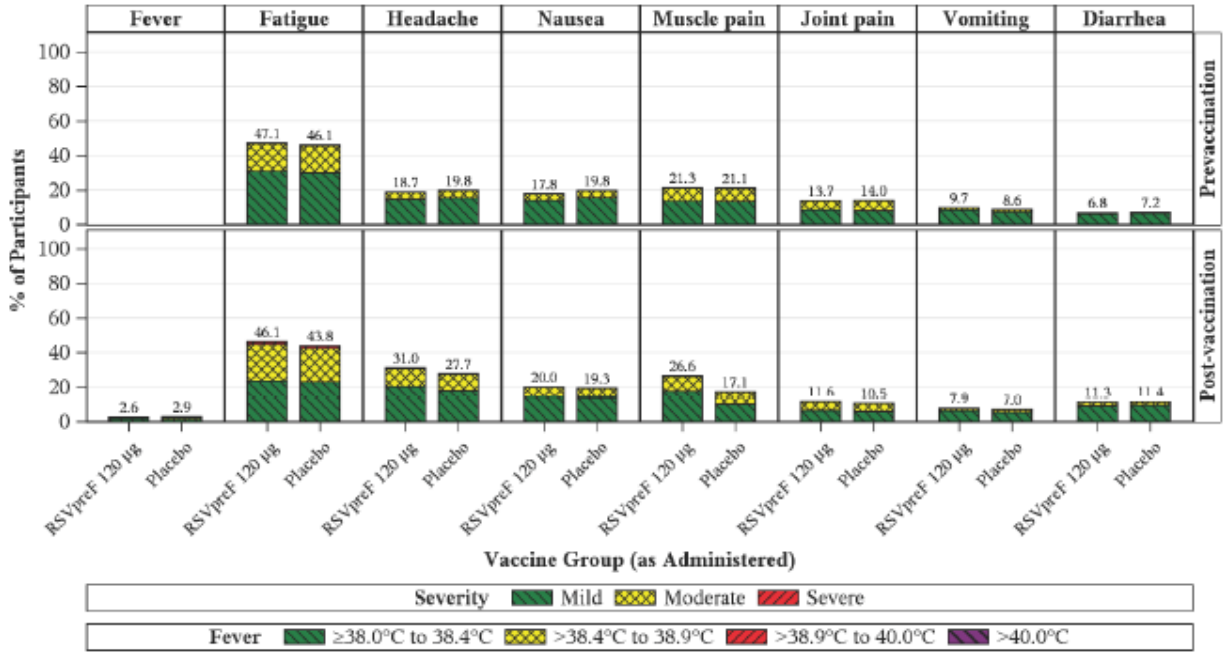


Figure 4 Participants Reporting Systemic Events by Maximum Severity - Maternal Participants - Safety Population



All AEs were collected through 1 month after vaccination (delivery may have occurred in this time) while SAEs and AESIs were collected through 6 months postdelivery. Overall, for each category of AE reported within 1 month after vaccination, proportions were similar between groups.

Table 21. Number (%) of Participants Reporting Adverse Events by Category Within 1 Month After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=3698)		Placebo (N[a]=3687)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Any event	516 (14.0)	(12.9, 15.1)	488 (13.2)	(12.2, 14.4)
Serious	160 (4.3)	(3.7, 5.0)	139 (3.8)	(3.2, 4.4)
Immediate[d]	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
Severe	66 (1.8)	(1.4, 2.3)	50 (1.4)	(1.0, 1.8)
Life-threatening	19 (0.5)	(0.3, 0.8)	11 (0.3)	(0.1, 0.5)
Related	13 (0.4)	(0.2, 0.6)	4 (0.1)	(0.0, 0.3)
AESIs	102 (2.8)	(2.3, 3.3)	95 (2.6)	(2.1, 3.1)
AE leading to withdrawal	0	(0.0, 0.1)	0	(0.0, 0.1)

a. N = number of participants in the specified vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event. For "any event", n = number of participants reporting at least 1 occurrence of any adverse event.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. An immediate AE is defined as any AE that occurred within the first 30 minutes after administration of the investigational product for maternal participants.

The most frequently reported AEs in the month after vaccination were in the SOCs of Pregnancy, puerperium and perinatal conditions (7.1% vs. 6.3%) and Infections and infestations (1.9% vs. 2.1%). By PT, the most frequently reported in both groups was premature delivery, which was solicited as an AESI (2.2% vs. 2.0%). AEs reported from delivery to 1 month after delivery were similar in the RSVpreF (16.4%) and placebo groups (15.9%). AEs were reported in ≤2.7% between 1 and 6 months after delivery.

Individual Tier 1 AEs (prespecified events of clinical importance) occurred at a similar frequency overall in both vaccine groups within 1 month of vaccination.

14.93. Tier 1 Adverse Events Reported Within 1 Month After Vaccination - Maternal Participants - Safety Population

	Vaccine Group (as Administered)				
	RSVpreF 120 µg (N[a]=3698)	Placebo (N[a]=3687)			
Preferred Term	n[b] (%)	n[b] (%)	Difference[c]	95% CI[d]	p-Value[d]
Eclampsia	3 (<0.1)	2 (<0.1)	0.03	(-0.12, 0.19)	0.657
Gestational hypertension	31 (0.8)	24 (0.7)	0.19	(-0.21, 0.60)	0.349
HELLP syndrome	2 (<0.1)	1 (<0.1)	0.03	(-0.10, 0.17)	0.565
Hypertension	10 (0.3)	9 (0.2)	0.03	(-0.22, 0.28)	0.823
Pre-eclampsia	36 (1.0)	32 (0.9)	0.11	(-0.34, 0.56)	0.635
Premature delivery	82 (2.2)	73 (2.0)	0.24	(-0.42, 0.90)	0.477
Superimposed pre-eclampsia	0	1 (<0.1)	0.03	(-0.08, 0.15)	0.317

AEs from vaccination through the 1-month follow-up visit that were considered related to vaccination were infrequent (0.4% vs. 0.1%) and occurred most commonly in the SOC of General disorders and administration site conditions. Most related AEs occurred after vaccination but before delivery but two AEs were reported in the RSVpreF group at delivery to 1 month after delivery. These were an SAE of eclampsia and premature delivery (see the corresponding related AE in the infant below).

AEs in infants born to vaccinees

AEs and SAEs in infants were captured from birth. All AEs were collected through 1 month after birth; SAEs (including congenital anomalies), AESIs and NDCMCs were collected up to 12 or 24 months. Overall, for each category of AE reported within 1 month after birth, proportions were similar for infants born to mothers in the RSVpreF and placebo groups.

One infant in the RSVpreF group had an AE assessed as related to maternal vaccination by the investigator. This concerned premature birth at 36 weeks and 5 days, which was relative day 86 to maternal vaccination (see also above).

Table 22. Number (%) of Participants Reporting Adverse Events by Category Within 1 Month After Birth - Infant Participants - Safety Population

	Maternal Vaccine Group (as Administered)			
	RSVpreF 120 µg (N[a]=3659)		Placebo (N[a]=3646)	
Adverse Event Category	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Any event	1391 (38.0)	(36.4, 39.6)	1291 (35.4)	(33.9, 37.0)
Serious	597 (16.3)	(15.1, 17.6)	587 (16.1)	(14.9, 17.3)
Severe	168 (4.6)	(3.9, 5.3)	142 (3.9)	(3.3, 4.6)
Life-threatening	34 (0.9)	(0.6, 1.3)	35 (1.0)	(0.7, 1.3)
Related	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
AESIs	306 (8.4)	(7.5, 9.3)	265 (7.3)	(6.4, 8.2)
Congenital Anomalies	205 (5.6)	(4.9, 6.4)	245 (6.7)	(5.9, 7.6)
NDCMCs	10 (0.3)	(0.1, 0.5)	6 (0.2)	(0.1, 0.4)
AE leading to withdrawal	0	(0.0, 0.1)	0	(0.0, 0.1)

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

The proportions of infants with any AE reported from birth to 24 months of age were 43.7% in the RSVpreF group and 41.5% in the placebo group. The most frequently reported of these were in the SOCs of Pregnancy, puerperium and perinatal conditions (16.9% vs. 15.7%), Congenital, familial and genetic disorders (8.8% vs. 8.9%) and Respiratory, thoracic and mediastinal disorders (8.3% in both groups). By PT, the most frequently reported was jaundice neonatal (7.3%) which was also reported in 6.9% of the placebo group.

The Tier 1 AE of premature baby occurred at a similar frequency in both groups (5.7% vs. 4.7%). Tier 2 AEs occurred at a similar frequency for both groups within 1 month of birth, the most frequently reported being jaundice neonatal (7.3% vs. 6.9%) and hyperbilirubinaemia neonatal (3.0% vs. 2.9%). Prematurity and low birth weight occurred at a similar frequency in both groups.

Serious adverse events and deaths

Deaths

In the final CSR there remained a single case of maternal death concerning a participant in the RSVpreF group in the Philippines who had postpartum haemorrhage and hypovolaemic shock, which was assessed by the investigator as not related to study intervention.

From time of the primary analysis through end of study there was one additional stillbirth reported (for an index pregnancy in the placebo group). There were no changes in the number of spontaneous abortions reported for subsequent pregnancies.

Table 23. Summary of Stillbirths, Maternal Deaths and Spontaneous Abortions - Maternal Participants - Safety Population

			Vaccine Group (as Administered)			
			RSVpreF 120 µg (N[a]=3698)		Placebo (N[a]=3687)	
Event Type	Time Interval	Preferred Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Stillbirth[d]	After vaccination to 6 months after delivery	Any event	10 (0.3)	(0.1, 0.5)	9 (0.2)	(0.1, 0.5)
		Foetal death#	6 (0.2)	(0.1, 0.4)	8 (0.2)	(0.1, 0.4)
		Stillbirth	4 (0.1)	(0.0, 0.3)	1 (<0.1)	(0.0, 0.2)
	After vaccination but before delivery	Any event	4 (0.1)	(0.0, 0.3)	3 (<0.1)	(0.0, 0.2)
		Foetal death#	3 (<0.1)	(0.0, 0.2)	3 (<0.1)	(0.0, 0.2)
		Stillbirth	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Delivery to 1 month after delivery	Any event	6 (0.2)	(0.1, 0.4)	6 (0.2)	(0.1, 0.4)
		Foetal death#	3 (<0.1)	(0.0, 0.2)	5 (0.1)	(0.0, 0.3)
		Stillbirth	3 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
Maternal Death	After vaccination to 6 months after delivery	Any event	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
		Hypovolaemic shock	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
		Postpartum haemorrhage	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Delivery to 1 month after delivery	Any event	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
		Hypovolaemic shock	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
		Postpartum haemorrhage	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Spontaneous Abortion[e]	After vaccination to 6 months after delivery	Any event	1 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)
		Abortion spontaneous	1 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)
	1 Month after delivery to 6 months after delivery	Any event	1 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)
		Abortion spontaneous	1 (<0.1)	(0.0, 0.2)	2 (<0.1)	(0.0, 0.2)

a. N = number of participants in the vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified adverse event or death term. For "any event", n = number of participants reporting at least 1 occurrence of any adverse event or death term.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
d. This event type includes AE records of stillbirth and foetal death.
e. These events are all related to second pregnancies in maternal participants.

There were 22 infant deaths from birth to 24 months of age: 8 (0.2%) in the RSVpreF group and 14 (0.4%) in the placebo group. This total includes 5 additional deaths vs. the prior CSR (3 in the RSVpreF group and 2 in the placebo group).

Table 24. Summary of Deaths - Infant Participants - Safety Population

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N*=3659)		Placebo (N*=3646)	
Time Interval	Death Details Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
Birth to 24 months of age	Any event	8 (0.2)	(0.1, 0.4)	14 (0.4)	(0.2, 0.6)
	Chronic hepatic failure	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Death	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Enterovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Escherichia sepsis	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Gastroenteritis	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Hepatic haematoma	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Ill-defined disorder	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Interstitial lung disease	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Left ventricular failure	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Low birth weight baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Meconium aspiration syndrome	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Meningitis	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Multiple organ dysfunction syndrome	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Neonatal asphyxia	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Neonatal respiratory distress	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Pneumonia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Premature baby	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Pulmonary hypertension	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Rhinovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Sepsis neonatal	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Skull base tumour	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Small for dates baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sudden infant death syndrome	0	(0.0, 0.1)	3 (<0.1)	(0.0, 0.2)
	Ventricular hypoplasia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
Birth to 1 month of age	Any event	3 (<0.1)	(0.0, 0.2)	5 (0.1)	(0.0, 0.3)
	Escherichia sepsis	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Meconium aspiration syndrome	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Multiple organ dysfunction syndrome	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Neonatal asphyxia	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Premature baby	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)

		Maternal Vaccine Group (as Administered)			
		RSVpreF 120 µg (N*=3659)		Placebo (N*=3646)	
Time Interval	Death Details Term	n[b] (%)	(95% CI)[c]	n[b] (%)	(95% CI)[c]
	Pulmonary hypertension	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sepsis neonatal	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
	Ventricular hypoplasia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
1 Month to 6 months of age	Any event	3 (<0.1)	(0.0, 0.2)	6 (0.2)	(0.1, 0.4)
	Death	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Enterovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Gastroenteritis	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Ill-defined disorder	1 (<0.1)	(0.0, 0.2)	1 (<0.1)	(0.0, 0.2)
	Interstitial lung disease	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Low birth weight baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Meningitis	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Neonatal respiratory distress	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Pneumonia	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Premature baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Rhinovirus infection	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Small for dates baby	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Sudden infant death syndrome	0	(0.0, 0.1)	2 (<0.1)	(0.0, 0.2)
6 Months to 12 months of age	Any event	1 (<0.1)	(0.0, 0.2)	3 (<0.1)	(0.0, 0.2)
	Gastroenteritis	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Hepatic haematoma	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Left ventricular failure	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
	Skull base tumour	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Sudden infant death syndrome	0	(0.0, 0.1)	1 (<0.1)	(0.0, 0.2)
12 Months to 24 months of age	Any event	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
	Chronic hepatic failure	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)

Note: Both primary and secondary causes of death are listed for each event.
a. N = number of participants in the vaccine group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified death term. For "any event", n = number of participants reporting at least 1 occurrence of any death term.
c. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.

SAEs

Proportions of maternal participants with any SAEs reported after vaccination to 6 months after delivery were similar in the RSVpreF group (16.6%) and placebo group (15.8%). Most occurred from delivery to 1 month after delivery (≤10.4%) and after vaccination but before delivery (≤7.4%).

After vaccination to 6 months after delivery, SAEs were most frequently reported in the SOC of Pregnancy, puerperium and perinatal conditions in the RSVpreF group (12.3%) and placebo group (11.6%). The most frequently reported by PT in the RSVpreF group were pre-eclampsia (1.8%), fetal distress syndrome (1.8%), gestational hypertension (1.2%), non-reassuring fetal heart rate pattern (1.0%) and arrested labour (1.0%). Corresponding rates in the placebo group were 1.4%, 1.8%, 1.1%, 0.8% and 1.2%.

SAEs assessed as related by the investigator were:
In the RSVpreF group:
☐ Pain in extremity (severe) with onset 2 days after vaccination and resolution after 6 days
☐ Premature labour (life-threatening) with onset 2 days after vaccination
☐ Eclampsia (life-threatening with onset 15 days after vaccination
The SAE of systemic lupus erythematosus in the RSVpreF group that was previously reported as related to study intervention by the investigator has since been re-assessed based on a rheumatological evaluation and is no longer considered vaccine-related.

The proportions of infants with any SAEs reported from birth to 24 months of age were similar in the RSVpreF group (19.0%) and placebo group (18.9%). Most SAEs occurred from birth to 1 month of age (≤16.3%) and none was considered related to maternal vaccination. SAEs were most frequently reported in the SOCs of Respiratory, thoracic and mediastinal disorders, Pregnancy, puerperium and perinatal conditions and Infections and infestations (4.5%, 3.9% and 3.6% in the RSVpreF group and 4.2%, 3.5% and 3.1%, respectively, in the placebo group. The most frequently reported SAEs by were jaundice neonatal, hyperbilirubinemia neonatal, premature baby and respiratory distress, with similar rates in both groups. Congenital anomalies were reported as SAEs in 5.6% and 6.7% (all were to be reported as SAEs, regardless of severity).

AESIs

The AESI of premature delivery was reported at a similar frequency for the RSVpreF and placebo groups (5.7% vs. 4.8%).

Low birth weight baby was reported for 5.1% vs. 4.3% of infants and prematurity for 5.7% vs. 4.7%. Developmental delay reported from birth and 24 months of age occurred in 0.1% vs. <0.1%.

Birth outcomes were similar for the RSVpreF and placebo groups. No meaningful differences were detected with respect to birth outcomes including GA at birth, Apgar scores, or birthweight. Most infants in both groups were born at term (≥93.6% of all infants; ≥37 weeks to <42 weeks GA) and had a normal birthweight (>2500 g). Most of the pre-term infants in all subgroups were near-term (≥34 to <37 weeks). Most (70.2%) were delivered via vaginal delivery and the median GA at delivery was 39.14 weeks for both groups. The median number of days between vaccination and delivery were similar (54.0 days vs. 55.0 days). Abnormal physical examination findings at birth were reported for 12.7% vs. 13.5%).

Discontinuation due to AES

It remains the case that one maternal participant in the placebo group withdrew from the study due to the AE of premature delivery. No infants were withdrawn due to AEs.

2.3.3. Discussion on clinical aspects

The following should be read in conjunction with the comments made, including the benefit-risk discussion, in the prior assessment reports.

Efficacy

The results reported in the CSR of December 2022 reflected the second interim efficacy analysis, which was conducted following the predicted end of the fourth RSV season and included 80 evaluable cases of MA-LRTI due to RSV with onset within 90 days of birth, of which 39 were severe MA-LRTI. Only RSV MA-LRTI cases fully adjudicated prior to taking a data snapshot were included in the second interim analysis. The results led the E-DMC to recommend stopping the study because the success criterion was met for one of the two primary efficacy endpoints. At the time of data cut-off for the second interim analysis, >75% of the pregnant women had completed the study and almost 80% of their infants had completed at least to month 6.

Enrolment for maternal participants was completed on 03 Oct 2022, i.e. after the data cut-off on 30 Sep 2022 used for the second interim analysis. All participants were followed-up for study completion after the decision to stop recruitment and the LPLV occurred on 27 October 2023. The final CSR describes data obtained for 7420 randomised maternal participants (vs. 7392 randomised at the time of the data cut-off for the second interim analysis) and for 7307 (vs. 7128 in the second interim analysis) of their live infants enrolled into the study.

In the final analysis for EAC-adjudicated cases over 180 days after birth, the lower bounds of the 95% CI (note that all CI reported for the final analysis are 95%) around the point estimates for VE were >30% for all and for severe RSV MA-LRTI. The final analysis reflected a relatively small difference in numbers of EAC-adjudicated RSV MA-LRTI and severe RSV MA-LRTI cases vs. the primary analysis. For example, for all RSV MA-LRTI, the two tables below show the numbers of cases – the first being the primary analysis and the second the final analysis. In both analyses, the point estimates for VE show only modest decreases as time elapsed from birth.

Table 14. RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

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

Abbreviations: EAC = endpoint adjudication committee; MA-LRTI = medically attended lower respiratory tract illness; RSV = respiratory syncytial virus.
a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations.
b. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases.
c. Confidence intervals are 99.5% CI at 90 days (as determined by the alpha spending function and adjusted using the Bonferroni procedure), and 97.58% CI at later intervals (based on 2-sided alpha of 0.0483 adjusted using the Bonferroni procedure).
d. Unadjusted 1-sided nominal p-value for the null hypothesis that vaccine efficacy ≤20%. Statistical significance cannot be claimed for these analyses due to the planned testing strategy and the failure to meet the statistical success criterion at 90 days for this endpoint.

Table 14. RSV-Positive MA-LRTIs, Confirmed by the EAC, Occurring Within 90, 120, 150, and 180 Days After Birth - Infant Participants - Evaluable Efficacy Population

	Maternal Vaccine Group (as Randomized)		
	RSVpreF 120 µg (N[a]=3585)	Placebo (N[a]=3563)	
Time Interval	Number of Cases (%)	Number of Cases (%)	Vaccine Efficacy[b] (%) (95% CI)
90 Days after birth	25 (0.7)	59 (1.7)	57.6 (31.3, 74.6)
120 Days after birth	40 (1.1)	88 (2.5)	54.5 (33.2, 69.5)
150 Days after birth	55 (1.5)	110 (3.1)	50.0 (30.3, 64.5)
180 Days after birth	67 (1.9)	132 (3.7)	49.2 (31.4, 62.8)

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

Beyond day 180, based on investigator-reported RSV MA-LRTI, vaccine efficacy decreased to 43.8% (25.6, 57.7) for cases up to 210 days and then dropped slightly over time to 33% (15.2, 47.1) by 360 days.

As noted previously, maternal vaccination against RSV does not protect against all-cause MA-LRTI. Moreover, the prior conclusions on efficacy against RSV-A and RSV-B (the latter being the subgroup causing the vast majority of cases in the study) are unchanged.

In the final analysis the distribution of maternal participants by GA at time of vaccination was very similar to that reported for the population included in the primary analysis. The final CSR does not repeat the analyses of EAC-adjudicated RSV MA-LRTI cases according to GA at time of vaccination and the Rapporteur does not request such analyses given the very small differences in subgroup numbers vs. the primary analysis. Therefore, the additional data do not allow further elucidation of the possible effect of GA at time of maternal vaccination on infant protection.

Immunogenicity

The immunogenicity results should be viewed in the light of the fact that data were obtained from selected sites/countries and not from a randomised subset of the entire study population.

The MAH explains that there was a need for laboratory prioritisation such that serology was completed on selected subsets from the maternal and infant evaluable immunogenicity populations, including:

- Maternal participants who delivered <14 days and <30 days after vaccination and their infants;
- Infants born at <37 weeks gestational age and their mothers;
- A random selection of maternal participants and their infants from countries from high to low middle income (US, Argentina, South Africa, the Philippines and the Gambia). In this strategy, 84 mother-infant pairs were selected at random except for the Philippines for which all were tested because there were <84 participants. Equal numbers were selected across vaccination groups and GA at vaccination windows (24 to <28 weeks, 28 to <32 weeks, and 32 to 36 weeks);
- Adolescents and their infants;
- Infants who had MA-LRTI due to RSV within 180 days of birth and their mothers.

Additional serology testing was done for regulatory purposes in specific regions.

The NA responses to vaccination in maternal participants and the infant transfer ratios were in keeping with data obtained from pregnant women in C3671003. In the majority of infant subgroups the combined RSV A/B maternal-to-infant placental transfer ratios in the RSVpreF group were >1 (range from 0.87 to 1.65). In contrast, transplacental antibody transfer ratios for infants born <14 days or between 14-29 days after maternal vaccination were 0.32 and 0.67, respectively. Furthermore, although the NA GMRs in infants born between 14-29 days after vaccination were ≥10 in the RSVpreF group compared with placebo, the GMR vs. the placebo group was 4.13 for infants born within 14 days of maternal vaccination.

Based on these limited analyses, the NA GMTs at birth were slightly lower in the infants who went on to have EAC-adjudicated RSV MA-LRTI vs. those who did not with combined RSV A/B GMTs of 19439 and 22147, respectively. For RSV A-, RSV B- and combined RSV A/B NA, the ratios between cases vs. non-cases ranged from 0.79 to 0.87, with upper bounds of the 95% CIs from 0.99 to 1.08. The transfer ratios did not differ appreciably between cases and non-cases within the RSVpreF group. Therefore, this limited analysis did not point to a threshold NA value that might broadly differentiate infants according to likely protection vs. non-protection.

Clinical safety

The additional safety data have not pointed to any new concerns in maternal or infant participants up to 24 months after birth. As previously noted, local reactions were reported more frequently in the RSVpreF group but they were mostly of mild to moderate severity and short-lived. Systemic events occurred at similar rates in vaccine and placebo groups. Importantly, rates for fever were low and most were ≤38.9°C.

The additional data do not point to any new issues regarding premature delivery (5.7% vs. 4.8%), infant condition at birth and infant development after birth.

Conclusions

It is agreed with the applicant that the final analysis results are consistent with the results of the primary analysis.

The descriptive analyses included in the final CSR support the conclusions drawn from the primary analysis. The current SmPC accurately reflects the primary analysis of efficacy and no change to the SmPC is proposed by the MAH or considered appropriate by the CHMP.

3. CHMP's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

None.