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U.S. FOOD & DRUG ADMINISTRATION

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

Review of Efficacy and Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO)

Immunization During the Second or Third Trimester of Pregnancy (24-36 weeks gestation) to Prevent RSV Lower Respiratory Tract Disease [LRTD] and Severe RSV LRTD in Infants, From Birth Through 6 Months of Age

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Division of Vaccines and Related Products Applications

Outline

- Introduction (Vaccine composition, dosage/administration, proposed indication)
- Overview of Clinical Studies
- Efficacy Data
- Safety Data
- Pharmacovigilance Plan
- Summary and Questions for VRBPAC

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RSVPreF Vaccine (ABRYSVO)

Vaccine composition*	Respiratory syncytial virus (RSV) recombinant stabilized prefusion F (preF) proteins • 60 µg RSVpreF from RSV A • 60 µg RSVpreF from RSV B
Dosage and administration	A single 0.5 mL dose administered intramuscularly in the late second or third trimester of pregnancy (24 through 36 weeks gestation)
Applicant's proposed indication	Prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth through 6 months of age by active immunization of pregnant individuals

*Presentation: Lyophilized antigen reconstituted with sterile water
Placebo: Lyophile match, containing excipients matched to vaccine formulation, minus the active ingredients

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Clinical Development - Total Exposure

Final Formulation ABRYSVO [120ug RSVPreF]: 3797 Maternal Participants (all studies)

Clinical Trial	Population	Country	120ug RSVpreF	Placebo/ Comparator
Phase 3: Safety, Efficacy **C3671008**	**Pregnant** individuals ≤49 yrs and their infants; vaccination at 24 0/7 to ≤36 0/7 weeks gestation	Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, US	**3682**	**3676**
Phase 2: Safety, Immunogenicity **C3671003**	**Pregnant** individuals 18-49 yrs and their infants; vaccination at 24 0/7 to ≤36 0/7 weeks gestation	Argentina, Chile, South Africa, US	**115**	**117**
Phase 2: Tdap co-admin **C3671004**	Nonpregnant individuals 18-49 yrs	US	141 (co-ad); 141 (RSVPreF alone)	141 (Tdap alone)
Lot Consistency **C3671014**	Adults 18-49 yrs	US	746	247
Phase 1/2: Safety, Immunogenicity, Dose-finding **C3671001**	Adults 18-49 yrs	US	93	53

Source: FDA-generated table

Study 1008: Two Primary Endpoints

Phase 3, ongoing, randomized, double-blinded, placebo-controlled

Primary Endpoint #1:
PCR-confirmed RSV MA-LRTD within 90, 120, 150, and 180 days after birth

Primary Endpoint #2:
PCR-confirmed *severe* RSV MA-LRTD (same timepoints)

Vaccine efficacy (VE) definition: 1- Risk Ratio (RR)

Statistical Criteria: Lower bound of the 2-sided multiplicity-adjusted 95% CI for VE >20%

- **Event-driven study** with a target of 124 adjudicated cases of RSV-associated MA-LRTD within 90 days from birth
- **Up to 10,000 pregnant individuals** were planned to be randomized (1:1) to receive a **single dose of RSVpreF or placebo**
- **Up to 2 Interim Analyses (IA)** planned

Study 1008: Interim Analyses

First Interim Analysis

After accrual of at least 43 RSV-associated MA-LRTD cases **within 90 days from birth**

- Conducted in April 2022 when 56 cases were accumulated

Second Interim Analysis

After accrual of at least 62 RSV-associated MA-LRTD cases **within 90 days from birth**

- Conducted in October 2022 when 80 cases were accumulated

Enrollment start	Data Cutoff Efficacy Endpoints	Data Cutoff Safety Endpoints
June 17, 2020	Sept 30, 2022	Sept 2, 2022

Study 1008: Study Success Criteria

Two primary efficacy endpoints: Infant RSV MA-LRTD and severe RSV MA-LRTD

- **Tested in parallel** using a Bonferroni multiplicity adjustment procedure
- **Trial success:** Multiplicity-adjusted CI lower bound for VE >20% for **either one** of the two primary endpoints at 90 days after birth
- **Vaccine efficacy:** Percentage reduction in the risk of MA-LRTD [severe MA-LRTD] due to RSV in the RSV vaccine group, relative to the placebo group

- Testing of the 2 primary endpoints follows a fixed sequence **across the time intervals** (90 days, 120 days, 150 days, and 180 days after birth)
- Testing for the endpoint at 120 days is conducted only upon success at 90 days, testing at 150 days is conducted only upon success at 120 days, etc.

Study 1008: Other Efficacy Endpoints

Secondary Endpoints

- VE against hospitalization due to RSV (up to 360 days after birth)
- VE against incidence of all-cause MA-LRTD (up to 360 days after birth)
- VE against MA-LRTD due to RSV within 210 to 360 days after birth

Statistical Criterion

- The 3 secondary efficacy endpoints are tested in parallel conditional upon success of at least one of the 2 primary efficacy endpoints through 180 days.
- Success criterion for the secondary efficacy endpoints: Multiplicity-adjusted CI lower bound for VE >0%.

Exploratory Endpoints

- VE against RSV MA-RTD (within 730 days after birth)
- VE against RSV-A /B MA-LRTD
- VE against RSV MA-LRTD (from 361 to 730 days after birth)

Study 1008: Primary Safety Objectives

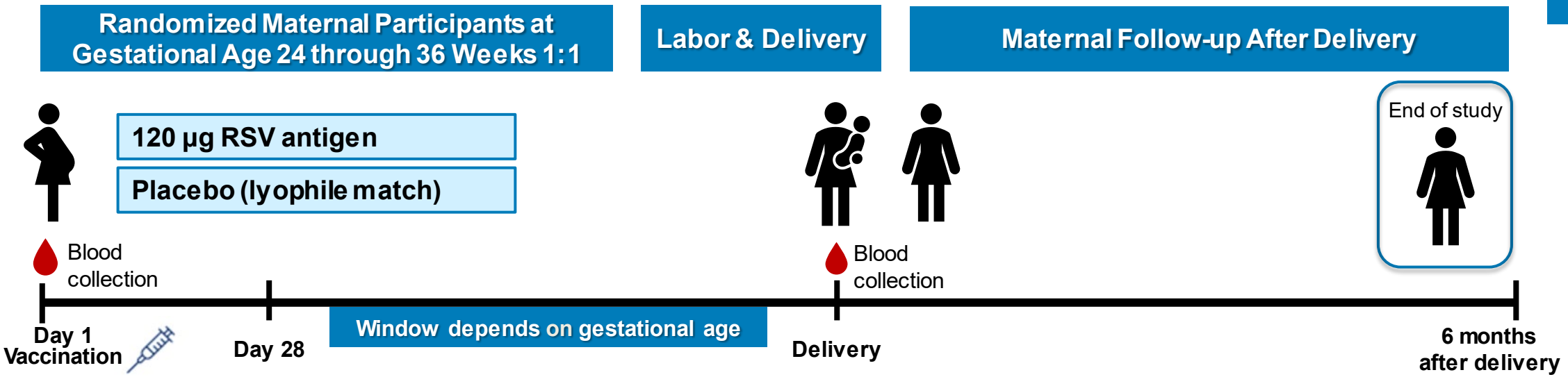
Infant Participants

- Adverse events (AEs) from birth to 1 month of age
- Birth outcomes: congenital anomalies and adverse events of special interest (AESIs) [prematurity, low birth weight (LBW) baby, developmental delay]
- Serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs) from birth to 24 months of age

Maternal Participants

- Solicited local and systemic reactions within 7 days after vaccination
- AEs through 1 month after vaccination
- SAEs through 6 months post-delivery

Study 1008 Design: Maternal Participants



E-diary 7 days

AEs collected for 1 month

SAEs collected throughout study

RTI surveillance period starts from vaccination until end of study.
MA-RTIs captured as study endpoints; no nasal swab collection (self-reported events).

Source: Adapted from Pfizer protocol, Study c3671008
Abbreviations: AE=adverse event; MA-RTIs=medically attended respiratory tract illness; RTI=respiratory tract illness; RSV=respiratory syncytial virus; SAE=serious adverse event

Study 1008: Disposition of Maternal Participants

Maternal Participants	RSVpreF N=3695[a] n (%)	Placebo N=3697 n (%)	Total N=7392[a] n (%)
Safety population	3681 (99.6)	3676 (99.4)	7357 (99.5)
Completed vaccination	3682 (99.6)	3676 (99.4)	7358 (99.5)
Completed study (6 months follow-up)	2840 (76.9)	2843 (76.9)	5683 (76.9)
Ongoing[b]	667 (18.1)	666 (18.0)	1333 (18.0)

Source: adapted from Pfizer CSR, Study 1008
Abbreviations: n=Number of participants in the specified category.
a. Randomized population, which is the denominator for the percentage calculations; b. Ongoing refers to participants who were randomized and have not yet completed or withdrawn.

Study 1008: Maternal Participants- Baseline Characteristics

Demographic Characteristic	RSVpreF N=3682 n (%)	Placebo N=3675 n (%)	Total N=7357 n (%)
White	2383 (64.7)	2365 (64.4)	4748 (64.5)
Asian	454 (12.3)	464 (12.6)	918 (12.5)
Black or African American	720 (19.6)	723 (19.7)	1443 (19.6)
American Indian or Alaskan Native	38 (1.0)	37 (1.0)	75 (1.0)
Native Hawaiian or Other Pacific Islander	9 (0.2)	12 (0.3)	21 (0.3)
Multiracial	30 (0.8)	21 (0.6)	51 (0.7)
Race not reported or unknown	48 (1.3)	53 (1.4)	101 (1.4)
Hispanic/Latino	1049 (28.5)	1075 (29.3)	2124 (28.9)
Not Hispanic/non-Latino	2603 (70.7)	2567 (69.9)	5170 (70.3)
Ethnicity not reported or unknown	30 (0.8)	33 (0.9)	63 (0.9)

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

Study 1008: Maternal Participants- Baseline Characteristics (cont'd)

Baseline Characteristic	RSVpreF N=3682 n (%)	Placebo N=3675 n (%)	Total N=7357 n (%)
Sex: Female	3682 (100.0)	3675 (100.0)	7357 (100.0)
Median age at vaccination (years)	29.0	29.0	29.0
Median gestational age (GA) at vaccination (weeks)	31.30	31.30	31.30
GA at vaccination ≥24 wks to <28 wks	941 (25.6)	909 (24.7)	1850 (25.1)
GA at vaccination ≥28 wks to <32 wks	1085 (29.5)	1128 (30.7)	2213 (30.1)
GA at vaccination ≥32 wks to ≤36 wks	1653 (44.9)	1632 (44.4)	3285 (44.7)
GA at vaccination >36 wks	3 (<0.1)	6 (0.2)	9 (0.1)

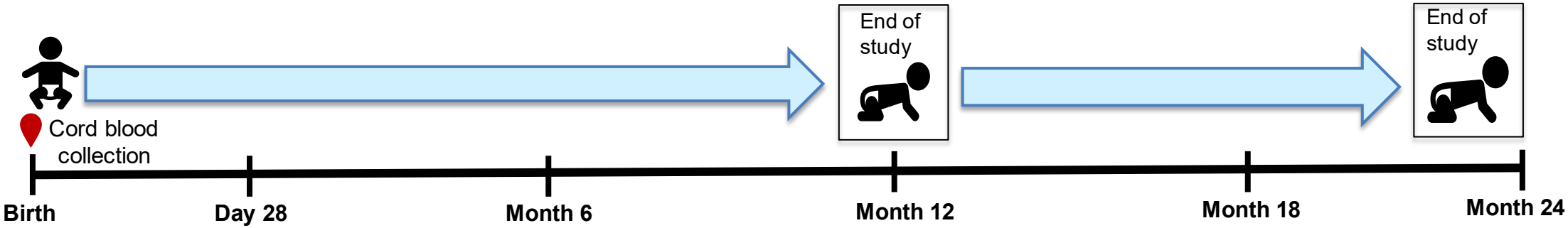
Source: adapted from Pfizer CSR, Study 1008
Abbreviations: N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=Number of participants in the specified category; GA=gestational age
Note: Participant 13081001 (RSVpreF group) is counted under ≥24 weeks to <28 weeks however actual age was 23 weeks 6 days.

Study 1008: Analysis Populations

Population (N)	Description
Evaluable efficacy, infant (**N=6975**)	All infant participants who met the following criteria: • Were eligible for the study • Were born to the maternal participants who received the investigational product to which they were randomized (RSVpreF or placebo) at least 14 days prior to delivery • Did not receive palivizumab or another monoclonal antibody targeting RSV • Had no major protocol violations • Did not have transfusions of more than 20 mL/kg of any blood products at <180 days
Safety, infant (**N=7126**)	All infant participants who were born to vaccinated maternal participants
Safety, maternal (**N=7357**)	All randomized maternal participants who received investigational product

Study 1008 Design: Infant Participants

Labor & Delivery	Infant Participants' RTI Surveillance Period [72 hours after delivery to 6 months after birth (Day 180)]	Infant Participants' RTI Surveillance Period* [6 months after birth (Day 181) to end of study]	Long-term Safety and RTI Surveillance (Infant participants enrolled during the first year of the study only)



Active RTI surveillance period via weekly contact. Follow-up participants for all MA-RTIs, including nasal swab collection.

RTI surveillance via monthly contact. Follow-up of participants for all MA-RTIs. Only hospitalization due to RTI and severe MA-LRTI events require nasal swab collection.

AEs collected for 1 month

SAEs and NDCMCs collected throughout the study

*Study completion up to Month 12 for all infant participants, except infant participants enrolled during the first year, which will be up to Month 24.

Source: Adapted from Pfizer protocol, Study c3671008

Abbreviations: AE=adverse event; NDCMC=newly diagnosed chronic medical condition; MA-LRTI=medically attended lower respiratory tract illness; RTI=respiratory tract illness; SAE=serious adverse event

Study 1008: Case Definitions for Infant Participants

Study Endpoints/Assessments	Study Definitions
Medically attended visit	Infant participant has been taken to or seen by an HCP (outpatient/inpatient visit, ED, UC, or home visit)
MA-RTD visit for infant participant	A medically attended visit **AND** 1 or more of the following RTD signs and symptoms: • Nasal discharge for 24 hours or more • Difficulty breathing, labored breathing, or rapid breathing for any duration • Cough • Inability to feed for any duration because of respiratory symptoms • Apnea • Any other respiratory symptom of concern
RSV-positive test[a]	RSV RT-PCR–positive test result by Pfizer central laboratory **OR** RSV-positive test result by certified laboratory with NAAT for RSV
MA-RTD due to RSV	An MA-RTD visit AND RSV-positive test result
MA-LRTD due to RSV	Infant with an MA-RTD visit **AND** RSV-positive test result **AND** one or more of the following: • Tachypnea (RR ≥60 bpm for <2 mos. [<60 days] of age or ≥50 bpm for ≥2 to 12 mos. of age, or ≥40 bpm for ≥12 to 24 mos. of age) • **OR** SpO2 <95% • **OR** Chest wall indrawing
Severe MA-LRTD due to RSV	Infant with an MA-RTD visit **AND** RSV-positive test result **AND** one or more of the following: • Tachypnea (RR ≥70 bpm for <2 mos. [<60 days] of age, ≥60 bpm for ≥2 mos. to 12 mos. of age, or ≥50 bpm for ≥12 to 24 mos. of age) • **OR** SpO2 <93% • **OR** High-flow nasal cannula or mechanical ventilation (i.e., invasive or noninvasive) • **OR** ICU admission for >4 hours • **OR** Unresponsive/unconscious

Study 1008: Disposition of Infant Participants

Infant Participants	RSVpreF N=3570[a] n (%)	Placebo N=3558[a] n (%)	Total N=7128 n (%)
Safety population	3568 (99.9)	3558 (100)	7126 (100)
Evaluable efficacy population	3495 (97.9)	3480 (97.8)	6975 (97.9)
Completed 6 months follow-up	2830 (79.3)	2824 (79.4)	5654 (79.3)
Completed 12 months follow-up	1631 (45.7)	1616 (45.4)	3247 (45.6)
Completed 24 months follow-up	3 (<0.1)	3 (<0.1)	6 (<0.1)
Ongoing	3343 (93.6)	3317 (93.2)	6660 (93.4)

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

Study 1008: Median Follow-up Duration In Days

Population	RSVpreF (range)	Placebo (range)
Evaluable efficacy population	274 (1-725)	270 (1-722)
Safety population (Maternal participants)	237 (1-679)	237 (1-712)
Safety population (Infant participants)	273 (1-725)	269 (1-722)

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Study 1008: Primary Efficacy Endpoints

Severe RSV-Positive MA-LRTDs, Evaluable Efficacy Population

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

Source: adapted from Pfizer CSR, Study 1008

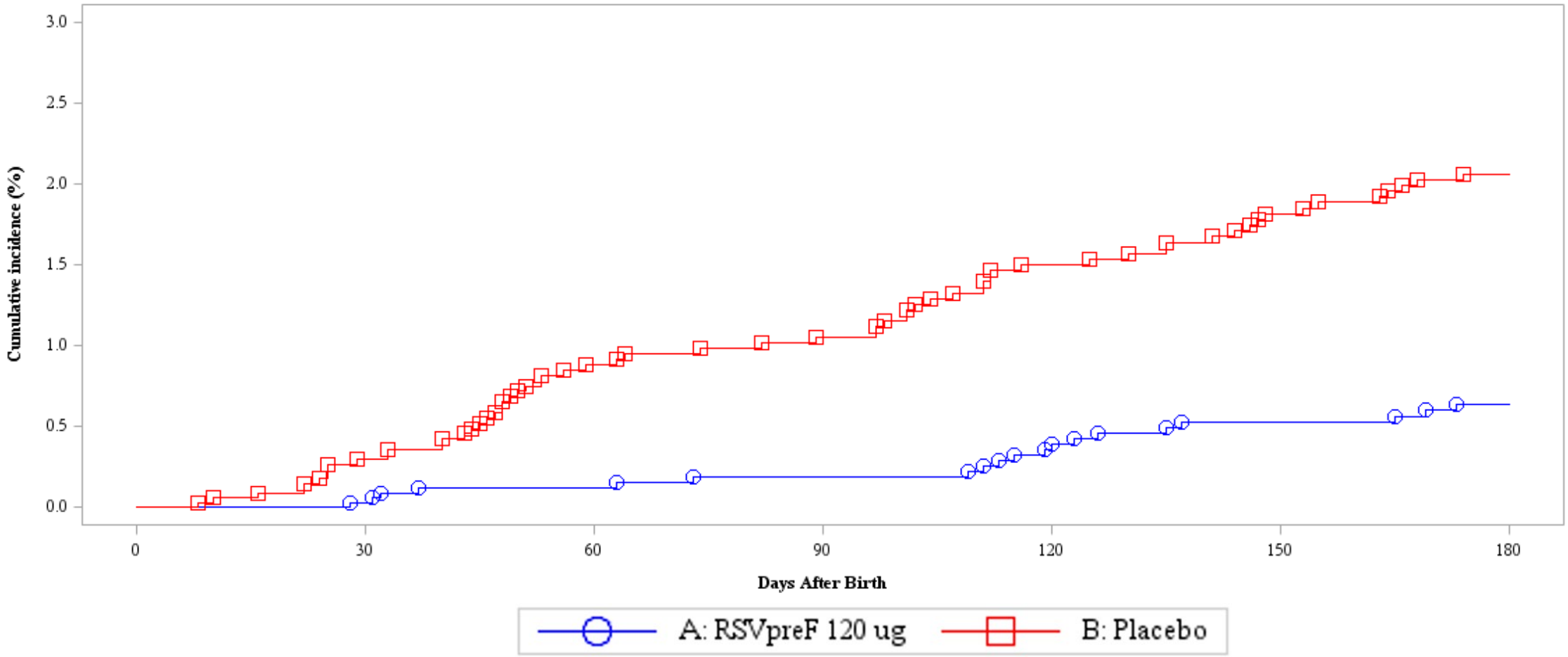
Abbreviations: MA-LRTD=medically attended lower respiratory tract disease; N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations; n=number of cases

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

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

Data cutoff date: Sept. 30, 2022

Study 1008: Cumulative Incidence Curve RSV-Positive Severe MA-LRTDs Within 180 Days After Birth, Infant Participants, Evaluable Efficacy Population



Source: Pfizer CSR 1008
Abbreviations: EAC=endpoint adjudication committee; MA-LRTI=medically attended lower respiratory tract illness; RSV=respiratory syncytial virus

Study 1008: Primary Efficacy Endpoints

RSV-Positive MA-LRTDs, Evaluable Efficacy Population

Time Interval	RSVpreF N=3495 n (%)	Placebo N=3480 n (%)	Vaccine Efficacy[a] (%) (CI)[b]
90 days after birth	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)
120 days after birth	35 (1.0)	81 (2.3)	56.8 (31.2, 73.5)
150 days after birth	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9)
180 days after birth	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)

Source: adapted from Pfizer CSR, Study 1008

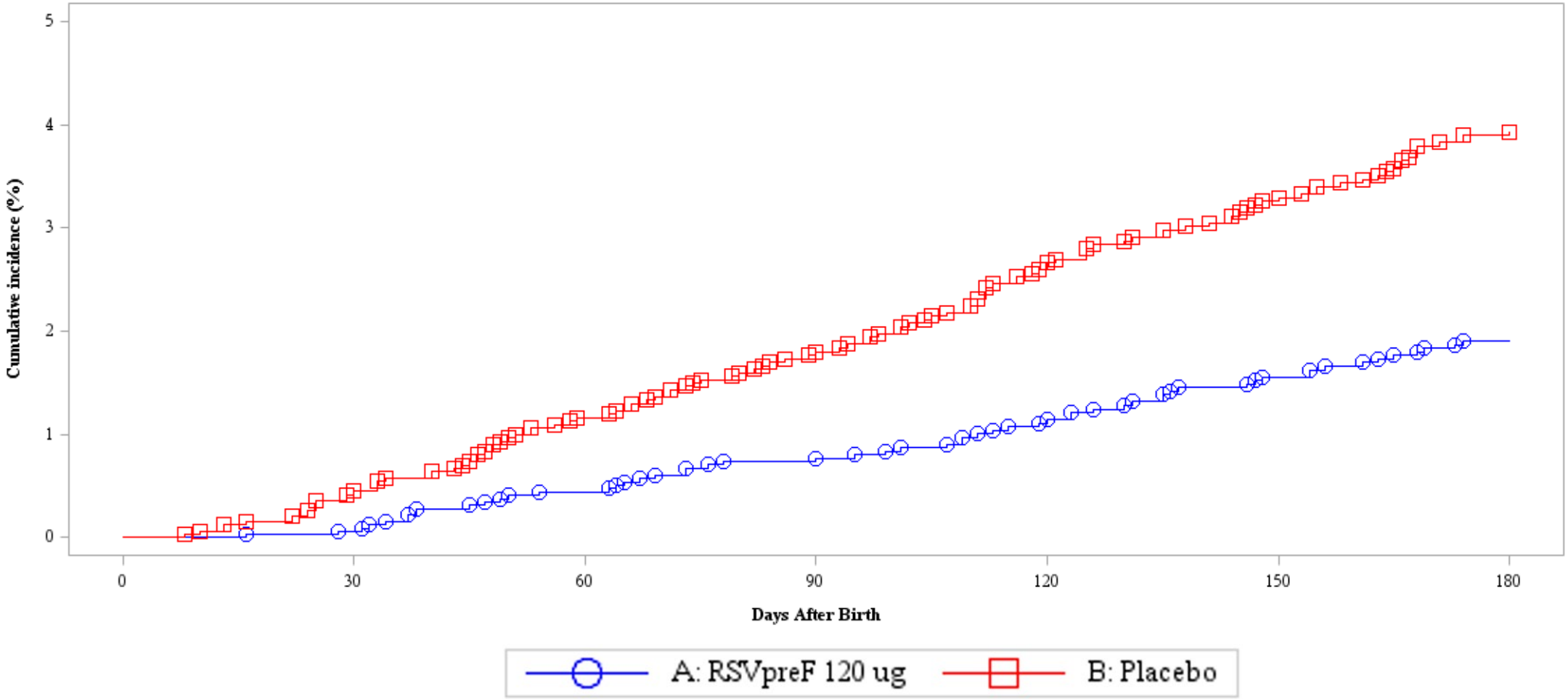
Abbreviations: MA-LRTD=medically attended lower respiratory tract disease; N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations; n=number of cases

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

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

Data cutoff date: Sept. 30, 2022

Study 1008: Cumulative Incidence Curve RSV-Positive MA-LRTDs Within 180 Days After Birth, Infant Participants, Evaluable Efficacy Population



Source: Pfizer CSR 1008
Abbreviations: EAC=endpoint adjudication committee; MA-LRTI=medically attended lower respiratory tract illness; RSV=respiratory syncytial virus

Study 1008: Secondary Efficacy Endpoints

Hospitalization Due to RSV, Evaluable Efficacy Population

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

Source: adapted from Pfizer CSR, Study 1008

Notes: N=number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations; n=number of cases

a. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using Bonferroni procedure and accounting for the primary endpoints results.

Study 1008: Secondary Efficacy Endpoints (cont'd)

MA-LRTD Due to RSV Within 210, 240, 270, and 360 Days After Birth

- Statistical success criterion was met (CI lower bound >0%) at all timepoints within 210 to 360 days after birth
- However, during the period from 181 to 360 days after birth, rates of RSV-confirmed MA-LRTD were similar between groups: 35 new cases in the RSVpreF group, and 39 new cases in the placebo group

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

- Results did not meet the statistical criterion for success for this endpoint at any measured timepoints through 360 days after birth

Study 1008 Exploratory Endpoints (Descriptive)

Time Interval	RSVpreF N=3495 # Cases	Placebo N=3480 # Cases	Vaccine Efficacy (%) (95% CI)
180 days after birth	--	--	--
MA-RTD due to RSV	157	253	37.9 (24.0, 49.5)
MA-LRTD due to RSV Subtype A	19	26	26.9 (-37.2, 61.8)
MA-LRTD due to RSV Subtype B	38	87	56.3 (35.4, 71.0)
Severe MA-LRTD due to RSV Subtype A	7	14	50.0 (-32.4, 82.9)
Severe MA-LRTD due to RSV Subtype B	11	44	75.0 (50.8, 88.4)
361 to 730 days after birth[a]	--	--	--
MA-LRTD due to RSV	4	6	33.3 (-181.1, 85.2)

Source: FDA-generated table
Abbreviations: RSV=respiratory syncytial virus; MA-LRTD=medically attended lower respiratory tract disease; CI=confidence interval
Notes: a. As of the data cutoff point, only 6 infant participants (3 in RSV preF group, 3 in placebo group) had completed 24 months of follow-up

Study 1008, Subgroup Analyses: Primary Efficacy Endpoints

VE consistent to those observed in the main analyses; clinically meaningful differences between subgroups generally not observed. However, these were limited by the numbers of cases in the subgroups and should be interpreted with caution.

- Gestational age at vaccination
- Country
- Country income level
- Exclusive breastfeeding
- Duration of breastfeeding
- Maternal smoking
- Number of household members
- Maternal age at vaccination

RSV MA-LRTDs By Subgroup Of Gestational Age At Vaccination

Subgroup Gestational Age at Vaccination	RSVpreF (N=3495) n	RSVpreF (N=3495) # cases (%)	Placebo (N=3480) n	Placebo (N=3480) # cases (%)	VE (%) (95% CI)
Interim analysis at 90 days	--	--	--	--	--
≥24 weeks to <28 weeks	890	6 (0.7)	866	13 (1.5)	55.1 (-26.6, 86.0)
≥28 weeks to <32 weeks	1030	4 (0.4)	1070	22 (2.1)	81.1 (44.4, 95.3)
≥32 weeks to ≤36 weeks	1572	14 (0.9)	1539	21 (1.4)	34.7 (-34.6, 69.3)
>36 weeks	3	0	5	0	-
Interim analysis at 180 days	--	--	--	--	--
≥24 weeks to <28 weeks	890	22 (2.5)	866	27 (3.1)	20.7 (-44.6, 57.0)
≥28 weeks to <32 weeks	1030	11 (1.1)	1070	35 (3.3)	67.4 (34.2, 85.0)
≥32 weeks to ≤36 weeks	1572	24 (1.5)	1539	55 (3.6)	57.3 (29.8, 74.7)

Source: adapted from Pfizer 1008 CSR
Abbreviations: RSV=respiratory syncytial virus; MA-LRTD=medically attended lower respiratory tract disease; VE=vaccine efficacy; CI=confidence interval
Note: This subgroup analysis did not appear in the FDA Briefing Document.

Severe RSV MA-LRTDs by Subgroup of Gestational Age at Vaccination

Subgroup Gestational Age at Vaccination	RSVpreF (N=3495) n	RSVpreF (N=3495) # cases (%)	Placebo (N=3480) n	Placebo (N=3480) # cases (%)	VE (%) (95% CI)
Interim analysis at 90 days	--	--	--	--	--
≥24 weeks to <28 weeks	890	4 (0.4)	866	11 (1.3)	64.6 (-19.4, 91.8)
≥28 weeks to <32 weeks	1030	1 (<0.1)	1070	11 (1.0)	90.6 (35.0, 99.8)
≥32 weeks to ≤36 weeks	1572	1 (<0.1)	1539	11 (0.7)	91.1 (38.8, 99.8)
>36 weeks	3	0	5	0	-
Interim analysis at 180 days	--	--	--	--	--
≥24 weeks to <28 weeks	890	11 (1.2)	866	19 (2.2)	43.7 (-24.6, 75.8)
≥28 weeks to <32 weeks	1030	2 (0.2)	1070	18 (1.7)	88.5 (51.8, 98.7)
≥32 weeks to ≤36 weeks	1572	6 (0.4)	1539	25 (1.6)	76.5 (41.3, 92.1)

Source: adapted from Pfizer 1008 CSR
Abbreviations: RSV=respiratory syncytial virus; MA-LRTD=medically attended lower respiratory tract disease; VE=vaccine efficacy; CI=confidence interval
Note: This subgroup analysis did not appear in the FDA Briefing Document.

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Maternal Safety - Study 1008

Overview of Adverse Events

Event	RSVpreF n/N (%)	Placebo n/N (%)
Immediate AEs within 30 minutes	1/3682 (<0.1)	1/3675 (<0.1)
Solicited injection site reactions within 7 days	1557/3663 (42.5)	378/3639 (10.4)
Solicited systemic adverse reactions within 7 days	2340/3663 (63.9)	2157/3640 (59.3)
Unsolicited non-serious AE within 30 days	412/3682 (11.2)	396/3675 (10.8)
SAEs	--	--
Within 30 days after vaccination	154/3682 (4.2)	137/3675 (3.7)
Day 1 through 6 months after delivery (data lock point)	598/3682 (16.2)	558/3675 (15.2)
Deaths to data lock point	1/3682 (<0.1)	0/3675
Withdrawal due to AE Day 1-6 months after delivery	0/3682	1/3675 (<0.1)
AESIs	--	--
Within 30 days after vaccination	99/3682 (2.7)	92/3675 (2.5)
Day 1 through 6 months after delivery (data lock point)	337/3682 (9.2)	280/3675 (7.6)
Premature delivery	**206/3682 (5.6)**	**174/3675 (4.7)**

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

Data cutoff date: Sept. 02, 2022

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

Local Reaction	RSVpreF % (N=3663)	Placebo % (N=3639)
Any redness[a]	7.2	0.2
Mild redness[a]	4.9	0.1
Severe redness[a]	**0.2**	**0**
Any swelling[a]	6.2	0.2
Mild swelling[a]	4.1	0.1
Severe swelling[a]	**0.1**	**0**
Any pain at injection site[b]	**40.6**	**10.1**
Mild pain at injection site[b]	36.0	9.3
Severe pain at injection site[b]	**0.1**	**0**
Any local reaction[c]	**42.5**	**10.4**
Mild local reaction[c]	35.4	9.4
Severe local reaction[c]	0.3	0

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

Median day of onset for *any* local reaction in RSVpreF group: Day 2
Median duration: 2-3 days

Solicited Systemic Events, by Maximum Severity Within 7 Days Af Vaccination, Maternal Participants, Safety Population - Study 100

Systemic Event	RSVpreF % (N=3663)	Placebo % (N=3638 to 3640)*
Fever (≥38.0°C)	2.6	2.9
38.0°C to 38.4°C	1.7	1.5
38.5°C to 38.9°C	0.8	1.2
39.0°C to 40.0°C	**<0.1**	**0.1**
>40.0°C	**<0.1**	**0.1**
Any fatigue[a]	46.1	43.8
Mild	23.4	22.7
Severe	**1.4**	**1.4**
Any headache[a]	31.0	27.6
Mild	20.2	17.9
Severe	**0.4**	**0.4**
Any muscle pain[a]	26.5	17.1
Mild	17.6	10.0
Severe	**0.4**	**0.3**
Any joint pain[a]	11.6	10.5
Mild	6.5	6.0
Severe	**0.2**	**<0.1**

Source: adapted from Pfizer sCSR, Study 1008

Notes: *N=number of participants reporting "yes" or "no" for at least 1 day. This value is the denominator for the percentage calculations and only 3 participants had missing data for an individual solicited adverse event; the percentage was the same regardless of the actual denominator; n=Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.

a. Mild=does not interfere with activity, moderate=some interference with activity, severe = prevents daily routine activity; b. Mild=1 to 2 times in 24 hours, moderate=>2 times in 24 hours, severe=requires intravenous hydration; c. Mild=2 to 3 loose stools in 24 hours, moderate=4 to 5 loose stools in 24 hours, severe = 6 or more loose stools in 24 hours; d. Any systemic event=any fatigue, any headache, any vomiting, any nausea, any diarrhea, any muscle pain or any joint pain.

Solicited Systemic Events, by Maximum Severity Within 7 Days After Vaccination, Maternal Participants, Safety Population - Study 1008 (cont'd)

Systemic Event	RSVpreF % (N=3663)	Placebo % (N=3638 to 3640)*
Any nausea[a]	20.0	19.3
Mild	14.4	13.8
Severe	**0.2**	**0.2**
Any vomiting[b]	7.8	7.0)
Mild	6.4	5.4
Severe	**0.2**	**<0.1**
Any diarrhea[c]	11.2	11.5)
Mild	9.1	9.4)
Severe	**0.1**	**0.2**
Any systemic event[d]	63.9	59.3

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

Median day of onset for *any* systemic event in RSVpreF group: Day 2
Median duration: 1 to 3 days

Maternal Participants - Unsolicited Non-Serious Adverse Events (AEs)

- Immediate AEs: 1 maternal participant in each group
- Unsolicited non-serious AEs within 1 month: 11.2% in RSVpreF group, 10.8% in placebo group
- Severe or Life-threatening AEs within 1 month: 2.2% in RSVpreF group, 1.5% in placebo group

- Most frequently reported AEs in maternal participants from vaccination through the 1-month follow-up visit for both groups were in the System Organ Class (SOC) of *Pregnancy, puerperium and perinatal conditions* (7.0% versus 6.2%) and *Infections and Infestations* (2.0% for both groups)
- By Preferred Term (PT), **premature delivery** (AESI) was most frequently reported AE in both groups within 1 month after vaccination
  - 2.1% in the RSVpreF group and 1.9% in the placebo group
- No maternal participants withdrew due to an AE within 1 month after vaccination

Maternal Participants - Related Adverse Events

- AEs from vaccination through 1 month assessed as related by investigator:
  - 0.4% in the RSVpreF group and 0.1% in the placebo group
  - Most in the SOC of *General disorders and Administration site conditions*
- All related AEs were reported after vaccination but before delivery (3.0% in RSVpreF group, 2.4% in placebo group), except for 2 related AEs reported from delivery to 1 month after delivery (RSVpreF group):
  - 1 SAE of eclampsia
  - 1 event of premature delivery (mild in severity, GA 36 wks/5 days, Day 86 post-vaccination)

Maternal Participants - Adverse Events of Special Interest (AESI)

- AESI within 1 month of vaccination: 2.7% in RSVpreF group, 2.5% in placebo group
- **Premature delivery after vaccination**:
  - 206/3682 **(5.6%)** [95% CI: 4.9%, 6.4%] in RSVpreF group
  - 174/3675 **(4.7%)** [95% CI: 4.1%, 5.5%] in placebo group
- One maternal participant in the placebo group withdrew from the study due to premature delivery

Maternal Participants - Non-Fatal Serious Adverse Events

- Within 1 month after vaccination: 4.2% in RSVpreF group, 3.7% placebo group
  - 1 related SAE of eclampsia (RSVpreF group)
- After vaccination to 6 months after delivery: 16.2% in RSVpreF group and 15.2% in the placebo group
- Most SAEs from delivery to 1 month after delivery (10.1% vs. 10.0%) and after vaccination but before delivery (7.2% vs. 6.1%)
- Most in the SOC of *Pregnancy, puerperium and perinatal conditions* (12.1% in RSVpreF group, 11.2% in placebo group)

SAEs assessed as *related* by the investigator (4 in RSVpreF group):

- Severe pain in multiple extremities – onset in vaccinated extremity 2 days post-vaccination
- Premature labor - onset 2 days after vaccination; did not result in preterm delivery
- Thrombocytopenia - 6 days post-vaccination with subsequent diagnosis of systemic lupus erythematous 5 months later
- Eclampsia - onset 15 days after vaccination

Maternal Safety - Serious Adverse Events Reported Within 1 Month After Vaccination, by System Organ Class

System Organ Class	RSVpreF N=3682 n (%)	Placebo N=3675 n (%)
Any Event	154 (4.2)	137 (3.7)
Blood and lymphatic system disorders	1 (<0.1)	1 (<0.1)
Cardiac disorders	8 (0.2)	8 (0.2)
Congenital, familial and genetic disorders	0	1 (<0.1)
Gastrointestinal disorders	0	3 (<0.1)
General disorders and administration site conditions	0	1 (<0.1)
Hepatobiliary disorders	5 (0.1)	6 (0.2)
Immune system disorders	1 (<0.1)	0
Infections and infestations	8 (0.2)	9 (0.2)
Injury, poisoning and procedural complications	4 (0.1)	2 (<0.1)

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

Maternal Safety - Serious Adverse Events Reported Within 1 Month After Vaccination, by System Organ Class (cont'd)

System Organ Class	RSVpreF N=3682 n (%)	Placebo N=3675 n (%)
Any Event	154 (4.2)	137 (3.7)
Investigations	2 (<0.1)	1 (<0.1)
Metabolism and nutrition disorders	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	3 (<0.1)	2 (<0.1)
Nervous system disorders	1 (<0.1)	1 (<0.1)
Pregnancy, puerperium and perinatal conditions	**120 (3.3)**	**99 (2.7)**
Psychiatric disorders	2 (<0.1)	0
Renal and urinary disorders	4 (0.1)	1 (<0.1)
Reproductive system and breast disorders	2 (<0.1)	2 (<0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1)
Skin and subcutaneous tissue disorders	0	1 (<0.1)
Vascular disorders	5 (0.1)	4 (0.1)

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

Data cutoff date: Sept. 02, 2022

Maternal / Fetal Deaths

- **1 death of maternal participant (RSVpreF)**
  - Post-partum hemorrhage and hypovolemic shock after delivery
- **18 intrauterine deaths**
  - 10 in RSVpreF, 8 in placebo
- **3 spontaneous abortions during subsequent pregnancies** (to 6 months after delivery)
  - 1 in RSVpreF, 2 in placebo group

Infant Safety Population - Study 1008

Overview of Adverse Events

Adverse Event Category	RSVpreF (N=3568) n (%)	Placebo (N=3558) n (%)
Any adverse event	1473 (41.3)	1403 (39.4)
Unsolicited non-serious AEs within 30 days	1012 (28.4)	931 (26.2)
SAEs	--	--
Within 30 days after birth	553 (15.5)	541 (15.2)
Up to 6 months after birth	595 (16.7)	585 (16.4)
Up to 12 months after birth	619 (17.3)	611 (17.2)
Up to data lock point	625 (17.5)	623 (17.5)
Deaths to data lock point	5 (0.1)	12 (0.3)
Congenital Anomalies	180 (5.0)	220 (6.2)
NDCMCs	--	--
Within 30 days after birth	6 (0.2)	6 (0.2)
Up to 6 months after birth	45 (1.3)	57 (1.6)
Up to 12 months after birth	75 (2.1)	83 (2.3)
Up to data lock point	87 (2.4)	99 (2.8)
AESIs	--	--
Within 30 days after birth	298 (8.4)	257 (7.2)
Up to 6 months after birth	334 (9.4)	282 (7.9)
Up to 12 months after birth	366 (10.3)	324 (9.1)
Up to data lock point	386 (10.8)	344 (9.7)
Premature Births	**202 (5.7)**	**169 (4.7)**
Withdrawals due to AE up to data lock point	0	0

Source: adapted from Pfizer CSR

Abbreviations: NDCMC=Newly Diagnosed Chronic Medical Condition; N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations; n=number of participants in the specified category. Notes: Major birth defects as defined by Centers for Disease Control and Prevention. Metropolitan Atlanta Congenital Defects Program (MACDP). https://www.cdc.gov/ncbddd/birthdefects/macdp.html.

Data cutoff date: Sept. 02, 2022

Infants - Unsolicited Non-Serious Adverse Events

- Any AE within 1 month after birth: 37.1% in RSVpreF group, 34.5% in placebo group
- Unsolicited non-serious AEs within 1 month after birth: 28.4% in RSVpreF group, 26.2% in placebo group
- Severe or life-threatening AEs: 5.1% in RSVpreF group, 4.5% in placebo group
- No infant participants were withdrawn from the study due to an AE

- One event of **prematurity** in the RSVpreF group was assessed by investigator as *related* to maternal vaccination:
  - 37-year-old maternal participant in second pregnancy; history of gestational diabetes, Raynaud's phenomenon, ADHD
  - Received RSVpreF at 24 weeks, 3 days gestation.
  - Hospitalized 4 days post vaccination with 2-day history of "decreased fetal movement" reported. Fetal movement was present on triage/per ultrasound. Pt was discharged home same day.
  - Live female infant delivered with no complications at 36 weeks, 5 days gestation, 85 days post vaccination.
  - Investigator's rationale for considering the premature delivery/premature birth to be related to the investigational product: Another cause for the premature delivery was not determined. "If the investigator does not know whether or not the IP caused the event, then the event will be handled as related to IP."

Infants - Adverse Events of Special Interest

- **AESIs:** Preterm birth (born at <37 weeks' gestation), LBW (birth weight 1001 to 2500 g), developmental delay
- **AESIs reported as SAEs:** Extremely preterm birth (<28 weeks), extremely LBW (≤1000 g)
- AESIs within 1 month after birth: 8.4% in RSVpreF group, 7.2% in placebo group

- **Low birth weight:** 5.1% [95% CI: 4.4, 5.8] vs. 4.4% [95% CI: 3.7, 5.0]
- **Premature births: 5.7%** [95% CI: 4.9, 6.5] vs. **4.7%** [95% CI: 4.1, 5.5]
  - Numerical imbalance noted in premature births
  - Difference in preterm birth rate noted in one upper middle income country between vaccine recipients (8.3%) and placebo recipients (4.0%)

Background incidence rate of premature birth: ~10%
(CDC, 2022; WHO, 2022)

Study 1008: Live Birth Outcomes

Gestational Age At Birth	RSVpreF (N= 3568) n (%)	Placebo (N= 3558) n (%)
24 wks to <28 wks	1 (<0.1)	1 (<0.1)
28 wks to <34 wks	**20 (0.6)**	**11 (0.3)**
34 wks to <37 wks	**180 (5.0)**	**157 (4.4)**
37 wks to <42 wks	3343 (93.7)	3356 (94.3)
≥42 wks	21 (0.6)	30 (0.8)
Outcome	--	--
Normal	3172 (88.9)	3149 (88.5)
Congenital malformation/anomaly	174 (4.9)	203 (5.7)
Other neonatal problem	219 (6.1)	200 (5.6)
LBW baby (≤2500 g)	181 (5.1)	155 (4.4)
Extremely LBW (≤1000 g)	1 (<0.1)	2 (<0.1)
VLBW (>1000 g to ≤1500 g)	3 (<0.1)	6 (0.2)
LBW (>1500 g to ≤2500 g)	177 (5.0)	147 (4.1)
Developmental delay	12 (0.3)	10 (0.3)

Source: adapted from Pfizer CSR, Study 1008

Abbreviations: LBW=low birth weight; VLBW=very low birth weight

Notes: a. N=number of participants in the specified vaccine group. This value is the denominator for the percentage calculations except Apgar scores; b. n=Number of participants with the specified characteristic; c. This value is the denominator for the percentage calculations for categories of Apgar scores at this specific timepoint; d. Developmental delay refers to an adverse event of special interest reported at any time after birth during the study period.

Time from Vaccination to Birth Among Preterm and At Term Births, Infant Participants, Safety Population

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

Source: Pfizer CSR 1008

Abbreviations: N=number of participants having birth date in the specified vaccine group. This value is the denominator for the percentage calculations; n = Number of participants in the specified category.

Note: Six participants have missing gestational age at birth in database, so are not included in counts above. Preterm/at term deliveries are determined based on gestational age at birth. Preterm=gestational age at birth less than 37 weeks. At term=gestational age at birth of 37 weeks or more. Number of days between vaccination and birth is calculated as birth date - vaccination date.

a. Percentages for this row are based on the number of preterm/at term deliveries, respectively.

Infants - Newly Diagnosed Chronic Medical Conditions (NDCMCs)

- NDCMCs within 1 month after birth: 0.2% of infant participants in both groups
- NDCMCs through 24 months after birth: 2.4% in the RSVpreF group and 2.8% in the placebo group
- “Asthma”-related diagnoses: 2.7% in the RSVpreF group and 3.1% in the placebo group
- No infant participants were withdrawn from the study due to an NDCMC

Infants - Non-Fatal Serious Adverse Events

- **Within 1 month after birth: 15.5% (RSVpreF) and 15.2% (placebo)**
- **From birth to 24 months of age: 17.5% (RSVpreF group) and 17.5% (placebo group)**

- Most in the SOC of *Respiratory, thoracic and mediastinal disorders*; *Pregnancy, puerperium and perinatal conditions*; and *Infections and infestations* (4.6%, 3.9%, and 3.0%, respectively in the RSVpreF group; 4.2%, 3.5%, and 2.5%, respectively in the placebo group).
- **Congenital anomalies were reported in 5.0% in the RSVpreF group and 6.2% in the placebo group**
- No infant SAEs were assessed by investigator as related to maternal vaccination

Infants - Fatal Serious Adverse Events

Infant Deaths:

- **17 infant deaths** were reported
- **5** (0.1%) in RSVpreF group, **12** (0.3%) in placebo group
- Neonatal deaths (first 28 days of life): **2** in RSVpreF group, **5** in placebo group
  - 1 infant in RSVpreF group: born at 10 days post-vaccination, extreme prematurity at 27 weeks, 3 days gestation, died on Day 4 of life
  - 1 infant in placebo group: cause of death "premature baby," bacterial meningitis, and sepsis

- One infant death adjudicated by EAC with possible cause of death **"acute respiratory illness due to RSV" (*placebo* group)**
  - Full term infant with normal birth outcome, presented with nasal discharge and cough at 114 days after birth, hospitalized, RSV PCR positive
  - Developed feeding problems following the acute respiratory illness, died 120 days after birth; cause of death reported by investigator as unknown

Phase 2 Study 1003: Design

Safety, tolerability, and immunogenicity of RSV vaccine formulations in maternal participants and their infants

- Pregnant individuals 18-49 years of age (and their infants) between 24 and 36 weeks gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy.

- 581 participants randomized to receive the following:

RSVpreF 120 µg	RSVpreF 120 µg + $Al(OH)_3$	RSVpreF 240 µg	RSVpreF 240 µg + $Al(OH)_3$	Placebo
115	117	116	114	117

- Safety follow-up approximately 12 months after delivery
- Study period: August 7, 2019 to September 30, 2021

Study 1003: Endpoints

Primary (Safety)

- Solicited local and systemic reactions 7 days after vaccination, AEs from vaccination to 1 month after vaccination; obstetric complications, MAEs, and SAEs throughout the study
- Birth outcomes, AEs to 1 month of age; SAEs and MAEs through 12 months of age in infants born to maternal participants

Secondary (Immunogenicity)

- Maternal-to-infant placental transfer ratio of RSV A- and RSV B-neutralizing antibody titers

Exploratory Efficacy Objective

- Rates of RSV-positive LRTD

Study 1003: Safety

Safety outcomes in maternal and infant participants similar to findings in Study 1008

- 1 fetal death (placebo group)
- No maternal or infant deaths reported during the study

Outcomes	RSVpreF 120 ug (N=115) n (%)	RSVpreF 120 ug +Al(OH)$_3$ (N=117) n (%)	RSVpreF 240 ug (N=116) n (%)	RSVpreF 240 ug + Al(OH)$_3$ (N=114) n (%)	Placebo (N=117) n (%)
Premature births	6 (5.3%)	4 (3.4%)	8 (7.1%)	4 (3.6%)	3 (2.6%)
Stillbirths	0	0	0	0	1

Source: FDA generated table adapted from Table 14.76 in CSR for Study 1003.

Study 1003: Immunogenicity

- Maternal-to-infant placental transfer ratio of RSV neutralizing titers was >1 for all vaccine groups

Study 1003: Exploratory Efficacy in Infants

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

Source: Pfizer CSR 1003

Abbreviations: VE: vaccine efficacy; CI=confidence interval; LRTD=lower respiratory tract disease

Notes: medically attended visit=infant participant has been taken to or seen by a healthcare provider (e.g., outpatient/inpatient visit, emergency room, urgent care, or home visit).

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

b. Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of RSVpreF cases divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group.

c. Defined as presence of one or more of the following physical examination signs: nasal flaring, lower chest wall indrawing or subcostal reactions, rhonchi, grunting, wheezing, crackles/rales/crepitations; plus 1 of the following: tachypnea (respiratory rate >60 breaths per minute (<2 months [<60 days] of age) or ≥45 breaths per minute (2 to 6 months [≥60 days to ≤180 days] of age)), use of mechanical ventilation (intubation or noninvasive positive pressure ventilation), difficulty feeding, signs of dehydration: sunken fontanelle, dry/sticky mucous membranes, tenting of skin.

d. Defined as a medically attended visit and presence of 1 of the following signs of LRTD: tachypnea (respiratory rate ≥60 breaths per minute (<2 months [60 days] of age) or ≥50 breaths per minute (≥2 to 12 months of age)), peripheral capillary oxygen saturation (SpO2) measured in room air <95%; chest wall indrawing.

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

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

Phase 2 Study 1004: Design

Placebo-controlled randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of RSVpreF when administered concomitantly with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy ***nonpregnant*** individuals 18-49 years of age.

A total of 713 participants were randomized 1:1:1:1:1 to 1 of 5 vaccine groups*:

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

*Each study vaccine or comparator was administered as a 0.5mL dose intramuscularly

Study 1004: Immunogenicity Objectives

Primary Immunogenicity

Non-inferiority of antibody responses to vaccine antigens in Tdap and RSVpreF when concomitantly administered

- Tetanus, Diphtheria: percentage of participants with antibody concentration ≥0.1 IU/mL
  - LL of 95% CI for difference in the percentage of participants with antibody concentration ≥0.1 IU/mL is >-10%
- Pertussis (PT, FHA, PRN): IgG GMCs
  - LL of 95% CI for GMC ratio is >0.67
- RSV A- and RSV B-neutralizing antibody titers
  - LL of 95% CI for GMC ratio is >0.5

Secondary Immunogenicity

Non-inferiority of RSV antibody responses to RSVpreF when concomitantly administered with Tdap

- RSV A- and RSV B-neutralizing antibody titers
  - LL of 95% CI for GMC ratio is >0.67

Study 1004: Safety

To evaluate the safety and tolerability RSVpreF when administered alone or concomitantly with Tdap

Endpoints:

- Solicited local and systemic reactions within 7 days after vaccination
- AEs within 1 month after vaccination
- Medically attended adverse events (MAEs) and SAEs to 1 month after vaccination

Study 1004: Immunogenicity Analyses

Pertussis Antibody GMCs at 1 Month After Tdap is Administered Concomitantly With RSVpreF or Saline Placebo, Evaluable Immunogenicity Population

Pertussis Component	RSVpreF 120 µg/Tdap GMC (n) (95% CI)[a]	Placebo/Tdap GMC (n) (95% CI)[a]	GMR (95% CI)
Anti-PT	40.47 (135) (34.71, 47.19)	45.90 (134) (37.43, 56.29)	0.80 (0.64, 1.00)
Anti-FHA	119.52 (135) (106.39, 134.27)	191.33 (134) (164.46, 222.59)	0.59 (0.50, 0.70)
Anti-PRN	148.29 (135) (126.01, 174.52)	257.05 (134) (211.55, 312.34)	0.60 (0.48, 0.76)

Source: Pfizer CSR
Abbreviations: FHA=filamentous hemagglutinin; GMC=geometric mean concentration; LLOQ=lower limit of quantitation; n=number of participants with valid and determinate assay results at the specified time point; PRN=pertactin; PT=pertussis toxin.
Note: The LLOQ values for each antibody were: Anti-PT = 0.9 EU/mL, Anti-FHA = 2.9 EU/mL, and Anti-PRN = 3.0 EU/mL. Assay results below the LLOQ were set to 0.5 × LLOQ; CIs were back transformations of CIs based on the Student t distribution for the mean logarithm of the titers.

Statistical criterion: **LL of 95% CI for GMC ratio is >0.67**

Study 1004: Safety Analyses

Solicited Adverse Reactions Within 7 Days After Vaccination

Adverse Reactions	RSVpreF 120 µg + Placebo N=141	RSVpreF 120 µg + Tdap N=141	Placebo + Tdap N=139
Pain at injection site[a]	57 (40.4%)	63 (44.7%)	36 (25.9%)
Systemic	--	--	--
Fatigue	60 (42.6%)	68 (48.2%)	61 (43.9%)
Headache	50 (35.5%)	59 (41.8%)	51 (36.7%)
Muscle Pain	49 (34.8%)	70 (49.6%)	48 (34.5%)

Injection Site Reactions

- Most frequently reported reaction
- Most mild to moderate
- Median duration 2 days

Systemic Reactions

- Frequency of events similar across vaccine groups
- Most common: fatigue, headache, muscle pain
- Most mild to moderate
- Median duration 1 to 3 days

Study 1004: Safety Analyses (cont'd)

AEs – Severe/Related:

- 1 in RSVpreF/placebo group (severe constipation)
- 1 in RSVpreF/Tdap group (severe lymphadenopathy)
  - Recorded in case report form (CRF) as 'enlarged lymph nodes-left axilla'; RSVpreF administered in left arm

MAEs:

- 2 in RSVpreF 120 µg/placebo, 3 in placebo/Tdap

SAEs:

- None reported within 1 month of vaccination
- 1 spontaneous abortion on Day 42 (RSVpreF 240 µg + $Al(OH)_3$ /placebo)

Outline

- Introduction (Vaccine composition, dosage/administration, proposed indication)
- Overview of Clinical Studies
- Efficacy Data
- Safety Data
- Pharmacovigilance Plan
- Summary and Questions for VRBPAC

Applicant's Proposed Pharmacovigilance Plan*

Safety specification	*Important identified risk(s):* • The Applicant did not note any important identified risk(s) *Important potential risks:* • Allergic reactions • Guillain-Barré syndrome (GBS) and other immune-mediated demyelinating conditions • Supraventricular arrhythmias in older adults *Missing information:* • Use in immunocompromised pregnant women • Use in immunocompromised older adults
Surveillance activities	Applicant will conduct passive and active surveillance activities for continued vaccine safety monitoring, including adverse event reporting and: • Planned postmarketing safety study to evaluate pregnancy and neonatal outcomes in women exposed to ABRYSVO during pregnancy, overall, and in pregnant women who are immunocompromised. • Planned postmarketing safety studies to assess GBS and atrial fibrillation in older adults vaccinated with ABRYSVO.

*Applicant's proposed PVP is under ongoing FDA review and a final determination of the safety specification and surveillance activities is pending. FDA plans to consolidate the PVPs from the proposed product use in pregnant women and proposed product use in older adults.

Outline

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Summary - Efficacy

The statistical criterion for study success (demonstration of VE >20% for at least one of the 2 primary endpoints) was met.

- **Effectiveness of RSVpreF immunization during pregnancy was demonstrated to prevent *severe* infant RSV MA-LRTD within 180 days**
  - VE 81.8% (99.5% CI: 40.6%, 96.3%) within 90 days
  - VE 69.4% (97.6% CI: 44.3%, 84.1%) within 180 days
- **Data suggest that RSVpreF immunization during pregnancy is effective in preventing RSV MA-LRTD in infants**
  - VE 57.1% (99.5% CI: 14.7%, 79.8%) within 90 days
  - VE 51.3% (97.6% CI: 29.4%, 66.8%) within 180 days

Summary - Efficacy

VE against RSV MA-LRTD within 210, 240, 270, and 360 days after birth *(Secondary Efficacy Endpoint):*

Statistical success criterion was met (a CI lower bound >0%) at all timepoints; *however*:

- Analyses represent *cumulative* RSV cases from Day 0
- Within 181 to 360 days after birth, the number of *new* cases of RSV-confirmed MA-LRTD were similar between treatment groups:
  - **35** new cases in the RSVpreF group; **39** new cases in the placebo group

VE against RSV MA-LRTD after 12 months of age (Exploratory Endpoint):

Within 361 to 730 days after birth, there were **4** cases of RSV-positive MA-LRTD in the RSVpreF group and **6** in the placebo group

Note: As of the data cutoff point, only 6 infant participants (3 in RSV preF group, 3 in placebo group) had completed 24 months of follow-up

Summary – Safety

- Total safety database: 3797 maternal participants received 120 µg RSVpreF vaccine (47% from US sites)
- Severe local reactions: 0.4% of maternal participants
- Severe systemic reactions: 2.7% of maternal participants
- Reactogenicity of RSVpreF in US participants and overall population comparable
- No meaningful differences between treatment groups in the overall rates of unsolicited AEs within 1 month after vaccination
- AEs and SAEs in infant participants were reported at a similar frequency across RSVpreF and placebo groups

Imbalance in rates of **premature birth/delivery**:

- Phase 3 study:
  - Premature births: 5.7% in RSVpreF vs. 4.7% in placebo group
  - Premature delivery: 5.6% in RSVpreF vs. 4.7% in placebo group
- Phase 2 study: Similar imbalance observed: 5.3% RSVpreF vs. 2.6% placebo group

Voting Questions for VRBPAC

1. Are the available data adequate to support the effectiveness of immunization with ABRYSVO during the second or third trimester of pregnancy (24-36 weeks gestational age) to prevent RSV lower respiratory tract disease [LRTD] and severe RSV LRTD in infants, from birth through 6 months of age?

   Please vote "Yes" or "No" or "Abstain"

2. Are the available data adequate to support the safety of immunization with ABRYSVO during the second or third trimester of pregnancy (24-36 weeks gestational age) to prevent RSV LRTD and severe RSV LRTD in infants, from birth through 6 months of age?

   Please vote "Yes" or "No" or "Abstain"

Thank You


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