Maternal RSV vaccine safety surveillance

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- The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the CDC
- The use of product trade names is for identification purposes only

Topics

- Background
- CDC vaccine safety monitoring for Pfizer RSV vaccines in pregnancy:
  - Vaccine Adverse Event Reporting System (VAERS)
  - V-Safe
  - Vaccine Safety Datalink (VSD)
- Summary

Key points up front

- In clinical trials among pregnant persons at 24–36 weeks' gestation, more preterm births were noted among Pfizer RSV vaccine recipients compared to placebo (differences not statistically significant)
- Post-licensure safety surveillance of the Pfizer RSV vaccine in pregnant persons was initiated during the 2023-2024 season
- Local and systemic (e.g., headache) adverse events were frequently reported in VAERS and V-safe after maternal Pfizer RSV vaccine which are consistent with its pre-licensure safety profile
- Pregnancy-specific (e.g., preterm delivery) conditions were frequently reported to VAERS as expected in a vaccine recommended at 32-36 weeks' gestational age
- Preliminary findings in the VSD suggest that the incidence of preterm births is 4.1% among pregnant persons who received Pfizer RSV vaccine during the 2023-2024 respiratory season. This was within the expected range of the incidence of preterm births at 32-36 weeks' gestation (3.1 - 6.1%) before introduction of this vaccine

Background

- In clinical trials among pregnant persons at 24–36 weeks' gestation, more preterm births were noted among Pfizer RSV vaccine recipients compared to placebo, but the differences were not statistically significant
  - To avoid the potential risk of preterm birth, FDA approved the maternal RSV vaccine (Pfizer) for use in pregnant persons at 32 through 36 weeks' gestational age[1]
- The label for Pfizer RSV vaccine notes potential risk of preterm birth under warnings and precautions section[1]
- In addition, more hypertensive disorders of pregnancy were observed among vaccine recipients compared to placebo recipients, but the differences were not statistically significant
- Post-licensure safety surveillance of the new Pfizer RSV vaccine in pregnant persons is of great importance to ensure maternal Pfizer RSV safety at the population level and the benefits of using the vaccine in pregnant persons to protect infants from RSV LRTD outweigh possible risks

RSV: respiratory syncytial virus; LRTD: lower respiratory tract disease

[1] https://www.fda.gov/media/168889/download

VAERS is the nation's early warning system for vaccine safety

CDC + FDA

VAERS

Vaccine Adverse Event Reporting System

Co-managed by
CDC and FDA
https://vaers.hhs.gov/

VAERS ADVERSE EVENT REPORTING SYSTEM (VAERS)

Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

- VAERS accepts all reports from all reporters without making judgments on causality or judging clinical seriousness of the event
- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

Approaches to analyzing VAERS data

- For more than a decade VAERS has been used as part of vaccine safety surveillance for vaccines used in pregnancy (e.g., influenza, Tdap, COVID-19)[1,2]
  - Descriptive analysis
  - Clinical review of individual reports
  - Aggregate descriptions of automated data (e.g., counts of reported adverse events)
  - Calculation of reporting rates for pregnancy outcomes (if doses of a vaccine administered in pregnancy or vaccination coverage data are available)
- Clinical review of infant's medical records at birth and for the first 3 months of life (enhanced surveillance)

[1]Moro et al. Obstetrics & Gynecology 140(3):p 421-427, September 2022. https://journals.lww.com/greenjournal/Fulltext/2022/09000/Safety_of_Booster_Doses_of_Coronavirus_Disease.11.aspx

[2]Moro et al. Vaccine. 34(20):p2349-2353, April 2016. https://www.sciencedirect.com/science/article/pii/S0264410X16300329?via%3Dihub

Characteristics of maternal Pfizer RSV vaccine reports submitted to VAERS (as of June 3, 2024)

Characteristics	N (%)
Number of reports	**121**
Maternal deaths	0
Pregnancy-specific adverse event(s) reports	52 (43)
Maternal age in years, median (range) [1]	32 (21-41)
Maternal age ≥ 35 years	24 (20)
Onset interval in days from vaccination to adverse event, median (interquartile range)	1 (0,4)
Gestational age[2] in weeks at time of vaccination, median (range)	34 (9,37)
Type of reporter	
Patient/relative[3]	60 (50)
Provider	36 (30)
Vaccine manufacturer	19 (16)
Other	6 (5)

[1] Age not provided in 15 reports; [2] Gestational age at vaccination available for 90 reports; unknown for 31 reports
[3] Pregnant persons represented 70% of those who reported a preterm delivery
From October 2023 through March 2024 an estimated 320,400 pregnant persons received RSV vaccine (Peacock. Implementation and Uptake of Nirsevimab and Maternal RSV Vaccine. Advisory Committee on Immunization Practices. June 28, 2024.

Most frequently reported MedDRA Preferred Terms[1] among reports (n=121) to VAERS following Pfizer RSV vaccination in pregnant persons (as of June 3, 2024)

Rank	MedDRA PT (not mutually exclusive)	N (%)
1	Premature delivery	29 (24)
2	Premature labor	18 (15)
3	Caesarean section	18 (15)
4	Uterine contractions during pregnancy	16 (13)
5	Headache	15 (12)
6	Nausea	13 (11)
7	Fever	13 (11)
8	Vomiting	12 (10)
9	Pain	11 (9)
10	Preterm premature rupture of membranes	10 (8)

[1] Medical Dictionary for Regulatory Activities Preferred Terms (https://www.meddra.org/how-to-use/basics/hierarchy)

From October 2023 through March 2024, an estimated 320,400 pregnant persons received RSV vaccine (Peacock. Implementation and Uptake of Nirsevimab and Maternal RSV Vaccine. Advisory Committee on Immunization Practices. June 28, 2024.

Adverse events among pregnant persons following Pfizer RSV vaccination in VAERS (as of June 3, 2024)

Adverse event	N (%)
Pregnancy specific	**52 (43)**
Premature delivery (< 37 weeks' gestation)	37 (31)
High blood pressure/gestational hypertension	4 (3)
Infant death[1]	1 (1)
Stillbirth (≥ 20 weeks' gestation)	3 (2)
Delivery/labor/contractions	3 (2)
Premature rupture of membranes	2 (2)
Other[2]	2 (2)
Non-pregnancy specific	**69 (57)**
General disorders and administration site conditions (mostly injection site and systemic reactions)	41 (34)
Vaccination errors[3]	21 (17)
Infections and infestations	3 (2)
Neurological disorders (Bell's palsy)	2 (2)
Other[4]	5 (4)

[1] 35-week infant with anoxic brain injury and neonatal death after emergent C-section, resuscitation, and hospital transfer 4 days after vaccination
[2] Other includes one report each of premature infant incorrectly classified as preterm (37w), a patient who underwent labor at 37 weeks, 6 days
[3] Vaccination errors included: eight reports of vaccine given outside recommended gestational period, six given outside season, three reports of an additional dose of RSV given during same season, before approval in two, subcutaneous route in one, storage issue for Covid-19 vaccine, not RSV. Three reports of adverse events with vaccination errors
[4] Other includes two reports of no adverse event, and one each of diarrhea, infant with jaundice, and a report of rash
From October 2023 through March 2024, an estimated 320,400 pregnant persons received RSV vaccine (Peacock. Implementation and Uptake of Nirsevimab and Maternal RSV Vaccine. Advisory Committee on Immunization Practices. June 28, 2024.
No verified cases of Guillain-Barre Syndrome reported

Preterm deliveries (as of June 3, 2024)

Classification[1]	N
Late preterm (34-36 weeks)	27
Early preterm (≥ 32 - <34 weeks)	7
Very preterm (28 - < 32 weeks)	0
Extremely preterm (< 28 weeks)	0
Unknown gestational age	3
Total	37**

[1] Based on ACOG and WHO definitions

Risk factors and clinical information[2]

- 22 reported a medical condition or complication that increased risk for preterm delivery (e.g., elevated blood pressure, history of preterm delivery)
- 12 had insufficient information (no medical records)
- 3 uncomplicated pregnancies (no reported factors)
- 8 deliveries were induced

[2] Median maternal age at vaccination was 33 years (range 25-40 years); median onset interval from vaccination to preterm birth was 3 days (range 0-31 days)

From October 2023 through March 2024, an estimated 320,400 pregnant persons received RSV vaccine (Peacock. Implementation and Uptake of Nirsevimab and Maternal RSV Vaccine. Advisory Committee on Immunization Practices. June 28, 2024.

Characteristics and outcomes of infants born to Pfizer RSV recipients

Characteristics	N (%)
Number of infants[1]	75
Premature at birth (< 37 weeks)[2]	38 (51)
Gestational age at birth (weeks) [3], median (range)	36 (32 – 41)
Infants at term	33 (44)
Sex	
Male	32 (43)
Female	34 (45)
Unknown sex	9 (12)
Infant deaths[4]	1
Infant born with low birth weight (< 2,500 g)	16 (21)
NICU admission[5]	24
Condition or reason for admission in NICU (not mutually exclusive) Respiratory distress Prematurity Fetal distress Unknown	 10 (42) 7 (29) 1 (4) 9 (38)

[1] 66 infants born of a single pregnancy; 3 from a multiple pregnancy; 3 data not reported
[2] Includes 6 infants from three twin pregnancies
[3] Gestational age at birth unknown for 4 reports
[4] 35-week infant with anoxic brain injury and neonatal death after emergent C-section, resuscitation, and hospital transfer 4 days after vaccination
[5] NICU admission unknown in 20 (39%) reports
From October 2023 through March 2024, an estimated 320,400 pregnant persons received RSV vaccine (Peacock. Implementation and Uptake of Nirsevimab and Maternal RSV Vaccine. Advisory Committee on Immunization Practices. June 28, 2024.

VAERS Summary

- Local and systemic symptoms (e.g., headache) were frequently reported in VAERS consistent with pre-licensure studies in pregnant persons
- In clinical trials among pregnant persons at 24–36 weeks' gestation, more preterm births were noted among Pfizer RSV vaccine recipients compared to placebo
- The label for Pfizer RSV vaccine notes potential risk of preterm birth under warnings and precautions section
- Patients (pregnant persons) were the most common reporters (50%) overall and represented 70% of those who reported a preterm delivery
- Reports of pregnancy specific conditions (e.g., preterm delivery) were not unexpected for a vaccine recommended at 32-36 weeks' gestation in pregnancy

V-safe

Characteristics of persons aged 16-49 years with reported RSV vaccination during pregnancy*

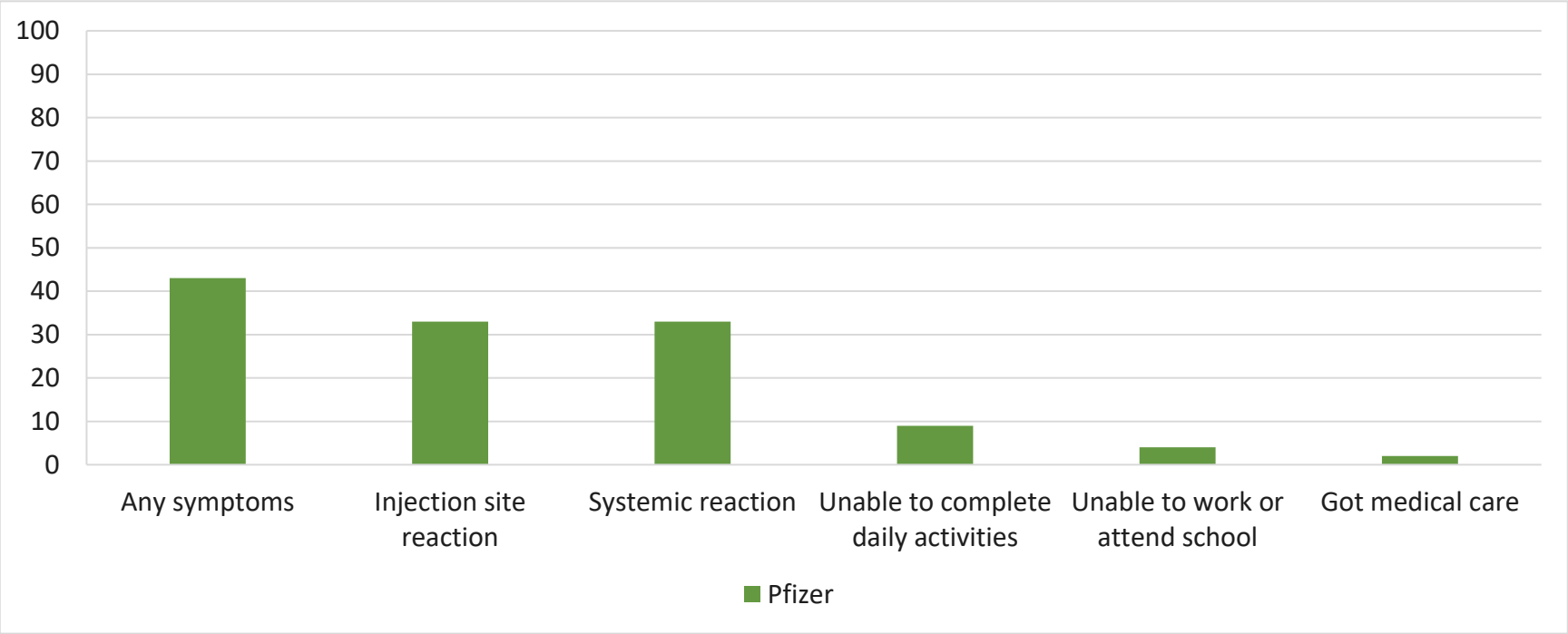
Characteristic	%
Age group, years	
16-34	58.4
35-49	41.6
Immunocompromised	**2**
Vaccine(s) co-administered	**12**
COVID-19	5.8
Influenza	0.7
Tetanus	4
Other	1.3

* For 1,116 V-safe participants aged 16-49 years enrolled in the maternal RSV protocol with ≥1 completed daily survey during August 21, 2023 – May 20, 2024

In Fall 2023 V-safe expanded to include RSV vaccine

- Surveys sent daily during the first week after vaccination, then weekly through week 6
- Daily surveys solicit adverse events and health impacts after vaccination
  - Local reactions (e.g., pain, redness, swelling)
  - Systemic reactions (e.g., fatigue, headache, muscle pain)
  - Health impacts (e.g., unable to perform normal daily activities, missed school or work, or received medical care)
  - Additional questions for persons who reported immunocompromise at vaccination
- Weekly surveys solicit new symptoms or conditions after vaccination
- Maternal RSV protocol includes additional questions about current and prior pregnancies

Reactions and health impacts reported for persons aged 16-49 years with reported RSV vaccination during pregnancy (n=1,116)*

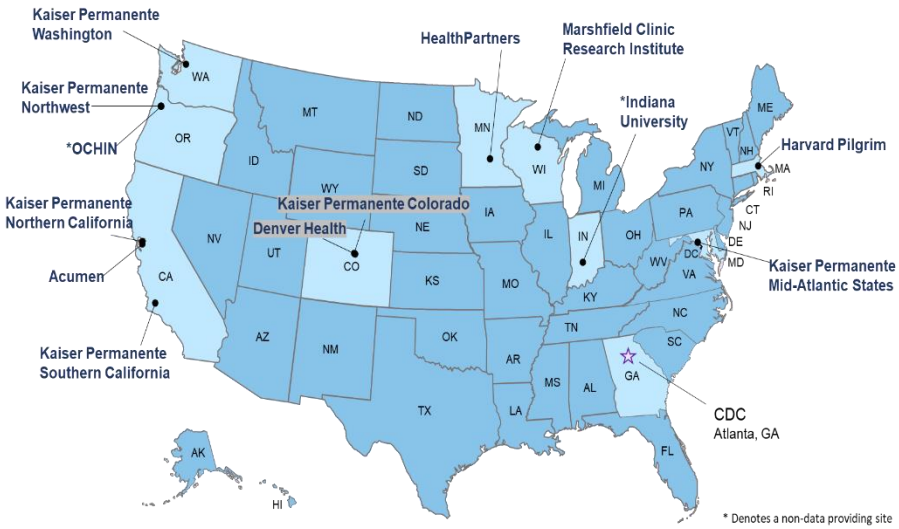


* For 1,116 V-safe participants aged 16-49 years enrolled in the maternal RSV protocol with ≥1 completed daily survey during August 21, 2023 – May 20, 2024

Vaccine Safety Datalink

Vaccine Safety Datalink (VSD) 2024

- Collaborative project between CDC and integrated healthcare organizations
- Monitors safety of vaccines used in the US, primarily through real-world data of rare and serious events following vaccination
- Includes data on ~15.5 million individuals across all sites annually
- ~ 115,000 annual live births
- Data is organized using a common data model with standardized coding systems



VSD Prenatal RSV Vaccine Surveillance

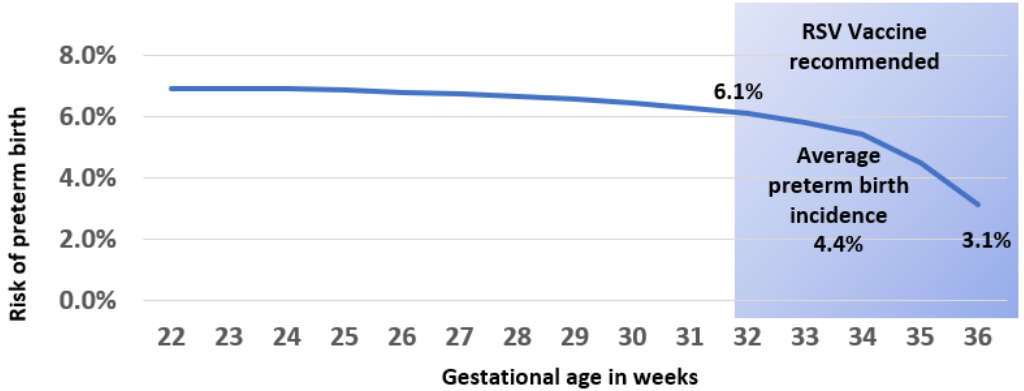
- Determine cumulative *historical* incidence rates of preterm birth among singleton pregnancies in the VSD reaching specified gestational ages from 22–36 weeks during 2017–2022

- Determine incidence of preterm births in RSV vaccinated pregnant persons[1,2]

[1]For RSV vaccines administered at 30 to less than 37 weeks' gestational age
[2]Pfizer RSV should be administered at 32 through 36 weeks' gestational age
https://www.fda.gov/media/168889/download

Preterm births in VSD – Historical incidence of preterm births and preterm births following RSV vaccine during pregnancy at 9 VSD sites

Incidence of preterm births among singleton pregnancies in the VSD reaching specified gestational ages from 22–36 weeks during 2017–2022



- In VSD, 10,295 RSV vaccines were administered at 30 to less than 37 weeks gestational age among pregnant persons during 2023–2024 respiratory season with 427 preterm births among vaccinees.
- **The preterm birth incidence was 4.1% which is *within the expected range* (3.1–6.1%) based on historical data.**

VSD 1:1 Matched analysis (ongoing)

- Pregnant persons, RSV vaccinated: unexposed at same gestational week
- Create propensity scores to account for confounding
- Outcomes
  - Acute safety outcomes (e.g., anaphylaxis, Guillain-Barré syndrome)
  - Preterm birth
  - Stillbirth
  - Preeclampsia/eclampsia/HELLP*
- 2023-2024 analysis pending, data available later this year

*Hemolysis, elevated liver enzymes, low platelet count

Summary

- Local and systemic symptoms were commonly reported in V-safe following Pfizer RSV vaccine in pregnant persons, with few reporting medical care for symptoms, consistent with pre-licensure studies[1]
- Local and systemic symptoms (e.g., headache) and pregnancy specific conditions (e.g., preterm delivery) were frequently reported in VAERS, as expected for a vaccine recommended for pregnant persons at 32-36 weeks' gestation
- Preliminary findings in the VSD suggest that the incidence of preterm births is 4.1% among pregnant persons who received Pfizer RSV vaccine during the 2023-2024 respiratory season. This was within the expected range of the incidence of preterm births at 32-36 weeks' gestation (3.1 - 6.1%) before introduction of this vaccine
- Post-licensure vaccine safety data from VAERS and V-safe during first season after maternal Pfizer RSV vaccine are consistent with pre-licensure safety profile
- CDC and FDA will continue to monitor maternal RSV vaccine safety in VAERS, V-safe and VSD

[1] https://www.fda.gov/vaccines-blood-biologics/abrysvo

Acknowledgements

- CDC Immunization Safety Office
  - VAERS Team
  - V-safe Team
  - Clinical Immunization Safety Assessment (CISA) Project
  - Vaccine Safety Datalink (VSD)
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- National Center for Immunization and Respiratory Diseases
  - Coronavirus and Other Respiratory Viruses Division

Preterm birth in Pfizer RSVpreF vaccine phase 3 trial data, comparing trial vs approved dosing interval

	Trial dosing interval (24–36 weeks gestation)[1]				Approved dosing interval (32–36 weeks gestation)[1,2]			
	RSVpreF vaccine group N=3,568		Placebo group N=3,558		RSVpreF vaccine group N=1,628		Placebo group N=1,604	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Preterm birth (<37 weeks gestation)	202	**5.7%** (4.9%, 6.5%)	169	**4.7%** (4.1%, 5.5%)	68	**4.2%** (3.3%, 5.3%)	59	**3.7%** (2.8%, 4.7%)

1. Package Insert - ABRYSVO (STN 125768) (fda.gov)

2. Pfizer response to ACIP, unpublished data, August 2023. In package insert, approved dosing interval reported as: **4.2% (68/1,631) in the RSVpreF group and 3.7% (59/1,610) in the placebo group.**

Select pregnancy-related serious adverse events at any time following vaccination[1,2]: Pfizer phase 3 trial, trial dosing interval (24–36 weeks gestation)

	RSVpreF Vaccine N= 3,682		Placebo N= 3,675	
Serious Adverse Reaction	n (%)	95% CI	n (%)	95% CI
All Maternal **Serious Adverse Events (SAEs)**	598 (16.2)	(15.1, 17.5)	558 (15.2)	(14.0, 16.4)
Pre-eclampsia	68 (1.8)	(1.4, 2.3)	53 (1.4)	(1.1, 1.9)
Gestational hypertension	41 (1.1)	(0.8, 1.5)	38 (1.0)	(0.7, 1.4)
Premature rupture of membranes	15 (0.4)	(0.2, 0.7)	16 (0.4)	(0.2, 0.7)
Preterm premature rupture of membranes	15 (0.4)	(0.2, 0.7)	10 (0.3)	(0.1, 0.5)
Hypertension	13 (0.4)	(0.2, 0.6)	6 (0.2)	(0.1, 0.4)
Maternal death[3]	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Fetal death[4]	10 (0.3)	(0.1, 0.5)	8 (0.2)	(0.1, 0.4)

1 Table 3 ABRYSVO package insert Package Insert - ABRYSVO (STN 125768) (fda.gov)

2 Includes all SAEs from vaccination to 6 months post-delivery (up to approximately 10 months, depending on the gestational age at the time of vaccination). In the phase 3 RCT, eclampsia occurred in 5 participants (3 in the RSVpreF group and 2 in the placebo group) and HELLP syndrome occurred in 5 participants (2 in the RSVpreF group and 3 in the placebo group).

3 There was one maternal death in the vaccine group due to postpartum hemorrhage that was not likely to be associated with vaccination.

4 A total of 18 intrauterine deaths were reported for the index pregnancy: 10 intrauterine deaths in the vaccine group (0.3%) and 8 intrauterine deaths in the placebo group (0.2%). The intrauterine deaths represented various clinical conditions and presentations resulting in fetal demise without clear evidence of a common pathophysiology.

Closing Slide / Disclaimer

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