

# **Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older**

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**MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)**

**Respiratory Syncytial Virus (RSV) Vaccine, Adults**

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# Outline

- Introduction
- Observed vs. Expected Analysis Summary
  - Study Methods and Results
- Self-Controlled Case Series (SCCS) Analysis
  - Study Methods and Results
- Discussion
- Conclusion



# Introduction

- Two\* RSV vaccines were approved for use in the U.S. in adults 60 years and older
  - RSVPreF3+AS01 (GSK - AREXVY)
  - RSVPreF (PFIZER - ABRYSVO)
- An imbalance in the rates of Guillain-Barré syndrome (GBS) between vaccine and placebo recipients was identified in clinical trials supporting licensure of RSV vaccines <sup>1, 2</sup>
- FDA is conducting a post-licensure RSV vaccine safety study using two designs:
  - Observed vs. Expected Analysis
  - Self-Controlled Case Series (SCCS) Analysis

\*mRNA-1345 (Moderna - mRESVIA®) was approved on May 31, 2024.

# Observed vs. Expected Analysis Summary



## Methods

- Evaluated risk of GBS following one dose of either RSVPreF3+AS01 or RSVPreF vaccines using a retrospective cohort design with the 2022 historical comparator
- Estimated the observed incidence rates (IRs) and compared to historical comparator (expected) rates, to obtain incidence rate ratios (IRRs) with 95% confidence intervals (CIs)
- Estimation of GBS positive-predictive value (PPV)-adjusted rates is based on multiple imputed datasets
  - Chart review, PPV for GBS: 71% (95% CI: 63%, 79%)<sup>3</sup>

# Observed vs. Expected Analysis Summary Results



	RSVPreF3+AS01	RSVPreF
<b>Inferential Analysis Results</b>		
Observed vs. Expected Analysis	<b>2.76 (95% CI: 1.32, 5.07)</b>	<b>6.94 (95% CI: 3.70, 11.87)</b>
PPV-Adjusted Analysis	2.75 (95% CI: 0.46, 5.04)	<b>6.91 (95% CI: 1.85, 11.97)</b>
GBS Cases per 1 million Doses	10.0	25.1
<b>Descriptive Analysis Results</b>		
Total RSV Vaccine Doses	<b>2,061,602</b>	
RSV Vaccine Doses	1,379,335	682,267
Observed GBS cases	<11	13

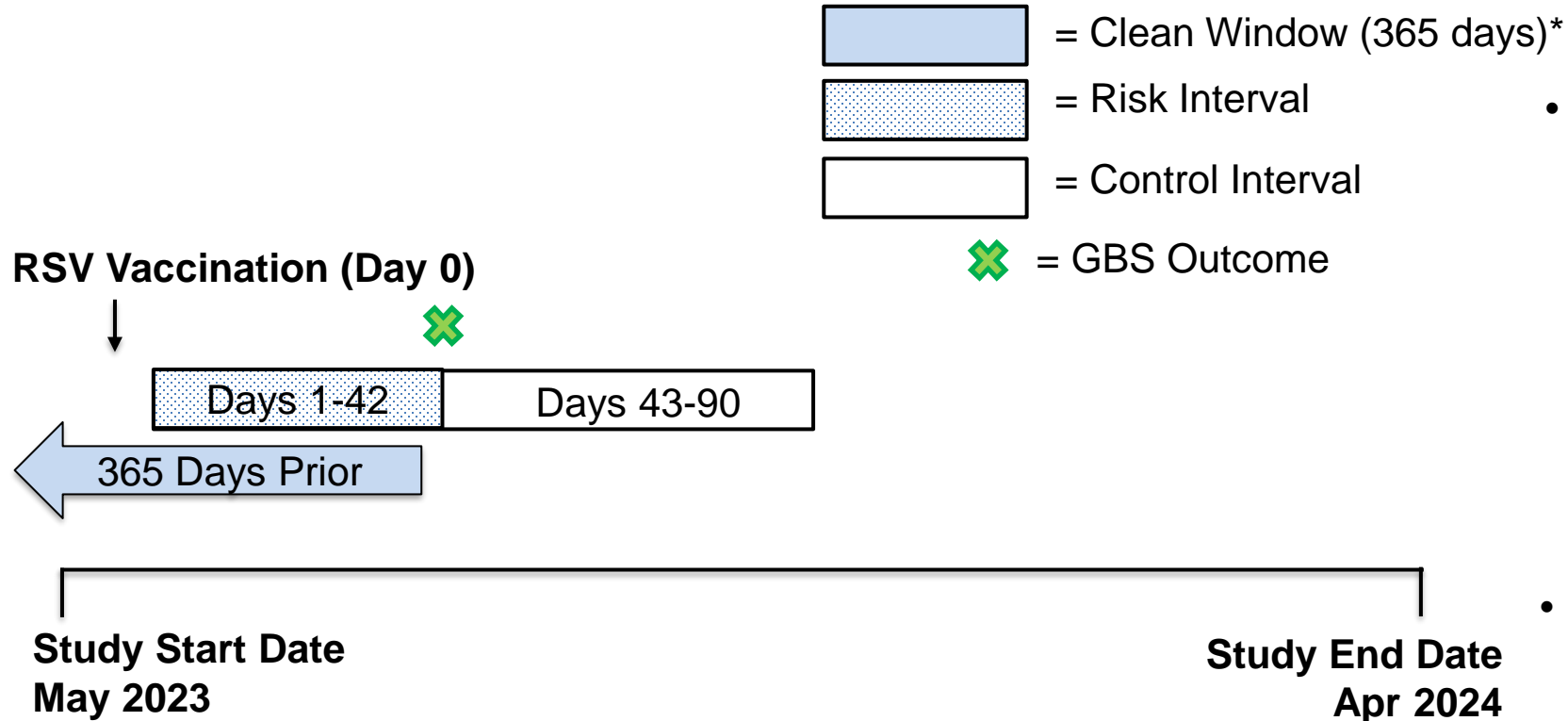
- **An elevated IRR was observed for GBS following RSV vaccination**
- **Only RSVPreF association was statistically significantly elevated in PPV-adjusted analysis**

# Motivation for SCCS Study



- The observed vs. expected analysis is a crude method with limited adjustments for confounding, utilizing aggregate historical incidence rates rather than individual historical persons as comparators, increasing the potential for confounding and bias
- The SCCS is a robust method that controls for time-invariant confounding and does not rely on historical background incidence rates

# Self-Controlled Case Series (SCCS) Design



## Population Inclusion Criteria:

- Enrolled in Medicare Fee-for-Service (FFS) during the clean window
- 65 years of age or older on RSV vaccination date
- No GBS outcome during the clean window

## Population Exclusion Criteria:

- Beneficiaries with no incident GBS outcome in the observation period

OR

- Beneficiaries who do not meet criteria to identify an incident outcome\*\*

\*The clean window is relative to the outcome date; risk and control intervals are relative to the vaccination date  
\*\*Outcomes that are considered 'incident' after implementing the outcome-specific cleaning window are included, and only first incident outcome in the observation period are retained

# SCCS Analysis: Study Methods



<b>Study Design</b>	Self-Controlled Case Series (SCCS) <sup>4, 5</sup>
<b>Data Sources and Study Population</b>	Centers for Medicare & Medicaid Services (CMS) Medicare Beneficiaries ages 65 years and older, enrolled in: <ul style="list-style-type: none"> <li>▪ Medicare FFS (Parts A and B) and Part D on the date of RSV vaccination</li> <li>▪ Medicare FFS and in 1-year prior</li> </ul>
<b>Study Period</b>	May 2023* – April 2024♦**
<b>GBS Outcome Definition</b>	<ul style="list-style-type: none"> <li>▪ Risk Interval: 1 - 42 days</li> <li>▪ Control Interval: 43 - 90 days</li> <li>▪ Care Setting: inpatient – primary position only; ICD-10-CM DGN G61.0</li> </ul>
<b>Statistical Analyses</b>	<ul style="list-style-type: none"> <li>▪ IRRs with 95% CIs</li> <li>▪ Absolute Risk: Attributable Risk (AR) with 95% CIs per 100,000 doses and 100,000 person-years (PY)</li> <li>▪ Adjustment for outcome-dependent observation time (Farrington) <sup>6</sup>, seasonality, PPV</li> </ul>

\*FDA approval dates for RSVPreF3+AS01 and RSVPreF were May 3, 2023 and May 31, 2023, respectively

♦Study end date for initial SCCS analysis was April 6, 2024

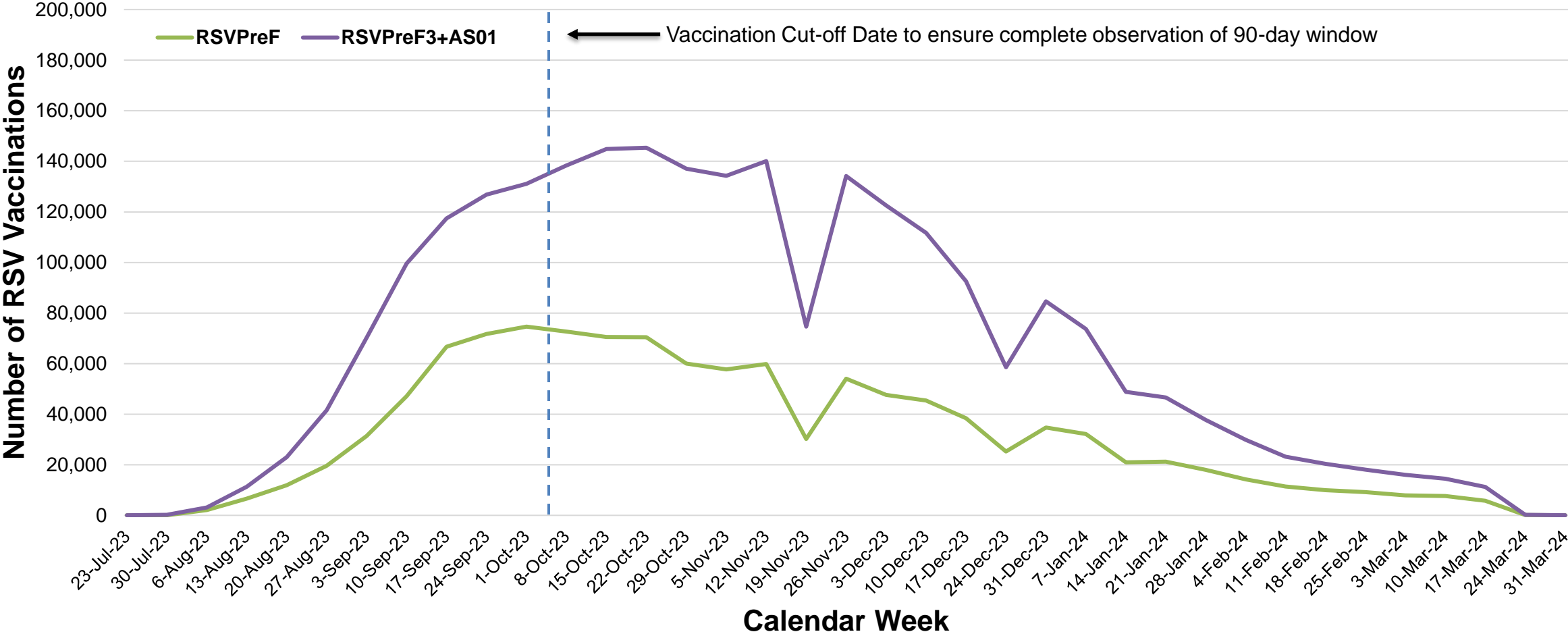
\*\*RSV vaccinations prior to October 8, 2023 to have complete observation in 90 days post-vaccination and is expected to have 90% or greater data-completeness



# SCCS Analysis: Vaccination Uptake Trends



### Weekly Vaccination Uptake Trends in RSV Vaccines, By Vaccine Type



Data Through Date: Apr 06, 2024



# SCCS Analysis: Descriptive Results

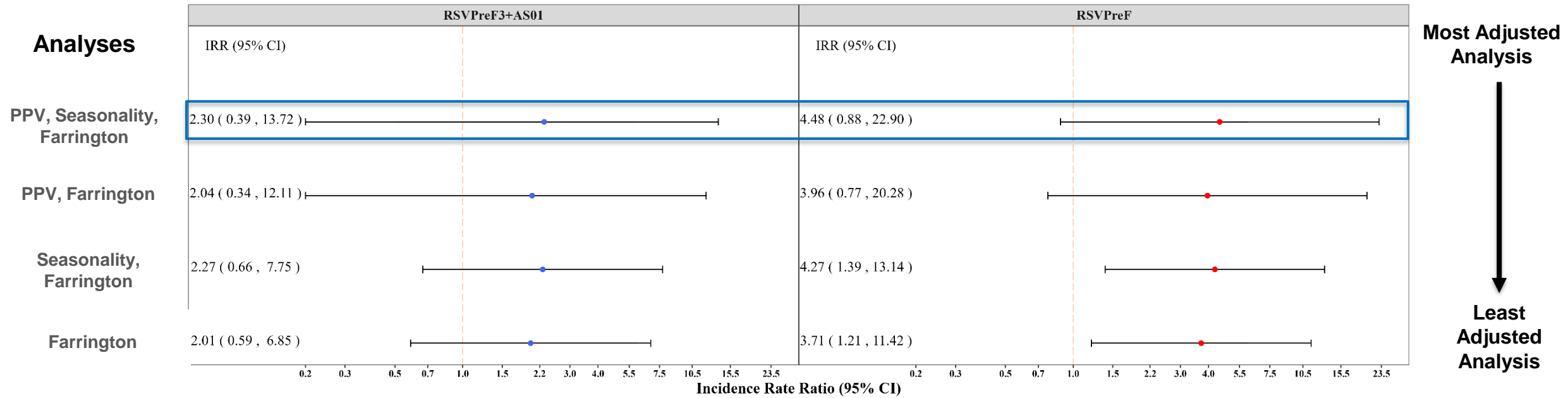
## Case Counts for GBS following RSV vaccination by Vaccine Type

Case Population Eligibility Criteria	RSV Vaccinations (n=1.33 M individuals; 1.33 M doses)*	
	RSVPreF3+AS01 (n= ~872k doses)*	RSVPreF (n= ~456k doses)*
Total GBS cases and total number of days in study period	160 cases [339 days]	92 cases [311 days]
GBS cases during 90-day observation period	105	74
Incident GBS cases after applying clean window restriction	55	36
<b>GBS cases qualifying for SCCS analysis</b> (vaccinated before Oct 8, 2023)	<b>11</b>	<b>17</b>

\* n = Medicare Beneficiaries that received RSV vaccination and eligible for SCCS analysis are presented

# SCCS Analysis: Results for GBS

IRR with 95% CI of GBS following RSV Vaccination Adjusted for Combinations of PPV, Seasonality *with* Outcome-Dependent Observation Time



- An elevated IRR was observed for GBS following RSVPreF vaccination with two analyses that had the least adjustments
- Results additionally adjusted for PPV were no longer statistically significant
  - **PPV, Seasonality with Farrington-Adjusted Analysis: 4.48 (95% CI: 0.88, 22.90)**
  - **PPV, with Farrington-Adjusted Analysis: 3.96 (95% CI: 0.77, 20.28)**

# SCCS Analysis: Results for GBS and RSV vaccination



Incidence Rate Ratio (IRR) and Attributable Risk (AR) of GBS - Adjusted for PPV, Seasonality and Outcome-Dependent Observation Time

Inferential Analysis Results	RSVPreF3+AS01	RSVPreF
Eligible Vaccinees	872,068	456,107
Cases in the Risk and Control Intervals	<11	12.1
IRR (95% CI)	2.30 (0.39, 13.72)	4.48 (0.88, 22.90)
AR per 100,000 Doses (95% CI)	0.32 (-0.30, 0.95)	1.57 (0.30, 2.85)
AR Per 100,000 PY (95% CI)	2.81 (-2.64, 8.26)	13.69 (2.59, 24.79)

# Discussion

## Strengths

- SCCS study design provides robust adjustment for potential time-invariant confounding
- Large database facilitates more precise evaluation of health outcomes
- Study findings are generalizable to U.S. population 65 years and older

## Limitations

- Potential outcome misclassification
- Potential misspecification of risk and control intervals
- Potential for residual confounding

# Discussion



## Observed vs. Expected Analysis

- An elevated IRR was observed for GBS following RSV vaccination, but only RSVPreF association was statistically significantly elevated  
PPV (chart review) adjustment
- Crude method that utilized aggregate historical comparator rates rather than individuals, increasing the potential for confounding
- Statistically significant results of GBS do not establish a causal association between RSV vaccines and GBS

# Discussion



## SCCS Analysis

- Although, an elevated IRR was observed for GBS following RSVPreF vaccination for two analyses that had fewer adjustments, the results were not statistically significant when adjusted for PPV
- Only cases, i.e., persons with an incident outcome contribute to the SCCS analysis
- Estimation of outcome risk occurs within, rather than between individuals, adjusting for time-invariant confounding

# Conclusion



- The results from two different types of analyses of potential GBS risk following RSV vaccination are mixed and highly uncertain
- These analyses do not provide clear, conclusive evidence of an elevated risk of GBS and an elevated risk cannot be ruled out at this time
- FDA is conducting medical chart review on GBS cases and will continue to evaluate the safety of RSV vaccines as more data are available
- FDA maintains that the benefits of RSV vaccination in preventing RSV hospitalizations outweigh the potential risks associated with the vaccines



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# Questions?