NON-INTERVENTIONAL STUDY
FINAL REPORT ABSTRACT

Title: A Post-Marketing Near Real-Time Safety Surveillance of Respiratory Syncytial Virus (RSV) Vaccine for Guillain-Barre Syndrome (GBS) among Older Adults in the United States

Date: 06 January 2026

Name and affiliation of the main author: Joanne Wu, ScD, MS, Director, Epidemiology, Safety Surveillance Research, Worldwide Safety Pfizer, Inc.

Keywords: Guillain-Barre Syndrome, Respiratory Syncytial Virus Vaccine, ABRYSVO, Near Real-Time Safety Surveillance

Rationale and background: The United States (US) Food and Drug Administration (FDA) approved RSVpreF (ABRYSVO®) respiratory syncytial virus (RSV) vaccine on 31 May 2023 for individuals 60 years of age or older to prevent severe RSV disease. Guillain-Barre syndrome (GBS) was designated as an important potential risk in the ABRYSVO US pharmacovigilance plan at the time of approval. This final study report provides rapid surveillance for the GBS risk following ABRYSVO vaccination by leveraging near real-time Medicare data for individuals aged 65 years or older across two RSV seasons (2023/2024 and 2024/2025) using a self-controlled risk interval design, as well as descriptive analysis of vaccine recipients aged 60-64 years from a large, nationally representative claims database. This non-interventional study was designated as a post-authorization safety study and was a post-marketing commitment to the FDA.

Research question and objectives: The research question was what is the incidence rate (IR) of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in the Centers for Medicare & Medicaid Services (CMS) Medicare databases and individuals aged 60-64 years enrolled in PharMetrics Plus database as compared to the expected IR of GBS in a comparable population?

Study design: This was a non-interventional cohort study among US Medicare beneficiaries aged 65 years or older and individuals aged 60-64 years enrolled in the PharMetrics Plus database. The indexing period for identifying ABRYSVO exposure in both databases was from 31 May 2023, the date of ABRYSVO's FDA approval for older adults, to 28 February 2025. The overall study period spanned the baseline period, indexing period, and follow-up period for the self-controlled risk interval (SCRI) and descriptive analyses, i.e., from 31 May 2022 to 23 May 2025.

The SCRI analysis compared the IR of GBS during the pre-specified post-vaccination risk interval (primary: days 1-21; secondary: days 1-42) to the post-vaccination control interval (days 43-84) within vaccinated individuals, which effectively controlled for time-invariant confounding within persons. To account for potential time-varying confounding due to seasonality of GBS, the study further adjusted for the estimated baseline risk of GBS over calendar months. In addition, positive predictive value (PPV) adjusted analyses were

conducted to mitigate bias due to outcome misclassification and uncertainty in the claims-identified cases of GBS.

Due to the limited sample size of individuals aged 60-64 years in the PharMetrics Plus database, analyses for this age group were pre-specified as descriptive only in the protocol and SCRI was not performed.

Setting: The source population was the US Medicare beneficiaries available in the CMS Medicare Fee-for-Service administrative database (referred to as the CMS Medicare databases including Medicare Parts A and B, with over 66 million individuals enrolled as of March 2024),[1] and individuals aged 60-64 years of age in the PharMetrics Plus database (approximately 3.1 million annual enrollees aged 60-64 years).[2]

Subjects and study size, including dropouts: Eligible individuals were required to receive a dose of the ABRYSVO vaccine (date of receipt defined as the index date) during the indexing period and had 12 months of baseline data. For Medicare beneficiaries, individuals were also required to be 65 years of age or older on the index date and had aged into Medicare. For commercially insured adults in the PharMetrics Plus database, individuals were required to be between 60 to 64 years at index date. In both databases, individuals were excluded if they received an RSV vaccine from any manufacturer other than Pfizer during the baseline and follow-up period, were missing information on sex, or had a GBS diagnosis during the baseline period or on the index date.

Of 3,966,220 individuals in CMS Medicare databases who received one dose of ABRYSVO during the indexing period, 1,584,636 (40%) individuals met all eligibility criteria and made up the final CMS study population. The largest attrition was due to the requirement of at least 12 months of continuous enrollment in Medicare Parts A and B before the index date (n=1,628,341; 41%).

In the PharMetrics Plus database, 355,928 individuals received one dose of ABRYSVO during the indexing period; only 13.6% (n=48,258) were 60-64 years of age on the index date. The final study population aged 60-64 years included 35,274 (10%) individuals.

Variables and data sources: The exposure of interest was defined as the receipt of a single dose of ABRYSVO vaccination during the indexing period, as identified by specific vaccine codes. The outcome of interest was GBS diagnosis, which was identified from claims using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code G61.0. An incident GBS case was defined as the first occurrence of a primary discharge diagnosis of GBS in the inpatient setting post-vaccination. In a recent FDA analysis evaluating GBS risk following RSV vaccination in Medicare data, the algorithm used in this study had an overall PPV of 68.0%, with a lower PPV of 62.3% in the post-

[1] Centers for Medicare & Medicate Services, CMS Fast Facts – March 2024 Version, URL: https://data.cms.gov/fact-sheet/cms-fast-facts.

[2] Baser O, Samayoa G, Yapar N, Baser E, Mete F. Use of open claims vs closed claims in health outcomes research. Journal of Health Economics and Outcomes Research. 2023;10(2):44.

vaccination risk interval of 1-42 days and a higher PPV of 81.8% in the post-vaccination control interval of 43-90 days (referred to as differential PPV adjustment in the analyses).[3] Individual demographic and clinical characteristics were captured during the baseline period. The study used the CMS Medicare databases with monthly data refreshes that included Medicare Parts A, B and D, and the PharMetrics Plus commercial claims database with monthly data refreshes.

Results: Among 35,274 individuals who were ABRYSVO-vaccinated individuals aged 60-64 years old in PharMetrics Plus, no GBS cases were observed during the 1-21- or 1-42-day post-vaccination risk interval nor in the 42-day control window in the combined 2023/2024 and 2024/2025 seasons.

Among 1,584,206 ABRYSVO-vaccinated Medicare beneficiaries aged 65 years and older, 26 cases in the 21-day primary risk interval, 38 cases in the 42-day primary risk interval, and 13 cases in the 42-day control interval were observed across both seasons. In the unadjusted SCRI model, the incidence rate ratio (IRR) for the 21-day primary risk interval compared to the control interval was 4.00 (95% CI: 2.05–7.78) and 2.92 (95% CI: 1.56–5.48) for the 42-day secondary risk interval. After adjusting for both differential PPV and seasonality, the risk of GBS in both the 21 and 42 days after ABRYSVO vaccination among Medicare beneficiaries aged 65 years and older was attenuated but remained borderline statistically significant in the primary risk interval (IRR=2.86 [95% CI: 1.03–7.94]) and was no longer statistically significant in the secondary risk interval (IRR=2.18 [95% CI: 0.85–5.60]). The adjusted attributable risk was 6.7 (95% CI: 0.3–8.9) and 8.1 (95% CI: –2.6–12.3) excess GBS cases per million vaccinations over the 21- and 42-day risk interval, respectively, with confidence intervals bordering or including the null (i.e., zero). For the primary risk interval, the risk was comparable between the 2023/2024 (differential PPV-adjusted IRR=2.47 [95% CI: 0.85–7.19]) and 2024/2025 (differential PPV-adjusted IRR=3.46 [95% CI: 0.52–23.04]) RSV seasons, and remained elevated after removal of GBS cases with infections in the 42 days prior to onset (differential PPV-adjusted IRR=3.71 [95% CI: 1.39–9.94]), a known risk factor of GBS.

Discussion: Based on approximately 1.6 million ABRYSVO doses analyzed over two seasons, the study suggests a small increased risk of GBS following ABRYSVO vaccination among US adults aged 65 years and older, with an estimated excess risk of 7-8 cases per million doses. The findings are consistent with FDA's separate analysis of Medicare data for the 2023/2024 season[3] and also align with findings from other published US and United Kingdom (UK) non-interventional studies using similar designs,[4,5,6] though absolute risk estimates vary across studies. These differences may reflect variations in the age of

[3] Lloyd PC, Shah PB, Zhang HT, Shah N, Nair N, Wan Z, et al. Evaluation of Guillain-Barré syndrome following Respiratory Syncytial Virus Vaccination among Medicare Beneficiaries 65 Years and Older. medRxiv.

[4] Stowe J, Watson C, Ramsay M, Andrews N. Assessing the risk of Guillain-Barré syndrome in older adults after bivalent RSV pre-F vaccination in England. medRxiv. 2025.

[5] Cullen LA, Gibbons CL, Shi T, Hasan T, Sullivan C, Marsh K, et al. RSV Vaccination Programme for Older Adults: A Scotland-Wide Study on RSVpreF Vaccine Safety. Vaccines. 2025;13(11):1088.

[6] Fry SE, Terebuh P, Kaelber DC, Xu R, Davis PB. Effectiveness and Safety of Respiratory Syncytial Virus Vaccine for US Adults Aged 60 Years or Older. JAMA Netw Open. 2025;8(5):e258322.

vaccinated populations and differences in case definitions and diagnostic accuracy. No GBS cases were observed among approximately 35,000 commercially insured individuals aged 60–64 years. However, results should be interpreted with caution given the rarity of GBS and the limited sample size in this age group.

While GBS following RSV vaccination warrants continued scientific scrutiny, the rare risk of GBS associated with the ABRYSVO, based on this study (and other similar available data including FDA's evaluation of GBS risk), is not anticipated to impact the overall benefit-risk profile of ABRYSVO. Pfizer's robust post-marketing surveillance will continue to monitor GBS risk to ensure that the benefit-risk profile of ABRYSVO remains favorable.

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Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
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NON-INTERVENTIONAL (NI) STUDY

FINAL STUDY REPORT

Study Information

Title	A Post-Marketing Near Real-Time Safety Surveillance of Respiratory Syncytial Virus (RSV) Vaccine for Guillain-Barre Syndrome (GBS) among Older Adults in the United States
Protocol number	C3671054
Version identifier of the study report	1.0
Date	06 January 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000267
Active substance	ABRYSVO® is a bivalent recombinant stabilized prefusion F protein subunit vaccine (Respiratory Syncytial Virus Vaccine). It consists of equal amounts of prefusion F antigens from the two major RSV subgroups: RSV subgroup A prefusion F (60 µg) and RSV subgroup B prefusion F (60 µg).
Medicinal product	RSVpreF (ABRYSVO®)
Research question and objectives	**Research question:** What is the incidence rate of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases and individuals aged 60–64 years enrolled in the IQVIA PharMetrics Plus claims database (PharMetrics Plus database) as compared to the expected incidence rate of GBS in a comparable population? **Research objectives:** • To conduct near real-time monitoring of the incidence of GBS following vaccination with ABRYSVO among individuals aged

	65 years of age or older enrolled in CMS Medicare databases using rapid cycle analysis (RCA) study design; and • To assess if there is an elevated risk of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases, using self-controlled risk interval (SCRI) study design; and • To descriptively monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60–64 years enrolled in PharMetrics Plus database.
Country(-ies) of study	United States
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Refer to Section 3 Investigators and Section 5 Milestones.

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Not applicable.

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Not applicable.

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Not applicable.

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The supplementary results tables are included in the stand-alone file named "C3671054_RSV Surveillance Final Study Report Supplementary Results."

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADI	Area deprivation index
AR	Attributable risk
BMI	Body mass index
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMS	Centers for Medicare & Medicaid Services
COVID-19	Coronavirus disease 2019
CMV	Cytomegalovirus
CPT	Current Procedural Terminology
EBV	Epstein-Barr virus
EU PAS	European Post Authorization Study
FDA	[US] Food and Drug Administration
FFS	Fee-for-Service
GBS	Guillain-Barre syndrome
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HEV	Hepatitis E virus

Abbreviation	Definition
HPV	Human Papillomavirus
ICD-10-CM	International Classification of Diseases, 10th revision, Clinical Modification
ID	Identifier
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IR	Incidence rate
IRR	Incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IP	Inpatient
IQR	Interquartile range
LRTD	Lower respiratory tract disease
MenACWY	Meningococcal ACWY vaccine
MenB	Meningococcal Serogroup B vaccine
N	Number
NDC	National Drug Codes
OP/PB	Outpatient
PASS	Post-Authorization Safety Study
PMR	Post-Marketing Requirement
PPV	Positive predictive value
P-y	Person-years
QBA	Quantitative bias analysis
QC	Quality control

Abbreviation	Definition
RCA	Rapid cycle analysis
RSV	Respiratory Syncytial Virus
RSVpreF	Respiratory Syncytial Virus Prefusion F protein
RWD	Real-world data
SAP	Statistical analysis plan
SCRI	Self-controlled risk interval
SD	Standard deviation
SES	Socioeconomic status
Td	Tetanus and diphtheria
Tdap	Tetanus, diphtheria, and pertussis
TNF-alpha	Tumor necrosis factor-alpha
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
US	United States

3. INVESTIGATORS

Name, degree(s)	Title	Affiliation
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Efe Eworuke, PhD	Principal, Epidemiology & Drug Safety	Epidemiology & Drug Safety, IQVIA, Inc.
Krystal Cantos, PhD	Associate Principal, Epidemiology & Drug Safety	Epidemiology & Drug Safety, IQVIA, Inc.

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Completion of feasibility assessment	29 February 2024	29 February 2024	
Draft protocol submission to the FDA	30 April 2024	30 April 2024	
Final protocol submission to the FDA	16 August 2024	16 August 2024	
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol	N/A	14 November 2024	
Start of data collection	19 August 2024	19 August 2024	
End of data collection	15 September 2025	17 November 2025	Delay is due to changes to the PharMetrics Plus data coverage and release schedule, implemented in August 2025.
Registration in the HMA-EMA Catalogue of RWD studies	Prior to the start of data collection	16 August 2024	
Interim report 1[1]	20 December 2024	20 December 2024	
Interim report 2[2]	21 February 2025	21 February 2025	
Interim report 3[3]	08 August 2025	08 August 2025	
Final study report[4]	30 January 2026		

Abbreviations: FDA, US Food and Drug Administration; HMA-EMA, Heads of Medicines Agencies – European Medicines Agency; RCA, rapid cycle analysis; RSV, respiratory syncytial virus; RWD, real-world data; SCRI, self-controlled risk interval.

[1] Interim report 1 included 2023/2024 RSV season SCRI and descriptive analysis report.

[2] Interim report 2 included a description of the population of RCA #1, with vaccination data from May 2023 through August 2024.

[3] Interim report 3 included all six RCAs, with vaccination data from May 2023 through January 2025.

[4] Final study report included 2023/2024 RSV season SCRI and descriptive analyses; 2024/2025 RSV season SCRI and descriptive analyses; and combined two seasons' SCRI and descriptive analyses.

6. RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a common, contagious virus that causes mild, cold-like symptoms but may cause severe disease with a need for hospitalization in infants and older adults.(1) The United States Food and Drug Administration (US FDA) approved Respiratory Syncytial Virus Prefusion F protein (RSVpreF) (ABRYSVO®) RSV vaccine on 31 May 2023 for individuals 60 years of age and older to prevent severe RSV disease.(2, 3) On 22 October 2024, the vaccine was approved for individuals 18 through 59 years of age who are at increased risk for lower respiratory tract disease (LRTD).(4) The Centers for Disease Control and Prevention (CDC) initially recommended that adults aged 60 years and older receive RSV vaccination using shared clinical decision-making.(3) Following the Advisory Committee on Immunization Practices (ACIP) meeting, the CDC further recommended on 26 June 2024 that all adults aged 75 years and older, and adults aged 60–74 years who are at increased risk for severe RSV disease, should receive the vaccine.(5, 6)

Guillain-Barre syndrome (GBS) is a rare, serious acute demyelinating disease, where nerve damage causes muscle weakness and sometimes paralysis.(7) GBS was an important potential risk in the US ABRYSVO pharmacovigilance plan at the time of approval; Pfizer has an ongoing Post-Marketing Requirement (PMR) Post-Authorization Safety Study (PASS),(8-10) protocol # C3671031, European Post Authorization Study (EU PAS) Register # EUPAS1000000267, that is planned over multiple RSV seasons to evaluate any small or modest risk of GBS (e.g., two-fold) following ABRYSVO vaccination using the fully adjudicated Centers for Medicare & Medicaid Services (CMS) Medicare claims. However, there is also a need to rapidly assess the risk of GBS following ABRYSVO administration, as exposures accrue to address the gap in safety evidence from prelicensure trials and early passive adverse event reporting.

Given the need for timely safety data, this PASS provided a timely assessment of GBS risk after ABRYSVO vaccination during the initial vaccine uptake period of the first two consecutive RSV seasons, 2023/2024 and 2024/2025, since FDA approval.

The first interim report, submitted to the FDA on 20 December 2024, evaluated ABRYSVO exposures in the 2023/2024 season using a comparative self-controlled risk interval (SCRI) design and noted a two-fold non-statistically significant increased risk of GBS following ABRYSVO vaccination among older adults (aged 65 years or older). The second and third interim study reports presented results from the rapid cycle analysis (RCA), an established method of near real-time surveillance, with six monthly assessments of a potential safety signal while exposures accrued by comparing observed incidence rates (IRs) of GBS to an expected background rate. A signal was detected for a modestly increased potential risk of GBS following ABRYSVO vaccination in RCA #1, after which GBS rates were descriptively monitored across subsequent RCAs. Cumulative unadjusted GBS IRs in the primary risk interval (1–21 days post-vaccination) increased slightly from 26.1 to 30.8 cases per 100,000 person-years (p-y) over the six RCAs, while rates in the secondary interval (1–42 days) remained relatively stable.

The final study report builds on these interim findings by presenting results from a SCRI analysis across both RSV seasons (2023/2024 and 2024/2025). This analysis provides a more robust evaluation of GBS risk following ABRYSVO vaccination by leveraging the full study period and controlling for time-invariant confounders within individuals. For this

reason, the comparative SCRI complements the RCA signal detection framework, and strengthens the vaccine safety study.(11)

This non-interventional study was designated as a PASS and was a post-marketing commitment to the FDA.

7. RESEARCH QUESTION AND OBJECTIVES

The research question for the overall study is: What is the IR of GBS following vaccination with ABRYSVO among older adults aged 65 years of age or older enrolled in CMS Medicare databases and individuals aged 60–64 years enrolled in the IQVIA PharMetrics Plus claims database (PharMetrics Plus database) as compared to the expected IR of GBS in a comparable population?

The research objectives are:

- To conduct near real-time monitoring of the incidence of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases using RCA study design; and
- To assess if there is an elevated risk of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases, using SCRI study design; and
- To descriptively monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60–64 years enrolled in PharMetrics Plus database.

This final study report presents results relevant to the second and third objectives. The first objective was addressed in the second and third interim reports.

8. AMENDMENTS AND UPDATES

All amendments to the protocol are listed in Table 1, and also available in Section 5 (Amendments and Updates) of the latest Protocol (**Appendix 2.1;** V2.0, 23 April 2025).

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	23 April 2025	Substantial	4. Abstract	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025 • Updated the study period end date for the RCA from 28 February 2025 to 21 February 2025 • Updated the years that will be used for	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition • The revised RCA study period aligns

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				background rate generation for the RCA • Revised the date of submission of Interim Report 3 from 20 June 2025 to 08 August 2025 • Revised description of CMS Medicare data from "primarily pre-adjudicated" to a mixture of pre-adjudicated and adjudicated • Updated wording for RCA statistical analysis text from "ratio of GBS rates between the ABRYSVO population and the comparator population" to "ratio of observed GBS rate and the expected GBS rate in the ABRYSVO population"	with the updated indexing period mentioned above • The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends, further outlined in Section 9.7.3.1 • The date of Interim Report 3 was extended to ensure all six RCA can be included in the report, given operational challenges and extended timeline encountered using Medicare data • The data source can be better described as a mixture of pre-adjudicated and adjudicated claims • A ratio of observed and expected rates better describes the statistical analysis for the RCA
			6. MILESTONES	• Added the date of registration in the HMA-EMA Catalogue and the EU PAS registration number • Revised the date of submission of Interim Report 3 from 20 June 2025 to 08 August 2025	• The protocol was registered in the HMA-EMA Catalogue on 16 August 2024 • The date of Interim Report 3 was extended to ensure all six RCA can be included in the report, given operational challenges

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					encountered using Medicare data
			7. RATIONALE AND BACKGROUND	• Updated recommendations for RSV vaccination added	• The Advisory Committee on Immunization Practices (ACIP) updated RSV vaccination recommendations in a 26 June 2024 meeting
			9.1.1 The Study Design of RCA Methodology	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025 • Updated the study period end date for the RCA from 28 February 2025 to 21 February 2025 • Renamed the "sensitivity risk interval" for the RCA to "secondary risk interval" and matched the indexing period to that of the primary risk interval • Updated the years that will be used for background rate generation for the RCA • Figure 1 and Figure 2 were updated to reflect the updated indexing periods for the RCA	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition • The revised RCA study period aligns with the updated indexing period mentioned above • The primary and secondary risk intervals will use the same indexing period to ensure that the same population is being evaluated in both, making the results more comparable • The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends, further

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					outlined in Section 9.7.3.1
			9.1.4. Study Population	• Figure 7 updated to reflect updated indexing periods for the RCA	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition
			9.2.1 Inclusion and Exclusion Criteria	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition
			9.3.2 Outcomes	• Included updated PPV for the GBS case definition	• To minimize potential outcome misclassification, the most updated data on PPV for the GBS case definition will be used for adjustment[1]
			9.3.3 Patient Characteristics	• Removed suramin from the list of medications being evaluated for use at baseline	• Suramin use is rare among population of interest[2]
			9.4.1 CMS Medicare Administrative Database	• Revised description of CMS Medicare data from “primarily pre-adjudicated” to a mixture of pre-	• The data source can be better described as a mixture of pre-

[1] Lloyd P. Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older. In: Office of Biostatistics and Pharmacovigilance Center for Biologics Evaluation and Research USFDA, editor. Meeting of the Advisory Committee on Immunization Practices (October 2024).

[2] Wiedemar N, Hauser DA, Mäser P. 100 years of suramin. Antimicrobial agents and chemotherapy. 2020;64(3):10.1128/aac. 01168-19.

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
				adjudicated and adjudicated	adjudicated and adjudicated claims
			9.7.3. The Statistical Analysis for the RCA	• Updated wording for RCA statistical analysis text from “ratio of GBS rates between the ABRYSVO population and the comparator population” to “ratio of observed GBS rate and the expected GBS rate in the ABRYSVO population”	• A ratio of observed and expected rates better describes the statistical analysis for the RCA
			9.7.3.1 The Background Rate of GBS	• Updated and added rationale for the years that will be used for background rate generation for the RCA	• The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends
			9.7.6.2 Positive Predictive Values (PPV)-Adjusted Quantitative Bias Analysis	• Added language to include updated PPVs for sensitivity analyses as they become available through the study duration	• To minimize potential outcome misclassification, the most updated data on PPV for the GBS case definition will be used for adjustment
			9.7.7.1. Removal of GBS Cases After Infection Diagnoses for the SCRI Analytic Population and the RCA Analytic Population	• Removed “and the RCA analytic population” from the header	• The header for this section did not accurately reflect the content of the section
			9.7.7.2. Secondary Risk Interval for the RCA Analytic Population	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025	• The primary and secondary risk intervals will use the same indexing period to ensure that the same population is being evaluated in both, making the

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					results more comparable
			9.7.7.3. Use of Published Background Rate of GBS for the RCA Analytic Population	• Section removed	• The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends
			9.7.7.4. Case-Centered GBS Analysis for the SCRI Analytic Population, the RCA Analytic Population and the Descriptive Analysis Population	• Clarified that selected demographic and clinical variables will be reported for the case-centered GBS analysis	• The full set of demographic and clinical variables will not be reported in case-centered GBS analyses as outlined the Statistical Analysis Plan. Updated for clarification.
			9.7.8 Summary of Statistical Analyses Presented in the Interim and Final Reports	• Revised the analyses that were included in Interim Report 2 and planned analyses for Interim Report 3 • Updated the indexing period end date for Interim Report 2 from 10 October 2024 to 10 August 2024 • Updated the indexing period end date for Interim Report 3 from 07 February 2025 to 10 January 2025	• The revised analyses for Interim Reports reflect the actual results that were presented in Interim Report 2 • The revised indexing period end date for Interim Report 2 reflects the actual data that were presented in Interim Report 2 • The revised Interim Report 3 end date aligns with the revised RCA indexing period, which allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture hospitalized

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
					GBS cases per outcome definition
			12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	• Revised text to clarify only the final study report will be uploaded to the HMA-EMA catalogues	• No interim reports will be uploaded to the HMA-EMA catalogues
			ANNEX 2. ADDITIONAL INFORMATION	• Updated the list of codes for RSV vaccination	• List of codes was updated as new ABRYSVO codes were added for the 2024/2025 season, and a new mRESVIA vaccine was approved

Abbreviations: CMS, Centers for Medicare & Medicaid Services; GBS, Guillain-Barre syndrome; HMA-EMA, Heads of Medicines Agencies – European Medicines Agency; PPV, positive predictive value; RCA, rapid cycle analysis; RWD, real-world data; SCRI, self-controlled risk interval.

9. RESEARCH METHODS

This final study report presents results from a SCRI analysis evaluating the risk of GBS following ABRYSVO vaccination among individuals aged 65 years of age or older enrolled in CMS Medicare databases. Additionally, a descriptive analysis was conducted to monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60–64 years enrolled in the PharMetrics Plus database. These analyses utilized data from the 2023/2024 and 2024/2025 RSV seasons, with analyses conducted separately by season as well as for the combined seasons. The research methods are summarized below, with further details described in the final study protocol (**Appendix 2.1**).

9.1. Study design

This was a non-interventional cohort study among adults aged 60 years and older exposed to ABRYSVO.

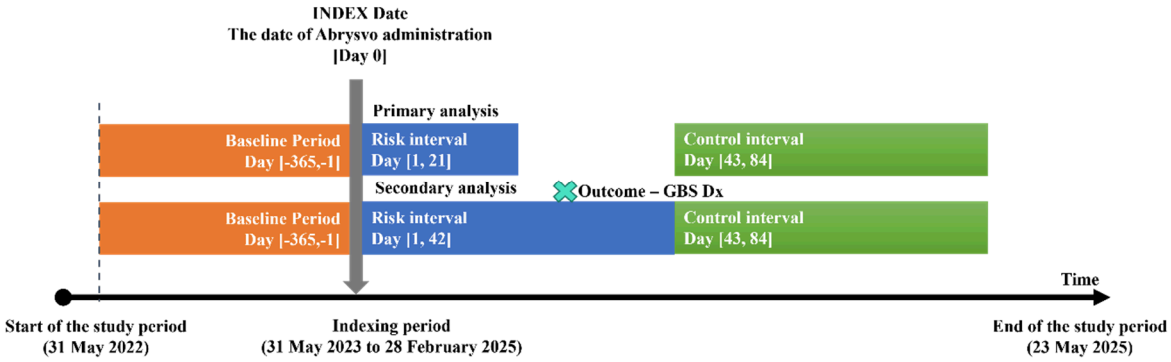
9.1.1. Study design of the SCRI analysis among ABRYSVO-vaccinated individuals aged 65 years and older

A SCRI analysis was conducted to evaluate potential risk of GBS following ABRYSVO vaccination among older adults aged 65 years and older, enrolled in CMS Medicare databases (Section 9.5). This design compared the IR of GBS during a pre-specified post-vaccination risk interval to a pre-specified post-vaccination control interval within a vaccinated individual, effectively controlling for time-invariant confounding.

Figure 1 illustrates the SCRI design, highlighting the index date (i.e., date of ABRYSVO administration), as well as the pre-specified risk and control intervals of a vaccinated individual. The primary risk interval for assessing incidence of GBS was 1–21 days following the index date (i.e., date of ABRYSVO vaccination); a secondary risk interval of 1–

42 days after the index date was also analyzed. The control interval spanned days 43–84 after the index date. The details of the key study periods are presented in Section 9.2.1.

Figure 1. Study design for SCRI analysis



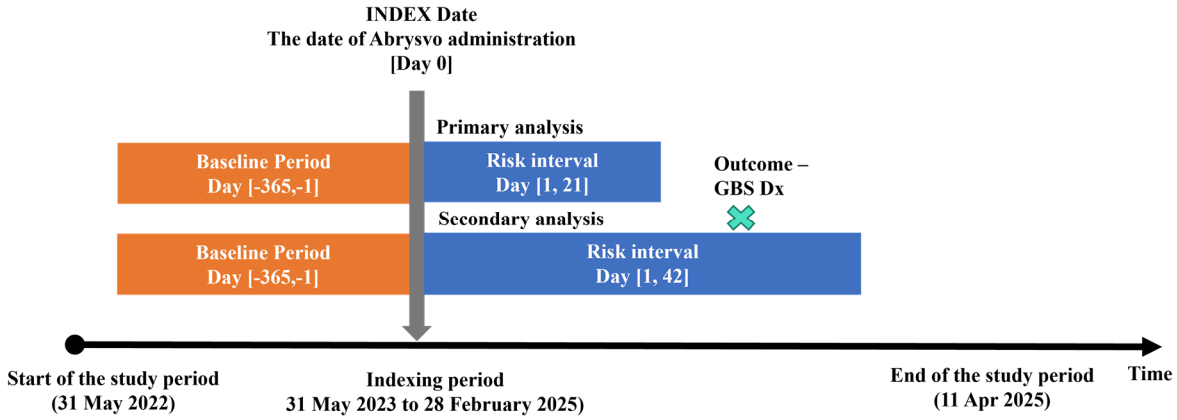
Abbreviations: Dx, diagnosis; GBS, Guillain-Barre Syndrome; SCRI, self-controlled risk interval.

9.1.2. Study design of the descriptive analysis among ABRYSVO-vaccinated individuals aged 60-64

Per the statistical analysis plan (SAP), a pre-specified descriptive analysis was conducted to evaluate the incidence of GBS following ABRYSVO vaccination among individuals aged 60–64 years and enrolled in the IQVIA PharMetrics Plus database. This design assessed the IR of GBS during a pre-specified post-vaccination risk interval.

Figure 2 illustrates the study design for the descriptive analysis, highlighting the index date (i.e., the date of ABRYSVO administration), as well as the pre-specified risk intervals of a vaccinated individual. For the primary analysis, the risk interval for assessing incidence of GBS was 1–21 days following the index date (i.e., date of ABRYSVO vaccination); for the secondary analysis, the risk interval was 1–42 days after the index date. The details of the key study periods are presented in Section 9.2.2.

Figure 2. Study design for descriptive analysis



Abbreviations: Dx, diagnosis; GBS, Guillain-Barre Syndrome.

9.2. Setting

The findings presented in this report cover the 2023/2024 and 2024/2025 RSV seasons. The indexing period for identifying ABRYSVO exposure in both databases was from 31 May 2023, the date of ABRYSVO's FDA approval in the older adult population, to 28 February 2025. The overall study period spanned the baseline period, indexing period, and follow-up period for the SCRI and descriptive analyses, i.e., from 31 May 2022 to 23 May 2025.

9.2.1. Setting of the SCRI analysis among ABRYSVO-vaccinated individuals aged 65 years and older

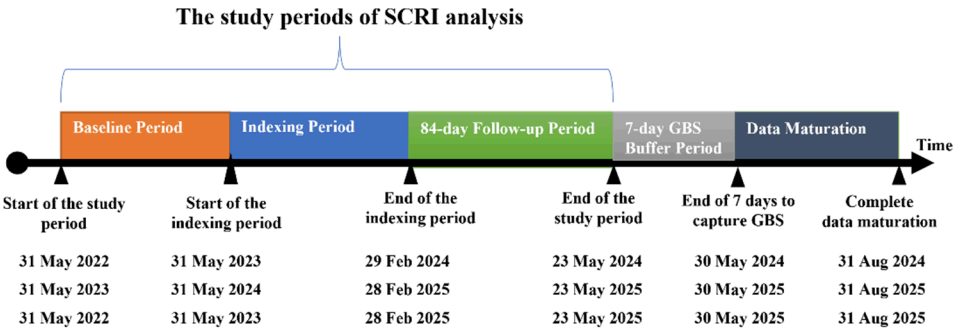
Figure 3 depicts the key study periods of the SCRI analysis for the 2023/2024, 2024/2025, and the combined season analysis, along with corresponding data maturation periods. The details of the components of the overall study period are provided below:

- **Study Periods:**
  - **2023/2024 Study Period:** 31 May 2022 – 23 May 2024
    - **Indexing period:** 31 May 2023 – 29 February 2024
  - **2024/2025 Study Period:** 31 May 2023 – 23 May 2025
    - **Indexing period:** 31 May 2024 – 28 February 2025
  - **Combined two season study period:** 31 May 2022 – 23 May 2025
    - **Indexing period:** 31 May 2023 – 28 February 2025[3]
- **Index Date:** The date of ABRYSVO administration
- **Baseline period:** 365 days prior to the index date
- **Follow-up period:** 1-84 days after the index date, and comprised of the:
  - **Post-vaccination risk period:** 1-21 and 1-42 days after the index date as the primary[4] and secondary risk interval, respectively
  - **Post-vaccination control period:** 43-84 days after the index date

[3] The indexing period ended in February as >90% of RSV vaccinations for the 2024/2025 RSV season were anticipated to be administered by that time, as a trade-off to balance timely analyses with data capture.

[4] Days 22-42 after the primary 1–21-day risk interval were considered a washout period and were not included in the primary analyses to avoid any carryover effects.

Figure 3. Study periods for the SCRI analysis spanning two RSV seasons



2023/2024 season analysis	31 May 2022	31 May 2023	29 Feb 2024	23 May 2024	30 May 2024	31 Aug 2024
2024/2025 season analysis	31 May 2023	31 May 2024	28 Feb 2025	23 May 2025	30 May 2025	31 Aug 2025
Analysis of both seasons	31 May 2022	31 May 2023	28 Feb 2025	23 May 2025	30 May 2025	31 Aug 2025

Abbreviations: CMS, Center for Medicare and Medicaid Services; GBS, Guillain-Barre syndrome; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.

Note: 1) 7-day GBS buffer period to accurately define date of GBS onset per outcome definition (Section 9.4.2); 2) The data maturation period allows for claims in the CMS Medicare Fee-for-Service (FFS) administrative database to be submitted in the system. Historically, approximately 90% of inpatient and outpatient claims are submitted to the CMS within two months after service date.(12)

9.2.2. Setting of the descriptive analysis among ABRYSVO-vaccinated individuals aged 60-64

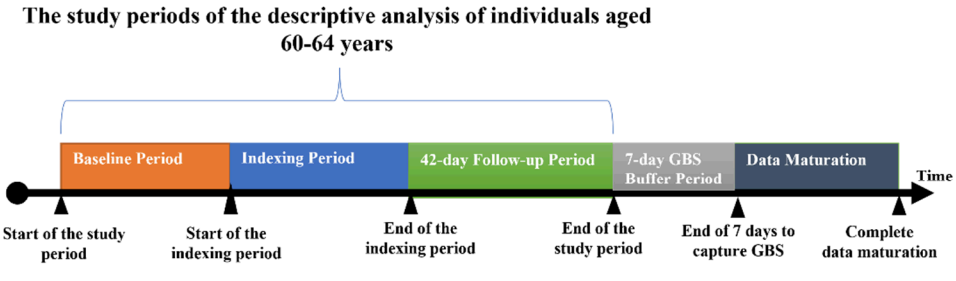
Figure 4 depicts the key study periods of the descriptive analysis for the 2023/2024, 2024/2025, and the combined season analysis, along with corresponding data maturation periods. The details of the components of the overall study period are provided below:

- **Study Periods:**
  - **2023/2024 Study Period:** 31 May 2022 – 11 April 2024
    - **Indexing period:** 31 May 2023 – 29 February 2024
  - **2024/2025 Study Period:** 31 May 2023 – 11 April 2025
    - **Indexing period:** 31 May 2024 – 28 February 2025
  - **Combined two season study period:** 31 May 2022 – 11 April 2025
    - **Indexing period:** 31 May 2023 – 28 February 2025[5]
- **Index Date:** The date of ABRYSVO administration
- **Baseline period:** 365 days prior to the index date
- **Follow-up period:** 1-42 days after the index date, and comprised of the:

[5] The indexing period ended in February as >90% of RSV vaccinations for the 2024/2025 RSV season were anticipated to be administered by that time, as a trade-off to balance timely analyses with data capture.

- **Post-vaccination risk period:** 1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively

Figure 4. Study periods for the descriptive analysis spanning two RSV seasons



2023/2024 season analysis	31 May 2022	31 May 2023	29 Feb 2024	11 Apr 2024	18 Apr 2024	01 Sept 2024
2024/2025 season analysis	31 May 2023	31 May 2024	28 Feb 2025	11 Apr 2025	18 Apr 2025	01 Nov 2025
Analysis of both seasons	31 May 2022	31 May 2023	28 Feb 2025	11 Apr 2025	18 Apr 2025	01 Nov 2025

Abbreviations: GBS, Guillain-Barre Syndrome; RSV, respiratory syncytial virus.

Note: 1) 7-day GBS buffer period to accurately define date of GBS onset per outcome definition (Section 9.4.2); 2) The data maturation period allows for claims in the PharMetrics Plus database to be fully adjudicated in the system.

9.3. Subjects

The study included adults aged 60 years and older in the US. The details for the study populations in the SCRI and descriptive analysis are described in Section 9.3.1 and 9.3.2, respectively.

9.3.1. Study population for SCRI analysis among ABRYSVO-vaccinated individuals aged 65 years and older

The source population for the SCRI analysis consisted of CMS Medicare Fee-for-Service (FFS) beneficiaries (Section 9.5.1) who received a single dose of ABRYSVO vaccine and were aged 65 years or older at the time of administration during the surveillance period.

9.3.1.1. Eligibility criteria

Inclusion criteria

The study included individuals from CMS Medicare databases who met the following inclusion criteria:

1. Received one dose of ABRYSVO vaccine administration (identified by specific current procedural terminology [CPT], national drug codes [NDC], or healthcare common procedure coding system [HCPCS] codes) between 31 May 2023 and 28 February 2025 (index date = date of ABRYSVO vaccination);

2. Were at least 65 years of age on the index date;

3. Aged into Medicare;[6]

4. Had at least 12 months of continuous enrollment in Medicare Parts A and B prior to the index date (i.e., the baseline period);

5. Had at least 3 months of continuous enrollment in Medicare Part D prior to the index date;

6. Had no record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.

Exclusion criteria

Individuals in CMS Medicare databases who met any of the following criteria were excluded from the study:

1. Missing sex information;

2. A GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.

9.3.2. Study population for descriptive analysis among ABRYSVO-vaccinated individuals aged 60–64

The source population for the descriptive analysis consisted of PharMetrics Plus enrollees (Section 9.5.2) who received a single dose of ABRYSVO vaccine and were aged 60–64 years at the time of administration during the surveillance period.

9.3.2.1. Eligibility Criteria

The study included individuals from the PharMetrics Plus database who met the following inclusion criteria:

1. Received one dose of ABRYSVO vaccine administration (identified by specific CPT, NDC, or healthcare common procedure coding system [HCPCS] codes) between 31 May 2023 and 28 February 2025 (index date = date of ABRYSVO vaccination);

2. Were 60-64 years of age on the index date;

3. Had at least 12 months of continuous enrollment in PharMetrics Plus with both medical and pharmacy benefits prior to the index date (i.e., the baseline period);

4. Had no record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.

[6] Beneficiaries who qualify due to disability may differ from beneficiaries who qualify due to age in demographic and clinical characteristics and are therefore excluded to reduce potential confounding.

Exclusion criteria

Individuals in the PharMetrics Plus database who met any of the following criteria were excluded from the study:

1. Missing sex information;

2. A GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.

9.4. Variables

9.4.1. Exposure

The exposure of interest was defined as an administration of the ABRYSVO vaccine during the indexing period (Section 9.2.1), as identified by a CPT code, HCPCS code or NDC during the indexing period.(13) Multiple records of the ABRYSVO vaccine for a unique patient identifier (ID) on the same day or within three days were deduplicated. The date of ABRYSVO vaccination was defined as the index date.

The code list for ABRYSVO vaccine and RSV vaccines from manufacturers other than Pfizer are listed in the SAP (**Appendix 4**). The list of RSV vaccine codes was reviewed and updated prior to starting analyses for the final study report.

9.4.2. Outcomes

The outcome of interest was the diagnosis of GBS, identified from inpatient and outpatient claims using International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) code G61.0. An incident GBS case was defined as the first occurrence of a primary discharge diagnosis of GBS in an inpatient setting after vaccination. The outcome date was defined as the date of hospitalization unless there was a claim with a GBS diagnosis in another medical setting (e.g., outpatient) in the prior 7 days. In that case, the earlier claim, irrespective of healthcare setting, was defined as the date of onset. Historically, this claims-based algorithm had a positive predictive value (PPV) of 71.2%–78.6% when validated against medical records using the Brighton criteria in Medicare data.(14-17) In a recent FDA analysis evaluating GBS risk following RSV vaccination in Medicare data, the algorithm had an overall PPV of 68.0%, with a PPV of 62.3% in the post-vaccination risk interval of 1-42 days, and 81.8% in the post-vaccination control interval of 43-90 days, based on chart review.(18)

9.4.3. Covariates

The patient characteristics of the ABRYSVO-vaccinated individuals, including demographics, clinical characteristics, and exposure characteristics were captured on the index date, during the baseline period and/or the follow-up period, as applicable. The variables that were assessed included but were not limited to those listed below and operational definitions are available in the SAP (**Appendix 4**).

Demographics:

- Age
- Sex
- Race/ethnicity (*CMS Medicare only*)

- Geographic region in the US
- Urban or rural residency (*CMS Medicare only*)
- Area Deprivation Index (ADI) rank
- Nursing home residency status (*CMS Medicare only*)
- Original reason of Medicare eligibility (*CMS Medicare only*)

ABRYSVO vaccination characteristics:

- Month and year of vaccination
- Care setting of vaccination
- Timing of vaccination (high respiratory season: September to February vs. low respiratory season: March to August)
- Record of ABRYSVO vaccination in both the 2023/2024 and 2024/2025 RSV seasons

Clinical characteristics:

- History of anaphylaxis
- Hospitalizations in the baseline period
- Infections in close proximity to vaccination (i.e., within 30 days prior to or after the index date).[7]
    - Any (includes any of the infections listed below)
    - Medically-attended infections: Upper or lower respiratory tract infections, gastrointestinal infections, and unspecified viral infections
    - Upper or lower respiratory tract infections (including diphtheria, whooping cough, streptococcal sore throat and scarlet fever, varicella with pneumonia, RSV, Coronavirus disease 2019 (COVID-19), acute sinusitis, acute tonsilitis, acute bronchitis, influenza, etc.)
    - Gastrointestinal infections (including cholera, typhoid and paratyphoid fevers, shigellosis, amoebic nondysenteric colitis, etc.)
    - Unspecified viral infection
    - Diarrhea
    - Fever
    - Campylobacter enteritis
    - Cytomegalovirus (CMV)
    - Epstein-Barr Virus (EBV)
    - Hepatitis E Virus (HEV)
    - Zika virus
- Frailty index(19-21)
- Charlson Comorbidity Index (CCI)(22).[8]
- Smoking status (ever)
- Body Mass Index (BMI)
- Immunocompromised status(23)

[7] Primary definition of one code in any clinical setting; Sensitivity definition of one inpatient (IP) claim or 2 outpatient (OP/PB) claims at least one day apart.

[8] The CCI used in this study assigned a score based on 19 conditions without incorporating age.

- Selected comorbidities[9]
  - Asthma
  - Blood disorders
  - Chronic lung disease
  - Diabetes
  - Heart disease
  - Kidney disease
  - Liver disorders
  - Neurological conditions
  - Malignant neoplasms
- Surgery (i.e., anesthesia or conscious sedation) in close proximity to vaccination (i.e., within 30 days prior to or after the index date)
- Trauma in close proximity to vaccination (i.e., within 30 days prior to or after the index date)
- Prior bone marrow transplant
- Other vaccines on the index date, in the baseline period, or in close proximity to ABRYSVO vaccination (i.e., within 30 days prior to or after the index date)
  - Any (includes any of the vaccinations listed below)
  - Seasonal influenza vaccine
  - COVID-19
  - RSV (other than ABRYSVO)
  - Tetanus and Diphtheria (Td) and Tetanus, Diphtheria, and Pertussis (Tdap)
  - Chickenpox (varicella)
  - Shingles (herpes zoster recombinant and/or live)
  - Human Papillomavirus (HPV)
  - Pneumococcal conjugate
  - Pneumococcal polysaccharide
  - Hepatitis A
  - Hepatitis B
  - Meningococcal ACWY Vaccine (MenACWY) and Meningococcal Serogroup B Vaccine (MenB)
  - Haemophilus influenzae type b
- Medications in the baseline period:
  - Tumor necrosis factor-alpha (TNF-alpha) antagonists
  - Immune checkpoint inhibitors
  - Immunosuppressant therapies
  - Isotretinoin

9.5. Data sources and measurement

The study utilized two data sources: the CMS Medicare FFS administrative database and the IQVIA PharMetrics Plus commercial claims database.

[9] Primary definition of one code in any clinical setting; Sensitivity definition of one inpatient (IP) claim or 2 outpatient (OP/PB) claims at least one day apart.

9.5.1. CMS Medicare Administrative databases

The study utilized the CMS Medicare FFS administrative database with monthly data refreshes that included Medicare Parts A, B, and D. The Medicare claims database has well-defined longitudinal data that captures healthcare service utilization for millions of beneficiaries across various care settings. Medicare Part A captures data from the inpatient setting, including critical access hospitals and skilled nursing facilities; approximately 90% of inpatient claims are submitted within two months after a healthcare encounter.(12) Medicare Part B covers doctors' services and outpatient care, including outpatient emergency departments and outpatient non-emergency departments, as well as professional services, non-laboratory, and laboratory services. Medicare Part D covers data from the outpatient pharmacy settings. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. The monthly data used in this study consisted of a mixture of pre-adjudicated and adjudicated claims; prior research has shown that the diagnosis codes rarely change (<0.5%) after adjudication.(12) The use of both adjudicated and pre-adjudicated claims data in this study enables near real-time assessments of safety signals.

9.5.2. IQVIA PharMetrics Plus database

The PharMetrics Plus database is one of the largest US health insurance claims databases comprised of fully adjudicated medical and pharmacy claims with approximately 3.1 million annual enrollees aged 60 to 64 years, and monthly data refreshes. Data contributors are largely commercial health plans, with an approximate 6-month data lag due to claims adjudication. PharMetrics Plus has diverse representation of geography, employers, payers, providers, and therapy areas, therefore, the database is representative of the commercially insured US national population for individuals under 65 years of age. In the post-launch and in-market phase, PharMetrics Plus has been utilized in providing robust insights in areas such as comparative effectiveness, medication adherence, patient cost analyses and also aids in pharmacovigilance and safety by tracking and analyzing the adverse effects of medications and vaccines.

9.6. Bias

Claims data are not collected for research purposes and thus are prone to coding errors, may have incomplete capture of variables of interest, and variable misclassification, which may have affected covariates (e.g., CCI, frailty index, nursing home residence, and presence of infections) as well as the exposure and outcome. GBS outcome events were not verified by chart review due to lack of access to Medicare medical records, but a validated algorithm directly developed from the Medicare data was employed, which has shown a high PPV of 71-78%.(14-17) In addition, a PPV-adjusted analysis was conducted as part of the SCRI analysis to minimize any bias due to outcome misclassification. Sensitivity definitions were also reported for covariates (e.g., nursing home residence defined using codes across different time windows) to address potential misclassification bias.

The CMS Medicare databases with monthly data refresh were also subject to a delay, i.e., “claims lag”, between when a service occurred and when the claim or encounter was considered adjudicated in the database. It is estimated that 91% of inpatient claims, 90% of outpatient, 96% of pharmacy claims and 87% of Carrier claims were submitted within two

months after service date.(12) In this analysis, under-ascertainment of outcomes due to data lag would be expected to occur more often in the control interval, given the control interval occurred the latest or closest to the study end date. To minimize under-ascertainment of outcomes due to data lag in the current analysis, outcome data in the follow-up period were allowed to mature for at least three months before initiating the analysis to account for the data lag. Therefore, if there were any bias due to the data lag, the amount of bias in SCRI results should be no more than 10% in the expected overestimation of GBS risk.

9.7. Study size

SCRI analysis among ABRYSVO-vaccinated individuals aged 65 years and older

Table 2 outlines the sample size calculations required for a conditional Poisson regression using the SCRI design, across different incidence rate ratios (IRR). To detect a lower IRR, the total number of GBS events needed would increase along with the number of vaccinated individuals required for both risk intervals. Specifically, to detect an IRR of 5.0, 15 GBS events were required, with an expected 1,153,846 and 566,038 vaccinated individuals for analysis in the 21-day and 42-day post-vaccination risk intervals, respectively. Conversely, to detect an IRR of 2.0, 69 GBS events were required, with significantly higher requirements of an estimated 8,846,154 and 4,339,623 individuals for the 21-day and 42-day post-vaccination risk intervals, respectively. Based on an expected background rate of 4.6 per 100,000 p-y for incident GBS in the Medicare population aged 65 years of age or older (24) and estimated uptake of ABRYSVO in the Medicare FFS dataset from 2023/2024 RSV season, the study was anticipated to be able to detect a high risk of GBS (5.0- fold or lower) with 80% power and an alpha level of 0.05 during a 21- or 42-day risk interval following vaccinations in each RSV season. Pooled analyses combining data from two RSV seasons was anticipated to achieve 80% power to detect a modest risk of GBS (e.g., 3.0- to 4.0-fold), depending on the length of the risk interval. Pfizer has a planned PMR PASS (protocol # C3671031) spanning 4.5 RSV seasons aiming to detect at least a 2-fold increased risk of GBS following ABRYSVO vaccination using fully adjudicated CMS Medicare claims data. The current PASS described in this protocol (protocol # C3671054) aimed to generate rapid safety evidence to help rule out a moderate risk of GBS until the results of the PMR PASS (protocol # C3671031) are available.

Table 2. Sample size calculations for the conditional Poisson regression using the SCRI design

IRR	Total number of GBS events needed	Number of events expected in control interval	Number of vaccinated individuals needed for 21-day period (N)	Number of vaccinated individuals needed for 42-day period (N)
5.0	15	3	1,153,846	566,038
4.5	17	4	1,538,462	754,717
4.0	20	4	1,538,462	754,717
3.5	23	6	2,307,692	1,132,075
3.0	29	8	3,076,923	1,509,434
2.5	41	12	4,615,385	2,264,151

Table 2. Sample size calculations for the conditional Poisson regression using the SCRI design

IRR	Total number of GBS events needed	Number of events expected in control interval	Number of vaccinated individuals needed for 21-day period (N)	Number of vaccinated individuals needed for 42-day period (N)
2.0	69	23	8,846,154	4,339,623

Abbreviations: GBS, Guillain-Barre syndrome; IRR, incidence rate ratio; SCRI, self-controlled risk interval.

Notes: Sample size calculations for the SCRI design were performed according to the method by Musonda et al.(25) The calculations assumed a 2-sided α=0.05, a power of 80%, a risk interval of 21 days, and a control interval of 21 days. Calculations were also performed using a 42-day risk interval and a 42-day control interval for secondary analyses. These calculations are based on an equal length of the control and risk interval and provide a conservative estimate of sample size as compared to calculations based on variable lengths of the control and risk interval.

Descriptive analysis among ABRYSVO-vaccinated patients aged 60-64

For the PharMetrics Plus analysis, the primary study population consisted of adults 60–64 years of age enrolled in healthcare plans captured in the PharMetrics Plus database without a prior history of GBS as assessed during a 12-month baseline period.

Due to the expected limited sample size in this narrow age group, analyses in PharMetrics Plus were pre-specified as descriptive, and no minimum sample size was required.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the SAP, which is dated, filed and maintained by the sponsor (**Appendix 4**).

9.9. Statistical methods

The statistical methods are briefly described below and detailed in the stand-alone SAP (**Appendix 4**).

9.9.1. Main summary measures

- The demographic and clinical characteristics of the study population were summarized using mean ± standard deviation (SD), median, and interquartile range (IQR) for continuous variables. The categorical variables were summarized using counts and proportions.
- The number of observed GBS cases and p-y of follow-up during the risk intervals were reported. Unadjusted and adjusted IRs and corresponding 95% confidence intervals (CIs) were presented per 100,000 p-y.
- For the SCRI analysis, the IRRs, corresponding 95% CIs and p-values were reported. The attributable risk (AR) and corresponding 95% CIs were also reported.

Note: To ensure compliance with CMS reporting rules to protect patient confidentiality, counts of one through 10 were reported as <11.

9.9.2. Main statistical methods

9.9.2.1. SCRI analysis of ABRYSVO-vaccinated individuals aged 65 years and older

The SCRI analysis was conducted for the overall study period, and for the 2023/2024[10] and 2024/2025 seasons separately. In the SCRI analysis, the IRR was estimated comparing the IR of GBS in a pre-specified risk interval as compared to a pre-specified control interval within the same individual (Section 9.1.1). A conditional Poisson regression model was used to estimate the IRR and 95% CI, offset by the length of observation time. The model included an indicator for the risk window as the predictor variable, an offset equal to the log of the window length and was conditional on an identification variable for the beneficiary. The model can be written as:

$$log(p) = \beta(risk\ window) + log(interval) + strata(beneficiary\ id)$$

where *p* is the risk of GBS, *interval* represents the length of the respective window in days, and *beneficiary id* is the term identifying the patient. In the primary analysis, the risk window is 1-21 days post-vaccination, and the control window is 43-84 days post-vaccination. In the secondary analysis, the risk window is 1-42 days post-vaccination, and the control window is 43- 84 days post-vaccination. Under this model, our null and alternative hypotheses were:

$$H_0: e^{\beta} = 1 \text{ (i.e., IRR = 1)}$$

$$H_a: e^{\beta} \neq 1 \text{ (i.e., IRR} \neq 1)$$

where e^{β} is the IRR of GBS in the risk window compared to the control window. Thus, the significance of the coefficient on the risk window variable at a pre-specified level indicated a significant association between RSV vaccination and GBS. The statistical significance was determined using a 2-sided hypothesis test of increase using a significance level of 0.05.

The AR was presented for both the primary (21-days risk window) and secondary (42-day risk interval) analyses, and was defined as:

- X events per one million doses
- X events per 100,000 p-y

The unadjusted and fully adjusted AR and 95% CIs were manually calculated using the following formulas.(26) The manual approach was used due to the computational intensity of bootstrapping to obtain the CI and the sensitivity of the AR to the small number of GBS cases.

$$\textbf{\textit{AR per million doses}} = \frac{1{,}000{,}000 * (IRR-1)IRR * \text{cases in the risk interval}}{\text{Number of eligible vaccinations}}$$

$$\textbf{\textit{AR per 100,000 person-years}} = \frac{100{,}000 * (IRR-1)IRR * \text{cases in the risk interval}}{\text{Total eligible person-years}}$$

[10] Data from the 2023/2024 season were derived from Interim Report 1 analyses and presented in this report.

9.9.2.2. Descriptive analysis of ABRYSVO-vaccinated individuals aged 60-64

The descriptive analysis was conducted for the overall study period, and for the 2023/2024[11] and 2024/2025 seasons separately. Given the more limited age range for commercially insured adults 60-64 years, analyses for this age group were primarily descriptive. The count and proportion of ABRYSVO-vaccinated individuals with incident GBS in the primary and secondary risk intervals were reported.

9.9.3. Missing values

Missing values were not imputed; they were reported separately in a distinct category, where applicable.

9.9.4. Sensitivity analyses

All sensitivity, subgroup, and additional analyses are described below.

9.9.4.1. Adjustments for SCRI analysis

PPV adjustment

A PPV adjustment was applied to assess bias due to outcome misclassification and uncertainty in the claims-identified cases of GBS. The PPV-adjusted analysis was performed using quantitative bias analysis (QBA) using PPVs available from prior studies that have conducted medical record review to validate GBS diagnoses following vaccine exposures. Two different PPV estimates were applied for adjustment as shown below. The fixed PPV was derived from historical validation studies in Medicare data, whereas the differential PPV was based on the most recent Medicare validation study. The differential PPV was selected for the fully adjusted model due to its recency, the more granular detail, and relevance, as it was generated from a study population similar to the one analyzed here.

i. Fixed PPV: 71.0% (95% CI: 63.0%, 79.0%) for both the risk and control intervals; (14-17) and;

ii. Differential PPV: 62.3% for the risk interval, and 81.8% for the control interval.(18)

Seasonality adjustment

Given that GBS may be associated with infections such as wild-type influenza, it may exhibit trends that correlate with specific times of the year (e.g., have higher incidence in the winter). To evaluate potential time-varying confounding, the study adjusted for the baseline risk of GBS over calendar months, which was estimated from the influenza population, combined with data from the National Respiratory and Enteric Virus Surveillance System[12] during the calendar months in the 2023/2024 season and was included as an offset term in the Poisson regression model.

[11] Data from the 2023/2024 season were derived from Interim Report 1 analyses and presented in this report.

[12] Available at: https://www.cdc.gov/nrevss/php/dashboard/index.html; last updated May 23, 2024.

PPV and seasonality adjustment

In the fully adjusted SCRI analysis, the differential PPV and seasonality adjustments were applied. The differential PPV was chosen as it is more recent, was estimated in the CMS Medicare population following ABRYSVO vaccination, and provides greater granularity.

9.9.4.2. Season-specific SCRI

Unadjusted and differential PPV-adjusted SCRI analyses were conducted for vaccinations restricted to the 2024/2025 RSV season. The differential PPV was selected due to its recency, the more granular detail, and relevance, as it was generated from a study population similar to the one analyzed here. Of note, while adjustment by PPV and seasonality was applied to the combined two-season analysis, only adjustment for differential PPV was performed in season-specific SCRI analyses, as it exerted the greatest influence on risk estimates, whereas seasonality did not. Limited sample size also necessitated this approach to maintain estimate stability.

Data from the 2023/2024 season were derived from Interim Report 1 analyses without reanalysis and were presented for descriptive comparison purposes.

9.9.4.3. Subgroup analyses

Stratified SCRI analyses were performed for the following subgroups:

i. Age: 65-74 vs. 75+

ii. CCI: 0-1 vs. 2+.[13]

iii. Co-vaccination status: yes vs. no

iv. Sex: male vs. female

Other subgroup analyses that were considered in the SAP were not performed due to sample size restrictions. Stratified unadjusted SCRI analyses were conducted for the above subgroups. If there appeared to be large differences in IRR between subgroups, then differential PPV-adjusted analyses were also conducted.

9.9.4.4. Time trend analysis

To examine any change in post-vaccination GBS risk over time in Medicare data, a risk time trend analysis was conducted for the SCRI analysis for the overall study period. An interaction term was included in the model, allowing the risk of GBS in the risk window to change over calendar time, while assuming it remains constant in the control window. Due to the low number of observations, linearity of change in GBS risk was assumed. The coefficient in the model represented change in risk per month since ABRYSVO approval date.

[13] The CCI used in this study assigned a score based on 19 conditions without incorporating age.

9.9.4.5. SCRI analysis excluding individuals with infection in the 42 days prior to the date of GBS onset

Since prior infection may be an important risk factor for GBS onset, the differential PPV-adjusted SCRI for the overall study period was conducted excluding individuals with medically-attended infections (≥1 ICD-10-CM code in any setting for a respiratory, gastrointestinal (GI) or unspecified viral infection) in the 42 days prior to the date of GBS onset.

9.9.4.6. Case-centered GBS analysis

A case-centered analysis was performed to better understand the severity and characteristics of the GBS cases identified in the analysis, the potential risk factors associated with GBS onset, and potential confounding factors with GBS assessment. This analysis included all GBS cases occurring in the ABRYSVO-vaccinated population, regardless of eligibility for the SCRI design. As a result, the number of cases analyzed here is slightly higher than the number included in the SCRI analyses. The following variables were described for hospitalized GBS cases during 42 days after vaccination:

- Demographic and clinical characteristics (age, sex, race, US region, ADI rank, nursing home residency status, CCI, frailty index, immunocompromised status);
- Mean time to onset of GBS following index date;
- GBS risk factors (e.g., trauma in 14 days before GBS onset, infection in 42 days before GBS onset, administration of non-RSV vaccines in 42 days before GBS onset, co-vaccination on the index date);
- Having diagnoses similar to GBS within 30 days before and after GBS onset;
- Neurologist encounter or diagnostic procedures within 45 days before or after GBS onset;
- Indicators of GBS severity:
    - Length of inpatient stay (days);
    - Death (including discharge to hospice care), respiratory failure, or intubation during hospitalization.(27)

9.9.5. Amendments to the statistical analysis plan

9.9.5.1. GBS Background rate used for seasonality adjustment

The protocol and SAP originally specified using the GBS background rate estimated from the 2022/2023 season for the seasonality adjustment. However, the GBS background rate from the 2023-2024 RSV season was applied, consistent with Interim Report 1, because it is more temporally aligned with the indexing period reflects the most recent circulation patterns, and is consistent with common practice in the literature.(28) In contrast, the 2022/2023 season precedes the indexing period and may not accurately capture seasonal dynamics.

9.9.5.2. Calculation of AR

The unadjusted and fully adjusted AR and 95% CIs were manually calculated due to the computational intensity of bootstrapping to obtain the CI and the sensitivity of the AR to the small number of GBS cases. This change was documented in the SAP amendment (V2.0, 23 April 2025) following significant delays in generating the AR and 95% CIs in the first

interim report using the original bootstrapping methods. The manually calculated results are expected to provide a close approximation of the bootstrapped estimates.

9.10. Quality control

The study was conducted according to the standard operating procedures of IQVIA and Pfizer. At IQVIA, all aspects of the study, from protocol development to the reporting of the results, were conducted within the framework of the IQVIA Quality Management System. A Quality Control (QC) plan for the study was developed and executed, which includes QC on study methodology, the SAP, programming, data management and analysis, study results, conclusions, and the study report. Furthermore:

- The study QC plan established ownership for the execution of the individual QC steps;
- The Principal in Charge of the study ensured that individuals responsible for the execution of specific QC steps had the knowledge, capability, and experience necessary to perform the assigned tasks;
- The result of the execution of the individual steps of the QC plan was documented and included the required corrective actions, if any. The execution of any required corrective action was also documented;
- The QC plan was subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study;
- IQVIA confidentiality agreements were signed by all employees and include data protection and strict prohibitions on reidentification attempts.

9.11. Protection of human subjects

Subject information and consent

Not applicable.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol was reviewed by an IRB, and it was determined that this study is exempt from IRB oversight.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and followed generally accepted research practices described in International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS).(29) The study was also conducted in accordance with good practices for real-world data (RWD) studies of treatment and/or comparative effectiveness: recommendations from the joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) special task force on real-world evidence in healthcare decision-making.(30)

The study also followed additional guidelines, including Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for

Pharmacoepidemiology,(31) the FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data,(32) and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association.(33)

10. RESULTS

The key study results are presented in Sections 10.1 through 10.5, and supplemental results can be found in **Appendix 8**.

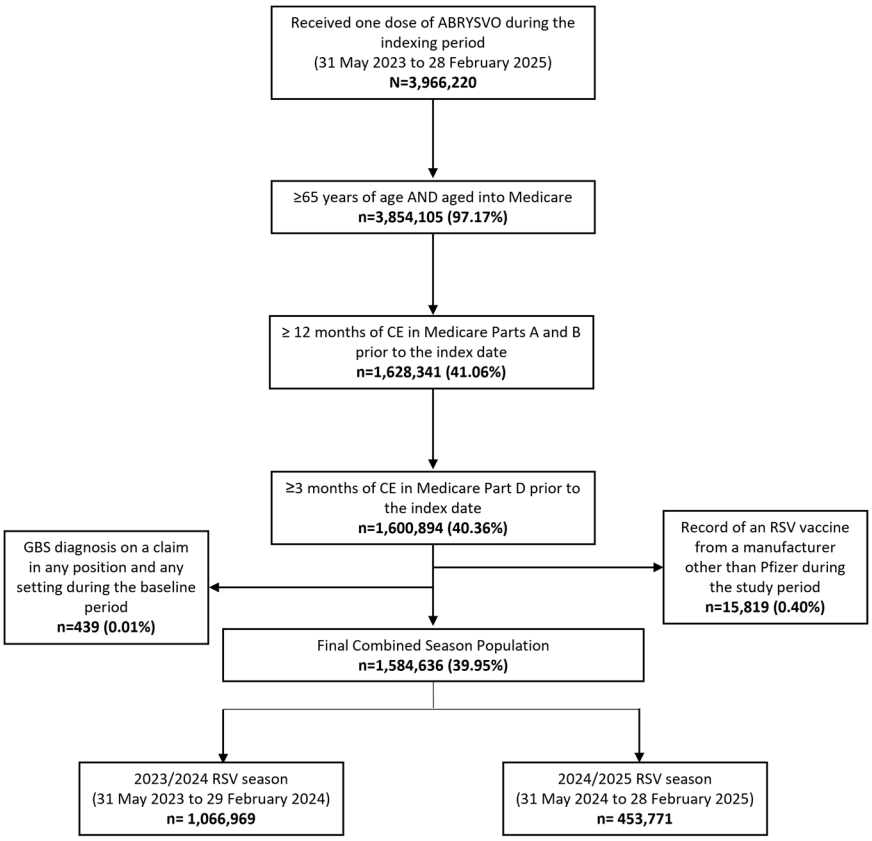
10.1. Participants

10.1.1. ABRYSVO-vaccinated individuals aged 65 years and older enrolled in CMS Medicare databases

Figure 5 shows the attrition of the ABRYSVO-vaccinated individuals enrolled in CMS Medicare databases, which includes individuals receiving ABRYSVO from 31 May 2023 to 28 February 2025. Of the 3,966,220 individuals who received one dose of ABRYSVO during the indexing period; 97.17% (n=3,854,105) were 65 years of age or older on the index date and aged into Medicare eligibility. The largest attrition was due to the requirement of at least 12 months of continuous enrollment in Medicare Parts A and B before the index date (n=1,628,341; 41.06%). Most of these patients (n=1,600,894; 40.36%) had at least 3 months of continuous enrollment in Medicare Part D. Additionally, 15,819 (0.40%) individuals were excluded for receiving a non-Pfizer RSV vaccine, and 439 individuals (0.01%) were excluded due to a claims-identified GBS diagnosis during the 12-month baseline period. The final study population aged 65 years and older included 1,584,636 individuals.

Among this population, 1,066,969 (67.3%) individuals were vaccinated in the 2023/2024 RSV season (indexing between 31 May 2023 to 29 February 2024); and 453,771 (28.6%) individuals were vaccinated in the 2024/2025 RSV season (indexing between 31 May 2024 to 28 February 2025). The detailed attrition for the individual season populations can be found in **Appendix 8 Tables 1a and 1b**.

Figure 5. Attrition of individuals aged 65 years and older enrolled in CMS Medicare databases



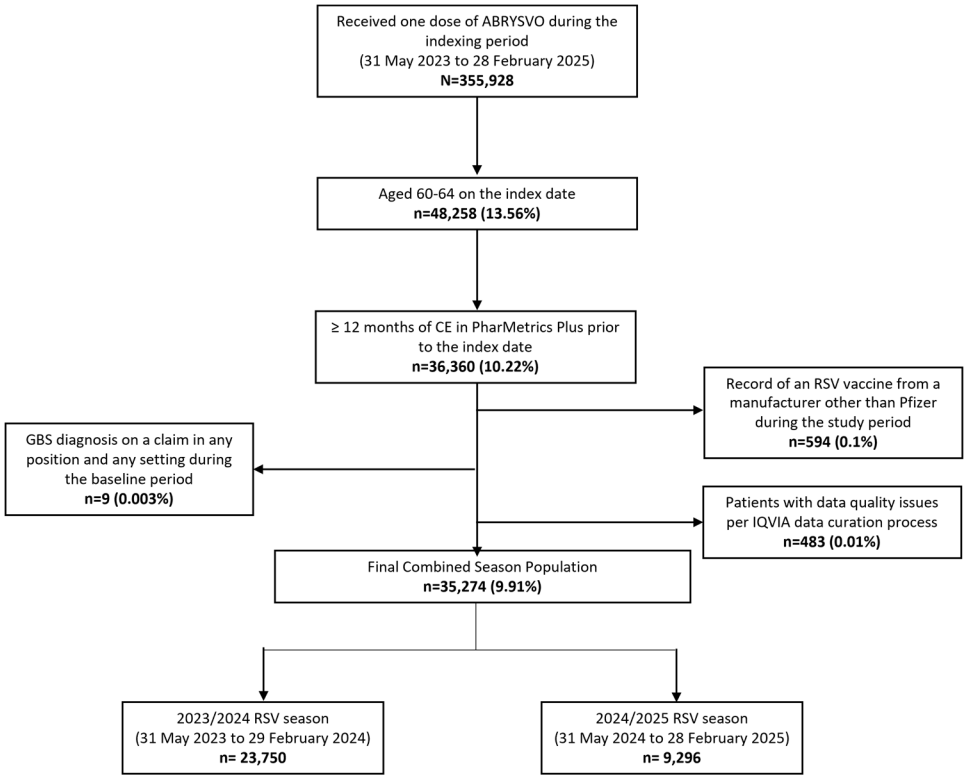
Abbreviations: CE, continuous enrollment; CMS, Centers for Medicare and Medicaid Services; GBS, Guillain-Barre syndrome; RSV, respiratory syncytial virus.
Note: The season-specific populations for 2023/2024 and 2024/2025 do not equal the combined season population because the combined season additionally includes the off-season period from March 1, 2024, through May 30, 2024. Additionally, a small number of records appearing in both seasons (n=14,671; <1%) were counted only once (in the first season).

10.1.2. ABRYSVO-vaccinated individuals aged 60-64 enrolled in PharMetrics Plus database

Figure 6 shows the attrition of the ABRYSVO-vaccinated individuals enrolled in the PharMetrics Plus database, which includes patients receiving ABRYSVO from 31 May 2023 to 28 February 2025. Of the 355,928 individuals who received one dose of ABRYSVO during the indexing period; only 13.6% (n=48,258) were 60-64 years of age on the index date. Most of these patients (n=36,360; 10.2%) had at least 12 months of continuous enrollment in the database. Among these individuals, 594 (0.2%) were excluded for receiving a non-Pfizer RSV vaccine, 483 (0.1%) were excluded for known data quality issues, and 9 (<0.1%) were excluded due to a claims-identified GBS diagnosis during the 12-month baseline period. The final study population aged 60-64 included 35,274 individuals.

Among this population, 23,750 (67.3%) individuals were vaccinated in the 2023/2024 RSV season (indexing between 31 May 2023 to 29 February 2024); 9,296 (26.4%) individuals were vaccinated in the 2024/2025 RSV season (indexing between 31 May 2024 to 28 February 2025). The detailed attrition for the individual season populations can be found in **Appendix 8 Tables 2a and 2b**.

Figure 6. Attrition of individuals aged 60-64 enrolled in the PharMetrics Plus database



Abbreviations: CE, continuous enrollment; GBS, Guillain-Barre syndrome; RSV, respiratory syncytial virus.
Note: The season-specific populations for 2023/2024 and 2024/2025 do not equal the combined season population because the combined season additionally includes the off-season period from March 1, 2024, through May 30, 2024. Additionally, a small number of records appearing in both seasons (n=159) were counted only once (in the first season).

10.2. Descriptive data

10.2.1. ABRYSVO-vaccinated individuals aged 65 years and older enrolled in CMS Medicare databases

Table 3 presents the key baseline demographic, clinical and exposure characteristics for the total ABRYSVO-vaccinated study population aged 65 years and older spanning the entire indexing period, and separately by the 2023/2024 and 2024/2025 RSV seasons. Additional baseline characteristics can be found in **Appendix 8 Tables 3a, 3b and 3c**.

Demographics

Among the 1,584,636 individuals included in the study population, the majority were aged 75 years or older (55.5%; n=879,620), with the largest age groups being 70–74 years (27.5%; n=435,204) and 75–79 years (26.0%; n=412,262). More than half of the population was female (57.8%; n=916,347), and most individuals were White (89.4%; n=1,416,681). The vaccinated population was distributed across the US regions, with the highest proportions in the South (31.7%; n=502,117) and Midwest (29.7%; n=470,354), followed by the West (20.8%; n=329,890) and Northeast (17.7%; n=281,180). About a third of the individuals (33.7%; n=533,848) resided in areas with ADI rank in the 1-30th percentile (high socioeconomic status [SES]). The middle range, ADI 41–70th percentile, included 512,629 individuals (32.4%), and the higher ADI ranks in 71-100th percentile (low SES) included 313,493 individuals (19.8%). Most individuals resided in urban areas (80.0%; n=1,267,305), while 11.5% (n=182,031) lived in rural areas. Nearly all were eligible for Medicare due to age (99.6%; n=1,578,697), and a small proportion had recent nursing home residency (1.5%; n=23,891) or had ever resided in a nursing home (3.9%; n=61,547).

The age distribution was similar across both seasons, but the 2024/2025 cohort included a slightly higher proportion of older individuals. In 2023/2024, 52.3% (n=557,973) of the population was aged 75 years or older, compared to 63.4% (n=287,581) in 2024/2025. The sex distribution was consistent, with females comprising 57.8% (n=616,218) of the population in 2023/2024 and 58.0% (n=263,015) in 2024/2025. Most individuals were White in both seasons (90.2%; n=962,203 in 2023/2024 and 88.2%; n=400,024 in 2024/2025), while the proportion of Black individuals increased from 2.7% (n=28,547) in 2023/2024 to 4.4% (n=19,911) in 2024/2025. Urban residency was similar (80.1%; n=854,953 in 2023/2024 vs. 79.6%; n=361,256 in 2024/2025) across the two seasons. The lower ADI rank (1-30th percentile; high SES) was slightly higher in 2023/2024 compared to 2024/2025 (34.4%; n=367,466 in 2023/2024 compared to 32.4%; n=147,100 in 2024/2025), and the middle ADI rank (41–70th percentile) was similar (32.1%; n=342,679 in 2023/2024 compared to 32.8%; n=148,747 in 2024/2025), showing a similar SES distribution across seasons. The recent nursing home residency was more common in 2024/2025 (2.2%; n=10,142) than in 2023/2024 (1.1%; n=11,718).

Clinical characteristics

Clinically, 9.4% (n=148,247) of individuals experienced any infection within 30 days before or after the index date as identified using one ICD-10-CM code in any setting, with 7.8% (n=123,137) having medically-attended respiratory, gastrointestinal, or unspecified viral infections. The mean frailty index was 1.29 (SD: 1.04), with 38.9% (n=617,026) classified as frail and 34.6% (n=547,488) as pre-frail. Over half of the population (54.2%; n=858,808) had a CCI of 2 or greater, and the mean CCI was 2.74 (SD: 3.14). Most individuals were not immunocompromised (91.1%; n=1,443,539), and only a small proportion had surgery (1.0%; n=16,194) or trauma (1.4%; n=22,337) in close proximity (in the 30 days prior to or after) vaccination. The majority were non-smokers (98.2%; n=1,556,435), and BMI data were missing for two-thirds of the population, but among those with data, most had BMI in the 20–29 range (14.9%; n=236,584).

Individuals vaccinated in 2024/2025 had slightly higher comorbidity and frailty. The mean CCI was 3.02 (SD: 3.28) in 2024/2025, compared to 2.61 (SD: 3.06) in 2023/2024. The

proportion with CCI ≥2 was 58.6% (n=266,022) in 2024/2025, versus 52.1% (n=555,444) in 2023/2024. The mean frailty index was higher in 2024/2025 (1.45; SD: 1.03) than in 2023/2024 (1.22; SD: 1.03), and the proportion classified as frail was 45.2% (n=204,988) in 2024/2025, compared to 36.2% (n=386,573) in 2023/2024. The remaining clinical characteristics were similar across both seasons.

Exposure characteristics

Nearly all individuals received ABRYSVO during the high respiratory season from September through February (91.2%; n=1,445,304). Almost all vaccinations were classified by administration codes as occurring in the pharmacy setting (99.1%; n=1,571,032); however, this is likely an overestimate because most vaccinations were identified via NDC, which are typically linked to Medicare Part D claims and can misclassify physician-administered vaccines as pharmacy-based. Over a third (41.0%; n=649,999) had another vaccine co-administered on the index date, most commonly seasonal influenza (25.3%; n=400,968) and COVID-19 (19.6%; n=310,806).

Slightly fewer vaccinations occurred during the high respiratory season (September–February) in 2024/2025 (90.5%; n=410,540) compared to 2023/2024 (97.0%; n=1,034,764). Co-administration of any vaccines on the index date was similar (42.0%; n=190,394 in 2024/2025 vs. 41.0%; n=436,996 in 2023/2024). Individual vaccine types were also similar across seasons, but the proportion receiving Tdap/Td was slightly higher in 2024/2025 (3.6%; n=16,232) than in 2023/2024 (1.1%; n=11,520), and shingles vaccine co-administration was also slightly higher (4.8%; n=21,721 in 2024/2025 vs. 2.7%; n=28,959 in 2023/2024).

It is noted that 14,671 individuals (0.9%) had vaccination records in both the 2023/2024 and 2024/2025 seasons after de-duplication. Whether this indicates potential off-label revaccination requires further investigation because claims errors cannot be ruled out. For the SCRI analysis, only the first recorded vaccination was considered.

Table 3. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 65 years and older

Characteristics	Combined two seasons		2023/2024 RSV season~		2024/2025 RSV season	
	N	%	N	%	N	%
Overall	1,584,636	100.00%	1,066,969	100.00%	453,771	100.00%
Demographics						
Age at ABRYSVO vaccination administration						
65-69	269,812	17.03%	194,040	18.19%	63,352	13.96%
70-74	435,204	27.46%	314,956	29.52%	102,838	22.66%
75-79	412,262	26.02%	264,698	24.81%	132,994	29.31%
80-84	260,483	16.44%	165,843	15.54%	84,677	18.66%
85-89	132,496	8.36%	81,633	7.65%	45,099	9.94%
90+	74,379	4.69%	45,799	4.29%	24,811	5.47%

Table 3. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 65 years and older

Characteristics	Combined two seasons		2023/2024 RSV season~		2024/2025 RSV season	
	N	%	N	%	N	%
Sex						
Male	668,289	42.17%	450,751	42.25%	190,756	42.04%
Female	916,347	57.83%	616,218	57.75%	263,015	57.96%
Race/Ethnicity						
Asian	26,449	1.67%	15,840	1.48%	8,729	1.92%
Black	52,073	3.29%	28,547	2.68%	19,911	4.39%
Hispanic	8,362	0.53%	4,390	0.41%	3,271	0.72%
American Indian/Alaskan Native	3,995	0.25%	2,440	0.23%	1,261	0.28%
White	1,416,681	89.40%	962,203	90.18%	400,024	88.16%
Other	24,856	1.57%	16,108	1.51%	7,549	1.66%
Missing/Unknown	52,220	3.30%	37,441	3.51%	13,026	2.87%
US region						
Northeast	281,180	17.74%	177,068	16.60%	94,223	20.76%
Midwest	470,354	29.68%	323,447	30.31%	126,903	27.97%
West	329,890	20.82%	234,506	21.98%	82,634	18.21%
South	502,117	31.69%	331,312	31.05%	149,633	32.98%
Other/Unknown	1,095	0.07%	636	0.06%	378	0.08%
Urban/Rural						
Urban	1,267,305	79.97%	854,953	80.13%	361,256	79.61%
Rural	182,031	11.49%	123,992	11.62%	50,824	11.20%
Missing/Unknown	135,300	8.54%	88,024	8.25%	41,691	9.19%
ADI rank*						
1-10 (th)	165,927	10.47%	114,643	10.74%	45,269	9.98%
11-20 (th)	170,312	10.75%	116,907	10.96%	47,391	10.44%
21-30 (th)	197,609	12.47%	135,916	12.74%	54,440	12.00%
31-40 (th)	188,248	11.88%	129,425	12.13%	51,500	11.35%
41-50 (th)	188,336	11.89%	127,083	11.91%	53,943	11.89%
51-60 (th)	165,583	10.45%	110,108	10.32%	48,516	10.69%
61-70 (th)	158,710	10.02%	105,488	9.89%	46,288	10.20%
71-80 (th)	136,435	8.61%	89,386	8.38%	40,829	9.00%
81-90 (th)	123,049	7.77%	80,324	7.53%	37,147	8.19%
91-100 (th)	54,009	3.41%	34,884	3.27%	16,397	3.61%
Missing/Unknown	36,418	2.30%	22,805	2.14%	12,051	2.66%
Original reason for Medicare eligibility						
Aged without ESRD	1,578,697	99.63%	1,063,481	99.67%	451,683	99.54%
Aged with ESRD	5,939	0.37%	3,488	0.33%	2,088	0.46%

Table 3. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 65 years and older

Characteristics	Combined two seasons		2023/2024 RSV season~		2024/2025 RSV season	
	N	%	N	%	N	%
Nursing home residency status on the index date (recent residency)±						
Resident	23,891	1.51%	11,718	1.10%	10,142	2.24%
Non-resident	1,560,745	98.49%	1,055,251	98.90%	443,629	97.76%
Nursing home residency status on the index date (any admission) ¥						
Resident (ever)	61,547	3.88%	34,778	3.26%	22,724	5.01%
Non-resident	1,523,089	96.12%	1,032,191	96.74%	431,047	94.99%
Clinical Characteristics						
Infections in close proximity (within 30 days prior to or after) the index date (Primary- one code in any setting)†						
Any‡	148,247	9.36%	100,111	9.38%	42,102	9.28%
Medically-attended infections (Respiratory, GI, unspecified viral infection) †	123,137	7.77%	83,948	7.87%	34,377	7.58%
Upper or lower respiratory tract infections	120,771	7.62%	82,486	7.73%	33,610	7.41%
GI infections	2,496	0.16%	1,504	0.14%	846	0.19%
Unspecified viral infection	553	0.03%	359	0.03%	156	0.03%
Infections in close proximity (within 30 days prior to or after) to the index date (Sensitivity- one code in IP or 2 codes in OP/PB setting)						
Any‡	37,976	2.40%	24,810	2.33%	11,439	2.52%
Medically-attended infections (Respiratory, GI, unspecified viral infection) †	29,194	1.84%	19,192	1.80%	8,711	1.92%
Upper or lower respiratory tract infections	28,170	1.78%	18,605	1.74%	8,333	1.84%
GI infections	1,059	0.07%	588	0.06%	410	0.09%
Unspecified viral infection	189	0.01%	121	0.01%	56	0.01%
Frailty index						
Mean and SD	1.29	1.04	1.22	1.03	1.45	1.03
Median and IQR	1	0.0, 2.0	1	0.0, 2.0	1	1.0, 2.0
Frail	617,026	38.94%	386,573	36.23%	204,988	45.17%
Pre-frail	547,488	34.55%	367,487	34.44%	157,719	34.76%
Non-frail	420,122	26.51%	312,909	29.33%	91,064	20.07%
CCI						
Mean and SD	2.74	3.14	2.61	3.06	3.02	3.28
Median and IQR	2	0.0, 4.0	2	0.0, 4.0	2	1.0, 4.0
0-1	725,828	45.80%	511,525	47.94%	187,749	41.38%
2+	858,808	54.20%	555,444	52.06%	266,022	58.62%
Immunocompromised status						
Yes	141,097	8.90%	93,374	8.75%	42,109	9.28%
No	1,443,539	91.10%	973,595	91.25%	411,662	90.72%

Table 3. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 65 years and older

Characteristics	Combined two seasons		2023/2024 RSV season~		2024/2025 RSV season	
	N	%	N	%	N	%
Surgery in close proximity (within 30 days prior to or after) the index date	16,194	1.02%	9,766	0.92%	5,553	1.22%
Trauma in close proximity (within 30 days prior to or after) the index date	22,337	1.41%	15,279	1.43%	6,276	1.38%
Ever smoker	28,201	1.78%	17,842	1.67%	8,989	1.98%
BMI						
≤19.9	21,897	1.38%	13,957	1.31%	6,919	1.52%
20-29	236,584	14.93%	159,607	14.96%	67,128	14.79%
30-39	215,275	13.59%	141,304	13.24%	64,575	14.23%
≥40	53,398	3.37%	34,780	3.26%	16,214	3.57%
Unknown	1,057,482	66.73%	717,321	67.23%	298,935	65.88%
Exposure Characteristics						
Vaccination record in both the 23/24 and 24/25 seasons	14,671	0.9%				
Timing of vaccination						
High respiratory season (September- February)	1,445,304	91.2%	1,034,764	97.0%	410,540	90.5%
Low respiratory season (March- August)	139,332	8.8%	32,205	3.0%	43,231	9.5%
Facility/provider type of ABRYSVO vaccination						
Hospital	<11	N/A	0	0.0%	<11	N/A
Office Visit	14,105	0.9%	6,676	0.6%	6,628	1.5%
Outpatient Institutional	5,044	0.3%	2,061	0.2%	2,531	0.6%
Pharmacy€	1,571,032	99.1%	1,060,908	99.4%	447,169	98.5%
Skilled Nursing Facility	0	0.0%	0	0.0%	0	0.0%
Home Health Agency	0	0.0%	0	0.0%	0	0.0%
Mass Immunization Center	N/A	N/A	N/A	N/A	N/A	N/A
Other	0	0.0%	0	0.0%	0	0.0%
Co-administered vaccinations (on index date)						
Any of the vaccines listed below	649,999	41.0%	436,996	41.0%	190,394	42.0%
Seasonal influenza	400,968	25.3%	284,247	26.6%	115,977	25.6%
COVID-19	310,806	19.6%	215,518	20.2%	85,408	18.8%
Tdap or Td	31,034	2.0%	11,520	1.1%	16,232	3.6%
Chickenpox (varicella)	14	0.0%	<11	N/A	<11	N/A
Shingles (herpes zoster recombinant and/or live)	58,376	3.7%	28,959	2.7%	21,721	4.8%
HPV	<11	N/A	<11	N/A	<11	N/A
Pneumococcal conjugate	56,347	3.6%	28,479	2.7%	23,267	5.1%

Table 3. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 65 years and older

Characteristics	Combined two seasons		2023/2024 RSV season~		2024/2025 RSV season	
	N	%	N	%	N	%
Pneumococcal polysaccharide	1,359	0.1%	547	0.1%	661	0.1%
Hepatitis A	3,084	0.2%	1,229	0.1%	1,296	0.3%
Hepatitis B	2,651	0.2%	964	0.1%	1,188	0.3%
MenACWY and MenB	126	0.0%	59	0.0%	46	0.0%
Haemophilus influenza type B	41	0.0%	<11	N/A	24	0.0%

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; GI, gastrointestinal; HPV, human papillomavirus; ICD-10-CM, International Classification of Diseases, 10th revision, Clinical Modification; IQR, interquartile range; MenACWY, meningococcal conjugate; MenB, meningococcal serotype B; N, number; N/A, not applicable; RSV, respiratory syncytial virus; SD, standard deviation; Td, tetanus and diphtheria; Tdap, tetanus, diphtheria, and pertussis; US, United States.
~ 2023/2024 demographic, clinical, and exposure characteristics were calculated in population using latest available data (n=1,066,969), which differs slightly from the data shown here and used in the first interim report to calculate IRR in the 2023/2024 season (n=1,066,945).
* A lower ADI rank indicates higher socioeconomic status, while a higher ADI rank indicates a lower socioeconomic status.
± Code admission or assessment in the 120 days prior to the index date.
¥ Code for admission during all available time (baseline and follow-up).
‡ Includes any of the following infections, symptoms, and types of pathogens: upper or lower respiratory tract infections, GI infections, unspecified viral infection, diarrhea, fever, campylobacter enteritis, cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Hepatitis E Virus (HEV) and Zika virus.
† Respiratory, gastrointestinal, or unspecified viral infection defined as presence of an ICD-10-CM code in any setting.
€ Most vaccinations were identified via NDC, which are typically associated with patient reimbursement through Medicare Part D claims and can misclassify physician-administered vaccines as pharmacy-based. Thus, this is likely an overestimate of administrations in the pharmacy setting.

10.2.2. ABRYSVO-vaccinated individuals aged 60-64 enrolled in PharMetrics Plus database

Table 4 presents the key baseline demographic, clinical and exposure characteristics for the total ABRYSVO-vaccinated study population aged 60-64 spanning the entire indexing period, and separately by the 2023/2024 and 2024/2025 RSV seasons. The full set of baseline characteristics results can be found in **Appendix 8 Tables 4a, 4b and 4c**.

Demographics

Among the 35,274 individuals aged 60-64, more than half of the population were female (60.0%; n=21,148), with the highest proportion of individuals in the Midwest (35.7%; n=12,587), followed by the West (25.0%; n=8,803), South (22.9%; n=8,068) and Northeast (16.5%; n=5,816). The sex distribution was consistent across the two seasons, with females comprising approximately 60% of the population in 2023/2024 (n=14,260) and 2024/2025 (n=5,659).

Clinical characteristics

Clinically, 8.5% (n=3,007) of individuals experienced any infection within 30 days before or after the index date, as identified using one ICD-10-CM code in any setting, with 7.4% (n=2,592) having medically-attended respiratory, gastrointestinal, or unspecified viral infections. The mean frailty index was 0.38 (SD: 0.49), with no individuals classified as frail and 37.9% (n=13,377) as pre-frail. Over a third of the population (37.9%; n=13,377) had a CCI of 2 or greater, and the mean CCI was 1.86 (SD: 2.64). Most individuals were not immunocompromised (99.2%; n=34,982), and only a small proportion had surgery (0.7%; n=249) or trauma (0.6%; n=216) in close proximity (in the 30 days prior to or on) vaccination. The majority were non-smokers (95.6%; n=33,716), and BMI data were missing for two-thirds of the population, but among those with data, most had BMI in the 30–39 range (15.0%; n=5,275).

Individuals vaccinated in 2024/2025 had slightly higher comorbidity and frailty. The mean CCI was 2.26 (SD: 2.85) in 2024/2025, compared to 1.69 (SD: 2.52) in 2023/2024. The proportion with CCI ≥2 was 45.6% (n=4,235) in 2024/2025, versus 34.4% (n=8,160) in 2023/2024. The mean frailty index was higher in 2024/2025 (0.46; SD: 0.50) than in 2023/2024 (0.34; SD: 0.47), and the proportion classified as pre-frail was 45.6% (n=4,235) in 2024/2025, compared to 34.4% (n=8,160) in 2023/2024. The remaining clinical characteristics were similar across both seasons.

Exposure characteristics

Most individuals received ABRYSVO during the high respiratory season from September through February (88.6%; n=31,267), and most were vaccinated at a pharmacy (74.2%; n=26,177). More than half (56.4%; n=19,904) had another vaccine co-administered on the index date, most commonly seasonal influenza (34.7%; n=12,252) and COVID-19 (29.5%; n=10,395).

Most vaccinations occurred during the high respiratory season (September–February) in both cohorts, but this was slightly less frequent in 2024/2025 (86.2%; n=8,012) compared to 2023/2024 (97.9%; n=23,255). Co-administration of vaccines on the index date was similar in the 2024/2025 season (59.8%; n=5,558) and the 2023/2024 season (56.2%; n=13,343) in 2023/2024).

It is noted that 159 individuals (0.5%) had vaccination records in both the 2023/2024 and 2024/2025 seasons after de-duplication. Whether this indicates potential off-label revaccination requires further investigation because claims errors cannot be ruled out.

Table 4. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 60-64

Characteristics	Combined two seasons		2023/2024 RSV Season		2024/2025 RSV Season	
	N	%	N	%	N	%
Overall	35,274	100.00%	23,750	100.00%	9,296	100.00%

Table 4. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 60-64

Characteristics	Combined two seasons		2023/2024 RSV Season		2024/2025 RSV Season	
	N	%	N	%	N	%
Demographics						
Age at ABRYSVO vaccination administration						
60-64	35,274	100.00%	23,750	100.00%	9,296	100.00%
Sex						
Male	14,126	40.05%	9,490	39.96%	3,637	39.12%
Female	21,148	59.95%	14,260	60.04%	5,659	60.88%
US region						
Northeast	5,816	16.49%	3,705	15.60%	1,788	19.23%
Midwest	12,587	35.68%	8,448	35.57%	3,310	35.61%
West	8,803	24.96%	6,203	26.12%	2,117	22.77%
South	8,068	22.87%	5,394	22.71%	2,081	22.39%
Other/Unknown	0	0.00%	0	0.00%	0	0.00%
HHS region						
Region 1	3,144	8.91%	2,036	8.57%	962	10.35%
Region 2	1,873	5.31%	1,147	4.83%	590	6.35%
Region 3	3,224	9.14%	2,102	8.85%	895	9.63%
Region 4	3,425	9.71%	2,155	9.07%	978	10.52%
Region 5	11,300	32.03%	7,587	31.95%	2,963	31.87%
Region 6	2,516	7.13%	1,862	7.84%	512	5.51%
Region 7	962	2.74%	626	2.64%	280	3.01%
Region 8	1,968	5.58%	1,550	6.53%	337	3.63%
Region 9	3,044	8.63%	1,818	7.65%	1,034	11.12%
Region 10	3,224	9.14%	2,407	10.13%	629	6.77%
Missing/Unknown	594	1.68%	460	1.94%	116	1.25%
ADI rank*						
1-10 (th)	1,801	5.11%	1,240	5.22%	471	5.07%
11-20 (th)	2,927	8.30%	1,965	8.27%	788	8.48%
21-30 (th)	2,693	7.63%	1,893	7.97%	639	6.87%
31-40 (th)	4,417	12.52%	2,978	12.54%	1,212	13.04%
41-50 (th)	4,601	13.04%	3,059	12.88%	1,262	13.58%
51-60 (th)	4,994	14.16%	3,322	13.99%	1,325	14.25%
61-70 (th)	6,125	17.36%	4,032	16.98%	1,678	18.05%
71-80 (th)	4,334	12.29%	2,930	12.34%	1,094	11.77%
81-90 (th)	2,222	6.30%	1,525	6.42%	544	5.85%
91-100 (th)	565	1.60%	346	1.46%	166	1.79%
Missing/Unknown	595	1.69%	460	1.94%	117	1.26%

Table 4. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 60-64

Characteristics	Combined two seasons		2023/2024 RSV Season		2024/2025 RSV Season	
	N	%	N	%	N	%
Clinical Characteristics						
Infections in close proximity (within 30 days prior to or after) the index date (Primary- one code in any setting)						
Any‡	3,007	8.52%	2,008	8.45%	816	8.78%
Medically-attended infections (Respiratory, GI, unspecified viral infection) †	2,592	7.35%	1,746	7.35%	694	7.47%
Upper or lower respiratory tract infections	2,550	7.23%	1,717	7.23%	684	7.36%
Gastrointestinal (GI) infections	43	0.12%	25	0.11%	14	0.15%
Unspecified viral infection	10	0.03%	5	0.02%	4	0.04%
Infections in close proximity to (within 30 days before or after) the index date (Sensitivity- one code in IP or 2 codes in OP/PB setting) †						
Any‡	722	2.05%	472	1.99%	205	2.21%
Medically-attended infections (Respiratory, GI, unspecified viral infection) †	568	1.61%	374	1.57%	159	1.71%
Upper or lower respiratory tract infections	554	1.57%	365	1.54%	154	1.66%
GI infections	18	0.05%	8	0.03%	9	0.10%
Unspecified viral infection	1	0.00%	1	0.00%	0	0.00%
Frailty index						
Mean and SD	0.38	0.49	0.34	0.47	0.46	0.50
Median and IQR	0	0.0,1.0	0	0.0,1.0	0	0.0,1.0
Frail	0	0.00%	0	0.00	0	0.00
Pre-frail	13,377	37.92%	8,160	34.36%	4,235	45.56%
Non-frail	21,897	62.08%	15,590	65.64%	5,061	54.44%
CCI						
Mean and SD	1.86	2.64	2	2.52	2	2.85
Median and IQR	1	0.0,2.0	2	0.0,4.0	2	1.0,4.0
0-1	21,897	62.08%	15,590	65.64%	5,061	54.44%
2+	13,377	37.92%	8,160	34.36%	4,235	45.56%
Immunocompromised status						
Yes	292	0.83%	185	0.78%	95	1.02%
No	34,982	99.17%	23,565	99.22%	9,201	98.98%
Surgery in close proximity (within 30 days before or after) the index date	249	0.71%	127	0.53%	96	1.03%
Trauma in close proximity (within 30 days before or after) the index date	216	0.61%	143	0.60%	62	0.67%
Ever smoker	1,558	4.42%	929	3.91%	498	5.36%

Table 4. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 60-64

Characteristics	Combined two seasons		2023/2024 RSV Season		2024/2025 RSV Season	
	N	%	N	%	N	%
BMI						
≤19.9	357	1.01%	239	1.01%	97	1.04%
20-29	4,245	12.03%	2,834	11.93%	1,108	11.92%
30-39	5,275	14.95%	3,447	14.51%	1,464	15.75%
≥40	2,266	6.42%	1,383	5.82%	731	7.86%
Unknown	23,131	65.58%	15,847	66.72%	5,896	63.43%
Exposure Characteristics						
Vaccination record in both the 23/24 and 24/25 seasons	159	0.45%				
Timing of vaccination						
High respiratory season (September- February)	31,267	88.64%	23,255	97.92%	8,012	86.19%
Low respiratory season (March-August)	4,007	11.36%	495	2.08%	1,284	13.81%
Facility/Provider type of ABRYSVO vaccination						
Hospital	0	0.00%	0	0.00%	0	0.00%
Office Visit	0	0.00%	0	0.00%	0	0.00%
Outpatient Institutional	0	0.00%	0	0.00%	0	0.00%
Pharmacy	26,177	74.21%	18,181	76.55%	6,580	70.78%
Skilled Nursing Facility	0	0.00%	0	0.00%	0	0.00%
Home Health Agency	0	0.00%	0	0.00%	0	0.00%
Mass Immunization Center	0	0.00%	0	0.00%	0	0.00%
Other	9,097	25.79%	5,569	23.45%	2,716	29.22%
Co-administered vaccinations (on index date)						
Any of the vaccines listed below	19,904	56.43%	13,343	56.18%	5,558	59.79%
Seasonal influenza	12,252	34.73%	8,798	37.04%	3,391	36.48%
COVID-19	10,395	29.47%	7,495	31.56%	2,662	28.64%
Tdap or Td	923	2.62%	346	1.46%	454	4.88%
Chickenpox (Varicella)	0	0.00%	0	0.00%	0	0.00%
Shingles (Herpes Zoster recombinant and/or live)	2,501	7.09%	1,097	4.62%	893	9.61%
HPV	3	0.01%	3	0.01%	0	0.00%
Pneumococcal conjugate	2,019	5.72%	937	3.95%	885	9.52%
Pneumococcal polysaccharide	46	0.13%	21	0.09%	17	0.18%
Hepatitis A	253	0.72%	109	0.46%	78	0.84%
Hepatitis B	378	1.07%	134	0.56%	128	1.38%
MenACWY and MenB	3	0.01%	1	0.00%	1	0.01%
Haemophilus influenza type B	0	0.00%	0	0.00%	0	0.00%

Table 4. Baseline demographic, clinical and exposure characteristics of ABRYSVO-vaccinated individuals aged 60-64

Characteristics	Combined two seasons		2023/2024 RSV Season		2024/2025 RSV Season	
	N	%	N	%	N	%

Abbreviations: ADI, area deprivation index; BMI, body mass index; CCI, Charlson comorbidity index; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; GI, gastrointestinal; HPV, human papillomavirus; ICD-10-CM, International Classification of Diseases, 10th revision, Clinical Modification; IQR, interquartile range; MenACWY, meningococcal conjugate; MenB, meningococcal serotype B; N, number; RSV, respiratory syncytial virus; SD, standard deviation; Td, tetanus and diphtheria; Tdap, tetanus, diphtheria, and pertussis; US, United States.
*A lower ADI rank indicates higher socioeconomic status, while a higher ADI rank indicates a lower socioeconomic status.
ǂ Includes any of the following infections, symptoms, and types of pathogens: upper or lower respiratory tract infections, GI infections, unspecified viral infection, diarrhea, fever, campylobacter enteritis, cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Hepatitis E Virus (HEV) and Zika virus.
† Respiratory, gastrointestinal, or unspecified viral infection defined as presence of an ICD-10-CM code in any setting.

10.3. Outcome data

10.3.1. GBS outcomes among ABRYSVO-vaccinated individuals aged 65 and older (SCRI population) enrolled in CMS Medicare databases

Table 5 summarizes GBS outcomes identified following vaccination in the ABRYSVO-vaccinated individuals aged 65 years and older in the risk and control intervals, overall and by RSV season.

Among the 1,584,636 ABRYSVO-vaccinated individuals aged 65 years and older, 1,584,206 (99.97%) had at least one day in the post-vaccination control interval and were included in the SCRI analytic population for the overall study period.

Among the 1,584,206 vaccinated individuals included in the overall analysis, 26 GBS cases were observed during the 21-day post-index primary risk interval, resulting in an unadjusted IR of 28.53 cases per 100,000 p-y (95% CI: 19.03–41.20). When stratified by RSV season, 16 GBS cases were observed in the 2023/2024 season[14] (n=1,066,800), with an unadjusted IR of 26.07 cases per 100,000 p-y (95% CI: 15.43– 41.43). In the 2024/2025 season (n=453,488), fewer than 11 cases were observed in the primary risk interval, with an unadjusted IR of 26.83 cases per 100,000 p-y (95% CI: 11.73– 53.07).

During the 42-day post-index secondary risk interval, 38 GBS cases were observed in the total population, corresponding to an unadjusted IR of 20.85 cases per 100,000 p-y (95% CI: 14.96–28.32). In the 2023/2024 season, 26 cases were observed (unadjusted IR: 21.18 per 100,000 p-y; 95% CI: 14.13–31.59), while in the 2024/2025 season, fewer than 11 cases were observed, with an unadjusted IR of 17.25 per 100,000 p-y (95% CI: 8.41- 31.65).

In the control interval (43–84 days post-index), 13 GBS cases were observed in the total population, yielding an unadjusted IR of 7.14 cases per 100,000 p-y (95% CI: 3.97–11.90). For the 2023/2024 season, fewer than 11 cases were observed (IR: 8.15 per 100,000 p-y;

[14] 2023/2024 RSV season results presented are from Interim Report 1.

95% CI: 4.14–14.53), and for the 2024/2025 season, fewer than 11 cases were observed (IR: 5.76 per 100,000 p-y; 95% CI:1.47–15.67).

Table 5. Incidence rate of GBS following ABRYSVO vaccination among individuals aged 65 years and older in SCRI analytic population, overall and by RSV season

	N	GBS Outcomes			
		Observed Number of Cases in Risk Interval	P-y	Unadjusted IR (per 100,000 p-y)	95% CI
The Primary Risk Interval (1–21 Days Post-index)					
Combined two seasons †	**1,584,206**	26	91,146.1	28.53	19.03- 41.20
2023/2024 RSV season	**1,066,699**	16	61,377.5	26.07	15.43- 41.43
2024/2025 RSV season	**453,488**	<11	--	26.83	11.73- 53.07
The Secondary Risk Interval (1–42 Days Post-index)					
Combined two seasons †	**1,584,206**	38	182,292.2	20.85	14.96- 28.32
2023/2024 RSV season	**1,066,699**	26	122,755.1	21.18	14.13- 30.59
2024/2025 RSV season	**453,488**	<11	--	17.25	8.41- 31.65
Control Interval (43-84 Days Post-index)					
Combined two seasons †	**1,584,206**	13	182124.2	7.14	3.97- 11.90
2023/2024 RSV season	**1,066,699**	<11	122,680.6	8.15	4.14- 14.53
2024/2025 RSV season	**453,488**	<11	--	5.76	1.47- 15.67

Abbreviations: CI, confidence interval; GBS, Guillain-Barre syndrome; IR, incidence rate; p-y, person-years; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.
† Indexing period is 31 May 2023 to 28 February 2025.

10.3.2. GBS outcomes among ABRYSVO-vaccinated individuals aged 60–64 years enrolled in PharMetrics Plus database

There were no GBS cases observed in 35,274 ABRYSVO-vaccinated individuals aged 60-64 years old during the 2,010.03 p-y of follow-up in the primary risk interval and 3,981.75 p-y of follow-up in the secondary risk interval. Additionally, no cases were observed in the control interval.

10.4. Main results

The results of the SCRI analysis among ABRYSVO-vaccinated individuals aged 65 years and older for the overall study period are shown in Figure 7 (primary risk interval) and Figure 8 (secondary risk interval), and **Appendix 8 Table 5**.

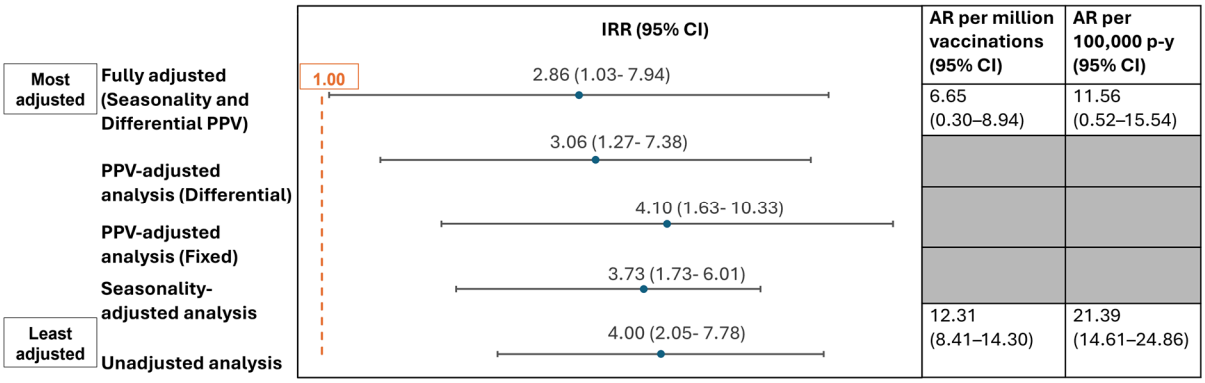
Primary Risk Interval (1–21 Days Post-index)

In the unadjusted SCRI model, the IRR for the primary risk interval compared to the control interval was 4.00 (95% CI: 2.05–7.78). After applying seasonality adjustment, the IRR was 3.73 (95% CI: 1.73–6.01), and with the fixed PPV adjustment, it was 4.10 (95% CI: 1.63–10.33). Applying differential PPVs attenuated the IRR to 3.06 (95% CI: 1.27–7.38). In the

fully adjusted model (adjusted for seasonality and differential PPVs), the IRR was 2.86 (95% CI: 1.03–7.94).

For unadjusted ARs in the primary risk interval, there were 12.31 (95% CI: 8.41–14.30) excess GBS cases per million vaccinations and 21.39 (95% CI: 14.61–24.86) excess cases per 100,000 p-y. After adjusting for seasonality and a differential PPV of 62.3% for cases in the risk interval, there were 6.65 (95% CI: 0.30–8.94) excess GBS cases per million vaccinations and 11.56 (95% CI: 0.52–15.54) excess cases per 100,000 p-y.

Figure 7. SCRI analysis of GBS risk in the overall study period for the primary risk interval: IRR and AR with corresponding 95% CI



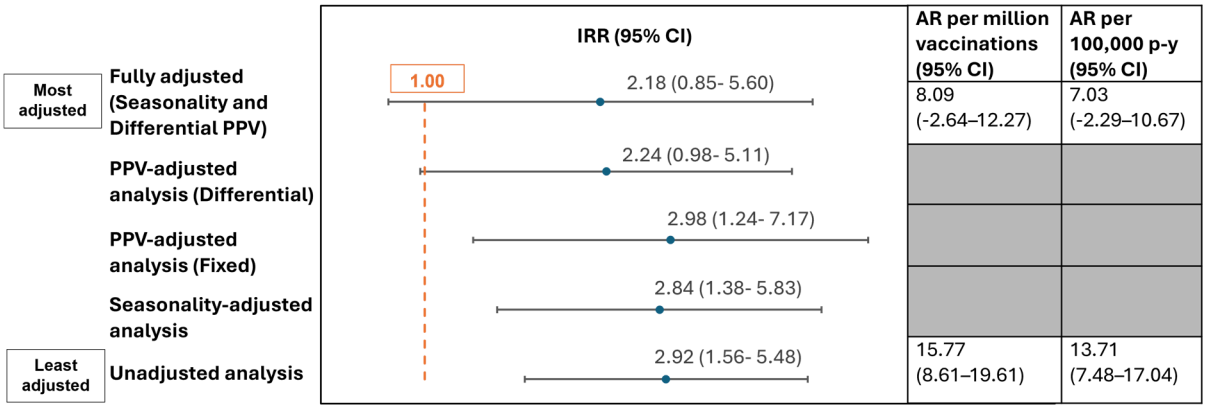
Abbreviations: AR, attributable risk; CI, confidence interval; GBS, Guillain-Barre Syndrome; IRR, incidence rate ratio; PPV, positive predictive value; p-y, person-years; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.
Note: Fixed PPV analysis used 71.0% (95% CI: 63.0%, 79.0%) for both the risk and control intervals;(14-17) and differential PPV analysis used 62.3% for the risk interval, and 81.8% for the control interval.(18)

Secondary Risk Interval (1–42 Days Post-index)

For the secondary risk interval, the unadjusted IRR was 2.92 (95% CI: 1.56–5.48). Seasonality adjustment yielded an IRR of 2.84 (95% CI: 1.38–5.83), and fixed PPV adjustment resulted in an IRR of 2.98 (95% CI: 1.24–7.17). When the differential PPV adjustment was applied, the IRR moved closer to the null at 2.24 (95% CI: 0.98–5.11). In the fully adjusted model (adjusted for seasonality and differential PPVs), the IRR was 2.18 (95% CI: 0.85–5.60).

For unadjusted ARs in the secondary risk interval, there were 15.77 (95% CI: 8.61–19.91) excess GBS cases per million vaccinations and 13.71 (95% CI: 7.48–17.04) excess cases per 100,000 p-y. After adjusting for seasonality and a PPV of 62.3% for cases in the risk interval, there were 8.09 (95% CI: -2.65–12.27) excess GBS cases per million vaccinations and 7.03 (95% CI: -2.29–10.67) excess cases per 100,000 p-y.

Figure 8. SCRI analysis of GBS risk in the overall study period for the secondary risk interval: IRR and AR with corresponding 95% CI



Abbreviations: AR, attributable risk; CI, confidence interval; GBS, Guillain-Barre Syndrome; IRR, incidence rate ratio; PPV, positive predictive value; p-y, person-years; SCRI, self-controlled risk interval.

Note: Fixed PPV analysis used 71.0% (95% CI: 63.0%, 79.0%) for both the risk and control intervals;(14-17) and; differential PPV analysis used 62.3% for the risk interval, and 81.8% for the control interval.(18)

10.4.1. Stratification by RSV season

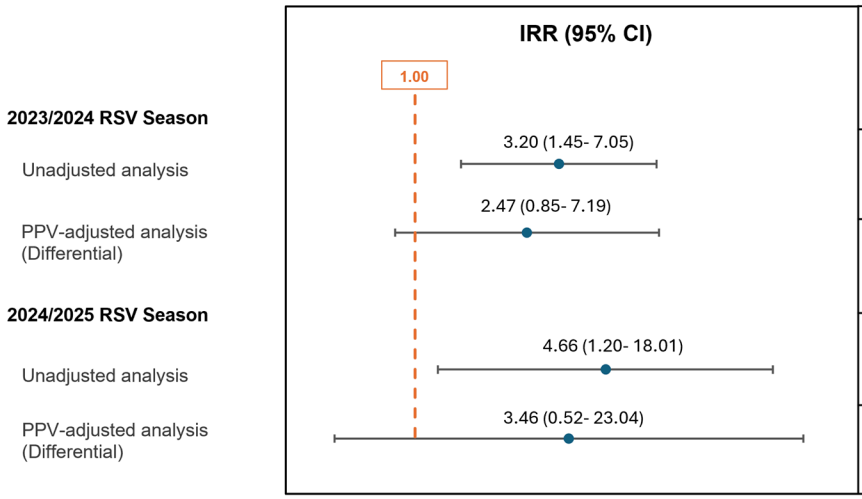
The results of the SCRI analysis among ABRYSVO-vaccinated individuals aged 65 and older stratified by RSV season are shown in Figure 9 (primary risk interval), Figure 10 (secondary risk interval), and **Appendix 8 Table 6**.

Primary Risk Interval (1–21 Days Post-index)

For the 2023/2024 RSV season, the unadjusted analysis yielded an IRR of 3.20 (95% CI: 1.45–7.05), which was attenuated to 2.47 for the differential PPV-adjusted analysis (95% CI: 0.85–7.19). The AR was 10.31 per million vaccinations (95% CI: 4.66–12.87) and 17.92 per 100,000 p-y (95% CI: 8.09–22.37) for the unadjusted analysis, and 5.56 per million vaccinations (95% CI: –1.65–8.05) and 9.67 per 100,000 p-y (95% CI: –2.87–13.98) for the differential PPV-adjusted analysis.

For the 2024/2025 RSV season, the unadjusted IRR was 4.66 (95% CI: 1.20–18.01), and the PPV-adjusted IRR was 3.46 (95% CI: 0.52–23.04). AR estimates were not calculatable because there were fewer than 11 cases in the risk interval.

Figure 9. SCRI analysis of GBS risk by RSV season for the primary risk interval: IRR and AR with corresponding 95% CI



	AR per million vaccinations (95% CI)	AR per 100,000 p-y (95% CI)
2023/2024 RSV Season		
Unadjusted analysis	5.56 (-1.65–8.05)	9.67 (-2.87– 13.98)
PPV-adjusted analysis (Differential)	10.31 (4.66–12.87)	17.92 (8.09–22.37)
2024/2025 RSV Season	Not Reportable*	Not Reportable*
Unadjusted analysis	Not Reportable*	Not Reportable*
PPV-adjusted analysis (Differential)		

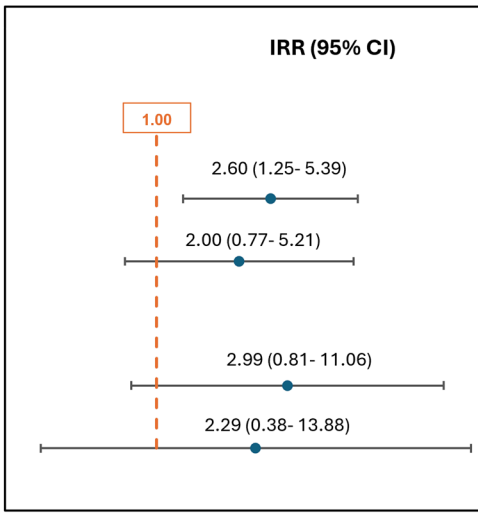
Abbreviations: AR, attributable risk; CI, confidence interval; GBS, Guillain-Barre Syndrome; IRR, incidence rate ratio; PPV, positive predictive value; p-y, person-years; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.
*Not reportable due to case count <11 in the risk interval.
Note: PPV-adjusted analysis used 62.3% for the risk interval, and 81.8% for the control interval.(18)

Secondary Risk Interval (1–42 Days Post-index)

For the 2023/2024 RSV season, the unadjusted analysis showed an IRR of 2.60 (95% CI: 1.25–5.39), while the PPV-adjusted analysis was 2.00 (95% CI: 0.77–5.21). The AR was 15.00 per million vaccinations (95% CI: 4.89–19.85) and 13.03 per 100,000 p-y (95% CI: 4.24–17.25) for the unadjusted analysis, and 7.59 per million vaccinations (95% CI: –4.54–12.27) and 6.60 per 100,000 p-y (95% CI: –3.94–10.66) for the PPV-adjusted analysis.

For the 2024/2025 RSV season, the unadjusted IRR was 2.99 (95% CI: 0.81–11.06), and the PPV-adjusted IRR was 2.29 (95% CI: 0.38–13.88). AR estimates were not calculable because there were fewer than 11 cases in the risk interval.

Figure 10. SCRI analysis of GBS risk by RSV season for the secondary risk interval: IRR and AR with corresponding 95% CI



	AR per million vaccinations (95% CI)	AR per 100,000 p-y (95% CI)
2023/2024 RSV Season		
Unadjusted analysis	15.00 (4.88- 19.85)	13.03 (4.24- 17.25)
PPV-adjusted analysis (Differential)	7.59 (-4.54–12.77)	6.60 (-3.94–10.66)
2024/2025 RSV Season		
Unadjusted analysis	Not Reportable*	Not Reportable*
PPV-adjusted analysis (Differential)	Not Reportable*	Not Reportable*

Abbreviations: AR, attributable risk; CI, confidence interval; GBS, Guillain-Barre Syndrome; IRR, incidence rate ratio; PPV, positive predictive value; p-y, person-years; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.
*Not reportable due to case count <11 in the risk interval.
Note: PPV-adjusted analysis used 62.3% for the risk interval, and 81.8% for the control interval.(18)

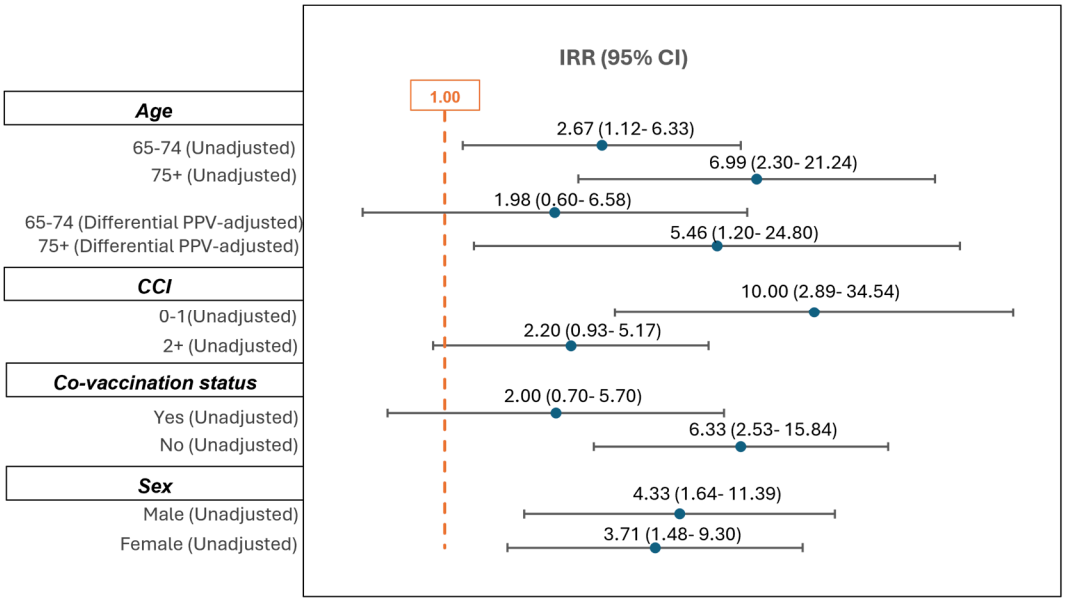
10.5. Other analyses

10.5.1. Subgroup SCRI analyses

The results of the SCRI analyses among ABRYSVO-vaccinated individuals aged 65 years and older stratified by age at index date, CCI, and co-vaccination status are shown in Figure 11 (primary risk interval), Figure 12 (secondary risk interval), and **Appendix 8 Table 7**. Given the small number of cases overall, unadjusted and differential PPV-adjusted models were prioritized to maintain model stability. If the bootstrapping model did not converge for IRR estimation in any subgroup, this is noted below.

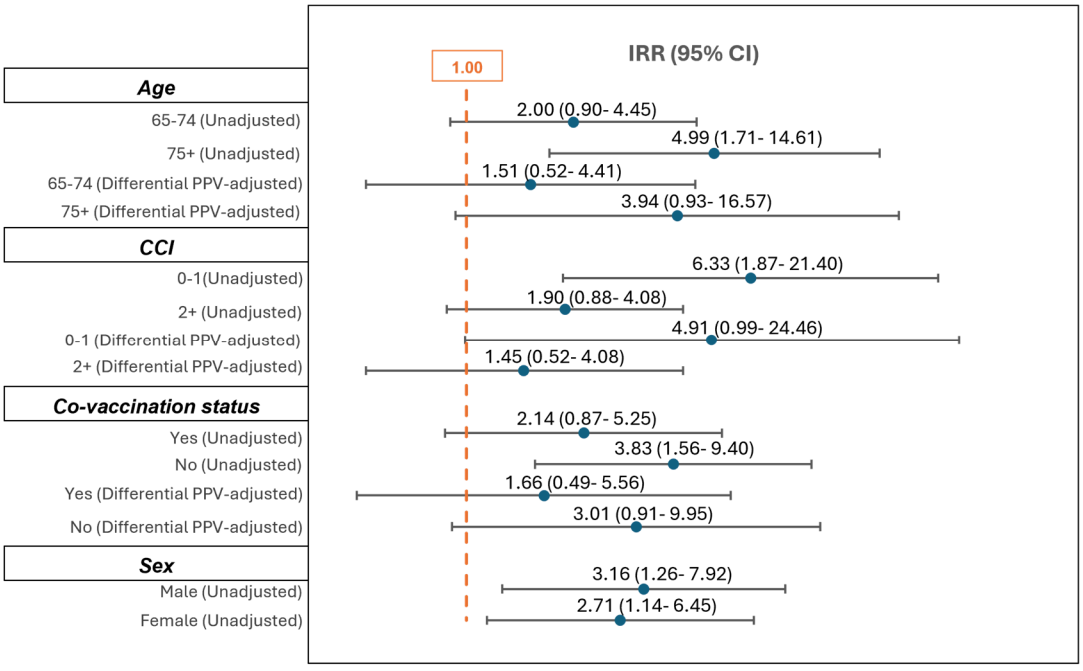
Results from subgroup analyses should be interpreted as exploratory and hypothesis-generating due to the small number of cases, which introduces greater uncertainty in the estimates. Formal statistical testing for interaction was not performed, also due to limited sample size.

Figure 11. Subgroup SCRI analyses of GBS risk by covariates of interest: primary risk interval



Abbreviations: CCI, Charlson comorbidity index; GBS, Guillain-Barre syndrome; IRR, incidence rate ratio; PPV, positive predictive value; SCRI, self-controlled risk interval.
Note: PPV-adjusted analysis used 62.3% for the risk interval, and 81.8% for the control interval.(18)

Figure 12. Subgroup SCRI analyses of GBS risk by covariates of interest: secondary risk interval



Abbreviations: CCI, Charlson comorbidity index; GBS, Guillain-Barre Syndrome; IRR, incidence rate ratio; PPV, positive predictive value; SCRI, self-controlled risk interval.
Note: PPV-adjusted analysis used 62.3% for the risk interval, and 81.8% for the control interval.(18)

Stratification by age

For the age subgroup analyses, individuals aged 75 years and older had a higher IRR of GBS following ABRYSVO vaccination compared to 65–74-year-olds in both unadjusted and PPV-adjusted analyses in the primary and secondary risk intervals, though 95% CIs were relatively wide and overlapping.

For the age-stratified unadjusted analysis in the primary risk interval, the IRR was 2.67 (95% CI: 1.12–6.33) for individuals aged 65–74 years and 6.99 (95% CI: 2.30–21.24) for those aged 75 years and older. After differential PPV adjustment, the IRR was 1.98 (95% CI: 0.60–6.58) for ages 65–74 years and 5.46[15] (95% CI: 1.20–24.80) for ages 75 years and older. The corresponding AR estimates per million vaccinations were 10.65 (95% CI: 1.82–14.33) and 13.64 (95% CI: 9.00–15.17) for the unadjusted analysis, and 5.25 (95% CI: -7.07–8.99) and 8.10[15] (95% CI: 1.65–9.52) for the adjusted analysis, for ages 65-74 years and 75 years and older respectively. When expressed per 100,000 p-y, the AR was 18.51 (95% CI: 3.17–24.91) and 23.72 (95% CI: 15.64–26.37) for the unadjusted analysis, and 9.12 (95% CI: -12.29–15.63) and 14.08[15] (95% CI: 2.87–16.55) for the adjusted analysis.

In the secondary risk interval, for the unadjusted analysis, the IRR was 2.00 (95% CI: 0.90–4.45) for ages 65–74 years and 4.99 (95% CI: 1.71–14.61) for ages 75 years and older. After adjustment, the IRR was 1.51 (95% CI: 0.52–4.41) for ages 65–74 years and 3.94[16] (95% CI: 0.93–16.57) for ages 75 years and older. The AR per million vaccinations was 12.77 (95% CI: -2.84–19.80) and 18.19 (95% CI: 9.44–21.29) for the unadjusted analysis, and 5.37 (95% CI: -14.68–12.04) and 10.57[16] (95% CI: -1.40–13.32) for the adjusted analysis, for aged 65-74 years and 75 years and older respectively. When expressed per 100,000 p-y, the AR was 11.10 (95% CI: -2.47–17.20) and 15.81 (95% CI: 8.21–18.41) for the unadjusted analysis, and 4.67 (95% CI: -12.76–10.46) and 9.19[16] (95% CI: -1.22–11.57) for the adjusted analysis.

Stratification by CCI

For the CCI subgroup analyses, individuals with a score of 0-1 had a higher IRR of GBS following ABRYSVO vaccination compared to those with a score of 2+ in both unadjusted and PPV-adjusted analyses in the primary and secondary risk intervals, though 95% CIs were wide and overlapping.

In the primary risk interval, in the unadjusted analysis, individuals with a score of 0–1 had an IRR of 10.00 (95% CI: 2.89–34.54; p=0.0003), whereas those with a score of 2 or higher had an IRR of 2.20 (95% CI: 0.93–5.17; p=0.0717). The AR per million doses was 18.60 (95% CI: 13.52–20.07) for scores 0–1 and 6.99 (95% CI: -0.96- 10.34) for scores 2 or higher. The AR per 100,000 p-y was 32.33 (95% CI: 23.49–34.88) for scores 0–1 and 12.15 (95% CI: -1.68- 17.96) for scores 2 or higher.

[15] 999 out of 1,000 models converged for these PPV-adjusted results.

[16] 998 out of 1,000 models converged for these PPV-adjusted results.

In the secondary risk interval, individuals with a score of 0–1 had an IRR of 6.33 (95% CI: 1.87–21.40; p=0.003), while those with a score of 2 or higher had an IRR of 1.90 (95% CI: 0.88–4.08; p=0.1012). The AR per million doses was 22.04 (95% CI: 12.18–24.95) for scores 0–1 and 10.48 (95% CI: -3.02 to 16.71) for scores 2 or higher. The AR per 100,000 p-y was 19.16 (95% CI: 10.58–21.69) for scores 0–1 and 9.11 (95% CI: -2.62 to 14.52) for scores 2 or higher.

For the PPV-adjusted analysis in the secondary risk interval, individuals with a score of 0–1 had an IRR of 4.91 (95% CI: 0.99–24.46; p=0.0521), whereas those with a score of 2 or higher had an IRR of 1.45.[17] (95% CI: 0.52–4.08; p=0.4789). The corresponding AR per million doses was 12.99 (95% CI: -0.16–15.64) for scores 0–1 and 4.28[17] (95% CI: -12.73–10.41) for scores 2 or higher. The AR per 100,000 p-y was 11.29 (95% CI: -0.14–13.59) for scores 0–1 and 3.72[17] (95% CI: -11.06–9.05) for scores 2 or higher.

Stratification by co-vaccination status

For the co-vaccination subgroup analyses, individuals without concomitant vaccination on index date had a higher IRR of GBS following ABRYSVO vaccination compared to those with concomitant vaccination in both the unadjusted and PPV-adjusted analyses in the primary and secondary risk intervals, though 95% CIs were wide and overlapping.

In the primary risk interval, the IRR was 2.00 (95% CI: 0.70–5.70; p=0.1951) among individuals receiving concomitant vaccines compared to 6.33 (95% CI: 2.53–15.84; p<0.0001) among those without. The AR per million doses was 17.12 (95% CI: 12.30–19.05) for those without concomitant vaccines, while risk was not estimable for those with concomitant vaccines. The AR per 100,000 p-y was 29.76 (95% CI: 21.38–33.11) for those without concomitant vaccines.

In the secondary risk interval, the IRR was 2.14 (95% CI: 0.87–5.25; p=0.0962) among those with concomitant vaccines compared to 3.83 (95% CI: 1.56–9.40; p=0.0034) among those without. The AR per million doses was 12.30 (95% CI: -3.45–18.68) for those with concomitant vaccines and 18.19 (95% CI: 8.84–22.00) for those without. The AR per 100,000 p-y was 10.68 (95% CI: -3.00–16.24) for those with concomitant vaccines and 15.81 (95% CI: 7.68–19.12) for those without.

For the PPV-adjusted analysis in the secondary risk interval, individuals receiving co-vaccination had an IRR of 1.66 (95% CI: 0.49–5.56; p=0.4139), whereas those without vaccination had an IRR of 3.01 (95% CI: 0.91–9.95; p=0.0713). The corresponding AR per million doses was 12.99 (95% CI: –0.16–15.64) for scores 0–1 and 4.28 (95% CI: -12.73-10.41) for scores 2 or higher. The AR per 100,000 p-y was 11.29 (95% CI: -0.14–13.59) for scores 0–1 and 3.72 (95% CI: –11.06–9.05) for scores 2 or higher.

Stratification by sex

[17] 996 out of 1,000 models converged for these PPV-adjusted results.

For the sex subgroup analyses, the IRRs of GBS following ABRYSVO vaccination were comparable among males and females in the unadjusted analyses, though 95% CIs were wide and overlapping.

In the primary risk interval, the IRR was 4.33 (95% CI: 1.64- 11.39; p=0.0030) among males compared to 3.71 (95% CI: 1.48- 9.30; p= 0.0052) among females. The AR per million doses was 14.96 (95% CI: 7.59- 17.75) for males, and 10.37 (95% CI: 4.60- 12.66) for females. The AR per 100,000 p-y was 26.01 (95% CI: 13.20- 30.85) for males, and 18.02 (95% CI: 8.00- 22.01) for females.

In the secondary risk interval, the IRR was 3.16 (95% CI: 1.26- 7.92; p=0.0139) among males compared to 2.71 (95% CI: 1.14- 6.45; p=0.0241) among females. The AR per million doses was 19.44 (95% CI: 5.87- 24.85) for males and 13.09 (95% CI: 2.55- 17.52) for females. The AR per 100,000 p-y was 16.89 (95% CI: 5.10- 21.59) for males and 11.37 (95% CI: 2.21- 15.23) for females.

10.5.2. SCRI sensitivity analyses

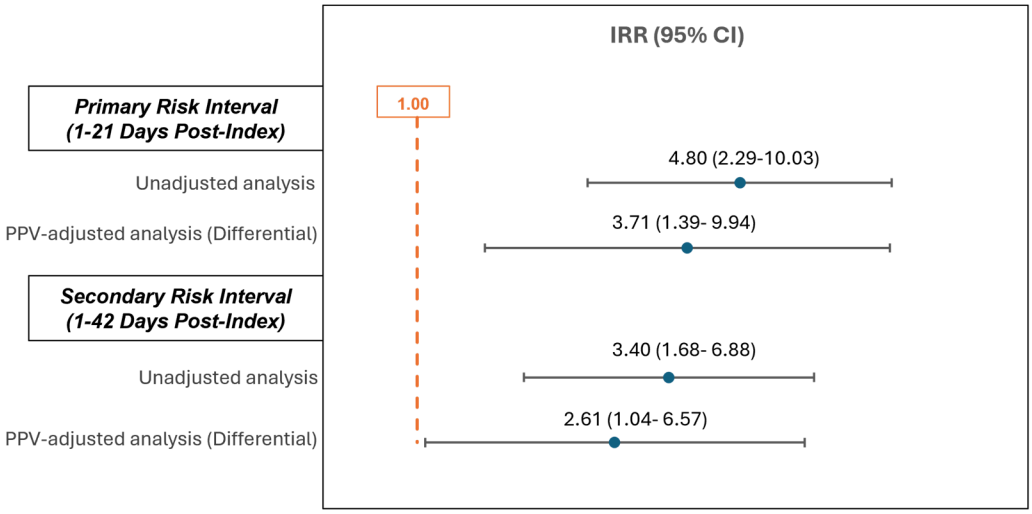
10.5.2.1. Exclusion of cases with medically-attended infections in the 42 days prior to date of GBS onset

The results for the sensitivity analysis removing cases with medically-attended infections in the 42 days prior to date of GBS onset are found in Figure 13 and **Appendix 8 Table 8**. Across risk intervals and unadjusted and PPV-adjusted analyses, there was a higher IRR of GBS following ABRYSVO vaccination when cases with medically-attended infections in the 42 days prior to GBS onset were removed from the risk and control intervals compared to the main analyses.

For the unadjusted analysis, in the primary risk interval, there were 24 cases observed over 91,145.7 p-y, corresponding to a rate of 26.33 per 100,000 p-y. In comparison, the control interval had fewer than 11 cases, with a rate of 5.49 per 100,000 p-y. The IRR was 4.80 (95% CI: 2.29–10.03). In the secondary risk interval, there were 34 cases over 182,291.39 p-y, corresponding to a rate of 18.65 per 100,000 p-y. The control interval again had fewer than 11 cases, with a rate of 5.49 per 100,000 p-y. The IRR was 3.40 (95% CI: 1.68–6.88).

For the PPV-adjusted analysis, in the primary risk interval, the IRR was 3.71 (95% CI: 1.39–9.94). In the secondary risk interval, the IRR was 2.61 (95% CI: 1.04-6.57).

Figure 13. SCRI analyses of GBS risk excluding cases with medically-attended infections in the 42 days prior to GBS onset



Abbreviations: GBS, Guillain-Barre Syndrome; IRR, incidence rate ratio; PPV, positive predictive value; SCRI, self-controlled risk interval.
Note: PPV-adjusted analysis used 62.3% for the risk interval, and 81.8% for the control interval.(18)

10.5.2.2. Exclusion of individuals with incomplete follow-up

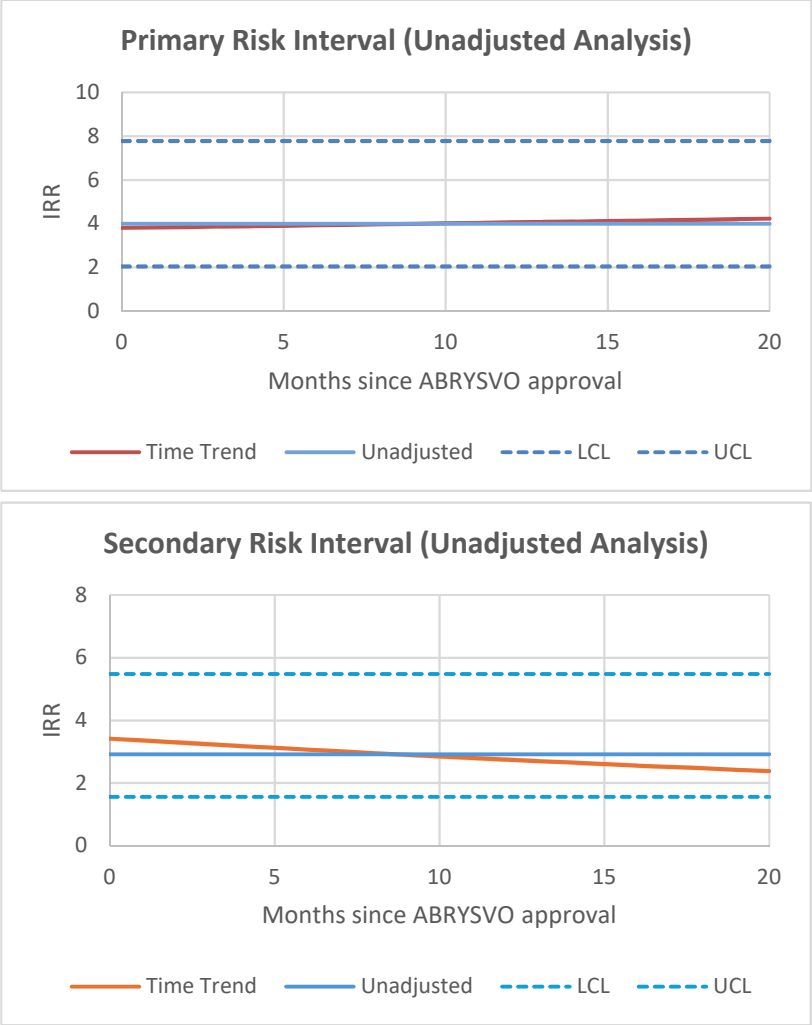
Per the SAP, a sensitivity analysis excluding individuals with incomplete follow-up was not conducted as nearly all individuals in the SCRI population (n=1,580,933; 99.8%) had complete follow-up during the 84-day post-vaccination period. Thus, excluding 0.2% of the population would have negligible impact on the IRR estimate.

10.5.2.3. Time trend analysis for the overall study period

Figure 14 shows the results from the time trend analyses of the primary and secondary risk intervals. For the 1–21-day primary risk interval, the monthly IRR change after ABRYSVO approval was 0.0053 (95% CI: -0.0618–0.0723; p-value= 0.878). For the 1–42-day secondary risk interval, the monthly IRR change was -0.0181 (95% CI: -0.0769–0.0407; p-

value= 0.546). Overall, the trend analysis did not suggest any appreciable changes in the risk of GBS overtime.

Figure 14. Time trend analyses for the unadjusted SCRI analysis of GBS risk in the overall study period: primary and secondary risk intervals



Abbreviations: GBS, Guillain-Barre Syndrome; IRR, incidence rate ratio; LCL, lower confidence limit; SCRI, self-controlled risk interval; UCL, upper confidence limit.

10.5.3. Characteristics of GBS cases among ABRYSVO-vaccinated individuals aged 65 years and older

Table 6 shows the characteristics of GBS cases that occurred within 42 days following ABRYSVO vaccination in Medicare beneficiaries aged 65 years and older. Note that characteristics for cases in the control interval were not examined due to low case counts (n=13), and most data would not be reportable per CMS reporting rules.

Among the 40 individuals[18] with GBS onset in 1-42 days post-index, the mean time to onset was 19.6 days (SD: 9.0), and the median was 16.0 days (IQR: 13.0–24.5). Of these individuals, 19 (47.5%) were aged 65–74 years, and 21 (52.5%) were aged 75 years or older. Twenty-one (52.5%) were male, and the majority were White (n=37; 92.5%). Thirteen (32.5%) individuals lived in areas with low deprivation index (high SES), and 14 (35.0%) in areas with medium deprivation index. Regional distribution showed 16 (40.0%) from the Midwest, while other regions had fewer than 11 individuals. None were recent nursing home residents at the time of vaccination, although 14 (35.0%) had evidence of a nursing home admission at any time during their baseline or follow-up.

In terms of clinical characteristics, 21 (52.5%) had a CCI of 2 or more, 14 (35.0%) classified as frail (score ≥2), and 14 (35.0%) as pre-frail. Fewer than 11 individuals were immunocompromised. All individuals (40; 100.0%) received ABRYSVO vaccination at a pharmacy. Within 45 days of GBS onset, 38 (95.0%) had a neurologist encounter, 38 (95.0%) underwent diagnostic procedures, and 36 (90.0%) had both. No individuals had diagnoses similar to GBS[19] within 30 days of GBS diagnosis. Medically-attended infections in the 42 days before onset were rare (<11 cases), and no gastrointestinal infections were reported. There were <11 cases with surgery within 42 days prior to onset, and no patients had evidence of trauma within 14 days prior to onset.

Regarding other vaccinations, 23 (57.5%) received at least one non-RSV vaccine in the 42 days prior to GBS onset, most commonly seasonal influenza (n=19; 47.5%) and COVID-19 (n=13; 32.5%). Co-administration on the index date occurred in 17 (42.5%), primarily influenza (n=13; 32.5%).

The mean length of inpatient stay was 12.7 days (SD: 9.0), with a median of 9.0 days (IQR: 6.0–18.0). Respiratory failure and intubation were not observed. At least one inpatient death occurred; however, the exact number cannot be reported in accordance with CMS requirements, which mandate masking any count less than 11. The cause of death could not be ascertained within the study.

Table 6. Characteristics of GBS cases in the 1-42 days after ABRYSVO vaccination

Characteristics	Individuals with GBS onset in 1-42 days after index date (N=40)	
	N	%
Mean time to onset of GBS following index date (days)		
Mean and SD	19.6	9.0

[18] This number is greater than the number reported for the SCRI analysis due to inclusion of GBS cases among all 1,584,636 ABRYSVO-vaccinated individuals aged 65 years and older, including individuals that did not have at last one day in the post-vaccination control interval.

[19] Brachial neuritis, myasthenia gravis, vasculitic neuropathy, diphthelic neuropathy, botulism, rhombencephalitis, or basal meningitis.

Table 6. Characteristics of GBS cases in the 1-42 days after ABRYSVO vaccination

Characteristics	Individuals with GBS onset in 1-42 days after index date (N=40)	
	N	%
Median and IQR	16.0	13.0- 24.5
Age on index date		
65-74	19	47.5%
75+	21	52.5%
Sex		
Male	21	52.5%
Female	19	47.5%
CCI		
0-1	19	47.5%
2+	21	52.5%
Frailty index		
Frail (2+)	14	35.0%
Pre-frail (1)	14	35.0%
Non-frail (0)	12	30.0%
Immunocompromised status		
Yes	<11	N/A
Race/Ethnicity		
White	37	92.5%
US Region		
Northeast	<11	N/A
Midwest	16	40.0%
West	<11	N/A
South	<11	N/A
ADI Rank		
Low deprivation (high SES): ADI rank 1 to 33	13	32.5%
Medium deprivation (middle SES): ADI rank 34 to 66	14	35.0%
High deprivation (low SES): ADI rank 67 to 100	12	30.0%
Facility/Provider type of ABRYSVO vaccination		
Pharmacy	40	100.0%
Hospital/ office visit	0	0.0%
Other	0	0.0%
Nursing home residency status (recent residency)*		
Resident	0	0.0%
Non-resident	40	100.0%
Nursing home residency status (any admission)†		

Table 6. Characteristics of GBS cases in the 1-42 days after ABRYSVO vaccination

Characteristics	Individuals with GBS onset in 1-42 days after index date (N=40)	
	N	%
Resident (Ever)	14	35.0%
Non-resident	26	65.0%
Neurologist encounter or diagnostic procedures within 45 days before or after GBS onset		
Neurologist encounter	38	95.0%
Diagnostic procedure	38	95.0%
Both	36	90.0%
Having diagnoses similar to GBS within 30 days before or after GBS diagnosis[^]		
No	40	100.0%
Infections in 42 days before GBS onset[‡]		
Medically-attended infections (Respiratory, GI, or unspecified viral infection)	<11	N/A
Upper or lower respiratory tract infections	<11	N/A
GI infections	0	0.0%
Unspecified viral infections	0	0.0%
Infections in 42 days before GBS onset[¥] (Sensitivity)		
Medically-attended infections (Respiratory, GI, or unspecified viral infection)	0	0.0%
Upper or lower respiratory tract infections	0	0.0%
GI infections	0	0.0%
Unspecified viral infections	0	0.0%
Surgery in 42 days before GBS onset	<11	N/A
Trauma in 14 days before GBS onset	0	0.0%
Non-RSV Vaccines Received in 42 days before GBS onset		
Any[±]	23	57.5%
Seasonal influenza vaccine	19	47.5%
COVID-19	13	32.5%
Shingles (Herpes Zoster recombinant and/or live)	<11	N/A
Pneumococcal	<11	N/A
Other[f]	<11	N/A
Vaccine co-administered on the index date		
Any±	17	42.5%
Seasonal influenza vaccine	13	32.5%
COVID-19	<11	N/A
Shingles (Herpes Zoster recombinant and/or live)	<11	N/A
Pneumococcal	0	0.0%
Other[f]	0	0.0%

Table 6. Characteristics of GBS cases in the 1-42 days after ABRYSVO vaccination

Characteristics	Individuals with GBS onset in 1-42 days after index date (N=40)	
	N	%
Indicators of GBS case severity		
Length of inpatient stay (days)		
Mean and standard deviation	12.7	9.0
Median and interquartile range	9.0	6.0- 18.0
Inpatient death	<11	N/A
Inpatient death (Sensitivity)‖	<11	N/A
Respiratory failure	0	0.0%
Intubation	0	0.0%

Abbreviations: ADI, area deprivation index; CCI, Charlson comorbidity index; COVID-19, coronavirus disease 2019; GBS, Guillain-Barré syndrome; GI, gastrointestinal; HPV, human papillomavirus; IQR, interquartile range; N/A, not applicable; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval; SD, standard deviation; SES, socioeconomic.
* Note: Record or admission into or assessment in a nursing home in the 120 days before the index date.
† Note: Record of admission into a nursing home during the baseline or follow-up period.
ﻉ Note: Includes brachial neuritis, myasthenia gravis, vasculitic neuropathy, diphthelic neuropathy, botulism, rhombencephalitis, or basal meningitis.(34)
ǂ Note: Defined as one code in any setting.
¥ Note: Defined as one code in the inpatient (IP) setting or 2 codes in the outpatient and professional billing (OP/PB) setting at least one day apart.
±Note: Includes any of the vaccines listed below.
f Note: Other vaccines include: Chickenpox, HPV, Hepatitis A, Hepatitis B, Meningococcal conjugate, and Haemophilus influenzae type b.
‖ Note: Includes admission into hospice care as a proxy for death.

10.6. Adverse events/adverse reactions

This study involves data that exist as structured data by the time of the study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. DISCUSSION

11.1. Key results

Risk of GBS following ABRYSVO vaccination over two seasons

In this analysis of approximately 1.6 million ABRYSVO-vaccinated Medicare beneficiaries aged 65 years and older, an increased risk of GBS following ABRYSVO vaccination was observed. While the unadjusted SCRI analysis suggested a statistically significantly increased risk of GBS following ABRYSVO vaccination was observed in both the 21-day and 42-day risk intervals. After further adjusting for differential PPV and seasonality, the risk of GBS was borderline statistically significant in the primary risk interval (2.86 [95% CI: 1.03-

7.94]) and was no longer statistically significant in the secondary risk interval (2.18 [95% CI: 0.85- 5.60]).

Across unadjusted and adjusted SCRI models, the risk was lower when the risk window was extended to 42 days, given most cases (68%) occurred within the first three weeks after vaccination. This is consistent with data reported in two recent studies in Scotland, where all cases presented before 21 days,(35) and England, where cases typically presented within 21-days post-vaccination.(36) If the true risk window following ABRYSVO vaccination is within the 21-day risk interval, then the risk estimate obtained using the 42-day secondary interval is likely diluted. It should be noted that adjusting for seasonality had minimal impact on IR and CI estimates. This was expected given the short risk and control intervals in this study, where seasonal variation was unlikely to influence results.

The unadjusted AR estimates indicated about 12 (95% CI: 8.4–14.3) and 16 (95% CI: 8.6–19.6) additional GBS cases per million vaccinations over the 21- and 42-day risk interval, respectively. After full adjustment (differential PPV and seasonality adjustment), the excess risk was about 7 (95% CI: 0.3–8.9) and 8 (95% CI: –2.6–12.3) additional GBS cases per million vaccinations with CIs bordering or including the null (i.e., zero). These results align with those of the FDA study, which found 9 (95% CI: –0.2–18.1) excess cases per million doses of ABRYSVO in the Medicare data during the 2023/2024 season.(18) These findings suggest an increased risk of GBS following ABRYSVO vaccination, primarily concentrated in the 21-day post-vaccination period, with a small absolute excess risk overall.

Among 35,274 individuals in the PharMetrics Plus population who were ABRYSVO-vaccinated commercially insured adults aged 60–64 years old, no GBS cases were observed during the 1-21- or 1-42-day post-vaccination risk interval, nor in the 42-day control window in the combined 2023/2024 and 2024/2025 seasons.

Changes in ABRYSVO-vaccinated population and risk of GBS in 2023/2024 vs. 2024/2025

Stratifications by season (2023/2024 vs. 2024/2025) were performed to further characterize the signal and identify any trends in GBS rates and ABRYSVO recipient characteristics over time. Of note, the number of ABRYSVO-vaccinated individuals identified in 2024/2025 was only about half the study population in 2023/2024.

The distribution of some key clinical characteristics appeared to be changing in the ABRYSVO-vaccinated population from the 2023/2024 to 2024/2025 season. Most demographic characteristics (sex, race/ethnicity, and US region) remained consistent when stratified by season. However, the 2024/2025 cohort had a higher proportion of older adults (63% aged 75+ vs. 52% in 2023/2024), more frail individuals (45% vs. 36%), and more individuals with significant comorbidities (59% with CCI ≥ 2 vs. 52%). Co-administration of other vaccines was similar (42% in 2024/2025 vs. 41% in 2023/2024) across the seasons, though there were slightly fewer ABRYSVO vaccinations occurring during the high respiratory season in 2024/2025 (91% vs. 97%).

The evolving population characteristics likely reflect changes in ACIP recommendations for RSV vaccination during this study period. Recommendations from the ACIP meeting on 29 February 2024 stated that the estimated benefits of RSV vaccination most clearly outweigh potential risks among adults aged 60 years and older who are at increased risk of

severe RSV disease.(3)The ACIP meeting on 26 June 2024 further recommended that all adults aged 75 years and older and adults aged 60–74 years who are at increased risk for severe RSV disease, should receive the vaccine. This represented a change from previous recommendations where the choice was based on shared clinical decision-making in adults aged 60 years and older.(6) Thus, changing demographics (older, frailer, more comorbid individuals) among those vaccinated beginning in the 2024/2025 season likely illustrates adherence to ACIP recommendations with a narrowing of the vaccinated population to individuals with more comorbid conditions at baseline.

Despite slight differences in clinical characteristics of the ABRYSVO-vaccinated population between the two seasons, a consistently increased risk of GBS was observed in both, with a numerically higher risk in the 2024–2025 season. Although formal statistical testing was not performed due to insufficient power, the risk estimates for the two seasons do not appear to differ significantly, as suggested by overlapping 95% CIs for season-specific IRRs and non-statistically significant slope from the risk time trend analysis.

Subgroup and sensitivity analyses including characteristics of GBS cases

Over the full study period, with individuals vaccinated from 31 May 2023 to 28 February 2025, there were 40 GBS cases observed within 42 days after receiving ABRYSVO, all among Medicare beneficiaries, with a median onset time of 16.0 (IQR: 13.0–24.5) days post-index. The distribution of most demographic and clinical variables for GBS cases was similar to the total ABRYSVO-vaccinated population, but there was a slightly higher proportion of males in the case population compared to the full study population (53% vs. 42%). This result is expected given male sex is a recognized risk factor for GBS.(37, 38) There were no respiratory failures or intubations noted during inpatient admission for the 40 GBS cases. At least one inpatient death was noted out of these cases, but the exact number could not be reported due to CMS Medicare data censoring rules. It is important to note that only the presence of inpatient death (including discharge to hospice care) was captured in this study, and not the cause of death in this older adult population.

About 58% of cases had received another vaccine (most often influenza [48%] or COVID-19 [33%]) in the preceding 42 days to GBS onset, and most (53%) GBS cases were comorbid with a CCI ≥ 2, though this was similar to the overall ABRYSVO-vaccinated Medicare population (54%). Finally, at least one (<11) case had an infection in the 42 days prior to GBS onset.

Since prior infection may be an important risk factor for GBS onset, the SCRI for the overall study period was re-run excluding individuals with medically-attended infections (≥1 ICD-10-CM code in any setting for a respiratory, GI or unspecified viral infection) in the 42 days prior to the date of GBS onset. A higher IRR of GBS after ABRYSVO-vaccination was observed across primary and secondary risk intervals in PPV-adjusted sensitivity analyses. Proportionally, more GBS cases were excluded from the control interval than from the risk interval, resulting in a more pronounced decrease in the IR within the control interval. This is sensible given cases in the control interval would be more likely to include situations where GBS onset was due to causes other than the ABRYSVO vaccine (such as infection), by design. Thus, results from this sensitivity analysis suggest that the increased risk of GBS after vaccination is unlikely to be confounded by prior infections.

To assess potential effect modification by age, sex, CCI, and co-vaccination status, given their evolving distribution over time (for age and CCI) and their high prevalence in the overall and case populations (for co-vaccination and CCI ≥ 2), subgroup analyses by age (60-74 years vs. 75+ years), CCI (2+ vs. 0-1), sex (male vs. female), and presence of concomitant vaccination on the index date (yes vs. no) were performed. Results from subgroup analyses should be interpreted as exploratory and hypothesis-generating due to the small number of cases, which introduces greater uncertainty in the estimates. Formal statistical testing for interaction was not performed due to insufficient power.

For age subgroup analyses, individuals aged 75 years and older had a higher IRR of GBS following ABRYSVO vaccination compared to 65–74-year-olds in both unadjusted (7.0 vs. 2.7, respectively) and PPV-adjusted (5.5 vs. 2.0) analyses in the primary risk interval. This is consistent with studies conducted in England and Scotland where ABRYSVO was recommended to those 75 years and older,(35, 36) and where generally higher risk estimates were reported than US studies including our own.(18, 39) In the study conducted by the United Kingdom Health Security Agency (UKHSA) in England, because chart review was not conducted for GBS cases, the authors performed a sensitivity analysis adjusting GBS cases using the same differential PPV values as in this study. Under this adjustment, the risk ratio was 2.5 with an AR of 12.1 cases per million vaccinations, bringing the results more in line with the IR and AR observed in the 75+ age group in this study. Although PPV values derived from the US population may not be directly applicable to the United Kingdom (UK) database, this comparison suggests that differences in GBS diagnostic certainty and age of the vaccinated population may partly explain the difference in the risk estimates between the US and UK studies.

In CCI-stratified analyses, there was a higher rate of GBS in the primary risk interval for those with a CCI of 0-1 compared to those with a CCI ≥ 2. It is important to note that the CCI used in this study did not include age in scoring, so it reflects only an individual's overall burden of disease separately from age. The higher IRR in the less comorbid group is likely driven by a lower baseline risk (i.e., control interval IR). For sex-stratified analyses, unadjusted results showed similar IRRs in males and females, suggesting no effect modification by sex. Finally, in co-vaccination-stratified analyses, there was a higher rate of GBS incidence in those without same day concomitant vaccination compared to those with same day co-vaccination. As previously mentioned, the study was not powered to examine these differences across all subgroup analyses, and the CIs were extremely wide for these IRRs (e.g., the CI for IRR of GBS in the primary risk interval for those with a CCI of 0-1 ranged from 2.9 to 34.5). Thus, no definitive conclusions can be drawn regarding statistically significant differences across subgroups. The CCI and co-vaccination subgroup analyses indicate that the associations between ABRYSVO vaccination and GBS are unlikely to be explained by concomitant vaccinations or higher burden of comorbidities among individuals receiving the ABRYSVO vaccination because an increased risk of GBS persisted in those without concomitant vaccination and with low CCI score, populations less prone to confounding.

11.2. Limitations

This study is subject to several limitations. First, this study is subject to misclassification, especially regarding GBS case status. GBS events were not verified by chart review due to lack of access to Medicare medical records. However, the vast majority of claims-identified GBS cases had a neurologist encounter or diagnostic procedures within 45 days of GBS

onset, and no one had any diagnosis similar to GBS within 30 days of onset, which provides supporting evidence for the validity of the identified GBS cases. Furthermore, the study employed a validated case definition and applied differential PPV adjustment for the risk and control intervals, based on the most recent validation study by the FDA,(18) to further mitigate the impact of outcome misclassification. This PPV-based approach has been applied in the first interim report for the 2023/2024 season, where results were very closely aligned with FDA's analysis that included chart review, further supporting the validity of this method.

A few GBS cases were removed from the SCRI analysis because they did not have at least one day of follow-up in the control window. To assess the impact of those excluded cases, a worst-case scenario was calculated. If these removed cases (and all individuals removed due to loss-to-follow-up in the risk interval) were also included in the primary risk interval analysis, assuming full follow-up for all individuals, the unadjusted IRR would be 3.08 (95% CI: 1.67-5.96). This estimate is comparable to the 4-fold unadjusted estimate from the primary analysis, suggesting the robustness of results even after excluding cases without a control interval by SCRI design.

The self-controlled design compares incidence in pre-specified risk and control intervals within an individual; however, it can be difficult to determine the timing when the rates of adverse events post-vaccination return to baseline. Although the risk window for GBS is well-studied for some exposures such as influenza vaccination, there could be bias arising from the misspecification of the risk interval for ABRYSVO. The study attempted to address this limitation by using two commonly used risk intervals for GBS with different lengths in the SCRI analysis.

Finally, though PharMetrics Plus is a large claims database representative of patients under 65 years of age on commercial health insurance plans, due to the narrow age band of 60-64, approximately 35,000 vaccinated individuals were included in the analysis and no GBS cases were observed. This may be attributable to the small sample size, and therefore results should be interpreted with caution.

This study also has several strengths. The SCRI design accounts for time-invariant confounders as the individual acts as their own control. This means even an unadjusted analysis should be less confounded than an analysis examining an ABRYSVO-vaccinated group with a comparator population. This study also used a large and fit-for-purpose database for evaluating the research question as it provided a representative source population for ABRYSVO recipients aged 65 years and older and captured a sizable proportion of exposures expected in the combined seasons. The study was powered to detect at least a 3.0- and 2.5-fold increase in GBS with 80% power for the primary and secondary risk intervals, respectively (see Section 9.7).

11.3. Interpretation

These results are consistent with findings from other safety studies of the ABRYSVO vaccine. Results using similar risk windows (secondary risk interval) and applying PPV adjustment methods most closely resemble findings in an FDA analysis of GBS risk in this population that includes chart review for GBS cases.(18) The FDA study also examined Medicare beneficiaries 65 years of age and older but included fewer ABRYSVO-vaccinated individuals given restriction to the 2023/2024 season. In the FDA analysis, an IRR of 2.0

(95% CI: 0.9–4.4) was identified in the fully adjusted 42-day risk interval, comparable to the secondary risk interval estimate of 2.2 (95% CI: 0.85, 5.60) identified in this study using similar parameters but across both seasons. A study by Fry et al. also examined ABRYSVO-vaccinated individuals aged 60 years or older from the Cosmos electronic health record database in the US and found a similar IRR of 2.4 (95% CI: 1.5–4.0) but a much higher AR.(39) This discrepancy may be due to inclusion of unverified GBS cases given lack of chart review or PPV adjustment in the study by Fry et al.(39) Besides the addition of a second season of data, this study adds to the existing knowledge and literature by providing estimates for a 21-day risk interval, a risk time trend analysis, and several sensitivity and subgroup analyses.

The relative and absolute GBS incidence estimates in this study were lower than that of two studies of ABRYSVO vaccination and GBS in England and Scotland.(35, 36) In the England study, an IRR of 3.3 (95% CI: 2.1–5.3) was identified, and in Scotland, the IRR was 16.6 (95% CI: 1.1–249.4). As previously mentioned, these estimates were obtained in an older population of 74- to 79- or 80-year-old adults. Additionally, GBS was identified using broader algorithms (e.g., the ICD-10 code for disorders of multiple cranial nerves was included in the Scotland-based study and treatment with intravenous immunoglobulin was included in the England-based study), thus making the estimates less comparable. The Scotland-based study had a much smaller sample size and used a different *pre-vaccination* control interval, which included only one GBS case. This resulted in greater uncertainty in the risk estimates and a tendency to overestimate risk, as the background rate of GBS is likely lower than usual during the period immediately before vaccination (i.e., the healthy vaccinee effect). Therefore, differences in study population age, GBS case definition, and key design elements collectively may contribute to the observed differences in the magnitude of risk between this study and the England and Scotland studies.

The current totality of evidence suggests a small increased risk of GBS after ABRYSVO vaccination. A planned PASS (C3671031) designated as a PMR will generate additional data and further elucidate the potential association between GBS and ABRYSVO. C3671031study will leverage data from at least four RSV seasons to achieve adequate statistical power to detect at least a 2-fold increased risk of GBS, with final results planned to be reported in May 2030.

11.4. Generalizability

Given the inclusion of ABRYSVO recipients from CMS Medicare databases, the data are expected to be generalizable to the older adult population (i.e., 65 years of age or older) within the US, as the study utilized a large and fit-for-purpose database for the source population. However, these results may have limited generalizability to individuals aged 60-64 years in the US as the PharMetrics Plus population only includes individuals who are enrolled in commercial health plans, so the results may not be generalizable to those uninsured or with other types of insurances.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Based on approximately 1.6 million ABRYSVO doses analyzed over two seasons, the study suggests a small increased risk of GBS following ABRYSVO vaccination among US adults aged 65 years and older, with an estimated excess risk of 7-8 cases per million doses. The findings are consistent with FDA's separate analysis of Medicare data for the 2023/2024 season and also align with findings from other published US and UK non-interventional studies using similar designs, although absolute risk estimates vary across studies. These differences may reflect variations in the age of vaccinated populations and differences in case definitions and diagnostic accuracy. No GBS cases were observed among approximately 35,000 commercially insured individuals aged 60–64 years. However, results should be interpreted with caution given the rarity of GBS and the limited sample size in this age group.

While GBS following RSV vaccination warrants continued scientific scrutiny, the rare risk of GBS associated with the vaccine, based on this study (and other similar available data including FDA's evaluation of GBS risk), is not anticipated to impact the overall benefit-risk profile of ABRYSVO. Pfizer's robust post-marketing surveillance will continue to monitor GBS risk to ensure that the benefit-risk profile of ABRYSVO remains favorable.

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15. LIST OF SOURCE TABLES AND FIGURES

Document Approval Record

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Document Title:	C3671054

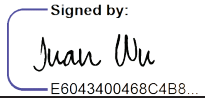
Signed By:	Date(GMT)	Signing Capacity
Younus, Muhammad	15-Jan-2026 13:27:05	Final Approval
De Bernardi, Barbara	16-Jan-2026 11:20:41	EUQPPV Approval

APPENDIX 1. SIGNATURES

PROTOCOL NUMBER:	C3671054
TITLE OF STUDY:	A Post-Marketing Near Real-Time Safety Surveillance of Respiratory Syncytial Virus (RSV) Vaccine for Guillain-Barre Syndrome (GBS) among Older Adults in the United States
STUDY REPORT VERSION:	Final Study Report – V1.0

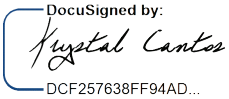
Confirmation: I confirm that this study report, which is final in content and has been printed from its definitive source, is a complete and accurate representation of the data and statistical analyses from this study.

Pfizer NI study lead/LIS1 study lead
Joanne Wu, ScD, MS

Signature: 

Date: 1/9/2026

IQVIA study lead
Krystal Cantos, PhD

Signature: 

Date: 1/9/2026

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Post-Marketing Near Real-Time Safety Surveillance of Respiratory Syncytial Virus Vaccine for Guillain-Barre Syndrome (GBS) among Older Adults in the United States
Protocol number	C3671054
Protocol version identifier	2.0
Date	23 April 2025
EU Post Authorization Study (PAS) register number	EUPAS1000000267
Active substance	ABRYSVO™ is a bivalent recombinant stabilized prefusion F protein subunit vaccine (Respiratory Syncytial Virus Vaccine). It consists of equal amounts of prefusion F antigens from the two major RSV subgroups: RSV subgroup A prefusion F (60 µg) and RSV subgroup B prefusion F (60 µg).
Medicinal product	RSVpreF (ABRYSVO™)
Research question and objectives	The research question is: What is the incidence rate of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases and individuals aged 60-64 years enrolled in the IQVIA PharMetrics Plus claims database (PharMetrics Plus database) as compared to the expected incidence rate of GBS in a comparable population? The research objectives are: • To conduct near real-time monitoring of the incidence of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases using RCA study design; and • To assess if there is an elevated risk of GBS following vaccination with ABRYSVO among individuals aged 65

	years of age or older enrolled in CMS Medicare databases, using SCRI study design; and • To descriptively monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database.
Country(ies) of study	United States
Author	**Pfizer:** Juan (Joanne) Wu, ScD, MS Associate Director, Epidemiology, Safety Surveillance Research, Worldwide Safety Pfizer, Inc. 66 Hudson Boulevard East, New York, NY 10001 United States **Sub-contractor (IQVIA):** Efe Eworuke, PhD Principal Krystal Cantos, PhD Associate Principal Epidemiology & Drug Safety, IQVIA 100 IMS Drive, Parsippany, NJ 07054 United States

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AIDS	Acquired Immunodeficiency Syndrome
AE	Adverse Event
AR	Attributable Risk
BMI	Body Mass Index
CAD	Coronary Artery Disease
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CHF	Congestive Heart Failure
CMS	Centers for Medicare & Medicaid Services
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPT	Current Procedural Terminology
EBV	Epstein-Barr Virus
EDB	Enrollment Database
FDA	Food and Drug Administration
FFS	Fee-for-Service
GBS	Guillain-Barre syndrome

Abbreviation	Definition
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
HBV	Hepatitis B Virus
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HMA-EMA	Heads of Medicines Agencies - European Medicines Agency
HPV	Human Papillomavirus
HSCT	Hematopoietic Stem Cell Transplantation
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases, 10th revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th revision, Procedure Coding System
IEA	International Epidemiological Association
IP	Inpatient
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
LRTD	Lower Respiratory Tract Disease
MDS	Minimum Data Set
MenACWY	Meningococcal ACWY Vaccine

Abbreviation	Definition
MenB	Meningococcal B Vaccine
NDC	National Drug Codes
OP/PB	Outpatient and Professional
PASS	Post-Authorization Safety Study
PMR	Post-marketing Requirement
PPV	Positive predictive value
QBA	Quantitative Bias Analysis
RCA	Rapid Cycle Analysis
RSV	Respiratory Syncytial Virus
RSVpreF	Respiratory Syncytial Virus Prefusion F protein
RWD	Real-World Data
SAP	Statistical Analysis Plan
SCRI	Self-Controlled Risk Interval
SD	Standard Deviation
SNF	Skilled Nursing Facility
SSD	Shared Systems Data
Td	Tetanus and Diphtheria Toxoids
Tdap	Tetanus, Diphtheria, and Pertussis
TNF	Tumor Necrosis Factor
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System
VTE	Venous Thromboembolism

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: A Post-Marketing Near Real-Time Safety Surveillance of Respiratory Syncytial Virus Vaccine for Guillain-Barre Syndrome (GBS) among Older Adults in the United States

Date: 23 April 2025, Version 2.0

Name and affiliation of the main author: Juan (Joanne) Wu, ScD, MS, Associate Director, Epidemiology, Safety Surveillance Research, Worldwide Safety Pfizer, Inc.

Rationale and background: The United States (U.S.) Food and Drug Administration (FDA) approved RSVpreF (ABRYSVO) Respiratory Syncytial Virus (RSV) vaccine on 31 May 2023 in individuals ≥60 years of age and on 21 August 2023 in pregnant individuals at 32 through 36 weeks gestational age. GBS is an important potential risk, which is mentioned in the ABRYSVO Risk Management Plan. Across all RSVpreF clinical trials, inflammatory neurologic events were reported in 3 of 20,255 adults aged ≥60 years within 42-days after vaccination with RSVpreF (1 case of GBS, 1 case of Miller Fisher syndrome [a variant of GBS] and 1 case reported as undifferentiated motor-sensory axonal polyneuropathy). On 09 November 2023, FDA informed Pfizer of a few potential cases of GBS among older adults receiving ABRYSVO that were reported to the FDA's Vaccine Adverse Event Reporting System (VAERS).

To rapidly monitor the risk of GBS, Pfizer proposes to conduct a near real-time surveillance of ABRYSVO among older adults in the U.S. This study will utilize both Rapid Cycle Analysis (RCA) and Self-Controlled Risk Interval (SCRI) analysis to detect and evaluate the risk of GBS following ABRYSVO vaccination. RCA is an established method of near real-time surveillance that periodically assesses data for safety signal as exposures accrue. The SCRI study design is a commonly used self-controlled method in vaccine safety studies, to evaluate the association between a transient exposure, such as vaccination, and an acute event, such as an adverse reaction. The complementary approaches of conducting an active surveillance study using an RCA for signal detection and a comparative SCRI analysis for signal evaluation is essential for a robust vaccine safety study, which combines the advantage of timely signal detection and the ability to perform an in-depth analysis that is hypothesis-driven and well-controlled for time-invariant confounders.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the FDA.

Research question and objectives:
Research question: What is the incidence rate of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in the Centers for Medicare & Medicaid Services (CMS) Medicare databases and individuals aged 60-64 years enrolled in PharMetrics Plus database as compared to the expected incidence rate of GBS in a comparable population?

The study objectives are:

- To conduct near real-time monitoring of the incidence of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases, using RCA study design; and
- To assess if there is an elevated risk of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases, using SCRI study design; and
- To descriptively monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database.

Study design: This will be a non-interventional cohort study among U.S. Medicare beneficiaries aged 65 years or older and individuals aged 60-64 years enrolled in PharMetrics Plus database. The full study period, which includes the baseline period, the indexing period (i.e., period for identification of ABRYSVO vaccinations), and the follow-up, will begin on 31 May 2022 and end on 23 May 2025, spanning two RSV seasons to rapidly assess if there is a high risk of GBS after RSV vaccination. The following approaches will be used to address the study objectives:

1. The Study Design of RCA Methodology using CMS Medicare Databases:

For signal detection, an RCA will be launched in the 2024/2025 RSV season, built upon cumulative data from the 2023/2024 RSV season, to periodically evaluate the incidence of GBS following vaccination with ABRYSVO compared to an estimated background rate in the CMS Medicare database, as the data become available on a monthly basis. The background rate will be estimated from a comparable population using the incidence rate of GBS after influenza vaccination in prior seasons before the approval of ABRYSVO. A secondary background rate will be based on the published background rate of GBS from the general CMS Medicare population.[1] A group sequential method will be utilized for the repeated testing of continuously accumulating data to minimize false positive signals. The RCA will use 1- 21 and 1- 42 days after the vaccination date (index date) as the primary and secondary risk intervals, respectively. The indexing period for both risk intervals will be from 31 May 2023 to 10 January 2025. The full study period of the RCA analysis will be from 31 May 2022 to 21 February 2025, including 365 days of the baseline period.

2. The Study Design of SCRI Methodology using CMS Medicare Databases:

As a comparative analysis to further evaluate the risk of GBS, an SCRI analysis will be conducted at the end of surveillance period in each of the 2023/2024 and 2024/2025 RSV seasons using the CMS Medicare databases. The SCRI will compare the incidence rate of

[1] Moll K, Lufkin B, Fingar KR, Zhou CK, Tworkoski E, Shi C, et al. Background rates of adverse events of special interest for COVID-19 vaccine safety monitoring in the United States, 2019–2020. Vaccine. 2023;41(2):333-53.

GBS during the pre-specified post-vaccination risk interval to the post-vaccination control interval within the vaccinated individuals, which effectively controls for time-invariant confounding. Finally, a pooled SCRI analysis using individual-level data from 2 RSV seasons will be conducted to allow for a comprehensive assessment of the association between ABRYSVO and GBS with higher statistical power. The indexing period of the SCRI analysis of the 2023/2024 RSV period for evaluating exposure to ABRYSVO will be from 31 May 2023 to 29 February 2024. The full study period for the 2023/2024 RSV season will be from 31 May 2022 to 23 May 2024, allowing 365 days of the baseline period and 84 days of post-vaccination follow-up period. The post-vaccination risk periods for the SCRI analysis are 1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively; and the post-vaccination control period is 43-84 days after the index date. For the 2024/2025 RSV season, the full study period will be from 31 May 2023 to 23 May 2025 (indexing period: 31 May 2024 through 28 February 2025). For the combined RSV season analysis, the full study period will be from 31 May 2022 to 23 May 2025 (indexing period: 31 May 2023 through 28 February 2025).

3. The Study Design of Descriptive Analysis of Individuals Aged 60-64 Years Enrolled in PharMetrics Plus Database:

Given the more limited age range for commercially insured adults 60-64 years, analyses for this age group will be primarily descriptive. For the descriptive analyses of GBS incidence following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database, the indexing period of the 2023/2024 RSV period for evaluating exposure to ABRYSVO will be from 31 May 2023 to 29 February 2024. The full study period for the 2023/2024 RSV season will be from 31 May 2022 to 11 April 2024, allowing 365 days of the baseline period and 42 days of post-vaccination follow-up period. The post-vaccination risk periods for the descriptive analysis are 1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively. For the 2024/2025 RSV season, the full study period will be from 31 May 2023 to 11 April 2025 (indexing period: 31 May 2024 to 28 February 2025). For the combined RSV season analysis, the full study period will be from 31 May 2022 to 11 April 2025 (indexing period: 31 May 2023 to 28 February 2025).

Setting: The source population will be the U.S. Medicare beneficiaries available in the CMS Medicare Fee-for-Service (FFS) administrative database (referred to as the CMS Medicare database), and individuals aged 60 – 64 years of age in PharMetrics Plus database.

Study Population: To be eligible for inclusion in the study, participants must meet eligibility criteria across the different RSV seasons. Participants eligible for the study will be required to receive one dose of the ABRYSVO vaccine, administered during the appropriate study indexing period for the 2023/2024 and 2024/2025 RSV seasons. Additional eligibility criteria include being 65 years of age or older on the index date and having aged into Medicare or being 60-64 years of age on the index date in the PharMetrics Plus database; having at least 12 months of continuous enrollment in Medicare Parts A and B for the CMS Medicare databases or having at least 12 months of continuous enrollment with medical and pharmacy benefits for PharMetrics Plus database; and having a minimum period of continuous enrollment (e.g., 3 months) in Medicare Part D prior to the index date (for the CMS Medicare

databases only). Participants must not have received an RSV vaccine from any manufacturer other than Pfizer during the baseline and follow-up period. Exclusion criteria include individuals with missing information on sex, and those with GBS diagnosis in any setting and any position on a claim (i.e., indicative of an existing GBS diagnosis) during the baseline period or on the index date.

Variables: Exposures, outcomes, and covariates will be identified within relevant care settings in the claims data. The care settings include inpatient (IP), and outpatient and professional (OP/PB) settings.

The exposure of interest is ABRYSVO vaccination, defined as an individual's first administration of the ABRYSVO vaccine during the indexing period, as identified by specific Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), or National Drug Codes (NDC) during the indexing period. To deduplicate exposure occurrences, multiple vaccine records containing the same ABRYSVO vaccine product, occurring on the same day or within 3 days will be deduplicated. The date of the first occurrence of the ABRYSVO vaccination will be defined as the index date.

The outcome of interest is GBS diagnosis, which will be identified from claims using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code G61.0. An incident GBS case will be defined as the first occurrence of a primary discharge diagnosis of GBS in the IP setting post-vaccination, where the date of the case's onset will be defined as the date of hospitalization unless there is a claim with a GBS diagnosis in another medical setting (e.g., OP) in the prior 7 days. In that case, the earlier claim, irrespective of healthcare setting, will represent the date of onset. This claims-based algorithm in the CMS Medicare database has a positive predictive value (PPV) of 71.2% – 78.6%.[2,3]

Patient characteristics, including demographics, clinical characteristics, medication use, vaccinations, and healthcare resource utilization will be captured during the baseline period and follow-up period, as applicable.

Data sources: The study will use the CMS Medicare databases with monthly data refreshes that include Medicare Parts A, B and D, and PharMetrics Plus commercial claims database. They are both claims databases that include well-defined longitudinal data that captures healthcare service utilization for millions of enrollees across multiple care settings including inpatient, outpatient emergency department and outpatient non-emergency department, professional services non-laboratory and laboratory, and pharmacy settings. The Medicare monthly data consists of a mixture of pre-adjudicated and adjudicated claims; prior research

[2] Goud R, Lufkin B, Duffy J, et al. Risk of Guillain-Barré syndrome following recombinant zoster vaccine in Medicare beneficiaries. JAMA Intern Med. 2021;181(12):1623-30.

[3] Perez-Vilar S, Hu M, Weintraub E, et al. Guillain-Barré syndrome after high-dose influenza vaccine administration in the United States, 2018-2019 season. J Infect Dis. 2021;223(3):416-25.

shows the diagnosis codes rarely change (<0.5%) after adjudication.[4,5,6] The PharMetrics Plus data consists of fully adjudicated claims.

Study size: All Medicare and commercially insured older adults who meet the eligibility criteria during the study period will be included. The sample size calculation outlines the number of individuals required for a conditional Poisson regression using the SCRI design, across different Incidence Rate Ratios (IRR). Based on preliminary counts through February 2024, approximately 1 million ABRYSVO-vaccinated individuals aged 65 years of age or older are expected to be included in the study for one RSV season. The study is anticipated to have 80% power to be able to detect a high to modest increased risk of GBS (5.0- fold or lower) in each RSV season. Pooled analysis combing data from 2 RSV seasons is anticipated to have 80% power to detect a modest increased risk of GBS (3.0- to 4.0- fold). Given the limited age range for commercially insured adults 60-64 years, analyses for this age group will be primarily descriptive.

Data analysis: Covariates will be assessed among the study populations of the SCRI, RCA and descriptive analysis. Patient demographics and clinical characteristics including age on index, gender, race, geographic region, concurrent vaccinations, and selected comorbidities will be reported. Continuous variables will be summarized using mean ± standard deviation (SD), median, and interquartile range. Categorical variables will be summarized using counts and proportions. 95% confidence intervals (CIs) will be provided where applicable.

To conduct near real-time surveillance using RCA, a group sequential testing approach will be used to compare the observed rates of GBS following vaccination to an expected incidence rate of GBS (referred to as the background rate). The background rate of GBS will be estimated using historical influenza-vaccinated population from the CMS FFS for the 2022 and 2023 influenza seasons. Each month, an exact sequential Poisson-based likelihood ratio test using unifying family group sequential methods will be conducted with cumulative monthly data, with the first monthly analysis launched in December 2024, which will include cumulative data from the 2023/2024 season and the initial uptake data in the 2024/2025 RSV season. The RR of GBS will be the target parameter, defined as the ratio of the observed GBS rate and the expected GBS rate in the ABRYSVO population. One-sided tests will be conducted where the null hypothesis is that the observed rate of GBS in the ABRYSVO cohort is no greater than 2 times the comparator rate.

The SCRI analysis will be conducted in the CMS Medicare databases. In the SCRI methodology, each ABRYSVO-vaccinated beneficiary will serve as their own control as the risk of experiencing GBS during a post-vaccination risk interval is compared to a post-

[4] BEST. Protocol: Evaluation of Multiple Safety Outcomes following Respiratory Syncytial Virus (RSV) Vaccination in Adults 60 Years and Older. 2023.

[5] US-HHS-CMS. Medicare Claims Maturity - Chronic Conditions Data Warehouse White Paper. 2.0 ed2017.

[6] Medicare Cf, Services M. Preliminary Medicare COVID-19 data snapshot. Retrieved September. 2021;5:2021.

vaccination control interval within the same individual. The study population will include all exposed individuals that meet the inclusion and exclusion criteria, but only individuals who develop GBS cases will contribute to the risk estimation. In the analysis, all GBS cases that occur within the specified risk and control intervals following vaccination will be included and the incidence will be estimated separately for the risk and control windows. A conditional Poisson regression model will be used to estimate the IRR and 95% CI, offset by the length of observation time. In addition, sensitivity analyses for addressing potential biases in the SCRI include a seasonality adjusted analysis to account for time-variant confounding, PPV-adjusted quantitative bias analysis for more comprehensive capture of the outcome using published PPV from Medicare data, and an approach adjusted for both seasonality and PPV. A final pooled SCRI analysis will be conducted by aggregating individual-level data from two seasons into one analytical file. Subgroup analyses and a risk trend analysis may also be conducted in the pooled SCRI analysis.

For commercially insured adults 60-64 years, the incidence of GBS after ABRYSVO vaccination will be described. Inferential analysis, SCRI, may be considered contingent on sample size. Other sensitivity analyses may include, but are not limited to, removal of GBS cases that occurred among individuals with prior infection diagnoses for the SCRI and RCA analytic population, a secondary risk interval for the RCA, alternative background rate comparation for the RCA, and a case-centered GBS analysis to evaluate the severity of GBS and relevant risk factors for the SCRI and RCA analytic populations, as well as the descriptive analysis population from PharMetrics Plus.

Detailed methodology for the statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP).

Milestones: The feasibility assessment was completed on 29 February 2024. The draft protocol will be submitted to the FDA by 30 April 2024; and the final protocol will be submitted to the FDA by 16 August 2024. Start of data collection is planned on 19 August 2024, pending FDA endorsement of the study protocol and SAP, and the end of data collection on 15 September 2025. The planned timeline includes three interim reports focusing on the analysis of the RSV seasons across two years, that are strategically scheduled: Interim report 1 will cover the 2023/2024 RSV season's SCRI and descriptive analysis (due to the FDA by 20 December 2024); Interim report 2 and Interim report 3 are due on 21 February 2025 and 08 August 2025, respectively, and will cover the RCA analyses in the 2024/2025 RSV season. The study concludes with a final report presenting the results of 2023/2024 and 2024/2025 RSV seasons' SCRI and descriptive analyses separately, as well as a pooled analysis for the SCRI and descriptive analysis findings from both seasons, to be submitted to the FDA by 30 January 2026.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	23 April 2025	Substantial	4. Abstract	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025 • Updated the study period end date for the RCA from 28 February 2025 to 21 February 2025 • Updated the years that will be used for background rate generation for the RCA • Revised the date of submission of Interim Report 3 from 20 June 2025 to 08 August 2025 • Revised description of CMS Medicare data from "primarily pre-adjudicated" to a mixture of pre-adjudicated and adjudicated • Updated wording for RCA statistical analysis text from "ratio of GBS rates between the ABRYSVO population and the comparator population" to "ratio of observed GBS rate and the expected GBS rate in the ABRYSVO population"	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition • The revised RCA study period aligns with the updated indexing period mentioned above • The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends, further outlined in Section 9.7.3.1 • The date of Interim Report 3 was extended to ensure all six RCA can be included in the report, given operational challenges and extended timeline encountered using Medicare data • The data source can be better described as a mixture of pre-adjudicated and adjudicated claims • A ratio of observed and expected rates better describes the statistical analysis for the RCA
			6. MILESTONES	• Added the date of registration in the HMA-EMA Catalogue and the EU PAS registration number	• The protocol was registered in the HMA-EMA Catalogue on 16 August 2024

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				• Revised the date of submission of Interim Report 3 from 20 June 2025 to 08 August 2025	• The date of Interim Report 3 was extended to ensure all six RCA can be included in the report, given operational challenges encountered using Medicare data
			7. RATIONALE AND BACKGROUND	• Updated recommendations for RSV vaccination added	• The Advisory Committee on Immunization Practices (ACIP) updated RSV vaccination recommendations in a 26 June 2024 meeting
			9.1.1 The Study Design of RCA Methodology	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025 • Updated the study period end date for the RCA from 28 February 2025 to 21 February 2025 • Renamed the "sensitivity risk interval" for the RCA to "secondary risk interval" and matched the indexing period to that of the primary risk interval • Updated the years that will be used for background rate generation for the RCA • Figure 1 and Figure 2 were updated to reflect the updated indexing periods for the RCA	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition • The revised RCA study period aligns with the updated indexing period mentioned above • The primary and secondary risk intervals will use the same indexing period to ensure that the same population is being evaluated in both, making the results more comparable • The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends, further outlined in Section 9.7.3.1

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			9.1.4. Study Population	• Figure 7 updated to reflect updated indexing periods for the RCA	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition
			9.2.1 Inclusion and Exclusion Criteria	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025	• The revised RCA indexing period allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture GBS cases per outcome definition
			9.3.2 Outcomes	• Included updated PPV for the GBS case definition	• To minimize potential outcome misclassification, the most updated data on PPV for the GBS case definition will be used for adjustment[7]
			9.3.3 Patient Characteristics	• Removed suramin from the list of medications being evaluated for use at baseline	• Suramin use is rare among population of interest[8]
			9.4.1 CMS Medicare Administrative Database	• Revised description of CMS Medicare data from "primarily pre-adjudicated" to a mixture of pre-adjudicated and adjudicated	• The data source can be better described as a mixture of pre-adjudicated and adjudicated claims
			9.7.3. The Statistical Analysis for the RCA	• Updated wording for RCA statistical analysis text from "ratio of GBS rates between the ABRYSVO population and the comparator population" to "ratio of observed GBS rate and the	• A ratio of observed and expected rates better describes the statistical analysis for the RCA

[7] Lloyd P. Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older. In: Office of Biostatistics and Pharmacovigilance Center for Biologics Evaluation and Research USFDA, editor. Meeting of the Advisory Committee on Immunization Practices (October 2024).

[8] Wiedemar N, Hauser DA, Mäser P. 100 years of suramin. Antimicrobial agents and chemotherapy. 2020;64(3):10.1128/aac. 01168-19.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				expected GBS rate in the ABRYSVO population"	
			9.7.3.1 The Background Rate of GBS	• Updated and added rationale for the years that will be used for background rate generation for the RCA	• The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends
			9.7.6.2 Positive Predictive Values (PPV)-Adjusted Quantitative Bias Analysis	• Added language to include updated PPVs for sensitivity analyses as they become available through the study duration	• To minimize potential outcome misclassification, the most updated data on PPV for the GBS case definition will be used for adjustment
			9.7.7.1. Removal of GBS Cases After Infection Diagnoses for the SCRI Analytic Population and the RCA Analytic Population	• Removed "and the RCA analytic population" from the header	• The header for this section did not accurately reflect the content of the section
			9.7.7.2. Secondary Risk Interval for the RCA Analytic Population	• Updated the indexing period end date for the RCA from 07 February 2025 to 10 January 2025	• The primary and secondary risk intervals will use the same indexing period to ensure that the same population is being evaluated in both, making the results more comparable
			9.7.7.3. Use of Published Background Rate of GBS for the RCA Analytic Population	• Section removed	• The most recent 2022 and 2023 data on influenza exposure before ABRYSVO approval will be used to estimate the GBS background rate to minimize potential biases from secular trends
			9.7.7.4. Case-Centered GBS Analysis for the SCRI Analytic Population, the RCA Analytic Population	• Clarified that selected demographic and clinical variables will be reported for the case-centered GBS analysis	• The full set of demographic and clinical variables will not be reported in case-centered GBS analyses as outlined the Statistical Analysis

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			and the Descriptive Analysis Population		Plan. Updated for clarification.
			9.7.8 Summary of Statistical Analyses Presented in the Interim and Final Reports	• Revised the analyses that were included in Interim Report 2 and planned analyses for Interim Report 3 • Updated the indexing period end date for Interim Report 2 from 10 October 2024 to 10 August 2024 • Updated the indexing period end date for Interim Report 3 from 07 February 2025 to 10 January 2025	• The revised analyses for Interim Reports reflect the actual results that were presented in Interim Report 2 • The revised indexing period end date for Interim Report 2 reflects the actual data that were presented in Interim Report 2 • The revised Interim Report 3 end date aligns with the revised RCA indexing period, which allows for two months of data maturation through 28 September 2024, covering the primary and secondary risk intervals and an additional 7 days to capture hospitalized GBS cases per outcome definition
			12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	• Revised text to clarify only the final study report will be uploaded to the HMA-EMA catalogues	• No interim reports will be uploaded to the HMA-EMA catalogues
			ANNEX 2. ADDITIONAL INFORMATION	• Updated the list of codes for RSV vaccination	• List of codes was updated as new ABRYSVO codes were added for the 2024/2025 season, and a new mRESVIA vaccine was approved

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	29 February 2024 (completed)
Draft protocol submission to the FDA	30 April 2024 (completed)
Final protocol submission to the FDA	16 August 2024 (completed)
Registration in the HMA-EMA Catalogue of RWD studies	16 August 2024 EU PAS number: EUPAS1000000267
Start of data collection*	19 August 2024
End of data collection	15 September 2025
Interim report 1** (2023/2024 RSV season SCRI and descriptive analysis)	20 December 2024 (completed)
Interim report 2 (2024/2025 RSV season 1st RCA report)	21 February 2025 (completed)
Interim report 3 (2024/2025 RSV season 2nd RCA report)	08 August 2025
Final study report to the FDA (2023/2024 RSV season SCRI and descriptive analysis; 2024/2025 RSV season SCRI and descriptive analysis; combined 2 seasons SCRI and descriptive analysis)	30 January 2026

* Start of data collection will occur after submission of final protocol and SAP finalization, which may be adjusted should there be any further feedback from the FDA.
** Timeline for the 1st interim report may be adjusted should there be any significant delay in start of data collection
Abbreviations: HMA-EMA, Heads of Medicines Agencies – European Medicines Agency; RWD, Real-World Data.

7. RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a common, contagious virus that causes mild, cold-like symptoms, but may cause severe disease with a need for hospitalization in infants and older adults.(1) RSV infection in older adults can result in Lower Respiratory Tract Disease (LRTD), which can lead to serious, life-threatening pneumonia and bronchiolitis. According to the Centers for Disease Control and Prevention (CDC), RSV infection causes approximately 60,000 – 120,000 hospitalizations and 6,000 – 10,000 deaths annually among adults ages 65 years of age and older.(1) The U.S. FDA approved RSVpreF (ABRYSVO) RSV vaccine on 31 May 2023 for individuals 60 years of age and older to prevent severe RSV and on 21 August 2023 for pregnant individuals at 32 through 36 weeks gestational age to protect newborns through passive immunity. (2, 3) On 22 October 2024, the vaccine was approved for individuals 18 through 59 years of age who are at increased risk for LRTD.(4) The CDC initially recommended that adults aged 60 years and older receive RSV vaccination using shared clinical decision-making.(5) Following the Advisory Committee on Immunization Practices (ACIP) meeting, the CDC further recommended on 26 June 2024 that all adults aged 75 years and older, and adults aged 60-74 years who are at increased risk for severe RSV disease, should receive the vaccine.(6, 7)

GBS is a rare, serious acute demyelinating disease, where damage to the nerve causes muscle weakness and sometimes paralysis.(8) Although the cause of GBS is not fully understood, the syndrome often follows infection with a virus or bacteria; furthermore, it has been found that there is an increased risk for GBS following vaccine administration, an association that was first observed after the 1976 swine flu vaccinations.(8, 9) GBS is a rare, serious acute demyelinating disease, where damage to the nerve causes muscle weakness and sometimes paralysis.(8) Although the cause of GBS is not fully understood, the syndrome often follows infection with a virus or bacteria; furthermore, it has been found that there is an increased risk for GBS following vaccine administration, an association that was first observed after the 1976 swine flu vaccinations.(8, 9)

Across all RSVpreF clinical trials, inflammatory neurologic events were reported in 3 of 20,255 adults aged ≥60 years within 42-days after vaccination with RSVpreF (1 case of GBS, 1 case of Miller Fisher syndrome [a variant of GBS] and 1 case reported as undifferentiated motor-sensory axonal polyneuropathy).(10) GBS is an important potential risk, which is mentioned in the ABRYSVO Risk Management Plan.(7) Pfizer has an ongoing Post-marketing Requirement (PMR) PASS (protocol # C3671031), that is planned over multiple RSV seasons to evaluate any small or modest risk of GBS (e.g., 2-fold) following ABRYSVO vaccination using the fully adjudicated CMS Medicare claims. The study's first interim report will be available in December 2026 and the final report in May 2030. On 09 November 2023, FDA informed Pfizer of a few potential cases of GBS among older adults receiving ABRYSVO that were reported to the FDA's Vaccine Adverse Event Reporting System (VAERS), highlighting a need to rapidly assess the risk of GBS following ABRYSVO administration.(11)

The proposed post-marketing safety study will provide a timely, targeted assessment of GBS after ABRYSVO vaccination during the initial vaccine uptake period of two consecutive RSV seasons, 2023/2024 and 2024/2025, that will address the gaps in safety evidence from

prelicensure trials and early passive adverse event reporting. The study will encompass two analytical approaches: a signal detection (RCA) and a comparative (SCRI) approach.

RCA is an established method of near real-time surveillance that periodically assesses data for safety signal as exposures accrue by comparing observed incidence rates of GBS to an expected background rate. To detect an early safety signal for GBS, Pfizer proposes to conduct a near real-time surveillance of risk of GBS following ABRYSVO among older adults in the U.S.

The SCRI study design is a commonly used method in vaccine safety studies, to evaluate the association between a transient exposure, such as vaccination, and an acute event, such as an adverse reaction. (12) This approach inherently controls for time-invariant confounders within an individual, such as genetic factors, chronic health conditions, as well as long-term lifestyle socio-economic status. To evaluate the risk of GBS following ABRYSVO, Pfizer proposes to conduct an SCRI analysis among older adults in the U.S.

The complementary approaches of conducting an active surveillance study using an RCA for signal detection, and a comparative SCRI analysis to further assess the risk for an adverse event following vaccination is essential for a robust vaccine safety study. It combines the advantage of timely signal detection and the ability to perform an in-depth analysis that is hypothesis-driven and well-controlled for time-invariant confounders. The approach ultimately ensures a robust measurement of the safety of vaccines in the indicated population.

This non-interventional study is designated as a PASS and is a post-marketing commitment to the FDA.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: What is the incidence rate of GBS following vaccination with ABRYSVO among older adults aged 65 years of age or older enrolled in CMS Medicare databases and individuals aged 60-64 years enrolled in the IQVIA PharMetrics Plus claims database (PharMetrics Plus database) as compared to the expected incidence rate of GBS in a comparable population?

The research objectives are:

- To conduct near real-time monitoring of the incidence of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases using RCA study design; and

- To assess if there is an elevated risk of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases, using SCRI study design; and

- To descriptively monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database.

9. RESEARCH METHODS

9.1. Study Design

This will be a non-interventional cohort study among older adults enrolled in CMS Medicare databases and PharMetrics Plus database (Section 9.4). The surveillance period for RSV vaccinations (i.e., the indexing period) will span 2 RSV seasons (i.e., 2023/2024 and 2024/2025 seasons), beginning on ABRYSVO's approval on 31 May 2023. Two RSV seasons are included to increase sample size and rapidly assess a modest to high risk (3- to 5-fold) of GBS after ABRYSVO vaccination while a separate, long-term PMR PASS (protocol # C3671031) spanning 4.5 RSV seasons or more is being conducted to detect any small risk of GBS (e.g., 2-fold) following ABRYSVO vaccination using the fully adjudicated claims in CMS Medicare. There will be descriptive monitoring of GBS incidence following ABRYSVO vaccination among adults aged 60-64 years of age.

The baseline period for an individual will be defined as 365 days prior to the date of the ABRYSVO administration (i.e., the index date), to assess the individual's demographic and clinical characteristics, and to rule out prevalent GBS cases. Two complementary approaches will be used to address the study objectives and evaluate the risk of GBS among individuals who receive ABRYSVO: RCA and SCRI. A patient-level case-centered analysis will also be conducted to better understand the severity and risk factors associated with all GBS cases identified in the analytic populations from two databases: CMS Medicare administrative databases and PharMetrics Plus database. The CMS Medicare database covers individuals aged 65 and older, while PharMetrics Plus data will cover individuals aged 60-64 years. Together, these two data sources will provide age representation for the currently approved indication for ABRYSVO for older adults. Given the more limited age range for commercially insured adults 60-64 years, analyses for this age group will be primarily descriptive based on available sample size.

9.1.1. The Study Design of RCA Methodology

For signal detection[9], an RCA will be conducted during the 2024/2025 RSV season, built upon cumulative data from the 2023/2024 RSV season, by periodically evaluating the near real-time incidence of GBS following vaccination as the data become available on a monthly basis. The observed number of GBS cases in the ABRYSVO-vaccinated population will be compared to an expected number of GBS cases based on an estimated background rate of GBS from a comparable population (Section 9.7.3.1). A group sequential testing approach will be used for repeated testing of continuously accumulating data to minimize false positive signals. The detailed study design and study periods of the RCA analysis are described in Section 9.1.1.1. The background rate of GBS will be estimated from individuals who received seasonal influenza vaccines using historical data across the 2022 and 2023 influenza seasons. The historical influenza-vaccinated population is expected to be more similar to ABRYSVO-vaccinated individuals in terms of demographics, clinical characteristics, and

[9] The RCA is a hypothesis-testing standard signal detection study with parameters in line with established rule-out risks. In our study, it is set up to provide early safety signals but will not be used to determine association between the exposure and outcome.

health-seeking behavior (Section 9.7.3.1). The RCA will allow timely safety signal detection of GBS risk following vaccination with ABRYSVO.

The indexing period for the RCA will be from 31 May 2023 (e.g., first date of ABRYSVO vaccination) to 10 January 2025 (e.g., last date of ABRYSVO vaccination). For the RCA, a primary risk interval of 1-21 days following the index date will be evaluated to allow sufficient time for data completion and to prioritize more timely analysis during the season. Currently, >90% GBS events that occurred after RSV vaccinations were within 21 days of vaccination.(13) A secondary risk interval of 1 – 42 days after the index date will also be assessed in the RCA.

The overall RCA study period will span the baseline period, indexing period, and follow-up period, i.e., from 31 May 2022 to 21 February 2025.

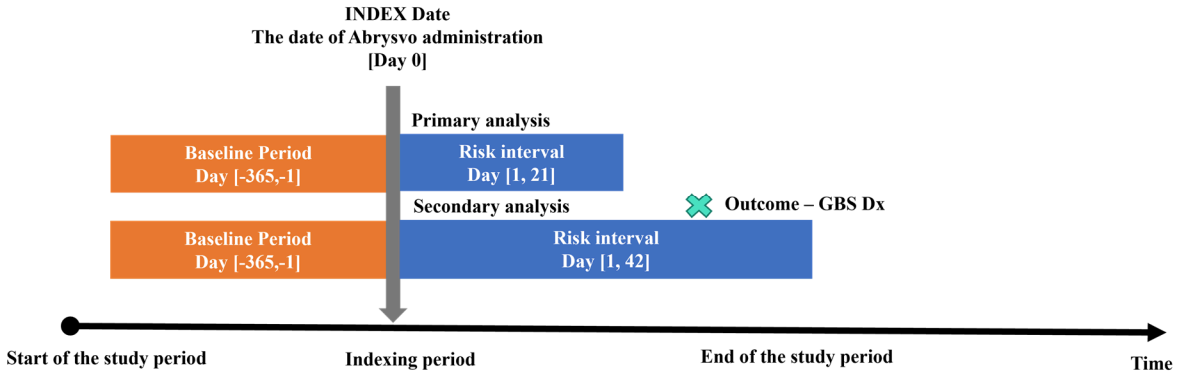
9.1.1.1. The Study Periods of RCA Methodology

The RCA analysis will be launched in the 2024/2025 RSV season, with cumulative data from the 2023/2024 RSV season. An early vaccination cutoff will be used in the RCA to balance the timeliness of in-season surveillance and the more complete capture of data to enhance results validity. The key study periods of the RCA analysis are described below:

- **Study Period:** 31 May 2022 – 21 February 2025
- **Indexing period (e.g., vaccination period):** 31 May 2023 – 10 January 2025
- **Index Date:** The date of ABRYSVO administration
- **Baseline period:** 365 days prior to the index date
- **Follow-up period:**
    - **Post-vaccination risk interval:** 1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively.

Figure 1 shows the study design and study period of the RCA analysis.

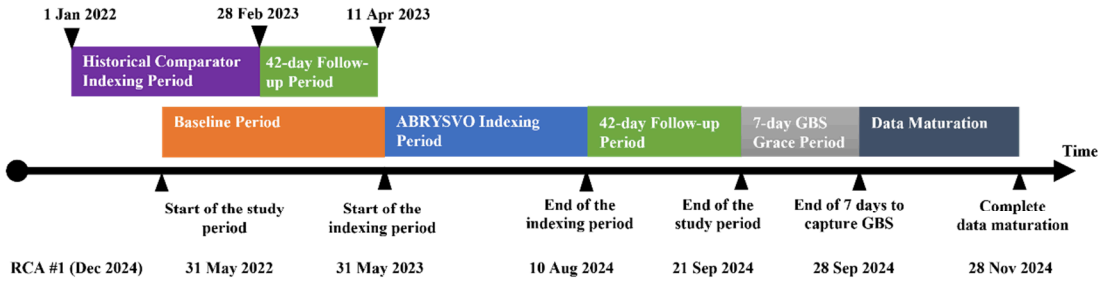
Figure 1. Study design and key study periods of the rapid cycle analysis



Abbreviations: Dx, diagnosis; GBS, Guillain-Barre Syndrome.

Figure 2 shows the study periods of the monthly RCA analysis.

Figure 2. The study periods of rapid cycle analysis during the 2023/2024 and 2024/2025 RSV seasons



RCA #1 (Dec 2024)	31 May 2022	31 May 2023	10 Aug 2024	21 Sep 2024	28 Sep 2024	28 Nov 2024
RCA #2 (Jan 2025)	31 May 2022	31 May 2023	10 Sep 2024	22 Oct 2024	29 Oct 2024	29 Dec 2025
RCA #3 (Feb 2025)	31 May 2022	31 May 2023	10 Oct 2024	21 Nov 2024	28 Nov 2024	28 Jan 2025
RCA #4 (Mar 2025)	31 May 2022	31 May 2023	10 Nov 2024	22 Dec 2024	29 Dec 2024	1 Mar 2025
RCA #5 (Apr 2025)	31 May 2022	31 May 2023	10 Dec 2024	21 Jan 2025	28 Jan 2025	28 Mar 2025
RCA #6 (May 2025)	31 May 2022	31 May 2023	10 Jan 2025	21 Feb 2025	28 Feb 2025	28 Apr 2025

Abbreviations: GBS, Guillain-Barre Syndrome; RCA, rapid cycle analysis.

Note: The data maturation period allows for claims in the CMS Medicare FFS administrative database to be completed in the system. Historically, approximately 90% of IP and OP claims are submitted to the CMS within 2 months after service date. (14, 15)

Note: The population for the RCA #1 was included in Interim report 2; the results of the RCA will be included in Interim report 3.

9.1.2. The Study Design of SCRI Methodology

In addition, as a comparative analysis, SCRI analyses will be conducted for the 2023/2024 and 2024/2025 RSV seasons, both separately and as a pooled analysis, to provide more conclusive evidence for the association between vaccination and GBS. The SCRI will assess the risk of GBS following ABRYSVO vaccination by comparing the incidence rate of GBS during the pre-specified post-vaccination risk interval to the pre-specified post-vaccination

control interval within the vaccinated individuals. The SCRI design effectively controls for time-invariant confounding. The detailed study design and study periods of the SCRI analysis are described in Section 9.1.2.1. A final pooled analysis using individual-level data from 2 RSV seasons (2023/2024 and 2024/2025) will be conducted which will allow for a more comprehensive and accurate assessment of the association between ABRYSVO and GBS with a larger sample size. The comparative SCRI analysis will assess the risk of GBS following vaccination as an in-depth analysis that is hypothesis-driven and well-controlled for time-invariant confounders.

The indexing period for the 2023/2024 RSV season SCRI analysis will be from 31 May 2023, starting from the date of ABRYSVO's approval, to 29 February 2024. The indexing period for the 2024/2025 RSV season SCRI analysis will be from 31 May 2024 to 28 February 2025. An early vaccination cutoff in February will be used as preliminary count data from the CMS for the 2023/2024 season indicate that ABRYSVO vaccinations peaked in October, and >90% of RSV vaccinations for the season are expected to have been administered by the end of February; this is also consistent with historical data for other seasonal vaccines such as influenza vaccines where >95% vaccinations of the season were administered by the end of February.(16, 17) Furthermore, the February end date allows sufficient time for completion of the claims in the CMS Medicare database before analysis begins (e.g., >90% IP and OP claim completeness within 2 months after service date). Previous studies have also shown that an early cutoff of the indexing period when assessing risk of GBS following influenza vaccination did not impact the results.(18) The indexing period for the combined two season analysis will be from 31 May 2023 following ABRYSVO's approval to 28 February 2025.The follow-up period for the SCRI analysis will consist of the post-vaccination risk interval of the individuals received ABRYSVO, defined as 1-21 and 1-42 days after the index date, as the primary and secondary risk intervals, respectively. These windows are consistent with the onset of GBS cases during the ABRYSVO clinical studies and also with previous vaccine safety studies that have evaluated the risk of GBS.(8, 12, 18, 19) The follow-up will also include the post-vaccination control interval, defined as 43-84 days after the index date. The total follow-up period of each patient will be 84 days for the SCRI analysis.

The overall SCRI study period will span the baseline period, indexing period, and follow-up period, i.e., from 31 May 2022 to 23 May 2025.

9.1.2.1. The Study Periods of SCRI Methodology

The SCRI analysis spans the 2023/2024 and 2024/2025 RSV seasons, and the follow-up period consists of the pre-specified post-vaccination risk and control intervals. The key study periods of the SCRI analysis are described below:

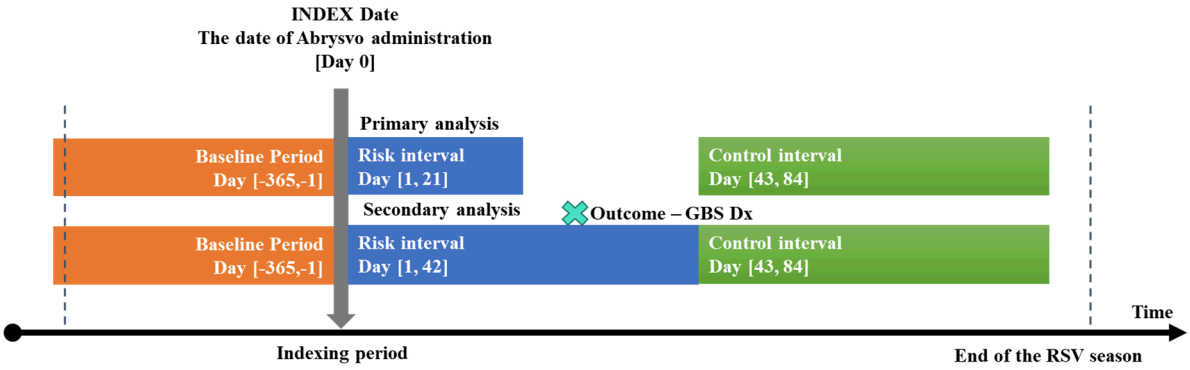
- **Study Periods:**
    - **2023/2024 Study Period:** 31 May 2022 – 23 May 2024
        - **Indexing period:** 31 May 2023 – 29 February 2024

- **2024/2025 Study Period:** 31 May 2023 – 23 May 2025
  - **Indexing period:** 31 May 2024 – 28 February 2025
- **Combined two season study period:** 31 May 2022 – 23 May 2025
  - **Indexing period:** 31 May 2023 – 28 February 2025

- Note: As detailed in Section 9.1.2, the indexing period will end in February as >90% of RSV vaccinations are anticipated to be administered by that time, as a trade-off to balance timely analyses and more complete data capture.
- **Index Date:** The date of ABRYSVO administration
- **Baseline period:** 365 days prior to the index date
- **Follow-up period:**
  - **Post-vaccination risk period:** 1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively. Days 22-42 after the primary 1-21 days risk interval will be considered a washout period and will not be included in the analyses to avoid any carryover effects.
  - **Post-vaccination control period:** 43-84 days after the index date

Figure 3 shows the study design and key study periods of the SCRI analysis.

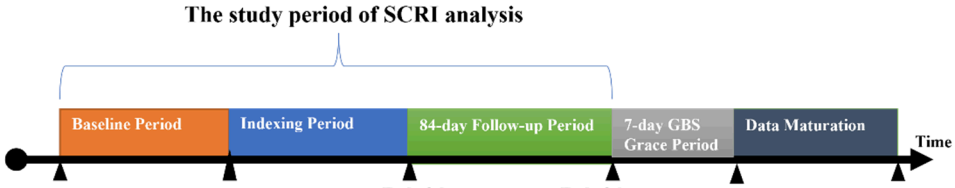
Figure 3. Study design of the self-controlled risk interval analysis



Abbreviations: Dx, diagnosis; GBS, Guillain-Barre syndrome; RSV, Respiratory Syncytial Virus.

Figure 4 shows the study period of SCRI analysis in relation to the RSV seasons.

Figure 4. The study period of self-controlled risk interval analysis during 2023/2024 and 2024/2025 RSV seasons



2023/2024 season analysis	31 May 2022	31 May 2023	29 Feb 2024	23 May 2024	30 May 2024	30 Jul 2024
2024/2025 season analysis	31 May 2023	31 May 2024	28 Feb 2025	23 May 2025	30 May 2025	30 Jul 2025
Analysis of both seasons	31 May 2022	31 May 2023	28 Feb 2025	23 May 2025	30 May 2025	30 Jul 2025

Abbreviations: GBS, Guillain-Barre Syndrome; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.

Note: The data maturation period allows for claims in the CMS Medicare FFS administrative database to be completed in the system. Historically, approximately 90% of Medicare IP and OP claims were submitted to the CMS within 2 months after service date. (14, 15)

9.1.3. The Descriptive Analysis of Individuals Aged 60-64 Years Enrolled in PharMetrics Plus Database

Given the more limited age range for commercially insured adults 60-64 years, analyses for this age group will be primarily descriptive based on available sample size. The inferential analysis, SCRI, may be considered contingent on sample size.

For the descriptive analyses of GBS incidence following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database, the indexing period of the 2023/2024 RSV period for evaluating exposure to ABRYSVO will be from 31 May 2023 to 29 February 2024. For the 2024/2025 RSV season, the indexing period will be from 31 May 2024 to 28 February 2025. For the combined RSV season analysis, the indexing period will be from 31 May 2023 to 28 February 2025.

The overall study period will span the baseline period, indexing period, and follow-up period, i.e., from 31 May 2022 to 11 April 2025.The detailed study design and study periods of the SCRI analysis are described in Section 9.1.3.1.

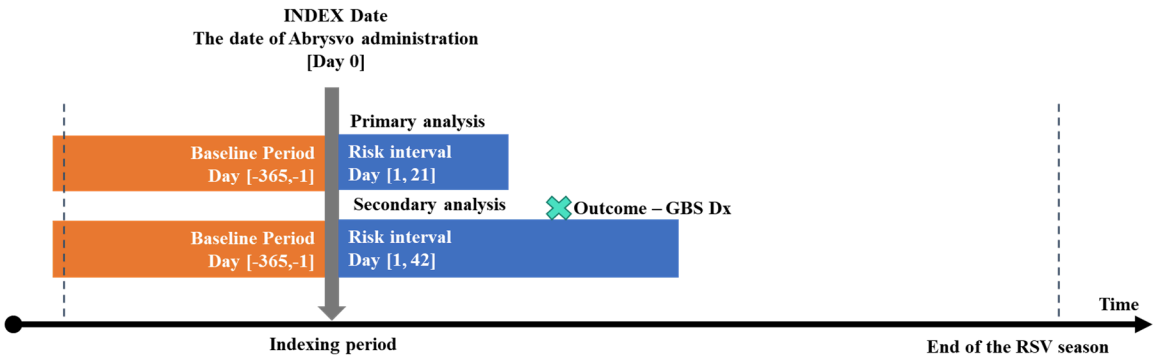
9.1.3.1. The Study Periods of Descriptive Analysis of Individuals Aged 60-64 Years Enrolled in PharMetrics Plus Database

The descriptive analysis spans the 2023/2024 and 2024/2025 RSV seasons, and the follow-up period consists of the pre-specified post-vaccination risk intervals. The key study periods of the descriptive analysis are described below:

- **Study Periods:**
  - **2023/2024 Study Period:** 31 May 2022 – 11 April 2024
    - **Indexing period:** 31 May 2023 – 29 February 2024
  - **2024/2025 Study Period:** 31 May 2023 – 11 April 2025
    - **Indexing period:** 31 May 2024 – 28 February 2025
  - **Combined two season study period:** 31 May 2022 – 11 April 2025
    - **Indexing period:** 31 May 2023 – 28 February 2025
- **Index Date:** The date of ABRYSVO administration
- **Baseline period:** 365 days prior to the index date
- **Follow-up period:**
  - **Post-vaccination risk period:** 1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively.

Figure 5 shows the study design and key study periods of the descriptive analysis.

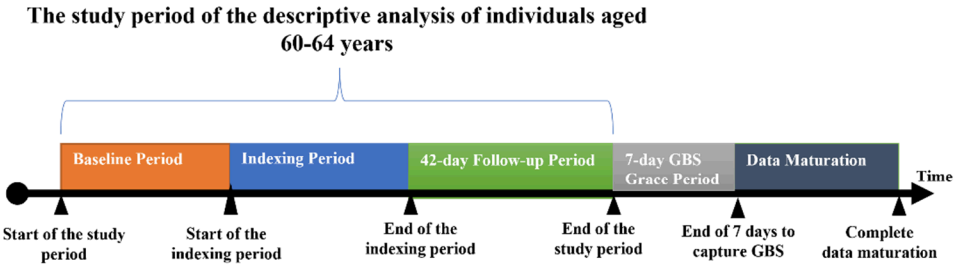
Figure 5. Study design of the descriptive analysis of individuals aged 60-64 years



Abbreviations: Dx, diagnosis; GBS, Guillain-Barre syndrome; RSV, Respiratory Syncytial Virus.

Figure 6 shows the study period of the descriptive analysis of individuals aged 60-64 years in relation to the RSV seasons.

Figure 6. The study period of the descriptive analysis of individuals aged 60-64 years during 2023/2024 and 2024/2025 RSV seasons



2023/2024 season analysis	31 May 2022	31 May 2023	29 Feb 2024	11 Apr 2024	18 Apr 2024	01 Sept 2024
2024/2025 season analysis	31 May 2023	31 May 2024	28 Feb 2025	11 Apr 2025	18 Apr 2025	01 Oct 2025
Analysis of both seasons	31 May 2022	31 May 2023	28 Feb 2025	11 Apr 2025	18 Apr 2025	01 Oct 2025

Abbreviations: GBS, Guillain-Barre syndrome; RSV, Respiratory Syncytial Virus.

Note: The PharMetrics Plus database contains fully-adjudicated claims with a data lag of approximately six months.(20) The indexing period for the descriptive analysis has accounted for the lag.

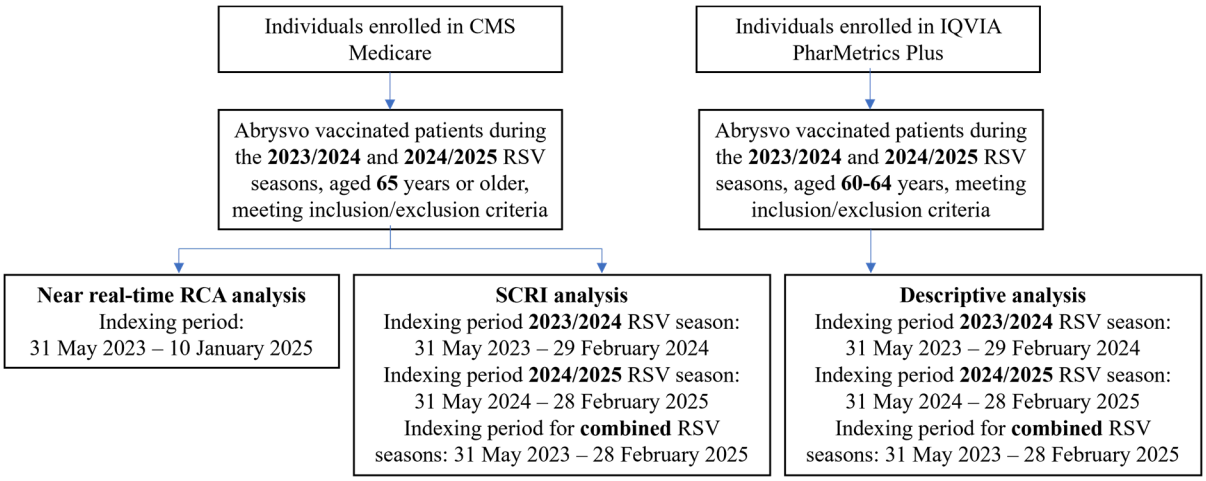
9.1.4. Study Population

The study population will include CMS Medicare FFS beneficiaries aged 65 years of age or older and PharMetrics Plus enrollees aged 60-64 years who receive one dose of ABRYSVO vaccine administration during the surveillance period and meet all other eligibility criteria (Section 9.2.1.1 and 9.2.1.2).

The SCRI analysis will be conducted in the study populations identified in both the 2023/2024 and 2024/2025 RSV seasons; the RCA analysis will be launched in the 2024/2025 RSV season, with cumulative data from the 2023/2024 RSV season (Figure 7).

The descriptive analysis for commercially insured adults aged 60-64 years will be conducted in the study populations identified in both the 2023/2024 and 2024/2025 RSV seasons (Figure 7).

Figure 7. The overall study design flowchart and population selection



Abbreviations: CMS, Centers for Medicare and Medicaid Services; RCA, rapid cycle analysis; RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.

9.2. Setting

The source population is U.S. Medicare beneficiaries available in the CMS Medicare FFS administrative database. This database includes Medicare Parts A, B, and D data, covering inpatient and outpatient encounters and drug/vaccine prescriptions. The source population also includes individuals aged 60-64 years in the PharMetrics Plus database, which provides comprehensive claims data on healthcare utilization, including inpatient and outpatient encounters, and drug/vaccine prescriptions.

Individuals aged 65 years of age or older in the CMS Medicare data and individuals aged 60-64 years in PharMetrics Plus database who receive ABRYSVO vaccine (i.e., exposure) who meet the eligibility criteria described in Sections 9.2.1.1 and 9.2.1.2 will be included in the study.

The ABRYSVO vaccine record will be identified using CPT (Current Procedural Terminology), HCPCS (Healthcare Common Procedure Coding System), and NDC (National Drug Code) codes. The details of the exposure and other inclusion and exclusion criteria are defined in Section 9.3.

9.2.1. Inclusion and Exclusion Criteria

9.2.1.1. Inclusion Criteria

Individuals in CMS Medicare databases must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during the respective indexing period:
    a. RCA analysis:
        i. 2023/2024 and 2024/2025 RSV seasons RCA analysis: 31 May 2023 to 10 January 2025 (Section 9.3.1);
    b. SCRI analysis:
        i. 2023/2024 RSV season SCRI analysis: 31 May 2023 to 29 February 2024;
        ii. 2024/2025 RSV season SCRI analysis: 31 May 2024 to 28 February 2025;
        iii. Combined two seasons SCRI analysis: 31 May 2023 to 28 February 2025;
2. At least 65 years of age on the index date (Section 9.3.3);
3. Medicare beneficiaries who aged into Medicare (Section 9.3.3);
    - Note: Beneficiaries who qualify due to disability differ from beneficiaries who qualify due to age in several ways, including their demographic, socioeconomic, and health status profiles. To reduce potential confounding from this specific frail Medicare population that could have a different association between vaccination and GBS, they are not included in the study population.
4. At least 12 months of continuous enrollment in Medicare Parts A and B prior to the index date (i.e., the baseline period) (Section 9.3.3);
5. A minimum period of continuous enrollment in Medicare Part D (e.g., 3 months) prior to the index date;
    - Note: this requirement is to balance subject attrition and adequate capture of recent prescriptions prior to vaccination. The minimum period of continuous enrollment in Medicare Part D will be specified in the SAP after feasibility assessment.

6. No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period (Section 9.3.1).

Individuals in the PharMetrics Plus database must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during the respective indexing period (Section 9.3.1):
    a. Indexing period for descriptive analysis:
        i. 2023/2024 RSV season analysis: 31 May 2023 to 29 February 2024;
        ii. 2024/2025 RSV season analysis: 31 May 2024 to 28 February 2025;
        iii. Combined two seasons analysis: 31 May 2023 to 28 February 2025;
2. Aged 60-64 years on the index date (Section 9.3.3);
3. At least 12 months of continuous enrollment with medical and pharmacy benefits in PharMetrics Plus database prior to the index date (i.e., the baseline period) (Section 9.3.3);
4. No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period (Section 9.3.1).

9.2.1.2. Exclusion Criteria

Individuals in CMS Medicare databases and the PharMetrics Plus database meeting any of the following criteria will not be included in the study:

1. Individuals without sex information (Section 9.3.3);
2. Individuals with a GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date (Section 9.3.2).

9.3. Variables

Exposures, outcomes, and covariates will be identified within relevant care settings in the claims data. The care setting of the IP and OP/PB settings used in this study are defined in Section 9.4.

9.3.1. Exposure

The exposure of interest is ABRYSVO vaccination, defined as an individual's first administration of the ABRYSVO vaccine during the indexing period (Section 9.1.1), as identified by a CPT code, HCPCS code or NDC during the indexing period. (21)

The study spans two RSV seasons, 2023/2024 and 2024/2025, and multiple vaccinations are not anticipated as ABRYSVO is currently not approved for re-vaccination and evidence

suggests that ABRYSVO provides protection for at least two RSV seasons that overlap with the study period. To deduplicate exposure occurrences, multiple vaccine records containing the same ABRYSVO vaccine product for a unique patient ID, occurring on the same day or within three days will be deduplicated. If the multiple vaccine records are more than three days apart for a unique patient ID, it will be flagged as off-label use and reported separately. The date of the first occurrence of the ABRYSVO vaccination will be defined as the index date.

The example code lists for ABRYSVO vaccine and RSV vaccines from a manufacturer other than Pfizer is listed in LIST OF CODES FOR RSV VACCINES. The list of RSV vaccine codes in the example code lists will be reviewed and updated periodically during the entire study period.

9.3.2. Outcomes

The outcome of interest is GBS diagnosis, which will be identified from IP and OP claims using ICD-10-CM code G 61.0.

An incident GBS case will be defined as the first occurrence of a primary discharge diagnosis of GBS in the IP setting post-vaccination. The date of the case's onset will be defined as the date of hospitalization unless there is a claim with a GBS diagnosis in another medical setting (e.g., OP) in the prior 7 days. In that case, the earlier claim, irrespective of healthcare setting, will represent the date of onset. This claims-based algorithm in Medicare data has a PPV of 71.2% – 78.6% when validated against medical records using the Brighton criteria and has been used to reliably identify GBS cases among Medicare beneficiaries.(9, 22, 23) In a recent FDA analysis evaluating GBS risk following RSV vaccination in the Medicare data, the algorithm for GBS had a PPV of 62.3% in the post-vaccination risk interval of 1-42 days and a PPV of 81.8% in the post-vaccination control interval of 43-90 days, based on chart review.(24)

The risk window of 42 days post-vaccination is generally recommended by the Brighton Collaboration GBS case definition. (19) Within the ABRYSVO clinical and surveillance studies, over 90% of GBS events have been found to occur within 21 days of vaccination.(13) In this study, for the RCA, the primary risk interval is defined as 1–- 21 days post-vaccination to prioritize timely analysis; a secondary risk interval of 1–- 42 days post-vaccination will also be analyzed. For the SCRI, the primary post-vaccination risk interval is defined as 1 – 21 days post-vaccination and the secondary post-vaccination risk interval is defined as 1 – 42 days post-vaccination. The control interval for the SCRI analysis is defined as 43 – 84 days post-vaccination. For the SCRI analysis, GBS diagnosis will be identified during the risk and the control intervals to compare the risk of GBS occurrence within the two intervals.

9.3.3. Patient Characteristics

Patient characteristics, including demographics, clinical characteristics, medications/vaccinations, and healthcare resource utilization will be captured during the baseline period and/or follow-up period, as applicable. Variables that will be assessed may

include, but are not limited to, those listed below. The final list of covariates and codes to identify those covariates will be defined in the SAP based on feasibility and availability.

Demographics:

- Age
- Sex
- Race/ethnicity
- Geographic region in the U.S.

ABRYSVO vaccination characteristics:

- Month and year of vaccination
- Care setting of vaccination

Clinical characteristics:

- History of anaphylaxis
- Previous anaphylaxis of vaccine component
- Hospitalizations in the baseline period and during the follow-up period
- Admission into nursing home/Skilled Nursing Facility (SNF) in the baseline period and during the follow-up period
- Infections in the baseline period and during the follow-up period
    - Upper or lower respiratory tract infections (including diphtheria, whooping cough, streptococcal sore throat and scarlet fever, varicella with pneumonia, RSV, COVID-19, acute sinusitis, acute tonsilitis, acute bronchitis, influenza, etc.)
    - Gastrointestinal infections (including cholera, typhoid and paratyphoid fevers, shigellosis, amebic nondysenteric colitis, etc.)
    - Unspecified viral infection
    - Diarrhea
    - Fever
    - Campylobacter enteritis
    - Cytomegalovirus (CMV)
    - Epstein-Barr Virus (EBV)
    - Hepatitis E Virus (HEV)
    - Zika virus
- Frailty index
- Charlson Comorbidity Index (CCI)
- Smoking status
- Body Mass Index (BMI)
- Immunocompromised status
- Selected comorbidities
    - Asthma
    - Blood disorders
    - Chronic lung disease

  - Diabetes
  - Heart disease
  - Kidney disease
  - Liver disorders
  - Neurological conditions
  - Malignant neoplasms
- Surgery (i.e., anesthesia or conscious sedation) in the baseline period and during the follow-up period
- Trauma in the baseline period and during the follow-up period
- Prior bone marrow transplant
- Immunizations on the index date, in the baseline period, in close proximity (e.g., within 30 days) to ABRYSVO exposure, and during the follow-up period
  - Seasonal influenza vaccine
  - COVID-19
  - RSV (other than Abrysvo)
  - Tetanus and Diphtheria (Td) and Tetanus, Diphtheria, Pertussis (Tdap)
  - Chickenpox (varicella)
  - Shingles (herpes zoster recombinant and/or live)
  - Human Papillomavirus (HPV)
  - Pneumococcal conjugate
  - Pneumococcal polysaccharide
  - Hepatitis A
  - Hepatitis B
  - Meningococcal ACWY Vaccine (MenACWY) and Meningococcal B Vaccine (MenB)
  - Haemophilus influenzae type b
  - Combined[10]
- Medication use in the baseline period and during the follow-up period including, but not limited to:
  - TNF-alpha antagonists
  - Immune checkpoint inhibitors
  - Immunosuppressant therapies
  - Isotretinoin

9.4. Data Sources

9.4.1. CMS Medicare Administrative Database

The study will use the CMS Medicare administrative database with monthly data refreshes that include Medicare Parts A, B and D. The study will be restricted to enrollees with FFS. The Medicare claims database includes well-defined longitudinal data that captures healthcare service utilization for millions of enrollees across multiple care settings. Medicare Part A captures the inpatient setting, including critical access hospitals and skilled nursing facilities; approximately 90% of inpatient claims are submitted in 2 months after a healthcare

[10] Presence of any concurrent vaccination.

encounter. (18) Medicare Part B covers doctors' services and outpatient care, including outpatient emergency department and outpatient non-emergency department, as well as professional services non-laboratory and laboratory. Medicare Part D covers the pharmacy setting. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. The monthly data consists of a mixture of pre-adjudicated and adjudicated claims; prior research shows that the diagnosis codes rarely change (<0.5%) after adjudication. (12, 14, 15) The use of adjudicated and pre-adjudicated claims data in this study enables near real-time assessment of a potential safety signal.

In this study, the variables will be identified within the relevant care settings. The IP setting represents hospital inpatient acute facility claims, which provide information on the care and services received by patients during the entire duration of inpatient care. These have more accurate diagnosis coding compared to professional claims, as provider facilities are reimbursed based on the types of diagnosis coded, which reflect the level of treatment required. The OP/PB setting represents all outpatient and professional services claims with non-laboratory places of service and captures the broad spectrum of outpatient care regardless of care setting or provider type. Claims with laboratory places of service are excluded as they often include “rule-out-diagnoses” that may not reflect true existing or underlying conditions present in patients.

The demographics of the Medicare FFS population and the coding system used in CMS Medicare data are substantial topics that encompass the broad characteristics of Medicare beneficiaries and the complex system for coding healthcare services, respectively. Below is an overview of both:

The Medicare FFS program covers a diverse population of older adults and some younger beneficiaries with disabilities. The majority of Medicare beneficiaries are aged 65 years of age or older, reflecting Medicare’s role as a health insurance program for older adults. The distribution between male and female beneficiaries in the Medicare FFS population tends to reflect that of the older adult population in the U.S., with a higher proportion of females, especially among the oldest age groups.

Medicare beneficiaries come from diverse socioeconomic backgrounds, but the program plays a critical role for lower-income individuals who might otherwise be unable to afford health insurance. The health status of Medicare FFS beneficiaries vary widely, from healthy individuals to those with multiple chronic conditions and serious disabilities. The program covers many individuals with high healthcare needs and expenditures. Medicare FFS beneficiaries are located across the United States, including both urban and rural areas, with distribution patterns reflecting the broader population distribution.

Medicare data utilizes several coding systems to document diagnoses, procedures, and equipment used in the care of beneficiaries. These include ICD-10-CM, used for diagnosis coding in all healthcare settings; ICD-10-PCS (Procedure Coding System), used for inpatient hospital procedure coding; CPT, used in billing process for medical procedures in medical, surgical, and diagnostic services in OP/PB services; HCPCS, also used for medical procedures, such as ambulance services and durable medical equipment; and NDC, used for a

prescription drug billing. The use of these coding systems ensures that Medicare billing is standardized, allowing for the efficient processing of claims and the collection of data for analysis and policy development.

9.4.2. IQVIA PharMetrics Plus Commercial Claims Database

The PharMetrics Plus database is one of the largest US health insurance claims databases comprised of fully adjudicated medical and pharmacy claims with approximately 3.1 million annual enrollees aged 60 to 64 years. Data contributors are largely commercial health plans, with an approximate 6-month data lag due to claims adjudication. PharMetrics Plus has diverse representation of geography, employers, payers, providers, and therapy areas, therefore the database is representative of the commercially insured US national population for individuals under 65 years of age. In the post-launch and in-market phase, PharMetrics Plus has been utilized in providing robust insights in areas such as comparative effectiveness, medication adherence, patient cost analyses and also aids in pharmacovigilance and safety by tracking and analyzing the adverse effects of medications and vaccines. (20)

The comprehensive patient insights provided by PharMetrics Plus are driven by several key attributes. For patient demographics, it includes the year of birth, gender, ZIP3 (the first three digits of the ZIP code), state, enrollment dates, and payer/plan type. PharMetrics Plus also details primary care and specialty visits, capturing event dates, diagnosis codes, ordered laboratory tests, procedure codes, and provider specialties, providing understanding of the nature of healthcare interactions of patients. Additionally, the information of medication use can be captured with data on fill and refill dates, retail, mail order, specialty medications, formulary status, status medications, quantity and days supplied, providing a comprehensive view of medication adherence and usage patterns.

Furthermore, the data offers insights into hospital admissions and discharges, including admission dates, inpatient length of stay, discharge status, diagnosis codes, inpatient procedures, ER visits, and provider specialties, enabling the assessment of healthcare utilization and patient outcomes. Similarly, for outpatient medication and vaccine administration, PharMetrics Plus records the date of administration, diagnosis codes, service units, procedure codes and provider specialties, ensuring comprehensive tracking of outpatient care.

9.5. Study Size

Medicare

All eligible Medicare beneficiaries aged 65 years of age or older who receive ABRYSVO during the surveillance period will be included. There were approximately 1,155,000 individuals vaccinated with ABRYSVO through February 2024; from prior experience, with approximately 15% attrition due to the requirement of continuous enrollment in Medicare Parts A, B and D, ~1 million individuals are expected to be eligible for the 2023/2024 season analysis. Assuming a similar uptake for the 2024/2025 season, for the pooled analysis, a sample size of ~2 million ABRYSVO exposures are anticipated by the end of study period.

Table 1 outlines the sample size calculations required for a conditional Poisson regression using the SCRI design, across different Incidence Rate Ratios (IRR). To detect a lower IRR, the total number of GBS events needed increases, as does the number of vaccinated individuals required for both risk intervals. Specifically, to detect an IRR of 5.0, 15 GBS events are needed, with 1,153,846 and 566,038 vaccinated individuals for analysis in the 21-day and 42-day post-vaccination risk intervals, respectively. Conversely, to detect an IRR of 2.0, 69 GBS events are needed, with significantly higher requirements of 8,846,154 and 4,339,623 individuals for the 21-day and 42-day post-vaccination risk intervals, respectively. Based on an expected background rate of 4.6 per 100,000 person-years for incident GBS in the Medicare population aged 65 years of age or older (25) and estimated uptake of ABRYSVO in the Medicare FFS dataset from 2023/2024 RSV season, the study is anticipated to be able to detect a high risk of GBS (5.0- fold or lower) with 80% power and an alpha level of 0.05 during a 21- or 42-day risk interval following vaccinations in each RSV season. Pooled analysis combing data from 2 RSV seasons is anticipated to have 80% power to detect a modest risk of GBS (e.g., 3.0- to 4.0-fold), depending on the length of the risk interval. Pfizer has an ongoing PMR PASS (protocol # C3671031) spanning 4.5 RSV seasons (or more) aiming to detect a 2-fold increased risk of GBS following ABRYSVO vaccination using the fully adjudicated CMS Medicare claims. The current PASS described in this protocol (protocol # C3671054) is aimed to generate rapid safety evidence to help rule out a modest or high risk of GBS until the results of the PMR PASS (protocol # C3671031) are available.

Table 1. Sample Size Calculations for the Conditional Poisson Regression Using the SCRI Design

IRR	Total number of GBS events needed	Number of events expected in control interval	Number of vaccinated individuals needed for 21-day period (N)	Number of vaccinated individuals needed for 42-day period (N)
5.0	15	3	1,153,846	566,038
4.5	17	4	1,538,462	754,717
4.0	20	4	1,538,462	754,717
3.5	23	6	2,307,692	1,132,075
3.0	29	8	3,076,923	1,509,434
2.5	41	12	4,615,385	2,264,151
2.0	69	23	8,846,154	4,339,623

Notes: Sample size calculations for the SCRI design were performed according to the method by Musonda et al.(26) The calculations are based on assuming a two-sided α=0.05, a power of 80%, and a risk interval of 21 and a control interval of 21 days. Calculations were also performed using a 42-day risk interval and a 42-day control interval for secondary analyses. These calculations are based on an equal length of the control and risk interval and provide a conservative estimate of sample size as compared to calculations based on variable lengths of the control and risk interval.

PharMetrics Plus

For the PharMetrics Plus analysis, the primary study population will consist of adults 60-64 years of age enrolled in healthcare plans captured in the PharMetrics Plus database without a prior history of GBS as assessed during a 12-month baseline period.

Based on medical and pharmacy claims through December 31, 2023, approximately 46,000 individuals between 60 and 64 years of age received ABRYSVO in the PharMetrics Plus database; 36,000 had one year of continuous medical and pharmacy benefits enrollment prior to ABRYSVO receipt. The PharMetrics Plus analysis will be descriptive in nature; the inferential analysis, SCRI, may be considered contingent on sample size.

9.6. Data Management

Datasets will be stored according to the third-party data vendor's procedures, and analytic programs will be stored according to IQVIA procedures with access restricted to study personnel. IQVIA confidentiality agreements are signed by all employees and include data protection and strict prohibitions on reidentification attempts. SAS® software (SAS Institute Inc., Cary, North Carolina, United States) or other appropriate analytical software will be used to access the raw data, manage the analytic datasets, and conduct data analyses. According to CMS Medicare reporting rules, values below 11 will be suppressed for any counts presented in the report.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of outcome definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Data Lag

In the analysis of CMS Medicare data, the approach to account for data lags in the RCA and SCRI is to delay the analysis for at least 60 days to allow for at least 90% capture of data for post-vaccination follow-up period. Prior research suggests that ≥90% of IP and OP claims were submitted to the CMS within 2 months after service date. (14, 15) While imposing a lag in the analysis negatively impacts the timeliness of safety assessment, it allows the data to be more complete and thus increases the validity of results. In a non-pandemic setting where the initial uptake for the RSV vaccines is modest, the trade-off between timeliness and validity is deemed acceptable, and a similar approach has been used in prior safety monitoring for Shingrix after the vaccine approval.(27) Data lags will be assessed during the interim reports and a lag longer than 60 days (e.g., 90 days) may be considered for the final analysis, as necessary and feasible, to accrue the most stable data.

The PharMetrics Plus data has a data lag of approximately 6 months due to claims adjudication and completeness, making it unsuitable for the monthly sequential monitoring component (i.e., RCA) of the study. However, it will effectively contribute to the descriptive analysis (SCRI may be considered contingent on sufficient sample size), to be conducted towards the end of each RSV season and at the final two-season pooled analysis. This

analytic arrangement accounts for the data lag and still generates timely safety data for GBS in individuals aged 60-64 years following exposure to ABRYSVO.

9.7.2. Description of ABRYSVO Recipients

Covariates will be assessed among the study population aimed for SCRI analysis, RCA analysis and the descriptive analysis for individuals aged 60-64 (Section 9.1.4). Patient demographic and clinical characteristics including age on index, gender, race, geographic region, concurrent immunizations, prior infections, and selected comorbidities will be reported. Demographic variables will be assessed on the index date or during the baseline period, as described in Section 9.3.3. If multiple records exist, the record closest to the index date will be used.

Continuous variables will be summarized using mean ± SD, median, and interquartile range. Categorical variables will be summarized using counts and proportions. 95% CIs will be provided where applicable.

9.7.3. The Statistical Analysis for the RCA

In order to conduct near real-time surveillance to monitor the risk of GBS following RSV vaccination, a group sequential testing approach will be used to compare the observed rates of GBS following vaccination to an expected incidence rate of GBS (referred to as the background rate; Section 9.7.3.1).(27, 28) Each month, an adjusted RR of GBS will be estimated to conduct an exact sequential Poisson-based likelihood ratio test using unifying family group sequential methods, previously described by Nelson et al. (27, 28) This methodology is suited for continuously accumulating data, enabling timely monitoring and decision-making regarding vaccine safety concerns.

The group sequential testing will be used to conduct sequential tests with cumulative monthly data, with the first monthly analysis starting December 2024 when >90% completeness in follow-up data for ABRYSVO vaccinations through 10 September 2024 are expected. The first RCA look will include cumulative data from the 2023/2024 RSV season and initial uptake data from the 2024/2025 season. A total of 6 monthly RCA looks are planned.

The RR of GBS will be the target parameter, defined as the ratio of the observed GBS rate and the expected GBS rate in the ABRYSVO population. We will conduct one-sided tests where the null hypothesis is that the observed rate of GBS in the ABRYSVO cohort is no greater than 2 times the comparator rate. The alternative hypothesis is that the observed rate in the ABRYSVO cohort is greater than 2 times than the comparator rate:

H_0: RR ≤ 2

H_a: RR > 2

In previous literature, a pre-specified the test margin with an overall alpha of 1% was used to obtain a null hypothesis of "RR ≤2.5" for assessing the risk of GBS following COVID-19 vaccination to avoid minimal risk increases that were unlikely to be clinically relevant.(29) In this study, the RR and test margin are more conservative to declare a safety signal.

The expected number of events under the null hypothesis will be used as the upper limit on number of tests to be conducted (i.e., the pre-specified surveillance length). Sequential testing will continue until a signal is observed (or the pre-specified surveillance length is reached), after which formal sequential analyses will be stopped and descriptive statistics will be monitored going forward until the end of the surveillance to increase the precision estimates for the incidence of GBS.

The RCA is meant to rapidly detect if there is a signal for an elevated risk of GBS following vaccination with ABRYSVO. In the monthly analyses, if the risk meets the signal threshold, rejecting the null does not imply a causal association and further steps will be taken to evaluate the robustness of signal and to characterize the signal, including:

1. Post-signal data quality assurance, including checking for possible duplications of vaccinations, GBS events or individuals; coding issues such as unexpected codes for vaccinations; and changes in claims recording processes.

2. A signal characterization will be performed to assess potential confouding factors, which will include a description of demographics, clinical characteristics, and GBS risk factors among the individuals who received ABRYSVO and had a GBS event.

Based on the post-signal data quality assurance check and the signal characterization, the RCA may be re-run to see if the positive signal persists when any potentially invalid GBS cases are excluded.

Lastly, an SCRI analysis will be conducted to further evaluate signals from the RCA results.

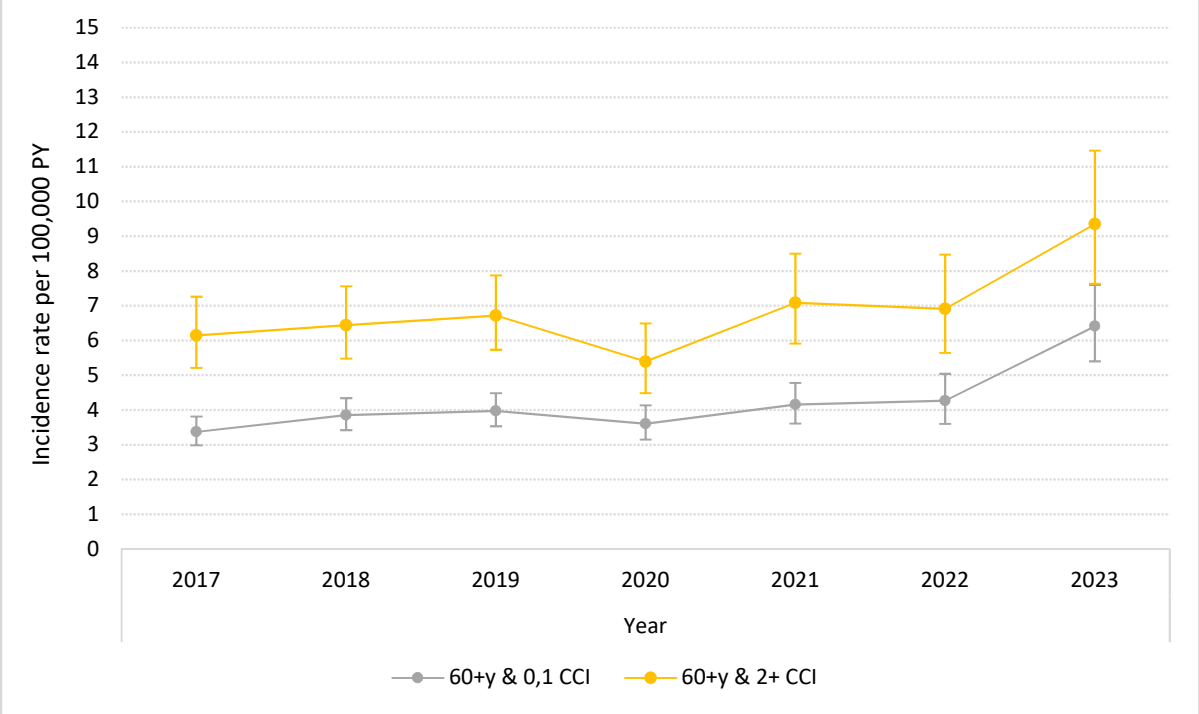
9.7.3.1. The Background Rate of GBS

The observed number of GBS cases in the ABRYSVO-vaccinated population will be compared to an expected number of GBS cases based on the background rate of GBS calculated for a historical influenza-vaccinated population from the CMS Medicare database. Although the background rate of GBS has been previously estimated from the general Medicare beneficiaries (25), we hypothesize that the historical influenza-vaccinated comparator group will have greater similarity to recipients of RSV vaccines than the general Medicare beneficiaries in terms of demographics, clinical characteristics and health-seeking behavior. Furthermore, the GBS rates of the historical comparator group will be adjusted for important covariates such as age, gender, and race to align with characteristics of the recipients of RSV vaccines; other variables (e.g., nursing home status) may also be included as feasible. Moreover, Medicare beneficiaries that are not qualified due to age will be excluded to match the inclusion criteria of the ABRYSVO-vaccinated study population.

The background rates of GBS will be estimated for individuals in the CMS Medicare database that received the seasonal influenza vaccines in the 2022 and 2023 influenza seasons (before ABRYSVO approval). This decision was influenced by recent literature indicating a 41.2% increase in the prevalence of GBS in North America between 1990 and 2019 and also an internal preliminary analysis in Optum's de-identified Market Clarity Data indicating a significant increase in annual incidence rates of GBS in older adults over time (Figure 8).(25, 30) This internal analysis was previously presented to the FDA in a document titled "Request for Comments and Advice Regarding RSV Vaccine Safety Study (28 August

2024).” Considering the updated knowledge regarding an increasing trend in incidence of GBS, it is more appropriate to use the more recent historical cohorts for background rate estimation to minimize biases due to secular trends.

Figure 8. Incidence rates of GBS among adults 60+ years of age by Charlson Comorbidity (CCI) (0,1 conditions versus 2+ conditions) in the United States from 2017-2023[11]



Abbreviations: CCI, Charlson Comorbidity Index; PY, person-years.

9.7.4. The Statistical Analysis for the SCRI

In the SCRI methodology, each ABRYSVO-vaccinated beneficiary serves as their own control as we assess the risk of experiencing GBS during a pre-defined post-vaccination risk interval to a post-vaccination control interval within the same individual (Section 9.1.2.1). The study population will include all exposed individuals that meeting the inclusion and exclusion criteria, but only individuals who develop GBS cases will contribute to the analysis. This approach inherently controls for time-invariant confounding variables and is a widely recognized method in vaccine safety research but may be susceptible to time-varying

[11] Pfizer’s preliminary analysis in Optum’s de-identified Market Clarity Data, previously presented to the FDA in a document titled “Request for Comments and Advice Regarding RSV Vaccine Safety Study (28 August 2024)”.

confounding, which can be minimized by choosing a control interval close to the risk interval.

In the analysis, GBS cases that occurred within the first 84 days following vaccination will be included and separated out into the risk and control window. The population summary statistics will be provided for each window.

A conditional Poisson regression model will be used to estimate the IRR and 95% CI, offset by the length of observation time. The model will include an indicator for the risk window as the predictor variable, an offset equal to the log of the window length and will condition on an identification variable for the beneficiary. The model can be written as:

$$log(p) = \beta(risk\ window) + log(interval) + strata(beneficiary\ id)$$

where p is the risk of GBS, *interval* represents the length of the respective window in days, and *beneficiary id* is the term identifying the patient. In the primary analysis, the risk window is 1-21 days post-vaccination, and the control window is 43-84 days post-vaccination. In the secondary analysis, the risk window is 1-42 days post-vaccination, and the control window is 43- 84 days post-vaccination. Under this model, our null and alternative hypotheses are:

H_0: $e^{\beta} = 1$ (i.e., IRR = 1)

H_a: $e^{\beta} \neq 1$ (i.e., IRR ≠ 1)

where e^{β} is the IRR of GBS in the risk window compared to the control window. Thus, the significance of the coefficient on the risk window variable at a pre-specified level will indicate a significant association between RSV vaccination and GBS. The statistical significance will be determined using a two-sided hypothesis test of increase using a significance level of 0.05.

The attributable risk (AR) will also be presented for both the primary (21-days risk window) and secondary (42-day risk interval) analyses, and will be defined as:

- X events per 1 million doses
- X events per 100,000 person-years

The AR per million vaccinations (or per 100,000 person-years) will be calculated by subtracting the expected number of events in the risk and control windows using the IRR estimated from the conditional Poisson regression and multiplying this by the total number of adjusted[12] GBS cases to obtain the expected number of cases in each period. The excess number of outcomes will be obtained by finding the differences between the expected number of cases in the risk and control window. The AR per 1,000,000 vaccine doses (or per 100,000 person-years) will then be calculated by dividing the excess number of outcomes associated with vaccination by the number of eligible doses (or eligible person-years) and multiplying by 1,000,000 (or 100,000 for person-years).

[12] When calculating the attributable risk (AR) for the primary risk window of 1-21 days post-vaccination, the number of cases in the control window must be divided by 2 to normalize the length of the risk window to the length of the control window. This will not be done for the secondary risk window of 1-42 days.

The analysis of AR does not presume a causal relationship between the ABRYSVO exposure and the GBS outcome. Rather, the analysis serves as a method to contextualize the additional risk (i.e., incidence) of the GBS outcome more intuitively, to identify the difference in risk in the exposed window compared to the unexposed window. The AR calculations can highlight associations but not definitively establish causal effect.

The final pooled SCRI analysis will be conducted by aggregating individual-level data from two seasons into one analytic file. Currently, only one dose of ABRYSVO is approved and recommended and evidence suggests RSV vaccines appear to provide protection for at least two RSV seasons. Therefore, revaccination is not anticipated during the study period. In the event where a patient had one more than one vaccination records in the pooled SCRI analysis, this will be flagged as an off-label use and numbers will be reported. Only the first exposure to ABRYSVO will be included in the pooled SCRI analysis.

To examine any change in post-vaccination GBS risk over time in Medicare data, a risk time trend analysis will be conducted using data from two seasons and will be further detailed in the SAP.

Additional adjusted analyses will be conducted and are described in Section 9.7.6.

9.7.4.1. Subgroup Analyses

Subgroup analyses may be conducted for the pooled SCRI analysis of 2023/2024 and 2024/2025 RSV seasons, pending sufficient sample size. The following is a list of stratification variables under consideration:

- Gender
- Age
- Race
- Concomitant Vaccines on the index date (Broad: yes vs. no; Individual vaccines: Combined, Influenza, Pneumococcal, COVID-19, Shingles, and others)
- Presence of prior infections (yes vs. no)

9.7.5. The Descriptive Analysis for Individuals Aged 60-64 years

Given the more limited age range for commercially insured adults 60-64 years, analyses for this age group will be primarily descriptive. Further inferential analysis (e.g., SCRI) may be considered contingent on sample size.

9.7.6. Sensitivity Analyses for the SCRI

This section outlines a multi-faceted approach to address potential biases and confounding in SCRI to evaluate the safety of ABRYSVO vaccination. Details of each analysis and any additional sensitivity analyses that may be conducted will be specified in the SAP.

9.7.6.1. Seasonality Adjustment

Given that GBS has been seen to be associated with infections such as wild-type influenza, it may exhibit trends that correlate with specific times of the year, which may introduce bias

into the analysis if not properly adjusted for. To evaluate potential time-varying confounding, the study will adjust for the changing risk of GBS over calendar months. Baseline outcome risk will be estimated from a similar population during the same calendar months in the 2022/2023 season and will be included as an offset term in the Poisson regression model.

9.7.6.2. Positive Predictive Values (PPV)-Adjusted Quantitative Bias Analysis

A PPV-adjusted analysis will be conducted to assess bias due to outcome misclassification and uncertainty in the claims-identified cases of GBS. Misclassification can occur if cases of GBS are under-identified or if other conditions are mistakenly classified as GBS.

The PPV-adjusted analysis will be performed using quantitative bias analysis (QBA) using PPVs available from prior studies that have conducted medical record review to validated GBS diagnoses following vaccine exposures.(12) The PPV estimate for GBS in CMS Medicare database for individuals aged 65 or older that will be used for adjustment in the study is 71.0% (95% CI: 63.0%, 79.0%).(9) For the SCRI analysis, differential PPV adjustment will also be used based on the FDA's October 2024 ACIP presentation, which reported different PPVs for GBS diagnosis in the risk and control intervals: 62.3% (48.8 - 74.1%) for claims-identified GBS cases during the 1-42 day risk interval and 81.8% (61.5 - 92.7%) during the 43-90 day control interval.(24) The study will integrate updated information on PPVs as they become available in the published literature or regulatory studies for the duration of the study.

9.7.6.3. The PPV-adjusted sensitivity analysis will also be conducted in the RCA.Seasonality and PPV-Adjusted Analysis

A seasonality and PPV-adjusted analysis may also be considered, as feasible, to account for both potential confounders that could bias outcome rate estimates.

9.7.6.4. SCRI Analysis Stratified by Individuals With and Without the Full Follow-up Period

In the primary analysis, incomplete follow-up for individuals (e.g., due to death, disenrollment, etc.) will be accounted for by using an offset term in the conditional Poisson regression model. To further evaluate potential biases associated with incomplete follow-up, if a significant number of individuals are lost to follow-up in the primary analysis, an SCRI analysis may be conducted requiring complete follow-up period of 84 days.

9.7.7. Additional Sensitivity Analyses

This section outlines further sensitivity analyses in SCRI and/or RCA that may be considered to evaluate the safety of ABRYSVO vaccination. Details of each analysis and any additional sensitivity analyses will be specified in the SAP.

9.7.7.1. Removal of GBS Cases After Infection Diagnoses for the SCRI Analytic Population

Prior infection has been found to be one of the most important risk factors for GBS.(31) In this study, we will conduct a sensitivity analysis, excluding individuals that have a prior respiratory or gastrointestinal infection within 1-42 days prior to GBS onset. These

individuals will not be included in the risk estimation for the SCRI analysis as their GBS onset may be related to their prior infection rather than the vaccination.

9.7.7.2. Secondary Risk Interval for the RCA Analytic Population

For the RCA, a secondary risk interval of 1-42 days post-index will be used a sensitivity analysis in lieu of the primary risk interval of 1-21 days post-index. The risk window of 42 days post-vaccination is generally recommended by the Brighton Collaboration GBS case definition as the most comprehensive risk interval, although current reports to VAERS suggest >90% of GBS events after RSV vaccinations occurred within 21 days and all are within 22 days. (19) Extending the window to 42 days helps ensure that all potential cases are captured, providing a comprehensive assessment of risk, and is consistent with the intervals defined for the SCRI. (9, 18, 19) Furthermore, a risk interval of 1-21 days will also be analyzed within this population to ensure comparability to the primary analysis.

9.7.7.3. Case-Centered GBS Analysis for the SCRI Analytic Population, the RCA Analytic Population and the Descriptive Analysis Population

To enhance the understanding of the severity and characteristics of the GBS cases identified in our analysis, and to better understand the risk factors of the individuals with GBS onset, a case-centered analysis will be performed to inform decisions regarding preventing severe outcomes. For each patient with a case of GBS identified, the following variables will be assessed:

- Selected demographics and clinical characteristics;
- Mean time to onset of GBS following index date;
- GBS risk factors (e.g., age, gender, preceding infections prior to onset, surgery within 42 days before GBS onset);
- Co-vaccination, stratified by risk and control intervals;
- Neurologist encounter surrounding the GBS diagnosis and diagnosing procedures received;
- Indicators of GBS severity: duration of IP stay, death (yes/no), respiratory failure or intubation. These variables will be assessed as part of the inpatient stay with a primary discharge diagnosis of GBS, following the definitions in the study of Shingles vaccination and GBS by Goud et al, 2021. (23)

9.7.8. Summary of Statistical Analyses Presented in the Interim and Final Reports

The conduct of the study involves the generation of several key reports. Interim report 1 delivers the SCRI analysis for the 2023/2024 RSV season. Interim report 2 and Interim report 3 will cover the RCA conducted during the 2024/2025 RSV season: Interim report 2 will cover an indexing period from 31 May 2023 to 10 August 2024, while Interim report 3 will extend the indexing period to 10 January 2025. The final report will include the SCRI

analysis for the 2023/2024 and the 2024/2025 RSV seasons. Additionally, this final report encompasses a pooled SCRI analysis that will combine the two consecutive seasons, and will also present any subgroup analyses, providing a comprehensive view of the safety profile of ABRYSVO. Table 2 summarizes the statistical analyses included in each interim and final report.

Table 2. Summary of Statistical Analyses in Interim and Final Reports

Milestone	Analysis Reported
Interim report 1	2023/2024 RSV season SCRI and descriptive analysis
Interim report 2	2024/2025 RSV season 1st RCA report (indexing period: 31 May 2023 – 10 August 2024)
Interim report 3	2024/2025 RSV season 2nd RCA report (indexing period: 31 May 2023 – 10 January 2025)
Final report to the FDA	2023/2024 RSV season SCRI and descriptive analysis 2024/2025 RSV season SCRI and descriptive analysis Combined 2 seasons SCRI and descriptive analysis Any pertinent subgroup and sensitivity analyses

9.8. Quality Control

The study will be conducted according to the standard operating procedures (SOPs) of IQVIA and Pfizer.

At IQVIA, all aspects of the study from protocol development to the reporting of the results will be conducted within the framework of the IQVIA Quality Management System. A Quality Control (QC) plan for the study will be developed and executed, which will include quality control on study methodology, the SAP, programming, data management and analysis, study results, conclusions, and the study report. Furthermore:

- The study QC plan will establish ownership for the execution of the individual QC steps;
- The Principal in Charge of the study will ensure that individuals responsible for the execution of specific QC steps will have the knowledge, capability, and experience necessary to perform the assigned tasks;
- The result of the execution of the individual steps of the QC plan will be documented, and will include the required corrective actions, if any. The execution of any required corrective action will also be documented;
- The QC plan will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study;
- IQVIA confidentiality agreements are signed by all employees and include data protection and strict prohibitions on reidentification attempts.

9.9. Limitations of the Research Methods

This study uses a large real-world data (RWD) source of U.S. older adults, which is representative of the patient population of interest. However, use of claims databases has limitations, especially regarding potential misclassification of study variables. In this study, the primary outcome of interest, GBS, will be identified based on a validated claims-based algorithm using ICD-10 codes in inpatient Medicare data. To account for the possibility of outcome misclassification, PPV-adjusted bias analysis will be conducted to assess the robustness of results.

In addition, the CMS Medicare database has a delay, i.e., "claims lag", between when a service occurs and when the claim or encounter appears in the database. It was estimated that 91% of inpatient claims, 90% of outpatient, 96% of pharmacy claims and 87% of Carrier claims were estimated to be submitted within 2 months after service date.(14, 15) Therefore, to ensure at least 90% data completeness for this study, data are allowed to mature and complete for a minimum period of 2 months after the end of follow-up period. If there is no association between ABRYSVO and GBS, the 90% data completeness is likely to overestimate the risk of GBS by no more than 10%. The PharMetrics Plus database, which consists of fully adjudicated claims, has a lag of approximately 6 months due to claim adjudication and completion.

Another potential limitation is the generalizability of these results to all older ABRYSVO-vaccinated individuals in the U.S. for which the vaccine is indicated (i.e., individuals 60 years of age and older). The CMS Medicare database is the optimal fit-for-use database for this study and primarily consists of individuals aged 65 years of age or older. Although a small portion of individuals aged less than 65 are also enrolled in Medicare, due to pre-existing comorbid conditions, they are not representative of the underlying population, and are excluded in this analysis to minimize confounding by pre-existing comorbidities. As such, a large and representative claims database, PharMetrics Plus, was selected to provide representation of individuals aged 60-64 years old. Considering more than 90% uptake of RSV vaccines were in individuals aged 65 and older, the ability to evaluate the risk of GBS in individuals aged 60-64 is anticipated to be limited. Lastly, despite the utilization of two large real-world databases, results of this study may not be generalizable to those uninsured or with other types of health insurances.

Each of the two study designs in the protocol have their own limitations.

9.9.1. SCRI Analysis

- Time-varying confounding is not accounted for in this study design, although this is minimized by using a short risk and control window adjacent to each other, and a seasonality adjustment for time-varying confounding in the sensitivity analysis.
- The planned study period is only powered to detect a modest to high risk of GBS based on the sample size expected (Section 9.5). However, Pfizer has an ongoing PMR PASS (C3671031) spanning 4.5 RSV seasons (or more) to detect a 2-fold increased risk of GBS following ABRYSVO vaccination using the fully adjudicated CMS Medicare claims.

9.9.2. RCA

- The signal detection of the observed rate of GBS in ABRYSVO recipients in comparison to the estimated background may be subject to residual confounding, although matching on key demographic characteristics will be conducted to increase comparability. Any signals from the RCA will need to be further evaluated in the SCRI analysis.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS).(32) The study will also be conducted in accordance with Good practices for RWD studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision-making. (32, 33)

The study will also follow additional guidelines, including guidelines for GPP issued by the International Society for Pharmacoepidemiology, the FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting, Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, and GEP guidelines issued by the IEA.(34)

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately. The interim and final study reports describing the study results will be disseminated to the regulators (i.e., the FDA). Data may be used in regulatory communications external to the FDA for contextualization purposes. Conference abstracts and/or manuscripts based on specific endpoints of interest may be developed for external publication purposes. The study will be registered and protocols as well as final study report will be posted in the HMA-EMA catalogues.

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ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

LIST OF CODES FOR RSV VACCINES

All codes will be reviewed prior to study initiation. Below are the codes used to identify RSV vaccinations.

Vaccine Name	Codes
ABRYSVO (RSVPreF)	CPT/HCPCS: 90678 (Respiratory Syncytial Virus vaccine, preF, subunit, bivalent, for intramuscular use) NDC: 0069020701, 00069034401, 00069034405, 00069034410, 00069246501, 00069246510, 00069246519
Arexvy (RSVPreF3 + AS01)	CPT/HCPCS: 90679 (Respiratory Syncytial Virus vaccine, preF, recombinant, subunit, adjuvated for intramuscular use) NDC: 58160072303, 58160074403, 58160084811
mRESVIA	CPT/HCPCS: 90683 (Respiratory Syncytial Virus vaccine, mRNA lipid nanoparticles, for intramuscular use) NDC: 80777034501, 80777034589, 80777034590, 80777034596

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Younus, Muhammad	25-Apr-2025 00:59:57	Final Approval
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Non-Interventional Study

C3671054

A Post-Marketing Near Real-Time Safety Surveillance of Respiratory Syncytial Virus Vaccine for Guillain-Barre Syndrome among Older Adults in the United States.

Statistical Analysis Plan

(SAP)

Version: 2.0

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AIDS	Acquired Immunodeficiency Syndrome
AE	Adverse Event
AR	Attributable Risk
BMI	Body Mass Index
CAD	Coronary Artery Disease
CBER	Center for Biologics Evaluation and Research
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CHF	Congestive Heart Failure
CMS	Centers for Medicare & Medicaid Services
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPT	Current Procedural Terminology
EBV	Epstein-Barr Virus
EDB	Enrollment Database
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration

Abbreviation	Definition
FFS	Fee-for-Service
GBS	Guillain-Barre syndrome
HBV	Hepatitis B Virus
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
HMA-EMA	Heads of Medicines Agencies - European Medicines Agency
HPV	Human Papillomavirus
HSCT	Hematopoietic Stem Cell Transplantation
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases, 10th revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th revision, Procedure Coding System
IP	Inpatient
IRB	Institutional Review Board
IRR	Incidence Rate Rati
LRTD	Lower Respiratory Tract Disease
MDS	Minimum Data Set
MenACWY	Meningococcal ACWY Vaccine
MenB	Meningococcal B Vaccine

Abbreviation	Definition
NDC	National Drug Codes
OP/PB	Outpatient and Professional
PASS	Post-Authorization Safety Study
PMR	Post-Marketing Requirements
PPV	Positive predictive value
PY	Person-years
QBA	Quantitative Bias Analysis
RCA	Rapid Cycle Analysis
RSV	Respiratory Syncytial Virus
RSVpreF	Respiratory Syncytial Virus Prefusion F protein
RWD	Real World Data
SAP	Statistical Analysis Plan
SCRI	Self-Controlled Risk Interval
SD	Standard deviation
SES	Socioeconomic status
SNF	Skilled Nursing Facility
SSD	Shared Systems Data
Td	Tetanus and Diphtheria Toxoids
Tdap	Tetanus, Diphtheria, and Pertussis
TNF	Tumor necrosis factor
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System
VTE	Venous thromboembolism

2. RATIONALE AND BACKGROUND

Note: In this document, any text taken directly from the non-interventional study protocol C3671054 is ***italicized***.

The United States (U.S.) Food and Drug Administration (FDA) approved Respiratory Syncytial Virus Prefusion F protein (*RSVpreF; ABRYSVO)* Respiratory Syncytial Virus (*RSV*) *vaccine on 31 May 2023 for individuals 60 years of age and older to prevent severe RSV and on 21 August 2023 in pregnant individuals at 32 through 36 weeks gestational age to protect newborns through passive immunity. (1, 2) On 22 October 2024, the vaccine was approved for individuals 18 through 59 years of age who are at increased risk for LRTD.(3) The CDC initially recommended that adults aged 60 years and older receive RSV vaccination using shared clinical decision-making. (4) Following the Advisory Committee on Immunization Practices (ACIP) meeting on 26 June 2024, the CDC further recommended that all adults aged 75 years and older, and adults aged 60-74 years who are at increased risk for severe RSV disease, should receive the vaccine.(5, 6) Guillain-Barre Syndrome (GBS) is an important potential risk, which is mentioned in the ABRYSVO Risk Management Plan. (7) Across all RSVpreF clinical trials, inflammatory neurologic events were reported in 2 of 20,255 adults aged ≥60 years within 42-days after vaccination with RSVpreF (1 case of GBS and 1 case of Miller Fisher syndrome [a variant of GBS]).(7) On 09 November 2023, FDA informed Pfizer of a few potential cases of GBS among older adults receiving ABRYSVO that were reported to the FDA's Vaccine Adverse Event Reporting System (VAERS).(8)*

The proposed post-marketing safety study, spanning two consecutive RSV seasons (2023/2024 and 2024/2025) *will provide a timely, targeted assessment of GBS after ABRYSVO vaccination that will address the gaps in safety evidence from prelicensure trials and early passive adverse event reporting. The study will encompass two analytical approaches: a signal detection [Rapid Cycle Analysis (RCA)] and a comparative [(Self-Controlled Risk Interval (SCRI)] approach. RCA is an established method of near real-time surveillance that periodically assesses data for safety signal as exposures accrue. The SCRI study design is a commonly used self-controlled method in vaccine safety studies, to evaluate the association between a transient exposure, such as vaccination, and an acute event, such as an adverse reaction. The complementary approaches of conducting an active surveillance study using an RCA for signal detection and a comparative SCRI analysis to further assess the risk for an adverse event following vaccination is essential for a robust vaccine safety study. It combines the advantage of timely signal detection and the ability to perform an in-depth analysis that is hypothesis-driven and well-controlled for time-invariant confounders. The approach ultimately ensures a robust measurement of the safety of vaccines in the indicated population.*

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the FDA.

3. STUDY OBJECTIVES AND HYPOTHESES

3.1. Primary Objectives

Research question: What is the incidence rate of GBS following vaccination with ABRYSVO among older adults aged 65 years of age or older enrolled in CMS Medicare databases and individuals aged 60-64 years enrolled in the IQVIA PharMetrics Plus claims database

(PharMetrics Plus database) as compared to the expected incidence rate of GBS in a comparable population?

The research objectives are:

- *To conduct near real-time monitoring of the incidence of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases using RCA study designs;*
- *To assess if there is an elevated risk of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases, using SCRI study design; and*
- *To descriptively monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database.*

3.2. Primary Hypothesis

3.2.1. RCA

The null hypothesis is that the observed rate of GBS in the ABRYSVO cohort is no greater than 2 times the comparator rate. The alternative hypothesis is that the observed rate in the ABRYSVO cohort is greater than 2 times than the comparator rate:

H_0: *Relative Risk (RR)* $\leqslant 2$

H_a: $RR > 2$

3.2.2. SCRI

The null hypothesis is that the incidence rate ratio (IRR) is equal to 1, i.e., the incidence rate of GBS is the same in the risk and control windows. The alternative hypothesis is that the IRR is not equal to 1, i.e., the incidence rate of GBS is different in the risk and control windows:

H_0: $e^{\beta} = 1$ *(i.e., IRR = 1)*

H_a: $e^{\beta} \neq 1$ *(i.e., IRR ≠ 1)*

where e^{β} *is the IRR of GBS in the risk window compared to the control window.*

4. RESEARCH METHODS

4.1. Study Design

This will be a non-interventional cohort study among older adults enrolled in CMS Medicare databases and PharMetrics Plus database (Section 4.4). The surveillance period for RSV vaccinations will span 2 RSV seasons (i.e., 2023/2024 and 2024/2025 seasons), beginning on ABRYSVO's approval on 31 May 2023. Two RSV seasons are included in order to increase sample size and rapidly assess a high risk (3- to 5-fold) of GBS after ABRYSVO vaccination while a separate, long-term PMR PASS (protocol # C3671031) spanning 4.5 RSV seasons or more is being conducted to detect any small or modest risk of GBS (e.g., 2-fold) following ABRYSVO vaccination using the fully-adjudicated claims in CMS Medicare and PharMetrics Plus databases.

The baseline period for an individual will be defined as 365 days prior to the date of the ABRYSVO administration (i.e., the index date), to assess the individual's demographic and clinical characteristics, and to rule out prevalent GBS cases. Two complementary approaches will be used to address the study objectives: *RCA and SCRI. A patient-level case-centered* sensitivity *analysis will be conducted to better understand the severity and risk factors associated with all GBS cases identified in the RCA and SCRI. Two data sources will be used for the study: CMS Medicare administrative databases and PharMetrics Plus database. The CMS Medicare database covers individuals aged 65 and older, while PharMetrics Plus data will cover individuals aged 60-64 years. Together, these two data sources will provide age representation for the currently approved indication for ABRYSVO. Given the more limited age range for commercially insured adults 60-64 years, analyses for this age group will be primarily descriptive based on available sample size.*

4.1.1. The Study Design of Rapid Cycle Analysis (RCA) Methodology

For signal detection[1], an RCA will be conducted during the 2024/2025 RSV season, built upon cumulative data from 2023/2024 RSV season, to periodically evaluate the near real-time incidence of GBS following vaccination as the data become available on a monthly basis. The observed number of GBS cases in the ABRYSVO-vaccinated population will be compared to an expected number of GBS cases based on an estimated background rate of GBS from a comparable population (*Section* 4.7.3.3). *A group sequential testing approach will be used for repeated testing of continuously accumulating data to minimize false positive signals. The background rate of GBS will be estimated from individuals who received seasonal influenza vaccines using historical data across the 2022 and 2023 influenza seasons. The historical influenza-vaccinated population is expected to be similar to ABRYSVO-vaccinated individuals in terms of demographics, clinical characteristics, and health-seeking behavior (Section* 4.7.3.3*). The RCA will allow timely safety signal detection of GBS risk following vaccination with ABRYSVO.*

The indexing period for the RCA will be from 31 May 2023 (e.g., first date of ABRYSVO vaccination) to 10 January 2025 (e.g., last date of ABRYSVO vaccination). For the RCA, a primary risk interval of 1-21 days following the index date will be evaluated to allow sufficient time for data completion and to prioritize more timely analysis during the season. Currently, >90% GBS events that occurred after RSV vaccinations were within 21 days of vaccination.(9) A secondary risk interval of 1 – 42 days after the index date will also be used in the RCA.

The overall RCA study period will span the baseline period, indexing period, and follow-up period, i.e., from 31 May 2022 to 21 February 2025.

[1] The RCA is a hypothesis-testing standard signal detection study with parameters in line with established rule-out risks. In our study, it is set up to provide early safety signals but will not be used to determine association between the exposure and outcome.

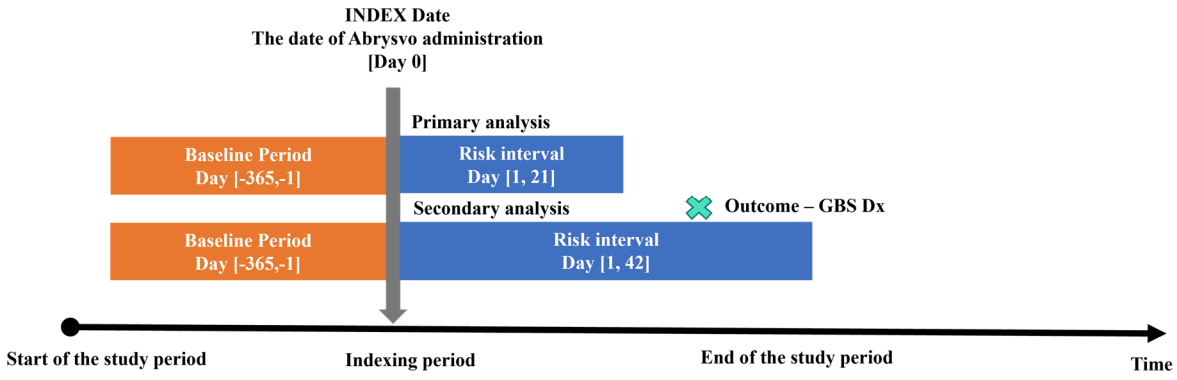
4.1.1.1. The Study Periods of Rapid Cycle Analysis (RCA) Methodology

The RCA analysis will focus on the 2023/2024 and 2024/2025 RSV seasons. The key study periods of the RCA analysis are described below:

- ***Study Period:*** *31 May 2022 – 21 February 2025*
- ***Indexing period (e.g., vaccination period):*** *31 May 2023 – 10 January 2025*
- ***Index Date:*** *The date of ABRYSVO administration*
- ***Baseline period:*** *365 days prior to the index date*
- ***Follow-up period:***
    - ***Post-vaccination risk interval:*** *1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively.* A patient's follow-up time will be censored at the first of: loss to follow-up (i.e., the date of disenrollment from Medicare FFS, including switching to Medicare Advantage), end of the follow-up period, or death. See Section 4.7.1 for more information on follow-up and censoring.

Figure 1 shows the study design and study period of an individual in the RCA.

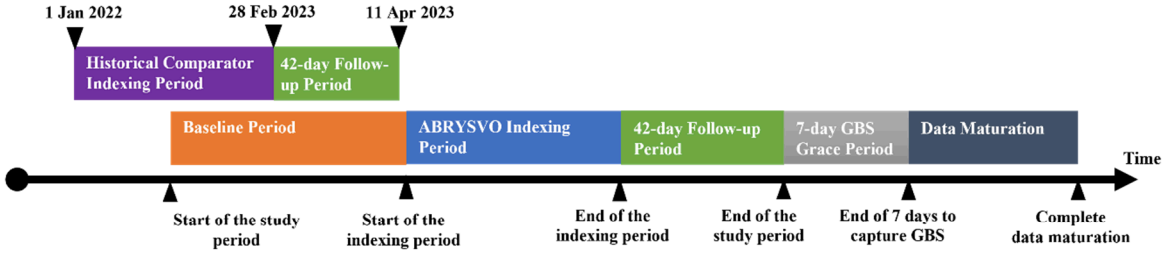
Figure 1. Study design and key study periods of the rapid cycle analysis



Abbreviations: Dx, diagnosis; GBS, Guillain-Barre Syndrome.

Figure 2 shows the specific study periods of the monthly RCA.

Figure 2. The study periods of rapid cycle analyses during the 2023/2024 and 2024/2025 RSV seasons



RCA #1 (Dec 2024)	31 May 2022	31 May 2023	10 Aug 2024	21 Sep 2024	28 Sep 2024	28 Nov 2024
RCA #2 (Jan 2025)	31 May 2022	31 May 2023	10 Sep 2024	22 Oct 2024	29 Oct 2024	29 Dec 2025
RCA #3 (Feb 2025)	31 May 2022	31 May 2023	10 Oct 2024	21 Nov 2024	28 Nov 2024	28 Jan 2025
RCA #4 (Mar 2025)	31 May 2022	31 May 2023	10 Nov 2024	22 Dec 2024	29 Dec 2024	1 Mar 2025
RCA #5 (Apr 2025)	31 May 2022	31 May 2023	10 Dec 2024	21 Jan 2025	28 Jan 2025	28 Mar 2025
RCA #6 (May 2025)	31 May 2022	31 May 2023	10 Jan 2025	21 Feb 2025	28 Feb 2025	28 Apr 2025

Abbreviations: RCA, rapid cycle analysis.

Note: The data maturation period allows for claims in the Centers for Medicare & Medicaid Services (CMS) Medicare Fee-for-Service (FFS) administrative database to be completed in the system. Over 90% of claims are submitted to the CMS within 2 months after service date. (10, 11)

Note: The population for the RCA #1 was included in Interim report 2; the results of RCA will be included in Interim report 3.

4.1.2. The Study Design of Self-Controlled Risk Interval (SCRI) Methodology

In addition, as a comparative analysis, SCRI analyses will be conducted for the 2023/2024 and 2024/2025 RSV seasons, both separately and as a pooled analysis, to provide more conclusive evidence for the association between vaccination and GBS. The SCRI will assess the risk of GBS following ABRYSVO vaccination by comparing the incidence rate of GBS during the pre-specified post-vaccination risk interval to the pre-specified post-vaccination control interval within the vaccinated individuals. The SCRI design effectively controls for time-invariant confounding. The detailed study design and study periods of the SCRI analysis are described in Section 4.1.2.1. A final pooled analysis using individual-level data from 2 RSV seasons (2023/2024 and 2024/2025) will be conducted by aggregating individual-level data from two seasons into one analytical file; this will allow for a more comprehensive and accurate assessment of the association between ABRYSVO and GBS with a larger sample size. The comparative SCRI analysis will assess the risk of GBS following vaccination as an in-depth analysis that is hypothesis-driven and well-controlled for time-invariant confounders.

The indexing period for the 2023/2024 RSV season SCRI analysis will be from 31 May 2023 following ABRYSVO's approval to 29 February 2024. The indexing period for the 2024/2025 RSV season SCRI analysis will be from 31 May 2024 to 28 February 2025. The indexing period will end in February as preliminary count data from Centers for Medicare & Medicaid Services (CMS) for the 2023/2024 season indicate that ABRYSVO vaccinations peaked in October, and >90% of RSV vaccinations for the season are expected to have been administered by the end of February; this is also consistent with historical data for other

seasonal vaccines such as influenza vaccines where >95% vaccinations of the season were administered by the end of February.(12, 13) Furthermore, the February end date allows sufficient time for completion of the claims in the CMS Fee-for-Service (FFS) database before analysis begins (e.g., >90% IP and outpatient (OP) claim completeness within 2 months after service date). Previous studies have also shown that an early cut-off of the indexing period when assessing risk of GBS following influenza vaccination did not impact the results.(14) The indexing period for the combined two season analysis will be from 31 May 2023 following ABRYSVO's approval to 28 February 2025.

The follow-up period for the SCRI analysis will consist of the post-vaccination risk interval of the individuals that received ABRYSVO, defined as 1-21 and 1-42 days after the index date, as the primary and secondary risk intervals, respectively. These windows are consistent with the onset of GBS cases during the ABRYSVO clinical studies and also with previous vaccine safety studies that have evaluated the risk of GBS.(14-17) The follow-up period will also include the post-vaccination control interval, defined as 43-84 days after the index date. The total follow-up period from the index date of each individual will be 84 days for the SCRI analysis.

The overall SCRI study period will span the baseline period, indexing period, and follow-up period, i.e., from 31 May 2022 to 23 May 2025.

4.1.2.1. The Study Periods of Self-Controlled Risk Interval (SCRI) Methodology

The SCRI analysis spans the 2023/2024 and 2024/2025 RSV seasons, and the follow-up period consists of the pre-specified post-vaccination risk and control intervals. The key study periods of the SCRI analysis are described below:

- ***Study Periods:***
  - ***2023/2024 Study Period:*** *31 May 2022 – 23 May 2024*
    - ***Indexing period:*** *31 May 2023 – 29 February 2024*
  - ***2024/2025 Study Period:*** *31 May 2023 – 23 May 2025*
    - ***Indexing period:*** *31 May 2024 – 28 February 2025*
  - ***Combined two season study period:*** *31 May 2022 – 23 May 2025*
    - ***Indexing period:*** *31 May 2023 – 28 February 2025*

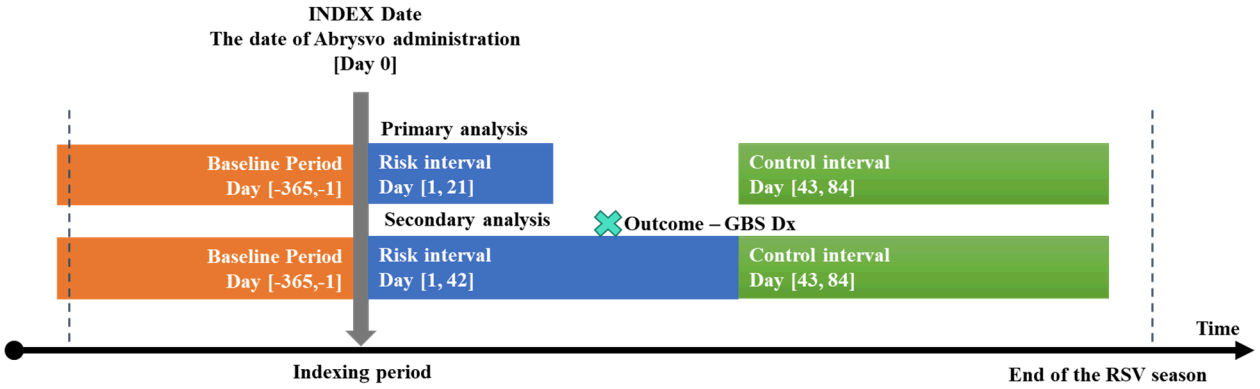
Note: As detailed in Section 4.1.2, the indexing period will end in February as >90% of RSV vaccinations are anticipated to be administered by that time, and to ensure timely analyses.

- ***Index Date:*** *The date of ABRYSVO administration*
- ***Baseline period:*** *365 days prior to the index date*

- ***Follow-up period:***
    - ***Post-vaccination risk period*****:** *1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively. Days 22-42 after the primary 1-21 days risk interval will be considered a washout period and will not be included in the analyses to avoid any carryover effects.*
    - ***Post-vaccination control period:*** *43-84 days after the index date*

Figure 3 shows the study design and key study periods of the SCRI analysis.

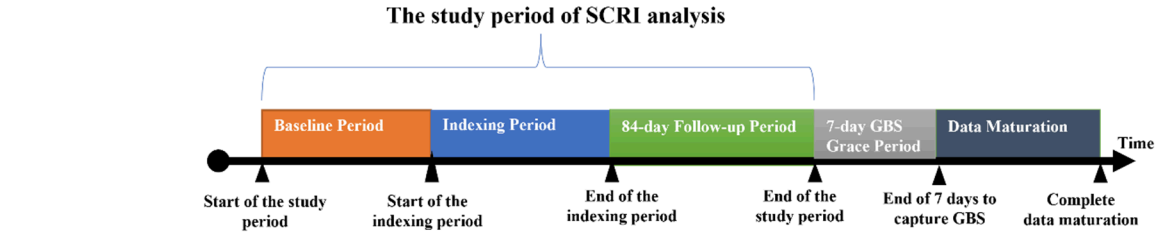
Figure 3. Study design of the self-controlled risk interval analysis



Abbreviations: Dx, diagnosis; GBS, Guillain-Barre syndrome; RSV, Respiratory Syncytial Virus.

Figure 4 shows the study period of SCRI analysis in relation to the RSV seasons.

Figure 4. The study period of self-controlled risk interval analysis during 2023/2024 and 2024/2025 RSV seasons



Abbreviations: RSV, respiratory syncytial virus; SCRI, self-controlled risk interval.

Note: The data maturation period allows for claims in the CMS Medicare FFS administrative database to be completed in the system. Over 90% of Medicare claims are submitted to the CMS within 2 months after service date. (10, 11)

4.1.3. The Study Design of Descriptive Analysis of Individuals Aged 60-64 Years Enrolled in PharMetrics Plus Database

For the descriptive analyses of GBS incidence following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database, the indexing period of the 2023/2024 RSV period for evaluating exposure to ABRYSVO will be from 31 May 2023 to 29 February 2024. For the 2024/2025 RSV season, the indexing period will be from 31 May 2024 to 28 February 2025. For the combined RSV season analysis, the indexing period will be from 31 May 2023 to 28 February 2025.

The overall study period will span the baseline period, indexing period, and follow-up period, i.e., from 31 May 2022 to 21 April 2025.The detailed study design and study periods of the descriptive analysis are described in Section 4.1.3.1.

Note: The PharMetrics Plus analysis will be descriptive in nature; the inferential analysis, SCRI, may be considered contingent on sample size.

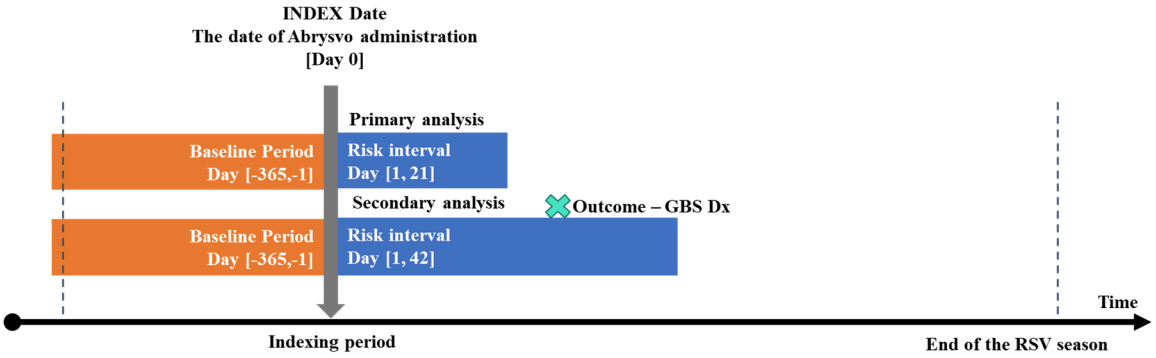
4.1.3.1. The Study Periods of Descriptive Analysis of Individuals Aged 60-64 Years Enrolled in PharMetrics Plus Database

The descriptive analysis spans the 2023/2024 and 2024/2025 RSV seasons, and the follow-up period consists of the pre-specified post-vaccination risk and control intervals. The key study periods of the descriptive analysis are described below:

- ***Study Periods:***
  - ***2023/2024 Study Period:*** *31 May 2022 – 11 April 2024*
    - ***Indexing period:*** *31 May 2023 – 29 February 2024*
  - ***2024/2025 Study Period:*** *31 May 2023 – 11 April 2025*
    - ***Indexing period:*** *31 May 2024 – 28 February 2025*
  - ***Combined two season study period:*** *31 May 2022 – 11 April 2025*
    - ***Indexing period:*** *31 May 2023 – 28 February 2025*
- ***Index Date:*** *The date of ABRYSVO administration*
- ***Baseline period:*** *365 days prior to the index date*
- ***Follow-up period:***
  - ***Post-vaccination risk period:*** *1-21 and 1-42 days after the index date as the primary and secondary risk interval, respectively.*

Figure 5 shows the study design and key study periods of the descriptive analysis.

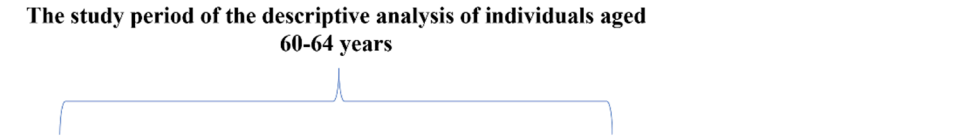
Figure 5. Study design of the descriptive analysis of individuals aged 60-64 years



Abbreviations: Dx, diagnosis; GBS, Guillain-Barre syndrome; RSV, Respiratory Syncytial Virus.

Figure 6 shows the study period of the descriptive analysis of individuals aged 60-64 years in relation to the RSV seasons.

Figure 6. The study period of the descriptive analysis of individuals aged 60-64 years during 2023/2024 and 2024/2025 RSV seasons



2023/2024 season analysis	31 May 2022	31 May 2023	29 Feb 2024	11 Apr 2024	18 Apr 2024	01 Sept 2024
2024/2025 season analysis	31 May 2023	31 May 2024	28 Feb 2025	11 Apr 2025	18 Apr 2025	01 Oct 2025
Analysis of both seasons	31 May 2022	31 May 2023	28 Feb 2025	11 Apr 2025	18 Apr 2025	01 Oct 2025

Abbreviations: RSV, Respiratory Syncytial Virus.

Note: The PharMetrics Plus database contains fully-adjudicated claims with a data lag of approximately six months.(18) The indexing period for the descriptive analysis has accounted for the lag.

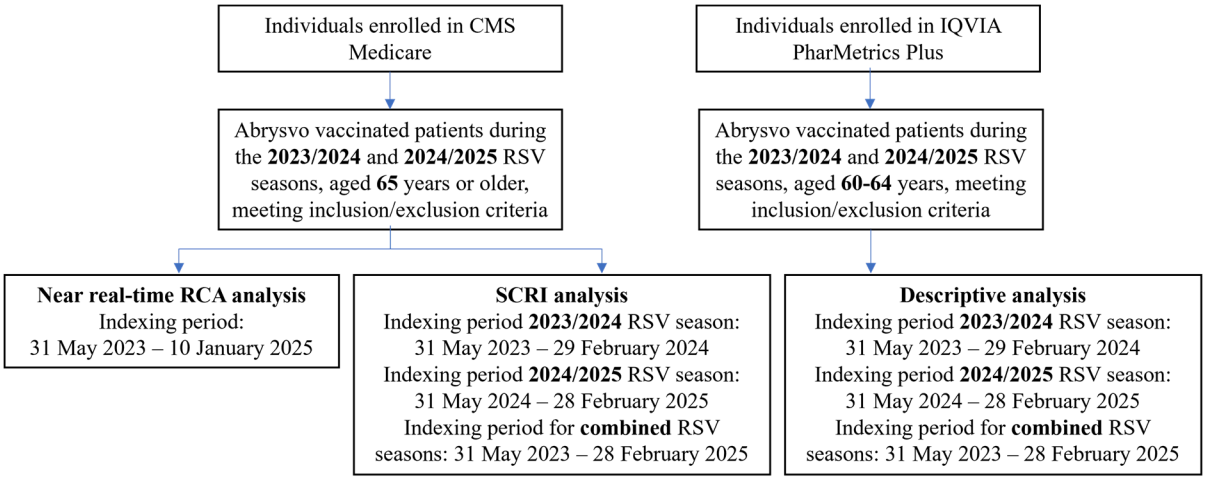
4.2. Study Population

The study population will include CMS Medicare FFS beneficiaries aged 65 years of age or older and PharMetrics Plus enrollees aged 60-64 years who receive one dose of ABRYSVO vaccine administration during the surveillance period and meet all other eligibility criteria (Section 4.2.2).

The SCRI analysis and descriptive analysis will be conducted in the study populations identified in both the 2023/2024 and 2024/2025 RSV seasons; the RCA analysis will be

launched in the 2024/2025 RSV season, with cumulative data from the 2023/2024 RSV season (Figure 7).

Figure 7. The overall study design flowchart and population selection



4.2.1. Setting

The source population is U.S. Medicare beneficiaries available in the CMS Medicare FFS administrative database. This database includes Medicare Parts A, B, and D data, covering inpatient and outpatient encounters and drug/vaccine prescriptions. The source population also includes individuals aged 60-64 years available in PharMetrics Plus database, which provides comprehensive claims data on healthcare utilization, including inpatient and outpatient encounters, as well as drug/vaccine prescriptions.

Individuals aged 65 years of age or older in the CMS Medicare data and individuals aged 60-64 years in the PharMetrics Plus database who receive ABRYSVO vaccine (i.e., exposure) who meet the eligibility criteria described in Section 4.2.2 will be included in the study.

The ABRYSVO vaccine record will be identified using CPT (Current Procedural Terminology), HCPCS (Healthcare Common Procedure Coding System), and NDC (National Drug Code) codes. The operational definitions of the exposure and other inclusion and exclusion criteria are defined in Section 4.3.

4.2.2. Inclusion and Exclusion Criteria

4.2.2.1. Inclusion Criteria

Individuals in CMS Medicare databases must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. *Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during the respective indexing period:*

    a. *RCA analysis:*

1) 2023/2024 and 2024/2025 RSV seasons RCA analysis: 31 May 2023 to 10 January 2025;

b. SCRI analysis:

1) 2023/2024 RSV season SCRI analysis: 31 May 2023 to 29 February 2024;

2) 2024/2025 RSV season SCRI analysis: 31 May 2024 to 28 February 2025;

3) Combined two seasons SCRI analysis: 31 May 2023 to 28 February 2025;

2. At least 65 years of age on the index date;

3. Medicare beneficiaries who aged into Medicare;

Note: Beneficiaries who qualify due to disability differ from beneficiaries who qualify due to age in several ways, including their demographic, socioeconomic, and health status profiles. To reduce potential confounding from this specific frail Medicare population that could have a different association between vaccination and GBS, they are not included in the study population.

4. At least 12 months of continuous enrollment in Medicare Parts A and B prior to the index date (i.e., the baseline period);

5. At least 3 months of continuous enrollment in Medicare Part D prior to the index date;

Note: this requirement is to balance subject attrition and adequate capture of recent prescriptions prior to vaccination.

6. No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.

Individuals in PharMetrics Plus database must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during the respective indexing period:

a. Indexing period for descriptive analysis:

1) 2023/2024 RSV season analysis: 31 May 2023 to 29 February 2024;

2) 2024/2025 RSV season analysis: 31 May 2024 to 28 February 2025;

3) Combined two seasons analysis: 31 May 2023 to 28 February 2025;

2. *Aged 60-64 years on the index date;*

3. *At least 12 months of continuous enrollment with medical and pharmacy benefits in the PharMetrics Plus database prior to the index date (i.e., the baseline period);*

4. *No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.*

4.2.2.2. Exclusion Criteria

Individuals in CMS Medicare databases and the PharMetrics Plus database meeting any of the following criteria will not be included in the study:

1. *Individuals without sex information;*

   Note: The sex information will be assessed in all available time, and defined based on the record closest to the index date.

2. *Individuals with a GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.*

4.2.3. Subgroups

Subgroup analyses may be conducted for the pooled analysis of 2023/2024 and 2024/2025 RSV seasons, pending sufficient sample size. Potential strata include gender, age, race, concomitant vaccines on the index date, and presence of prior infections. The details of the subgroup analyses are specified in Section 4.7.3.4.2.

4.3. Variables

Exposures, outcomes, and covariates will be identified within relevant care settings in the claims data, including the IP and OP/PB care settings. The operational definitions of all study variables are listed in Table 1.

4.3.1. Exposure

The exposure of interest is ABRYSVO vaccination, defined as an individual's first administration of the ABRYSVO vaccine during the indexing period (Section 4.1), as identified by a CPT code, HCPCS code or NDC during the indexing period.(19) The date of the first administration of the ABRYSVO vaccine is defined as the Index Date. The operational definitions related to the exposure are outlined in Table 1.

The study spans two RSV seasons, 2023/2024 and 2024/2025, and multiple vaccinations are not anticipated as ABRYSVO is not approved for re-vaccination. To deduplicate exposure occurrences, multiple vaccine records containing the same ABRYSVO vaccine product, occurring on the same day or within three days will be deduplicated. The date of the first occurrence of the ABRYSVO vaccination will be defined as the index date. If the multiple vaccine records are more than three days apart within the same season, only the first record will count towards the analysis. If the multiple vaccine records are more than

three days apart for a unique patient ID, it will be flagged as off-label use and reported separately, and only the first record will count towards the analysis.

The code lists for ABRYSVO vaccine and RSV vaccines from a manufacturer other than Pfizer are presented in Appendix B.1. The list of RSV vaccine codes in the example code lists will be reviewed and updated periodically during the entire study period.

4.3.2. Outcomes

The outcome of interest is GBS diagnosis, which will be identified from IP and OP/PB claims using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code G61.0 (Appendix B.2).

An incident GBS case will be defined as the first occurrence of a primary discharge diagnosis of GBS in the IP setting post-vaccination. The date of the case's onset will be defined as the date of hospitalization (i.e., inpatient admission date) unless there is a claim with a GBS diagnosis in another medical setting (e.g., OP) in the prior 7 days. In that case, the earlier claim, irrespective of healthcare setting, will represent the date of onset. This claims-based algorithm in Medicare data has a positive predictive value (PPV) of 71.2% – 78.6% when validated against medical records using the Brighton criteria and has been used to reliably identify GBS cases among Medicare beneficiaries.(20-22) In a recent FDA analysis evaluating GBS risk following RSV vaccination in the Medicare data, the algorithm had a PPV of 62.3% in the post-vaccination risk interval of 1-42 days and a PPV of 81.8% in the post-vaccination control interval of 43-90 days, based on chart review.(23) The operational definitions relevant to the outcome are outlined in Table 1.

The risk window of 42 days post-vaccination is generally recommended by the Brighton Collaboration GBS case definition. (16) Within the ABRYSVO clinical and surveillance studies, over 90% of GBS events have been found to occur within 21 days of vaccination.(9) In this study, for the RCA, the risk interval is defined as 1-21 days post-vaccination; a secondary risk interval of 1-42 days post-vaccination will also be analyzed. For the SCRI, the primary postvaccination risk interval is defined as 1 – 21 days post-vaccination with days 22-42 acting as a washout period to avoid carry over effects from the former to the latter. *The secondary postvaccination risk interval is defined as 1 – 42 days post-vaccination* with no washout period applied to the secondary risk interval. *The control interval for the SCRI analysis is defined as 43 – 84 days post-vaccination. For the SCRI analysis, GBS diagnosis will be identified during the risk and the control intervals to compare the risk of GBS occurrence within the two intervals* (*Section* 4.1.2).

A case-centered analysis will also be performed to enhance the understanding of the severity and characteristics of GBS cases identified in the analysis. The variables included in the case-centered analysis are outlined in Table 1.

4.3.3. Patient Characteristics

Patient characteristics, including demographics, clinical characteristics, medications/ vaccinations, and healthcare resource utilization will be captured during the baseline period and/or follow-up period, as applicable. The operational definitions of individual characteristics are listed in Table 1. If the operational definition of the variables in PharMetrics Plus database is different from the operational definition in CMS Medicare databases, it is defined in a separate column.

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Exposure Characteristics				
Index Date	Analysis anchor, exposure characteristics	Defined as the date of the first eligible record of the ABRYSVO vaccination during the indexing period. The NDC and CPT codes to identify ABRYSVO are listed in Appendix B.1.	Same	Indexing period, defined in Section 4.2.2.1
Month and year of ABRYSVO vaccination	Analysis anchor, exposure characteristics	Defined as the month and year of the Index Date, in the format of MMM-YYYY. Reported as a categorical variable with the categories from May-2023 through Feb-2025.	Same	Index Date, Day 0
RSV season of ABRYSVO vaccination	Analysis anchor, exposure characteristics	Defined as the season of the Index Date. Reported as a categorical variable with the following values: - 2023/2024 RSV season (i.e., 31 May 2023 to 29 February 2024) - 2024/2025 RSV season (i.e., 31 May 2024 to 28 February 2025)	Defined as the season of the Index Date. Reported as a categorical variable with the following values: - 2023/2024 RSV season (i.e., 31 May 2023 to 29 February 2024) - 2024/2025 RSV season (i.e., 31 May 2024 to 28 February 2025)	Index Date, Day 0
Timing of vaccination	Exposure characteristics, subgroup identifier	Defined based on the month of the Index Date, and reported in the following categories: - High respiratory season (i.e., vaccination month from September to February) - Low respiratory season (i.e., vaccination month from March to August)	Same	Index Date, Day 0

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Facility/provider type of ABRYSVO vaccination	Exposure characteristics	Facility or provider type will be assessed at the time of first valid ABRYSVO vaccination during the study period. Reported as a categorical variable with the following categories: - Hospital - Office Visit - Pharmacy - Skilled Nursing Facility - Home Health Agency - Mass Immunization Center - Other - Missing/unknown	Same	Index Date, Day 0
Co-administered vaccinations on index date	Exposure characteristics	Defined as ≥1 NDC or CPT code of vaccinations of interest on the Index Date. Reported as a binary variable (1: yes; 0: no) for the receipt of the following vaccinations: - Seasonal influenza vaccine - COVID-19 - Tetanus diphtheria and pertussis (Tdap or Td) - Chickenpox (Varicella) - Shingles (Herpes Zoster recombinant and/or live) - Human papillomavirus (HPV) - Pneumococcal conjugate - Pneumococcal polysaccharide - Hepatitis A - Hepatitis B - Meningococcal conjugate (MenACWY) and serogroup B (MenB)	Same	Index Date, Day 0

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		- Haemophilus influenza type B - Any (Presence of any above vaccination) The code list is specified in Appendix B.3.		
Vaccines in close proximity to index date	Exposure characteristics	Defined as ≥1 NDC or CPT code of vaccinations of interest in close proximity (within 30 days) to the Index Date. Reported as a binary variable (1: yes; 0: no) for the receipt of the following vaccinations: - Seasonal influenza vaccine - COVID-19 - Tdap or Td - Chickenpox (Varicella) - Shingles (Herpes Zoster recombinant and/or live) - HPV - Pneumococcal conjugate - Pneumococcal polysaccharide - Hepatitis A - Hepatitis B - MenACWY and MenB - Haemophilus influenza type B - Any (Presence of any above vaccination) The code list is specified in Appendix B.3.	Same	30 days before and after the Index Date, Day [-30, 30]
Inclusion and Exclusion Criteria				
Receiving one dose of ABRYSVO vaccine administration during the 2023/2024 RSV season for SCRI analysis	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when Index Date was identified between 31 May 2023 and 29 February 2024.	Binary variable (1: yes; 0: no) to be true when Index Date was identified	2023/2024 RSV season

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
			between 31 May 2023 and 29 February 2024.	
Receiving one dose of ABRYSVO vaccine administration during the 2024/2025 RSV season for SCRI analysis	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when Index Date was identified between 31 May 2024 and 28 February 2025.	Same	2024/2025 RSV season (31 May 2024 to 28 February 2025)
Receiving one dose of ABRYSVO vaccine administration during the combined two season for SCRI analysis	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when Index Date was identified between 31 May 2023 and 28 February 2025.	Same	The combined two season (31 May 2023 to 28 February 2025)
Receiving one dose of ABRYSVO vaccine administration during the 2024/2025 RSV season for RCA analysis	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when Index Date was identified between 31 May 2023 and 28 February 2025.	Not applicable	2024/2025 RSV season (31 May 2024 to 28 February 2025)
At least 65 years of age on the index date	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when Age on index ≥65.	Not applicable	Index Date, Day 0
Aged 60-64 on the index date	Inclusion criteria	Not applicable	Binary variable (1: yes; 0: no) to be true when Age on index ≥60 and <64.	Index Date, Day 0
Medicare beneficiaries who aged into Medicare	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when Original reason for Medicare eligibility = “Aged without End-Stage Renal Disease (ESRD)” OR “Aged with ESRD”.	Not applicable	N/A
12 months of continuous enrollment in Medicare Parts A and B prior to the index date	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when individuals have 12 months of continuous enrollment in Medicare Parts A and B prior to the Index Date.	Not applicable	Baseline period, Day [-365, -1]
12 months of continuous enrollment in PharMetrics Plus prior to the index date	Inclusion criteria	Not applicable	Binary variable (1: yes; 0: no) to be true when	Baseline period, Day [-365, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
			individuals have 12 months of continuous enrollment in PharMetrics Plus prior to the Index Date.	
3 months of continuous enrollment in Medicare Parts D prior to the index date	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when individuals have 3 months of continuous enrollment in Medicare Part D prior to the Index Date.	Not applicable	3 months prior to the Index Date, Day [-90, -1]
No record of an RSV vaccine from a manufacturer other than Pfizer	Inclusion criteria	Binary variable (1: yes; 0: no) to be true when individuals have no record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period. The code list of exclusionary vaccination is specified in Appendix B.1.	Same	The baseline and follow-up period
Individuals without sex information	Exclusion criteria	Binary variable (1: yes; 0: no) to be true when individuals have no sex information.	Same	All available data
Individuals with a GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date	Exclusion criteria	Binary variable (1: yes; 0: no) to be true when individuals have a GBS diagnosis on a claim in any position and any setting during the baseline period or on the Index Date.	Same	The baseline and on the Index Date, Day [-365,0]
Demographic Characteristics				
Age on index	Baseline characteristic, potential confounder, subgroup identifier	Defined as a person's age at the time of vaccination in the unit of years. Reported as a categorical variable with the following age groups: - 65-69 - 70-74	Defined as a person's age at the time of vaccination in the unit of years. Age is computed by taking the number of years between index date and birth date.	Index Date, Day 0

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		- 75-79 - 80-84 - 85-89 - 90+	Reported as a categorical variable with only one age group: 60-64.	
Gender	Baseline characteristic, potential confounder, subgroup identifier	Reported as a categorical variable with the following groups: - Male - Female	Same	Index Date/ all available time, using record closest to Index Date
Race/ethnicity	Baseline characteristic, potential confounder, subgroup identifier	Reported as a categorical variable with the following groups: - White - Black - Asian - Hispanic - American Indian/ Alaskan Native - Other - Missing/Unknown	Same Note: Race/ethnicity information may not be complete in PharMetrics Plus.	Index Date/ all available time, using record closest to Index Date
US Region	Baseline characteristic, potential confounder, sub-group identifier	Reported as a categorical variable with the following groups: - Northeast - Midwest - West - South	Same	Index Date/ all available time, using record closest to Index Date
Health and Human Services (HHS) region	Baseline characteristic, potential confounder, subgroup identifier	The HHS region will be assigned based on persons' state of residence closest to the index date. Reported as a categorical variable with the following groups:	The HHS region information will be linked via 3-digit zip codes that is closest to the index date. Reported as a categorical variable with the following groups:	Index Date/ all available time, using record closest to Index Date

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		- Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont) - Region 2 (New Jersey, New York, Puerto Rico, and the Virgin Islands) - Region 3 (Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia) - Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee) - Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) - Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas) - Region 7 (Iowa, Kansas, Missouri, and Nebraska) - Region 8 (Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming) - Region 9 (Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, and Republic of Palau)	- Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont) - Region 2 (New Jersey, New York, Puerto Rico, and the Virgin Islands) - Region 3 (Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia) - Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee) - Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) - Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas) - Region 7 (Iowa, Kansas, Missouri, and Nebraska) - Region 8 (Colorado, Montana, North Dakota, South	

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		- Region 10 (Alaska, Idaho, Oregon, and Washington) - Missing/unknown	Dakota, Utah, and Wyoming) - Region 9 (Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, and Republic of Palau) - Region 10 (Alaska, Idaho, Oregon, and Washington) - Missing/unknown	
Urban/rural	Baseline characteristic, potential confounder, subgroup identifier	Reported as a categorical variable based on the core-based statistical area, which categorizes areas as micropolitan (Rural) or metropolitan (Urban), will be assigned based on the Medicare beneficiary's residential address closest to the index date. (17) - Urban - Rural - Missing/unknown	Not available	Index Date/ all available time, using record closest to Index Date
Area Deprivation Index (ADI) rank	Baseline characteristic	The ADI is an index of seventeen socioeconomic indicators which includes block group measures of education, employment, income, housing, household composition, and household resources. A	Not available	Index Date/ all available time, using records closest to Index Date

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		higher ADI index indicates lower socioeconomic status (SES). To protect the patient privacy, the block group level ADI will be cross-walked to 9-digit zip code level, aggregated as the median of ADI at 3- to 5-digit zip code level and linked to Medicare enrollees using 3- to 5-digit zip code from Medicare enrollment file based on the zip code closest to the index date. Reported as a categorical variable by ranking of the ADI: - 1-10 (th) - 11-20 (th) - 21-30 (th) - 31-40 (th) - 41-50 (th) - 51-60 (th) - 61-70 (th) - 71-80 (th) - 81-90 (th) - 91-100 (th) - Missing/Unknown		
Original reason for Medicare eligibility	Baseline characteristic, inclusion criteria	The original reason for Medicare entitlement, reported as a categorical variable: - Aged without ESRD - Aged with ESRD	Not applicable	All available time, using record closest to Index Date
Nursing Home Residency Status (Recent Residency)	Baseline characteristic,	Reported as a categorical variable, based on the presence of a code for nursing home	Not available	Baseline period, Day [-120, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
	Subgroup identifier	admission or assessment during the ascertainment window: - Resident - Non-resident		
Nursing Home Residency Status (Any Admission)	Baseline characteristic, Subgroup identifier	Reported as a categorical variable, based on the presence of a code for nursing home admission during the ascertainment window: - Resident (ever) - Non-resident	Not available	All available time, using record closest to Index Date
Clinical Characteristics, Medication Use, and Healthcare Resource Utilization				
History of anaphylaxis	Clinical characteristics	Binary variable (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of anaphylaxis in IP/OP/PB settings during the baseline period. The code list is specified in Appendix B.4.	Same	Baseline period, Day [-365, -1]
Hospitalization in the baseline period	Healthcare resource utilization	Binary variable (1: yes; 0: no) defined as ≥1 events/encounters in IP settings in the baseline period.	Same	Baseline period, Day [-365, -1]
Number of hospitalizations in the baseline period	Healthcare resource utilization	Among patients with hospitalization in the baseline period, continuous variable defined as number of events/encounters in IP setting in the baseline period.	Same	Baseline period, Day [-365, -1]
Admission into nursing home/SNF in the baseline period	Healthcare resource utilization	Binary variable (1: yes; 0: no) defined as admission status change of the nursing home/SNF, specifically admission into nursing home/SNF in the baseline period.	Same	Baseline period, Day [-365, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Infections in close proximity to the index date	Clinical characteristics, Subgroup identifier	Binary variables (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of infections in IP/OP/PB settings in the ascertainment window: - Medically-attended infections (respiratory, gastrointestinal [GI], unspecified viral infection) - Upper or lower respiratory tract infections (including diphtheria, whooping cough, streptococcal sore throat and scarlet fever, varicella with pneumonia, RSV, COVID-19, acute sinusitis, acute tonsilitis, acute bronchitis, influenza, etc) - GI infections (including cholera, typhoid and paratyphoid fevers, shigellosis, amebic nondysenteric colitis, etc) - Unspecified viral infection - Diarrhea - Fever - Campylobacter enteritis - Cytomegalovirus (CMV) - Epstein-Barr Virus (EBV) - Hepatitis E Virus (HEV) - Zika virus - Any The code list is specified in Appendix B.6. One variable will be created for each infection condition listed above. And another variable will	Same	30 days before and after the index date, Day [-30, 30]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		be created for presence of any condition listed above.		
Infections in close proximity to the index date (Sensitivity)	Clinical characteristics, Subgroup identifier	Binary variables (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of infections in IP setting OR ≥2 ICD-10-CM codes of infections in the OP/PB setting at least one day apart in the baseline period: - Medically-attended infections (respiratory, GI, unspecified viral infection) - Upper or lower respiratory tract infections (including diphtheria, whooping cough, streptococcal sore throat and scarlet fever, varicella with pneumonia, RSV, COVID-19, acute sinusitis, acute tonsilitis, acute bronchitis, influenza, etc) - GI infections (including cholera, typhoid and paratyphoid fevers, shigellosis, amebic nondysenteric colitis, etc) - Unspecified viral infection - Diarrhea - Fever - Campylobacter enteritis - CMV - EBV - HEV - Zika virus - Any The code list is specified in Appendix B.6.	Same	30 days before and after the index date, Day [-30, 30]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		One variable will be created for each infection condition listed above. And another variable will be created for presence of any condition listed above.		
Frailty index	Clinical characteristics, subgroup identifier	Determined by the cumulated score of age and Charlson comorbidity index. Patient age will contribute to the score based on the following categories: ≤75 years = 0 score, 76-80 years = 1 score, ≥81 years = 2 scores. Charlson comorbidity index will contribute to the score based on the following categories: ≤1 CCI = 0 score, ≥2 CCI = 1 score.(24-26) The frailty index will be reported in the following categories: - Frail (2+ score) - Pre-frail (1 score) - Non-frail (0 score) The code list is specified in Appendix B.4.	Same	Baseline period, Day [-365, -1]
Charlson Comorbidity Index (CCI)	Clinical characteristics, subgroup identifier	Reported as a continuous variable, CCI will be assessed based on presence of comorbidities, identified by ICD-10-CM diagnosis codes in IP/OP/PB settings in the baseline period. Each comorbidity category has an associated weight (from 1 to 6) based on the adjusted risk of	Same	Baseline period, Day [-365, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		mortality or resource use. There are 19 comorbidity categories in total and does not include age adjustment. (27) The CCI will also be reported in categories such as: - 0-1 - ≥2 The code list is specified in Appendix B.4.		
Smoking Status	Clinical characteristics	Binary variable (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of tobacco use or nicotine dependence during the baseline period. The code list is specified in Appendix B.4. Note: This variable may be under-reported in claims data.	Same	Baseline period, Day [-365, -1]
Body Mass Index (BMI)	Clinical characteristics	Reported as a categorical variable, identified by ICD-10-CM codes in the baseline period. BMI will be reported in the categories: - ≤19.9 - 20-29 - 30-39 - ≥40 - Unknown The code list is specified in Appendix B.4. Note: This variable may be under-reported in claims data.	Same	Baseline period, Day [-365, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Selected comorbidity conditions	Clinical characteristics	Binary variables (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of conditions in IP/OP/PB settings during the baseline period. The categories of comorbidity conditions are derived from the algorithm by Center for Biologics Evaluation and Research (CBER) (17). - Asthma - Blood Disorders - Chronic Lung Disease - Diabetes - Heart Disease - Kidney Disease - Liver Disorders - Neurological / Neurodevelopmental Conditions - Malignant Neoplasms The code list is specified in Appendix B.5. One variable will be created for each comorbidity category.	Same	Baseline period, Day [-365, -1]
Selected comorbidity conditions (Sensitivity)	Clinical characteristics	Binary variables (1: yes; 0: no) defined as ⩾1 ICD-10-CM codes of infections in IP setting OR ⩾2 ICD-10-CM codes of infections in the OP/PB setting at least one day apart during the baseline period. The categories of comorbidity conditions are derived from the algorithm by CBER(17). - Asthma	Same	Baseline period, Day [-365, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		- Blood Disorders - Chronic Lung Disease - Diabetes - Heart Disease - Kidney Disease - Liver Disorders - Neurological / Neurodevelopmental Conditions - Malignant Neoplasms The code list is specified in Appendix B.5. One variable will be created for each comorbidity category.		
Immunocompromised status	Clinical characteristics, subgroup identifier	Binary variables (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of immunocompromised conditions in IP/OP/PB settings during the baseline period. The categories of immunocompromised conditions are derived from the validated algorithm by Greenberg *et al.* (28) and an adapted version by CBER(17) and will be evaluated during the baseline period. - Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) - Hematological Malignancy and Related Conditions - Immune deficiencies (treatment-dependent)	Same	Baseline period, Day [-365, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		- Immune deficiencies (treatment-independent) - Solid Malignancy - Transplant and Related Conditions - Rheumatological / Inflammatory Conditions - Dialysis - Other intermediate conditions The code list is specified in Appendix B.5.		
Surgery in close proximity to the index date	Clinical characteristics	Binary variable (1: yes; 0: no) defined as ≥1 CPT/HCPCS codes of surgery in IP settings in 30 days before and after the index date. The code list is specified in Appendix B.7.	Same	30 days before and after the index date, Day [-30, 30]
Trauma in close proximity to the index date	Clinical characteristics	Binary variable (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of trauma in IP/OP/PB settings in 30 days before and after the index date. The code list is specified in Appendix B.4.	Same	30 days before and after the index date, Day [-30, 30]
Bone marrow transplant in the baseline period	Clinical characteristics	Binary variable (1: yes; 0: no) defined as ≥1 CPT/HCPCS codes of bone marrow transplant in IP settings in the baseline period. The code list is specified in Appendix B.7.	Same	Baseline period, Day [-365, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Vaccines in the baseline period	Clinical characteristics	Defined as ≥1 NDC or HCPCS/CPT code of vaccinations of interest in baseline period. Reported as a binary variable (1: yes; 0: no) for the receipt of the following vaccinations: - Any - Seasonal influenza vaccine - COVID-19 - Tdap or Td - Chickenpox (Varicella) - Shingles (Herpes Zoster recombinant and/or live) - HPV - Pneumococcal conjugate - Pneumococcal polysaccharide - Hepatitis A - Hepatitis B - MenACWY and MenB - Haemophilus influenza type B The code list is specified in Appendix B.3.	Same	Baseline period, Day [-365, -1]
Selected medication use in the baseline period	Medication use	Binary variables (1: yes; 0: no) defined as ≥1 NDC or HCPCS/CPT codes of medication in any settings in the baseline period: - TNF-alpha antagonists - Immune checkpoint inhibitors - Immunosuppressant therapies - Isotretinoin The code list is specified in Appendix B.8.	Same	90 days before and on the index date, Day [-90, -1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		One variable will be created for each medication listed above.		
Outcome Variables				
Date of GBS onset	Outcome variables	An incident GBS case will be defined as the first occurrence of a primary discharge diagnosis of GBS in the IP setting post-vaccination during the follow-up period. The date of the case's onset will be defined as the date of hospitalization unless there is a claim with a GBS diagnosis in another medical setting (e.g., OP) in the prior 7 days. In this case, the date of onset will be the date of the GBS diagnosis code in another medical setting within 7 days before the first occurrence of a primary discharge diagnosis of GBS in the IP setting post-vaccination. The ICD-10-CM codes to identify GBS onset are listed in Appendix B.2. Note: An additional 7 days beyond the end of the listed ascertainment windows will be used to identify ICD-10-CM codes for GBS in the IP setting. However, these GBS cases will only be included if there is a GBS ICD-10-CM code for GBS in the OP setting that is both within 7	Same	Follow-up period, (CMS Medicare: Day [1, 84]; PharMetrics Plus: Day [1, 42])

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		days prior to the IP claim and within the listed ascertainment windows.		
Time from index date to GBS onset	Outcome variables	Duration of time from Index Date to Date of GBS onset. Reported as continuous variable in the unit of days.	Same	Follow-up period, (CMS Medicare: Day [1, 84]; PharMetrics Plus: Day [1, 42])
GBS onset in the primary risk interval	Outcome variables	Binary variable (1: yes; 0: no) defined as the Date of GBS onset occurring during the primary risk interval (i.e., 1-21 days after the Index Date).	Same	Primary risk interval, Day [1, 21]
GBS onset in the secondary risk interval	Outcome variables, sensitivity analysis	Binary variable (1:yes; 0:no) defined as the Date of GBS onset occurring during the secondary risk interval (i.e., 1-42 days after the Index Date).	Same	Secondary risk interval, Day [1, 42]
Date of GBS onset in the control interval (of SCRI analysis only)	Outcome variables	Binary variable (1:yes; 0:no) defined as the Date of GBS onset occurring during the control interval of SCRI analysis (i.e., 43-84 days after the Index Date).	Not applicable	Control interval (of SCRI analysis only), Day [43, 84]
Censoring date (for SCRI analysis)	Outcome variables	The date of last clinical encounter, date of death, or the end of the control interval of SCRI analysis (i.e., 84 days after the Index Date), whichever occurs first.	Not applicable	Follow-up period, Day [1, 84]
GBS Case-centered Analysis				
Age on index date	GBS case-centred analysis subgroup analysis	Defined as a person's age at the time of vaccination in the unit of years. Reported as a categorical variable with the following age groups: - 65-74 - 75+	Not applicable	Index Date, Day 0

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Race/Ethnicity	GBS case-centred analysis, subgroup analysis	Reported as a categorical variable with the following categories: - White - Black - Other	Same Note: Race/ethnicity information may not be complete in PharMetrics Plus.	Index Date/ all available time, using record closest to Index Date
ADI Rank	GBS case-centred analysis	Reported as a continuous variable or a categorical variable with the following categories: - Low Deprivation (High socioeconomic status [SES]): ADI rank 1 to 33 - Medium Deprivation (Middle SES): ADI rank 34 to 66 - High Deprivation (Low SES): ADI rank 67 to 100	Not available	Index Date/ all available time, using record closest to Index Date
Frailty Index	GBS case-centred analysis	Reported as a categorical variable with the following categories (25, 26): - Frail (2+) - Pre-frail (1) - Non-frail (0)	Same	Index Date/ all available time, using record closest to Index Date
Facility/Provider type of ABRYSVO Vaccination	GBS case-centred analysis	Reported as a categorical variable with the following categories: - Pharmacy - Hospital/Office Visit - Other	Same	Index Date
Neurologist encounter or diagnostic procedures within 45 days of GBS diagnosis	GBS case-centred analysis	Reported as a categorical variable with the following categories (29): - Neurologist encounter - Diagnostic procedure - Both	Same	45 days before and after the date of GBS onset, Day [Date of GBS onset- 45, Date of GBS onset+45]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Selected diagnoses similar to GBS within 30 days of GBS diagnosis	GBS case-centred analysis	Defined as the presence of ≥1 ICD code in IP/OP/PB setting for the following conditions that are similar to GBS: - Brachial neuritis - Myasthenia gravis - Vasculitic Neuropathy - Diphthelic neuropathy - Botulism - Rhombencephalitis - Basal meningitis	Same	30 days before and after the date of GBS onset, Day [Date of GBS onset- 30, Date of GBS onset +30]
Infections in 42 days before GBS onset	GBS case-centered analysis	Binary variables (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of infections in IP/OP/PB settings within 42 days before the Date of GBS onset: - Any - Medically-attended infections (respiratory, GI or unspecified viral infections) - Upper or lower respiratory tract infections (including diphtheria, whooping cough, streptococcal sore throat and scarlet fever, varicella with pneumonia, RSV, COVID-19, acute sinusitis, acute tonsilitis, acute bronchitis, influenza, etc) - GI infections (including cholera, typhoid and paratyphoid fevers, shigellosis, amebic nondysenteric colitis, etc) - Unspecified viral infection	Same	Within 42 days before the Date of GBS onset, Day [Date of GBS onset- 42, Date of GBS onset-1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		The code list is specified in Appendix B.6. One variable will be created for each infection condition listed above. And another variable will be created for presence of any condition listed above.		
Infections in 42 days before GBS onset (Sensitivity)	GBS case-centered analysis	Binary variables (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of infections in IP setting *OR* ≥2 ICD-10-CM codes of infections in the OP/PB setting at least one day apart within 42 days before the Date of GBS onset: - Any - Medically-attended infections (respiratory, GI or unspecified viral infections) - Upper or lower respiratory tract infections (including diphtheria, whooping cough, streptococcal sore throat and scarlet fever, varicella with pneumonia, RSV, COVID-19, acute sinusitis, acute tonsilitis, acute bronchitis, influenza, etc) - GI infections (including cholera, typhoid and paratyphoid fevers, shigellosis, amebic nondysenteric colitis, etc) - Unspecified viral infection The code list is specified in Appendix B.6.	Same	Within 42 days before the Date of GBS onset, Day [Date of GBS onset- 42, Date of GBS onset-1]

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
		One variable will be created for each infection condition listed above. And another variable will be created for presence of any condition listed above.		
Surgery in 42 days before GBS onset	GBS case-centered analysis	Binary variable (1: yes; 0: no) defined as ≥1 CPT/HCPCS codes of surgery in IP/OP/PB settings within 42 days before the Date of GBS onset. The code list is specified in Appendix B.7.	Same	Within 42 days before the Date of GBS onset, Day [Date of GBS onset- 42, Date of GBS onset-1]
Trauma in 14 days before GBS onset	Clinical characteristics	Binary variable (1: yes; 0: no) defined as ≥1 ICD-10-CM codes of trauma in IP/OP/PB settings within 14 days before the Date of GBS onset. The code list is specified in Appendix B.4.	Same	Within 14 days before the Date of GBS onset, Day [Date of GBS onset- 14, Date of GBS onset-1]
Co-administered vaccinations on index date	GBS case-centred analysis, subgroup analysis	Defined as ≥1 NDC or CPT code of vaccinations of interest on the Index Date. Reported as a binary variable (1: yes; 0: no) for the receipt of the following vaccinations: - Any - Seasonal influenza vaccine - COVID-19 - Shingles (Herpes Zoster recombinant and/or live) - Pneumococcal - Other The code list is specified in Appendix B.3.	Same	Index Date

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
Non-RSV vaccines received in 42 days prior to GBS onset	Exposure characteristics	Defined as ≥1 NDC or CPT code of vaccinations of interest in 42 days before the Date of GBS onset. Reported as a binary variable (1: yes; 0: no) for the receipt of the following vaccinations: - Any - Seasonal influenza vaccine - COVID-19 - Shingles (Herpes Zoster recombinant and/or live) - Pneumococcal - Other The code list is specified in Appendix B.3.	Same	42 days before Date of GBS onset, Day [Date of GBS onset- 42, Date of GBS onset - 1]
Length of inpatient stay due to GBS onset	GBS case-centered analysis	Continuous variable defined as date from the admission to IP setting to the date of discharge, where the primary discharge diagnosis of the IP stay is GBS. The ICD-10-CM codes to identify GBS onset are listed in Appendix B.2.	Same	Time starting from the Date of GBS onset
Death	GBS case-centered analysis	Binary variable (1: yes; 0: no) defined as record of death after Date of GBS onset, defined as the reason for discharge from an inpatient stay.	Binary variable (1: yes; 0: no) using a proxy measure of death, inferred based on the following rules: following the Date of GBS onset, if the patient has a loss of eligibility, examine the claims of mortality flags for the last 60 days of eligibility; if the claims stream ends prior to loss	Duration of inpatient stay due to GBS onset

Table 1. Operational definitions of study variables

Variable	Role	Operational Definition – CMS Medicare	Operational Definition – PharMetrics Plus (if different)	Ascertainment Window
			of eligibility, assess the mortality flags in the last 60 days before the last claim. In patients with mortality flags, the date of the last claim is ascertained as the date of death. (30) The code list of mortality flags is specified in Appendix B.9.	
Death (Sensitivity)	GBS case-centered analysis	Binary variable (1: yes; 0: no) defined as record of death or hospice care after Date of GBS onset as the reason for discharge from an inpatient stay.	None[2]	Duration of inpatient stay due to GBS onset
Respiratory failure due to GBS onset	GBS case-centered analysis	Binary variable (1: yes; 0: no) defined as ≥1 diagnosis codes of respiratory failure during inpatient stay where the primary discharge diagnosis of the IP stay is GBS. The code list is specified in Appendix B.9.	Same	Duration of inpatient stay due to GBS onset

[2] The primary definition for death in PharMetrics Plus is already a proxy that includes hospice care. Therefore, no additional sensitivity definitions will be included.

4.4. Data Source

4.4.1. CMS Medicare Administrative Database

The study will use the CMS Medicare administrative database with monthly data refreshes that include Medicare Parts A, B and D. The study will be restricted to enrollees with FFS. The Medicare claims database includes well-defined longitudinal data that captures healthcare service utilization for millions of enrollees across multiple care settings. Medicare Part A captures the inpatient setting, including critical access hospitals and skilled nursing facilities; approximately 90% of inpatient claims are submitted in 2 months after a healthcare encounter. (10, 11) Medicare Part B covers doctors' services and outpatient care, including outpatient emergency department and outpatient non-emergency department, as well as professional services non-laboratory and laboratory. Medicare Part D covers the pharmacy setting. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. The monthly data consists of a mixture of pre-adjudicated and adjudicated claims; prior research shows that the diagnosis codes rarely change (<0.5%) after adjudication. (10, 11) The use of adjudicated and pre-adjudicated claims data in this study enables near real-time assessment of a potential safety signal.

In this study, the variables will be identified within the relevant care settings. The IP setting represents hospital inpatient acute facility claims, which provide information on the care and services received by patients during the entire duration of inpatient care. These have more accurate diagnosis coding compared to professional claims, as provider facilities are reimbursed based on the types of diagnosis coded, which reflect the level of treatment required. The OP/PB setting represents all outpatient and professional services claims with non-laboratory places of service and captures the broad spectrum of outpatient care regardless of care setting or provider type. Claims with laboratory places of service are excluded as they often include "rule-out-diagnoses" that may not reflect true existing or underlying conditions present in patients.

The demographics of the Medicare FFS population and the coding system used in CMS Medicare data are substantial topics that encompass the broad characteristics of Medicare beneficiaries and the complex system for coding healthcare services, respectively. Below is an overview of both:

The Medicare FFS program covers a diverse population of older adults and some younger beneficiaries with disabilities. The majority of Medicare beneficiaries are aged 65 years of age or older, reflecting Medicare's role as a health insurance program for older adults. However, a significant minority are younger individuals who qualify due to disability. The distribution between male and female beneficiaries in the Medicare FFS population tends to reflect that of the older adult population in the U.S., with a higher proportion of females, especially among the oldest age groups.

Medicare beneficiaries come from diverse socioeconomic backgrounds, but the program plays a critical role for lower-income individuals who might otherwise be unable to afford health insurance. The health status of Medicare FFS beneficiaries vary widely, from healthy individuals to those with multiple chronic conditions and serious disabilities. The program covers many individuals with high healthcare needs and expenditures. Medicare FFS beneficiaries are located across the United States, including both urban and rural areas, with distribution patterns reflecting the broader population distribution.

Medicare data utilizes several coding systems to document diagnoses, procedures, and equipment used in the care of beneficiaries. These include ICD-10-CM, used for diagnosis coding in all healthcare settings; ICD-10-PCS (Procedure Coding System), used for inpatient hospital procedure coding; CPT, used in billing process for medical procedures in medical, surgical, and diagnostic services in outpatient and professional services; and HCPCS, also used for medical procedures, such as ambulance services and durable medical equipment. The use of these coding systems ensures that Medicare billing is standardized, allowing for the efficient processing of claims and the collection of data for analysis and policy development. Note that cells containing <11 patients in these data will be masked.

4.4.2. IQVIA PharMetrics Plus Commercial Claims Database

The PharMetrics Plus database is one of the largest U.S. health insurance claims databases comprised of fully-adjudicated medical and pharmacy claims with approximately 3.1 million annual enrollees aged 60 to 64 years. Data contributors are largely commercial health plans, with a 6-month data lag due to claims adjudication. PharMetrics Plus has diverse representation of geography, employers, payers, providers, and therapy areas, therefore the database is representative of the commercially insured U.S. national population for individuals under 65 years of age. In the post-launch and in-market phase, PharMetrics Plus has a been utilized in providing robust insights in areas such as comparative effectiveness, medication adherence, patient cost analyses and also aids in pharmacovigilance and safety by tracking and analyzing the adverse effects of medications and vaccines. (18)

The comprehensive patient insights provided by PharMetrics Plus are driven by several key attributes. For patient demographics, it includes the year of birth, gender, ZIP3 (the first three digits of the ZIP code), state, enrollment dates, and payer/plan type. PharMetrics Plus also details primary care and specialty visits, capturing event dates, diagnosis codes, ordered laboratory tests, procedure codes, and provider specialties, providing understanding of the nature of healthcare interactions of patients. Additionally, the information of medication use can be captured with data on fill and refill dates, retail, mail order, specialty medications, formulary status, status medications, quantity and days supplied, providing a comprehensive view of medication adherence and usage patterns.

Furthermore, the data offers insights into hospital admissions and discharges, including admission dates, inpatient length of stay, discharge status, diagnosis codes, inpatient procedures, ER visits, and provider specialties, enabling the assessment of healthcare utilization and patient outcomes. Similarly, for outpatient medication and vaccine administration, PharMetrics Plus records the date of administration, diagnosis codes, service units, procedure codes and provider specialties, ensuring comprehensive tracking of outpatient care.

4.5. Sample Size and Power Calculations

Medicare

All eligible Medicare beneficiaries aged 65 years of age or older who receive ABRYSVO during the surveillance period will be included. Currently, there were approximately 1,155,000 individuals vaccinated with ABRYSVO through February 2024 for CMS Medicare and approximately 40,000 individuals aged 60-64 vaccinated with ABRYSVO in PharMetrics

Plus; from prior experience, with 15% attrition due to the requirement of continuous enrollment in Medicare Parts A, B and D, ~1 million individuals are anticipated to be eligible for the 2023/2024 season analysis. Assuming a similar uptake for the 2024/2025 season, for the pooled analysis, a sample size of ~2 million ABRYSVO exposures are anticipated by the end of study period.

Table 2 outlines the sample size calculations required for a conditional Poisson regression using the SCRI design, across different IRR. To detect a lower IRR, the total number of GBS events needed increases, as does the number of vaccinated individuals required for both risk intervals. Specifically, to detect an IRR of 5.0, 15 GBS events are needed, with 1,153,846 and 566,038 vaccinated individuals for analysis in the 21-day and 42-day post-vaccination risk intervals, respectively. Conversely, to detect an IRR of 2.0, 69 GBS events are needed, with significantly higher requirements of 8,846,154 and 4,339,623 individuals for the 21-day and 42-day post-vaccination risk intervals, respectively. Based on an expected background rate of 4.6 per 100,000 person-years for incident GBS in the Medicare population aged 65 years of age or older (31) and estimated uptake of ABRYSVO in the Medicare FFS dataset from 2023/2024 RSV season, the study is anticipated to be able to detect a highly elevated risk of GBS (5.0- fold or lower) with 80% power and an alpha level of 0.05 during a 21- or 42-day risk interval following vaccinations in each RSV season. Pooled analysis combing data from 2 RSV seasons is anticipated to have 80% power to detect a modest risk of GBS (e.g., 3.0- to 4.0-fold). Pfizer has an ongoing PMR PASS (protocol # C3671031) spanning 4.5 RSV seasons or more to detect any small or modest risk of GBS (e.g., 2-fold) following ABRYSVO vaccination using the CMS Medicare database. The current PASS described in this protocol (protocol # C3671054) is aimed to generate rapid safety evidence until the results of the PMR PASS (protocol # C3671031) are available.

Table 2. Sample size calculations for the conditional Poisson regression using the SCRI design

IRR	Total number of GBS events needed	Number of events expected in control interval	Number of vaccinated individuals needed for 21-day risk period (N)	Number of vaccinated individuals needed for 42-day risk period (N)
5.0	15	3	1,153,846	566,038
4.5	17	4	1,538,462	754,717
4.0	20	4	1,538,462	754,717
3.5	23	6	2,307,692	1,132,075
3.0	29	8	3,076,923	1,509,434
2.5	41	12	4,615,385	2,264,151
2.0	69	23	8,846,154	4,339,623

Notes: Sample size calculations for the SCRI design were performed according to the method by Musonda et al.(32) The calculations are based on assuming a two-sided α=0.05, a power of 80%, and for the 4th column, a risk interval of 21 and a control interval of 42 days. Calculations were also

Table 2. Sample size calculations for the conditional Poisson regression using the SCRI design

IRR	Total number of GBS events needed	Number of events expected in control interval	Number of vaccinated individuals needed for 21-day risk period (N)	Number of vaccinated individuals needed for 42-day risk period (N)

performed using a 42-day risk interval and a 42-day control interval for secondary analyses in the final column. These calculations are based on an equal length of the control and risk interval and provide a conservative estimate of sample size as compared to calculations based on variable lengths of the control and risk interval. For all sample size calculations, each individual must be included in the risk and control intervals.

PharMetrics Plus

For the PharMetrics Plus analysis, the primary study population will consist of adults 60-64 years of age enrolled in healthcare plans captured in the PharMetrics Plus database without a prior history of GBS as assessed during a 12-month baseline period.

Based on medical and pharmacy claims through December 31, 2023, approximately 46,000 individuals between 60 and 64 years of age received ABRYSVO in the PharMetrics Plus database. The PharMetrics Plus analysis will be descriptive in nature; the inferential analysis, SCRI, may be considered contingent on sample size.

4.6. Missing Data

When missing data occur, no imputation will be made, and all statistics will be calculated with non-missing values. Counts and percentages of missing values will be presented in the tables where applicable.

4.7. Statistical Methodology and Analyses

The attrition of individuals and their demographic and clinical characteristics will be described using summary statistics, categorized by analytical cohorts. Analytical cohorts will be built separately depending on whether an individual is qualified for RCA and/or the SCRI [Table shell 1a], or the descriptive analysis for PharMetrics Plus [Table shell 1b] and will be specific to the RSV season of interest.

For each cohort, continuous variables will be summarized using means and standard deviations, while binary and categorical variables will be summarized using counts and proportions.

An RCA analysis will be used to monitor the risk of GBS following ABRYSVO vaccination using a group sequential testing approach. The methodology enables near real-time surveillance, comparing observed rates of GBS after ABRYSVO vaccination to the background rates of GBS. The raw and adjusted relative risk (RR) of GBS will be estimated monthly in the 2024/2025 RSV season, based on cumulative vaccination data from the 2023/2024 RSV season, and a group sequential Poisson-based likelihood ratio test will be used to test if it is above the pre-specified RR threshold of 2, adjusting for multiple comparisons. If a signal of GBS is detected, signal verification will be performed to rule out bias due to other GBS risk factors.

The SCRI methodology will evaluate the risk of GBS following ABRYSVO vaccination by comparing the incidence of GBS during pre-specified risk and control windows within the same individual after ABRYSVO vaccination. This method inherently controls for time-invariant confounders. A conditional Poisson regression model will be used to estimate IRRs and 95% confidence intervals (CIs). The null hypothesis states that the IRR equals 1, which means there is no increased risk of GBS after ABRYSVO vaccination; the alternative hypothesis is that the IRR is not equal to 1. A significance level of 0.05 will be used for testing. The Attributable Risk (AR) will be calculated to contextualize the additional risk of GBS, presenting the excess number of cases per million vaccine doses and per 100,000 person-years. This calculation helps to highlight associations without presuming causality.

Together, the RCA and SCRI methodologies will allow for timely signal detection and the ability to perform an in-depth analysis that is hypothesis-driven and well-controlled for time-invariant confounders. See Appendix A: Table Shells for table shells.

4.7.1. Index Date and Follow-up

The index date will be defined as the date of the first ABRYSVO vaccination for each individual within the study period of interest, i.e., the 2023/2024 and/or the 2024/2025 RSV season. This date serves as the study anchor for the baseline period, and the follow-up period [Table shell 4].

The risk intervals of the follow-up time refer to the time period following the index date during which the individual is considered at risk of developing the study outcome (e.g., GBS onset) due to exposure. In the control intervals of the follow-up time, the same individual is considered unexposed to vaccination and will be used to compare the risk of the study outcome (e.g., GBS onset) against the exposed period.

The follow-up periods of the RCA, SCRI and descriptive analyses are described in Section 4.1.1.1, 4.1.2.1, and 4.1.3.1. The follow-up periods are also summarized below:

- RCA, where the follow-up ends at the end of the risk interval.
  - Risk interval: 1-21 days post-index
  - Secondary risk interval: 1-42 days post-index
- SCRI, where the follow-up ends at the end of the control interval.
  - Primary risk interval: 1-21 days post-index, with days 22-42 acting as a “washout period” not included in the analysis to avoid any carryover effects
  - Secondary risk interval: 1-42 days post-index
  - Control interval: 43-84 days post-index
- Descriptive analysis in PharMetrics Plus, where the follow-up ends at the end of the risk interval.
  - Risk interval: 1-21 days post-index
  - Secondary risk interval: 1-42 days post-index

Censoring occurs when an individual's follow-up period is cut short due to reasons other than the occurrence of the study endpoint (i.e., GBS onset). This ensures that the analysis only includes time during which individuals are truly at risk of experiencing the endpoint. A patient's follow-up time will be censored at the first of: loss to follow-up (i.e., the date of disenrollment from Medicare FFS, including switching to Medicare Advantage), end of the follow-up period, or death (i.e., the date of death will be the censoring date).

4.7.2. Risk Window Definitions

In the RCA, the primary risk interval will be 1-21 days following the index date. A secondary risk interval of 1 – 42 days after the index date will also be used in the RCA with a shortened indexing period.

In the SCRI and descriptive analyses, 1-21 and 1-42 days after the index date will be used as the primary and secondary risk intervals, respectively. Days 22-42 after the primary 1-21 days risk interval will be considered a washout period and will not be included in the analyses to avoid any carryover effects.

4.7.3. Primary Analyses

4.7.3.1. Data Lag

In the analysis of CMS Medicare data, the approach to account for data lags in the RCA and SCRI is to delay the analysis for at least 60 days post-data cut-off to allow for at least 90% capture of data for post-vaccination risk and control intervals. Prior research suggests that ≥ 90% of IP and OP claims were submitted to the CMS within 2 months after service date. (10, 11) While imposing a lag in the analysis negatively impacts the timeliness of safety assessment, it allows the data to be more complete and thus increases the validity of results. In a non-pandemic setting where the initial uptake for the RSV vaccines is modest, the trade-off between timeliness and validity is deemed acceptable, and a similar approach has been used in prior safety monitoring for Shingrix after product approval.(33) Data lags will be assessed during the interim reports and a lag longer than 60 days (e.g., 90 days) may be considered for the final analysis, as necessary and feasible, to accrue the most stable data.

The PharMetrics Plus data has a longer data lag of approximately 6 months due to claims adjudication and completeness, making it unsuitable for the monthly sequential monitoring component (i.e., RCA) component of the study. However, it will effectively contribute to the descriptive analysis (SCRI may be considered contingent on sufficient sample size), to be conducted towards the end of each RSV season and at the final two-season pooled analysis. This analytic arrangement accounts for the data lag and still generates timely safety data for GBS in individuals aged 60-64 years following exposure to ABRYSVO. (Section 4.1.3.1).

4.7.3.2. Description of ABRYSVO Recipients

Covariates will be assessed among the study population aimed for SCRI, RCA and the descriptive analysis in PharMetrics Plus (Section 4.3.3). Individual demographic and clinical characteristics including but not limited to age on index, gender, race, geographic region, and ADI [Table shell 2 and Table shell 3]. Demographic variables will be assessed on the index date or during the baseline period. If multiple records exist, the record closest to the

index date will be used. Concurrent immunizations, prior infections, selected comorbidities, healthcare resource utilization and selected medication use in the baseline period will be reported.

Continuous variables will be summarized using mean, standard deviation (SD), median, and interquartile range (IQR). Categorical variables will be summarized using counts and proportions. 95% CIs will be provided where applicable.

4.7.3.3. The Statistical Analysis for the RCA

In order to conduct near real-time surveillance to monitor the risk of GBS following RSV vaccination, a group sequential testing approach will be used to compare the observed rates of GBS following vaccination to an incidence rate of GBS from a suitable comparator population (referred to as the background rate; Section 4.7.3.3.1.3) [Table shell 5a-1].(33-35) *Each month, an adjusted RR of GBS will be estimated to conduct an exact sequential Poisson-based likelihood ratio test using unifying family group sequential methods* [Table shell 5b], *previously described by Nelson et al.(33-35) This methodology is suited for continuously accumulating data, enabling timely monitoring and decision-making regarding vaccine safety concerns.* Adjustment of the RR refers to accounting for differences in the distribution of selected variables between the RSV vaccinated individuals and the historical comparator group of influenza-vaccinated individuals.

The group sequential testing will be used to conduct sequential tests with cumulative monthly data, with the first monthly analysis starting December 2024 when >90% completeness in follow-up data for ABRYSVO vaccinations through 10 September 2024 are expected. The first RCA look will include data from the complete 2023/2024 and part of the 2024/2025 RSV seasons. To avoid spurious signals from a few early events, sequential testing for GBS will commence when a minimum of three GBS cases have been accrued.

The RR of GBS will be the target parameter, defined as the ratio of the observed GBS rate and the expected GBS rate in the ABRYSVO population. We will conduct one-sided tests where the null hypothesis is that the observed rate of GBS in the ABRYSVO cohort is no greater than 2 times the comparator rate. The alternative hypothesis is that the observed rate in the ABRYSVO cohort is greater than 2 times than the comparator rate:

H_0: *RR ≤ 2*

H_a: *RR > 2*

In previous literature, a pre-specified the test margin with an overall alpha of 1% was used to obtain a null hypothesis of "RR ≤ 2.5" for assessing the risk of GBS following COVID-19 vaccination to avoid minimal risk increases that were unlikely to be clinically relevant.(36) In this study, the RR and test margin are more conservative to allow for early detection of a safety signal.

The expected number of events under the null hypothesis will be used as the upper limit on number of tests to be conducted (i.e., the pre-specified surveillance length), described further in Section 4.7.3.3.1.3*. Sequential testing will continue until a signal is observed or the pre-specified surveillance length is reached (Section* 4.7.3.3.3*), after which signal detection of the GBS rates will continue, which will increase the precision of the incidence estimates until the end of the study period.*

The RCA is meant to rapidly detect if there is a signal for an elevated risk of GBS following vaccination with ABRYSVO. In the monthly analyses, if the risk meets the signal threshold, rejecting the null does not imply a causal association and further steps will be taken to evaluate the robustness of signal and to characterize the signal, described in Section 4.7.3.3.4.

4.7.3.3.1. The Historical Comparator Group

The historical comparator group will be used to estimate the background rate of GBS in the RCA analysis. The historical group will be chosen from an influenza-vaccinated population aged ⩾65 years of age or older from the CMS Medicare database. The detailed inclusion and exclusion criteria are described in Sections 4.7.3.3.1.1 and 4.7.3.3.1.2, respectively, which mimics the eligibility criteria for the ABRYSVO exposed cohort to increase comparability. The historical influenza comparator cohort is expected to be significantly larger than the ABRYSVO-vaccinated cohort. Therefore, a sampling method may be used to create the comparator cohort for generating the background rate. To reduce the total sample size and preserve statistical power, a 10% random sample will be taken from the non-GBS cases in the influenza-vaccinated cohort, stratified by age, gender, race/ethnicity and time of vaccination, along with all individuals that were GBS cases during the primary or secondary risk intervals. Descriptive statistics of demographic and clinical characteristics will be calculated separately for events and non-events and a weighted sum of the characteristics will be computed accounting for the under-sampling of non-events. This approach, called under-sampling of the non-events for rare event data, has been commonly used in rare-event studies.(37, 38) The estimated probability of having a GBS event using the sample can be adjusted to generate an unbiased estimated probability based on the method described by Wang 2020.(39) This approach has limitations given the GBS rate will not be directly generated from the full influenza-vaccinated cohort. However, the stratified random sampling approach reduces the random error introduced by random sampling.

The distribution of selected baseline characteristics will be presented for the historical comparator group and the ABRYSVO groups, to assess variables that should be accounted for to enhance comparability with the ABRYSVO-vaccinated cohort [Table Shell 5a-2]. The candidate variables include but are not limited to:

- Gender (male vs. female)
- Age (65-74, 75+)
- Race/ethnicity (Black, Other, White)
- Nursing home residency status (yes vs. no)
- Immunocompromised status (yes vs. no)
- Timing of vaccination (high vs. low season)
- CCI (0-1, 2+)

4.7.3.3.1.1. Inclusion Criteria

Individuals in the historical comparator group must be enrolled in the CMS Medicare databases and must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Receiving one dose of influenza vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during the influenza season;

2. At least 65 years of age on the index date;

3. Medicare beneficiaries who aged into Medicare;

   Note: Beneficiaries who qualify due to disability differ from beneficiaries who qualify due to age in several ways, including their demographic, socioeconomic, and health status profiles. To reduce potential confounding from this specific frail Medicare population that could have a different association between vaccination and GBS, they are not included in the study population.

3. At least 12 months of continuous enrollment in Medicare Parts A and B prior to the index date (i.e., the baseline period); and

4. At least 3 months of continuous enrollment in Medicare Part D prior to the index date.

4.7.3.3.1.2. Exclusion Criteria

Individuals meeting any of the following criteria will not be included in the study:

1. Individuals without sex information;
2. Individuals with a GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.

4.7.3.3.1.3. The Background Rate of GBS

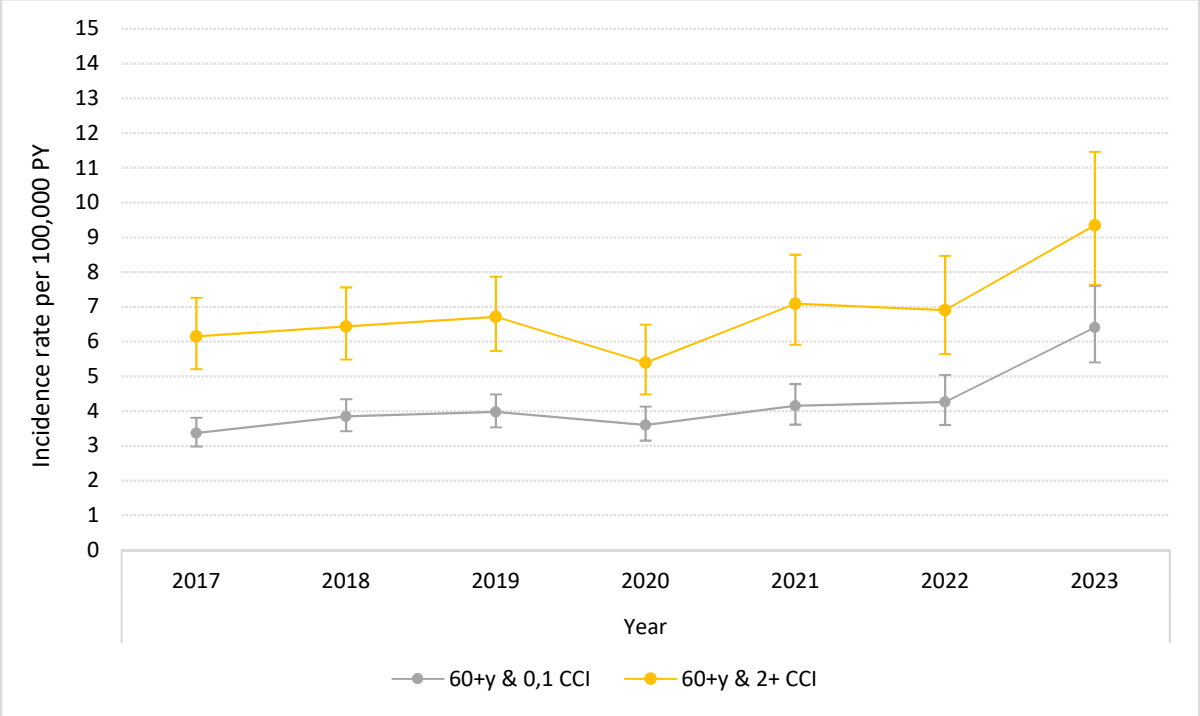
The observed number of GBS cases in the ABRYSVO-vaccinated population will be compared to an expected number of GBS cases based on the background rate of GBS calculated for a historical influenza-vaccinated population from the CMS Medicare database, described in Section 4.7.3.3.1. *Although the background rate of GBS has been previously estimated from the general Medicare beneficiaries (31), we hypothesize that the historical influenza-vaccinated comparator group will have greater similarity to recipients of RSV vaccines than the general Medicare beneficiaries in terms of demographics, clinical characteristics and health-seeking behavior.*

The background rate of GBS will be estimated for individuals in the CMS Medicare database that received the seasonal influenza vaccines in the 2022 and 2023 influenza seasons before ABRYSVO approval. This decision was influenced by recent literature indicating a 41.2% increase in the prevalence of GBS in North America between 1990 and 2019 and also an internal preliminary analysis in Optum's de-identified Market Clarity Data indicating a significant increase in annual incidence rates of GBS in older adults over time (Figure 8).(31, 40) This internal analysis was previously presented to the FDA in a document titled

"Request for Comments and Advice Regarding RSV Vaccine Safety Study (28 August 2024)." Considering the updated knowledge regarding an increasing trend in incidence of GBS, it is more appropriate to use the more recent historical cohorts for background rate estimation to minimize biases due to secular trends.

In Table shell 5a-1, the background rate GBS in the historical influenza-vaccinated comparator group will be reported. The characteristics of this comparator group will be presented in Table shell 5a-2.

Figure 8. Incidence rates of GBS among adults 60+ years of age by Charlson Comorbidity (CCI) (0,1 conditions versus 2+ conditions) in the United States from 2017-2023[3]



Abbreviations: CCI, Charlson Comorbidity Index; PY, person-years.

Stratum-specific GBS rates will be estimated via logistic regression from the historical comparator group, and the total number of expected outcomes among the ABRYSVO-vaccinated population will be computed as a weighted average across all selected covariate strata. Given GBS is a rare event, the statistical power of a logistic regression model is limited by the number of GBS cases. After reviewing the demographic and clinical characteristics of the RSV vaccinated cohort and the historical comparator influenza-vaccinated cohort, candidate variables for inclusion in the logistic regression will be selected

[3] Pfizer's preliminary analysis in Optum's de-identified Market Clarity Data, previously presented to the FDA in a document titled "Request for Comments and Advice Regarding RSV Vaccine Safety Study (28 August 2024)."

for the model based on *a priori* knowledge of the variable as a confounder of vaccination type and GBS as well as based on descriptive differences in the distribution of the variable between the two cohorts. Collinearity between the independent variables will be checked. A conditional index > 10 will be considered as the presence of high collinearity. A model selection will be conducted after checking collinearity. Given the importance of the variables, age and CCI may be forced in the model.

4.7.3.3.2. Boundaries for Group Sequential Tests

A total of six tests are planned (see Section 4.1.1). The approach described by Nelson et al, 2013, will be followed.(35) In brief, a unified group family method with Pocock's boundary will used to compute the sequential stopping boundary. With a Pocock boundary, the sequential stopping boundary can be presented as C (T, α, Δ) or C(T=6, α = 0.05, Δ = 1/2), in which T is the number of tests planned, α is the significant level, and Δ is an index that determines the shape of the threshold over time (Δ = ½ for Pocock's boundary). The null hypothesis H_0 will be rejected at test t if the log likelihood ratio (LLR) exceeded this preset stopping threshold. The critical value, C, will be computed via simulation at each sequential test and accounted for any changes over time in the confounder distribution in the study population and any difference between the planned and the actual number of ABRYSVO vaccines observed at the time of the test. The critical value, C, will be computed as following steps:

Step 1. The number of expected GBS cases under the null hypothesis among ABRYSVO recipients (E_t) will be computed for the six sequential tests. To compute the expected number of GBS following ABRYSVO vaccination, the 2022 and 2023 influenza seasons before ABRYSVO approval will be used.

Given H_0: RR= 2.0, the expected GBS rate in the ABRYSVO group (R_A) under the null hypothesis is twice the GBS rate in the historical comparator group (R_H). R_H during the specified period above is the number of GBS cases divided by number of patients in the historical comparator group times 100,000 to get a GBS rate per 100,000 doses. The expected numbers of GBS cases in the ABRYSVO group at test *t* (E_t) will be estimated by $2R_H \times n_t/100{,}000$, where n_t is number of patients in the ABRYSVO group at test *t*. The expected numbers of GBS cases will be estimated before the analysis of the first test starts and will not be re-estimated for the tests that are already conducted.

Step 2. Using E_t estimated in Step 1, the number of GBS cases observed at each of the six sequential tests (O_t) will be simulated under the null Poisson distribution with mean E_t.

Step 3. For each of the six sequential tests, the relative risk $RR_t = O_t/E_t$. Since the one-sided alternative hypothesis $RR_t>1$ then, RR_t will be set to 1 if its computed values < 1. The Poisson log likelihood ratio LLR_t test statistic will be computed as:

$$LLR_t = E_t - O_t + O_t \times \log(RR_t)$$

Step 4. Identify the maximum log likelihood ratio (LLR_{max}) among six tests.

Step 5. Repeat Step 1-4 100,000 times.

Step 6. The critical value C will be the 95th percentile of LLRmax across all 100,000 simulated datasets, which ensures the Type I error is 5%.

4.7.3.3.3. Group Sequential Tests

For each of the six sequential tests, LLR statistic will be computed using a Poisson likelihood ratio test to compare the observed number of GBS cases among accrued ABRYSVO recipients with the expected number based on historical comparator data. If historical comparator group cannot be appropriately adjusted to match the distribution of patient characteristics in the ABRYSVO group, further covariate adjustment will be conducted in the Poisson regression model. The LLR statistic will be compared against the pre-calculated boundary value at each test. If the LLR statistic is greater than the boundary value, H_0 will be rejected. Further investigation of the GBS cases will be conducted as described in Section 4.7.3.3.5.

4.7.3.3.4. Programming Verification Check

Regardless of whether the H_0 is rejected, the following programming verification checks will be performed to ensure the robustness of analysis:

- Check for duplications of vaccinations, safety outcomes, or persons (e.g., if subsequent claims are counted as new episodes of vaccination or AESIs)
- Check for coding issues (e.g., unexpected codes for vaccinations)
- Check for changes in claims recording processes
- Check for unusual variability in claim accrual by process date and by service date

4.7.3.3.5. Signal Characterization

In the monthly analyses, if the H_0 is rejected, *further steps will be taken to evaluate the robustness of signal and to characterize the signal, including:*

- Evaluate patient's diagnoses, vaccinations, treatments, and procedures surrounding the date of each case (This is part of the case-centered analysis)
- Evaluate the geographical distribution of cases, checking for over or under-representation of state or regions
- Evaluate the distribution of demographic and clinical characteristics among the cases and compare with the distribution of these characteristics in the population used to calculate the background rate
    - Check for over- or under-representation of certain demographics; estimate relative risks within patient strata (e.g., NSH, sex, age, race, CCI, immunocompromised status)
    - Summarize covariate distributions of vaccinated individuals compared to comparator population
- Assess the frequency of individual codes, the clinical setting of cases and specialty of diagnosing physicians and compare to historical periods
- Assess whether there was a change in diagnostic criteria or guidelines of detecting GBS
- Assess for temporal clustering of cases in the risk window through temporal scans

Based on the post-signal data quality assurance check and signal characterization, the RCA may be re-run to assess if the positive signal persists when any potentially invalid GBS cases are excluded.

Lastly, an SCRI analysis will be conducted to further evaluate signals from the RCA results.

4.7.3.3.6. Sensitivity Analyses for the RCA

4.7.3.3.6.1. PPV-adjusted Quantitative Bias Analysis

As described for the SCRI in Section 4.7.3.4.3.2, a PPV-adjusted analysis will be conducted for the RCA analytic population for both the primary and secondary risk intervals [Table Shell 5b].

4.7.3.4. *The Statistical Analysis for the SCRI*

The SCRI analysis will be conducted separately in the CMS Medicare databases and PharMetrics Plus database.

Note: Based on feasibility numbers, approximately 40,000 individuals with ABRYSVO exposure are anticipated in the PharMetrics Plus database in one season, which would not allow the conduct of SCRI. Therefore, a descriptive analysis of this database will be performed for the 2023/2024 and 2024/2025 RSV seasons as well as the pooled analysis, and the inferential SCRI may be conducted if sufficient exposures are accrued (~100,000) to detect an IRR of 10 or less or if scientific exploration is needed.

In the SCRI methodology, each ABRYSVO-vaccinated beneficiary serves as their own control as we assess the risk of experiencing GBS during a pre-defined post-vaccination risk interval to a post-vaccination control interval within the same individual (Section 4.1.2.1). The study population will include all exposed individuals that meeting the inclusion and exclusion criteria, but only individuals who develop GBS cases will contribute to the risk estimation. This approach inherently controls for time-invariant confounding variables and is a widely recognized method in vaccine safety research but may be susceptible to time-varying confounding, which can be minimized by choosing a control interval close to the risk interval.

In the analysis, GBS cases that occurred within the first 84 days following vaccination will be included and separated out into the risk and control window [Table Shell 6a]. *The population summary statistics will be provided for each window.*

A conditional Poisson regression model will be used to estimate the IRR and 95% CI, offset by the length of observation time. The model will include an indicator for the risk window as the predictor variable, an offset equal to the log of the window length and will condition on an identification variable for the beneficiary. The model can be written as:

$$log(p) = \beta(risk\ window) + log(interval) + strata(beneficiary\ id)$$

where p is the risk of GBS, interval represents the length of the respective window in days, and beneficiary id is the term identifying the patient. In the primary analysis, the risk window is 1-21 days post-vaccination, and the control window is 43-84 days post-vaccination. In the secondary analysis, the risk window is 1-42 days post-vaccination, and the control window is 43- 84 days post-vaccination. Under this model, our null and alternative hypotheses are:

H_0: $e^{\beta} = 1$ *(i.e., IRR = 1)*

H_a: $e^{\beta} \neq 1$ (i.e., IRR $\neq$ 1)

Where e^{β} is the IRR of GBS in the risk window compared to the control window. Thus, the significance of the coefficient on the risk window variable at a pre-specified level will indicate a significant association between RSV vaccination and GBS. The statistical significance will be determined using a two-sided hypothesis test of increase using a significance level of 0.05 [Table Shell 6a].

The AR will also be presented for both the primary (21-days risk window) and secondary (42-day risk interval) analyses [Table shell 6a], *and will be defined as:*

- *X events per 1 million doses*
- *X events per 100,000 person-years*

The crude and fully-adjusted AR and 95% confidence intervals (CI) can be manually calculated using the following formulas.(41)

$$\textbf{AR per million doses} = \frac{1{,}000{,}000 * \frac{IRR-1}{IRR} * cases\ in\ the\ risk\ interval}{Number\ of\ eligible\ vaccinations}$$

$$\textbf{AR per 100,000 person-years} = \frac{100{,}000 * \frac{IRR-1}{IRR} * cases\ in\ the\ risk\ interval}{Total\ eligible\ person-years}$$

In the formulas above, the number of cases in the risk interval is conditional on seasonality trends during the study period, adjusted for PPV. Findings from the first interim report suggest that seasonality adjustment had minimal impact on the IRR of GBS following ABRYSVO vaccination; thus, the GBS case numbers adjusted for PPV *only* should closely approximate the number of cases adjusting for both seasonality and PPV. Bootstrapping may be attempted to provide a more accurate estimate for AR in the final study report, pending sufficient timeline.(17) The estimation of standard error of the AR will be attempted by bootstrap resampling 10,000 times. For each iteration, this study will sample the beneficiaries with outcomes with replacement and calculate the AR. The standard error is then calculated as the square root of the variance of the 10,000 AR values.

The analysis of AR does not presume a causal relationship between the ABRYSVO exposure and the GBS onset. Rather, the analysis serves as a method to contextualize the additional risk (i.e., incidence) of the GBS onset more intuitively, to identify the difference in risk in the exposed window compared to the unexposed window. The AR calculations can highlight associations but not definitively establish causal effect.

The final pooled SCRI analysis will be conducted by aggregating individual-level vaccination data from two seasons into one analytic file.

Additional adjusted analyses will be conducted and are described in Section 4.7.3.4.3*.*

4.7.3.4.1. Pooled SCRI Analysis for the 2023/2024 and 2024/2025 RSV Seasons

The pooled SCRI analysis aims to evaluate the risk of GBS following RSV vaccination by combining data from the 2023/2024 and 2024/2025 RSV seasons. The analysis population will include all individuals who received the RSV vaccine during the entire indexing period

and meet the inclusion and exclusion criteria for the SCRI analysis. The index date and follow-up periods are specified in Section 4.1 and 4.2.

The individual-level data for individuals that receive the vaccine in either season will be aggregated into a single analytical file. Currently, only one dose of ABRYSVO is approved and recommended and evidence suggests RSV vaccines appear to provide protection for at least two RSV seasons. Therefore, revaccination is not anticipated during the study period. In the event where a patient had one more than one vaccination records in the pooled SCRI analysis, this will be flagged as an off-label use and numbers will be reported. Only the first exposure to ABRYSVO will be included in the pooled SCRI analysis. A conditional Poisson regression will be used to estimate the IRR and 95% CIs.

4.7.3.4.1.1. Risk Time Trend analysis for Pooled SCRI Analysis

To examine any change in post-vaccination GBS risk over time in Medicare data, a risk time trend analysis will be conducted for the SCRI analysis *using the sample pooled from two seasons.* (22) An SCRI model will be fit as the following:

$$\log\big(E(Y|X)\big) = \beta_1(risk\ window) + \beta_2(risk\ window \times vaccination\ timing) + \log(window\ length) + strata(patient\ ID)$$

Where:
$Y = GBS\ outcome$
$risk\ window = binary\ term\ indicating\ risk\ or\ control\ window$
$vaccination\ timing = days\ since\ Abrysvo\ approval\ date$
$window\ length = interval\ (risk\ or\ control\ window\ length)$
$patient\ ID = term\ identifying\ the\ patient$

The model allows the risk of GBS in the risk window to change over calendar time, while assuming it remains constant in the control window over calendar time. Due to the low number of observations, we assume linearity of change in GBS risk. $Exp(\beta_2)$ represents the change in risk per unit time since ABRYSVO approval date. High vs. low season timing of vaccination may also be added to the model.

4.7.3.4.2. Subgroup Analyses

Subgroup analyses may be conducted for the pooled analysis of 2023/2024 and 2024/2025 RSV seasons, pending sufficient sample size [Table shell 6b]. *The following is a list of stratification variables under consideration:*

- Gender (male vs. female);
- Age, where potential subgroups below will be determined based on sample size:
  - 65-74 vs 75+
- Race, where the subgroups are specified below:
  - White, Black, Other
- Concomitant vaccines on the index date, where there are binary subgroups and categorical subgroups:
  - Binary subgroups: yes vs. no; and

- Subgroups by individual vaccines: Influenza, Pneumococcal, COVID-19, Shingles, and Other;

- Presence of prior infections in close proximity (within 30 days) of index date (yes vs. no).

4.7.3.4.3. Sensitivity Analyses for the SCRI

This section outlines a multi-faceted approach to address potential biases and confounding in SCRI to evaluate the safety of ABRYSVO vaccination [Table shell 6a].

4.7.3.4.3.1. Seasonality Adjustment

Given that GBS has been seen to be associated with infections such as wild-type influenza, it may exhibit trends that correlate with specific times of the year, which may introduce bias into the analysis if not properly adjusted for. To evaluate potential time-varying confounding, the study will adjust for the changing risk of GBS over calendar months. Baseline outcome risk will be estimated from a similar population during the same calendar months in the 2022/2023 season and will be included as an offset term in the Poisson regression model.

The seasonality adjustment methodology is to use data from the World Health Organization and the National Enteric Virus Surveillance System to determine weekly influenza rates and determine the expected rate of GBS. Seasonality of influenza will be measured and introduced into the SCRI analysis in the following manner:

1) Choosing Seasonality Metric: the weekly rate of confirmed influenza will be calculated as the total positive influenza count (the sum of positive tests for all sub-strains of influenza (A (H1N1), A (H3), A (unidentified), B, Bvic, Byam, H3N2v)) divided by the total number of specimens submitted.
2) Defining “high” and “low” Seasons for Each Region: weeks with an influenza rate in the upper 25th percentile (i.e., 10 weeks) will be deemed to be in the “high” influenza season while the remaining weeks (i.e., 30 weeks) will be deemed to be in the “low” influenza season, for each HHS region.
3) Estimating Regional Baseline Risk: expected weekly number of GBS cases for each region will be estimated using the fitted value from a Poisson regression model.
    a. Influenza season (“high” or “low”), as determined in (2), was the independent variable (dummy for “high” influenza season)
    b. Log of total FFS beneficiaries enrolled for each respective week and region will be used as the offset.
4) Calculating Weekly GBS Predicted Probability: the weekly number of GBS cases will be predicted for each regional model and divided by the number of FFS beneficiaries from that region in that week to get a predicted GBS rate by region and week.
5) Calculating Weighted National GBS Predicted Probability for Each Week: the weekly predicted GBS probabilities from (4) will be aggregated by region and weighted using the proportion of observed number of FFS beneficiaries in each region as the weight.

6) Calculating Cumulative Risk: Poisson regression model will be used to estimate cumulative risk in risk interval and control interval for each beneficiary included in the SCRI analysis.

    a. Cumulative risk will be calculated by summing weekly national baseline risk of GBS for risk and control period.

    b. Risk of getting GBS in a particular week will be partially dependent on not having gotten it in previous weeks in the corresponding window period (risk or control). This dependence of risk among weeks will be taken into account by multiplying each risk estimate for week q by (1 – pw) for each w, where pw is the risk for week w and w runs from 1 to (q – 1) ii. Using the above-mentioned variables, the cumulative risk for a 6-week risk interval beginning in week 1 will be calculated as such: Cumulative Risk = p1 + (1 – p1)*p2 + … + (1 – p1)* … * (1 – p5)*p6

7) Running New SCRI Model with Seasonality Measure: a conditional Poisson regression used for SCRI analysis conducted as before, with the following difference: new offset term will be the log of cumulative estimated risk for the interval instead of the log of length of interval in days.

4.7.3.4.3.2. Positive Predictive Values (PPV)-Adjusted Quantitative Bias Analysis

A PPV-adjusted analysis will be conducted to assess bias due to outcome misclassification and uncertainty in the claims-identified cases of GBS. Misclassification can occur if cases of GBS are under-identified or if other conditions are mistakenly classified as GBS.
The PPV-adjusted analysis will be performed using quantitative bias analysis (QBA) using PPVs available from prior studies that have conducted medical record review to validated GBS diagnoses following vaccine exposures. (17) The PPV estimate for GBS in CMS Medicare database for individuals aged 65 or older that will be used for adjustment in the study is 71.0% (95% CI: 63.0%, 79.0%).(20)

For the SCRI analysis, differential PPV adjustment will also be used based on the FDA's October 2024 ACIP presentation, which reported different PPVs for GBS diagnosis in the risk and control intervals: 62.3% (48.8 - 74.1%) for claims-identified GBS cases during the 1-42 day risk interval and 81.8% (61.5 - 92.7%) during the 43-90 day control interval.(23)_ Additional PPV adjustments may be considered to integrate updated information on PPVs as they become available in the published literature or regulatory studies for the duration of the study.

Methodology described by Perez-Vilar *et al.*(14, 21) will be used to conduct the PPV-adjusted analysis. In brief, for all claims-identified GBS cases, multiple imputations will be conducted by applying the PPV by sampling with probability equal to the PPV of 71.2% derived from the medical record review of GBS cases from the 2015–2016 influenza season. (20) The PPV did not consider cases with insufficient evidence as confirmed GBS cases. (16) This imputation will be done by creating multiple datasets where the status of the claim – identified GBS cases will be imputed by randomly assigning them the status of 'confirmed' with probability equal to the PPV. There will be 1,000 imputed datasets generated, and estimates will be combined using the method developed by Schenker and Rubin. (14, 21, 42)

Each imputed dataset i will generate a GBS rate $\widehat{Q_i}$, and a variance U_i.

Assume the true GBS rate is Q. The normal-based inference for Q is based on the statement that $\left(Q-\hat{Q}\right)\sim N(0,T)$.

$\hat{Q}=(\sum_{i=1}^{m}\widehat{Q_i})/m$, where m = 1000 in this case.

$\hat{Q}$ is the estimate of GBS rate based on 1000 imputations.

$$\hat{T}=\widehat{W}+(\frac{m+1}{m})\hat{B}$$

where $\widehat{W}=(\sum_{i=1}^{m}U_i)/m$ is the average within-imputation variance, and $\hat{B}=\sum_{i=1}^{m}\left(\widehat{P_i}-\hat{P}\right)^2/(m-1)$ is the between-imputation variance of $Q-\hat{Q}$.

Assuming normality of the coefficient estimates, p-values for imputed analyses will be computed by dividing the coefficient estimate by the model's standard error to arrive at the z-statistic.

4.7.3.4.3.3. Seasonality and PPV-Adjusted Analysis

A seasonality and PPV-adjusted analysis using the methods described in Sections 4.7.3.4.3.1 and 4.7.3.4.3.2 will also be performed to account for both potential confounders that could bias outcome rate estimates.

4.7.3.4.3.4. SCRI Analysis Stratified by Individuals With and Without the Full Follow-up Period

In the primary analysis, incomplete follow-up for individuals (e.g., due to death, disenrollment, etc.) will be accounted for by using an offset term in the conditional Poisson regression model. To further evaluate potential biases associated with incomplete follow-up, if a significant number of individuals (e.g., up to 20%) *are lost to follow-up in the primary analysis, an SCRI analysis may be conducted requiring complete follow-up period of 84 days.*

4.7.3.5. The Statistical Analysis for Descriptive Analysis in PharMetrics Plus

Based on medical and pharmacy claims through December 31, 2023, approximately 46,000 individuals between 60 and 64 years of age received ABRYSVO in the PharMetrics Plus database, which would not allow the conduct of SCRI *(Section 4.7.3.4)*. Therefore, a descriptive analysis reporting the GBS incidence rates in the primary and secondary risk intervals will be performed in this database for the 2023/2024 and 2024/2025 RSV seasons as well as the pooled analysis [Table shell 7]. The inferential SCRI may be conducted if sufficient exposures are accrued (~100,000) to detect an IRR of 10 or less or if scientific exploration is needed.

4.7.4. Additional Sensitivity Analyses

This section outlines further sensitivity analyses in SCRI and/or RCA that may be conducted to evaluate the safety of ABRYSVO vaccination.

4.7.4.1. Case-Centered GBS Analysis for the SCRI Analytic Population, the RCA Analytic Population and the Descriptive Analysis Population

To enhance the understanding of the severity and characteristics of the GBS cases identified in our analysis, and to better understand the risk factors of the individuals with GBS onset, a case-centered analysis will be performed to inform decisions regarding preventing severe outcomes. For each patient with a case of GBS identified during the follow-up period of RCA analysis, SCRI analysis or the descriptive analysis, *the following variables will be assessed:*

- Time from the index date to date of GBS onset (reported as mean, SD, median, and IQR);
- Gender (male vs. female);
- Age (65-74 vs. 75+);
- Race/Ethnicity (White, Black, and other);
- Facility/ provider type of ABRYSVO vaccination;
- Nursing home residency status (CMS Medicare databases only);
- Neurologist encounter within 45 days of GBS diagnosis and diagnosing procedures received;
- Selected diagnoses similar to GBS within 30 days of GBS onset;
- Geographical region (Northeast, Midwest, South and West);
- Risk factors of GBS:
    - Charlson Comorbidity Index (0-1 vs. 2+);
    - Frailty Index (frail, pre-frail, vs. non-frail);
    - Immunocompromised status (yes vs. no);
    - Infections within 42 days before date of GBS onset (yes vs. no; if yes, upper or lower respiratory tract infections, GI infections, other, hospitalized, and non-hospitalized);
    - Surgery in 42 days before date of GBS onset (yes vs. no);
    - Trauma in 14 days before date of GBS onset (yes vs. no);
    - Vaccination during the 42 days prior to GBS onset (yes vs. no; if yes, Influenza, COVID-19, Shingles, Pneumococcal, and Others);

- Co-vaccination on the index date (yes vs. no; if yes, Influenza, COVID-19, Shingles, Pneumococcal, and Others);

- GBS case severity:
  - Duration of IP stay after the date of GBS onset (reported as mean, SD, median, and IQR);
  - Death after the date of GBS onset (yes vs. no);
  - Respiratory failure after the date of GBS onset (yes vs. no);
  - Intubation after the date of GBS onset (yes vs. no).

Based on the sample size, the case-centered analysis for the SCRI may be stratified by whether the date of GBS onset is during the risk or control windows [Table shell 8].

4.7.4.2. Removal of GBS Cases After Infection Diagnoses for the SCRI Analytic Population

Prior infection has been found to be one of the most important risk factors for GBS.(43) In this study, we will conduct a sensitivity analysis, excluding individuals that have a prior respiratory or gastrointestinal infection within 1-42 days prior to GBS onset. (43) In this study, we will conduct a sensitivity analysis, excluding individuals that have a prior respiratory or gastrointestinal infection within 1-42 days prior to GBS onset. These individuals will not be included in the risk estimation for the SCRI analysis as their GBS onset may be related to their prior infection rather than the vaccination.

4.7.5. Post-hoc Analyses

Not applicable.

4.7.6. Summary of Statistical Analyses Presented in the Interim and Final Reports

The conduct of the study involves the generation of several key reports. Interim report 1 delivers the SCRI analysis for the 2023/2024 RSV season. Interim report 2 and Interim report 3 will cover the RCA for the 2023/2024 and 2024/2025 RSV seasons: Interim report 2 will cover an indexing period from 31 May 2023 to 10 August 2024, while Interim report 3 will extend the indexing period to 10 January 2025. The final report will include the SCRI analysis for the 2023/2024 and the 2024/2025 RSV seasons. Additionally, this final report encompasses a pooled SCRI analysis that will combine the two consecutive seasons, and will also present any subgroup analyses, providing a comprehensive view of the safety profile of ABRYSVO. Table 3 summarizes the statistical analyses included in each interim and final report.

Table 3. Summary of statistical analyses in interim and final report

Milestone	Analysis Reported
Interim report 1	2023/2024 RSV season SCRI and descriptive analysis
Interim report 2	2023/2024 and 2024/2025 RSV season 1st RCA report (Indexing period: 31 May 2023 – 10 August 2024)
Interim report 3	2023/2024 and 2024/2025 RSV season 2nd RCA report (Indexing period: 31 May 2023 – 10 January 2025)
Final report to the FDA	2023/2024 RSV season SCRI and descriptive analysis 2024/2025 RSV season SCRI and descriptive analysis Combined 2 seasons SCRI and descriptive analysis Any pertinent subgroup and sensitivity analyses

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6. APPENDICES

6.1. Appendix A: Table Shells

Table shells will be provided in the standalone document titled “C3671054_RSV Near Real Time Surveillance_SAP_Table Shells_v2.0.pdf”. The titles of table shells are listed below:

- Table 1a. Attrition of Individuals Who Received ABRYSVO Vaccines, Enrolled in CMS Medicare During the <RSV Season>
- Table 1b. Attrition of Individuals Who Received ABRYSVO Vaccines, Enrolled in PharMetrics Plus During the <RSV Season>
- Table 2. Demographic Characteristics of Individuals Who Received ABRYSVO Vaccines, Enrolled in <Data Source> During the <RSV Season> for the <SCRI Analytic or RCA Analytic> Population
- Table 3. Characteristics of Individuals Who Received ABRYSVO Vaccines, Enrolled in <Data Source> During the <RSV Season> for the <SCRI Analytic or RCA Analytic or Descriptive Analysis> Population
- Table 4. Exposure Characteristics of Individuals Who Received ABRYSVO Vaccines, Enrolled in <Data Source> During the <RSV Season> for the <SCRI Analytic or RCA Analytic or Descriptive Analysis> Population
- Table 5a-1. GBS Background Rate Calculated from Individuals Who Received Influenza Vaccines, Enrolled in CMS Medicare During the Selected Influenza Seasons
- Table 5a-2. Demographic and Clinical Characteristics of Individuals Who Received Influenza Vaccines, Historical Comparator Population
- Table 5b. Statistics for GBS Outcome in CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine for the <RCA Analytic> Population by <Primary or Secondary> Risk Intervals
- Table 6a. Statistics for GBS Outcome in CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine for the <SCRI Analytic > Population in Risk and Control Intervals
- Table 6b. Statistics for GBS Outcome in CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine for the <SCRI Analytic > Population in Risk and Control Intervals – Subgroup Analyses
- Table 7. Statistics for GBS Outcome in PharMetrics Plus Enrollees Among Persons Receiving ABRYSVO Vaccine for the Descriptive Analysis Population in the Primary and Secondary Risk Intervals
- Table 8. Case-Centered GBS Characteristics for the <SCRI Analytic or RCA Analytic or Descriptive Analysis> Population

Please note that these are exemplary table shells for illustrative purposes. Final presentation of data may vary in the reports.

6.2. Appendix B: Code Lists

Appendix B.1 List of Codes for RSV Vaccines

Vaccine Name	Code Type	Code	Manufacturer/Descriptions
ABRYSVO (RSVPreF)	NDC	00069-0207-01	ABRYSVO single dose vial
		00069-0344-01	0.5 mL solution for intramuscular injection, 1-dose carton (2 mL vial, 1 mL prefilled syringe, vial adapter)
		00069-0344-05	0.5 mL solution for intramuscular injection, 5-dose carton
		00069-0344-10	ABRYSVO respiratory syncytial virus vaccine kit
		00069-2465-01	Respiratory Syncytial Virus Vaccine Injection, Powder, Lyophilized, For Solution (1 vial in 1 carton/ 0.5 mL in 1 vial)
		00069-2465-10	Respiratory Syncytial Virus Vaccine Injection, Powder, Lyophilized, For Solution (10 vial in 1 carton/ 0.5 mL in 1 vial)
		00069-2465-19	Respiratory Syncytial Virus Vaccine Injection, Powder, Lyophilized, For Solution
	CPT	90678	Respiratory Syncytial Virus vaccine, preF, subunit, bivalent, for intramuscular use
Arexvy (RSVPreF3 + AS01)	NDC	58160-0723-03	Respiratory Syncytial Virus vaccine, preF, recombinant (1 kit in 1 carton/ 0.5mL solution in 1 vial)
		58160-0744-03	Respiratory Syncytial Virus vaccine, preF, recombinant (1 kit in 1 carton/ 0.5mL solution in 1 vial)
		58160-0848-11	Arexvy vaccine kit
	CPT	90769	Respiratory Syncytial Virus vaccine, preF, recombinant, subunit, adjuvated for intramuscular use
mRESVIA	NDC	80777-0345-01	mRESVIA suspension vaccine kit
		80777-0345-89	Respiratory Syncytial Virus vaccine (2 syringe in 1 carton/0.5 mL in one syringe)
		80777-0345-90	Respiratory Syncytial Virus vaccine (1 syringe in 1 carton/0.5 mL in one syringe)
		80777-0345-96	Respiratory Syncytial Virus vaccine (10 syringe in 1 carton/0.5 mL in one syringe)
	CPT	90683	Respiratory Syncytial Virus vaccine, mRNA lipid nanoparticles, for intramuscular use

Abbreviation: NDC, National Drug Code; CPT, Current Procedural Terminology.

Vaccine Name	Code Type	Code	Manufacturer/Descriptions

Source: Coding Guide for ABRYSVO Administration, Food and Drug Administration. Approval of ABRYSVO™. Updated May 31, 2023. Accessed June 5, 2023.
URL:https://www.fda.gov/media/168890/download

Appendix B.2 List of Codes for GBS Outcome Diagnosis

Code Type	Code	Descriptions
ICD-10-CM	G61.0	Guillain-Barre syndrome

Abbreviation: ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Appendix B.3 List of Codes for Vaccinations of Interests

The comprehensive code list of exclusionary vaccinations and co-vaccinations of interest will be detailed in the standalone document entitled "C3671054_Pfizer_RSV_Surveillance_Code_List_of_Vaccinations_of_Interest.pdf".

Appendix B.4 List of Codes for Clinical Characteristics

The comprehensive code list of anaphylaxis diagnosis, diagnosis codes for frailty, diagnosis codes for Charlson Comorbidity Index, and trauma will be detailed in the standalone document entitled
"C3671054_Pfizer_RSV_Surveillance_Code_List_of_Clinical_Characteristics_Part 1.pdf".
"C3671054_Pfizer_RSV_Surveillance_Code_List_of_Clinical_Characteristics_Part 2.pdf".

Appendix B.5 List of Codes for Diagnosis of Selected Comorbidities

The comprehensive code list of selected comorbidities of interest will be detailed in the standalone document entitled
"C3671054_Pfizer_RSV_Surveillance_Code_List_of_Selected_Comorbidities.pdf".

Appendix B.6 List of Codes for Infections of Interest

The comprehensive diagnosis codes of infections of interest, including COVID-19 infection, will be detailed in the standalone document entitled
"C3671054_Pfizer_RSV_Surveillance_Code_List_of_Infections_of_Interest.pdf".

Appendix B.7 List of Codes for Procedures of Interest

The comprehensive procedure codes of surgery and bone marrow transplant will be detailed in the standalone document entitled
"C3671054_Pfizer_RSV_Surveillance_Code_List_of_Procedures_of_Interest.pdf".

Appendix B.8 List of Codes for Medications of Interest

The comprehensive drug codes of medications of interest will be detailed in the standalone document entitled
"C3671054_Pfizer_RSV_Surveillance_Code_List_of_Medications_of_Interest.pdf".

Appendix B.9 List of Codes for Case-centered Analysis

The comprehensive drug codes of medications of interest will be detailed in the standalone document entitled "C3671054_Pfizer_RSV_Surveillance_Code_List_of_Case-centered_Analysis.pdf".

Document Approval Record

Document Name:	C3671054_SAP- RSV NEAR REAL TIME SURVEILLANCE STUDY_V 2.0_23APR2025
Document Title:	C3671054_SAP- RSV NEAR REAL TIME SURVEILLANCE STUDY_V 2.0_23APR2025

Signed By:	Date(GMT)	Signing Capacity
Kelly, Scott	25-Apr-2025 16:17:26	Manager Approval
Cai, Bing	28-Apr-2025 13:32:28	Scientific Review

NON-INTERVENTIONAL (NI) STUDY

Appendix 8
Supplementary Information

Study Information

Title	A Post-Marketing Near Real-Time Safety Surveillance of Respiratory Syncytial Virus (RSV) Vaccine for Guillain-Barre Syndrome (GBS) among Older Adults in the United States
Protocol number	C3671054
Version identifier of the study report	1.0
Date	06 January 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000267
Active substance	ABRYSVO® is a bivalent recombinant stabilized prefusion F protein subunit vaccine (Respiratory Syncytial Virus Vaccine). It consists of equal amounts of prefusion F antigens from the two major RSV subgroups: RSV subgroup A prefusion F (60 µg) and RSV subgroup B prefusion F (60 µg).
Medicinal product	RSVpreF (ABRYSVO®)
Research question and objectives	**Research question:** What is the incidence rate of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases and individuals aged 60-64 years enrolled in the IQVIA PharMetrics Plus claims database (PharMetrics Plus database) as compared to the expected incidence rate of GBS in a comparable population? **Research objectives:** • To conduct near real-time monitoring of the incidence of GBS following vaccination with

	ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases using rapid cycle analysis (RCA) study design; and • To assess if there is an elevated risk of GBS following vaccination with ABRYSVO among individuals aged 65 years of age or older enrolled in CMS Medicare databases, using self-controlled risk interval (SCRI) study design; and • To descriptively monitor the incidence of GBS following vaccination with ABRYSVO in individuals aged 60-64 years enrolled in PharMetrics Plus database.
Country(-ies) of study	United States
Author	***Pfizer:*** Joanne Wu, ScD, MS Director, Epidemiology, Safety Surveillance Research, Worldwide Safety Pfizer, Inc. 66 Hudson Boulevard East, New York, NY 10001 United States ***IQVIA:*** Efe Eworuke, PhD Principal Epidemiology & Drug Safety, IQVIA 100 IMS Drive, Parsippany, NJ 07054 United States Krystal Cantos, PhD Associate Principal Epidemiology & Drug Safety, IQVIA 25 Thompson Pl, Boston, MA 02210 United States

LIST OF TABLES

Table 1a. Attrition of Individuals who Received an ABRYSVO Vaccine, Enrolled in CMS Medicare During the 2023/2024 RSV Season

		Individuals Who Received ABRYSVO Vaccines, Enrolled in CMS Medicare During the 2023/2024 RSV Season		
		Exclude	Include	Percent Change
Step	**Study Criteria**	**n**	**n**	
Inclusion Criteria				
1	Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during 31 May 2023 to 29 February 2024;		2537241	100.00%
2	≥ 65 years of age on the index date;	61802	2475439	97.56%
3	Medicare beneficiaries who aged into Medicare*;	752	2474687	97.53%
4	≥ 12 months of continuous enrollment in Medicare Parts A and B prior to the index date (i.e., the baseline period); Applied filter to remove MA;	1388450	1086237	42.81%
5	≥ 3 months of continuous enrollment in Medicare Parts D prior to the index date;	17289	1068948	42.13%
6	No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.	1718	1067230	42.06%
Exclusion Criteria				
	Individuals meeting any of the following criteria will not be included in the study:			
1	Missing sex information;	0	1067230	42.06%
2	GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.	285	1066945	42.05%

Abbreviations: CMS, Centers for Medicare & Medicaid Services; CPT, Current Procedural Terminology; GBS, Guillain-Barre Syndrome; HCPCS, Healthcare Common Procedure Coding System; IRR, Incidence Rate Ratio; MA, Medicare Advantage; n, Number; NDC, National Drug Code; RSV, Respiratory Syncytial Virus.

* Beneficiaries who qualify due to disability differ from beneficiaries who qualify due to age in several ways, including their demographic, socioeconomic, and health status profiles. To reduce potential confounding from this specific frail Medicare population that could have a different association between vaccination and GBS, they are not included in the study population.

Note: 2023/2024 demographic, clinical, and exposure characteristics were calculated in the population using latest available data (n=1,066,969), which differs slightly from the data shown here and used in the first interim report to calculate IRR in the 2023/2024 season (n=1,066,945).

Table 1b. Attrition of Individuals who Received an ABRYSVO Vaccine, Enrolled in CMS Medicare During the 2024/2025 RSV Season

		Individuals who Received ABRYSVO Vaccines, Enrolled in CMS Medicare During the 2024/2025 RSV season		
		Exclude	Include	Percent Change
Step	Study Criteria	n	n	
Inclusion Criteria				
1	Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during 31 May 2024 to 28 February 2025;		1,221,228	100.00%
2	≥ 65 years of age on the index date;	38,982	1,182,246	96.81%
3	Medicare beneficiaries who aged into Medicare*;	625	1,181,621	96.76%
4	≥ 12 months of continuous enrollment in Medicare Parts A and B prior to the index date (i.e., the baseline period); Applied filter to remove MA;	707,055	474,566	38.86%
5	≥ 3 months of continuous enrollment in Medicare Parts D prior to the index date;	7,365	467,201	38.26%
6	No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.	13,293	453,908	37.17%
Exclusion Criteria				
	Individuals meeting any of the following criteria will not be included in the study:			
1	Missing sex information;	0	453,908	37.17%
2	GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.	137	453,771	37.16%

Abbreviations: CMS, Centers for Medicare & Medicaid Services; CPT, Current Procedural Terminology; GBS, Guillain-Barre Syndrome; HCPCS, Healthcare Common Procedure Coding System; MA, Medicare Advantage; n, Number; NDC, National Drug Code; RSV, Respiratory Syncytial Virus.
* Beneficiaries who qualify due to disability differ from beneficiaries who qualify due to age in several ways, including their demographic, socioeconomic, and health status profiles. To reduce potential confounding from this specific frail Medicare population that could have a different association between vaccination and GBS, they are not included in the study population.

Table 2a. Attrition of Individuals who Received an ABRYSVO Vaccine, Enrolled in PharMetrics Plus During the 2023/2024 RSV Season

		Individuals Who Received ABRYSVO Vaccines, Enrolled in PharMetrics Plus During the 2023/2024 RSV Season		
		Exclude	Include	Percent Change
Step	Study Criteria	n	n	
Inclusion Criteria				
1	Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during 31 May 2024 to 28 February 2025;		226,558	100.00%
2	Aged 60-64 years on the index date;	194,808	31,750	14.01%
3	≥ 12 months of continuous enrollment in PharMetrics Plus with both medical and pharmacy benefits prior to the index date (i.e., the baseline period);	7,413	24,337	10.74%
4	No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.	245	24,092	10.63%
Exclusion Criteria				
	Individuals meeting any of the following criteria will not be included in the study:			
1	Missing sex information;	0	24,092	10.63%
2	Patients with other data quality issues per IQVIA standard data curation process;	338	23,754	10.48%
3	GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.	4	23,750	10.48%

Abbreviations: CPT, Current Procedural Terminology; GBS, Guillain-Barre Syndrome; HCPCS, Healthcare Common Procedure Coding System; n, Number; NDC, National Drug Code; RSV, Respiratory Syncytial Virus.

Table 2b. Attrition of Individuals who Received an ABRYSVO Vaccine, Enrolled in PharMetrics Plus During the 2024/2025 RSV Season

		Individuals Who Received ABRYSVO Vaccines, Enrolled in PharMetrics Plus During the 2024/2025 RSV Season		
		Exclude	Include	Percent Change
Step	**Study Criteria**	**n**	**n**	
Inclusion Criteria				
1	Receiving one dose of ABRYSVO vaccine administration (identified by specific CPT, HCPCS, or NDC codes) during 31 May 2024 to 28 February 2025;		107,966	100.00%
2	Aged 60-64 years on the index date;	94,586	13,380	12.39%
3	≥ 12 months of continuous enrollment in PharMetrics Plus with both medical and pharmacy benefits prior to the index date (i.e., the baseline period);	3,643	9,737	9.02%
4	No record of an RSV vaccine from a manufacturer other than Pfizer during the baseline and the follow-up period.	314	9,423	8.73%
Exclusion Criteria				
	Individuals meeting any of the following criteria will not be included in the study:			
1	Missing sex information;	0	9,423	8.73%
2	Patients with other data quality issues per IQVIA standard data curation process;	126	9,297	8.61%
3	GBS diagnosis on a claim in any position and any setting during the baseline period or on the index date.	1	9,296	8.61%

Abbreviations: CPT, Current Procedural Terminology; GBS, Guillain-Barre Syndrome; HCPCS, Healthcare Common Procedure Coding System; n, Number; NDC, National Drug Code; RSV, Respiratory Syncytial Virus.

Table 3a. Demographic Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Overall	1,584,636	100.00%	1,066,969	100.00%	453,771	100.00%
Age at ABRYSVO Vaccination Administration						
60-64						
65-69	269,812	17.03%	194,040	18.19%	63,352	13.96%
70-74	435,204	27.46%	314,956	29.52%	102,838	22.66%
75-79	412,262	26.02%	264,698	24.81%	132,994	29.31%
80-84	260,483	16.44%	165,843	15.54%	84,677	18.66%
85-89	132,496	8.36%	81,633	7.65%	45,099	9.94%
90+	74,379	4.69%	45,799	4.29%	24,811	5.47%
Sex						
Male	668,289	42.17%	450,751	42.25%	190,756	42.04%
Female	916,347	57.83%	616,218	57.75%	263,015	57.96%
Race/Ethnicity						
Asian	26,449	1.67%	15,840	1.48%	8,729	1.92%
Black	52,073	3.29%	28,547	2.68%	19,911	4.39%
Hispanic	8,362	0.53%	4,390	0.41%	3,271	0.72%
American Indian/Alaskan Native	3,995	0.25%	2,440	0.23%	1,261	0.28%
White	1,416,681	89.40%	962,203	90.18%	400,024	88.16%
Other	24,856	1.57%	16,108	1.51%	7,549	1.66%
Missing/Unknown	52,220	3.30%	37,441	3.51%	13,026	2.87%
US Region						
Northeast	281,180	17.74%	177,068	16.60%	94,223	20.76%
Midwest	470,354	29.68%	323,447	30.31%	126,903	27.97%
West	329,890	20.82%	234,506	21.98%	82,634	18.21%

Table 3a. Demographic Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
South	502,117	31.69%	331,312	31.05%	149,633	32.98%
Other/Unknown	1,095	0.07%	636	0.06%	378	0.08%
HHS Region						
Region 1	94,727	5.98%	59,860	5.61%	31,755	7.00%
Region 2	145,970	9.21%	90,445	8.48%	50,168	11.06%
Region 3	163,165	10.30%	108,797	10.20%	48,051	10.59%
Region 4	246,380	15.55%	161,040	15.09%	74,670	16.46%
Region 5	319,368	20.15%	216,495	20.29%	88,864	19.58%
Region 6	144,731	9.13%	96,196	9.02%	42,487	9.36%
Region 7	134,034	8.46%	96,150	9.01%	32,628	7.19%
Region 8	80,646	5.09%	59,281	5.56%	18,353	4.04%
Region 9	164,237	10.36%	109,648	10.28%	47,378	10.44%
Region 10	91,378	5.77%	69,057	6.47%	19,417	4.28%
Missing/Unknown	0	0.00%	0	0.00%	0	0.00%
Urban/Rural						
Urban	1,267,305	79.97%	854,953	80.13%	361,256	79.61%
Rural	182,031	11.49%	123,992	11.62%	50,824	11.20%
Missing/Unknown	135,300	8.54%	88,024	8.25%	41,691	9.19%
ADI Rank*						
1-10 (th)	165,927	10.47%	114,643	10.74%	45,269	9.98%
11-20 (th)	170,312	10.75%	116,907	10.96%	47,391	10.44%
21-30 (th)	197,609	12.47%	135,916	12.74%	54,440	12.00%
31-40 (th)	188,248	11.88%	129,425	12.13%	51,500	11.35%
41-50 (th)	188,336	11.89%	127,083	11.91%	53,943	11.89%

Table 3a. Demographic Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
51-60 (th)	165,583	10.45%	110,108	10.32%	48,516	10.69%
61-70 (th)	158,710	10.02%	105,488	9.89%	46,288	10.20%
71-80 (th)	136,435	8.61%	89,386	8.38%	40,829	9.00%
81-90 (th)	123,049	7.77%	80,324	7.53%	37,147	8.19%
91-100 (th)	54,009	3.41%	34,884	3.27%	16,397	3.61%
Missing/Unknown	36,418	2.30%	22,805	2.14%	12,051	2.66%
Original Reason for Medicare Eligibility						
Aged without ESRD	1,578,697	99.63%	1,063,481	99.67%	451,683	99.54%
Aged with ESRD	5,939	0.37%	3,488	0.33%	2,088	0.46%
Nursing Home Residency Status on the Index Date (Recent Residency)†						
Resident	23,891	1.51%	11,718	1.10%	10,142	2.24%
Non-resident	1,560,745	98.49%	1,055,251	98.90%	443,629	97.76%
Nursing Home Residency Status on the Index Date (Any Admission)‡						
Resident (ever)	61,547	3.88%	34,778	3.26%	22,724	5.01%
Non-resident	1,523,089	96.12%	1,032,191	96.74%	431,047	94.99%

Abbreviations: ADI, Area Deprivation Index; CMS, Centers for Medicare & Medicaid Services; ESRD, End-Stage Renal Disease; HHS, Health and Human Services; N, Number; RSV, Respiratory Syncytial Virus; SES, Socioeconomic Status; US, United States.
*A lower ADI rank indicates higher SES, while a higher ADI rank indicates a lower SES.

† Record or admission into or assessment in a nursing home in the 120 days before the index date.

‡ Record of admission into a nursing home during the baseline or follow-up period.

Table 3b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Overall	1,584,636	100.00%	1,066,969	100.00%	453,771	100.00%
History of anaphylaxis	1,633	0.10%	1,055	0.10%	514	0.11%
Number of hospitalizations in the baseline period among those with a hospitalization						
Mean and SD	1.55	1.07	1.51	1.01	1.62	1.14
Median and IQR	1	1.0, 2.0	1	1.0, 2.0	1	1.0, 2.0
Admission into nursing home/SNF in the baseline period	52,285	3.30%	29,156	2.73%	19,597	4.32%
Infections in close proximity (within 30 days prior to or after) the index date*	.		.		.	
Any†	148,247	9.36%	100,111	9.38%	42,102	9.28%
Medically-attended infections (Respiratory, GI, unspecified viral infection)	123,137	7.77%	83,948	7.87%	34,377	7.58%
Upper or lower respiratory tract infections	120,771	7.62%	82,486	7.73%	33,610	7.41%
GI infections	2,496	0.16%	1,504	0.14%	846	0.19%
Unspecified viral infection	553	0.03%	359	0.03%	156	0.03%
Diarrhea	23,432	1.48%	15,292	1.43%	7,036	1.55%
Fever	10,968	0.69%	6,918	0.65%	3,530	0.78%
Campylobacter enteritis	64	0.00%	42	0.00%	18	0.00%
CMV	381	0.02%	236	0.02%	126	0.03%
EBV	99	0.01%	67	0.01%	23	0.01%
HEV	<11	N/A	<11	N/A	<11	N/A
Zika virus	<11	N/A	<11	N/A	<11	N/A
Infections in close proximity (within 30 days prior to or after) to the index date (Sensitivity)‡					.	
Any†	37,976	2.40%	24,810	2.33%	11,439	2.52%
Medically-attended infections (Respiratory, GI, unspecified viral infection)	29,194	1.84%	19,192	1.80%	8,711	1.92%
Upper or lower respiratory tract infections	28,170	1.78%	18,605	1.74%	8,333	1.84%

Table 3b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
GI infections	1,059	0.07%	588	0.06%	410	0.09%
Unspecified viral infection	189	0.01%	121	0.01%	56	0.01%
Diarrhea	7,601	0.48%	4,892	0.46%	2,349	0.52%
Fever	2,492	0.16%	1,521	0.14%	826	0.18%
Campylobacter enteritis	26	0.00%	17	0.00%	<11	N/A
CMV	207	0.01%	130	0.01%	68	0.01%
EBV	31	0.00%	22	0.00%	<11	N/A
HEV	<11	N/A	<11	N/A	<11	N/A
Zika virus	<11	N/A	<11	N/A	0	0.00%
Frailty Index			.			
Mean and SD	1.29	1.04	1.22	1.03	1.45	1.03
Median and IQR	1	0.0, 2.0	1	0.0, 2.0	1	1.0, 2.0
Frail	617,026	38.94%	386,573	36.23%	204,988	45.17%
Pre-frail	547,488	34.55%	367,487	34.44%	157,719	34.76%
Non-frail	420,122	26.51%	312,909	29.33%	91,064	20.07%
CCI			.		.	
Mean and SD	2.74	3.14	2.61	3.06	3.02	3.28
Median and IQR	2	0.0, 4.0	2	0.0, 4.0	2	1.0, 4.0
0-1	725,828	45.80%	511,525	47.94%	187,749	41.38%
2+	858,808	54.20%	555,444	52.06%	266,022	58.62%
Selected comorbidity conditions*			.		.	
Asthma	175,745	11.09%	118,719	11.13%	50,172	11.06%
Blood Disorders	466,022	29.41%	298,427	27.97%	147,104	32.42%
Chronic Lung Disease	271,803	17.15%	175,286	16.43%	84,522	18.63%
Diabetes	454,339	28.67%	289,219	27.11%	143,967	31.73%
Heart Disease	495,125	31.25%	319,238	29.92%	155,042	34.17%

Table 3b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Kidney Disease	492,516	31.08%	314,611	29.49%	156,475	34.48%
Liver Disorders	117,814	7.43%	76,520	7.17%	36,293	8.00%
Neurological/Neurodevelopmental Conditions	829,412	52.34%	547,504	51.31%	246,468	54.32%
Malignant Neoplasms	709,793	44.79%	482,572	45.23%	202,021	44.52%
Selected comorbidity conditions (Sensitivity)‡						
Asthma	116,102	7.33%	77,916	7.30%	33,590	7.40%
Blood Disorders	312,930	19.75%	196,783	18.44%	101,621	22.39%
Chronic Lung Disease	199,502	12.59%	128,211	12.02%	62,280	13.72%
Diabetes	396,404	25.02%	251,345	23.56%	126,335	27.84%
Heart Disease	358,560	22.63%	229,566	21.52%	113,790	25.08%
Kidney Disease	363,671	22.95%	228,998	21.46%	118,321	26.08%
Liver Disorders	59,453	3.75%	37,816	3.54%	18,991	4.19%
Neurological/Neurodevelopmental Conditions	628,839	39.68%	410,447	38.47%	190,651	42.01%
Malignant Neoplasms	513,243	32.39%	346,315	32.46%	148,464	32.72%
Immunocompromised status	.		.		.	
Yes	141,097	8.90%	93,374	8.75%	42,109	9.28%
No	1,443,539	91.10%	973,595	91.25%	411,662	90.72%
Surgery in close proximity (within 30 days prior to and after) the index date	16,194	1.02%	9,766	0.92%	5,553	1.22%
Trauma in close proximity (within 30 days prior to and after) the index date	22,337	1.41%	15,279	1.43%	6,276	1.38%
Prior bone marrow transplant	192	0.01%	105	0.01%	71	0.02%
Vaccines in the baseline period	.		.		.	
Any¥	1,362,060	85.95%	943,143	88.39%	363,684	80.15%
Seasonal influenza	1,176,086	74.22%	811,137	76.02%	315,669	69.57%
COVID-19	952,025	60.08%	687,831	64.47%	229,626	50.60%
Tdap or Td	122,772	7.75%	87,301	8.18%	30,771	6.78%

Table 3b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Chickenpox (Varicella)	68	0.00%	49	0.00%	14	0.00%
Shingles (Herpes Zoster recombinant and/or live)	168,256	10.62%	122,947	11.52%	36,185	7.97%
HPV	115	0.01%	83	0.01%	27	0.01%
Pneumococcal conjugate	180,810	11.41%	124,277	11.65%	47,982	10.57%
Pneumococcal polysaccharide	20,054	1.27%	16,643	1.56%	2,756	0.61%
Hepatitis A	9,712	0.61%	7,086	0.66%	2,120	0.47%
Hepatitis B	11,687	0.74%	8,138	0.76%	2,892	0.64%
Meningococcal conjugate (MenACWY) and serogroup B (MenB)	1,587	0.10%	1,095	0.10%	426	0.09%
Haemophilus influenza type b	824	0.05%	556	0.05%	238	0.05%
Selected medication use in the baseline period	.		.		.	
TNF-alpha antagonists	4,132	0.26%	2,798	0.26%	1,179	0.26%
Immune checkpoint inhibitors	4,148	0.26%	2,663	0.25%	1,337	0.29%
Immunosuppressant therapies	7,595	0.48%	5,089	0.48%	2,214	0.49%
Isotretinoin	86	0.01%	67	0.01%	17	0.00%
Smoking status	.		.		.	
Smoker (ever)	28,201	1.78%	17,842	1.67%	8,989	1.98%
BMI	.		.		.	
≤19.9	21,897	1.38%	13,957	1.31%	6,919	1.52%
20-29	236,584	14.93%	159,607	14.96%	67,128	14.79%
30-39	215,275	13.59%	141,304	13.24%	64,575	14.23%
≥40	53,398	3.37%	34,780	3.26%	16,214	3.57%
Unknown	1,057,482	66.73%	717,321	67.23%	298,935	65.88%

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CMS, Centers for Medicare & Medicaid Services; CMV, Cytomegalovirus; COVID-19, Coronavirus Disease 2019; EBV, Epstein-Barr Virus; GI, Gastrointestinal; HEV, Hepatitis E Virus; HPV, Human Papillomavirus; IQR, Interquartile Range; IP, Inpatient; MenACWY, Meningococcal Conjugate; MenB, Meningococcal Serotype B; N, Number; N/A, Not Applicable; OP/PB, Outpatient and Professional Billing; RSV, Respiratory Syncytial Virus; SD, Standard Deviation; SNF, Skilled Nursing Facility; Td, Tetanus and diphtheria; Tdap, Tetanus diphtheria and pertussis; TNF, Tumor Necrosis Factor.

Table 3b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%

* Note: Defined as one code in any setting.

† Note: Includes any of the infections, symptoms, and types of pathogen listed in the table.

‡ Note: Defined as one code in the IP setting or two codes in the OP/PB setting at least one day apart.

¥ Note: Includes any of the vaccines listed below.

Table 3c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Overall	1,584,636	100.00%	1,066,969	100.00%	453,771	100.00%
RSV season of ABRYSVO vaccination						
2023/2024 RSV season	1,066,969	67.33%	1,066,969	100.00%		
2024/2025 RSV season	453,771	28.64%			453,771	100.00%
Month and Year of ABRYSVO Vaccination						
May-23	0	0.00%	0	0.00%		
Jun-23	0	0.00%	0	0.00%		
Jul-23	0	0.00%	0	0.00%		
Aug-23	32,205	2.03%	32,205	3.02%		
Sep-23	213,135	13.45%	213,135	19.98%		
Oct-23	297,960	18.80%	297,960	27.93%		
Nov-23	213,450	13.47%	213,450	20.01%		
Dec-23	161,544	10.19%	161,544	15.14%		
Jan-24	104,834	6.62%	104,834	9.83%		

Table 3c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Feb-24	43,841	2.77%	43,841	4.11%		
Mar-24	27,632	1.74%				
Apr-24	21,632	1.37%				
May-24	15,097	0.95%			465	0.10%
Jun-24	11,321	0.71%			11,321	2.49%
Jul-24	11,004	0.69%			11,004	2.43%
Aug-24	20,441	1.29%			20,441	4.50%
Sep-24	69,494	4.39%			69,494	15.31%
Oct-24	115,921	7.32%			115,921	25.55%
Nov-24	83,703	5.28%			83,703	18.45%
Dec-24	61,886	3.91%			61,886	13.64%
Jan-25	49,942	3.15%			49,942	11.01%
Feb-25	29,594	1.87%			29,594	6.52%
Vaccination record in both the 23/24 and 24/25 seasons	14,671	0.93%				
Timing of vaccination						
High respiratory season (September-February)	1,445,304	91.21%	1,034,764	96.98%	410,540	90.47%
Low respiratory season (March-August)	139,332	8.79%	32,205	3.02%	43,231	9.53%
Facility/Provider Type of ABRYSVO Vaccination*						
Hospital	<11	N/A	0	0.00%	<11	N/A
Office Visit	14,105	0.89%	6,676	0.63%	6,628	1.46%
Outpatient Institutional	5,044	0.32%	2,061	0.19%	2,531	0.56%
Pharmacy	1,571,032	99.14%	1,060,908	99.43%	447,169	98.55%
Skilled Nursing Facility	0	0.00%	0	0.00%	0	0.00%

Table 3c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Home Health Agency	0	0.00%	0	0.00%	0	0.00%
Mass Immunization Center	N/A	N/A	N/A	N/A	N/A	N/A
Other	0	0.00%	0	0.00%	0	0.00%
Co-administered vaccinations (on Index Date)						
Any †	649,999	41.02%	436,996	40.96%	190,394	41.96%
Seasonal influenza	400,968	25.30%	284,247	26.64%	115,977	25.56%
COVID-19	310,806	19.61%	215,518	20.20%	85,408	18.82%
Tdap or Td	31,034	1.96%	11,520	1.08%	16,232	3.58%
Chickenpox (Varicella)	14	0.00%	<11	N/A	<11	N/A
Shingles (Herpes Zoster recombinant and/or live)	58,376	3.68%	28,959	2.71%	21,721	4.79%
HPV	<11	N/A	<11	N/A	<11	N/A
Pneumococcal conjugate	56,347	3.56%	28,479	2.67%	23,267	5.13%
Pneumococcal polysaccharide	1,359	0.09%	547	0.05%	661	0.15%
Hepatitis A	3,084	0.19%	1,229	0.12%	1,296	0.29%
Hepatitis B	2,651	0.17%	964	0.09%	1,188	0.263%
MenACWY and MenB	126	0.01%	59	0.01%	46	0.01%
Haemophilus influenza type B	41	0.00%	<11	N/A	24	0.01%
Vaccines in close proximity (within 30 days prior to or after) the Index Date						
Any †	1,096,841	69.22%	769,808	72.15%	297,742	65.62%
Seasonal influenza	807,825	50.98%	587,972	55.11%	218,625	48.18%
COVID-19	711,191	44.88%	535,978	50.23%	161,320	35.55%
Tdap or Td	57,494	3.63%	27,634	2.59%	25,367	5.59%
Chickenpox (Varicella)	32	0.00%	11	0.00%	16	0.00%

Table 3c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in CMS Medicare

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Shingles (Herpes Zoster recombinant and/or live)	96,902	6.12%	56,075	5.26%	31,337	6.91%
HPV	40	N/A	20	0.00%	17	0.00%
Pneumococcal conjugate	106,572	6.73%	61,420	5.76%	38,445	8.47%
Pneumococcal polysaccharide	3,913	0.25%	2,315	0.22%	1,299	0.29%
Hepatitis A	6,082	0.38%	3,198	0.30%	2,145	0.47%
Hepatitis B	6,200	0.39%	3,211	0.30%	2,265	0.50%
MenACWY and MenB	513	0.03%	312	0.03%	165	0.04%
Haemophilus influenza type B	262	0.02%	142	0.01%	101	0.02%

Abbreviations: CMS, Centers for Medicare & Medicaid Services; COVID-19, Coronavirus Disease 2019; HPV, Human Papillomavirus; MenACWY, Meningococcal Conjugate; MenB, Meningococcal Serotype B; N, Number; N/A, Not Applicable; NDC, National Drug Codes; RSV, Respiratory Syncytial Virus; Td, Tetanus and Diphtheria; Tdap, Tetanus Diphtheria and Pertussis.
* Note: Most vaccinations were identified via NDC, which are typically associated with patient reimbursement through Medicare Part D claims and can misclassify physician-administered vaccines as pharmacy-based. Thus, this is likely an overestimate of administrations in the pharmacy setting.
† Note: Includes any of the vaccines listed below.

Table 4a. Demographic Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Overall	35,274	100.00%	23,750	100.00%	9,296	100.00%
Age at ABRYSVO Vaccination Administration						
60-64	35,274	100.00%	23,750	100.00%	9,296	100.00%
Sex						
Male	14,126	40.05%	9,490	39.96%	3,637	39.12%
Female	21,148	59.95%	14,260	60.04%	5,659	60.88%
US Region						
Northeast	5,816	16.49%	3,705	15.60%	1,788	19.23%
Midwest	12,587	35.68%	8,448	35.57%	3,310	35.61%
West	8,803	24.96%	6,203	26.12%	2,117	22.77%
South	8,068	22.87%	5,394	22.71%	2,081	22.39%
Other/Unknown	0	0.00%	0	0.00%	0	0.00%
HHS Region						
Region 1	3,144	8.91%	2,036	8.57%	962	10.35%
Region 2	1,873	5.31%	1,147	4.83%	590	6.35%
Region 3	3,224	9.14%	2,102	8.85%	895	9.63%
Region 4	3,425	9.71%	2,155	9.07%	978	10.52%
Region 5	11,300	32.03%	7,587	31.95%	2,963	31.87%
Region 6	2,516	7.13%	1,862	7.84%	512	5.51%
Region 7	962	2.74%	626	2.64%	280	3.01%
Region 8	1,968	5.58%	1,550	6.53%	337	3.63%
Region 9	3,044	8.63%	1,818	7.65%	1,034	11.12%
Region 10	3,224	9.14%	2,407	10.13%	629	6.77%
Missing/Unknown	594	1.68%	460	1.94%	116	1.25%
ADI Rank*						

Table 4a. Demographic Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
1-10 (th)	1,801	5.11%	1,240	5.22%	471	5.07%
11-20 (th)	2,927	8.30%	1,965	8.27%	788	8.48%
21-30 (th)	2,693	7.63%	1,893	7.97%	639	6.87%
31-40 (th)	4,417	12.52%	2,978	12.54%	1212	13.04%
41-50 (th)	4,601	13.04%	3,059	12.88%	1262	13.58%
51-60 (th)	4,994	14.16%	3,322	13.99%	1325	14.25%
61-70 (th)	6,125	17.36%	4,032	16.98%	1678	18.05%
71-80 (th)	4,334	12.29%	2,930	12.34%	1094	11.77%
81-90 (th)	2,222	6.30%	1,525	6.42%	544	5.85%
91-100 (th)	565	1.60%	346	1.46%	166	1.79%
Missing/Unknown	595	1.69%	460	1.94%	117	1.26%

Abbreviations: ADI, Area Deprivation Index; HHS, Health and Human Services; N, Number; RSV, Respiratory Syncytial Virus; US, United States.

*A lower ADI rank indicates higher SES, while a higher ADI rank indicates a lower SES.

Table 4b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Overall	35,274	100.00%	23,750	100.00%	9,296	100.00%
History of anaphylaxis	85	0.24%	56	0.24%	17	0.18%
Number of hospitalizations in the baseline period among those with a hospitalization						
Mean and SD	0.14	0.61	0.11	0.53	0	0.77
Median and IQR	0	0.0, 0.0	0	0.0, 0.0	0	0.0, 0.0
Infections in close proximity (within 30 days before or after) the index date*						
Any†	3,007	8.52%	2,008	8.45%	816	8.78%
Medically-attended infections (Respiratory, GI, unspecified viral infection)	2,592	7.35%	1,746	7.35%	694	7.47%
Upper or lower respiratory tract infections	2,550	7.23%	1,717	7.23%	684	7.36%
GI infections	43	0.12%	25	0.11%	14	0.15%
Unspecified viral infection	10	0.03%	5	0.02%	4	0.04%
Diarrhea	381	1.08%	244	1.03%	108	1.16%
Fever	203	0.58%	117	0.49%	70	0.75%
Campylobacter enteritis	2	0.01%	2	0.01%	0	0.00%
CMV	10	0.03%	7	0.03%	3	0.03%
EBV	2	0.08%	1	0.00%	1	0.01%
HEV	0	0.00%	0	0.00%	0	0.00%
Zika virus	0	0.00%	0	0.00%	0	0.00%
Infections in close proximity (within 30 days prior to or after) to the index date (Sensitivity)‡						
Any†	722	2.05%	472	1.99%	205	2.21%
Medically-attended infections (Respiratory, GI, unspecified viral infection)	568	1.61%	374	1.57%	159	1.71%
Upper or lower respiratory tract infections	554	1.57%	365	1.54%	154	1.66%
GI infections	18	0.05%	8	0.03%	9	0.10%

Table 4b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Unspecified viral infection	1	0.00%	1	0.00%	0	0.00%
Diarrhea	116	0.33%	77	0.32%	32	0.34%
Fever	65	0.18%	35	0.15%	24	0.26%
Campylobacter enteritis	2	0.01%	2	0.01%	0	0.00%
CMV	5	0.01%	4	0.02%	1	0.01%
EBV	1	0.00%	0	0.00%	1	0.01%
HEV	0	0.00%	0	0.00%	0	0.00%
Zika virus	0	0.00%	0	0.00%	0	0.00%
Frailty Index						
Mean and SD	0.38	0.49	0	0.47	0	0.50
Median and IQR	0	0.0, 1.0	0	0.0, 1.0	0	0.0, 1.0
Frail	0	0.00%	0	0.00%	0	0.00%
Pre-frail	13,377	37.92%	8,160	34.36%	4,235	45.56%
Non-frail	21,897	62.08%	15,590	65.64%	5,061	54.44%
CCI						
Mean and SD	1.86	2.64	2	2.52	2	2.85
Median and IQR	1	0.0, 2.0	2	0.0, 4.0	2	1.0, 4.0
0-1	21,897	62.08%	15,590	65.64%	5,061	54.44%
2+	13,377	37.92%	8,160	34.36%	4,235	45.56%
Selected comorbidity conditions*						
Asthma	5,043	14.30%	3,154	13.28%	1,595	17.16%
Blood Disorders	5,342	15.14%	3,287	13.84%	1,708	18.37%
Chronic Lung Disease	5,325	15.10%	3,141	13.23%	1,811	19.48%
Diabetes	9,753	27.65%	5,876	24.74%	3,081	33.14%
Heart Disease	5,594	15.86%	3,437	14.47%	1,753	18.86%

Table 4b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Kidney Disease	5,519	15.65%	3,417	14.39%	1,686	18.14%
Liver Disorders	2,933	8.31%	1,784	7.51%	953	10.25%
Neurological/Neurodevelopmental Conditions	17,497	49.60%	11,452	48.22%	4,862	52.30%
Malignant Neoplasms	7,935	22.50%	5,500	23.16%	2,034	21.88%
Selected comorbidity conditions (Sensitivity)‡						
Asthma	3,108	8.81%	1,901	8.00%	1,012	10.89%
Blood Disorders	3,416	9.68%	2,048	8.62%	1,146	12.33%
Chronic Lung Disease	4,100	11.62%	2,371	9.98%	1,447	15.57%
Diabetes	8,734	24.76%	5,231	22.03%	2,787	29.98%
Heart Disease	3,740	10.60%	2,249	9.47%	1,207	12.98%
Kidney Disease	3,848	10.91%	2,307	9.71%	1,242	13.36%
Liver Disorders	1,569	4.45%	923	3.89%	535	5.76%
Neurological/Neurodevelopmental Conditions	13,219	37.48%	8,547	35.99%	3,761	40.46%
Malignant Neoplasms	5,063	14.35%	3,443	14.50%	1,354	14.57%
Immunocompromised status						
Yes	292	0.83%	185	0.78%	95	1.02%
No	34,982	99.17%	23,565	99.22%	9,201	98.98%
Surgery in close proximity (within 30 days prior to and after) the index date	249	0.71%	127	0.53%	96	1.03%
Trauma in close proximity (within 30 days prior to and after) the index date	216	0.61%	143	0.60%	62	0.67%
Prior bone marrow transplant	15	0.04%	11	0.05%	3	0.03%
Vaccines in the baseline period						
Any¥	26,937	76.37%	19,485	82.04%	5,688	61.19%
Seasonal influenza	21,742	61.64%	16,277	68.53%	3,970	42.71%
COVID-19	15,654	44.38%	12,486	52.57%	2,312	24.87%

Table 4b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Tdap or Td	3,324	9.42%	2,290	9.64%	801	8.62%
Chickenpox (Varicella)	9	0.03%	6	0.03%	3	0.03%
Shingles (Herpes Zoster recombinant and/or live)	4,436	12.58%	3,061	12.89%	979	10.53%
HPV	11	0.03%	9	0.04%	2	0.02%
Pneumococcal conjugate	3,883	11.01%	2,575	10.84%	1,034	11.12%
Pneumococcal polysaccharide	284	0.81%	210	0.88%	57	0.61%
Hepatitis A	576	1.63%	379	1.60%	134	1.44%
Hepatitis B	961	2.72%	589	2.48%	271	2.92%
MenACWY and MenB	64	0.18%	45	0.19%	18	0.19%
Haemophilus influenza type B	24	0.07%	20	0.08%	4	0.04%
Selected medication use in the baseline period						
TNF-alpha antagonists	254	0.72%	159	0.67%	77	0.83%
Immune checkpoint inhibitors	107	0.30%	60	0.25%	44	0.47%
Immunosuppressant therapies	416	1.18%	259	1.09%	136	1.46%
Isotretinoin	15	0.04%	7	0.03%	8	0.09%
Smoking status						
Smoker (ever)	1,558	4.42%	929	3.91%	498	5.36%
BMI						
≤19.9	357	1.01%	239	1.01%	97	1.04%
20-29	4,245	12.03%	2,834	11.93%	1,108	11.92%
30-39	5,275	14.95%	3,447	14.51%	1,464	15.75%
≥40	2,266	6.42%	1,383	5.82%	731	7.86%
Unknown	23,131	65.58%	15,847	66.72%	5,896	63.43%

Abbreviations: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; CMV, Cytomegalovirus; COVID-19, Coronavirus Disease 2019; EBV, Epstein-Barr Virus; GI, Gastrointestinal; HEV, Hepatitis E Virus; HPV, Human Papillomavirus; IQR, Interquartile Range; MenACWY, Meningococcal Conjugate; MenB,

Table 4b. Clinical Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%

Meningococcal Serotype B; N, Number; RSV, Respiratory Syncytial Virus; SD, Standard Deviation; Td, Tetanus and Diphtheria; Tdap, Tetanus Diphtheria and Pertussis; TNF, Tumor Necrosis Factor.
* Note: Defined as one code in any setting.

† Note: Includes any of the infections, symptoms, and types of pathogen listed in the table.

‡ Note: Defined as one code in the inpatient (IP) setting or two codes in the outpatient and professional billing (OP/PB) setting at least one day apart.

¥ Note: Includes any of the vaccines listed below.

Table 4c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Overall	35,274	100.00%	23,750	100.00%	9,296	100.00%
RSV season of ABRYSVO vaccination						
2023/2024 RSV season	23,750	67.33%	23,750	100.00%	0	0.00%
2024/2025 RSV season	9,296	26.35%	0	0.00%	9,296	100.00%
Month and Year of ABRYSVO Vaccination						
May-23	0	0.00%	0	0.00%	0	0.00%
Jun-23	0	0.00%	0	0.00%	0	0.00%
Jul-23	0	0.00%	0	0.00%	0	0.00%
Aug-23	495	1.40%	495	2.08%	0	0.00%
Sep-23	4,125	11.69%	4,125	17.37%	0	0.00%
Oct-23	6,968	19.75%	6,968	29.34%	0	0.00%
Nov-23	4,761	13.50%	4,761	20.05%	0	0.00%
Dec-23	4,121	11.68%	4,121	17.35%	0	0.00%

Table 4c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Jan-24	2,210	6.27%	2,210	9.31%	0	0.00%
Feb-24	1,070	3.03%	1,070	4.51%	0	0.00%
Mar-24	942	2.67%				
Apr-24	752	2.13%				
May-24	553	1.57%	0	0.00%	19	0.20%
Jun-24	404	1.15%	0	0.00%	404	4.35%
Jul-24	337	0.96%	0	0.00%	337	3.63%
Aug-24	524	1.49%	0	0.00%	524	5.64%
Sep-24	1,673	4.74%	0	0.00%	1,673	18.00%
Oct-24	2,217	6.29%	0	0.00%	2,217	23.85%
Nov-24	1,534	4.35%	0	0.00%	1,534	16.50%
Dec-24	1,278	3.62%	0	0.00%	1,278	13.75%
Jan-25	796	2.26%	0	0.00%	796	8.56%
Feb-25	514	1.46%	0	0.00%	514	5.53%
Vaccination record in both the 23/24 and 24/25 seasons	159	0.45%				
Timing of vaccination						
High respiratory season (September-February)	31,267	88.64%	23,255	97.92%	8,012	86.19%
Low respiratory season (March- August)	4,007	11.36%	495	2.08%	1,284	13.81%
Facility/Provider Type of ABRYSVO Vaccination						
Hospital	0	0.00%	0	0.00%	0	0.00%
Office Visit	0	0.00%	0	0.00%	0	0.00%
Outpatient Institutional	0	0.00%	0	0.00%	0	0.00%
Pharmacy	26,177	74.21%	18,181	76.55%	6,580	70.78%

Table 4c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Skilled Nursing Facility	0	0.00%	0	0.00%	0	0.00%
Home Health Agency	0	0.00%	0	0.00%	0	0.00%
Mass Immunization Center	0	0.00%	0	0.00%	0	0.00%
Other	9,097	25.79%	5,569	23.45%	2,716	29.22%
Co-administered vaccinations (on Index Date)						
Any*	19,904	56.43%	13,343	56.18%	5,558	59.79%
Seasonal influenza	12,252	34.73%	8,798	37.04%	3,391	36.48%
COVID-19	10,395	29.47%	7,495	31.56%	2,662	28.64%
Tdap or Td	923	2.62%	346	1.46%	454	4.88%
Chickenpox (Varicella)	0	0.00%	0	0.00%	0	0.00%
Shingles (Herpes Zoster recombinant and/or live)	2,501	7.09%	1,097	4.62%	893	9.61%
HPV	3	0.01%	3	0.01%	0	0.00%
Pneumococcal conjugate	2,019	5.72%	937	3.95%	885	9.52%
Pneumococcal polysaccharide	46	0.13%	21	0.09%	17	0.18%
Hepatitis A	253	0.72%	109	0.46%	78	0.84%
Hepatitis B	378	1.07%	134	0.56%	128	1.38%
MenACWY and MenB	3	0.01%	1	0.00%	1	0.01%
Haemophilus influenza type B	0	0.00%	0	0.00%	0	0.00%
Vaccines in close proximity (within 30 days prior to or after) the Index Date						
Any*	26,477	75.06%	18,305	77.07%	7,017	75.48%
Seasonal influenza	19,060	54.03%	14,027	59.06%	4,952	53.27%
COVID-19	16,442	46.61%	12,483	52.56%	3,674	39.52%
Tdap or Td	1,663	4.71%	795	3.35%	687	7.39%

Table 4c. Exposure Characteristics of Individuals who Received an ABRYSVO Vaccine in PharMetrics Plus

Characteristics	Combined two seasons (31 May 2023- 28 Feb 2025)		2023/2024 RSV season (31 May 2023- 29 Feb 2024)		2024/2025 RSV season (31 May 2024- 28 Feb 2025)	
	N	%	N	%	N	%
Chickenpox (Varicella)	4	0.01%	1	0.00%	3	0.03%
Shingles (Herpes Zoster recombinant and/or live)	3,400	9.64%	1,695	7.14%	1,124	12.09%
HPV	7	0.02%	6	0.03%	1	0.01%
Pneumococcal conjugate	3,029	8.59%	1,549	6.52%	1,231	13.24%
Pneumococcal polysaccharide	97	0.27%	57	0.24%	28	0.30%
Hepatitis A	400	1.13%	197	0.83%	115	1.24%
Hepatitis B	617	1.75%	276	1.16%	195	2.10%
MenACWY and MenB	21	0.06%	11	0.05%	7	0.08%
Haemophilus influenza type B	3	0.01%	3	0.01%	0	0.00%

Abbreviations: COVID-19, Coronavirus Disease 2019; HPV, Human Papillomavirus; MenACWY, Meningococcal conjugate; MenB, Meningococcal serotype B; N, number; RSV, Respiratory Syncytial Virus; Tdap, tetanus diphtheria and pertussis.

* Note: Includes any of the vaccines listed below.

Table 5. SCRI Analysis of CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine for the Combined Season Population in Risk and Control Intervals

	Outcomes during Risk Interval				Outcomes during Control Interval				Poisson Analysis		
	No. of Out-comes	P-Y	Rate per 100,000 P-Y	95% CI	No. of Outcomes	P-Y	Rate per 100,000 P-Y	95% CI	IRR	95% CI	p-value
The Primary Risk Interval (1 - 21 Days Post-index)											
Unadjusted analysis	26	91146.10	28.53	19.03 - 41.20	13	182124.21	7.14	3.97 - 11.90	4.00	2.05 - 7.78	<.0001
Seasonality-adjusted analysis	26	91146.10	28.53	19.03 - 41.20	13	182124.21	7.14	3.97 - 11.90	3.73	1.73 - 6.01	<.0001
PPV-adjusted analysis (71%)*	18.46	91146.10	20.25	13.40 - 29.86	9.23	182124.21	5.07	3.02 - 8.66	4.10	1.63 -10.33	0.0028
PPV-adjusted analysis (Differential)†	16.20	91146.10	17.77	11.70 - 27.14	10.63	182124.21	5.84	3.41 - 9.38	3.06	1.27 - 7.38	0.0126
Fully adjusted†‡	16.20	91146.10	17.77	11.70 - 27.14	10.63	182124.21	5.84	3.41 - 9.38	2.86	1.03 - 7.94	0.0432
The Secondary Risk Interval (1 - 42 Days Post-index)											
Unadjusted analysis	38	182292.20	20.85	14.96 - 28.32	13	182124.21	7.14	3.97 - 11. 90	2.92	1.56 -5.48	0.0009
Seasonality-adjusted analysis	38	182292.20	20.85	14.96 - 28.32	13	182124.21	7.14	3.97 - 11. 90	2.84	1.38 - 5.83	0.0044
PPV-adjusted analysis (71%)*	26.98	182292.20	14.8	10.21 - 20.25	9.23	182124.21	5.07	3.01 - 8.66	2.98	1.24 - 7.17	0.0145
PPV-adjusted analysis (Differential)†	23.67	182292.20	12.99	8.88 - 18.27	10.63	182124.21	5.84	3.41 - 9.38	2.24	0.98 - 5.11	0.055
Fully adjusted†‡	23.67	182292.20	12.99	8.88 - 18.27	10.63	182124.21	5.84	3.41 - 9.38	2.18	0.85 - 5.60	0.1067

Abbreviations: CI, Confidence Intervals; CMS, Centers for Medicare & Medicaid Services; IRR, Incidence Rate Ratio; No., Number; PPV, Positive Predictive Value; P-Y, Person-Years; SCRI, Self-Controlled Risk Interval.
*PPV adjustment (71% for both the risk and control interval) has been applied to the number of outcomes reported in this row.
† PPV adjustment (62.3% for risk interval and 81.8% for control interval) has been applied to the number of outcomes reported in this row.
‡ Seasonality- and PPV-adjusted (differential) analysis.
Note: This population is smaller than the ABRYSVO-vaccinated group in the attrition table because the SCRI model includes only patients with at least one day in the control interval.

Table 6. Season-Specific SCRI Analyses of CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine

	Outcomes during Risk Interval			Outcomes during Control Interval			Poisson Analysis		
	No. of Out-comes	Rate per 100,000 P-Y	95% CI	No. of Out-comes	Rate per 100,000 P-Y	95% CI	IRR	95% CI	P-value
2023/2024 RSV Season									
The Primary Risk Interval (1 - 21 Days Post-index)									
Unadjusted analysis	16	26.07	15.43 - 41.43	<11	8.15	4.14 - 14.53	3.2	1.45-7.05	0.0039
PPV-adjusted analysis (differential)*	9.97	16.24	8.95 - 25.68	<11	6.67	3.91 - 11.76	2.47	0.85-7.19	0.0967
The Secondary Risk Interval (1 - 42 Days Post-index)									
Unadjusted analysis	26	21.18	14.13 - 30.59	<11	8.15	4.14 - 14.53	2.6	1.25-5.39	0.0103
PPV-adjusted analysis (differential)*	16.20	13.20	8.69 - 20.15	<11	6.67	3.91 - 11.76	2.00	0.77-5.21	0.1558
2024/2025 RSV Season									
The Primary Risk Interval (1 - 21 Days Post-index)									
Unadjusted analysis	<11	26.83	11.73- 53.07	<11	5.76	1.47- 15.67	4.66	1.20- 18.01	0.0258
PPV-adjusted analysis (differential)*	<11	16.72	8.44 - 33.60	<11	4.71	2.09 - 10.70	3.46	0.52- 23.04	0.1987
The Secondary Risk Interval (1 - 42 Days Post-index)									
Unadjusted analysis	<11	17.25	8.41- 31.65	<11	5.76	1.47- 15.67	2.99	0.81- 11.06	0.0999
PPV-adjusted analysis (differential)*	<11	10.75	5.39 - 19.6	<11	4.71	2.09 - 10.70	2.29	0.38- 13.88	0.3671

Abbreviations: CI, Confidence Intervals; CMS, Centers for Medicare & Medicaid Services; IRR, Incidence Rate Ratio; No., Number; PPV, Positive Predictive Value; P-Y, Person-Years; RSV, Respiratory Syncytial Virus; SCRI, Self-Controlled Risk Interval.

Table 7. Subgroup SCRI Analyses of CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine

	Outcomes during Risk Interval		Outcomes during Control Interval		Poisson Analysis		
	No. of Outcomes	Rate per 100,000 P-Y	No. of Outcomes	Rate per 100,000 P-Y	IRR	95% CI	P-value
Unadjusted analyses							
Age at ABRYSVO Vaccination Administration (Primary Risk Interval)							
65-74 years	12	29.59	<11	11.10	2.67	1.12 - 6.33	0.0262
75+ years	14	27.67	<11	3.96	6.99	2.30 - 21.24	0.0006
Age at ABRYSVO Vaccination Administration (Secondary Risk Interval)							
65-74 years	18	22.19	<11	11.10	2.00	0.90 - 4.45	0.0897
75+ years	20	19.77	<11	3.96	4.99	1.71 - 14.61	0.0033
Concomitant Vaccines on the Index Date (Primary Risk Interval)							
Yes	<11	18.72	<11	9.37	2.00	0.70 - 5.70	0.1951
No	19	35.35	<11	5.587	6.33	2.53 - 15.84	<.0001
Concomitant Vaccines on the Index Date (Secondary Risk Interval)							
Yes	15	20.06	<11	9.37	2.14	0.87 - 5.25	0.0962
No	23	21.39	<11	5.59	3.83	1.56 - 9.40	0.0034
CCI (Primary Risk Interval)							
0-1	15	35.92	<11	3.59	10.00	2.89 - 34.54	0.0003
2+	11	22.27	<11	10.14	2.20	0.93 - 5.17	0.0717
CCI (Secondary Risk Interval)							
0-1	19	22.75	<11	3.59	6.33	1.87- 21.40	0.0030
2+	19	19.24	<11	10.14	1.90	0.88 - 4.08	0.1012
Sex (Primary Risk Interval)							
Male	13	33.82	<11	7.81	4.33	1.64 - 11.39	0.0030
Female	13	24.66	<11	6.65	3.71	1.48 - 9.30	0.0052
Sex (Secondary Risk Interval)							

Table 7. Subgroup SCRI Analyses of CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine

	Outcomes during Risk Interval		Outcomes during Control Interval		Poisson Analysis		
	No. of Outcomes	Rate per 100,000 P-Y	No. of Outcomes	Rate per 100,000 P-Y	IRR	95% CI	P-value
Male	19	24.71	<11	7.81	3.16	1.26 - 7.92	0.0139
Female	19	18.02	<11	6.65	2.71	1.14 - 6.45	0.0241
PPV-adjusted analyses (differential)*							
Age at ABRYSVO Vaccination Administration (Primary Risk Interval)							
65-74 years	7.48	18.43	<11	9.08	1.98	0.60 - 6.58	0.2630
75+ year†	8.72	17.24	<11	3.24	5.46	1.20 - 24.80	0.0279
Age at ABRYSVO Vaccination Administration (Secondary Risk Interval)							
65-74 years	11.21	13.82	<11	9.08	1.51	0.52 - 4.41	0.4463
75+ years‡	12.46	12.32	<11	3.24	3.94	0.93 - 16.57	0.0617
Concomitant Vaccines on the index date (Secondary Risk Interval)							
Yes	9.35	12.50	<11	7.66	1.66	0.49 - 5.56	0.4139
No	14.33	13.33	<11	4.57	3.01	0.91 - 9.95	0.0713
CCI (Secondary Risk Interval)							
0-1	11.84	14.17	<11	2.94	4.91	0.99 - 24.46	0.0521
2+ ¥	11.84	11.98	<11	8.29	1.45	0.52 - 4.08	0.4789

Abbreviations: CCI, Charlson Comorbidity Index; CI, Confidence Intervals; CMS, Centers for Medicare & Medicaid Services; IRR, Incidence Rate Ratio; No., Number; PPV, Positive Predictive Value; P-Y, Person-Years; SCRI, Self-Controlled Risk Interval.
*Note: PPV adjustment (62.3% for risk interval and 81.8% for control interval) has been applied to the number of outcomes reported in this row.
†Note: 999 out of 1,000 imputation models converged.
‡Note: 998 out of 1,000 imputation models converged.
¥Note: 996 out of 1,000 imputation models converged.

Table 8. Sensitivity SCRI Analysis of CMS Medicare Enrollees Among Persons Receiving ABRYSVO Vaccine, Excluding Individuals with Infections in the 42 Days Prior to GBS Onset

	Outcomes during Risk Interval			Outcomes during Control Interval		Poisson Analysis		
	No. of Outcomes	P-Y	Rate per 100,000 P-Y	No. of Outcomes	Rate per 100,000 P-Y	IRR	95% CI	P-value
The Primary Risk Interval (1 - 21 Days Post-index)								
Unadjusted analysis	24	91145.70	26.33	<11	5.49	4.80	2.29 - 10.03	<.0001
PPV-adjusted analysis (differential)*	14.952	91145.70	16.40	<11	4.49	3.71	1.39 - 9.94	0.0091
The Secondary Risk Interval (1 - 42 Days Post-index)								
Unadjusted analysis	34	182291.39	18.65	<11	5.49	3.40	1.68 - 6.88	0.0007
PPV-adjusted analysis (differential)*	21.18	182291.39	11.62	<11	2.78	2.61	1.04 - 6.57	0.0414

Abbreviations: CI, Confidence Intervals; CMS, Centers for Medicare & Medicaid Services; GBS, Guillain-Barre syndrome; IRR, Incidence Rate Ratio; No., Number; PPV, Positive Predictive Value; P-Y, Person-Years; SCRI, Self-Controlled Risk Interval.
*Note: PPV adjustment (62.3% for risk interval and 81.8% for control interval) has been applied to the number of outcomes reported in this row.