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
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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

Principal Investigator(s) of the Protocol

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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. <u>The Study Design of RCA Methodology using CMS Medicare Databases:</u>

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. <u>The Study Design of SCRI Methodology using CMS Medicare Databases:</u>

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. <u>The Study Design of Descriptive Analysis of Individuals Aged 60-64 Years Enrolled in PharMetrics Plus Database:</u>

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.

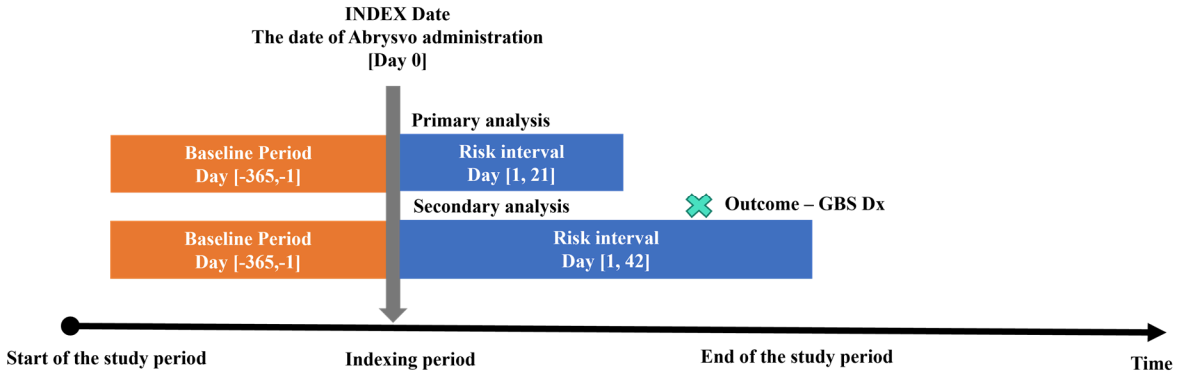
9.1.1.1. The Study Periods of RCA Methodology

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.

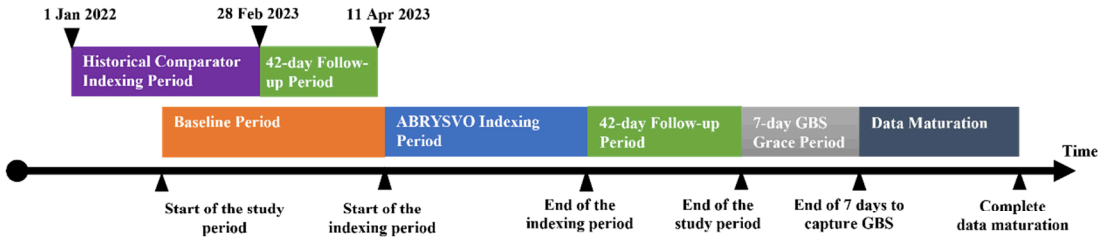
Figure 1. Study design and key study periods of the rapid cycle analysis



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:

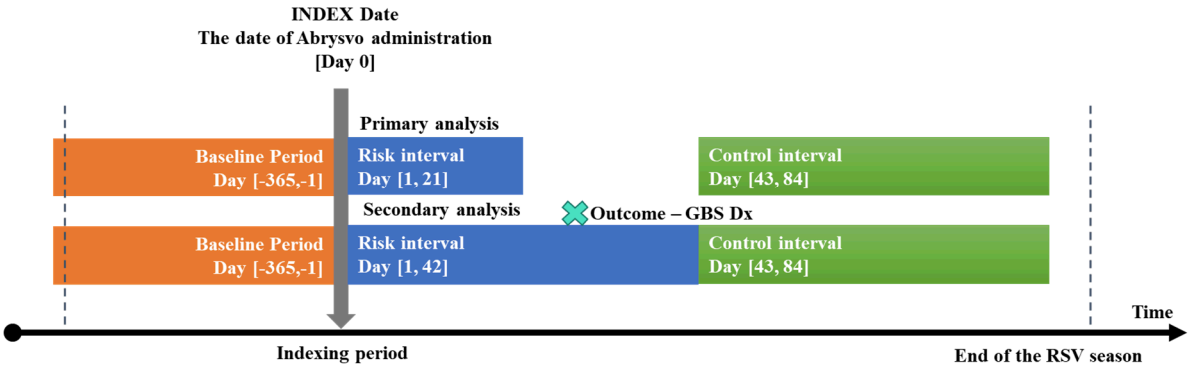
- **Study Periods:**
    - **2023/2024 Study Period:** 31 May 2022 – 23 May 2024
        - **Indexing period:** 31 May 2023 – 29 February 2024

- **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.

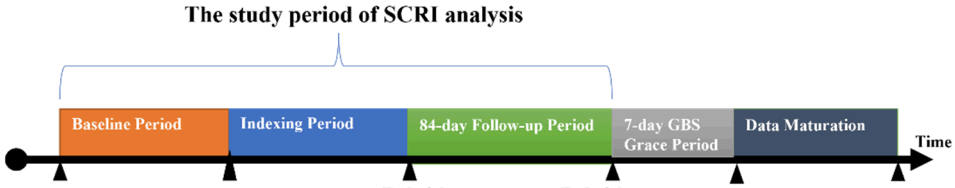
Figure 3. Study design of the self-controlled risk interval analysis



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.

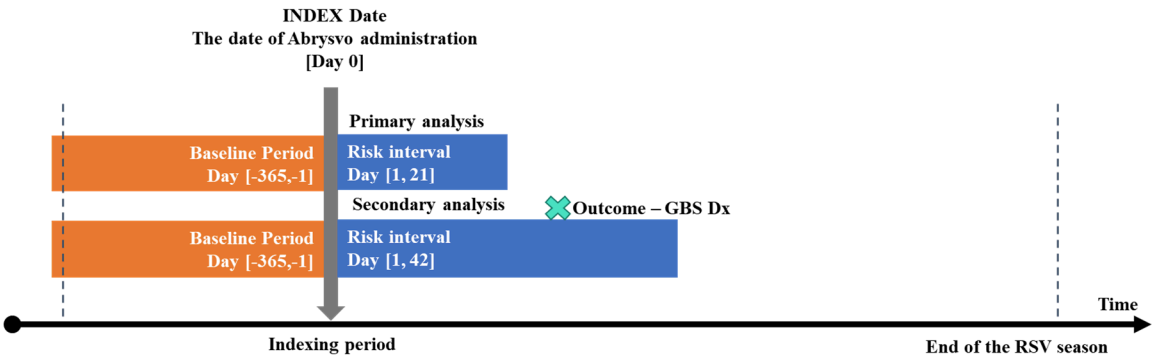
9.1.3.1. The Study Periods of Descriptive Analysis of Individuals Aged 60-64 Years Enrolled in PharMetrics Plus Database

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.

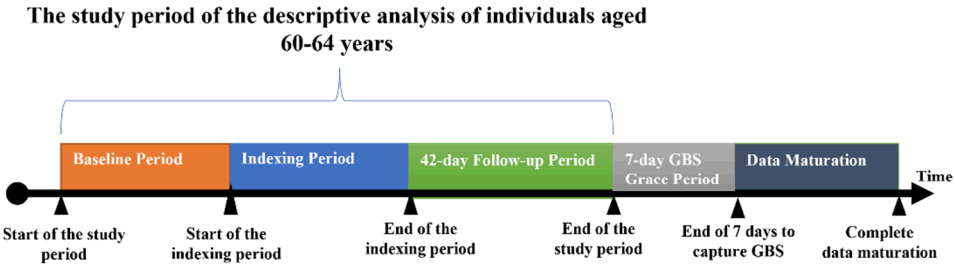
Figure 5. Study design of the descriptive analysis of individuals aged 60-64 years



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.

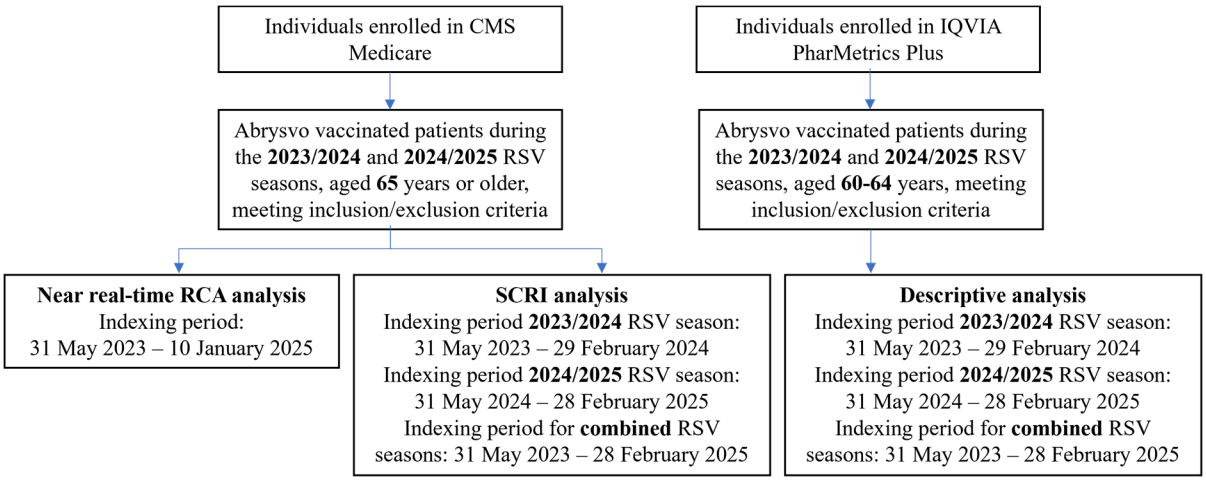
9.1.4. Study Population

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.

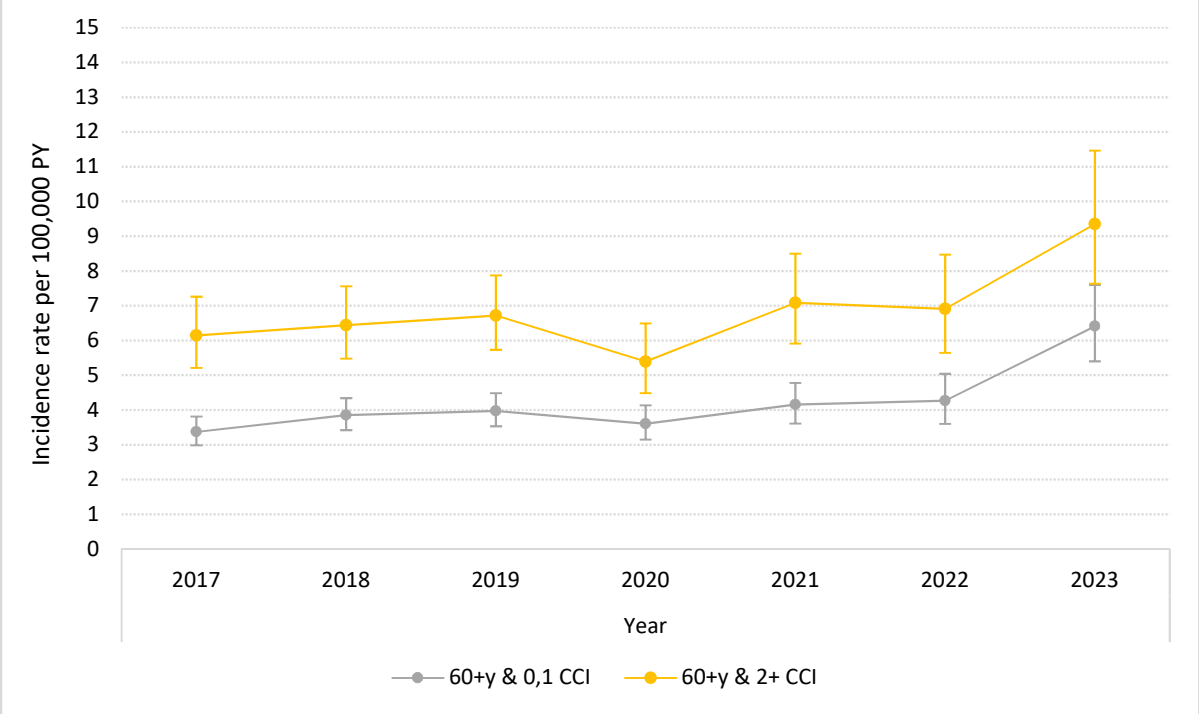
9.7.3.1. The Background Rate of GBS

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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14. LIST OF TABLES

15. LIST OF FIGURES

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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