PASS INFORMATION

Title:	A targeted safety study, EPI-ZOSTER-030 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 50 years of age in the United States.
Protocol version identifier:	209452 (EPI-ZOSTER-030 VS US DB)
Date of last version of the protocol:	Final: 19 August 2020 Amendment 1 Final: 17 May 2021 Amendment 2 Final: 13 June 2022 Amendment 3 Final:18 Sep 2024
EU PAS Register No:	*EUPAS37156*
Active substance:	VZV glycoprotein E (gE)
Medicinal product(s):	*Shingrix* (Recombinant Zoster Vaccine, RZV)
Product reference:	For EMA: MEA/H/C/004336 For FDA: IND number 13857
Procedure number:	EMEA/H/C/004336/MEA/009.1
Marketing Authorization Holder (MAH):	GlaxoSmithKline Biologicals SA. Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	The study will address the question of whether *Shingrix*, or recombinant zoster vaccine, is associated with an increased risk of new-onset Guillain-Barré syndrome (GBS), gout, polymyalgia rheumatica (PMR), giant cell arteritis (GCA), supraventricular tachycardia (SVT), or ischemic optic neuropathy (ION) within specified time periods after vaccination in people ≥ 50 years of age enrolled beginning in January 2018 at any of the participating US Sentinel ***Research*** Partners. SVT and ION will be investigated as secondary objectives.
Country of study:	United States
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BASED ON GSK BIOLOGICALS' PROTOCOL TEMPLATE FOR POST-AUTHORIZATION SAFETY STUDIES V17.0

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2. LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ASO	Administrative-services-only
ATE	Average Treatment Effect
CBER	Center for Biologics Evaluation and Research (Food and Drug Administration)
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CPT	Current Procedural Terminology
CSR	Clinical Study Report
CW	Control Window
EKG	Electrocardiogram
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU PAS	European Union Electronic Register of Post-Authorization Studies
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
FQHC	Federally Qualified Health Center
GBS	Guillain-Barré syndrome
GCA	Giant Cell Arteritis
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HOI	Health Outcome of Interest
HPHC	Harvard Pilgrim Health Care
HPHCI	Harvard Pilgrim Health Care Institute
HZ	Herpes Zoster
ICD-9-CM	International Classification of Diseases, ninth revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, tenth revision, Clinical Modification
IEC	Independent Ethics Committee

IMEDS	Innovation in Medical Evidence Development and Surveillance
ION	Ischemic Optic Neuropathy
IPPE	Initial Preventive Physical Exam
IRB	Institutional Review Board
NDC	National Drug Code
NIST	National Institute of Standards and Technology
PCORnet	Patient-Centered Clinical Research Network
pIMD	Potential Immune-Mediated Disorders
PMR	Polymyalgia Rheumatica
PPS	Personalized Prevention Plan of Service
QA	Quality Assurance
RR	Relative Risk
RW	Risk Window
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SCCS	Self-Controlled Case Series
SCDM	Sentinel Common Data Model
SCRI	Self-Controlled Risk Interval
SOP	Standard Operating Procedure
SVT	Supraventricular Tachycardia
VZV	Varicella Zoster Virus
ZVL	Zoster Vaccine Live

3. RESPONSIBLE PARTIES

Principal investigator	Richard Platt, Harvard Medical School & Harvard Pilgrim Health Care Institute
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4. ABSTRACT

Title	A targeted safety study, EPI-ZOSTER-030 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 50 years of age in the United States.
Version and date of the protocol	Final: 19 August 2020 Amendment 1 Final: 17 May 2021 Amendment 2 Final: 13 June 2022 ***Amendment 3 Final: 18 Sep 2024***
Main author	PPD, Harvard Medical School & Harvard Pilgrim Health Care Institute
Rationale and background	*Shingrix*, or recombinant zoster vaccine (RZV), is a subunit, adjuvanted vaccine that was approved by the Food and Drug Administration (FDA) in October 2017 and by the European Medicines Agency (EMA) in March 2018 for the prevention of herpes zoster (HZ) in adults ≥ 50 years of age. The Advisory Committee on Immunization Practices recommends RZV vaccination for the prevention of HZ in immunocompetent adults ≥ 50 years of age. In pre-licensure clinical trials, which are not designed to assess rare outcomes, numerical differences between the RZV and Placebo groups were noted for certain conditions, including: 1) polymyalgia rheumatica (PMR), 2) giant cell arteritis (GCA), 3) gout, 4) ischemic optic neuropathy (ION), and 5) supraventricular tachycardia (SVT). The Centers for Disease Control and Prevention (CDC) detected a statistical signal for Guillain-Barré syndrome (GBS) during post-licensure safety surveillance of RZV using the Vaccine Safety Datalink. CDC applied an iterative algorithm that preferentially maximizes sensitivity over specificity that was designed for hypothesis (signal) generation. This safety study will use a large, distributed data network in the US to rigorously evaluate the real-world safety of RZV, focusing on the specific outcomes listed above. The network is comprised of several large national and regional healthcare systems that currently participate in the FDA's Sentinel Surveillance System.

Research question and objectives	This study is a targeted safety study and a post-authorization safety study. The study will address the question of whether there is an increased risk of new-onset GBS, gout, PMR, GCA, SVT, or ION within specified time periods after *Shingrix* vaccination in people ≥ 50 years of age enrolled starting in January 2018 at any of the participating US ***Research*** Partners. SVT and ION will be examined as secondary objectives.
Study design	A self-controlled risk interval design will be used to study the risk of GBS, gout, and SVT (a secondary outcome). A retrospective cohort design with concurrent controls will be used to study the risk of PMR, GCA, and ION (a secondary outcome).
Population	The study population will be US commercially insured people ≥ 50 years of age on or after 1/1/2018 who are members of participating Sentinel ***Research*** Partners.
Variables	The exposure is receipt of at least one dose of RZV. Variables to be collected include RZV exposure; preventive care visits; occurrence of health outcomes of interest; and several covariates, including age, sex, ***Research*** Partner, region of residence within the US, calendar year-month, concomitant vaccinations and certain comorbidities.
Data sources	This study will be conducted using data provided by ***five*** US ***Research*** Partners in the FDA's Sentinel System. Four of these are national insurers (Aetna, ***a CVS Health Company***; Carelon Research; Humana; Optum), and one, Harvard Pilgrim Health Care, is a regional insurer. The study will use curated data that are formatted to the FDA Sentinel Common Data Model specifications, which permits the use of publicly available Sentinel analytic tools.
Study size	Sample size calculations together with preliminary data suggest that the study will ultimately have at least 80% power to reject the null hypothesis of no association if the true relative risk is ≥4 for GBS, ≥2 for gout, ≥2 for PMR, and ≥3 for GCA.
Data analysis	The analysis plan will include descriptive measures to characterize exposed and unexposed individuals, conditional Poisson regression models for the self-controlled risk interval (SCRI), and Cox proportional hazards regression models for the cohort design outcomes.
Milestones	The milestones are 14 September 2020 (Actual date) for start of data collection, Q2, 2025 (Tentative) for end of data

collection and final report submitted to FDA's Center for Biologics Evaluation and Research (CBER) and to EMA 31 March 2027.

Note: the above timelines are tentative and subject to change.

5. AMENDMENTS AND UPDATES

Protocol amendment 2 (dated 13 June 2022) was amended to address the following analytical updates.

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
3	18 Sep 2024	• Data partner name changed to research partner	Throughout the protocol	• Aligned with new Sentinel terminology
		• Clarified the possibility of inclusion of ASO members • Clarified 1 year look back for gout, and continuous enrollment without gaps during follow-up for SCRI	Section 9.2	• Some research partners may have the ability to include ASO members and their medical records. • Clarifications added that were not previously explicit
		• Clarified the invalidity of doses prior to Sept 2017 (i.e. approval), counting of dose number, and dose 2 inclusion period. • Clarified comparator cohorts for each dose, and the sampling of comparators	Sections 9.3.1	• Any observed doses prior to approval of the vaccine are not included. • Separate comparators are selected for each cohort, and if more comparators are identified during the accrual period than needed per the sample size calculation then sampling will be conducted due to chart review
		• Footnotes for references added to table 2	Section 9.3.2	• Administrative update
		• Clarified the selection process for obtaining 25% of PMR cases for chart review, cases for	Section 9.3.3	• To ensure the ability to meet 25% criteria, research

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
		the final and sensitivity analysis, and PPV calculation		partners will be advised to continue requesting charts until 25% of charts are retrieved. • As only 25% of PMR cases will be chart reviewed, the final analysis will include claims-based cases, with sensitivity analysis conducted if PPV is found to be <70% • The methodology for the PPV calculation was not previously specified
		• Clarified covariate for immunocompromising status	Section 9.3.4	• Conditions and therapies to be included
		• Adjustment made to description of data sources	Section 9.4	• Some research partners have changed their names and descriptions needed to be updated
		• Updates made to tables 3 to 5 headers and footnotes • Clarified accrual periods based on sample size calculations	Section 9.5	• To align with GSKs updated style guide. • To clarify that accrual periods of RZV, and cases is planned to meet sample size targets. Additionally due to the need for chart review comparators

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
				will be sampled if more cases are accrued then needed per planned sample size target
		Added sensitivity analysis for; • asymptomatic SVT • Unobtainable/incomplete charts	Section 9.7.2.1.1	• Upon expert consultation asymptomatic short-run SVT is not clinically important therefore these cases are not included in the primary analysis, but added sensitivity analysis where they will be captured • Some charts may not be obtainable or may have incomplete information that prevents adjudication of the case. These cases cannot be included in the primary analysis as they will not be adjudicated, but sensitivity analysis will be conducted to test any potential bias.
		• Primary analytic models are to be weighted by inverse probability of treatment weights to estimate population-average treatment effect	Section 9.7.2.2.1	• Propensity score methods were seen as superior for confounding control and to increase the

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
				likelihood of outcome model convergence
		• In secondary analysis dose 1 follow-up time will be censored at dose 2 (if dose 2 is received within the 183-day follow-up after dose 1) to avoid double counting of events	Section 9.7.2.2.2	• Individuals only contribute a single event to the analytic model
		• Clarified sensitivity analysis for PMR due to the 25% chart review • Added bias analysis for unobtainable/incomplete charts • Added sensitivity analysis to test IPTW sample	Section 9.7.2.2.3	• As only 25% of PMR cases will be chart reviewed, the final analysis will include claims-based cases, with sensitivity analysis conducted if PPV is found to be <70% • Some charts may not be obtainable or may have incomplete information that prevents adjudication of the case. These cases cannot be included in the primary analysis as they will not be adjudicated, but sensitivity analysis will be conducted to test any potential bias. • If results in the IPT weighted sample are not significant this may be due to insufficient

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
				sample. Sensitivity analysis may be conducted to adjust the IPT weighted sample.

6. MILESTONES

Milestone	Planned date
Start of data collection[1]	14 Sep 2020 (Actual date)
End of data collection[2]	Q2, 2025 (Tentative)
Final report submitted to the FDA's CBER and to EMA	31 Mar 2027

Note: the above timelines are tentative and subject to change.
[1] Start of study activities
[2] Date analytic dataset with chart confirmed cases of last health outcome available for analysis

7. RATIONALE AND BACKGROUND

Herpes zoster, the result of reactivation of latent VZV in dorsal root ganglia, most commonly presents as a painful vesicular dermatomal rash. However, complications such as postherpetic neuralgia, as well as disseminated disease in the immunocompromised population, can lead to significant disability and morbidity [Austin, 2021]. There are an estimated 1 million cases of HZ in the US annually, resulting in $5 billion in healthcare expenditures per year [McLaughlin, 2013]. Risk factors for HZ include older age and immunocompromising conditions [Kawai, 2017; Thomas, 2004].

Shingrix, or RZV, is a subunit, adjuvanted VZV vaccine. It is approved for the prevention of HZ in adults ≥ 50 years of age in several countries within Europe and the US. RZV is a two-dose vaccine; in Europe, Doses 1 and 2 should be given 2 months apart, with the possibility of extending the timing of Dose 2 to 6 months. In the US, RZV is given 2 to 6 months apart. Since this study is being conducted in the US, the recommended dosing schedule in the US will be considered. The Advisory Committee on Immunization Practices (ACIP) recommendations for RZV include the following: 1) RZV (as two doses 2 to 6 months apart) is recommended for immunocompetent adults aged 50 years and older; 2) RZV is recommended for immunocompetent adults previously vaccinated with the live zoster vaccine (*Zostavax* [ZVL]); and 3) RZV is preferred over ZVL [Dooling, 2018]. Vaccine efficacy against HZ in the pivotal Phase III studies was 97.2% in adults ≥ 50 years of age (ZOE-50)[Lal, 2015] and 91.5% in adults ≥ 70 years of age [Cunningham, 2016]. Pooled safety analysis of clinical data from these ***2*** Phase ***3*** studies included a total of 14,645 RZV and 14,660 placebo recipients, with a median follow-up duration of 4.4 years [Curtis, 2012; Sentinel Initiative, 2024]. The pooled analysis demonstrated a comparable incidence of unsolicited AEs in the day 7 through day 29 follow-up period (excluding day 0 through day 6 where reactogenicity was observed to

be higher in RZV versus placebo recipients) ***between the RZV and Placebo groups*** [Lopez-Fauqued, 2019]. ***Similar findings were noted for*** SAEs, and potential immune-mediated disorders (pIMDs) and specific SAEs and pIMDs were within the expected incidence for the study age group [Lopez-Fauqued, 2019].

On descriptive analyses, there were numerical differences in AEs for some specific conditions, including 1) polymyalgia rheumatica (PMR), 2) GCA, 3) gout, and 4) ION. During the entire post-vaccination follow-up period, PMR was reported by 32 (0.2% [95% confidence interval [CI]: 0.1-0.3]) and 29 (0.2% [95% CI: 0.1-0.3]) subjects in the RZV and Placebo groups, respectively. GCA was reported by 6 (0.04 % [95% CI: 0.0-0.1]) and 3 (0.02% [95% CI: 0.0-0.1]) subjects in the RZV and Placebo groups, respectively. Within the 30-day period following the last vaccination, there were 27 (0.18% [95% CI: 0.12-0.27]) and 8 (0.05% [95% CI: 0.02-0.11]) subjects in the RZV and Placebo groups, respectively, who reported an event of gout or gouty arthritis (relative risk [RR] 3.38 [95% CI: 1.49- 8.60]). Among subjects without a known history of gout at study entry, 19 subjects in the RZV group versus 3 subjects in the Placebo group reported new-onset gout in the 30-day period following the last vaccination. For ION at specific follow-up timepoints post-vaccination, 1 versus 0 cases at ≤ 30 days and 2 versus 0 cases at ≤ 365 days were reported in RZV and Placebo groups, respectively.

With respect to clinical trials, numerical differences were also noted between the RZV group and the Placebo group on pooled analyses with respect to other clinical outcomes, including supraventricular tachycardia (SVT): 6 (0.04% [95% CI: 0.02-0.09]) and 0 (0.00% [95% CI: 0.00-0.03]) subjects in the RZV and Placebo groups, respectively, in the 365-day follow-up period post-last vaccination.

With respect to reports of GBS, there were 2 cases reported in the RZV group and 3 in the Placebo group during the entire post-vaccination follow-up period. Recent RZV post-licensure safety surveillance by the ***CDC*** detected a statistical signal using Vaccine Safety Datalink Rapid Cycle Analysis, using an algorithm that preferentially maximizes sensitivity over specificity. Specifically, at the time of the preliminary signal, there were 3 presumptive (i.e., ICD-10-CM based) observed events compared to 0.57 expected events when comparing RZV to a historical cohort of ZVL users, with an RR of 5.25 [Shimabukuro, 2019]. As of the most recent publicly available analysis, 5 presumptive events have been observed compared to 1.6 expected with an RR of 3.18. Of these 5, one case was confirmed as Brighton Criteria level 2, one case was confirmed as Brighton Criteria level 3 (with probable respiratory infection prior to GBS symptom onset), and three cases were ruled out as not being representative of true incident cases post-vaccination.

Based on the clinical trial data and the clinical importance of some events which were too rare to be assessed in clinical trials, further evaluation is warranted using real-world data. Robust data on the risk of these outcomes following administration of RZV are currently lacking. Furthermore, data on the use of RZV in complex patient populations are critical in assessing the safety of the vaccine in the real-world setting. An observational study utilizing a large and comprehensive distributed data network will therefore provide a valuable opportunity to rigorously evaluate the real-world safety of RZV, including in

heterogeneous, complex populations, with a focus on the specific safety outcomes outlined above.

8. RESEARCH QUESTION AND OBJECTIVES

The study will address the question of whether there is an increased risk of new-onset GBS, gout, PMR, GCA, SVT, or ION within specified time periods after RZV vaccination in people ≥ 50 years of age enrolled starting in January 2018 at any of the participating ***Research*** Partners. A SCRI design will be used for GBS, gout, and SVT. A cohort design using a concurrent preventive care visit comparison group will be used for PMR, GCA, and ION.

Primary objectives

1. To assess the risk of new-onset GBS within 42 days after RZV vaccination using an SCRI design
2. To assess the risk of new-onset gout within 30 days after RZV vaccination using an SCRI design
3. To assess the risk of new-onset PMR within 183 days after RZV vaccination using a cohort design
4. To assess the risk of new-onset GCA within 183 days after RZV vaccination using a cohort design

Secondary objectives

1. To assess the risk of new-onset SVT within 30 days after RZV vaccination using an SCRI design
2. To assess the risk of new-onset ION within 183 days after RZV vaccination using a cohort design

9. RESEARCH METHODS

9.1. Study design

- This study is a targeted safety study and a post-authorization safety study that will assess the risk of new-onset GBS, gout, and SVT following RZV exposure using an SCRI design; this study will also assess the risk of new-onset PMR, GCA, and ION following RZV exposure using a retrospective cohort design.
- The study population will be comprised of approximately 2 million commercially -insured US adults ≥50 years of age who received at least one dose of RZV.
- RZV exposure will be defined as receipt of at least one dose of vaccine; secondary analyses will be conducted to assess the risk of outcomes when Dose 2 is received, e.g., 2-6 months after Dose 1 (per US dosing recommendation).

- This study will be conducted using health data held by ***Research*** Partners that participate in the FDA's Sentinel System (described in Section 9.4).

SCRI design for Primary Objectives 1 & 2 and Secondary Objective 1:

To study the risk of new-onset GBS, gout, and SVT after RZV exposure, we will use the SCRI design, which has been used in a number of vaccine safety studies [Baker 2019; Klein, 2010; Yih, 2014; Yih, 2016]. This design is a special (and simpler) case of both the case-crossover [Maclure, 1991] and the self-controlled case series (SCCS) [Farrington, 1995; Farrington, 1996; Petersen, 2016] designs, in which the cumulative numbers of cases in pre-specified risk and control intervals (or "windows") are compared ***(approximating a relative risk)***. The analysis is conditioned on the individual, and only those RZV vaccinees having the health outcome of interest (HOI) in either the risk or the control interval contributes to the analysis. The SCRI design is ideal for assessing acute outcomes and transient exposures.

The unique strength of self-controlled designs is that they control for all time-fixed potential confounders, such as sex, race/ethnicity, and chronic disease status. However, potential time-varying confounders, such as age, seasonality, and possibly medication use, may introduce bias unless they are explicitly controlled for within the analysis. In the current study, time-varying confounding may not be a concern. For example, age would not likely act as a strong confounder in the age groups receiving RZV, as HOI risk does not change dramatically by age over the course of a few months, and seasonality could not act as a confounder unless both RZV receipt and the HOI had a seasonal pattern.

Cohort design for Primary Objectives 3 & 4 and Secondary Objective 2:

The 183 days (6 month) follow-up period post-RZV administration for new-onset PMR, GCA, and ION makes the use of the SCRI design impractical, due primarily to the possibility of time-varying confounding and overlapping observation windows for Doses 1 and 2. In general, self-controlled designs, including the SCCS design, of which the SCRI design is a special case, are not ideal for the study of non-acute outcomes or outcomes with insidious onset, due to the difficulty of specifying the most appropriate risk interval and the introduction of time-varying confounding when follow-up extends more than a few weeks post-exposure.

Thus, we will instead use a cohort design that compares the hazard of these HOIs after RZV exposure with the hazard after preventive care visits or age-appropriate screenings (e.g., colonoscopies) among those who have not received RZV. For simplicity, in the remainder of the protocol, we will refer to the comparator group in terms of preventive care visits, rather than in terms of "preventive care visits or screenings." Further details of the preventive care visit comparator group are described in Section 9.3.1 below.

The use of a concurrent comparator group (i.e., a comparator group that is observed during the same period of time as the RZV exposed group) as opposed to a historical preventive care visit comparator group avoids potential confounding related to time (e.g., changes in HOI coding practices over time). Given that the HOIs assessed using the cohort design are rare, the study design will be unmatched so as to not arbitrarily reduce the size of the comparison group, which would reduce statistical power. Potential

confounding differences between RZV vaccinees and preventive care visit seekers (e.g., age, sex, certain chronic conditions, calendar time, etc.) will be adjusted for in multivariable Cox proportional hazards regression models (described in Section 9.7.2.2 below).

9.2. Setting

The Sentinel ***Research*** Partners are discussed in Section 9.4. The study population will be commercially insured people in the US who are ≥ 50 years of age at the time of their qualifying visit date (i.e., RZV vaccination date for RZV recipients or preventive care visit date for cohort study comparators) during the study period, from 1/1/2018 on. Administrative-services-only enrollees will be excluded, as their medical records ***may not be*** available for review; ***however, ASO enrollees may be considered for inclusion on an as-needed basis, if allowable and medical records are available***.

9.2.1. SCRI design inclusion criteria

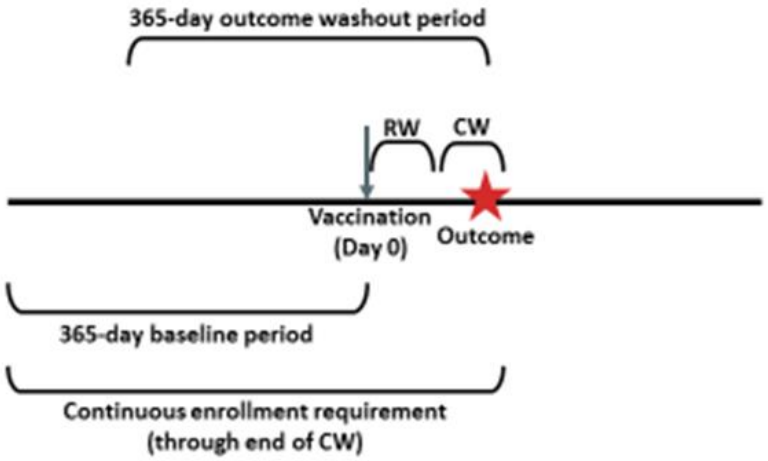
Additional inclusion requirements for the SCRI analyses of new-onset GBS, gout, and SVT are illustrated in Figure 1and consist of:

- RZV vaccination
- First-in-365-days case of the HOI in the risk or control interval (i.e., definition of an incident case)
- 365 days (1 year) of continuous enrolled time, allowing 45-days gap, prior to RZV receipt for GBS and SVT, ***and the secondary definition of gout***
- 730 days (2 years) of continuous enrolled time, allowing a 45-days gap, prior to RZV receipt for gout, to allow for a more specific definition of incident, versus prevalent gout, to be implemented
- Continuous enrollment ***(without gaps)*** through the end of the respective control interval during a period when data for the respective ***Research*** Partner are determined to be ≥ 90% complete for the outcomes of gout and SVT.
- Continuous enrollment ***(without gaps)*** through the end of the respective control interval plus 14 days during a period when data for the respective ***Research*** Partner are determined to be ≥ 90% complete for the outcome of GBS. The 14 “extra” days are to ensure capture of GBS cases with symptom onset in windows of interest but no diagnosis code until later, e.g., GBS symptom onset on Day 82 after RZV receipt (determined by chart review) but no GBS hospitalization or diagnosis code until Day 85, which would be outside of the windows of interest. Further details on medical record review for GBS are described in Section 9.3.3 below.

The use of a first-in-X-days definition of HOI incidence is important and customary with the SCRI design, to establish an equal opportunity for a case to be ascertained regardless of where in the follow-up (risk + control) period it might appear.

The requirement of a defined amount of follow-up time, e.g., through the end of the control interval plus 14 days, will exclude people who die before that time. However, because the HOIs addressed in this study are usually not fatal, we do not expect this requirement to produce any appreciable bias in our analyses.

Figure 1 Illustration of temporal inclusion criteria for SCRI analyses



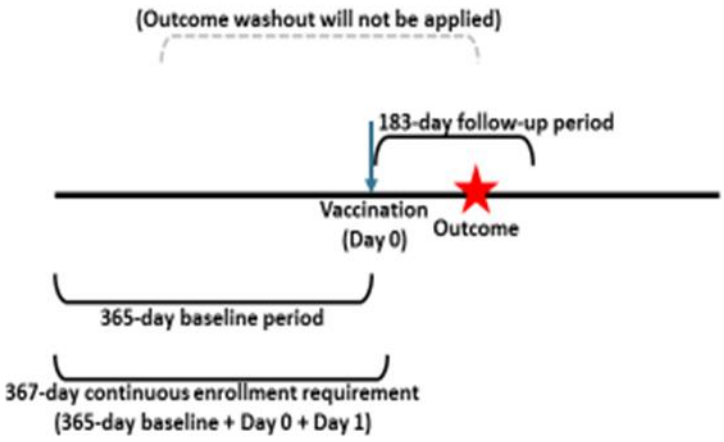
RW = risk window; CW = control window. For the gout primary definition, the outcome washout period will be 730 instead of 365 days, and the continuous enrollment requirement will extend 365 days further to the left than shown.

9.2.2. Cohort design inclusion criteria

Inclusion requirements for the cohort analyses of new-onset PMR, GCA and ION (beyond those in the first paragraph of this section) are illustrated in Figure 2 and are:

- RZV vaccination or eligible preventive care visit with 365 days of enrolled time, allowing 45-days gap, before the index date (vaccination or preventive care visit) during a period when data for the respective ***Research*** Partner are determined to be ≥ 90% complete.
- For a preventive care visit to be eligible as a comparator, the person must not have had RZV at any time (in available history) prior to the visit or on the day of the visit. Unlike the SCRI design, the outcome washout/exclusion period anchored on the outcome date (red star in Figure 2) will not be applied. Rather, as is customary for the cohort design, patients must not have had the HOI at any point in the whole baseline period prior to vaccination or the preventive care visit in order to exclude prevalent cases of the HOI prior to the index date.

Figure 2 Illustration of temporal inclusion criteria for cohort analyses



9.3. Variables

9.3.1. Exposures

RZV exposure will be defined as receipt of at least one dose of RZV for the primary analyses; all-dose as well as dose-specific analyses will be performed. RZV vaccination will be identified by means of CPT code 90750, and NDC codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11. ***RZV records observed before September 2017 (the month prior to approval) will be considered invalid.***

We will define duplicate RZV vaccination records as those occurring within 27 days after a previous RZV vaccination record (i.e., on Days 1-27, where the day of the previous record is Day 0). Duplicate records will be deleted. After deduplication, we will exclude from analysis all RZV doses beyond two per study subject, ***with dose number assigned based on the ordinal number of records observed after September 1, 2017. Dose 2 exposures will be eligible for analysis only if the individual's Dose 1 was included in the analysis, and if the gap between doses was <365 days.***

Preventive care visits for comparison with RZV vaccinations will be identified by means of CPT, ICD-10, and Healthcare Common Procedure Coding System (HCPCS) codes, as shown in Table 1. The presence of any of the below codes qualifies as an eligible "preventive care visit."

Table 1 Codes to be used to identify comparison visits for cohort analyses

Z00.00	Encounter for general adult medical examination without abnormal findings	Diagnosis	ICD-10-CM
Z00.01	Encounter for general adult medical examination with abnormal findings	Diagnosis	ICD-10-CM
Z12.11	Encounter for screening for malignant neoplasm of colon	Diagnosis	ICD-10-CM
Z12.31	Encounter for screening mammogram for malignant neoplasm of breast	Diagnosis	ICD-10-CM
Z12.39	Encounter for other screening for malignant neoplasm of breast	Diagnosis	ICD-10-CM

Z13.820	Encounter screening for osteoporosis	Diagnosis	ICD-10-CM
99386	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 40-64 years	Procedure	CPT-4
99387	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 65 years and older	Procedure	CPT-4
99396	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	Procedure	CPT-4
99397	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 65 years and older	Procedure	CPT-4
45378	Screening colonoscopy	Procedure	CPT-4
77067	Screening mammogram	Procedure	CPT-4
77080	Osteoporosis screening	Procedure	CPT-4
77081	Osteoporosis screening	Procedure	CPT-4
G0438	Annual wellness visit; includes a personalized prevention plan of service (PPS), initial visit	Procedure	HCPCS
G0439	Annual wellness visit, includes a personalized prevention plan of service (PPS), subsequent visit	Procedure	HCPCS
G0468	Federally qualified health center (FQHC) visit, initial preventive physical exam (IPPE) or annual wellness visit (AWV)	Procedure	HCPCS
S5190	Wellness assessment, performed by nonphysician	Procedure	HCPCS

Dates of RZV exposure and preventive care visits will be collected. All preventive care visits that meet inclusion requirements will be identified, and one per patient will be randomly selected as the index date. The preventive care visit definition for the comparator group for the cohort analyses was selected based on having demonstrated greatest comparability to RZV recipients on a number of patient characteristics that may be important potential confounders (e.g., comorbidities) compared to alternative comparator definitions. (The comparison was conducted as part of feasibility assessment in four ***Research*** Partners.) ***Separate comparator cohorts will be selected for each HOI, and a single set of comparators used for analysis of both RZV doses. Comparators may be sampled if necessary to achieve the numbers needed to meet study power (see Section 9.5).***

9.3.2. Outcomes

Case-finding algorithms for the HOIs are listed in Table 2 below. Primary outcomes are GBS, gout, PMR, and GCA. Secondary outcomes are SVT and ION.

Table 2 Case-finding algorithms

1	2	3	4	5	6	7	8	9	10
Outcome (1° or 2°) (Study design) Chart review plan	ICD-10 code(s) for case ascertainment	ICD-9 code(s)[a]	Validation statistics[b]	Other requirements[c]	Settings for case ascertainment	Risk interval	Look back period and settings to determine incidence	What to look back for	What to look back from
GBS (1°), primary def. (SCRI) Chart review; PPV to be calculated DO NOT REQUIRE DRUG COVERAGE	G61.0 (GBS)[Sentinel GBS]	357.0[Sentinel GBS]		None	Inpatient; primary position OR Diagnosis in any setting followed by an inpatient claim within 7 days	Days 1-42	1 year; inpatient; primary position	Same as in Col. 2&3	HOI
GBS (1°), secondary def.[e] (SCRI) Chart review; PPV to be calculated DO NOT REQUIRE DRUG COVERAGE	G61.0 (GBS) [Sentinel GBS]	357.0[Sentinel GBS]	Sensitivity 79.7%, PPV 61.8% (inpatient; primary position)[Bogliun, 2002]	None	Inpatient; primary position	Days 1-42	1 year; inpatient; primary position	Same as in Col. 2&3	HOI
Gout (1°) (SCRI) No chart review REQUIRE DRUG COVERAGE	M10.* *[Sentinel coding trend analysis for gout]*, M1A.* *[Sentinel coding trend analysis for gout]*	274.*[Sentinel coding trend analysis for gout], [Singh 2007], [Harrold 2007]; 274.0 [Meier 1997]	PPV 89.5% (outpatient; any position; diagnosis code + increased abnormal high serum urate level or newly started gout	Gout-specific oral medications (allopurinol, colchicine, probenecid, febuxostat) prescribed within 3 months after diagnosis date	All settings[d]; any position	Days 1-30	Primary def. : 2 years Secondary def.: 1 year; all settings	Any code in Col. 2, 3, or 5 (refer to drug list)	HOI

1	2	3	4	5	6	7	8	9	10
Outcome (1° or 2°) (Study design) Chart review plan	ICD-10 code(s) for case ascertainment	ICD-9 code(s)[a]	Validation statistics[b]	Other requirements[c]	Settings for case ascertainment	Risk interval	Look back period and settings to determine incidence	What to look back for	What to look back from
			drug treatment (allopurinol, colchicine, probenecid, indomethacin or other potent non-steroidal anti-inflammatory agents)[Meier,1997]						
SVT (2°) (SCRI) Chart review; PPV to be calculated DO NOT REQUIRE DRUG COVERAGE	I47.1	427.0 [Sidney, 2005]	PPV 91.7% (inpatient; primary position) [Sidney, 2005]	None	Inpatient, ED; any position	Days 1-30	1 year; all settings	Same as in Col. 2&3	HOI
PMR (1°) (Cohort) Chart review; PPV to be calculated REQUIRE DRUG COVERAGE	M35.3 (PMR) M31.5 (GCA with PMR)	725 [Bernatsky, 2011]	Sensitivity 99.5%, Specificity 92.2%, PPV 78.7% (inpatient; any position; ≥1 diagnosis code or physician billing (≥2 billing claims	Oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone) prescriptions; 1st dispensing date within 6 months after diagnosis date	All settings[d]; any position	Days 1-183	1 year; all settings	Same as in Col. 2&3 (not Col. 5)	Exposure

1	2	3	4	5	6	7	8	9	10
Outcome (1° or 2°) (Study design) Chart review plan	ICD-10 code(s) for case ascertainment	ICD-9 code(s)[a]	Validation statistics[b]	Other requirements[c]	Settings for case ascertainment	Risk interval	Look back period and settings to determine incidence	What to look back for	What to look back from
			by any physician with the diagnosis code, ≥8 weeks apart but within 2 years, or >1 claim by a rheumatologist or internist); true-positive additionally required ≥1 rheumatologist diagnosis code with no requirement of glucocorticoid prescriptions) [Bernatsky, *2011*]	and 2nd dispensing date within 6 months after 1st dispensing date					
GCA (1°) (Cohort) Chart review; PPV to be calculated REQUIRE DRUG COVERAGE	M31.6 (Other GCA) M31.5 (GCA with PMR) M31.9 (Necrotizing vasculopathy, unspecified)	446.5 [England,*2017*], [Gale,*2019*]	NA	Same as for PMR	All settings[d]; any position	Days 1-183	1 year; all settings	Same as in Col. 2&3 (not Col. 5)	Exposure

1	2	3	4	5	6	7	8	9	10
Outcome (1° or 2°) (Study design) Chart review plan	ICD-10 code(s) for case ascertainment	ICD-9 code(s)[a]	Validation statistics[b]	Other requirements[c]	Settings for case ascertainment	Risk interval	Look back period and settings to determine incidence	What to look back for	What to look back from
ION (2°), primary def. (Cohort) Chart review; PPV to be calculated REQUIRE DRUG COVERAGE	H47.01*	377.41	NA	Exclude patients who had lumbar spine surgery or coronary artery bypass graft (CABG) surgery [Rubin, 2016], [Rubin, 2017] within 30 days before ION diagnosis date	All settings[d]; any position	Days 1-183	1 year; all settings	Same as in Col. 2&3	Exposure
ION (2°), secondary def. Chart review; PPV to be calculated REQUIRE DRUG COVERAGE	Same as above except also require: Outpatient dispensing of oral prednisone (≥40 mg/day) within 4 weeks after the initial encounter with ION ICD code *AND* ICD-10 diagnosis code for GCA (M31.6, M31.5, M31.9) within the 3 months prior to or *the 3 months* after the initial encounter with ION ICD code *The aim of this secondary definition is to restrict the outcome to arteritic ION (versus non-arteritic ION)								

Col: Column. Def: Definition. ED: Emergency Department. GBS: Guillain-Barré syndrome. GCA: Giant cell arteritis. HOI: Health outcome of interest. ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification. ICD-10-CM: International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification. ION: Ischemic optic neuropathy. NA: Not available. NPV: Negative predictive value. PMR: Polymyalgia rheumatica. PPV: Positive predictive value. Ref: Reference. SCRI: Self-controlled risk interval. SVT: Supraventricular tachycardia. 1°: Primary. 2°: Secondary.

[a] ICD-9 code(s) will be used for mapping to develop ICD-10 algorithms when validated ICD-10 algorithms are not available, as well as for assessing background frequencies/rates of the outcomes of interest from January 1, 2015 to September 30, 2015 without regard to RZV vaccination.

[b] For ICD-9-CM codes; "NA" means no performance characteristics are available for same or similar algorithm.

[c] Based on external expert opinion.

[d] All settings: Inpatient, Emergency Department, and outpatient settings.

[e] The secondary definition of GBS will be used for descriptive monitoring queries. Potential GBS cases for medical record review will be identified based on the primary GBS definition

9.3.3. Medical record review

Medical record review will be conducted for all identified potential cases (i.e., cases identified based on the claims-based primary HOI definitions as defined in Table 2) of all HOIs except gout and PMR. The gout algorithm, which was developed in consultation with an external expert (rheumatologist), requires a gout diagnosis code followed by a gout-specific drug dispensing within 3 months and excludes cases with either a gout diagnosis code or a gout drug in the prior period (Table 2). This algorithm is expected to have a high positive predictive value, based on validation of a similar algorithm in the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) era [Meier, 1997] together with ICD-9-CM-to-ICD-10-CM trend analysis in the Sentinel system, which demonstrates continuity in gout incidence from the ICD-9-CM to ICD-10-CM eras [Sentinel coding trend analysis for gout, n.d.].

The number of algorithm-identified cases of PMR is expected to be the highest of the primary outcomes based on results of our feasibility assessment. Therefore, for the outcome of PMR, a 25% random sample of potential cases ascertained in the 183 days after RZV vaccination, and a 25% random sample of potential cases ascertained in the 183 days after preventive care comparison visits will be chart reviewed ***to estimate the PPV of the algorithm***. ***To ensure that we obtain 25%, chart review will proceed until 25% of cases have charts obtained***. The final analysis for PMR will include all claims-identified cases ***given that the chart review is only being conducted on a 25% sample of PMR cases. The PPV obtained from the 25% random sample of cases will be reported***. If the PPV is <70% for the claims-based algorithm to detect PMR, ***sensitivity analyses will include chart confirmed and confirmed/probable cases identified from the 25% chart review sample***. Additional sensitivity analysis may be conducted, and details are provided in the SAP. For the process of medical record review, clinical data appropriate to the HOI will be ascertained. For example, for potential cases of GBS, clinical documentation (e.g., admission, discharge, and progress notes; neurology consultation), electromyography testing, neurologic imaging, and laboratory results will be solicited. The ***Research Partners*** will use vendors to obtain the records and redact personal identifiers from the records prior to providing them to the study team for further processing.

On the basis of the medical records obtained, board-certified clinical experts will adjudicate the cases, classifying them into confirmed, probable, possible, and ruled out, using published criteria for these categories, e.g., Brighton Collaboration criteria for GBS. Adjudicators will be blinded to potential cases' vaccination status. Adjudication of 20 randomly chosen cases (or all if less than 20) by at least two adjudicators will be done in order to compare case classifications, resolve any discrepancies, and refine the case-classification rules. Cases beyond the 20 can be either multiply-adjudicated or adjudicated by a single expert, to be determined on the basis of the degree of concordance found during double-adjudication of the first 20 cases, the total number of potential cases, and the availability of adjudicators.

After case adjudication, the respective analysis or analyses will be conducted using confirmed cases. ***The PPVs will be calculated as the number of confirmed cases divided by all successfully adjudicated cases.*** Confirmation of arteritic ION cases (secondary

definition table 2) will be considered during chart review. However, if distinguishing arteritic ION cases during chart review is not feasible then arteritic ION cases will be identified as chart confirmed ION cases who met the secondary claims-based arteritic ION definition. For the cohort design outcomes of PMR, GCA, and ION, where the duration of follow-up is 183 days, the date of onset of the confirmed HOI will be the date of the ICD-10 code for both the RZV and comparator groups. For gout, which will be assessed via SCRI analysis, date of onset will also be the date of the ICD-10 code. However, for GBS, the earliest date of onset will be designated as the first date of the onset of signs and/or symptoms suggestive of GBS based on medical record review. This approach will provide greater accuracy for the true date of GBS onset versus date of hospitalization or claims codes, which is particularly important with the short risk and control intervals being used for the SCRI design. For the SCRI design outcome of SVT, the date of onset will be designated as the date of the ICD-10 code. Given that symptoms of SVT can be nonspecific (e.g., lightheadedness) and subject to patient recall, using the date of the ICD-10 code is preferred as this indicates when the patient has symptoms that prompt medical attention and would most likely have an electrocardiogram (EKG) at this time confirming SVT.

Additionally, the study team may decide to conduct sensitivity analyses incorporating additional levels of diagnostic certainty, for example, probable cases in addition to confirmed ones.

9.3.4. Covariates

Covariates to be evaluated using curated data formatted to the SCDM structure include the following, some of which will be used to adjust or stratify the cohort analyses during modeling:

- ***Research Partner***
- Region of residence within US (as defined by Census Bureau (4 regions))
- Calendar year of vaccination or preventive care visit
- Calendar month of vaccination or preventive care visit
- Age in years at vaccination or preventive care visit (aggregated into age groups: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80+ years)
- Sex
- Race and ethnicity
- Concomitant vaccinations at index date (e.g., influenza, pneumococcal)
- Certain immunocompromising conditions ***or therapies*** (e.g., solid organ or stem cell transplant, cancer, autoimmune/inflammatory conditions, ***steroid use***)
- Certain other comorbidities (e.g., diabetes mellitus, congestive heart failure, chronic kidney disease, chronic pulmonary disease, stroke)

9.3.5. Potential confounding variables and effect modifiers

The self-controlled nature of the SCRI design means that time-fixed traits will not act as confounders. Regarding potential time-varying confounders, increasing age is not expected to significantly change one's risk of GBS or gout over the course of a few months. However, the occurrence of GBS as well as the occurrence of gout are known to vary seasonally. If RZV administration also has a seasonal pattern, seasonality would then operate as a confounder. We will conduct analyses unadjusted for seasonality as our primary SCRI analysis for each of these two HOIs and we will also conduct additional secondary analyses adjusted for seasonality.

The cohort analyses will adjust for ***Research*** Partner, year and/or month of index encounter, age, and sex, at a minimum. Patient characteristics that are risk factors specific to the HOIs and/or relatively common conditions that are indicative of functional status or illness severity will also be considered. Interaction terms will be used during modeling to check for effect modification by ***Research*** Partner, sex, and other covariates that could plausibly operate as effect modifiers.

In this population 50 years of age and older, approximately 4 per 100 individuals in the US population will have an immunocompromising condition [Harpaz, 2016]. The SCRI analyses will control for these conditions automatically. In the cohort analyses, such conditions could produce bias if associated both with receipt of RZV and with the HOI. Ultimately, RZV may be recommended (as opposed to simply not being contraindicated) for immunocompromised patients. To the extent that immunocompromising conditions and their treatment are also associated with an increased or decreased risk of the HOIs to be studied using the cohort design, analyses unadjusted for these conditions could be biased.

Based on identified imbalances in immunocompromising conditions (or other covariates) between the RZV and comparison groups that seem likely to confound our cohort analyses, we will consider options, including the use of propensity scores, to ensure comparability of the RZV and control groups based on confounders that we can measure using these database sources.

9.4. Data sources

This study will be conducted using health plan data held by five ***Research*** Partners that participate in the FDA's Sentinel System. Four are national insurers that update their curated Sentinel database three to four times per year (Aetna, ***Carelon Research [formerly HealthCore]***, Humana, and Optum); HPHC is a regional insurer that updates its data once per year. This study will use the most recently available approved database at each ***Research*** Partner at the time of analysis. All ***Research*** Partners are expected to contribute data for all the analysis detailed in the protocol and statistical analysis plan. However, if a ***Research*** Partner cannot contribute to specific analysis, then alternative approaches to conducting the analysis may be considered including excluding the impacted ***Research*** Partner if appropriate sample size can be maintained, or meta-analytical approaches to combine estimates obtained from analysis conducted individually at the ***Research*** Partner(s), or other appropriate analytical or methodological

solutions. In addition to providing claims data, the ***Research*** Partners will provide scientific input and feedback to support this study.

The Sentinel System is an active surveillance system that uses routine querying and analytical tools to evaluate electronic healthcare data from a distributed data network for monitoring the safety of regulated medical products in the United States, established under the Sentinel Initiative [Behrman, 2011; Platt, 2018]. The average enrollment length for patients across data sources in Sentinel is similar to other claims databases of members with medical and pharmacy coverage; about 25% of patients have over three years of enrollment, and patients with chronic conditions such as diabetes and older members typically have longer than average enrollment periods within these databases.

Brief descriptions of the Research Partners are provided below:

- Aetna***, a CVS Health Company,*** is one of the nation's leading healthcare benefits companies, serving 38 million people with information and resources to help them make better-informed decisions about their healthcare***. CVS Health CTS*** became an FDA Sentinel ***RP*** in 2010 and continues to be one of the largest contributors of data for public health purposes.
- **Harvard Pilgrim Health Care** is one of the country's premier health plans. It is a large non-profit health plan with diverse enrollees across New England. Approximately 3.7 million researchable lives are available for study by HPHCI, a research and academic partnership between Harvard Medical School and HPHC. HPHCI also participates in the Innovation in Medical Evidence Development and Surveillance (IMEDS) program as the IMEDS Analytic Center. Among HPHC's population aged 50 years or older with both medical and drug coverage, 80% are 50-64 years of age and 20% are 65+ years of age. HPHC offers Medicare Advantage.
- ***Carelon Research (formerly*** HealthCore, Inc.***),*** a wholly owned, independently operating subsidiary of ***Elevance Health,*** uses real-world data to conduct outcomes, health economics, pharmacoepidemiologic, and late phase research***. Carelon Research curates the Healthcare*** Integrated Research Database ***(HIRD®),*** a proprietary, fully integrated, longitudinal claims database that combines medical, pharmacy, and laboratory information drawn from ***88*** *million unique individuals with medical coverage and more than* ***67*** million individuals with medical and pharmacy claims information since 2006***.*** In addition***, Carelon*** Research has the ability to link claims data in the ***HIRD*** to complementary data sources, including inpatient and outpatient medical records, national vital statistics records, cancer and vaccine registries (state-by-state), disease and device registries, member and provider surveys, and point of care clinical data. Using these resources***, Carelon Research*** conducts a range of real-world research designed to meet client needs, including retrospective database studies, medical record review studies, cross-sectional and longitudinal patient and provider surveys, and prospective site-based studies, including pragmatic clinical trials.
- **Humana** Healthcare Research is a health economics and outcomes research subsidiary of Humana, which focuses on treatment effectiveness, drug safety, adherence, medical and pharmacy benefit design, disease management programs, and other healthcare services. Humana has been an active collaborator and ***Research***

Partner in the FDA Sentinel System, the Patient-Centered Outcomes Research Institute's, National Patient-Centered Clinical Research Network (PCORnet), and several Distributed Research Network initiatives. More than 12.4 million people are available for research within this health system. Of Humana's population 50 years of age or older with both medical and drug coverage, approximately 28% are 50-64, and 72% are 65+ years of age. Humana offers Medicare Advantage.

- **Optum *was*** initially founded as Epidemiology Research Institute, and later acquired in 1999 by Ingenix (renamed to Optum), Optum Epidemiology has a nearly 40-year history in regulatory drug safety research. Optum Epidemiology scientists leverage their extensive applied experience with real-world data sources to inform the design and implementation of clinical and pharmacoepidemiology research; safety profile and effectiveness evaluations; and risk assessment. Optum's rich data assets include the Optum Research Database comprised of administrative claims data from health plans of a large US national health insurer, with data beginning in 1993. For 2017, data are available for approximately 14.6 million commercially insured individuals with medical and pharmacy coverage. Additional Optum data assets include administrative claims data from Medicare Advantage plans and Electronic Health Records.

The ***Research*** Partners use the SCDM [Curtis, 2012; *Sentinel coding trend analysis for gout*, n.d.] for standardization of demographic and clinical data elements. Publicly available routine analytical tools (i.e., reusable, modular Statistical Analysis System [SAS] programs) designed to be executed against the SCDM permit rapid queries, including descriptive analyses and complex methodologies (e.g., comparative analyses), across ***Research*** Partners. Specific information in the SCDM includes, but is not limited to, the following types of data:

- **Enrollment data**: One record per covered individual per unique enrollment span is included in the SCDM. Individuals are assigned a unique identifier by their insurer, which is linkable to all other data in the SCDM. Due to changes in employment status, individuals may be enrolled multiple times with the same insurer, and the length of each given enrollment "span" may vary substantially. Each record in the enrollment file indicates the patient identifier, enrollment start and end dates, and whether the patient was enrolled in medical coverage, pharmacy coverage, or both during that range. Likewise, a final field indicates whether the ***Research*** Partner can request medical charts for a given patient during a given enrollment span.
- **Demographic data**, including birth date, sex, race/ethnicity, and ZIP code of their most recently recorded primary residence.
- **Pharmacy dispensing data**, including the date of each prescription dispensing, the NDC identifier associated with the dispensed product, the nominal days' supply, and the number of individual units (pills, tables, vials, etc.) dispensed. Products purchased over the counter or at some cash-only retail locations selling prescription drug products (e.g., through the Walmart Prescription Program) are not captured.
- **Medical encounter data**, including the healthcare provider most responsible for the encounter as well as the facility in which the encounter occurred and its ZIP code. Admission and discharge dates (if applicable) are also included, as is the encounter

type (either an ambulatory visit, an Emergency Department visit, an inpatient hospital stay, a non-acute inpatient stay, or an otherwise unspecified ambulatory visit). Discharge disposition (alive, expired, or unknown) as well as discharge status (to where a patient was discharged) are also included for inpatient hospital stays and non-acute inpatient stays. Finally, laboratory data are available for some, but not all, of the ***Research*** Partners; and the level of completeness for laboratory information for those ***Research*** Partners with such data varies [Raebel, 2014].

- **Diagnosis data**, including the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type. Diagnoses are recorded with ICD-9-CM and ICD-10-CM codes. For inpatient hospital and non-acute inpatient stay encounters, the SCDM includes both principal and non-principal discharge diagnosis data.
- **Procedure data**, including the procedure date, its associated encounter identifier, admission date, provider identifier, and encounter type. Procedures are coded as ICD-9-CM and ICD-10-CM Procedure Coding System procedure codes, CPT categories II, III, or IV codes, revenue codes, as well as HCPCS levels II and III codes.

9.5. Study size

Estimated numbers of cases and vaccinations needed to detect an association between RZV vaccination and the respective outcome under different RR scenarios, with 80% power, a two-sided test, and a Type 1 error probability of 0.05, are shown in Table 3 (for gout and GBS), Table 4 (for PMR), and Table 5 (for GCA) below.

For example, in the case of GBS, to reject the null hypothesis when the true RR is ≥4, 20 chart confirmed cases would be needed in the risk and control intervals together. Using the conservative background incidence of 2/100,000 person-years for 50+ year olds, approximately 2 million vaccinations would be needed to generate that number of cases under this scenario. Due to the dose spacing and the possibility of the Dose 1 control window overlapping the RW for Dose 2, the full 42-day control window for Dose 1 for GBS may not be observed; we expect this to occur in about 50% of 2-dose vaccine recipients based on internal GSK data from 2018-2019 regarding timing of dose 2 receipt in the US). Therefore, the average length of the control window observed would be about 36 days.

Table 3 Estimated numbers of cases and vaccinations needed to detect an association between vaccination and the respective outcome using an SCRI design, with 80% power, a two-sided test, and alpha of 0.05, under different RR scenarios, assuming the background incidence rates shown

Outcome (RW length)	Incidence	Alpha	Power	RR	Total events needed*	CW length (days)	Scalar of CW length as fraction of 1 year	Cases expected in CW, N	CWs needed/100 000	Vaccinations needed, N**	Vaccinated people needed, N***
Gout (30 days)	2/1000 PY	0.05	0.8	2	68	30	0.082136	23	140	140,000	70,000
				2.5	40			11	67	67,000	33,500
GBS (42 days)	2/100,000 PY	0.05	0.8	3	30	36	0.0985626	8	41	4,100,000	2,050,000
				4	20			4	20	2,000,000	1,000,000

CW = control window; GBS = Guillain-Barré syndrome; N = number; PY = person-years; RR = relative risk; RW = risk window; SCRI = self-controlled risk interval.

* Total events needed were calculated using the method described by [Musonda, 2006].

** Expected vaccinations were obtained by assuming the control window was truly not a period of increased risk of GBS due to vaccination, scaling the background incidence (2/100,000 person-years) to the length of the control window, and dividing the number of cases expected in the control window, given the total number needed in both windows, by the background incidence scaled to the control window length. The estimated incidence of 2/100,000 person-years is conservative, obtained by taking the lowest incidence for the age range from Table 3 of [Shui, 2012] --3.99/100,000 person-years for females 50-64 years of age--and dividing by 2, in view of the reported positive predictive value of 55% for confirmed and probable cases. The algorithm in the current study is more specific than the one used by [Shui, 2012]., but the positive predictive value is expected to be higher as a consequence.

*** Approximate numbers, assuming that individuals receive 2 doses

Table 4 Sample sizes for PMR, using cohort design and up to 6 months of follow-up

Outcome	Age Group	Study Design	Exposed Time (years)	Regr.	Alpha (two-sided)	Power	RR	Baseline Response	Total Cohort Sample Size, N	Vaccinated Population N	Control Population N
PMR	50+	1:4 ratio	0.5	Poisson	0.05	80%	2	0.000119	1,491,486	298,298	1,193,188
							2.5		824,334	164,867	659,467
							3		559,238	111,848	447,390
							3.5		421,984	84,397	337,587

N = number; PMR = polymyalgia rheumatica; Regr. = regression; RR = relative risk.

Poisson Regression, Numeric Results when X1 is Binomial with Proportion = 0.5, Phi (Over-Dispersion Parameter) = 1.0000, R-Squared of X1 with Other X's = 0

Sample sizes calculated by GSK using the PASS software (NCCS Statistical Software, 2013, version 12.0.2)

Table 5 Sample sizes for GCA, using cohort design and up to 6 months of follow-up

Outcome	Age Group	Study Design	Exposed Time (years)	Regr.	Alpha (two-sided)	Power	RR	Baseline Response	Total Cohort Sample Size, N	Vaccinated Population N	Control Population N	Total Cohort Sample Size Adjusted *, N	Vaccinated Population Adjusted*, N	Control Population Adjusted*, N
GCA	50+	1:4 ratio	0.5	Poisson	0.05	80%	2	0.000022	8,067,579	1,613,516	6,454,063	9,681,095	1,936,219	7,744,876
							2.5		4,458,893	891,779	3,567,114	5,350,672	1,070,135	4,280,537
							3		3,024,965	604,993	2,419,972	3,629,958	725,992	2,903,966
							3.5		2,282,550	456,510	1,826,040	2,739,060	547,812	2,191,248

GCA = giant cell arteritis; N = number; Regr. = regression; RR = relative risk.

Poisson Regression, Numeric Results when X1 is Binomial with Proportion = 0.5, Phi (Over-Dispersion Parameter) = 1.0000

Sample sizes calculated by GSK using the PASS software (NCCS Statistical Software, 2013, version 12.0.2

* Sample size estimate augmented by 20% to adjust for unobtainable charts.

The calculations for the cohort analyses are based on a cohort design with a 4 unexposed to 1 exposed ratio. We expect to have a considerably larger control population with our unmatched cohort design—descriptive statistics suggest there will be about 11 times as many preventive care control visits as RZV vaccinations. Thus, we expect to need fewer vaccinations than shown to achieve 80% power to reject the null hypothesis if true RRs are of these magnitudes.

We expect that the estimated sample sizes for the SCRI design with ***cases*** (Table 3) and the cohort design with vaccinees and the unvaccinated comparators (Table 4 and Table 5) needed to detect the specified RRs (≥ 4 for GBS, ≥ 2 for gout, ≥ 2 for PMR, and ≥ 3 for GCA) with 80% power will be attainable.

Except for gout (where we will include all cases identified from claims at the time of analysis given that chart review is not needed), the study accrual period for the primary objectives will be defined based on meeting the case count (for GBS) or vaccinated and comparator (for PMR and GCA) as defined by the sample size calculations. For cohort analysis, the study accrual periods will be based on meeting the sample size target for Dose 1 RZV exposed individuals, adjusted for projected incompleteness of chart retrieval. If more comparators are accrued during the time period needed for the RZV cohort, then comparators will be sampled to meet the sample size required for power as outlined in Tables 4 and 5.

9.6. Data management

9.6.1. Data handling conventions

HPHCI, located in Boston, Massachusetts, will serve as the Coordinating Center for the proposed study. HPHCI staff or contractors will be responsible for writing and distributing SAS programs that can be used to evaluate data from the administrative claims databases at participating ***Research*** Partners. The distributed network will allow ***Research*** Partners to maintain physical and operational control of their data while allowing use of the data to meet the study needs. The HPHCI will maintain a secure distributed querying web-based portal to enable secure distribution of analytic queries, data transfer and document storage. The system will meet all required State and Federal security guidelines for health data (e.g., Federal Information Security Management Act [FISMA], Health Insurance Portability and Accountability Act of 1996), specifically FISMA compliant for FISMA security controls as specified in the National Institute of Standards and Technology (NIST) Special Publication 800-53 (NIST and Joint Task Force Transformation Initiative 2017).

9.6.2. Resourcing needs

HPHCI brings expertise in conducting multi-site evaluations using disparate electronic healthcare data systems, including extensive work with the Health Care Systems Research Network, the Vaccine Safety Datalink, FDA Sentinel, the National Institutes of Health, Health Care Systems Research Collaboratory, IMEDS, the Biologics and Biosimilars Collective Intelligence Consortium and PCORnet. HPHC will oversee all

project activities, including scientific leadership, management of the partnership, coordination of activities with the ***Research*** Partners and other participants, oversight of the project plan and budgets, establishment of secure infrastructure used for collaboration, and training related to use of the SCDM and associated querying tools. The ***Research*** Partners will establish and maintain the administrative, hardware, and software capabilities and capacity to respond to data requests in a timely manner. They will also provide data science support with epidemiologic review.

9.7. Data analysis

Whenever possible, publicly available Sentinel analytic tools will be used for the distributed analyses; these are the same tools used by FDA for similar analyses. Modifications to the tools may be needed to meet study objectives, in which case the SAS programming data QA Standard Operating Procedures (SOP) will be followed (see Section 9.8). All the statistical calculations will be done in SAS 9.2 or higher.

9.7.1. Descriptive analyses

Descriptive statistical analyses of the study population will be conducted. These will include frequency distributions of RZV vaccinees and those in the preventive-care comparison group by age group, sex, race, and relevant comorbidities. Settings of RZV vaccination, patterns of concomitant vaccination, and temporal patterns of RZV vaccination will also be described. Temporal patterns will be illustrated by histograms of the number of RZV vaccinations by year-month and of the number of days between the two doses for two-dose recipients. Time to event data for each HOI will be collected through the respective follow-up period and graphed.

The recommended RZV vaccination schedule in Europe is 0 and 2 months, with the option of giving Dose 2 within 2-6 months after Dose 1 if necessary. The EMA wishes to see whether a meaningful number of study subjects receive Dose 2 within 2 months after Dose 1 in order to determine the applicability of the study results to the European context. In accordance with this request, we will calculate and report the proportion of all 2-dose recipients receiving the second dose on Days 28-60 after the first dose.

In addition, we will report on the number of confirmed GBS cases with evidence in their medical records of respiratory or gastrointestinal infection (including COVID-19) in the 42 days prior to onset of GBS symptoms, including in which post-RZV windows (risk vs. control) these GBS cases occurred. If deemed appropriate by the study team, an ad hoc sensitivity SCRI analysis will be conducted like the primary SCRI analysis but with these cases excluded.

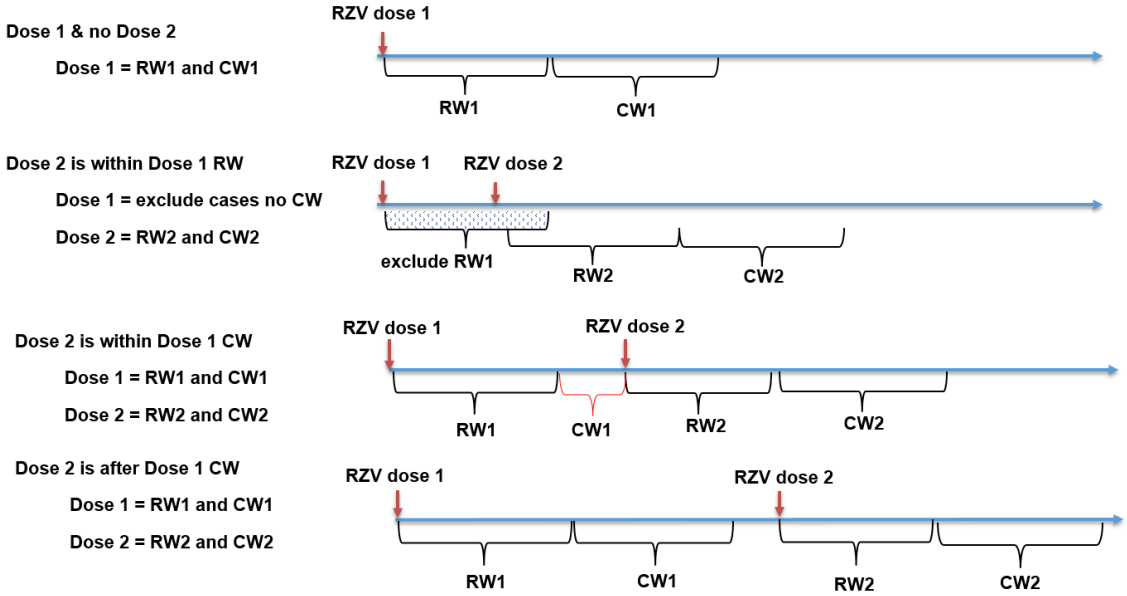
9.7.2. Analyses for primary and secondary objectives

9.7.2.1. Primary Objectives 1 & 2 and Secondary Objective 1 (SCRI design)

As described in Section 9.1, we will use the SCRI design to assess the risk of new-onset GBS, gout, and SVT after receipt of RZV vaccine. In an SCRI analysis, comparisons of risk are made within each individual, so each individual serves as his/her own control. Only those RZV vaccinees having the HOI in either the risk or the control interval

contribute to the analysis. Day 0 is the day of vaccination. For GBS, the risk during Days 1-42 after RZV vaccination will be compared with the risk in a post-vaccination control interval starting on Day 43 after Dose 1. For gout and SVT, the risk during Days 1-30 after RZV vaccination will be compared with the risk in a post-vaccination control interval starting on Day 31 after Dose 1. Details of the primary, secondary, and sensitivity analyses, including length of control intervals, are shown in Table 6 and Figure 3.All analyses will use conditional Poisson regression.

Figure 3 Illustration of SCRI design with variable spacing between Dose 1 and Dose 2



RW1: Risk window for dose 1; RW2: Risk window for dose 2; CW1: Control window for dose 1; CW2: Control window for dose 2

Table 6 Planned self-controlled risk interval analyses for GBS, gout and SVT

#	Category of analysis (short description)	Doses to include	Exclusions*	Dose 1 control interval	Risk estimate
GBS—risk window (RW) for all doses is Days 1-42 (6 ***weeks***) after the dose; control window (CW) for all doses starts on Day 43 after the dose					
1	Primary (Dose 1 CW censored at receipt of Dose 2)	1 and 2 without distinguishing	*	Maximum of Days 43-84 after Dose 1, censored at Dose 2	For any dose
2	Sensitivity (restricted to 2-dose recipients with 60-183-day dose spacing per US dosing recommendations, subset of #1)	1 and 2 without distinguishing	People not getting Dose 2 60-183 days inclusive after Dose 1	Maximum of Days 43-84 after Dose 1, censored at Dose 2	For any dose, in people who get 2 doses 60-183 days apart
3	Secondary (3-***week*** CW for both doses)	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 43-63 after Dose 1 (3 ***weeks***)	For any dose
4	Secondary (6-***week*** CW for both doses)	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 43-84 after Dose 1 (6 ***weeks***)	For any dose
5	Sensitivity (Dose 1, subset of #4)	Just Dose 1	Dose 1 CW cases if also in Dose 2 RW	Days 43-84 after Dose 1 (6 ***weeks***)	For Dose 1
6	Sensitivity (Dose 2, subset of #4)	Just Dose 2	None	N.a.	For Dose 2
Gout and SVT—risk window (RW) for all doses is Days 1-30 after the dose; control window (CW) for all doses starts on Day 31 after the dose					
7	Primary (Dose 1 CW censored at receipt of Dose 2)	1 and 2 without distinguishing	*	Maximum of Days 31-60 after Dose 1, censored at Dose 2	For any dose
8	Sensitivity (restricted to 2-dose recipients with 60-183-day dose spacing per US dosing recommendations, subset of #7)	1 and 2 without distinguishing	People not getting Dose 2 60-183 days inclusive after Dose 1	Maximum of Days 31-60 after Dose 1, censored at Dose 2	For any dose, in people who get 2 doses 60-183 days apart

#	Category of analysis (short description)	Doses to include	Exclusions*	Dose 1 control interval	Risk estimate
9	Secondary (30-d CW for both doses)	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 31-60 after Dose 1	For any dose
10	Sensitivity (Dose 1, subset of #9)	Just Dose 1	Dose 1 CW cases if also in Dose 2 RW	Days 31-60 after Dose 1	For Dose 1
11	Sensitivity (Dose 2, subset of #9)	Just Dose 2	None	N.a.	For Dose 2

GBS = Guillain-Barré syndrome; SVT = supraventricular tachycardia .

* Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW—no Dose 1 CW would exist.

We will estimate the relative incidence of GBS and gout in the post-RZV RW relative to the ***CW*** using conditional Poisson regression. Our primary analysis will not employ explicit adjustment for confounding, since all time-fixed covariates are inherently controlled for by design.

Primary analyses will analyze both dose 1 and 2 without distinguishing between doses (Table 6, Rows 1 and 7). For individuals receiving 2 doses, the Dose 1 CW will be censored if Dose 2 is received during the Dose 1 CW; Dose 1 events will be excluded from the analysis if Dose 2 is received during the Dose 1 risk interval (no corresponding control interval). Secondary and sensitivity analysis related to dose spacing (Table 6, rows 2 and 8), adjustments of the window length (Table 6 rows 3-4 and 9) and specific doses (Table 6, rows 5-6 and 10-11) are also planned.

9.7.2.1.1. Additional secondary or sensitivity analyses

In additional to the main analysis as detailed in Table 6, several sensitivity or secondary analysis of the primary analysis (Table 6 rows 1 and 7) to address other study design aspects are detailed below and in the SAP.

Seasonality-adjusted sensitivity analysis

We will also conduct an additional secondary analysis for GBS and gout adjusted for seasonality ***by means of an offset term as detailed in the SAP.***

Sensitivity analysis for the secondary definition of gout

The number of gout cases identified by the secondary HOI definition (i.e. 1-year lookback - Table 2 column 8) will be reported. Sensitivity analysis with the 1-year lookback will be conducted using the primary SCRI analytical approach (Table 6 Row 7).

Sensitivity analysis including asymptomatic short-run SVT cases

An additional sensitivity analysis will be performed including both confirmed cases and events identified by adjudicators as asymptomatic short-run SVT. Asymptomatic short-run SVT was defined for adjudication purposes as ECG evidence of SVT of less than 6 minutes' duration with no accompanying symptoms, based on a 6-minute threshold of subclinical atrial fibrillation required for inclusion in clinical trials [Healey, 2024; Kirchhof, 2023]. Cases with this designation will not be included in the primary analysis.

Inclusion of unobtainable/incomplete charts

In the SCRI analysis for GBS and SVT as detailed in Table 6, only confirmed cases will be included as outcomes in the main analysis. Cases where charts were unobtainable (i.e. charts could not be retrieved from providers) or incomplete (i.e. unable to adjudicate the case due to lack of information in the chart) will not be included in the primary analysis as these cases cannot be adjudicated. Therefore, a sensitivity analysis of the primary analysis may be conducted to include a proportion of GBS and SVT cases with unobtainable or incomplete charts after adjusting the count by the window-specific PPVs. This method is consistent with a published FDA study

[Goud, 2021]. In this sensitivity analysis, for GBS, the event date will be defined as the claims-based diagnosis date for any unadjudicated cases.

Sensitivity analysis to evaluate the impact of the COVID-19 pandemic

Sensitivity analyses will exclude exposures from the analytical cohort for which follow-up ended after February 1, 2020. For HOIs to be studied using the SCRI design (GBS, Gout, SVT), vaccinations (and their cases) for which follow-up ends after February 1, 2020 will be excluded. For GBS, any doses administered on or after October 26, 2019 (and their cases) will be excluded to allow a full 84 days (plus 14 days) of follow-up before February 1, 2020. For Gout and SVT, any doses administered on or after December 2, 2019 (and their cases) will be excluded to allow a full 60 days of follow-up before February 1, 2020. Descriptive analyses will be conducted if the exclusion of data as described above limits the ability to conduct the analysis.

9.7.2.2. Primary Objectives 3 & 4 and Secondary Objective 2 (retrospective cohort design)

We will use a retrospective cohort study design with Cox proportional hazards modeling to assess the risks of new-onset PMR, GCA, and ION within 6 months after RZV vaccination. The risk of each HOI in the 183 days risk interval after RZV will be compared with the risk of the HOI in the 183 days period following preventive-care visits that occur during the study period by people who have not received RZV at any prior point. If a patient has multiple qualifying comparison preventive-care visits during the study period, we will use one randomly selected comparison visit for that patient. ***Individuals can contribute to the comparator cohort and subsequently to the exposed cohort upon receipt of RZV Dose 1.***

In order not to arbitrarily reduce the size of the comparison group, which would reduce statistical power, and in view of the planned adjustment for confounding, these analyses will be unmatched. Maximizing power is critical in safety settings, where the HOIs are often rare. The statistical power of this unmatched cohort design is expected to be higher than with many other designs, since it leverages the large sample size of the comparator preventive care visit group.

Censoring events

Follow-up time will be censored upon the earliest occurrence of any of the following:

- The respective HOI
- ZVL (*Zostavax*) receipt
- RZV receipt (for preventive-care visit comparators)
- Disenrollment
- Death
- ***Research*** Partner end date
- End of the 183 days of follow-up.

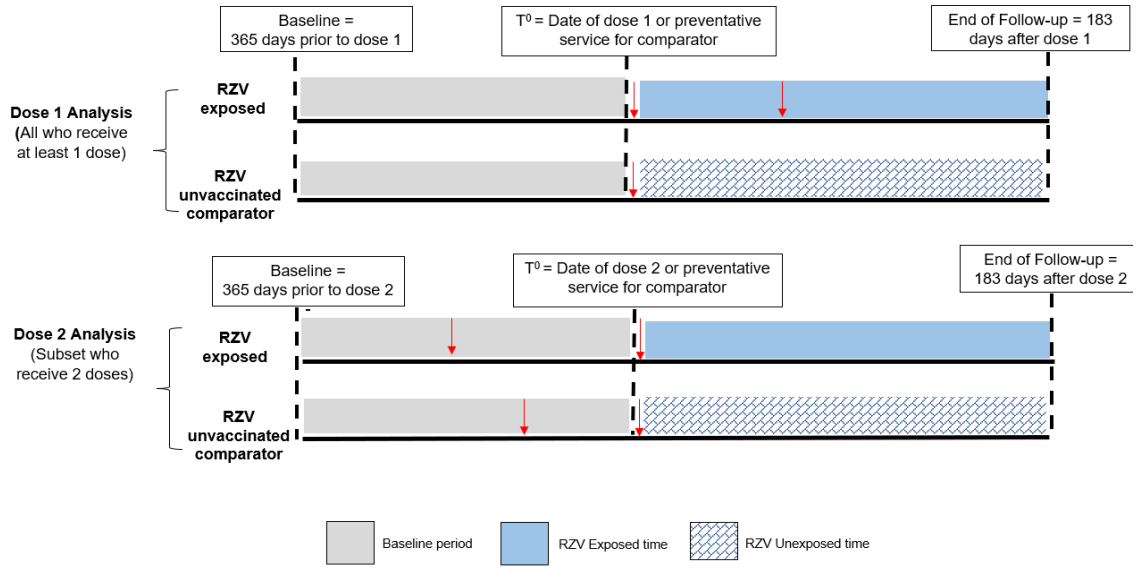
9.7.2.2.1. Primary analyses

In the primary analyses, we will fit a separate model for each dose (i.e., one model will include the cohort of all subjects who receive Dose 1 and a second model will include the ***subgroup of Dose 1-exposed individuals*** who also receive Dose 2 ***within 365 days of Dose 1); the same comparator population will be used for both analyses***. The Dose 1 ***primary*** analysis will be performed with 183 days of follow-up regardless of if and when the person receives Dose 2. Separate models will be fit for two main reasons:

1. The cohort of those who receive Dose 1 may differ from the sub-cohort who receive two doses, and we want to understand and be able to interpret effects in the context of these potential differences. For instance, those who experience an adverse event after receipt of Dose 1 may not go on to receive a second dose.
2. Although from a clinical perspective an individual may be considered "exposed" and at risk starting with receipt of Dose 1, separate models allow us to estimate the potentially differing effects of RZV receipt on adverse event risk by dose number, freeing us from the assumption that effects are the same across doses.

Figure 4 shows the baseline ascertainment period (1 year prior to the respective dose or preventive care visit), index date, and maximum follow-up period (183 days) for exposed and unexposed individuals in these primary, dose-specific cohort analyses.

Figure 4 Illustration of baseline ascertainment period, index date, and end of follow-up for exposed and unexposed individuals in the primary, dose-specific cohort analyses



Hazard ratios will be used to quantify the association between RZV receipt and the risk of each HOI. A Cox proportional hazards regression model will be used to estimate the hazard ratio, comparing hazard of each HOI after RZV vaccination with hazard after preventive care visits. This is a semi-parametric model in that it assumes a parametric form for the effects of the explanatory variables and an unspecified form for the underlying survival function. The general form of a Cox proportional hazards regression model can be written as:

$$h(t, \overline{x_i}) = \lambda_0(t) \cdot exp\left[\beta_1 \cdot x_{i,1} + \cdots + \beta_k \cdot x_{i,k}\right]$$

where, $h(t)$ is the expected hazard at time t; $\lambda_0(t)$ is the baseline hazard function and represents the hazard when all predictors are equal to 0. The effect estimate generated from Cox proportional hazards model is hazard ratio, expressed as:

$$HR(1,0,\beta) = \frac{h(x=1,\beta)}{h(x=0,\beta)} = \exp(\beta)$$

where x (1,0) denotes the exposure status, and β is the estimated parameter from the regression model. Violations of the proportional hazard assumption ***will be evaluated. We may*** evaluate ***this assumption*** using graphical approaches by plotting the log[-log(S(t))] versus log(t) and the Schoenfeld residuals by time, ***and*** by testing the interaction between ***exposure*** and log(t). Non-parallel lines or non-zero slope in the graphical approach ***or*** a significant interaction term would indicate a violation of the proportional hazards assumption. If the proportional hazard assumption is violated, an interaction term of time and the ***exposure*** will be included in the model.

Individuals will be followed for the occurrence of each HOI from their index date (i.e., the date of RZV vaccine for RZV vaccinees or the date of the preventive care visit for the comparison group) until the first censoring event: HOI, ZVL receipt, death, disenrollment, ***Research Partner*** end date, or the end of the 183 days follow-up period. For those in the comparator group, follow-up will additionally be censored at the time of receipt of RZV (if this should occur during the 183 days follow-up period). Thus, some individuals in the analysis may contribute person-time to both the comparison group and (subsequently) to the RZV-vaccinated group. Specifically, individuals initially identified to be in the comparator group who later become exposed to RZV vaccine within 183 days of their preventive care visit will be censored from the comparator group and will contribute person-time to the RZV vaccine group starting on the date of their RZV vaccination. We will compute robust standard errors for clustered survival data ***using a sandwich estimator*** to account for the within-person correlation ***for individuals included in analyses multiple times and for the use of weights [Austin, 2016***; Lin, 1989). ***Additional methodology such as bootstrapping may also be considered to account for within-person correlations [Austin, 2016].*** Once an individual receives RZV vaccine, any subsequent preventive care visit will *not* be eligible for selection as the individual's one index comparator event.

As the analysis compares RZV exposed and preventative care comparators, adjustment for additional potential confounders ***assessed*** in the 12-month baseline prior ***to the index*** date ***is needed.*** Such confounders may include immunocompromising conditions, receipt of steroids, and/or measures of health care utilization***. Multivariable adjustment may be considered, however, more advanced confounder adjustment approaches (e.g., propensity score stratification or weighting) may be needed if*** there is need to adjust for a large number of potential confounders.

Analytic models will use IPTW as the preferred approach to control for confounding and estimate the population- ATE, or the treatment effect that would be observed if the

entire population received RZV versus did not receive RZV. IPTW is a weighting method based on an individual's propensity score (PS), or the predicted probability they are in the RZV exposed (versus comparator) group, conditional on baseline covariates. A logistic regression model will be used to estimate the conditional probability of receiving the RZV vaccine predicted by the baseline covariates observed in the 365 days preceding the index date (i.e., RZV exposed vaccination date or RZV unexposed preventive care visit date). To estimate the ATE, the following weight form is used in analyses:

$$w_{ATE} = \frac{A}{e} + \frac{1-A}{1-e} \qquad w_{stableATE} = \Pr(A=1)\frac{A}{e} + \Pr(A=0)\frac{1-A}{1-e}$$

where A is the treatment indicator (A = 1 if exposed and A = 0 if unexposed), and the propensity score $\boldsymbol{e = Pr(A = 1 \mid X)}$ ***with X denoting the vector of covariates. Stabilized weights are intended to reduce variability due to instability in estimation that can be induced by subjects with very large weights.***

Propensity score adjustment by IPTW allows for adjustment by all potential confounders without overparameterization of the inferential regression model. All baseline covariates (as detailed in the SAP) that are hypothesized confounders will be included in the propensity score model, as will covariates that are weakly associated with the outcome, as inclusion of these variables can reduce bias (Brookhart 2006). After estimating propensity scores, non-overlapping areas of the propensity score distribution between the RZV exposed and RZV unvaccinated comparator cohorts will be removed ("non-overlap trimming").

The performance of IPTW for controlling confounding will be assessed by examining the balance of covariates using standardized mean differences between exposed and comparator in IPT weighted data. Additional trimming may be implemented if extreme weights or covariate imbalance is observed.

9.7.2.2.2. Secondary analyses

In secondary analyses, we will fit models by combining information from the two doses together to determine if additional precision can be gained by leveraging information across all doses. ***As in the primary analysis, Dose 2 exposures will only be assessed among patients whose Dose 1 was included in the study and if the gap between doses was no more than 365 days. If an individual received their second dose 2 within the 183-day follow-up period for dose 1, then their follow-up after Dose 1 will be censored at receipt of Dose 2 in order to avoid overlapping follow-up time or duplicate events***. In one secondary analysis, we will use a partly conditional model ***to combine information from each exposed group to*** generate one ***combined*** hazard ratio that estimates the association between receipt of RZV and adverse event risk rather than two separate dose-specific hazard ratios. In the other secondary analysis, we will fit a time-dependent Cox model to estimate separate effect estimates for Doses 1 and 2 in the combined model. We do not expect the estimated effects for Dose 1 and Dose 2 to change much compared with the separate models, but precision should improve.

In both of these secondary analyses, we will compute robust standard errors for clustered survival data to account for the within-person correlation for people who contribute both post-preventive care visit follow-up (unexposed) time and post-RZV follow-up (exposed) time and also to account for the correlation between doses received by the same person in the combined dose analysis. ***Other methods (e.g., bootstrapping) for estimating the variance may be considered as necessary.***

Secondary *analysis of Dose 1 and Dose 2 yielding* ***a combined*** *risk estimate.* A partly conditional survival model will be used in the secondary analysis of combined doses. Since an individual may contribute more than one observation in the analysis (i.e., Dose 1 and Dose 2), this model is appropriate, as it estimates the effect of longitudinal ***exposures*** (in this case, dose) on survival [Gong, 2013; Zheng, 2005].

Whereas typically survival is modeled as the time from study entry to the event, i.e., event time, D_i, in partly conditional survival analysis, regression parameters depend upon the time of measurement, S_i, for the predictor (i.e., dose receipt) and the follow-up time ***between*** the ***exposure and event***, $D_i - S_i$. This is considered partly conditional since the hazard function that is being modeled conditions on the covariate history through S_i. ***Therefore, individuals receiving a Dose 2 during the follow-up period after Dose 1 will have their Dose 1 follow-up window censored such that any HOI event can be included in the analysis only one time. Weights for analysis will be based on the dose-specific IPTW.***

As mentioned above, standard errors will be calculated using a robust sandwich estimator ***(or other methods as appropriate e.g., bootstrapping)*** for repeated measures survival data [Lin, 1989].

Single model yielding separate *Dose 1 and Dose 2 risk estimates.* To generate a separate risk estimate for each dose in a combined analysis, where a binary indicator defines the Dose 1 and Dose 2 RWs, a time-varying Cox proportional hazards regression model will be used. In the time-dependent model, we allow the RW to vary for each dose***.*** ***Follow-up will be defined as the 183 days*** after Dose 1***, regardless of whether Dose 2 is received during that time. As such,***

- ***the time after Dose 1*** until ***(a)*** Dose 2 ***(if received within 183 days of Dose 1)*** or ***(b)*** end of follow-up (if no Dose 2 occurs) defines the Dose 1 RW, and
- the time from Dose 2 until end of follow-up ***(183 days after Dose 1)*** defines the Dose 2 RW.

Thus, a subject who receives two doses ***within <183 days*** will contribute time to the Dose 1 RW and the Dose 2 RW. In the unvaccinated comparators the time from index date to end of follow-up is considered unexposed time.

A general form of time-dependent Cox models can be written as:

$$h_i(t,x) = \lambda_0(t) \exp[\beta_1 x_{i1} + \ldots. \beta_2 x_{i2}(t)]$$

where x_{i1} represents a time-independent variable, and x_{i2} represents the time-dependent variable. This analysis will use the full cohort and obtain estimates for both doses

whereas the primary separate dose analysis either ignores Dose 2 or includes only the subset of the sample who received two doses. ***The Dose 1 IPTW will be used for all observations***.

This analysis allows us to use the full cohort to compare the findings to the primary separate dose analysis. The primary Dose 1 analysis ignores Dose 2, and as such the events after Dose 2 may be attributed to Dose 1, thereby increasing the HR for Dose 1 (and it is unknown which dose carries the highest risk). The primary Dose 2 analysis only includes individuals who did not experience the event after Dose 1, which could reflect potentially the more robust individuals. This could bias the estimate towards the null, and it is difficult to determine whether the estimate is a function of the vaccine or the characteristics of the Dose 2 subgroup. The time-varying model for this analysis uses the entire cohort, and attributes events to the respective dose risk window yielding a HR for each dose. Therefore, the full cohort sensitivity analysis allows us to estimate the hazard for each individual dose risk and to compare the results with the primary analysis estimates.

The effect estimates generated from the time-dependent Cox proportional hazards model will be a hazard ratio for Dose 1 relative to unexposed and a hazard ratio for Dose 2 relative to unexposed. Both hazards are generated in the same model with the full cohort, using time since the Dose 1 index date or the preventive care visit.

9.7.2.2.3. Sensitivity, supplemental, and bias analyses

Restriction to doses compliant with US dosing recommendations

As a sensitivity analysis for each of the secondary analyses, we will fit the combined Cox proportional hazards regression model as described above but restricted to just the subgroup of patients who received two doses ***in the span of*** 2 and 6 months, ***inclusive*** (60 and 183 days, as per US dosing recommendations).

Confirmed case sensitivity analysis for PMR

As the final analysis for PMR will include all claims-identified cases, a sensitivity analysis may be conducted using the 25% PMR chart review sample. This sensitivity analysis using the primary analytic approach and based on adjudicated case classifications may be conducted if the PPV obtained from the 25% chart reviewed sample is found to be <70%. We will calculate the PPV two ways: using a narrow case definition of only adjudicated confirmed cases and using a broad case definition of both confirmed and probable adjudicated cases.

This sensitivity analysis will use the primary analytic model. We will perform the analysis twice, using the narrow case definition and the broad case definition, as defined above. Cases selected for chart review that were adjudicated as possible, ruled out, or incomplete will be included as non-cases in the analytic cohort along with a 25% sample of claims-based non-cases. These claims-based non-cases will be sampled from the Dose 1, Dose 2, and comparator cohorts using the same methodology used to

sample cases for medical record review (i.e., by RP) for a total analytic sample of 25% of the primary analysis cohort.

Bias analysis for unobtainable/incomplete charts

In the main analysis for GCA and ION, only confirmed cases will be considered as true cases and counted as events. However, there will be cases where the chart was not obtainable or incomplete and therefore the case could not be adjudicated. In the main analysis these cases will be considered as non-events (and individuals will be censored at their claims-based event date).

However, if the proportion of charts that are unobtainable or incomplete differ substantially between the RZV and comparator cohorts, we may obtain a biased HR from analyses that consider only the chart confirmed cases as true outcomes. Therefore, we will compare the proportion of unobtainable and incomplete charts between RZV and comparators and if there is substantial difference between the two groups, we may perform a sensitivity analysis of the primary analysis for GCA and ION that brings both adjudicated and non-adjudicated claims-based cases into the analysis. This sensitivity analysis would count all claims-based events as HOIs and adjust the estimated HR by the ratio of the estimated PPV in the exposed to the estimated PPV in the unexposed, per [Brenner,1993]. This method assumes algorithm sensitivity is nondifferential with respect to exposure.

Bias analysis to test for unmeasured confounders for the cohort design analysis.

One assumption underlying the cohort analyses is that there are no unobserved confounders related to RZV exposure and the study outcomes of interest, given the observed covariates. Unobservable factors, related to illness severity and health status, could influence RZV receipt and the outcomes of interest. The goal of the bias analysis is to estimate the magnitude of effect of an unobserved confounder needed to change the statistical inference.

Supplemental analysis ***excluding ever-exposed comparators***

Some individuals in the analysis may contribute person-time both to the comparison group and (subsequently) to the RZV-vaccinated group. At CBER's request, a supplemental analysis will be conducted for the primary analysis, excluding from the control arm those subjects who ***were observed in our data to receive*** RZV at any point, so that each subject contributes person-time to only one arm.

Sensitivity analysis for secondary definition (i.e., arteritic) of ION

Classification of ION cases as arteritic (secondary definition Table 2) will be considered during chart review. If distinguishing arteritic ION cases during chart review is feasible then sensitivity analysis using the primary analysis for the cohort design may be conducted with chart confirmed arteritic ION cases. Alternatively, if distinguishing arteritic ION cases during chart review is not feasible then sensitivity analysis may be based on validated ION cases that met the secondary arteritic claims-based definition without chart confirming their status as arteritic ION. The number of arteritic ION cases

will be reported and if a sufficient number of artertic ION cases are identified then sensitivity analysis will be conducted for arteritic ION using the primary analysis for the cohort design as described in Figure 4 (i.e., a separate model for each dose) . ***If the PPV of the ION algorithm is <70%, it is possible that this analysis may not be feasible.***

Sensitivity analysis related to influenza vaccine during follow-up for PMR and GCA

Given that influenza vaccine has been associated with PMR and GCA and influenza vaccine is seasonal, a descriptive assessment of influenza vaccine during follow-up will be conducted. If a meaningful difference in influenza vaccination rates between vaccinated and comparator ***is*** observed, sensitivity analysis aligned with the primary analytical approach (Figure 4) for PMR and GCA will be performed adding influenza vaccination as a censoring event.

Sensitivity analysis to evaluate the impact of the COVID-19 pandemic

In sensitivity analyses ***for HOIs to be studied using*** the cohort ***design (PMR, GCA, ION), February 1, 2020 will be included as a censoring event. Any doses administered (or preventative care visits for comparators) on or*** after February 1, 2020 will be excluded. These sensitivity analyses will allow for an evaluation of the robustness of the primary findings after excluding cases and vaccinations during the COVID-19 pandemic. The sensitivity analyses will be descriptive if the exclusion of subjects after February 1, 2020 compromises the sample size such that there is insufficient power to generate meaningful estimates. Such descriptive analysis will report the incidence rate (or cumulative incidence) for the cohort design.

Sensitivity analysis to test IPTW sample

If the effect estimates of our IPTW adjusted primary analysis is non-significant, it is possible that this may be due to insufficient sample size of the IPT weighted sample. In this situation, we may consider calculating the RR that the IPT weighted sample is powered to detect, or we may conduct sensitivity analysis after re-estimating the sample size to account for IPTW using methods described by [Austin, 2021]. This sensitivity analysis will be aligned with the primary analytical model and use claims -based cases to define the HOI. The resulting HR will be adjusted to account for differential misclassification of the outcome (multiply the resulting HR by PPV_exposed / PPV_unexposed).

9.7.2.3. Temporal scan statistics and avoidance of temporal bias (potential sensitivity analysis)

Temporal scan statistics will be used as a supplemental method for assessing the possibility of an association between RZV vaccination and an HOI during the respective follow-up period, if any of the above-specified analyses of the HOI suggest that an association may exist. This method evaluates whether there is any statistically significant temporal clustering of cases, the existence of which would support, albeit not confirm, an association. Just as with the SCRI method (see Section 9.2), the use of a consistent, first-in-X-days definition of incident HOI cases is necessary in order to establish an equal opportunity for a case to be ascertained regardless of where in the follow-up period it

might appear and to thereby avoid temporal bias. Thus, in data extraction, an inclusive cohort will be established to start with, without explicitly restricting it to those without HOIs in the 12-month baseline period. From this cohort, a sub-cohort restricted to those without the respective HOI in the 12-month baseline period will be drawn for each cohort analysis.

9.7.3. Conduct of analyses

The details of data extraction and preparation of analysis datasets will be presented in a supplement to the SAP.

The phased sequence of analyses to be conducted to detect increased risks of importance for public health are presented in Table 7. The sequence of analysis takes into consideration the number of doses needed from the sample size tables, follow-up times, data lag, and chart review where applicable and reflects some uncertainties. Notably, the timeline is based on projecting partial data on RZV vaccination from 2018, under somewhat conservative assumptions. We will continue to monitor these assumptions through periodic descriptive analyses as data accumulate, particularly in view of the expected significant increase in 2019 supply, and sequence of analysis may be adjusted as the study progresses. A comprehensive final study report will be prepared upon completion of all primary and secondary analyses. This final study report will be submitted to the FDA CBER and EMA.

Table 7 Sequence of analyses to be conducted

Outcome	Target risk to detect	Analysis Sequence
Gout	RR of ≥2	Phase 1
SVT	N.a.	Phase 2
PMR	RR of ≥2	
GCA	RR of ≥3	Phase 3
GBS	RR of ≥4	
ION	N.a.	

GBS = Guillain-Barré syndrome; GCA = giant cell arteritis; ION = ischemic optic neuropathy; N.a. = Not Applicable; PMR = polymyalgia rheumatica; RR = relative risk; SVT = supraventricular tachycardia.

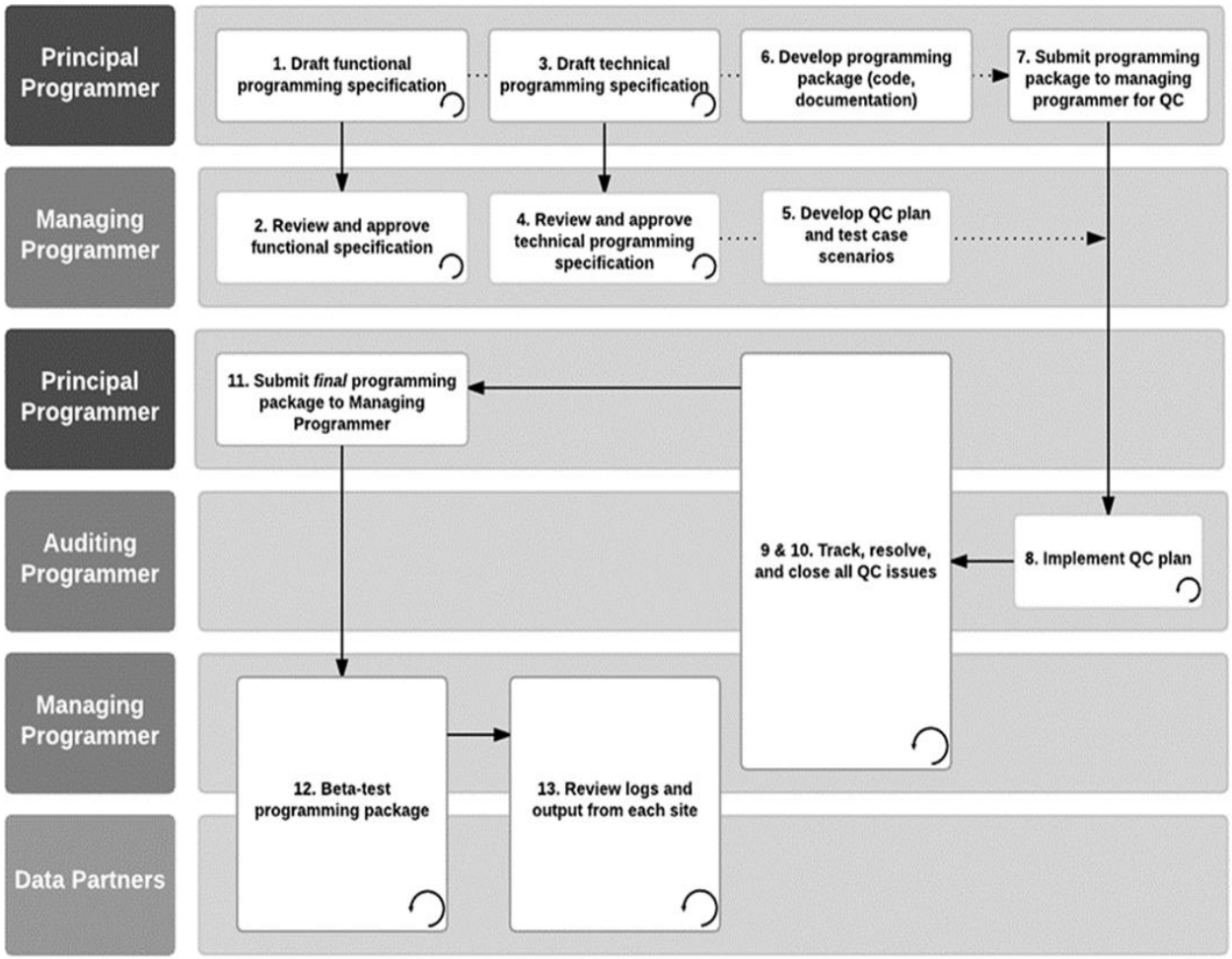
9.8. Quality control

As described above, the distributed network utilizes a common data model that enables data standardization across ***Research*** Partners. Furthermore, each of the participating ***Research*** Partners has experience with this data model given its role as an active participant in the Sentinel System. This study will use the same data QA procedures as the Sentinel System and the same curated datasets used by FDA to conduct Sentinel analyses. The QA approach assesses consistency with the SCDM, evaluates adherence to data model requirements and definitions, evaluates logical relationships between data model tables, and reviews trends in medical and pharmacy services use within and across ***Research*** Partners. Full QA processes and details on the Sentinel data curation approach are documented on the Sentinel website [Sentinel Initiative, 2024]. The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data quality assurance (U.S. Food and Drug Administration [FDA, 2013]).

In addition to QA of data elements, HPHCI adopts standard SAS programming QA and quality control processes used by the Sentinel System to check SAS programs and deliverables. Figure 5 illustrates the SOPs for SAS programming QA and quality control in the Sentinel System.

By signing onto this protocol, the investigators agree to be responsible for implementing and maintaining a quality management system with written development procedures and functional area SOPs to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

Figure 5 Standard Operating Procedure for SAS Programming Quality Assurance and Quality Control in the Sentinel System



9.9. Limitations of the research methods

The possibility of confounding and bias is a concern in any observational epidemiologic study. In the proposed study, the use of the SCRI design for GBS, gout, and SVT guards against confounding by many of the covariates that can confound other designs, including chronic disease status (if stable over the course of the 2-3-month follow-up period). Nonetheless, if RZV administration in the study population has a seasonal pattern—for example, due to the timing of vaccine shortages—seasonality would be a potential confounder, especially in the case of GBS, which also has a seasonal pattern. Therefore, we will conduct secondary analyses that explicitly adjust for seasonality. In the cohort analyses to be used to study PMR, GCA, and ION, our proposed use of a concurrent preventive care visit as the comparison group will mitigate against large differences between RZV vaccinees and comparators, as both will be seekers of preventive health care. Potential measurable confounding differences between the two groups such as age, sex, Research Partner, and calendar time will be adjusted ***using propensity score based weighting.***

An important potential limitation of the study is that adequate sample size might be difficult to achieve. There are several reasons for this: (a) several of the HOIs are rare; (b) depending on the ***Research*** Partner, there is a 9-12-month lag in the data as well as generally some incompleteness toward the most recent end of a given period of data supplied; and (c) some of the case-finding algorithms require up to 12 months of follow-up to identify potential cases, e.g., PMR and GCA, which have a post-***diagnosis*** code medication requirement. Also, COVID-19 is reducing the number of RZV and preventive care visits. We will run occasional queries on ***Research*** Partners' accumulating data to monitor RZV dose counts and HOI case counts to determine when statistical power is sufficient to conduct analysis for each HOI.

As in any study relying on administrative data, case-finding algorithms are rarely if ever perfectly sensitive and specific. Our algorithms are based on algorithms found to have high positive predictive value in published case validation studies. Furthermore, for all HOIs except for gout, medical record review and adjudication by clinical experts will be carried out and only chart confirmed ***GBS, GCA, ION, and SVT*** cases included in analysis. A ***sensitivity analysis using chart-confirmed PMR cases will also be conducted, in addition to the claims-based primary analysis if the algorithm PPV is low.***

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information and consent

All parties will ensure protection of patients' personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, high standards of confidentiality and protection of patient personal data will be maintained.

The study will be conducted with a waiver of informed consent. This study will involve numerous individuals from multiple health plans and delivery systems. Thus, it could not be practically conducted without a waiver of informed consent. The proposed study has minimal risk; potential breaches of privacy and confidentiality are the primary study risks, and these risks will be minimized by ensuring that rigorous security procedures are applied to data collection, management, and transfer. Some of these procedures include using a study identification number in place of direct patient identifiers; transferring data using secure, encrypted websites; and ensuring that appropriate data transfer agreements are in place between institutions prior to data sharing. Additionally, only trained and authorized study staff will be allowed to access study data, and secure data storage methods, such as password protected electronic files and locked paper files, will be used by all participating ***Research*** Partners and the data Coordinating Center.

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

As the Coordinating Center for the current study, HPHCI has the responsibility to obtain approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from an IRB/IEC. Participating ***Research*** Partners can either cede IRB review to HPHCI or seek approval from their local IRB. All correspondence with the IRB/IEC will be retained in the Investigator File.

10.3. Ethical conduct of the study

The study will be conducted in accordance with all legal and regulatory requirements. Additionally, we will adhere to commonly accepted research practices, including those described in the following guidance documents: European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [Anes, 2012]. Guidelines for GPP issued by the International Society for Pharmacoepidemiology [ISPE, 2008], FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [FDA, 2005], and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets (U.S. Food and Drug Administration [FDA, 2013]).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The current non-interventional safety study will be based on secondary use of data previously captured from consumers or healthcare professionals for other purposes. Data to be used in this study will include medical chart reviews (including follow-up on data with healthcare professionals) and electronic healthcare records. Therefore, the submission of individual cases of adverse events/adverse reactions is not required (Module VI.C.1.2.1.2 and GVP Module VIII.11.).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Study information from this protocol will be posted on publicly available registers following finalization of the protocol. The study will also be registered with the European Union Electronic Register of Post-Authorization Studies (EU PAS Register® (http://www.encepp.eu/encepp_studies/indexRegister.shtml) prior to data collection.

GSK also aims to publish the results of these studies in the searchable, peer-reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. At the time of publication, this protocol will be fully disclosed. Any publications will follow guidelines, including those for authorship (e.g., guidelines established by the International Committee of Medical Journal Editors 2018) and for reporting of observational studies in epidemiology (e.g., Strengthening the Reporting of Observational Studies in Epidemiology 2007) [Von, 2007].

Posting of study protocols and results will be done according to the following:

Observational studies evaluating a product:

- The key design elements of this protocol and results summaries will be posted on the GSK Clinical Study register in compliance with the applicable regulations/GSK policy according to the timelines described below.
- Protocol summaries will be registered prior to study start.
- Results summaries along with redacted protocol and SAP will be posted within 12 months of analysis completion date.
- Where required by regulation, summaries will also be posted on applicable national or regional registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results.

- GSK also aims to publish the results of these studies in the searchable, peer-reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. Any publications will follow guidelines, including those for authorship (e.g., guidelines established by the International Committee of Medical Journal Editors 2018) and for reporting of observational studies in epidemiology (e.g., Strengthening the Reporting of Observational Studies in Epidemiology (STROBE,) 2007) [Musonda, 2006].

  Post-authorization safety study studies:

- Protocol summaries for non-interventional post-authorization safety studies will be registered along with redacted protocol in the EU PAS register prior to study start.
- Redacted CSR will be submitted in the EU PAS register within 12 months of end of ***analysis completion.***
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results.

12.2. Provision of study reports to regulatory authorities

The final study report will provide an overview of the study background, objectives, methods, and findings and will be submitted to regulatory agency authorities by the vaccine manufacturer. Final study results, as well as the main methodological components developed as part of this study, will be disseminated as oral or poster presentations at scientific meetings and as peer-reviewed publications.

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	209452	19-Aug-2020	List of stand-alone documents
2	209452	19-Aug-2020	Glossary of terms
3	209452	17-May-2021	List of principal and coordinating investigators
4	209452	19-Aug-2020	Sponsor Information
5	*209452*	*13 June 2022*	*Amendments to the protocol*
6	*209452*	*13 June 2022*	*Protocol Amendment 2 Sponsor Signatory Approval*
7	*209452*	*13 June 2022*	*Protocol Amendment 2 Pharmacovigilance Signatory Approval*
8	*209452*	*13 June 2022*	*Protocol Amendment 2 Investigator Agreement*
9	209452	19-Aug-2020	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Adverse event:	Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Database:	A database is a set of pre-existing tables and views containing data. The term "pre-existing" implies that the analysis will be done on retrospective data and the term "views" implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc.).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-) encoding via CRF/eCRF and retesting of human biological samples.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study **(Synonym of End of Trial)**	For studies without collection of human biological samples or imaging data: Last subject last visit
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
eTrack:	GSK's tracking tool for clinical/ epidemiological trials.
Key coded information:	Refers to encoded or otherwise pseudo-anonymized PII from which direct identifiers have been removed and replace by a unique identifier or random code. Key coded PII shall not be considered anonymized information.

Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post-Authorization Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorization and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorization' means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).
Prospective study:	A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study objectives. A prospective study usually involves primary data collection.
Protocol amendment:	The International Council on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. Note: Any change that falls under the definition of a protocol amendment (e.g., a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.

Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Surveillance	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 List of principal and coordinating investigators

The list of investigators and their contact details are available upon request.

Annex 4 Sponsor Information

Sponsor: ***Huifeng Yun, Head, Viral Non-Respiratory Epidemiology, GSK***

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Annex 5 Amendments to the protocol

GLAXOSMITHKLINE BIOLOGICALS SA **Vaccines R & D** **Protocol Amendment 3**	
eTrack study number and Abbreviated Title:	209452 (EPI-ZOSTER-030 VS US DB)
Amendment number:	Amendment 3 Final
Amendment date:	18 Sep 2024
Rationale/background for changes: ***Protocol Amendment 3 dated 11 September 2024 was primarily amended to add clarity and/or updates to the analysis.***	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Section Number and title	**Changes made**
All relevant sections throughout entire protocol	
The term data partner was updated to research partner	
PASS INFORMATION **Section 3: Responsible Parties**	
Authors Contributing authors	• PPD ~~, Harvard Medical School & Harvard Pilgrim Health Care Institute~~ • PPD ***, Harvard Medical School & Harvard Pilgrim Health Care Institute*** ~~• PPD , GSK~~ ~~• PPD , GSK~~ ~~• PPD , GSK~~ ~~•~~ PPD ***, GSK***
MAH contact person Sponsor contact	PPD ~~, Clinical and Epidemiology Project Lead, GSK~~ ***Huifeng Yun, MD, PhD***

	Head, Viral Non-Respiratory Epidemiology
Section 3. Responsible Parties	
Investigators	• ~~Aaron B. Mendelsohn~~, • ***Sophie E. Mayer***
Section 4. Abstract	
Data Source	This study will be conducted using data provided by ***five*** US ~~Data~~ ***Research*** Partners in the FDA's Sentinel System. ~~At least four Data Partners will participate in this study~~. Four of these are national insurers (Aetna, ~~HealthCore, Inc.~~ ***a CVS Health Company; Carelon Resesarch***; Humana; Optum), and one, Harvard Pilgrim Health Care, is a regional insurer. The study will use curated data that are formatted to the FDA SCDM specifications, which permits the use of publicly available Sentinel analytic tools.

Section 7: Rationale and Background

Pooled safety analysis of clinical data from these ~~two~~ ***2*** Phase ~~III~~ ***3*** studies included a total of 14,645 RZV and 14,660 placebo recipients, with a median follow-up duration of 4.4 years (Curtis, 2012; Sentinel Initiative, 2024). The pooled analysis demonstrated a comparable incidence of unsolicited AEs in the day 7 through day 29 follow-up period (excluding day 0 through day 6 where reactogenicity was observed to be higher in RZV versus placebo recipients) ***between the RZV and Placebo groups*** (Lopez-Fauqued, 2019). ***Similar findings were noted for*** SAEs, and potential immune-mediated disorders (pIMDs) ~~between the RZV and Placebo groups~~ and specific SAEs and pIMDs were within the expected incidence for the study age group (Lopez-Fauqued, 2019)

Section 9.1: Study design

This design is a special (and simpler) case of both the case-crossover (Maclure, 1991) and the self-controlled case series (SCCS) Petersen, 2016) designs, in which the cumulative numbers of cases in pre-specified risk and control intervals (or "windows") are compared ***(approximating a relative risk)***.

Section 9.2: Setting

The Sentinel ***Research*** Partners are discussed in Section 9.4. The study population will be commercially insured people in the US who are ≥ 50 years of age at the time of their qualifying visit date (i.e., RZV vaccination date for RZV recipients or preventive-care visit date for cohort study comparators) during the study period, from 1/1/2018 on. ASO enrollees will be excluded, as their medical records ~~are~~ ***may not be*** available for review;

however, ASO enrollees may be considered for inclusion on an as-needed basis, if allowable and medical records are available.

Section 9.2.1: SCRI design inclusion criteria

- 365 days (1 year) of continuous enrolled time, allowing 45-days gap, prior to RZV receipt for GBS and SVT, ***and the secondary definition of gout***
- Continuous enrollment ***(without gaps)*** through the end of the respective control interval during a period when data for the respective ~~Data~~ ***Research*** Partner are determined to be ≥ 90% complete for the outcomes of gout and SVT.
- Continuous enrollment ***(without gaps)*** through the end of the respective control interval plus 14 days during a period when data for the respective ~~Data~~ ***Research*** Partner are determined to be ≥ 90% complete for the outcome of GBS.

Section 9.3.1: Exposures

RZV exposure will be defined as receipt of at least one dose of RZV for the primary analyses; all-dose as well as dose-specific analyses will be performed. RZV vaccination will be identified by means of CPT code 90750, and NDC codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11. ***RZV records observed before September 2017 (the month prior to approval) will be considered invalid.***

We will define duplicate RZV vaccination records as those occurring within 27 days after a previous RZV vaccination record (i.e., on Days 1-27, where the day of the previous record is Day 0). Duplicate records will be deleted. After deduplication, we will exclude from analysis all RZV doses beyond two per study subject, ***with dose number assigned based on the ordinal number of records observed after September 1, 2017. Dose 2 exposures will be eligible for analysis only if the individual's Dose 1 was included in the analysis, and if the gap between doses was <365 days.***

Separate comparator cohorts will be selected for each HOI, and a single set of comparators used for analysis of both RZV doses. Comparators may be sampled if necessary to achieve the numbers needed to meet study power (see Section 9.5).

Section 9.3.2: Outcomes

References: [1]Sentinel coding trend analysis for GBS. [2] Bogliun, 2002; [3]Sentinel coding trend analysis for gout; [4]Singh 2007; [5]Harrold 2007; [6]Meier 1997; [7]Sidney 2005; [8] Bernatsky 2011; [9]England 2017; [10]Gale 2019; [11]Rubin 2016; [12]Rubin 2017

Section 9.3.3: Medical record review

Therefore, for the outcome of PMR, a 25% random sample of potential cases ascertained in the 183 days after RZV vaccination, and a 25% random sample of potential cases ascertained in the 183 days after preventive care comparison visits will be chart reviewed ***to estimate the PPV of the algorithm***. ***To ensure that we obtain 25%,*** ~~we will seek a random sample of 35%~~ ***chart review will proceed until 25% of cases have charts***

obtained. The final analysis for PMR will include all claims-identified cases ~~if the PPV obtained from the 25% random sample is found to be ≥70%~~ ***given that the chart review is only being conducted on a 25% sample of PMR cases. The PPV obtained from the 25% random sample of cases will be reported***. If the PPV is <70% for the claims-based algorithm to detect PMR, ~~the final analysis~~ ***sensitivity analyses will include chart confirmed and confirmed/probable cases identified from the 25%*** ~~random~~ ***chart review sample***.

After case adjudication, the respective analysis or analyses will be conducted using confirmed cases. ***The PPVs will be calculated as the number of confirmed cases divided by all successfully adjudicated cases.***

Section 9.3.4: Covariates

- ~~Data~~ ***Research Partner***
- Certain immunocompromising conditions ***or therapies*** (e.g., solid organ or stem cell transplant, cancer, autoimmune/inflammatory conditions, ***steroid use***)

Section 9.4: Data sources

This study will be conducted using health plan data held by five ~~Data~~ ***Research*** Partners that participate in the FDA's Sentinel System. Four are national insurers that update their curated Sentinel database three to four times per year (Aetna, ***Carelon Research [formerly HealthCore]***, Humana, and Optum); HPHC is a regional insurer that updates its data once per year. This study will use the most recently available approved database at each ~~Data~~ ***Research*** Partner at the time of analysis. All Research Partners are expected to contribute data for all the analysis detailed in the protocol and statistical analysis plan. However, if a ~~Data~~ ***Research*** Partner cannot contribute to specific analysis, then alternative approaches to conducting the analysis may be considered including excluding the impacted ~~Data~~ ***Research*** Partner if appropriate sample size can be maintained, or meta-analytical approaches to combine estimates obtained from analysis conducted individually at the ~~Data~~ ***Research*** Partner(s), or other appropriate analytical or methodological solutions. In addition to providing claims data, the ~~Data~~ ***Research*** Partners will provide scientific input and feedback to support this study.

Brief descriptions of the Research Partners are provided below:

- *Aetna****, a CVS Health Company,*** is one of the nation's leading healthcare benefits companies, serving 38 million people with information and resources to help them make better-informed decisions about their healthcare***. CVS Health CTS*** ~~Aetna~~ became an FDA Sentinel ~~Data Partner~~ ***RP*** in 2010 and continues to be one of the largest contributors of data for public health purposes. ~~Of Aetna's 50+ year old population with both medical and drug coverage, approximately 52% are 50-64 years of age and approximately 48% are 65+ years of age. Aetna offers Medicare Advantage; however, approximately 32% of Aetna's Medicare Advantage participants have only the medical plan and not the drug plan.~~
- ***Carelon Research (formerly*** HealthCore, Inc.***),*** a wholly owned, ~~subsidiary of Anthem, Inc~~ ***independently operating*** subsidiary of ***Elevance Health,*** uses real-world data to conduct outcomes, health economics, pharmacoepidemiologic, and late

phase research***. Carelon Research curates the*** ~~HealthCore~~ ***Healthcare*** Integrated Research Database ~~is~~ ***(HIRD®),*** a proprietary, fully integrated, longitudinal claims database that combines medical, pharmacy, and laboratory information drawn from ~~72.5~~ ***88*** million unique individuals with medical coverage and more than ~~51~~ ***67*** million ~~lives~~ ***individuals*** with medical and pharmacy claims information since 2006***.*** In addition***, Carelon Research*** ~~HealthCore Integrated Research Environment~~ has the ability to link ~~the~~ claims data in the ~~HealthCore Integrated Research Database~~ ***HIRD*** to complementary data sources, including inpatient and outpatient medical records, national vital statistics records, cancer and vaccine registries (state-by-state), disease and device registries, member and provider surveys, and point of care clinical data. Using these resources***,*** ~~HealthCore~~ ***Carelon Research*** conducts a range of real-world research designed to meet client needs, including retrospective database studies, medical record review studies, cross-sectional and longitudinal patient and provider surveys, and prospective site-based studies, including pragmatic clinical trials. ~~Of HealthCore's population aged 50 or older from 2006 through mid-2019 with both medical and drug coverage, 57% were 50-64 years old and 43% were 65+ years old; some of the latter are covered under Medicare Advantage.~~

- **Optum ~~(UnitedHealth)~~** was initially founded as Epidemiology Research Institute, and later acquired in 1999 by Ingenix (renamed to Optum), Optum Epidemiology has a nearly 40-year history in regulatory drug safety research.

Section 9.5: Study size

We expect that the estimated sample sizes for the SCRI design with ~~vaccinees~~ ***cases*** (Table 3) and the cohort design with vaccinees and the unvaccinated comparators (Table 4 and Table 5) needed to detect the specified RRs (≥ 4 for GBS, ≥ 2 for gout, ≥ 2 for PMR, and ≥ 3 for GCA) with 80% power will be attainable.

Except for gout (where we will include all cases identified from claims at the time of analysis given that chart review is not needed), the study accrual period for the primary objectives will be defined based on meeting the case count (for GBS) or vaccinated and comparator (for PMR and GCA) as defined by the sample size calculations. For cohort analysis, the study accrual periods will be based on meeting the sample size target for Dose 1 RZV exposed individuals, adjusted for projected incompleteness of chart retrieval. If more comparators are accrued during the time period needed for the RZV cohort, then comparators will be sampled to meet the sample size required for power as outlined in Tables 4 and 5.

Section 9.7.2.1: Primary Objectives 1 & 2 and Secondary Objective 1 (SCRI design)

Primary analyses will analyze both dose 1 and 2 without distinguishing between doses (Table 6, Rows 1 and 7). For individuals receiving 2 doses, the Dose 1 CW will be censored if Dose 2 is received during the Dose 1 CW; Dose 1 events will be excluded from the analysis if Dose 2 is received during the Dose 1 risk interval (no corresponding control interval). Secondary and sensitivity analysis related to dose spacing (Table 6, rows 2 and 8), adjustments of the window length (table 6 rows 3-4 and 9) and specific doses (Table 6, rows 5-6 and 10-11) are also planned.

Section 9.7.2.1.1: Additional secondary or sensitivity analyses

In additional to the main analysis as detailed in Table 6, several sensitivity or secondary analysis of the primary analysis (Table 6 rows 1 and 7) to address other study design aspects are detailed below and in the SAP.

Seasonality-adjusted sensitivity analysis

We will also conduct an additional secondary analysis for GBS and gout adjusted for seasonality ***by means of an offset term as detailed in the SAP.***

Sensitivity analysis including asymptomatic short-run SVT cases

An additional sensitivity analysis will be performed including both confirmed cases and events identified by adjudicators as asymptomatic short-run SVT. Asymptomatic short-run SVT was defined for adjudication purposes as ECG evidence of SVT of less than 6 minutes' duration with no accompanying symptoms, based on a 6-minute threshold of subclinical atrial fibrillation required for inclusion in clinical trials (Healey, 2024;, Kirchhof, 2023). Cases with this designation will not be included in the primary analysis.

Inclusion of unobtainable/incomplete charts

In the SCRI analysis for GBS and SVT as detailed in Table 6, only confirmed cases will be included as outcomes in the main analysis. Cases where charts were unobtainable (i.e. charts could not be retrieved from providers) or incomplete (i.e. unable to adjudicate the case due to lack of information in the chart) will not be included in the primary analysis as these cases cannot be adjudicated. Therefore, a sensitivity analysis of the primary analysis may be conducted to include a proportion of GBS and SVT cases with unobtainable or incomplete charts after adjusting the count by the window-specific PPVs. This method is consistent with a published FDA study (Goud, 2021). In this sensitivity analysis, for GBS, the event date will be defined as the claims-based diagnosis date for any unadjudicated cases.

Section 9.7.2.2: Primary Objectives 3 & 4 and Secondary Objective 2

Individuals can contribute to the comparator cohort and subsequently to the exposed cohort upon receipt of RZV Dose 1.

~~The analysis will be conducted using SAS 9.2 or higher.~~

Section 9.7.2.2.1: Primary analyses

In the primary analyses, we will fit a separate model for each dose (i.e., one model will include the cohort of all subjects who receive Dose 1 and a second model will include the ~~cohort~~ ***subgroup of*** ~~subjects~~ ***Dose 1-exposed individuals*** who also receive Dose 2 ***within 365 days of Dose 1); the same comparator population will be used for both analyses***. The Dose 1 ***primary*** analysis will be performed with 183 days of follow-up regardless of if and when the person receives Dose 2. Separate models will be fit for two main reasons:

Violations of the proportional hazard assumption ***will be evaluated. We may*** evaluate ***this assumption*** using ~~a~~ graphical approache***s*** by plotting the log[-log(S(t))] versus log(t) and the Schoenfeld residuals by time, ***and*** by testing the interaction between ~~the covariates~~ ***exposure*** and log(t). Non-parallel lines or non-zero slope in the graphical approach ***or*** a significant interaction term ~~and a significant supremum test~~ would indicate a violation of the proportional hazards assumption. If the proportional hazard assumption is violated, an interaction term of time and the ~~variable of interest~~ ***exposure*** will be included in the model.

We will compute robust standard errors for clustered survival data ***using a sandwich estimator*** to account for the within-person correlation ~~between post-preventive care visit follow-up time and post-RZV follow-up time on the same person~~ ***for individuals included in analyses multiple times and for the use of weights*** (Austin, 2016; Lin & Wei, 1989). ***Additional methodology such as bootstrapping may also be considered to account for within-person correlations (Austin, 2016).*** Once an individual receives RZV vaccine, any subsequent preventive care visit will *not* be eligible for selection as the individual's one index comparator event.

~~Primary models will be adjusted for at least sex, age, and Data Partner. For comparison, some secondary models will be implemented, adjusting for additional potential confounders defined to occur in the 12-month baseline prior to the date of the first dose of RZV. Such confounders may include immunocompromising conditions, receipt of steroids, and/or measures of health care utilization. If there is need to adjust for a large number of potential confounders, propensity score stratification or weighting may be used.~~

~~Primary models will be adjusted for at least sex, age, and Data Partner. For comparison, some secondary models will be implemented adjusting~~ ***As the analysis compares RZV exposed and preventative care comparators, adjustment*** for additional potential confounders ~~defined to occur~~ ***assessed*** in the 12-month baseline prior to the ~~date of the first dose of RZV~~ ***index date is needed.*** Such confounders may include immunocompromising conditions, receipt of steroids, and/or measures of health care utilization. ***Multivariable adjustment may be considered, however, more advanced confounder adjustment approaches (e.g., propensity score stratification or weighting) may be needed*** if there is need to adjust for a large number of potential confounders ~~propensity score stratification or weighting may be used~~.

~~It is worth noting that if propensity scores are to be used, they will be used for confounder adjustment in the analysis, rather than for matching. Compared with design-based confounder adjustment methods like matching, strategies applied in the analysis phase permit greater analytic flexibility39. For example, when using regression adjustment or weighting, it is straightforward to conduct subgroup sensitivity analyses (e.g., by age group, gender, etc.) by simply segmenting the cohort into subgroups and rerunning the main regression or weighted regression analysis within each subgroup to estimate subgroup-specific effects. With propensity score matching, however, subgroup analyses are challenged by the fact that a propensity score-matched set that may contain subjects in multiple categories of a subgroup variable of interest (e.g., a man and woman may be in the same matched set because they have a similar propensity score). Thus, it is~~

~~less straightforward to break apart the analytic dataset into subgroups for analysis (e.g., matched sets containing both men and women cannot easily be split out into gender subgroups).~~

Analytic models will use inverse probability of treatment weighting (IPTW) as the preferred approach to control for confounding and estimate the population-ATE, or the treatment effect that would be observed if the entire population received RZV versus did not receive RZV. IPTW is a weighting method based on an individual's propensity score (PS), or the predicted probability they are in the RZV exposed (versus comparator) group, conditional on baseline covariates. A logistic regression model will be used to estimate the conditional probability of receiving the RZV vaccine predicted by the baseline covariates observed in the 365 days preceding the index date (i.e., RZV exposed vaccination date or RZV unexposed preventive care visit date). To estimate the ATE, the following weight form is used in analyses:

$$w_{ATE} = \frac{A}{e} + \frac{1-A}{1-e} \qquad w_{stableATE} = \Pr(A=1)\frac{A}{e} + \Pr(A=0)\frac{1-A}{1-e}$$

where A is the treatment indicator (A = 1 if exposed and A = 0 if unexposed), and the propensity score $\boldsymbol{e = Pr(A = 1 \mid X)}$ ***with X denoting the vector of covariates. Stabilized weights are intended to reduce variability due to instability in estimation that can be induced by subjects with very large weights.***

Propensity score adjustment by IPTW allows for adjustment by all potential confounders without overparameterization of the inferential regression model. All baseline covariates (as detailed in the SAP) that are hypothesized confounders will be included in the propensity score model, as will covariates that are weakly associated with the outcome, as inclusion of these variables can reduce bias (Brookhart 2006). After estimating propensity scores, non-overlapping areas of the propensity score distribution between the RZV exposed and RZV unvaccinated comparator cohorts will be removed ("non-overlap trimming").

The performance of IPTW for controlling confounding will be assessed by examining the balance of covariates using standardized mean differences between exposed and comparator in IPT weighted data. Additional trimming may be implemented if extreme weights or covariate imbalance is observed.

Section 9.7.2.2.2: Secondary analyses

In secondary analyses, we will fit models by combining information from the two doses together to determine if additional precision can be gained by leveraging information across all doses. ~~Second~~ ***As in the primary analysis, Dose 2 exposures will only be assessed among patients whose Dose 1 was included in the study and if the gap between doses*** ~~received~~ ***was no more than*** ~~1 year~~ ***365 days. If an individual received their second dose 2 within the 183-day follow-up period for dose 1, then their follow-up after*** ~~first dose will be excluded from these secondary analyses~~ ***Dose 1 will be censored at receipt of Dose 2 in order to avoid overlapping follow-up time or duplicate events***. In one secondary analysis, we will use a partly conditional ~~survival~~ model ***to*** ~~estimate a~~

~~single hazard ratio across both doses. In other words, we will~~ ***combine information from each exposed group to*** generate one ***combined*** hazard ratio that estimates the association between receipt of RZV and adverse event risk rather than two separate dose-specific hazard ratios. In the other secondary analysis, we will fit a time-dependent Cox model to estimate separate effect estimates for Doses 1 and 2 in the combined model ~~as done in the primary analyses~~. We do not expect the estimated effects for Dose 1 and Dose 2 to change much compared with the separate models, but precision should improve.

In both of these secondary analyses, we will compute robust standard errors for clustered survival data to account for the within-person correlation for people who contribute both post-preventive care visit follow-up (unexposed) time and post-RZV follow-up (exposed) time and also to account for the correlation between doses received by the same person in the combined dose analysis. ~~With this method, a single case of an HOI occurring in both the 6 months after a patient's Dose 1 and the (overlapping) 183 days after their Dose 2 will not be treated as two independent events. For simplicity in these combined analyses, we will define the baseline period for potential confounders as the 12 months prior to receipt of Dose 1, because using separate baseline periods would complicate the use of propensity scores (should those be needed) and we do not expect confounder status to change substantially during the interval between doses. Censoring follow-up at HOI occurrence will prevent non-incident HOI cases from being counted after each dose.~~ ***Other methods (e.g., bootstrapping) for estimating the variance may be considered as necessary.***

~~Combined~~ ***Secondary*** *analysis of Dose 1 and Dose 2 yielding* ~~one~~ ***a combined*** *risk estimate.* A partly conditional survival model will be used in the secondary analysis of combined doses. Since an individual may contribute more than one observation in the analysis (i.e., Dose 1 and Dose 2), this model is appropriate, as it estimates the effect of longitudinal ~~measures~~ ***exposures*** (in this case, dose) on survival ~~allowing for repeated measures for each individual~~ (Gong, 2013; Zheng, 2005).

Whereas typically survival is modeled as the time from study entry to the event, i.e., event time, D_i, in partly conditional survival analysis, regression parameters depend upon the time of measurement, S_i, for the predictor (i.e., dose receipt) and ~~time of measurement for the event to measure~~ the follow-up time ~~since~~ ***between*** the ~~measurement~~ ***exposure and event***, $D_i - S_i$. This is considered partly conditional since the hazard function that is being modeled conditions on the covariate history through S_i. ~~As a result, there are multiple event times for each individual which corresponds with the repeated measures for each dose~~ ***Therefore, individuals receiving a Dose 2 during the follow-up period after Dose 1 will have their Dose 1 follow-up window censored such that any HOI event can be included in the analysis only one time. Weights for analysis will be based on the dose-specific IPTW.***

~~A general form of the regression model for the hazard is shown below,~~

$$\lambda_{ik}(t* \mid \mathbf{Z}_{ik}, 0 \le s_{ik} \le T_i) = g[\lambda_0(t*, s), \boldsymbol{\beta}(t*, s)^{\mathrm{T}} \mathbf{Z}_{ik}]$$

~~where T_i is the time to event (or censor) for subject i, s_{ik} denotes measurement times for each dose, $t* = t - s_{ik}$ measures the follow-up time since dose, $g(\lambda, \eta)$ is a link function, λ~~

~~$_0(t^*, s)$, is the baseline hazard, $\beta(t^*, s)$ is the regression coefficient, and Z_{ik} is a vector of covariates associated with subject i, at time s_{ik}.~~

The analysis will be conducted using SAS 9.2 or higher. As mentioned above, standard errors will be calculated using a robust sandwich estimator ***(or other methods as appropriate e.g., bootstrapping)*** for repeated measures survival data.**Error! Reference source not found.**

~~Combined analysis of~~ ***Single model yielding separate*** *Dose 1 and Dose 2* ~~yielding separate~~ *risk estimates.* To generate a separate risk estimate for each dose in a combined analysis, where a binary indicator defines the Dose 1 and Dose 2 RWs, a time-varying Cox proportional hazards regression model will be used. In the time-dependent model, we allow the RW to vary for each dose**.** ~~The time~~ ***Follow-up will be defined as the 183 days*** after Dose 1***, regardless of whether Dose 2 is received during that time. As such,***

- ***the time after Dose 1*** until ***(a)*** Dose 2 ***(if received within 183 days of Dose 1)*** or ***(b)*** end of follow-up (if no Dose 2 occurs) defines the Dose 1 RW, and
- the time from Dose 2 until end of follow-up ***(183 days after Dose 1)*** defines the Dose 2 RW.

Thus, a subject who receives two doses ***within <183 days*** will contribute time to the Dose 1 RW and the Dose 2 risk window. In the unvaccinated comparators the time from index date to end of follow-up is considered unexposed time.

The Dose 1 IPTW will be used for all observations.

Section 9.7.2.2.3: Sensitivity, supplemental and bias analysis

Restriction to doses compliant with US dosing recommendations

As a sensitivity analysis for each of the secondary analyses, we will fit the combined Cox proportional hazards regression model as described above but restricted to just the subgroup of patients who received two doses ~~between~~ ***in the span of*** 2 and 6 months, ***inclusive*** (60 and 183 days, as per US dosing recommendations) ~~inclusive apart~~.

Confirmed case sensitivity analysis for PMR

As the final analysis for PMR will include all claims-identified cases, a sensitivity analysis may be conducted using the 25% PMR chart review sample. This sensitivity analysis using the primary analytic approach and based on adjudicated case classifications may be conducted if the PPV obtained from the 25% chart reviewed sample is found to be <70%. We will calculate the PPV two ways: using a narrow case definition of only adjudicated confirmed cases and using a broad case definition of both confirmed and probable adjudicated cases.

This sensitivity analysis will use the primary analytic model. We will perform the analysis twice, using the narrow case definition and the broad case definition, as defined above. Cases selected for chart review that were adjudicated as possible, ruled out, or incomplete will be included as non-cases in the analytic cohort along with a 25% sample of claims-based non-cases. These claims-based non-cases will be sampled

from the Dose 1, Dose 2, and comparator cohorts using the same methodology used to sample cases for medical record review (i.e., by RP) for a total analytic sample of 25% of the primary analysis cohort.

Bias analysis for unobtainable/incomplete charts

In the main analysis for GCA and ION, only confirmed cases will be considered as true cases and counted as events. However, there will be cases where the chart was not obtainable or incomplete and therefore the case could not be adjudicated. In the main analysis these cases will be considered as non-events (and individuals will be censored at their claims-based event date).

However, if the proportion of charts that are unobtainable or incomplete differ substantially between the RZV and comparator cohorts, we may obtain a biased HR from analyses that consider only the chart-confirmed cases as true outcomes. Therefore, we will compare the proportion of unobtainable and incomplete charts between RZV and comparators and if there is substantial difference between the two groups, we may perform a sensitivity analysis of the primary analysis for GCA and ION that brings both adjudicated and non-adjudicated claims-based cases into the analysis. This sensitivity analysis would count all claims-based events as HOIs and adjust the estimated HR by the ratio of the estimated PPV in the exposed to the estimated PPV in the unexposed, per Brenner and Gefeller (1993). This method assumes algorithm sensitivity is nondifferential with respect to exposure.

Supplemental analysis ***excluding ever-exposed comparators***

Some individuals in the analysis may contribute person-time both to the comparison group and (subsequently) to the RZV-vaccinated group. At CBER's request, a supplemental analysis will be conducted for the primary analysis, excluding from the control arm those subjects who ~~received~~ ***were observed in our data to receive*** RZV at any point, so that each subject contributes person-time to only one arm.

Sensitivity analysis for secondary definition (i.e., arteritic) of ION

If the PPV of the ION algorithm is <70%, it is possible that this analysis may not be feasible

Sensitivity analysis to evaluate the impact of the COVID-19 pandemic

~~Sensitivity~~ ***In sensitivity*** analyses ~~will exclude exposures from~~ ***for HOIs to be studied using*** the cohort ***design (PMR, GCA, ION), February 1, 2020 will be included as a censoring event. Any doses administered (or preventative care visits for comparators) on or*** after February 1, 2020 will be excluded. ~~These sensitivity analyses will be conducted for each HOI and will be aligned with the primary (1°) SCRI and cohort analysis as described in Table 6 and sections 9.7.2.2~~ These sensitivity analyses will allow for an evaluation of the robustness of the primary findings after excluding cases and vaccinations during the COVID-19 pandemic. The sensitivity analyses will be descriptive if the exclusion of subjects after February 1, 2020 compromises the sample size such that there is insufficient power to generate meaningful estimates. Such descriptive analysis

will report the ~~number of cases in the risk and control windows (for the SCRI design) or the~~ incidence rate (or cumulative incidence) for the cohort design.

Sensitivity analysis to test IPTW sample

If the effect estimates of our IPTW adjusted primary analysis is non-significant, it is possible that this may be due to insufficient sample size of the IPT weighted sample. In this situation, we may consider calculating the RR that the IPT weighted sample is powered to detect, or we may conduct sensitivity analysis after re-estimating the sample size to account for IPTW using methods described by Austin et al. 2021. This sensitivity analysis will be aligned with the primary analytical model and use claims -based cases to define the HOI. The resulting HR will be adjusted to account for differential misclassification of the outcome (multiply the resulting HR by PPV_exposed / PPV_unexposed).

Section 9.8 Quality control

The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data QA ~~specifically, "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (Guidance), section IV.E "Best Practices – Data Sources: QA and Quality Control", published in May 2013 (FDA 2013)~~**~~Error! Reference source not found.~~**~~.~~

Section 9.9: Limitations of research methods

Potential measurable confounding differences between the two groups such as age, sex, ~~Data~~ ***Research*** Partner, and calendar time will be adjusted ~~for in multivariable regression models. Propensity scores (PS) will also be considered to address confounding if there is the requirement for adjustment for a large number of variables~~ ***using propensity score based weighting.***

As in any study relying on administrative data, case-finding algorithms are rarely if ever perfectly sensitive and specific. Our algorithms are based on algorithms found to have high positive predictive value in published case validation studies. Furthermore, for all HOIs except for gout, medical record review and adjudication by clinical experts will be carried out and only chart-confirmed ***GBS, GCA, ION, and SVT*** cases included in analysis. A ***sensitivity analysis using chart-confirmed PMR cases will also be conducted, in addition to the claims-based primary analysis if the algorithm PPV is low.***

Section 12.1 :Posting of information on publicly available registers and publication policy

Redacted CSR will be submitted in the EU PAS register within 12 months of end of ~~data collection~~ ***analysis completion***

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Vaccines R & D
Protocol Amendment 2

eTrack study number and Abbreviated Title:	209452 (EPI-ZOSTER-030 VS US DB)
Amendment number:	Amendment 2 Final
Amendment date:	13 June 2022
Rationale/background for changes: ***Protocol Amendment 2 dated 13 June 2022 was amended to add clarity regarding the analytical approach, which was not previously specified in the protocol, and to include sensitivity analysis to evaluate the impact of the COVID-19 pandemic.***	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Section Number and title	**Changes made**
Marketing Authorization Holder	
MAH contact person:	PPD Clinical and Epidemiology Project Lead, GSK ~~Vaccines~~
Section 3: Responsible Parties **Annex 4 Sponsor information** **Annex 6 Sponsor Protocol Amendment 2 Signatory Approval** **Annex 7 Protocol Amendment 2 Investigator Agreement**	
Principal investigator	***Richard Platt*** ~~Jeffrey S Brown~~, Harvard Medical School & Harvard Pilgrim Health Care Institute
Sponsor Contact	***Agnes Mwakingwe-Omari*** ***Clinical and*** Epidemiology ***Project*** Lead GSK 14200 Shady Grove Rd Rockville, MD 20850 +1 202-525-0130

Investigators	***Harvard Medical School & Harvard Pilgrim Health Care Institute*** • ~~W. Katherine Yih~~ • ~~Young Hee Name~~ • ~~Jennifer C. Nelson~~
Contributing authors	***GSK ~~Vaccines~~*** PPD
Section 4: Abstract	
Main author	PPD ~~, Harvard Medical School & Harvard Pilgrim Health Care Institute~~
Rationale and background	~~After licensure, using an algorithm that preferentially maximizes sensitivity over specificity, the Vaccine Safety Datalink detected a statistical signal for Guillain-Barré syndrome (GBS) during active surveillance for RZV safety.~~ ***The Centers for Disease Control and Prevention (CDC) detected a statistical signal for GBS during post-licensure safety surveillance of RZV using the Vaccine Safety Datalink. CDC applied an iterative algorithm that preferentially maximizes sensitivity over specificity that was designed for hypothesis (signal) generation.***

Section 9.2 Setting

- 365 days (1 year) of ***continuous*** enrolled time, ***allowing 45-days gap***, prior to RZV receipt for GBS and SVT

- 730 days (2 years) of ***continuous*** enrolled time, ***allowing a 45-days gap***, prior to RZV receipt for gout, to allow for a more specific definition of incident, versus prevalent gout, to be implemented
- ***Continuous*** enrollment through the end of the respective control interval during a period when data for the respective Data Partner are determined to be ≥ 90% complete for the outcomes of gout and SVT.
- **Continuous** enrollment through the end of the respective control interval plus 14 days during a period when data for the respective Data Partner are determined to be ≥ 90% complete for the outcome of GBS. The 14 "extra" days are to ensure capture of GBS cases with symptom onset in windows of interest but no diagnosis code until later, e.g., GBS symptom onset on Day 82 after RZV receipt (determined by chart review) but no GBS hospitalization or diagnosis code until Day 85, which would be outside of the windows of interest. Further details on medical record review for GBS are described in Section 9.3.3 below.

Inclusion requirements for the cohort analyses of new-onset PMR, GCA ***and ION*** (beyond those in the first paragraph of this section) are illustrated in Figure 2 and are:

- RZV vaccination or eligible preventive care visit with 365 days of enrolled time, ***allowing 45-days gap***, before the index date (vaccination or preventive care visit) during a period when data for the respective Data Partner are determined to be ≥ 90% complete.

Section 9.3.1 Exposures

Dates of RZV exposure and preventive care visits will be collected. ***All preventive care visits that meet inclusion requirements will be identified, and one per patient will be randomly selected as the index date.*** The preventive care visit definition for the comparator group for the cohort analyses was selected based on having demonstrated greatest comparability to RZV recipients on a number of patient characteristics that may be important potential confounders (e.g., comorbidities) compared to alternative comparator definitions. (The comparison was conducted as part of feasibility assessment in four Data Partners.)

Section 9.3.2 Outcomes

Table 2 footnotes added

[a] ICD-9 code(s) will be used for mapping to develop ICD-10 algorithms when validated ICD-10 algorithms are not available, as well as for assessing background frequencies/rates of the outcomes of interest from January 1, 2015 to September 30, 2015 without regard to RZV vaccination.
[b] For ICD-9-CM codes; "NA" means no performance characteristics are available for same or similar algorithm.
[c] Based on external expert opinion.
[d] All settings: Inpatient, Emergency Department, and outpatient settings.

[e] ***The secondary definition of GBS will be used for descriptive monitoring queries. Potential GBS cases for medical record review will be identified based on the primary GBS definition.***

Section 9.3.3 Medical record review

Medical record review will be conducted for all identified potential cases ***(i.e., cases identified based on the claims-based primary HOI definitions as defined in Table 2)*** of all HOIs except gout and PMR.

To ensure that we obtain 25%, we will seek a random sample of 3~~0~~%. ***The final analysis for PMR will include all claims-identified cases if the PPV obtained from the 25% random sample is found to be ≥70%. If the PPV is <70% for the claims-based algorithm to detect PMR, the final analysis will include chart confirmed cases identified from the 25% random sample. Additional sensitivity analysis may be conducted and details are provided in the SAP.***

After case adjudication, the respective analysis or analyses will be conducted using confirmed cases. ***Confirmation of arteritic ION cases (secondary definition table 2) will be considered during chart review. However, if distinguishing arteritic ION cases during chart review is not feasible then arteritic ION cases will be identified as chart-confirmed ION cases who met the secondary claims-based arteritic ION definition.*** For the cohort design outcomes of PMR, GCA, and ION, where the duration of follow-up is 183 days, the date of onset of the confirmed HOI will be the date of the ICD-10 code for both the RZV and comparator groups. ***For gout, which will be assessed via SCRI analysis, date of onset will also be the date of the ICD-10 code.***

Section 9.3.4 Covariates

- Region of residence within US (as defined ~~by either Department of Health and Human Services (11 regions) or~~ Census Bureau (4 regions))
- Calendar year~~ month~~ of vaccination or preventive care visit
- **Calendar month of vaccination or preventive care visit**
- Concomitant vaccinations ***at index date*** (e.g., influenza, pneumococcal)

Section 9.3.5 Potential confounding variables and effect modifiers

We will conduct analyses unadjusted for seasonality as our primary SCRI analysis for each of these two HOIs and ~~If descriptive statistics show a seasonal pattern in RZV administration,~~ we will also conduct ~~an~~ **additional secondary** ~~the~~ analyses adjusted for seasonality.

Section 9.4 Data sources

All data partners are expected to contribute data for all the analyses detailed in the SAP. However, if a data partner cannot contribute to a specific analysis, then alternative approaches to conducting the analysis may be considered including excluding the impacted data partner if appropriate sample size can be maintained, or meta-analytical approaches to combine estimates obtained from analysis conducted

individually at the data partner(s), or other appropriate analytical or methodological solutions.

Section 9.5 Study size

~~The~~ ***We expect that the*** estimated sample sizes for the SCRI design with vaccinees (Table 3) and the cohort design with vaccinees and the unvaccinated comparators (Table 4 and Table 5) needed to detect the specified RRs (≥ 4 for GBS, ≥ 2 for gout, ≥ 2 for PMR, and ≥ 3 for GCA) with 80% power ~~are~~ ***will be*** attainable.

Section 9.7.2.1 Primary Objectives 1 & 2 and Secondary Objective 1 (SCRI design)

~~If and only if descriptive analyses show a seasonal pattern in RZV administration,~~ We will **also** conduct an additional secondary analysis for GBS and gout adjusted for seasonality.

Sensitivity analysis for the secondary definition of gout

The number of gout cases identified by the secondary HOI definition (i.e. one – year lookback - Table 2 column 8) will be reported. Sensitivity analysis with the 1-year lookback will also be conducted using the primary SCRI analytical approach (Table 6, Row 7).

Section 9.7.2.2 Primary Objectives 3 & 4 and Secondary Objective 2 (retrospective cohort design)

Censoring events

Follow-up time will be censored upon the earliest occurrence of any of the following:

- The respective HOI
- ZVL (*Zostavax*) receipt
- RZV receipt (for preventive-care visit comparators)
- Disenrollment
- Death
- ***Data Partner end date***
- End of the 183 days of follow-up.

Primary analysis

Individuals will be followed for the occurrence of each HOI from their index date (i.e., the date of RZV vaccine for RZV vaccinees or the date of the preventive care visit for the comparison group) until the first censoring event: HOI, ZVL receipt, death, disenrollment, ***Data Partner end date***, or the end of the 183 days follow-up period. For those in the comparator group, follow-up will additionally be censored at the time of receipt of RZV ~~or ZVL vaccine~~ (if this should occur during the 183 days follow-up period).

Once an individual receives RZV vaccine, any subsequent preventive care visit will *not* be eligible ~~to contribute time to the comparator group~~ ***for selection as the individual's one index comparator event.***

Secondary analysis
The analysis will be conducted using SAS ***9.2 or higher***. As mentioned above, standard errors will be calculated using a robust sandwich estimator for repeated measures survival data

Sensitivity analysis
Sensitivity analysis for secondary definition (i.e., arteritic) of ION

Classification of ION cases as arteritic (secondary definition Table 2) will be considered during chart review. If distinguishing arteritic ION cases during chart review is feasible then sensitivity analysis using the primary analysis for the cohort design may be conducted with chart confirmed arteritic ION cases. Alternatively, if distinguishing arteritic ION cases during chart review is not feasible then sensitivity analysis may be based on validated ION cases that met the secondary arteritic claims-based definition without chart confirming their status as arteritic ION. The number of arteritic ION cases will be reported and if a sufficient number of artertic ION cases are identified then sensitivity analysis will be conducted for arteritic ION using the primary analysis for the cohort design as described in Figure 4 ***(i.e., a separate model for each dose).***

Sensitivity analysis related to Influenza vaccine during follow-up for PMR and GCA

Given that influenza vaccine has been associated with PMR and GCA and influenza vaccine is seasonal, a descriptive assessment of influenza vaccine during follow-up will be conducted. If a meaningful difference in influenza vaccination rates between vaccinated and comparator are observed, sensitivity analysis aligned with the primary analytical approach (Figure 4***)) for PMR and GCA will be performed adding influenza vaccination as a censoring event.***

Sensitivity analysis to evaluate the impact of the COVID-19 pandemic

Sensitivity analyses will exclude exposures from the analytical cohort for which follow-up ended after February 1, 2020. These sensitivity analyses will be conducted for each HOI and will be aligned with the primary (1°) SCRI and cohort analysis as described in Table 6 and sections 9.7.2.2. These sensitivity analyses will allow for an evaluation of the robustness of the primary findings after excluding cases and vaccinations during the COVID-19 pandemic. The sensitivity analyses will be descriptive if the exclusion of subjects after February 1, 2020 compromises the sample size such that there is insufficient power to generate meaningful estimates. Such descriptive analysis will report the number of cases in the risk and control windows (for the SCRI design) or the incidence rate (or cumulative incidence) for the cohort design.

Section 9.7.3 Conduct of analysis

Table 7 Sequence of analyses to be conducted

Outcome	Target risk to detect	Analysis Sequence
Gout	RR of ≥2	Phase 1
~~GBS~~ ***SVT***	~~RR of ≥4~~ ***N.a.***	Phase 2
PMR	RR of ≥2	
GCA	RR of ≥3	Phase 3
~~SVT~~ ***GBS***	~~N.a.~~ ***RR of ≥4***	
ION	N.a.	

N.a. = Not Applicable.

Section 9.9 Limitations of the research methods

Nonetheless, if RZV administration in the study population has a seasonal pattern—for example, due to the timing of vaccine shortages—seasonality would be a potential confounder, especially in the case of GBS, which also has a seasonal pattern. Therefore, ~~if RZV vaccination indeed appears to have a seasonal pattern~~, we will conduct secondary analyses that explicitly adjust for seasonality.

Section 12.1 Posting of information on publicly available registers and publication policy

- Results summaries ***along with redacted protocol and SAP*** will be posted within 12 months of analysis completion date.
- ***GSK also aims to publish the results of these studies in the searchable, peer-reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. Any publications will follow guidelines, including those for authorship (e.g., guidelines established by the International Committee of Medical Journal Editors 2018) and for reporting of observational studies in epidemiology (e.g. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE,) 2007)***
- Protocol summaries for non-interventional post-authorization safety studies will be registered ***along with redacted protocol*** in the EU PAS register prior to study start.
- ***Redacted Clinical Study Report (CSR)*** ~~Results summaries~~ will be submitted ***in the*** EU PAS register within 12 months of end of data collection.

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	209452	19-Aug-2020	List of stand-alone documents
2	209452	19-Aug-2020	Glossary of terms
3	209452	17-May-2021	List of principal and coordinating investigators
4	209452	19-Aug-2020	Sponsor Information
5	209452	**13-June-2022**	Amendments ~~and administrative changes~~ to the protocol
6	209452	**13-June-2022**	Protocol Amendment ~~1~~ **2** Sponsor Signatory Approval
7	209452	**13-June-2022**	Protocol Amendment ~~1~~ **2** Investigator Agreement
8	209452	19-Aug-2020	ENCePP checklist for study protocols

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Vaccines R & D
Protocol Amendment 1

eTrack study number and Abbreviated Title:	209452 (EPI-ZOSTER-030 VS US DB)
Amendment number:	Amendment 1 Final
Amendment date:	17 May 2021
Rationale/background for changes:	
Protocol dated 19 August 2020 was amended to address feedback received from regulatory authorities.	

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Section Number and title	**Changes made**
PASS information	
EU PAS Register Number	EUPAS37156
Authors	• PPD , Harvard Medical School & Harvard Pilgrim Health Care Institute
Contributing authors	• PPD Harvard Medical School & Harvard Pilgrim Health Care Institute • PPD , GSK Vaccines • PPD , GSK Vaccines • PPD , GSK Vaccines • PPD , GSK Vaccines • PPD GSK Vaccines
Marketing Authorization Holder	
MAH contact person:	PPD Clinical and Epidemiology Project Lead, GSK Vaccines

Section 3: Responsible Parties	
Principal investigator	Jeffrey S Brown ~~W. Katherine Yih~~, Harvard Medical School & Harvard Pilgrim Health Care Institute
Sponsor Contact	O'Mareen Spence, PhD ~~Josephine Ocran Appiah, MD, MPH, MSc~~ ~~CRDL Zoster Vaccine~~ ***Epidemiology Lead*** ~~Clinical & Epidemiology Development~~ GSK 14200 Shady Grove Rd Rockville, MD 20850 +1 202-525-0130
Investigators	Harvard Medical School & Harvard Pilgrim Health Care Institute • Sheryl A Kluberg • Dongdong Li
Contributing authors	GSK Vaccines PPD
Section 4: Abstract	
Main author	PPD Harvard Medical School & Harvard Pilgrim Health Care Institute
Variables	The exposure is receipt of at least one dose of RZV. Variables to be collected include RZV exposure; preventive care visits; occurrence of health outcomes of interest; and several co-variates, including age, sex, Data Partner, region of residence within the US, calendar year-month, ~~RZV dose number,~~ concomitant vaccinations and certain comorbidities. ~~and healthcare setting of exposure~~.
Milestones	The milestones are ~~September 15, 2020~~ 14 September 2020 (Actual date) for start of data collection, ~~September 30, 2024~~ Q2, 2025 (Tentative) for end of data collection and final report submitted to FDA's Center for Biologics

	Evaluation and Research (CBER) and to EMA 31 March 2027 ~~March 31, 2027.~~ Note: the above timelines are tentative and subject to change.
Section 6: Milestone	
Milestone	Planned date
Start of data collection[1]	14~~5~~ Sep 2020 (Actual date)
End of data collection[2]	~~30 Sep.2024~~ Q2, 2025 (Tentative)
Final report submitted to the FDA's CBER and to EMA	31 Mar 2027
Note: the above timelines are tentative and subject to change. *[1] Start date of study activities* *[2] Date analytic dataset with chart-confirmed cases of last health outcome available for analysis*	

Section 9.3.1 Exposures

We will define duplicate RZV vaccination records as those occurring within 27 days after a previous RZV vaccination record (i.e., on Days 1-27, where the day of the previous record is Day 0). Duplicate records will be deleted. After deduplication, we will exclude from analysis all RZV doses beyond two per study subject.

Section 9.3.4 – Covariates

- ~~Type of code capturing RZV vaccination (CPT, NDC)~~
- ~~RZV dose number~~
- ~~Care setting of exposure (e.g., ambulatory, pharmacy, etc.)~~
- ~~Care setting of diagnosis (e.g., ambulatory, Emergency Department, inpatient)~~

Section 9.7.1 Descriptive analyses

The recommended RZV vaccination schedule in Europe is 0 and 2 months, with the option of giving Dose 2 within 2-6 months after Dose 1 if necessary. The EMA wishes to see whether a meaningful number of study subjects receive Dose 2 within 2 months after Dose 1 in order to determine the applicability of the study results to the European context. In accordance with this request, we will calculate and report the proportion of all 2-dose recipients receiving the second dose on Days 28- 60 after the first dose.

In addition, we will report on the number of confirmed GBS cases with evidence in their medical records of respiratory or gastrointestinal infection (including COVID-19) in the 42 days prior to onset of GBS symptoms, including in which post-RZV windows (risk vs. control) these GBS cases occurred. If deemed appropriate by the study team, an ad hoc

sensitivity SCRI analysis will be conducted like the primary SCRI analysis but with these cases excluded.

Section 9.7.2.2 - Primary Objectives 3 & 4 and Secondary Objective 2 (retrospective cohort design)

Bias analysis to test for unmeasured confounders for the cohort design analysis.

One assumption underlying the cohort analyses is that there are no unobserved confounders related to RZV exposure and the study outcomes of interest, given the observed covariates. Unobservable factors, related to illness severity and health status, could influence RZV receipt and the outcomes of interest. The goal of the bias analysis is to estimate the magnitude of effect of an unobserved confounder needed to change the statistical inference.

Supplemental analysis

Some individuals in the analysis may contribute person-time both to the comparison group and (subsequently) to the RZV-vaccinated group. At CBER's request, a supplemental analysis will be conducted for the primary analysis, excluding from the control arm those subjects who received RZV at any point, so that each subject contributes person-time to only one arm.

Annex 5 Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209452 (EPI-ZOSTER-030 VS US DB)
Date of protocol amendment	Amendment 3 Final: 18 Sep 2024
Title	A targeted safety study, EPI-ZOSTER-030 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 50 years of age in the United States.
Sponsor signatory	Huifeng Yun, Head, Viral Non-Respiratory Epidemiology, GSK

Signature _____

Date _____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

Annex 6 Protocol Amendment 3 Pharmacovigilance Signatory Approval

eTrack study number and Abbreviated Title	209452 (EPI-ZOSTER-030 VS US DB)
Date of protocol amendment	Amendment 3 Final: 18 Sep 2024
Title	A targeted safety study, EPI-ZOSTER-030 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 50 years of age in the United States.
Sponsor signatory	Peggy Webster, VP, Head of Clinical Safety and Pharmacovigilance, GSK

Signature _____

Date _____

Note: In order to comply with the pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) must be involved in the review, content approval and sign off (in addition to sponsor signatory) of Post-Authorization Safety studies (PASS) protocols (GVP Module 1). This also applies to Targeted Safety Study (TSS) protocols.

Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the QPPV approval.

Annex 7 Protocol Amendment 3 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, ENCePP guide for methodological standards in pharmacoepidemiology, the International Society of Pharmacoepidemiology guidelines for GPP, and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions and to implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	209452 (EPI-ZOSTER-030 VS US DB)
Date of protocol amendment	Amendment 3 Final: 18 Sep 2024
Title	A targeted safety study, EPI-ZOSTER-030 VS, to evaluate the safety of *Shingrix* in adults ≥50 years of age in the United States.
Investigator name	Richard Platt, Harvard Medical School & Harvard Pilgrim Health Care Institute
Signature	_____
Date	_____

Annex 8 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	Section 6
1.1.2 End of data collection[2]	☒	☐	☐	Section 6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Section 12.1
1.1.6 Final report of study results.	☒	☐	☐	Section 6

COMMENTS:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	Section 4, Section 8, and Section 9
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Section 8
2.1.2 The objective(s) of the study?	☒	☐	☐	Section 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	Section 8, Section 9.1, and Section 9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	Section 4, and Section 9.5
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

COMMENTS:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	Section 9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 9.1, and Section 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	Section 9.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	Section 9.7.2.1, and Section 9.7.2.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	Section 11

COMMENTS:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☐	☐	☐	Section 9.1, and Section 9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	Section 9.2
	4.2.2 Age and sex	☒	☐	☐	Section 9.1, and Section 9.2
	4.2.3 Country of origin	☒	☐	☐	Section 9.1, and Section 9.2
	4.2.4 Disease/indication	☒	☐	☐	Section 9.1, and Section 9.2
	4.2.5 Duration of follow-up	☒	☐	☐	Section 8, Section 9.3.2, Section 9.7.2.1, and Section 9.7.2.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Section 9.1, Section 9.2, Section 9.3.1, and Section 9.5

COMMENTS:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Section 9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorized according to time windows?	☒	☐	☐	Section 9.7.2.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section 9.3.1, and Section 9.7.2
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	Section 9.1, Section 9.2.2, Section 9.3.1, and Section 9.7.2.2

COMMENTS:

5.2. Chart validation of RZV exposure will not be done. Regarding the potential problem of RZV codes appearing that do not represent true instances of vaccination, it seems unlikely in this claims-based system. Affirmative coding for vaccination in the Sentinel system has been found to be accurate. Regarding the potential problem of missed RZV vaccinations, this is not a concern for the SCRI analyses, as only vaccinated cases are used. For the cohort analyses, all subjects will have both medical and drug coverage, thus their RZV vaccinations, even if occurring in a pharmacy setting, will be captured.

5.3. Post-exposure follow-up time in the SCRI analyses will be categorized as at risk and presumed not-at risk.

5.4. Dose-specific analyses will be done.

5.5. Although dose-specific analyses will be done and post-exposure risk intervals for outcomes take into account putative biological mechanisms, no detailed consideration of the pharmacokinetics and pharmacodynamics of RZV appears in the protocol.

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	Section 4, 8, and 9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Section 9.3.2, and 9.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	Section 9.3.2, 9.3.3, 9.7.2.1.1, and 9.7.2.2.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

COMMENTS:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	Section 9.1, 9.3.5, and 9.7.2.2.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	Section 9.1, 9.3.5, and 9.7.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	Section 9.1, 9.3.3, 9.3.5, 9.7.2.2.1, and 9.7.2.2.3

COMMENTS:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	Section 9.3.5, and 9.7.2.2.1

COMMENTS:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Section 9.3.1, and 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Section 9.3.2, 9.3.3, and 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	Section 9.3.4, and 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Section 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 9.3.1, and 9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Section 9.3.2, 9.3.3, and 9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	Section 9.3.4, and 9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Section 9.4

COMMENTS:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	Section 9.1, and 9.7.2
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	Section 9.5
10.3	Are descriptive analyses included?	☒	☐	☐	Section 9.7.1
10.4	Are stratified analyses included?	☒	☐	☐	Section 9.3.4, and 9.7.2
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	Section 9.3.5, and 9.7.2.2.1
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	Section 9.7.2.2.1, and 9.7.2.2.3
10.7	Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	Section 9.3.3, 9.7.2.2.1, and 9.7.2.2.3

COMMENTS:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Section 9.6
11.2	Are methods of quality assurance described?	☒	☐	☐	Section 9.8
11.3	Is there a system in place for independent review of study results?	☐	☒	☐	

COMMENTS:

11.3. There is not a system in place for independent review of the study result. However, study deliverables including data tables and summaries of results (study reports) will be reviewed by all stakeholders including the HPHCI, the participating Research partners, and GSK staff (including persons not directly involved in the study). Additionally, the study will be submitted to the FDA and EMA for their review and approval.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	Section 9.7.2.1.1, and 9.7.2.2.3
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	Section 9.7.2.2.1, and 9.7.2.2.3
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	Section 9.5

COMMENTS:

12.1. The protocol does not explicitly discuss the magnitude or direction of bias from selection bias, but the designs and comparator populations were chosen to mitigate bias. Primary cohort analyses use trimming to guard against residual confounding, and sensitivity analysis has been included to estimate the magnitude of effect of an unobserved confounder needed to change the statistical inference. Additional sensitivity analyses have been included for both SCRI and cohort designs to address potential differential outcome misclassification. Multiple analyses per design (including secondary and sensitivity) will provide evidence for or against the existence of bias in the primary analyses.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	Section 10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Section 9.6.1, 10.1, and 10.3,

COMMENTS:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Section 5

COMMENTS:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	Section 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 12

COMMENTS:

Name of the main author of the protocol amendment 3:

Sheryl A Kluberg, Harvard Medical School & Harvard Pilgrim Health Care Institute

Note: The Sponsor confirms his/her agreement with the completed ENCePP checklist by signing the Protocol Sponsor Signatory Approval page.

Signature Page for 209452 TMF-19899192 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 16-Sep-2024 15:25:44 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 18-Sep-2024 11:26:11 GMT+0000

Signature Page for TMF-19899192 v1.0

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