PASS INFORMATION

Title:	Safety and effectiveness of Recombinant Zoster Vaccine (RZV) in adults ≥18 years of age with Systemic lupus erythematosus (SLE) or Multiple sclerosis (MS)
Protocol version identifier:	215104 (EPI-ZOSTER-041 VS US DB)
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EU PAS Register No:	***EUPAS107073***
Active substance:	VZV glycoprotein E (gE)
Medicinal product(s):	*Shingrix* (Recombinant Zoster Vaccine, RZV)
Product reference:	For EMA: EU/1/18/1272/001, EU/1/18/1272/002 For FDA: IND number 13857
Procedure number:	EMEA/H/C/004336
Marketing Authorization Holder(s) (MAH):	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89, 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives *(Amended 12 Dec 2025)*:	This study will evaluate the safety and vaccine effectiveness (VE) of *Shingrix*, or recombinant zoster vaccine (RZV), in adults ≥18 years of age (YOA) with pre-existing systemic lupus erythematosus (SLE) or multiple sclerosis (MS). The primary safety objective is to assess the risk of ***hospitalized*** SLE flare within 90 days following any RZV dose in adults ≥18 YOA with pre-existing SLE. CCI [redacted] CCI [redacted] CCI [redacted]

	CCI [redacted] CCI [redacted] The primary effectiveness objective is to estimate the VE of 2 doses of RZV in preventing Herpes Zoster (HZ) in adults ≥18 YOA with pre-existing SLE or MS, respectively.
Country of study:	United States
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MARKETING AUTHORIZATION HOLDER

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1. TABLE OF CONTENTS

PAGE

1.1. LIST OF TABLES

PAGE

1.2. LIST OF FIGURES

PAGE

2. LIST OF ABBREVIATIONS (Amended 12 Dec 2025)

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AID	Autoimmune disease
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CTS	Clinical trial services
CW	Control window
DMT	Disease modifying therapy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FFS	***Fee-for-Service Medicare (excludes Part C plans)***
GSK	GlaxoSmithKline
HCPCS	Healthcare Common Procedure Coding System
HPHC	Harvard Pilgrim Health Care
HPHCI	Harvard Pilgrim Health Care Institute
HZ	Herpes Zoster
HR	***Hazard ratio***
ICD-10-CM	***International Classification of Diseases, Tenth Revision, Clinical Modification***
IM	Intramuscular
IPTW	***Inverse-probability-of-treatment weight***
IRB	Institutional Review Board
IV	Intravenous
MS	Multiple sclerosis
PASS	Post-Authorization Safety Study
PHN	Post-herpetic neuralgia
PO	By mouth
PPV	Positive Predictive Value
RCT	Randomized controlled trial

RW	Risk window
RZV	Recombinant zoster vaccine
SAP	Statistical Analysis Plan
SCDM	Sentinel Common Data Model
SCRI	Self-controlled risk interval
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus Disease Activity Index
SQ	Subcutaneous
TSS	Targeted Safety Study
US	United States
VE	Vaccine effectiveness
VZV	Varicella Zoster Virus
YOA	Years of age
ZVL	Zoster vaccine live

3. RESPONSIBLE PARTIES (*Amended 12 Dec 2025)*

Principal Investigator	Richard Platt Harvard Medical School & Harvard Pilgrim Health Care Institute
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Investigators *(Amended 12 Dec 2025)*	**University of Pennsylvania, Perelman School of Medicine** • Michael D. George (Scientific Lead) • Alexis R. Ogdie (Co-Scientific Lead) • **Harvard Pilgrim Health Care Institute** • Sheryl Kluberg
Study Teams *(Amended 12 Dec 2025)*	**Harvard Pilgrim Health Care Institute** • PPD • • • • • • • • **University of Pennsylvania** • PPD • • ***Biostatistics Consultant*** • PPD

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4. ABSTRACT

Title	Safety and effectiveness of RZV in adults ≥18 years of age with Systemic lupus erythematosus (SLE) or Multiple sclerosis (MS).
Version and date of the protocol	Amendment *3* Final: *12 Dec 2025*
Main authors	PPD, University of Pennsylvania
Rationale and background	Patients with autoimmune diseases, such as SLE and MS, or who are immunosuppressed, are at increased risk of HZ. In July 2021, the FDA approved an expanded indication of *Shingrix* (recombinant zoster vaccine, RZV) for use in adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy. RZV provides a substantial benefit in preventing HZ in these populations, however, data on the safety and effectiveness of RZV in adults with SLE or MS are limited. In addition, assessing the safety of RZV in this population is important given a hypothetical risk of SLE flares or MS relapses with vaccinations due to immune activation.
Research question and objectives *(Amended 12 Dec 2025)*	This study is a targeted safety study and a post-authorization safety study. • The primary safety objective is to assess the risk of ***hospitalized*** SLE flare within 90 days following any RZV dose in adults ≥18 years with pre-existing SLE**.** CCI [redacted] • The primary effectiveness objective is to estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 YOA with pre-existing SLE or MS, respectively.
Study design	A retrospective cohort study will be used to evaluate safety and VE.

Population ***(Amended 12 Dec 2025)***	The study population will include: US adults ≥18 YOA who are diagnosed with SLE or MS and are members of participating ***Research*** Partners in the US FDA Sentinel System or ***enrolled in FFS*** Medicare
Variables ***(Amended 12 Dec 2025)***	Key variables will include: • Primary exposure: RZV vaccination on or after 01 January 2018 • Primary safety outcome: ***Hospitalized*** SLE flare within 90 days of RZV vaccination CCI [redacted] • Primary VE outcome: HZ diagnosis • Other variables: Disease severity, medications used in treating SLE and MS, comorbid conditions, health care utilization and sociodemographic characteristics.
Data sources ***(Amended 12 Dec 2025)***	This study will be conducted using health plan data held by ***up to 6 Research*** Partners that participate in the FDA's Sentinel System and ***FFS*** Medicare. The ***Sentinel Research Partners*** participating in the study include CVS Health***/Aetna***, ***Point32Health*** (Harvard Pilgrim Health Care ***and Tufts Health Plan), Carelon Research (formerly*** HealthCore***)***, HealthPartners, Humana, and Kaiser Permanente Mid-Atlantic. The study will use curated data ***from all sites*** that are formatted to the FDA SCDM specifications, which permits the use of publicly available Sentinel analytic tools.
Study size ***(Amended 12 Dec 2025)***	***For the primary safety objective,*** the sample size needed to detect a ***50***% increase in the risk of ***hospitalized*** SLE flares (HR=1.***51***, absolute increase in risk of ***0.25***% over 90 days) with 80% power is as follows: • ***10 864*** vaccinated ***with SLE (assuming baseline flare incidence of 3 per 100 person-years)*** • ***44 367*** unvaccinated ***with SLE (assuming baseline incidence of 2 per 100 person-years)***

For VE, the sample size needed to detect VE of at least 50% (HR=0.5) reduction in HZ with 80% power is as follows:

- SLE: ***1,001*** vaccinated patients and ***4,225*** unvaccinated patients (assuming baseline HZ incidence of 20 ***per*** 1000 person-years)
- MS: ***2,001*** vaccinated patients and ***8,544*** unvaccinated patients (assuming baseline HZ incidence of 10 ***per*** 1000 person-years)

Data analysis

The analysis plan will include descriptive measures to characterize vaccinated and unvaccinated individuals. Cox proportional hazards regression models will be used to compare outcomes in vaccinated and unvaccinated patients using propensity scores to balance potential confounders.

5. AMENDMENTS AND UPDATES

Protocol Amendment 2 (dated 10 August 2023) was primarily updated to amend the study safety objectives and associated safety outcome definitions. A pre-planned chart review sub-validation of previously defined safety outcomes (severe SLE flare and any MS relapse) demonstrated PPVs for these outcomes <70%, below the pre-defined threshold that necessitated an alternative approach to identify outcomes in final safety analyses.

Following the completion of the chart review sub-validation in December 2024, the outcome algorithms were refined considering the results of the chart review and expert clinical guidance. Additionally, CCI [redacted] CCI [redacted] CCI [redacted] ***Given these needed changes to the objectives and outcome definitions, subsequent updates to the study variables, sample size estimates, and analytic approach were made for alignment with the new objectives and outcome definitions. Additionally, two Sentinel Research Partners will not be participating in the final study.***

Amendment number	Date	Amendment or update	Section of study protocol	Reason
3	12 Dec 2025	Updates to outcome algorithms for MS and SLE safety objectives	9.4.3.1, 9.4.3, 9.10	The previously planned chart review validation of a random sample of ~100 severe Garris flare cases and ~100 MS relapse cases was completed in December 2024, with results demonstrating PPVs <70% (the *a priori* planned cut-point). Performance of different components of the algorithm and expert guidance led to revisions of the algorithms as defined in Table 2 and 3. Outcome descriptions are updated throughout the Protocol.
		Updates to safety objectives	8, 8.1, 8.2, 8.3, 9.8.2	Changes to objectives reflect new outcome definitions CCI [redacted]
		Updates to study data availability, planned dates	6	Reflect most current information on data availability and timelines for interim and final analyses. Data availability is updated throughout.
		Updates to participating research sites	9.5.1	1 commercial Sentinel Research Partner elected not to participate in the final

Amendment number	Date	Amendment or update	Section of study protocol	Reason
				safety study; throughout, the number of participating Research Partners has been updated. Updated descriptions provided for most Research Partners based on current information. Medicare data source has been clarified as "fee-for-service" throughout the Protocol.
		Updates to power calculations	9.6	Target study sample sizes updated to reflect rates of the new outcome observed in most recent monitoring queries (where indicated). Updated methodology does not require simulation given certainty regarding outcome frequency. Relevant information from Appendix 3 moved into the main body of the Protocol. Power calculations for interim analyses removed as no longer applicable.
		1. Removal of exploratory effectiveness objectives and sensitivity analyses related to 1-dose VE 2. Addition of footnotes	8.6, 8.5, 9.8.3.1.1	1. As 1-dose VE is already considered a secondary objective, exploratory and sensitivity objectives related to it were removed, given they are being conducted for the primary effectiveness objective of 2-dose VE. 2. Footnotes indicate feasibility will be considered as well for secondary and exploratory effectiveness objectives and descriptive results may be provided instead.
		Updates to preparatory research queries	9.1	Amended to include information on monitoring query and assessment of new outcome algorithms. Tense updated throughout.
		Remove exclusion made for individuals with RZV doses <28 days apart	9.3.1, 9.8.1	Receipt of doses <28 days apart occurred infrequently in monitoring and interim analyses (<5%). Clinical experts indicated these individuals need not be excluded from safety analyses nor their outcome

Amendment number	Date	Amendment or update	Section of study protocol	Reason
				frequencies described separately.
		Covariate updates: 1. Race/ethnicity data included wherever available 2. Removal of disability as reason for Medicare eligibility 3. Prior flare/relapse covariates updated 4. Durable medical equipment (DME) updated to commercial data only 5. Addition of comorbidities of interest 6. Addition of covariate assessing immunosuppressive therapy within 3 months of index 7. Noting grouping of covariates or categories may be implemented in PS models 8. Ublituximab and mycophenolic acid added to MS medications 9. Subheadings added	9.4.4	1. Capture of race/ethnicity data has improved among Sentinel Research Partners and is available at all sites (with some missingness) 2. Data on reason for Medicare eligibility not available 3. Reflect new outcome definitions 4. DME claims not available in FFS Medicare 5. New comorbidities added during monitoring based on clinical input 6. Replaces a sensitivity analysis for effectiveness 7. Update to enhance feasibility 8. Updates reflecting current clinical practice 9. Subheadings added for readability
		Added language that individual Research Partners may be excluded from selected analyses for which they lack adequate sample size	9.5.1	This challenge was noted in the interim analysis. Language added to document this approach and retain flexibility for the final analysis.
		Removal of information related to chart review	(previously) 9.7.3	Chart review sub-validation completed in 2024, no further applicability to study conduct
		Removal of information related to interim analysis	9.8	No longer relevant as interim analysis has been completed in July 2024
		Removed of assessment of temporal distribution of flares and relapses	9.8.1 (Descriptive analyses)	Preliminary assessment for SLE flares conducted in interim analysis; clinical experts indicate no further exploration required
		1. Additional information provided on analytic approach for primary safety objective (e.g., IPTW, accounting for correlation between doses).	9.8.2.1, 9.8.3, 9.8.3.1 (Primary analyses)	1. For clarification. Further technical details provided in the SAP. 2. As propensity-score based methods are of primary interest prefer to refine PS models instead

Amendment number	Date	Amendment or update	Section of study protocol	Reason
		2. Removal of language related to including imbalanced covariates in outcome models. 3. Specify proportional hazards to be assessed using Kaplan-Meier plots and other diagnostic approaches		of producing covariate-adjusted estimates. 3. Detail not previously included
		Removal of: 1. Assessment of any severity SLE flare 2. Assessment of alternative follow-up periods 3. Chart-confirmed analysis	9.8.2.2 (Secondary analyses for safety)	1. No longer applicable based on updated SLE safety outcomes 2. No longer applicable based on clinical guidance 3. No longer applicable, chart review not conducted for final analysis
		1. Sensitivity analyses updated to use methodology of secondary safety analyses only (stratified by dose) 2. Add sensitivity analysis using alternative outcome definitions 3. Remove analysis using “any severity” flare for washout 4. Remove analysis using longer washout	9.8.2.2.1 (Sensitivity analyses for safety)	1. Reduce computational intensity, avoid assumptions regarding dose-specific effects 2. These alternative definitions are of clinical relevance, but more subject to misclassification than primary definitions. 3. No longer applicable based on new outcome definitions 4. No longer applicable based on clinical guidance
		Section added for exploratory MS safety objectives	9.8.2.3	Notes inferential analyses will not be conducted.
		1. Removal of analysis of individuals with treatment-changes around their index date 2. Removal of analysis including post-index medications as time-varying covariates 3. Removal of analysis restricting to individuals with 2+ years of pre-index enrolment	9.8.3.1.1 (Sensitivity analyses for effectiveness)	1. Replaced with a descriptive covariate (see 9.4.4) 2. Determined infeasible in a distributed data setting. Marginal structural models would be necessary to properly account for time-varying covariates 3. Expected to have low power, removed due to limited utility

6. MILESTONES (*Amended 12 Dec 2025*)

Milestone	Planned date
Start of data collection[a]	~Q1 2023 (start of data extraction)
Interim study report in ≥18 YOA of VE in MS/SLE and safety in SLE[b]	~Q1-2 2024
End of data collection[c]	~***Q3*** 2026 (The date from which the analytical dataset is completely available.)
Final report of study results	~Q1 2027

MS: Multiple sclerosis; Q: calendar quarter; RZV: recombinant zoster vaccine; SLE: Systemic lupus erythematous; VE: vaccine effectiveness; YOA: Years of age

a. Start of study activities including the start of data extraction.
b. Date analytic dataset available for analysis (***using*** last RZV vaccination ***accrued through September*** 2023).***The interim report included cohort studies assessing effectiveness in the overall SLE cohort and overall MS cohort ≥18 years old and*** safety in the SLE cohort. ***Safety in the MS cohort was not*** included in interim ***analyses but instead*** chart review ***to validate the MS relapse*** algorithm ***was prioritized and initiated during this time***.
c. Date analytic dataset available for analysis (***the date of*** last RZV vaccination entering the cohort ***varies by Research Partner*** and ***is based on most recent data available at the time of analytic*** data ***extract (last recent data availability anticipated to be April 2025 or later for Sentinel Research Partners and end 2023 for FFS Medicare***).

7. RATIONALE AND BACKGROUND (*Amended 12 Dec 2025)*

HZ, also known as shingles, is caused by reactivation of VZV and often appears as a painful, pruritic rash which can resolve on its own within 1-2 weeks. Herpes zoster affects at least 1 million people in the US each year and the lifetime prevalence is approximately 25-33% [CDC, 2021; Bowsher, 1999]. Additionally, over 95% of adults above the age of 50 have evidence of VZV seropositivity and are thus at risk for developing HZ [Johnson, 2015]. ***VZV*** can also cause ocular or auricular involvement and encephalitis. Post-herpetic neuralgia, a chronic neuropathic pain at the site of the HZ infection, is a common complication of HZ.

Patients who are immunosuppressed are at increased risk for HZ and potentially the complications of HZ. Disseminated HZ, a rare and potentially deadly manifestation of VZV infection is more likely to occur in immunocompromised patients and has a mortality of 5-10% in this population [Johnson, 2015]. Furthermore, certain medications are associated with HZ based on their degree of immunosuppression or specific mechanisms of action.

Beyond immunosuppression, other risk factors for HZ include age, physical trauma, malignancy and other comorbidities including rheumatic disease and autoimmune diseases, depression, diabetes and chronic renal disease [Marra, 2020]. Patients with SLE and MS may be particularly at higher risk for VZV reactivation given their treatment with immunosuppressive medication [Borba, 2010; Manouchehrinia, 2017]. One meta-

analysis found that the risk of HZ in patients with SLE was twice that of the general population [Kawai, 2017].

Herpes zoster is a vaccine preventable illness. The first HZ vaccine available was a live attenuated Oka-strain vaccine, or *Zostavax*, approved by the US FDA in May 2006 for adults ≥60 YOA and in March 2011 for adults 50 to 59 YOA. It should be noted that *Zostavax* has never been recommended for use in adults 50 to 59 YOA by the ***ACIP*** and was withdrawn from the US market in November 2020. *Zostavax* is a live vaccine, limiting its use in immunocompromised populations.

Recombinant zoster vaccine or *Shingrix*, an adjuvanted recombinant vaccine, was approved by the FDA in October 2017 for adults ≥50 YOA and in July 2021 for adults ≥18 YOA who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy. ***RZV*** is currently recommended for use in adults ≥50+ YOA [Dooling, 2018] and immunocompromised adults ≥19 YOA by the ACIP [Anderson, 2022].

RZV is a 2-dose vaccine with demonstrated efficacy in preventing HZ in 2 Phase III RCTs, ZOE-50 and ZOE-70 [Lal, 2015;Cunningham, 2016]. Vaccine efficacy in these trials demonstrated 97.2% in adults ≥50 YOA (ZOE-50) and 89.8% in adults ≥70 YOA (ZOE-70). The majority of the adverse events AE reported in this set of trials included pain and erythema at the injection site and myalgia. In a post marketing observational study, an increased risk of Guillain-Barré syndrome was observed during the 42 days following vaccination with RZV, although available evidence is insufficient to establish a causal relationship [Goud, 2021].

Six clinical trials have been conducted assessing RZV in immunocompromised adults ≥18 YOA [Stadtmauer, 2014; Berkowitz, 2015; Bastidas, 2019; Vink, 2019; Dagnew, 2019; Vink, 2020]. The trials enrolled patients with autologous hematopoietic stem cell transplant (2 trials), hematologic malignancies, renal transplant, solid tumor receiving chemotherapy, and HIV-infection. Efficacy in preventing HZ evaluated among autologous hematopoietic stem cell transplant recipients and adults with hematological malignancies was 68.2% and 87.2%, respectively [Bastidas, 2019; Dagnew, 2019].

The safety and efficacy of RZV in patients with pre-existing SLE and MS, were not evaluated in clinical trials. Therefore, there is a critical need for real-world evidence related to the safety and effectiveness of RZV in this target population who are at increased risk of HZ and its complications. One study, which evaluated the effectiveness of RZV in a subgroup of patients ≥65 YOA enrolled in Medicare with AID (including MS and SLE) reported 1-***dose*** and 2-dose VE***s*** of 57.7% and 68.0%, respectively [Izurieta, 2021]. Nevertheless, more research is needed to provide evidence on the benefits-risk profile of RZV, particularly among adults ≥18 YOA for which current data is very limited. Data on the safety of RZV in adults with SLE and MS is also needed. There is a hypothetical association between adjuvanted vaccines and flares of autoimmune disease immediately post-vaccination [Guimarães, 2015]. While this has been a concern, the risk with different vaccines on flare/relapse appears to be small if present at all according to current studies [Murdaca, 2014; Frederiksen, 2017; Garg, 2018; Mok, 2019; Huttner, 2020; Tonacio, 2021; Ciampi, 2022]. Additionally, 1 study

using administrative data examined patients ≥50 YOA with AID (including SLE) and did not find evidence of increased flares after RZV [Curtis, 2021]. Thus, evidence is lacking which quantifies the potential risk of SLE flares or MS relapses following vaccination with RZV.

The goal of this study is to evaluate the safety and effectiveness of RZV in patients with SLE and MS. The study will utilize a large, distributed data network in the US to address these questions.

8. RESEARCH OBJECTIVES (*Amended 12 Dec 2025)*

The study will address the question of whether adults ≥18 YOA with SLE are at increased risk of ***hospitalized*** SLE flares CCI [redacted] CCI [redacted]. ***The study*** will also assess the real-world effectiveness of RZV in preventing HZ in these populations. The specific objectives are as follows:

8.1. Primary safety objective:

1. To assess the risk of ***hospitalized*** flare within 90 days following any RZV dose in adults ≥18 years with pre-existing SLE

8.2. Secondary safety objective:

1. To assess the risk of ***hospitalized*** flare within 90 days following RZV in adults ≥18 years with pre-existing SLE, stratified by RZV dose

8.3. Exploratory safety objective:

CCI [redacted]

8.4. Primary effectiveness objectives:

1. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years with pre-existing SLE
2. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years with pre-existing MS

8.5. Secondary effectiveness objectives[1]:

1. To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥18 years with pre-existing SLE
2. To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥18 years with pre-existing MS
3. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years with SLE, stratified by age (18-49; ≥50 years) and sex
4. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years with MS, stratified by age (18-49; ≥50 years) and sex
5. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years with SLE, by time since vaccination and time interval between 2 doses
6. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years with MS, by time since vaccination and time interval between 2 doses
7. To estimate the incidence of PHN in RZV vaccinated (2 doses) and unvaccinated adults ≥18 years with pre-existing SLE
8. To estimate the incidence of PHN in RZV vaccinated (2 doses) and unvaccinated adults ≥18 years with pre-existing MS

CCI [redacted]

[1] ***Secondary VE objectives will be conducted only if sample size allows. In the event of small sample sizes, the study team may instead choose to report descriptive incidence rates. For secondary VE objectives 3 and 4, further stratification by race/ethnicity will be conducted if adequate race/ethnicity data are available. While the populations of participating Research Partners represent the general insured population, race/ethnicity data is not available for all participants.***

CCI [redacted]

9. RESEARCH METHODS

9.1. Study Preparation Queries (*Amended 12 Dec 2025)*

We ***conducted*** several queries ***(called descriptive and monitoring)*** prior to the interim and final analyses. These queries ***involved*** obtaining and aggregating ***descriptive*** data from all sources in Section 9.6 except for the CMS ***FFS*** Medicare data. The queries ***were*** descriptive in nature and used to identify the number of persons with SLE and MS vaccinated with RZV, overall and by patient demographic and clinical characteristics of interest, as well as unvaccinated individuals with SLE and MS, ***and the frequency of planned and investigational outcome definitions***. The information from the queries ***informed*** the finalization of the ***study methodology***, specifically to refine and tailor the analytical approaches to be most appropriate with the expected final sample size (extrapolated from the descriptive queries results)***, select final outcome algorithms and assess study power, and assess*** the distribution of patients across meaningful subgroups (e.g., selection of variables for propensity score analyses).

9.2. Overview of study design (*Amended 12 Dec 2025)*

- A retrospective cohort study will be ***implemented*** to evaluate ***all objectives***.
- The study population will be comprised of US adults ≥18 YOA who are diagnosed with SLE or MS and who are commercially insured and enrolled in 1 of ***the*** participating ***Sentinel Research Partners***, or who are enrolled in ***FFS*** Medicare.
- Vaccinated patients will include adults who received at least 1 dose of RZV on or after 01 January 2018 ***until the most recent data available at each Research Partner***. Unvaccinated patients with SLE or MS will be included as ***comparators***.
- To evaluate safety ***of RZV***, RZV exposure will be defined as receipt of at least 1 dose of vaccine. The primary analysis will evaluate the risk of ***hospitalized*** SLE flares after any RZV dose. Secondary analyses will be conducted to assess the risk of ***hospitalized*** SLE flares separately after Dose 1 and Dose 2 of RZV. CCI [redacted] CCI [redacted] CCI [redacted]
- To evaluate the effectiveness of RZV, the primary RZV exposure will be defined as receipt of 2 doses of RZV (given ≥28 days apart as per prescribing information, as patients who are immunocompromised qualify for a shorter vaccination schedule). Secondary analyses will examine effectiveness after 1 dose of RZV.
- Data sources include ***6*** selected ***Research*** Partners that participate in the FDA's Sentinel System ***and FFS*** Medicare. Patients enrolled in Medicare will be analyzed separately from patients enrolled in Sentinel ***Research*** Partners.
- All analyses will be conducted separately among patients diagnosed with SLE and MS.

9.3. Rationale for retrospective cohort study design *(Amended 12 Dec 2025)*

Assessment of safety objectives

A retrospective cohort study will be conducted to compare the hazard of ***hospitalized*** SLE flares ***using Cox proportional hazard models*** or ***describe the occurrence of*** CCI [redacted] CCI [redacted] (Figure 1). Two base cohorts will be identified consisting of patients diagnosed with SLE and separately of patients diagnosed with MS; the safety analyses will be conducted separately among patients diagnosed with SLE and MS. A 90-day follow-up period was defined based on input from subject matter experts (board certified neurologists and rheumatologists) who recommended that ***hospitalized*** SLE flares or CCI [redacted] CCI [redacted] might be expected to occur within 4-8 weeks of a trigger but that these events may not come to medical attention immediately, CCI [redacted] CCI [redacted]

A strength of the cohort design is that it allows an estimation of the incidence of SLE flares or MS relapses after vaccination. However, a challenge to this design is that patients may tend to be vaccinated during a period of lower disease activity, and both disease activity and disease severity may be different in vaccinated versus unvaccinated patients. This challenge necessitates rigorous methods to account for confounding through implementation of propensity score methods.

A self-controlled design such as a SCRI study was considered, given that this is a common study design in vaccine safety studies [Baker, 2015]. A SCRI study is a special case of a self-controlled case series in which there is a fixed CW relative to the date of vaccination, as opposed to using all available patient-time [Baker, 2015; Cadarette, 2021]. The analysis is conditioned on the individual. Only patients receiving RZV vaccination with the outcome of interest in either the risk or the control interval contribute to the analysis. The SCRI study design is ideal when there are transient exposures and acute outcomes with short, well-defined risk windows, as is sometimes the case in vaccine studies [Klein, 2010; Yih, 2014; Baker, 2015; Yih, 2016; Baker, 2019]. While the SCRI design has advantages in that it controls for time-fixed potential confounders (such as disease severity), several limitations limit its usefulness for assessing safety outcomes in this study. Notably, uncertainty of the appropriate risk window is a major limitation, variable spacing of RZV vaccine doses would affect full capture of risk windows and CW and there is potential seasonality of flares and relapses in SLE and MS [Duarte-Garcia, 2012; Harding, 2017]. This design also has reduced power compared to a cohort study making capture of clinically important differences in SLE flares or MS relapses challenging. For these reasons, a cohort study will be used for safety analyses.

Assessment of effectiveness objectives

To assess VE, a retrospective cohort design will be used to compare the hazard of HZ in patients with SLE or MS who received 2 doses of RZV relative to unvaccinated ***comparators*** using Cox proportional hazards models (Figure 2). A cohort design is used

to evaluate the VE of RZV as a long follow-up period post-RZV exposure is needed to assess new onset HZ. The potential for healthy-user bias (patients who are vaccinated may more frequently have other healthy behaviors), as well as differing characteristics among vaccinated and unvaccinated patients related to comorbidities, health status, disease activity, medications, and other factors necessitates rigorous methods to account for confounding, such as propensity score methods (e.g., through inverse probability weighting).

The retrospective cohort design will also be implemented to evaluate the incidence of PHN among vaccinated and unvaccinated patients.

9.4. Study population

The study population will be selected from adults enrolled in participating Sentinel ***Research*** Partners or ***FFS*** Medicare (Section 9.6) who are diagnosed with SLE or MS. Starting on 01 January 2018, the cohort will accrue commercially insured and Medicare beneficiaries in the US diagnosed with SLE or MS who are ≥18 YOA at their index date (i.e., RZV vaccination date for RZV recipients or assigned index date for unvaccinated ***comparators***, see Sections 9.4.1 and 9.4.2). The 365 days prior to the index date will define the baseline period. All analyses will be conducted separately in SLE and MS populations. Co-existence of SLE and MS is rare – while it is not required that the SLE and MS cohorts be mutually exclusive, overlap is expected to be minimal. Details of inclusion and exclusion criteria are defined in Sections 9.4.1 and 9.4.2.

9.4.1. Study population to evaluate the safety of RZV (*Amended 12 Dec 2025)*

A retrospective cohort study will be used to assess the safety of RZV in patients with SLE ***with respect to hospitalized SLE flare*** CCI [redacted] CCI [redacted] (Figure 1). Vaccinated patients will include adults who received at least 1 dose of RZV. Unvaccinated ***individuals with SLE or MS*** will serve as comparators.

Inclusion:

- Age ≥18 years at the index date. The index date will be defined separately for each dose among vaccinated patients. Unvaccinated patients will be assigned an index date as described below.
- Received at least 1 dose of RZV (for vaccinated individuals) on or after 01 January 2018 ***until the most recent data available at each Research Partner***.
- For ***Sentinel Research Partners***: 365 days of continuous enrollment with medical and prescription coverage (allowing ≤45-day administrative gaps in coverage) prior to the index date (baseline period).
- For ***FFS*** Medicare: continuous enrollment in Medicare part A/B/D (with no part C) 1 year prior to the index date (allowing 1 month gap in enrollment***).***
- Met criteria for SLE or MS prior to the index date (see Section 9.5.1).

Exclusion:

- Any previous RZV doses prior to the index date using all available data (for comparator patients only) or a first RZV dose prior to 01 January 2018 (for vaccinated patients).
- ***Treatment-based or hospitalized*** flares ***in patients with SLE*** CCI [redacted] CCI [redacted], ***in*** the 90 days prior to the index date (to ensure capture of incident SLE flares or MS relapses, as defined in Section 9.5.3.1) ***regardless of the evaluated outcome definition.***
- Diagnosis of HIV/AIDs, cancer and solid organ transplant or stem cell transplant during the baseline period.

Note: Sex is required for matching and in rare cases in which sex is missing or classified as "Other," this will also be an exclusion.

Definition of the index date:

- For RZV vaccinated patients the index date is the date of RZV vaccination (Dose 1 or Dose 2). Patients with 2 RZV doses can contribute 2 observations to the study with 2 distinct index dates (with follow-up after the first dose censored at the time of the second dose, if the second dose is received before Day 90, as detailed below). Additional RZV doses after the first 2 will not be included and ***will*** serve as censoring events as detailed below.
- Unvaccinated patients will be matched to vaccinated patients by ***Research*** Partner, sex, and age ***(within 5 years)***, and assigned the same index date as the vaccinated patients, to ensure calendar year and seasonality is balanced across groups. These unvaccinated patients must not have had any RZV doses at any time prior to this index date using all available data. More detail on matching is provided below.

End of follow-up/censoring:

Patients will be followed from the index date until the earliest of:

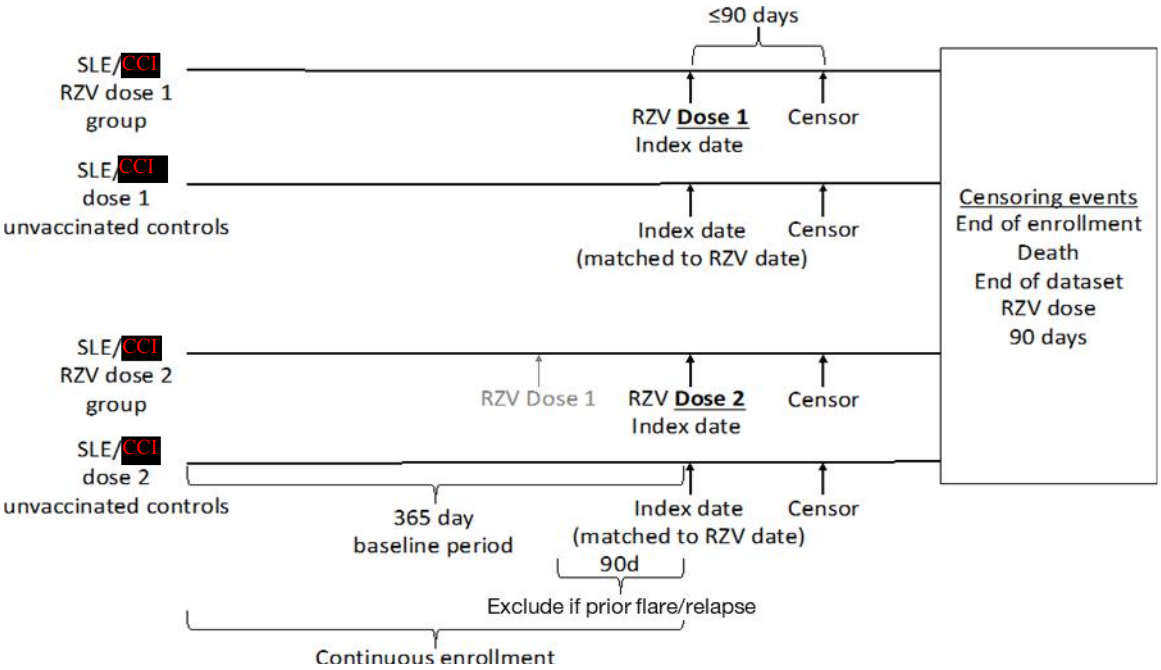
- Occurrence of the ***outcome of interest***
- End of enrollment (medical or prescription coverage)
- Death
- End of data availability and/or end of study period
- RZV dose (any subsequent dose for vaccinated patients or first RZV dose for ***comparators***)
- End of 90-day follow-up ***period***

Selection of unvaccinated *comparators*:

In order to ensure unvaccinated patients have similar calendar time and seasonality to the vaccinated patients, unvaccinated patients will first be matched to vaccinated patients and assigned the index date of the vaccinated patient. Unvaccinated patients will be matched to each vaccinated patient by data partner, sex, and age to ensure an overall sample size of 4 times unvaccinated to vaccinated (i.e., sample size ratio of 4:1). The unvaccinated patient will then be assigned the same index date as the matched vaccinated patient. This process is akin to risk set sampling in case- control studies. Matching will proceed without replacement unless there are insufficient unvaccinated patients in which case matching with replacement will be allowed.

Matching will be performed separately for the RZV Dose 1 cohort and the RZV Dose 2 cohort. The same unvaccinated patients can serve as ***comparators*** for both cohorts, although index dates will differ.

Figure 1 Cohort design to assess vaccine safety



9.4.2. Study population to evaluate the effectiveness of RZV (*Amended 12 Dec 2025*)

The primary analysis will evaluate vaccine effectiveness of 2 doses of RZV (Figure 2). A secondary analysis will evaluate vaccine effectiveness after 1 dose of RZV (Figure 3), censoring at the time of a second RZV dose. Specific inclusion/exclusion criteria for the cohort analyses assessing RZV effectiveness are similar to the safety analyses except that SLE flares or MS relapses in the 90 days prior to the index date are not exclusions (since HZ is the outcome for VE). Additional exclusions related to previous HZ or live zoster vaccine (ZVL) are needed as detailed below.

Inclusion:

- Age ≥18 years at the index date.
- Meet criteria for SLE or MS prior to the index date (see Section 9.5.1).
- For ***Sentinel Research Partners***: 365 days of continuous enrollment (allowing administrative gaps ≤45 days) prior to the index date (baseline period) to 30 days after the index date.
- For ***FFS*** Medicare: continuous enrollment in Medicare part A/B/D (with no part C) one-year prior to the index date (allowing 1 month gap in enrollment) ***to 30 days after the index date***.
- For vaccinated patients only: Received 2 doses of RZV starting on or after 01 January 2018, separated by ≥28 days (recommendations for the general population are for RZV doses to be separated by 2 to 6 months but shorter dosing intervals of 1-2 months are an option for immunocompromised patients).
  - In secondary analysis evaluating 1 dose VE of RZV, the inclusion requirement is for at least 1 dose of RZV on or after 01 January 2018 (Figure 3). As such the 1 dose VE cohort will include patients who received only 1 RZV dose, as well as those who ***ultimately*** received 2 doses (***but*** will be censored upon receipt of Dose 2).

Exclusion:

- Any previous RZV doses prior to the index date (for unvaccinated patients) or a first RZV dose prior to 01 January 2018 (for vaccinated patients) using all available data.
- Receipt of RZV doses <28 days apart.
  - ACIP recommends a third dose of RZV if patients receive a second dose <28 days after their first dose, which could affect VE [Anderson, 2022]. This scenario is expected to be rare, and patients receiving doses within 28 days will be excluded, since VE may be different in this population.
- Receipt of ZVL (Zoster Vaccine Live, *Zostavax*) during the baseline period since this may affect rates of HZ.
- Diagnoses of HZ or PHN during the baseline period
  - This exclusion refers to diagnoses of HZ or PHN from hospital, emergency department, or ambulatory visits ***(all care settings)*** even if not accompanied by an anti-viral dispensing.
- Prescription fill for oral acyclovir, valacyclovir, or famciclovir during the baseline period to avoid patients with prior HZ diagnoses and because of challenges in ascertaining new episodes of HZ in patients receiving these therapies chronically for other indications.
- Diagnoses of HZ or PHN or prescription fills for oral acyclovir, valacyclovir, or famciclovir within 30 days after the index date
  - Individuals with HZ occurring within 30 days after the index date for both exposed and unexposed groups will be excluded to allow time for the

development of immunity (for RZV vaccinated individuals) and because it is unclear if HZ began before or after index date [Sun, 2021; Izurieta, 2021].

- Censoring events (i.e., loss of enrollment, death, end of data/study period, ZVL vaccination) within 30 days after the index date (before the start of follow-up).
- Diagnosis of HIV/AIDs, cancer and solid organ transplant or stem cell transplant during the baseline period

Note: Sex is required for matching and in rare cases in which sex is missing or classified as "Other," this will also be an exclusion.

Definition of the index date:

- ***For*** primary ***VE objectives 1 and 2, secondary VE objectives 3-8 and*** CCI [redacted] CCI [redacted] which ***evaluate*** 2-dose VE, the index date is the date of the second RZV dose.
- ***For*** secondary ***VE objectives 1 and 2*** evaluating 1-dose VE, the index date is the date of the first RZV dose.
- Unvaccinated patients will be matched to vaccinated patients and assigned the same index date as the vaccinated patients, to ensure calendar year and seasonality is balanced across groups. These unvaccinated patients must not have had any RZV doses at any time prior to this index date using all available data. More detail on matching is provided in Section 9.4.1 above.

Follow-up/censoring:

- Patients will be followed from Day 31 after the index date (to allow the development of immunity after vaccination) until the earliest of:
  - ***Outcome of interest (i.e.,*** HZ ***or PHN)***
  - End of enrollment
  - Death
  - End of data availability
  - RZV dose
    - For 2-dose VE, vaccinated patients will be censored upon receipt of a third dose.
    - For 1-dose VE, vaccinated patients will be censored upon receipt of their second dose.
    - ***For all VE analyses, unvaccinated patients will be censored upon receipt of any RZV dose.***
  - ZVL vaccination

Selection of unvaccinated comparators:

The same selection process described in the safety analysis Section 9.4.1 will be used to select an overall sample size of unvaccinated that is 4 times the vaccinated (i.e., sample size ratio of 4:1), matched on data partner, sex, and age ***(±5 years)***.

Unvaccinated patients will be assigned the same index date as the matched vaccinated patient.

Figure 2 Cohort design to assess vaccine effectiveness - 2 dose VE

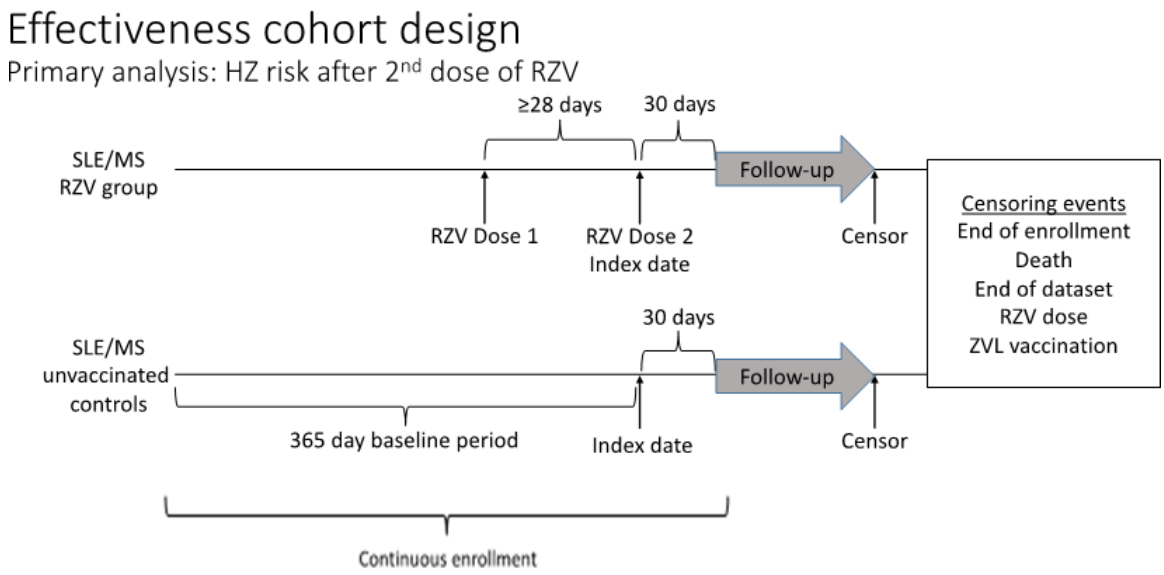
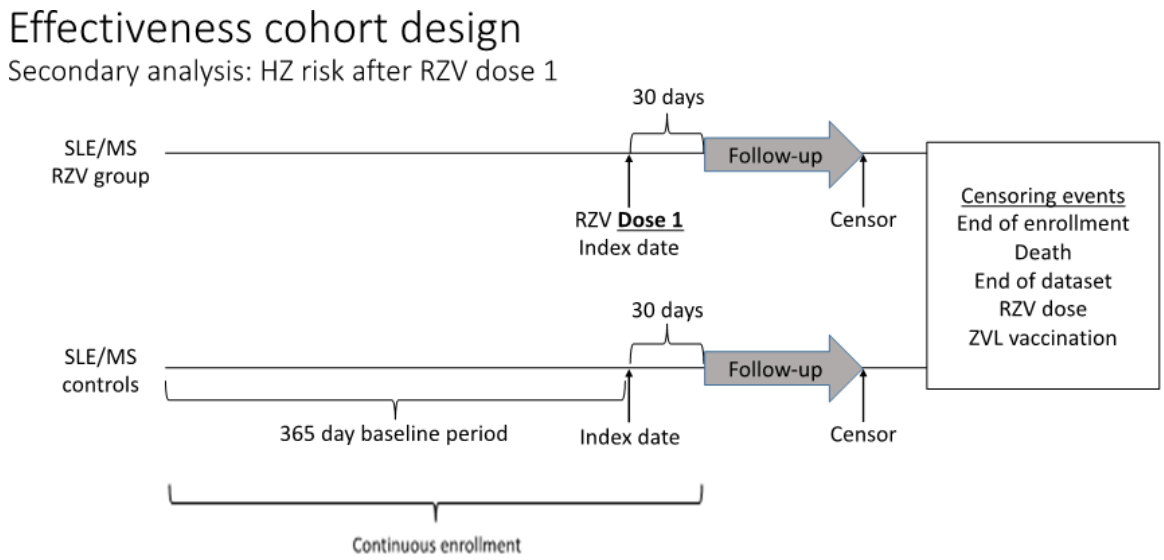


Figure 3 Cohort design to assess vaccine effectiveness - 1-dose VE



9.5. Variables

9.5.1. Definitions of SLE and MS *(Amended 12 Dec 2025)*

Systemic Lupus Erythematosus:

- ≥3 visits/encounters for SLE ***(see Table 1)***, each at least 30 days apart from each other, including inpatient, ambulatory, and emergency department (ED) diagnoses (all care settings), any position, in the entire enrollment history prior to the index date [Chibnik, 2010; Hiraki, 2012; Feldman, 2013; Feldman, 2015].
  - Because defining SLE requires 3 diagnoses spaced in time, the 1-year baseline period may not be sufficient to capture SLE diagnoses in some cases, leading to the use of the entire enrollment history prior to the index date to identify SLE.
  - In addition, the following will be required to ensure that the diagnosis of SLE is a current diagnosis (rather than a historical or rule-out diagnosis that was later considered to be incorrect): 1 inpatient, 1 ED or 2 ambulatory diagnoses for SLE ≥30 days apart during the 365 day baseline period [Lokhandwala, 2021].

One validation study using electronic health record data found a PPV of 75% for ≥3 SLE encounters [Barnado, 2017]. This definition has also been used as part of the validated lupus nephritis algorithms which provides a sub-population that can be identified with high confidence.

Multiple Sclerosis:

- ≥3 MS-related claims of any combination of encounters ***with ICD-10-CM diagnosis codes (see Table 1)*** from any care setting (inpatient [any position], ambulatory, ED), or MS-specific disease-modifying therapy (DMT) fills/infusions (see Table 8 for medication list) during the 1-year baseline period, requiring at least 1 of these to be an encounter with a diagnosis of MS. Of note, because a combination of visit diagnoses and DMT will meet the definition of MS, a look-back period >1 year is not needed to identify patients with MS, unlike in SLE where more time is needed to allow 3 SLE diagnoses to occur.
  - This algorithm for MS has demonstrated a PPV of 95-97% and sensitivity of 85-93% [Culpepper, 2019].
  - The Neurology subject matter experts who provided consultation on the study noted that some patients who are managed well may only have one visit per year but that almost all patients will be treated with DMT, making an algorithm that includes both diagnoses and DMT more optimal.

Table 1 ICD-9-CM and ICD-10-CM diagnosis codes for SLE and MS

Diagnosis	*Diagnosis code(s)*
Systemic lupus erythematosus (SLE)	*ICD-10: M32.1*, M32.8, M32.9, ICD-9: 710.0*
Multiple sclerosis (MS)	*ICD-10: G35*

ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, 9th revision, Clinical Modification

9.5.2. Exposures (*Amended 12 Dec 2025)*

- For the primary safety objective ***1*** to evaluate safety after any dose, RZV exposure is defined as receipt of at least 1 dose of RZV.
- For the secondary safety objective ***1 and*** CCI [redacted] to evaluate safety stratified by RZV dose, RZV exposure is defined as receipt of Dose 1 and receipt of Dose 2, separately.
- For the primary ***VE objectives 1 and 2***, ***secondary VE objective 3-8 and*** CCI [redacted] CCI [redacted] to evaluate 2-dose VE, RZV exposure is defined as receipt of 2 doses of RZV occurring ≥28 days apart.
- For secondary ***VE*** objectives ***1 and 2*** evaluating 1-dose VE, RZV exposure is defined as receipt of 1 dose of RZV. The 1 dose VE cohort will include patients who received only 1 RZV dose, as well as those who received 2 doses (for those who ***ultimately*** receive 2 doses, follow-up will be censored upon receipt of Dose 2).
- RZV vaccination will be identified using Current Procedural Terminology (CPT) code 90750 or National Drug ***Codes (NDCs) provided in a separate code list (and refreshed prior to each analysis) (see Annex 1).*** Using both CPT codes and NDCs will allow for identification of vaccinations occurring at office visits or at retail pharmacies. Assessment for the presence of new CPT and NDC codes indicating RZV at the time of analysis will be undertaken to ensure that capture is complete.

9.5.3. Outcomes of interest (*Amended 12 Dec 2025)*

Table 2 Overview of outcomes

Objectives	Outcome of interest	Sensitivity outcome definitions
Safety		
Primary safety objective	SLE: ***Hospitalized*** flare	N/A
Secondary safety objective	SLE: ***Hospitalized*** flare	***SLE: Treatment-based flare, and hospitalized or treatment-based flare, respectively***
CCI [redacted]		
Effectiveness		
Primary VE objective	Herpes Zoster	N/A
Secondary VE objectives	Herpes Zoster, PHN	N/A
CCI [redacted]		

N/A: not applicable

9.5.3.1. Outcomes to evaluate safety objectives *(Amended 12 Dec 2025)*

9.5.3.1.1. Safety outcomes for SLE

The primary outcome in all safety analysis among patients diagnosed with SLE is ***hospitalized SLE flare as defined in Table 3 using a claims-based algorithm. Treatment-based flares and hospitalized or treatment-based flares will be assessed as sensitivity outcome definitions for safety secondary objective 1 (risk of flare, stratified by RZV dose). All relevant codes are provided in a standalone code list (see Annex 1).***

Revised algorithms for final analyses were informed by results from the chart-based sub-validation of the Garris severe flare algorithm [Garris, 2013] ***used for interim analyses, which had an overall PPV <70% but suggested acceptable performance of a hospitalized SLE flare algorithm. Treatment-based SLE flares will also be assessed as a clinically meaningful and more frequent outcome for sensitivity analyses, after modifications based on the observation from the chart review which suggested more specific treatment criteria were needed.***

The revised outcomes will not be separately adjudicated.

Table 3 Algorithms for identifying SLE flare

Algorithm	Criteria	Objective
Hospitalized SLE flare	*Inpatient admission with SLE in the primary diagnosis position* *OR* *Inpatient admission with a SLE-related condition[a] in the primary diagnosis position with an inpatient SLE diagnosis code during the same hospitalization* *OR* *Inpatient incident ESRD[b] in the primary diagnosis position with an inpatient SLE diagnosis code during the same hospitalization* *Flare date = date of inpatient admission, or date of emergency department admission if the patient was admitted to the emergency department, with any diagnosis, during the previous day.*	• Safety primary objective 1 • Safety secondary objective 1
Treatment-based SLE flare	*New initiation (no use in prior 183 days) of rituximab, cyclophosphamide, or mycophenolate[c]* *OR* *Initiation[d] of glucocorticoids with average daily prednisone equivalent dose (PED) ≥40mg for >14 days.* *Flare date = date of medication dispensing*	*Sensitivity outcome definition for safety secondary objective 1*
Hospitalized or treatment-based SLE flare	*Either of the above.* *Flare date = earliest observed flare of either type.*	*Sensitivity outcome definition for safety secondary objective 1*

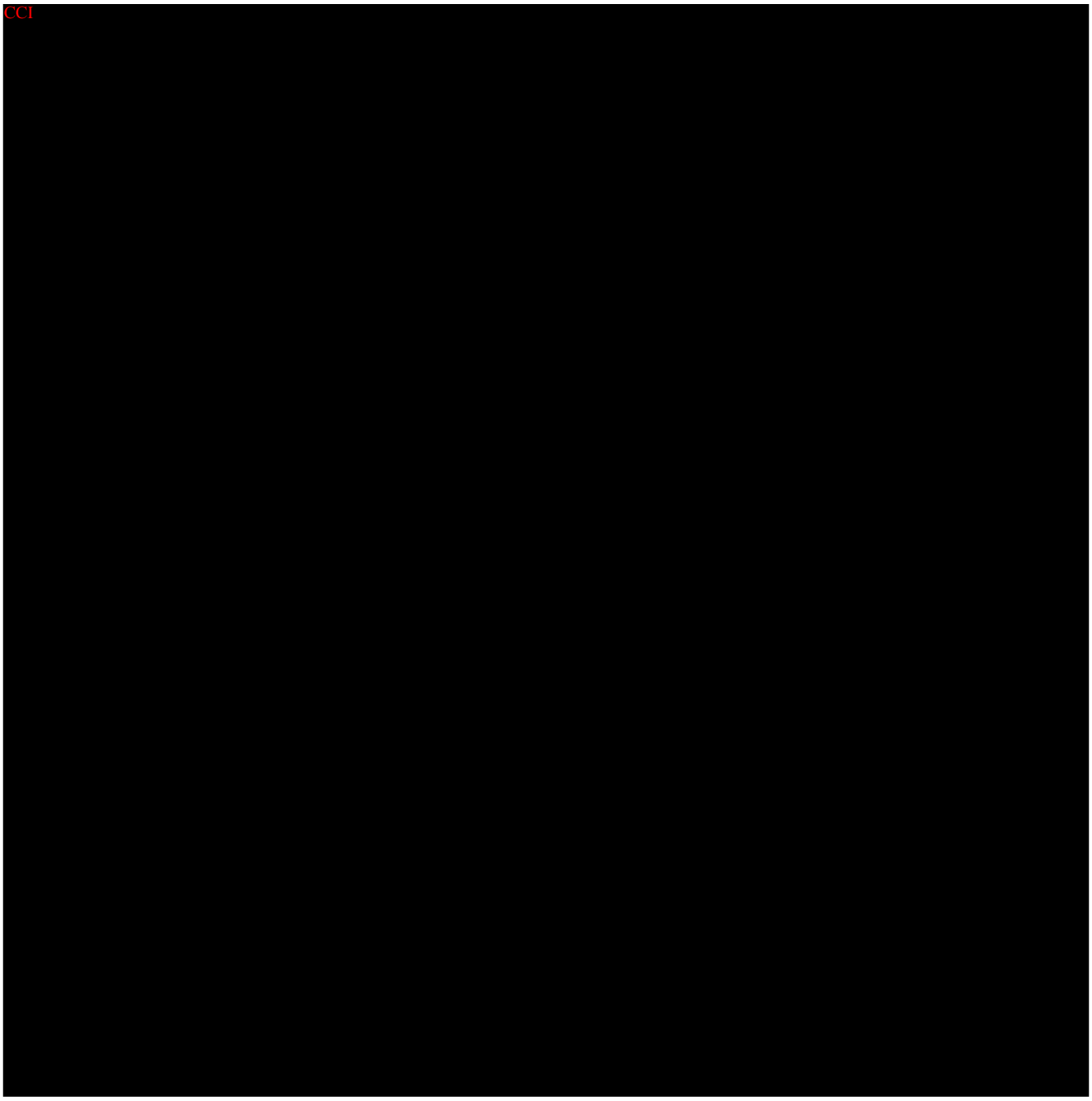
ESRD = end-stage renal disease; SLE = systemic lupus erythematosus

[a] SLE-related conditions for primary outcome definition: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, optic neuritis, pulmonary hemorrhage, stroke/TIA, acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, ischemic necrosis of bone, nephritis, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis, vasculitis (excluding aortitis).

[b] Incident ESRD defined based on no evidence of ESRD in the prior 365 days (any care setting).

[c] For the treatment-based SLE flare outcome, the washout for prior use will be based on days' supply for dispensings; when procedure codes are used to identify treatments, fixed treatment durations of 30 days for cyclophosphamide infusions and of 183 days for rituximab infusions will be used for washout.

[d] New glucocorticoid initiation excludes events with evidence of glucocorticoids within prior 60 days or if prior active glucocorticoid prescription within 60 days, prior fill was for a daily dose <40 mg PED. Further information on glucocorticoid dose conversion factors is provided in the SAP.



CCI

[redacted]

9.5.3.2. Outcomes to evaluate effectiveness objectives (Amended 12 Dec 2025)

9.5.3.2.1. Primary effectiveness outcome

The primary outcome to evaluate the VE of RZV is <u>Herpes Zoster</u>.

HZ can be identified with a high PPV >80% based on diagnosis codes, with additional accuracy established through requirement for use of an antiviral medication [Zhang, 2012]. A recent study showed a high PPV of 97.5% for an ICD-10 code for HZ accompanied by either a prescription or laboratory test results [Baxter, 2018]. Based on these data, and as done in multiple previous studies, the claims-based algorithm to identify HZ will require the following [Zhang, 2012; Izurieta, 2021]:

- An ICD-10-***CM*** diagnosis code for HZ (B02.xx) from any care setting (inpatient, emergency department, or ambulatory visit)

  AND

- Dispensing for an oral antiviral (acyclovir, valacyclovir, or famciclovir) within 7 days before or after the HZ diagnosis
- The HZ date is the date of the encounter with the HZ diagnosis code. ***HZ diagnosis codes and medications are provided in a standalone code list***.

9.5.3.2.2. Secondary effectiveness outcome

A secondary VE objective is to evaluate the incidence of ***PHN***. PHN has been examined in administrative claims data among patients diagnosed with HZ by using diagnoses of PHN in combination with a prescription for PHN treatment with PPV of 78-96% [Klompas, 2011; Klein, 2019]. This is a joint outcome that requires both a HZ code and a PHN code within 90-180 days (a HZ code without a PHN code in the correct range will not be a censoring event as the intent is to identify the first episode that meets the criteria for PHN). An algorithm based on these studies modified by [Izurieta, 2021], will be used (codes and medications ***provided in a standalone code list***) [Izurieta, 2021]:

- At least 1 subsequent ICD-10-***CM*** diagnosis code B02.xx in the 90-180 days after the initial HZ event.

  AND at least 1 of the following

a. At least 1 incident dispensing for anti-PHN drugs (anti-epileptic, gabapentinoid, anti-depressant, or opioid analgesics) in the 0-60 days after the first HZ diagnosis without an anti-PHN drug in this drug class in the 365 days prior to initial HZ event (each drug class handled separately). The 0–60 day interval to identify anti-PHN medications is used as in [Izurieta, 2021] because therapy for pain is typically started by clinicians in the first 60 days after HZ diagnosis.

b. An ICD-10-***CM*** diagnosis B02.2x (HZ with other nervous system involvement) in the 90-180 days after HZ onset.

c. A new ICD-10-***CM*** diagnosis M79.2 (neuralgia and neuritis, unspecified) or M54.10 (radiculopathy, site unspecified) in the 0-180 days after HZ onset, without neuralgia or radiculopathy in the 365 days prior to HZ onset.

- Patients meeting all these criteria will be assigned the PHN outcome date at the time of the HZ event for which PHN is observed as has been done previously, assuming the pain initiated at the time of the HZ event. Patients who have at least 180 days of follow-up after the HZ event but who do not meet criteria for PHN continue to contribute follow-up time until they have an episode meeting the criteria for PHN or another censoring event occurs, since they are at risk for a future HZ event complicated by PHN. Patients who do not meet criteria for PHN but who have less than 180 days of follow-up after the HZ event will be censored at the time of their HZ diagnosis.

9.5.4. Covariates (Amended 12 Dec 2025)

To address potential confounding due to differences between vaccinated and unvaccinated cohorts (see directed acyclic graphs in Appendix 1 and Appendix 2), multiple covariates will be assessed and balanced across the exposure groups using propensity scores. A list of covariates to be considered followed by a detailed description of select covariates is included below. Key potential effect modifiers of interest will also be assessed in stratified analyses, which are detailed in the analysis Section 9.9. ***Variables described in Table 5 may be redefined, combined, or excluded as needed due to sample size or to facilitate analysis***. ***All codes to identify covariates are provided in a separate standalone code list (see Annex 1).***

Table 5 Covariates of interest

	Analyses in which covariates will be included			
Covariates	**Cohort study evaluating *safety***		**Cohort study evaluating RZV effectiveness**	
	SLE	**MS[a]**	**SLE**	**MS**
Demographics				
Age in categories: 18--49, 50-59, 60-69, ≥70	x	x	x	x
Sex	x	x	x	x
Race/Ethnicity (***where available***)	x	x	x	x
Data partner (de-identified in the final report)	x	x	x	x
Calendar year of the index date	x	x	x	
Month of the index date (to capture seasonality)	x	x	x	x

	Analyses in which covariates will be included			
Covariates	**Cohort study evaluating *safety***		**Cohort study evaluating RZV effectiveness**	
	SLE	**MS[a]**	**SLE**	**MS**
Region of residence within US Census Bureau (4 regions)	x	x	x	x
Proxies of disease severity in SLE (other than medication use) measured during the baseline period				
Lupus nephritis (as defined ***in Section 9.5.4.1***)	x		x	
SLE disease severity (mild, moderate, or severe – see ***Section 9.5.4.1 and*** Table 6)	x		x	
Number of ***hospitalized*** SLE flares in ***0***-365 days prior the index date (as defined above)[b]	x		x	
Number of ***treatment-based*** SLE flares in ***0***-365 days prior the index date (as defined above)[b]	x		x	
CCI		x		x
Other health characteristics				
Average glucocorticoid dose (oral and IV) in prednisone equivalents in the 90 days prior to the index date ***(categorical)***[c]	x	x	x	x
Immunosuppressive/immunomodulatory therapies[d] (each medication will be an individual covariate – see ***Section 9.5.4.2 and*** Table 7 and Table 8 for specific medications and time frame for measurement)	x	x	x	x
Opioid prescription fill in the 90 days prior to the index date	x	x	x	x
Comorbidities – diabetes mellitus, congestive heart failure or cardiomyopathy, chronic kidney disease, chronic obstructive pulmonary disease, stroke, depression, ***hypertension, hyperlipidemia, fibromyalgia, obesity, smoking status***, rheumatoid arthritis, inflammatory bowel disease, Combined Comorbidity Index [Gagne, 2011; Sun, 2017]	x	x	x	x
Prior pneumococcal vaccination using all data prior to the index date, as a proxy for health behaviors	x	x	x	x
Influenza vaccination in the 365 days prior to the index date (vaccines administered outside of office visits or pharmacies, for example in workplace settings, will not be captured)	x	x	x	x
Prior HZ infection >365 days prior to the index date (all available data)			x	x
Prior ZVL (Zoster Vaccine Live, Zostavax) >365 days prior to the index date using all available data			x	x
Durable medical equipment codes (wheelchair, walker, oxygen, hospital bed, lift) in the 365 days prior to the index date ***(in commercial data only)***	x	x	x	x
COVID-19 infection in the 90 days prior to the index date	x	x	x	x
COVID-19 vaccination in the 90 days prior to the index date	x	x	x	x
New immunosuppressive therapy/immunomodulatory therapy[d] within 3 months following index (descriptive only)			x	x
Healthcare utilization				
Number of ED visits in the 365 days prior to the index date (categorized 0, 1, 2-3, ≥4)	x	x	x	x
Number of hospitalizations in the 365 days prior to the index date (categorized 0, 1, ≥2)	x	x	x	x
Number of ambulatory visits in the 365 days prior to the index date (continuous, quartiles)	x	x	x	x

Codes for covariates ***are provided in a standalone code list.***

CCI

[b] ***Individuals with hospitalized and treatment-based flares/relapses in 90 days prior to the index date are excluded from the safety cohort. Therefore, these analyses the covariates for prior flares or relapses will identify those events in the 91-365 days pre-index.***
[c] ***Further information on glucocorticoid dose conversion factors is provided in the SAP.***
[d] ***Medications may be grouped in descriptive tables as needed for modelling or masking of small cells.***

9.5.4.1. Proxies for SLE disease severity

Lupus nephritis

Among patients meeting the definition for SLE, the presence lupus nephritis will be assessed as a proxy for severe disease, as:

- ≥1 visits/encounters with ICD-10-CM diagnoses of lupus nephritis (M32.14) from inpatient, ambulatory, or ED visits (all care settings) in the year prior to the index date (any diagnosis position) [Li, 2021].

  OR

- ≥3 visits/encounters with ICD-10-CM diagnoses of acute or chronic glomerulonephritis, acute or chronic renal failure, nephritis or nephrotic syndrome, renal failure or proteinuria from inpatient, ambulatory, or ED visits (all care settings), any position, in the year prior to the index date [Chibnik, 2010].

The presence of ≥3 ICD-9-CM diagnoses for renal disease (acute or chronic glomerulonephritis, acute or chronic renal failure, nephritis or nephrotic syndrome, renal failure or proteinuria) has shown a positive predictive value (PPV) of 80% for the identification of lupus nephritis [Chibnik, 2010]. A study of the lupus nephritis ICD-10-CM code M32.14 showed high PPV for lupus nephritis of 94% although low sensitivity of 33% [Li, 2021].

SLE disease severity

A validated algorithm by Garris et al. for SLE severity has been shown to predict subsequent healthcare costs and correlates with clinical disease activity measures [Garris, 2013; Speyer, 2020; Hammond, 2021; Lokhandwala, 2021]. Given changes in ***SLE treatment since this algorithm was developed, use of rituximab (currently used off-label for severe disease manifestations) is included to define severe disease [Rydén-Aulin, 2016]. Further information on the algorithms used to define SLE disease severity are provided in Table 6.***

Table 6 Algorithm for defining SLE disease severity

Mild disease
Does not meet the criteria for moderate or severe disease.
Moderate disease
Had no filled prescriptions for cyclophosphamide or rituximab or ***mycophenolate/mycophenolic acid or*** oral corticosteroid with ≥60 mg/day of prednisone equivalent dose[a] and no claims with a diagnosis of a 'severe' condition
AND
Met 1 or both of the following any time during the follow-up period:
Had ≥1 non-laboratory claims with a diagnosis of a condition listed as 'moderate', where the diagnosis occurs in any position on the claim
OR

Had ≥1 filled prescription for an oral corticosteroid with a prednisone-equivalent dose of ≥7.5 mg/day and <60 mg/day[a] or for an immunosuppressive agent (other than cyclophosphamide or rituximab) ***or mycophenolate/mycophenolic acid***).
Moderate conditions: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, hepatitis (non-viral), ischemic necrosis of bone, nephritis, renal impairment other than nephritis or end stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis, vasculitis (excluding aortitis) – codes ***are provided in a standalone code list***.
Severe disease
a) Had ≥1 filled prescriptions for cyclophosphamide or rituximab or ***mycophenolate/mycophenolic acid or*** oral corticosteroid with a prednisone equivalent dose of ≥60 mg/day[a]
OR
b) Had ≥1 non-laboratory claims with a diagnosis listed as 'severe', where the diagnosis occurs in any position on the claim.
Severe conditions: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end stage renal disease, optic neuritis, pulmonary hemorrhage, stroke/TIA – codes ***are provided in a standalone code list***.

[a] ***Further information on glucocorticoid dose conversion factors is provided in the SAP.***

9.5.4.2. Therapies for SLE and MS

Therapies to treat SLE and MS are described in Table 7and Table 8, including by medication class. Procedure codes and NDCs to assess these therapies are provided in a standalone code list.

Table 7 SLE immunosuppressive/immunomodulatory therapies

Immunosuppression category	Medications (generic name)	Time frame for measurement prior to the index date indicating active use
Anti-malarial (non-immunosuppressing)	Hydroxychloroquine, chloroquine	90 days
Less immunosuppressive	Methotrexate	90 days
	Azathioprine	90 days
	Mycophenolate mofetil, mycophenolic acid	90 days
	Tacrolimus, cyclosporine, voclosporin	90 days
	Belimumab SQ	90 days
	Belimumab IV	90 days
	Anifrolumab IV	90 days
Highly immunosuppressive	Rituximab IV	183 days
	Cyclophosphamide PO	90 days
	Cyclophosphamide IV	90 days

Note: infusion therapies dosed monthly are considered an active treatment if they have been received in the past 90 days to account for interruptions in infusion treatments. IV = intravenous, PO = by mouth; SQ = subcutaneous

Table 8 MS Immunosuppressive/immunomodulatory therapies (i.e., DMT)

Effectiveness/Immunosuppression category	Medications (generic name)	Time frame for measurement prior to the index date indicating active use
Highly effective and immunosuppressive	Alemtuzumab IV	365 days
	Cladribine PO	365 days
	Mitoxantrone IV	90 days (dosed every 1-3 months)
Highly effective and immunosuppressive, anti-CD20	Rituximab IV	183 days
	Ocrelizumab IV	183 days
	Ofatumumab SQ	90 days
	Ublituximab IV	***183 days***
Highly effective and immunosuppressing, SP1 receptor modulators	Fingolimod, Siponimod, ozanimod, ponesimod	90 days
Highly effective and less immunosuppressive therapies	Natalizumab IV	90 days (dosed every 4-6 weeks)
Less effective and less immunosuppressive therapies	Fumarates: dimethyl fumarate, diroximel fumarate, monomethyl fumarate	90 days
	Glatiramer acetate SQ or IM	90 days
	IVIG	90 days
	Interferon beta SQ or IM: recombinant human interferon beta- 1b, recombinant human interferon-1a, Pegylated recombinant interferon beta-1a	90 days
	Teriflunomide	90 days
	Azathioprine, methotrexate, mycophenolate mofetil***/mycophenolic acid*** (all uncommonly used)	90 days

Note: infusion therapies dosed monthly are still considered an active treatment if they have been received in the past 90 days to account for interruptions in treatment.
IV = intravenous, IM = intramuscular, PO = by mouth; SQ = subcutaneous

9.6. Data sources (*Amended 12 Dec 2025)*

9.6.1. Research Partners

This study will be conducted using health plan data held by ***six Research*** Partners that participate in the FDA's Sentinel System. ***Three*** are national insurers that update their curated Sentinel database 3 to 4 times per year (CVS Health/Aetna, ***Carelon [formerly*** HealthCore***], and*** Humana***); Point32Health (***Harvard Pilgrim Health Care ***and Tufts Health Plan), HealthPartners,*** and Kaiser Permanente Mid-Atlantic States are regional insurers. This study will use the most recently available approved SCDM of the research portion of the population at each ***Research*** Partner at the time of analysis. In addition to providing claims data, the ***Research*** Partners will provide scientific input and feedback to support this study.

In the event that a Research Partner has inadequate sample size to perform any of the specified analyses for this study, the study team may choose to exclude this Partner from the respective analysis.

To ensure greater capture of persons with SLE and MS exposed to RZV beyond those covered by commercial insurers, we will also use data from CMS to examine ***FFS Medicare beneficiaries,*** including older patients ≥65 as well as patients <65, given the substantial number of younger patients with SLE and MS who have Medicare due to disability [Garris, 2015]. CMS Research Identifiable Files (RIF) will be obtained and transformed into the Sentinel Common Data Model (SCDM) using publicly available tools. The proposed CMS RIF data contain patient-level information from Medicare beneficiaries with full fee-for-service inpatient and outpatient medical coverage (Parts A & B***) and prescription drug coverage (Part D).***

Brief descriptions of the ***Research*** Partners are provided below:

- Aetna, a CVS Health company, is one of the leading healthcare benefits companies ***in the US, currently*** serving ***39*** million people***.*** Aetna became ***part of the Sentinel System in 2008. Aetna's SCDM captures longitudinal information on dispensed prescriptions, inpatient and outpatient diagnoses, inpatient and outpatient treatments and procedures, and outpatient laboratory results. The healthcare experience for over 41 million individuals is available for research, covering all ages. As of January 2025,*** CVS Health ***includes approximately 4.2 million members aged 18 years and older actively enrolled with ≥365 days of medical and prescription coverage who are research eligible. Among them, approximately 1.7 million are 18-59 years of age***.
- ***Point32Health is the second largest New England based health plan. It provides care to 2.2 million individuals under the names, Harvard Pilgrim Health Care and Tufts Health Plan. Harvard Pilgrim Health Care participated in the Sentinel System and HPHCI is currently a site for the CDCs Vaccine Safety Datalink. As of September 2023, there are approximately 248 000 current members with both medical and drug coverage, who are ≥50 years of age, and are research eligible. Although Point32Health is smaller than the other RPs, it has the important advantages of being the institutional home of HPHCI. Designated HPHCI personnel have direct access to certain Point32Health data, providing the ability to work directly with source data to understand apparent anomalies in any analyses performed within this distributed data network.***
- ***Carelon Research (formerly*** HealthCore***)*** 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 ***approximately 88*** million unique individuals with medical coverage and more than ***67*** million ***individuals withmedical*** and pharmacy claims information since 2006. In addition, ***Carelon*** Research ***can*** 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. ***Carelon Research has been a partner within the Sentinel Initiative since 2008. As of January 2025, Carelon Research includes approximately 94 million members aged 18 years and older years actively enrolled***

with ≥365 days of medical and prescription coverage who are research eligible. Among them, approximately 14.9 million are 18-59 years of age.

- **HealthPartners** ***is an active collaborator and RP in the FDA Sentinel System.*** HealthPartners is the largest consumer-governed ***non-profit health care*** organization in the ***country***, providing care, coverage, research, and education to ***improve health and well-being in partnership with*** its members***,*** patients ***and community. Included under HealthPartners' umbrella are Regions Hospital, HealthPartners Care Group, HealthPartners Center for Memory & Aging, Park Nicollet Methodist Hospital and HealthPartners Institute. HealthPartners has formal relationships with hospitals and clinics throughout Minnesota and western Wisconsin, including Westfields Hospital (New Richmond, WI), Lakeview Hospital (Stillwater, MN), Hudson Hospitals and Clinics (Hudson, WI), Amery Hospital and Clinic (Amery, WI), St Francis Regional Medical Center (Shakopee, MN), Hutchinson Health (Hutchinson, MN), TRIA Orthopedic Center, and Physicians Neck and Back Clinic. Founded in 1957, the HealthPartners family of care*** serves more than 1.8 million medical and dental health plan members***. As of September 2023, there are approximately 247 000 current members with both medical and drug coverage, who are ≥50*** years ***of age,*** and ***are*** research ***eligible.*** HealthPartners ***is one*** of the ***top-ranked commercial*** health ***plans*** in ***Minnesota and is also one of the highest rated plans*** in the ***nation, according to the National Committee for Quality Assurance's Health Insurance Plan Rankings 2021- 2022***.
- Kaiser Permanente Mid-Atlantic States (KPMAS) is an integrated healthcare delivery system providing comprehensive medical services, and currently serving ***between 750 000 and*** 800 000 members at 35 Kaiser Permanente Medical Centers in the District of Columbia (DC), Maryland, and northern Virginia. KPMAS is composed of the Kaiser Foundation Health Plan of the Mid-Atlantic States, a non-profit health care organization with more than ***8000*** employees, and the Mid-Atlantic Permanente Medical Group (MAPMG), a multi-specialty group practice of over ***1,700*** physicians (including internal medicine/family practice, obstetricians/gynecologists, pediatricians, and specialists) and support personnel who provide or arrange health care for members of the health plan.
- Humana Healthcare Research (HHR) a subsidiary of Humana Inc., ***is an active collaborator 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 for vaccine safety. Humana includes members throughout the US, with the highest concentration of members in the South. As of October 2024, Humana includes approximately 4.2 million members aged 18 years and older actively enrolled with ≥365 days of medical and prescription coverage who are research eligible. Among them, approximately 0.3 million are 18-59 years of age.***
- Medicare provides health insurance to US residents aged 65 and over, as well as to younger individuals in special populations. It is estimated that over 98% of adults aged 65 years and over are enrolled in Medicare, making Medicare data one of the richest sources of utilization information in the country. Furthermore, over 99% of deaths in the US among persons aged 65 and older are accounted for by the Medicare program. ***There are over 66 million beneficiaries enrolled in the Medicare program***

as of December 2023, allowing for detailed sub-group analyses with reduced concerns about loss of statistical power [Medicare Tables and Reports, 2022].

9.6.2. Sentinel System and Common Data Model

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 US, established under the Sentinel Initiative [Sentinel Initiative , 2021]. 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. The system does not link patients who have enrollment periods with more than 1 Data Partner.

The ***Research*** Partners use the Sentinel Common Data Model (SCDM) [Sentinel] 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 Data 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. The data are organized as:

- Ambulatory Visits (AV): includes visits at outpatient clinics, same day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes Emergency Department encounters. Transfer from AV facility to an ED facility starts a new encounter at the new facility
- Emergency Department (ED): includes ED encounters that become inpatient stays through hospital admission. In this scenario, ED is 1 encounter, Inpatient Hospital Stay after admission from the ED is a second encounter. ED data should be identified before hospitalization data to ensure that ED with subsequent admission won't be rolled up in the hospital event. Transfer from one ED facility to another ED facility starts a new encounter at the new facility. Excludes urgent care visits.
- Inpatient Hospital Stay (IP): includes all inpatient stays, same-day hospital discharges, and other acute hospital care where the discharge is after the admission date. Transfer from one facility to another starts a new encounter at the new facility.
- Non-Acute Institutional Stay (IS): includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays. Transfer from one facility to another starts a new encounter at the new facility.
- Other Ambulatory Visit (OA): includes other non-overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

When capturing ambulatory visits, OA and AV settings will be used. IP will be used when capturing only inpatient settings (IS will only be used when all settings is specified). ED will be used when capturing only ED settings. All setting (AV, ED, IP, IS, OA) will be used when capturing “any care settings”. Any revisions to this implementation will be reflected in the technical specifications.

- 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 Healthcare Common Procedure Coding System (HCPCS) levels II and III codes.

9.7. Study Sample Size *(Amended 12 Dec 2025)*

As this study uses a real-world database, study sample size is dependent on real world uptake of RZV. As such, all patients meeting eligibility criteria at the time of analysis will be included in the final analytical cohort. The sample size estimates below provide guidance on the minimum sample meeting eligibility criteria that will need to be accrued in the database to provide 80% power to detect a specific effect size. It is possible that at the time of analysis more patients than estimated below will be vaccinated and included in the analysis. If less patients are accrued at the time of analysis than estimated below, a decision can be made regarding whether the accrual should be extended. Alternatively, given the sample accrued at the time of analysis, an estimate can also be made to determine the effect size for which the sample is 80% powered to detect.

All power calculations below evaluate necessary sample sizes for different effect sizes ***(minimum detectable HRs)*** with a power of 80% and alpha of 0.05. The primary method for the sample size calculation ***uses*** the Schoenfeld formula [Schoenfeld, 1983] for log rank test to calculate the needed number of events per group in the cohort study, and uses the observed or literature-based incidence rate of outcomes, observed average length of follow-up, and assumed attrition rate to calculate the required numbers of vaccinated and unvaccinated subjects. The specific steps are described below. ***All power calculations are performed using R open-source statistical software.***

a. To calculate the sample size for comparing two survival functions based on log-rank test, the Schoenfeld formula [Schoenfeld, 1983] for the needed total number of events is

$$N.events = \frac{(z_{1-\alpha/2}+z_{\beta})^2}{p_1 * p_2 (log\ HR)^2}$$

where:

- $z_{1-\alpha/2}$ ***and*** z_{β} ***are standard normal percentiles (here,*** α ***=0.05,*** β***=0.80,*** $z_{1-\alpha/2}$***=1.96,*** z_{β}***=0.84),***
- p_1 ***and*** p_2 ***are the proportions to be allocated to groups 1 and 2 (here, p1=0.2 and p2=0.8 to reflect the targeted 1:4 ratio for the sample sizes of the vaccinated and unvaccinated groups), and***
- ***HR is calculated as log(1-incidence.Vac)/log(1-incidence.unVac), where:***

incidence.Vac =1−(1−incidence.unVac)^HR [Schoenfeld, 1983].

b. Now we need to calculate the proportion of patients in the cohort study who will have outcome, as:

$$d = incidence.Vac * (p_1) + incidence.unVac * (1 - p_1)$$

c. Number of needed person-year is then:

$$N.person.years = N.events/d$$

d. Numbers of events for vaccinated and unvaccinated groups are:

$$N.event.Vac = N.person.years * p_1 * incidence.Vac$$

$$N.event.unVac = N.person.years * p_2 * incidence.unVac$$

e. Number of needed person-years per group is:

$$n.vaccine.grp = N.event.Vac / incidence.Vac$$

$$n.unvaccine.grp = N.event.unVac / incidence.unVac$$

f. Number of needed subjects per group is calculated by dividing follow-up time in years by a function of attrition rate, as follows:

$$nsubj.vaccine.grp = \frac{ceiling((n.vaccine.grp/avg.followup.time)}{(1-attrition.vaccinated)\text{^}avg.followup.time}$$

$$nsubj.unvaccine.grp = \frac{ceiling((n.unvaccine.grp/avg.followup.time)}{(1-attrition.unvaccinated)\text{^}avg.followup.time}$$

where attrition rate is assumed to be 7% among the vaccinated and 15% among the unvaccinated (due to the receipt of RZV among the unvaccinated).

Follow-up for safety is 0.25 years, based on the 90-day follow-up period used in this analysis. ***Follow-up for effectiveness is 1.32 years, based on the shortest observed follow-up time of any cohort observed during the interim analysis, though the follow-up may be longer for the final analysis.***

9.7.1. Power calculations for safety analyses

Power calculations for ***primary*** safety ***objective 1*** assessing the risk of ***hospitalized*** SLE flares include the following assumptions:

- A ***hospitalized*** flare rate in ***unvaccinated*** SLE ***comparators*** of ***between 1-6*** per 100 person-years ***was assumed based on the results of monitoring analyses completed in October 2025 among commercially insured patients. The results of this monitoring analyses revealed a background rate of hospitalized flare among unvaccinated adults of 1.97*** per 100 person-years***, with rates for sensitivity flare outcome definitions ranging from 5.00 to 6.64 per 100 person-years.***
- A ***50%*** increase in the risk of ***hospitalized*** SLE flares (***target HR=1.51, 0.25***% absolute increase in risk over 90 days) would be important to detect, although sample size needs for other effect sizes ***were*** assessed.
  - The maximum amount of follow-up time after each vaccine dose is 90 days. The actual amount of follow-up time is likely to be less than 90 days for many patients, especially after RZV dose 1 (because of censoring at RZV Dose 2). Because patients can contribute follow-up time after both vaccine doses ***to the primary safety objective***, however, the total amount of follow-up time will be more than 90 days in most patients – the 90 day estimates below are conservative. ***They do not otherwise account for the combining of information from the Dose 1 and Dose 2 analyses.***

- A cohort of patients without vaccination will be identified to achieve a ratio of 4:1 (unvaccinated to vaccinated).
- Censoring rate of 7% per year in the RZV vaccinated group (due to death, ***flare***, or end of enrollment) and 15% in the RZV unvaccinated group (due to death, ***flare***, end of enrollment, or RZV vaccination), based on estimates from prior studies.
- ***Power calculations were not estimated for secondary or*** CCI [redacted] ***safety objectives.***

Table 9 Sample size calculation for final SLE safety analyses under a range of assumed incidence rates for unvaccinated and vaccinated group and assumed *minimal detectable* hazard ratio under *a 4:1 matched* cohort design

Incidence rate of *hospitalized* flare in unvaccinated	Incidence rate *of hospitalized flare* in vaccinated	Effect size (percent increase in risk)	*Minimum Detectable* Hazard Ratio	Required number of unvaccinated patients (after adjusting for attrition)	Required number of vaccinated patients (after adjusting for attrition)
1	*2*	*100%*	*2.01*	*28,328*	*6,925*
1	*1.75*	*75%*	*1.76*	*44,992*	*11,173*
1	*1.5*	*50%*	*1.50*	*89,567*	*21,996*
1	*1.4*	*40%*	*1.40*	*132,475*	*32,586*
1	*1.3*	*30%*	*1.30*	*222,041*	*54,207*
2	*4*	*100%*	*2.02*	*13,956*	*3,463*
2	*3.5*	*75%*	*1.76*	*22,288*	*5,471*
2	*3*	*50%*	*1.51*	*44,367*	*10,864*
2	*2.8*	*40%*	*1.41*	*65,405*	*16,004*
2	*2.6*	*30%*	*1.30*	*109,771*	*26,790*
3	*6*	*100%*	*2.03*	*9,165*	*2,241*
3	*5.25*	*75%*	*1.77*	*14,723*	*3,573*
3	*4.5*	*50%*	*1.51*	*29,162*	*7,153*
3	*4.2*	*40%*	*1.41*	*43,051*	*10,575*
3	*3.9*	*30%*	*1.31*	*72,349*	*17,756*
4	*8*	*100%*	*2.04*	*6,770*	*1,683*
4	*7*	*75%*	*1.78*	*10,832*	*2,681*
4	*6*	*50%*	*1.52*	*21,559*	*5,296*
4	*5.6*	*40%*	*1.41*	*31,869*	*7,858*
4	*5.2*	*30%*	*1.31*	*53,532*	*13,084*
5	*10*	*100%*	*2.05*	*5,333*	*1,304*
5	*8.75*	*75%*	*1.79*	*8,582*	*2,098*
5	*7.5*	*50%*	*1.52*	*16,997*	*4,184*
5	*7*	*40%*	*1.41*	*25,246*	*6,171*
5	*6.5*	*30%*	*1.31*	*42,326*	*10,342*
6	*12*	*100%*	*2.07*	*4,375*	*1,088*
6	*10.5*	*75%*	*1.79*	*7,016*	*1,711*
6	*9*	*50%*	*1.52*	*14,027*	*3,442*
6	*8.4*	*40%*	*1.42*	*20,763*	*5,092*
6	*7.8*	*30%*	*1.31*	*34,856*	*8,514*

Note: Incidence rates are given per ***100*** person-year***s*** (although absolute rates are lower given a 90-day follow-up period).

Results of the monitoring queries conducted in October 2025 indicate a sample of 9544 dose 1 vaccinated, 7456 dose 2 vaccinated and 110893 unvaccinated individuals with pre-existing SLE are available among commercial Research Partners with data through April 2025. As such, it is expected that the primary safety objective will reach appropriate 80% power to detect a HR=1.51, assuming an incidence rate of 2 per 100 person years among unvaccinated and 3 per 100 person years among vaccinated (in line with observed rates among the unvaccinated). Notably, as we expect similar rates among the commercially insured and Medicare populations, the same sample size target is applied to both populations. Further, it is expected the sample would increase at the time the final analysis is completed given that a longer duration of data will be available at that time.

9.7.2. Power calculations for effectiveness analyses

Power calculations for the effectiveness analyses include the following assumptions:

- The incidence of HZ in unvaccinated adults >65 YOA in the general population is approximately 10 ***per*** 1000 person-years [Izurieta, 2021], but a meta-analysis showed an approximately 2-fold higher risk in patients with SLE [Kawai, 2017]. Studies in SLE have shown rates of HZ of approximate 15-20 per 1000 person-years even among younger patients [Chakravarty, 2013; Chen, 2014; Yun, 2016]. Rates of HZ in MS are lower than in SLE, although are similar to that seen in the >65 YOA general population even among younger patients with MS, with an expected overall rate of HZ in the MS population of approximately 10 ***per*** 1000 person-years and a rate of approximately 8 ***per*** 1000 person-years in patients 18-49 YOA [Chen, 2014].
- Greater number of unvaccinated than vaccinated patients (4:1 ratio).
- Average follow-up time of ***1.32*** years based on ***the shortest observed follow-up in any cohort during the interim analysis. This is expected to be a conservative approach***.
- Possible lower effectiveness given immunosuppression: expect 70% VE but evaluate sample size needs for lower VE (range 40-70%).
- Censoring rate of 7% per year in the RZV vaccinated group (due to death, HZ occurrence, or end of enrollment) and 15% in the RZV unvaccinated group (due to death, HZ occurrence, end of enrollment, or RZV vaccination) based on estimates from prior studies.

Based on these results, with a baseline incidence of HZ of 20/1000 person-years in SLE in the overall population and VE of 50% (HR=0.5), sample size requirements are 912 vaccinated patients with SLE with 4,474 unvaccinated patients to provide 80% power. Results of the monitoring queries conducted in October 2025 indicate a sample of 9544 dose 1 vaccinated, 7456 dose 2 vaccinated and 110893 unvaccinated individuals with pre-existing SLE are available among commercial Research Partners with data through April 2025, therefore this sample size target is feasible.

With a baseline incidence of HZ of 10 per 1,000 person-years in MS and VE of 50% (HR=0.5), sample size requirements are 1,727 vaccinated patients with MS with 8,648 unvaccinated patients to provide 80% power. Among patients with MS, 11689 dose 1 vaccinated, 9284 dose 2 vaccinated and 123 761 unvaccinated individuals were identified in monitoring queries conducted in October 2025 among commercial Research Partners with data through April 2025, therefore this sample size target is feasible.

It is expected that sample size will be sufficient to detect an even smaller effect size (e.g., VE of 40%) as shown in Table 10.

Table 10 Sample size calculation for final effectiveness analyses under a range of assumed incidence rates for unvaccinated and vaccinated group and assumed assumed *minimal detectable* hazard ratio under *a 4:1 matched* cohort design

Incidence rate in unvaccinated	Incidence rate in vaccinated	Effect size (percent reduction)	Hazard Ratio	Required person- years for vaccinated patients	Required person-years for unvaccinated patients	Required number of vaccinated patients (after adjusting for attrition)	Required number of unvaccinated patients (after adjusting for attrition)
20	*6*	*70%*	*0.30*	*500*	*1,600*	*417*	*1,503*
15	*4.5*	*70%*	*0.30*	*667*	*2,134*	*557*	*2,004*
10	*3*	*70%*	*0.30*	*1,000*	*3,200*	*834*	*3,005*
8	*2.4*	*70%*	*0.30*	*1,250*	*4,000*	*1,043*	*3,756*
20	*8*	*60%*	*0.40*	*750*	*2,650*	*626*	*2,488*
15	*6*	*60%*	*0.40*	*1,000*	*3,534*	*834*	*3,318*
10	*4*	*60%*	*0.40*	*1,500*	*5,400*	*1,251*	*5,070*
8	*3.2*	*60%*	*0.40*	*1,875*	*6,750*	*1,564*	*6,338*
20	*10*	*50%*	*0.50*	*1,200*	*4,500*	*1,001*	*4,225*
15	*7.5*	*50%*	*0.50*	*1,600*	*6,000*	*1,334*	*5,634*
10	*5*	*50%*	*0.50*	*2,400*	*9,100*	*2,001*	*8,544*
8	*4*	*50%*	*0.50*	*3,000*	*11,375*	*2,502*	*10,680*
20	*12*	*40%*	*0.60*	*2,084*	*8,100*	*1,738*	*7,605*
15	*9*	*40%*	*0.60*	*2,778*	*10,800*	*2,317*	*10,140*
10	*6*	*40%*	*0.60*	*4,167*	*16,300*	*3,475*	*15,304*
8	*4.8*	*40%*	*0.60*	*5,209*	*20,375*	*4,343*	*19,129*

Note: Incidence rates are given per 1,000 person-years. All power calculations performed using R statistical software.

9.8. Data management

9.8.1. 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 Data Partners. The distributed network will allow Data Partners to maintain physical and operational control of their data while allowing use of the data to meet the study needs. HPHCI will maintain a secure distributed querying web-based portal to enable secure distribution of analytic queries, data transfer and document storage.).

9.8.2. 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. HPHCI 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.

9.9. 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 quality assurance (QA) Standard Operating Procedures (SOP) will be followed. All the statistical calculations will be done in SAS 9.***4*** or higher. An outline of planned analyses is described below. Additional analysis details will be provided in the SAP.

9.9.1. Descriptive analyses *(Amended 12 Dec 2025)*

All analyses will be conducted separately in SLE and MS populations. First, descriptive analyses of the study populations will be conducted comparing the baseline characteristics in the vaccinated and unvaccinated groups.

Additionally, temporal patterns of vaccination will be evaluated using histograms of the number of RZV vaccinations ***and outcomes*** by year-month. The COVID-19 pandemic could potentially impact results by affecting not only the rates of vaccination, but more

importantly the capture of outcomes, with patients avoiding interactions with the healthcare system early in the pandemic beginning March 2020 [George, 2020; Moynihan, 2021; George, 2021]. Vaccination rates will be examined descriptively to evaluate the trend in RZV vaccination and to determine when RZV vaccination rates begin to rebound after 01 March 2020. This examination will inform what time period is the most likely to be potentially affected by the pandemic in the planned analyses. Sensitivity analyses will be conducted excluding the time period most likely to be affected by the pandemic (***see Sections 9.9.2.2.1 and 9.9.3.1***).

Descriptive information on the number of days between the 2 doses for 2-dose recipients, with the frequency of shorter intervals <2 months between doses of particular interest in this population. Additionally, the frequency of receiving RZV doses <28 days apart will be ***described***. Distributions of ***study outcomes***, by vaccination status, will be collected through the follow-up period and graphed ***using Kaplan Meier curves***.

9.9.2. Analysis for safety objectives *(Amended 12 Dec 2025)*

9.9.2.1. Primary safety objective 1

To evaluate ***risk of hospitalized SLE flare*** after any dose of RZV, separate cohorts will be created for RZV dose 1 and RZV Dose 2, each with matched unvaccinated comparators. This approach allows potential confounders to be balanced separately at RZV Dose 1 and RZV Dose 2, which is particularly important given that doses may at times be separately significantly in time, while important confounders such as medications may also change over this timeframe. In addition, this approach simplifies the key secondary analysis that separately assesses RZV Dose 1 and RZV Dose 2 ***(see Section 9.9.2.2).***

Following matching of unvaccinated to vaccinated patients on data partner, sex, and age and the assignment of a matched index date in unvaccinated patients as described in Section 9.4.1, propensity scores based on the likelihood of receiving RZV Dose 1 versus no RZV vaccination will be calculated using logistic regression models with RZV vaccination as the dependent variable and independent variables as outlined in Table 5. Propensity scores will be used to balance measured confounders, through inverse probability weighting, among patients receiving RZV Dose 1 and comparator patients with no prior RZV vaccination. Calendar month and year of the index date will also be included in the propensity score to ensure balance is maintained. The same process will be used to calculate propensity scores for the cohort of patients receiving RZV Dose 2 matched to unvaccinated patients. An unvaccinated patient may serve as a comparator for both the Dose 1 and Dose 2 cohorts, although separate index dates will be applied.

Covariate balance will be assessed before and after applying propensity scores using standardized mean differences, with ***absolute*** standardized differences >0.1 suggestive of important imbalance [Austin, 2009a; Austin, 2009b]. Any imbalanced factors after weighting suggests residual confounding, therefore ***adjustments to the propensity score model or alternative modeling strategies will be considered***.

The risk of hospitalized SLE flares will be assessed in each cohort (Dose ***1 or Dose 2)*** using time-to-event analysis with Cox proportional hazard models, assessing violations of the proportional ***hazard*** assumptions (***based on visual assessment of Kaplan-Meier plots and additional diagnostics [e.g., Schoenfeld residual or log(−log) plots]).***

To assess the risk of hospitalized SLE flares after any dose of RZV, risk assessments after RZV Dose 1 and Dose 2 will be combined to provide a single risk estimate using the bootstrapping method outlined in the SAP; specialized methods are required to properly account for the correlation between two estimated risks given the expected overlap in the two cohorts.

- Patients will be followed until the earliest of:
- Occurrence of ***hospitalized*** SLE flare
- End of enrollment
- Death
- End of data availability or study period
- RZV dose (***any subsequent*** dose for vaccinated patients or first RZV dose in the case of ***unvaccinated comparators***)
- End of 90-days of follow-up

9.9.2.2. Secondary safety objective 1

This analyses will use the same methods (IPTW Cox proportional hazards models) as the primary analyses, except risk assessments after RZV Dose 1 and Dose 2 ***will be reported separately; they will not*** be combined to provide a single risk estimate; ***thus no bootstrapping will be performed***. ***This analysis will also inform whether there is evidence for different effects by dose***.

9.9.2.2.1. Sensitivity analyses for secondary safety objective 1

The following sensitivity analysis detailed below will be conducted for secondary safety objective 1. These analyses will use the same methods (i.e. IPTW Cox proportional hazards regression) as described in Section 9.9.2.2

- ***Repeating analyses using sensitivity outcome definitions of treatment-based SLE flare, and hospitalized or treatment-based SLE flare (as defined in Table 2***
- Repeating the analyses restricted to patients with SLE who are currently treated with a non-glucocorticoid immunosuppressive/immunomodulatory therapy at the index date (expected to have even less misclassification of SLE or MS diagnoses)
- Repeating the ***analyses*** after excluding patients who also have administration of other ***influenza, pneumococcal or COVID-19*** vaccinations within 7 days before or after receipt of RZV to avoid flare/relapse outcomes that could be related to a different vaccine

- Repeating the analyses after excluding time during the height of the COVID-19 pandemic as outlined ***in Section 9.9.1***
- Repeating the Dose 2 analysis limiting to patients who received Dose 2 within 6 months after Dose 1

9.9.2.2.2. Stratified analyses for secondary safety objective 1

Pre-specified stratified analyses will be undertaken to assess potential effect modifiers that could result in differential risks of ***hospitalized*** SLE flares after RZV. ***Stratified analyses will use the same methods (i.e., Cox proportional hazards regression) as described in Section 9.9.2.2, except strata will be treated as separate cohorts and*** propensity scores will be recalculated within each ***strata*** to ensure covariate balance ***in each analysis***. ***If any strata has inadequate*** sample size***, exposure or outcome counts to allow for regression modelling, descriptive results will be shared instead of inferential results.***

Specific strata for the final analyses are as follows:

- Age (18-49, ≥50)
- Sex (male, female)
- Race/ethnicity (where race/ethnicity data is available in sufficient numbers)

SLE disease severity:

- SLE disease severity (mild, moderate, severe)
- Lupus nephritis (yes, no)

CCI [redacted]

- CCI [redacted] ***Table 3.*** CCI [redacted]

9.9.3. Analysis of effectiveness objectives *(Amended 12 Dec 2025)*

We will use a retrospective cohort design with Cox proportional hazards modeling to assess the risks of HZ and incidence of PHN after RZV vaccination. In the primary analysis patients receiving a second dose of RZV separated by ≥28 days after Dose 1 will be compared to patients with no prior RZV vaccination.

Following matching of unvaccinated to vaccinated patients on data partner, sex, and age and the assignment of a matched index date in unvaccinated patients as described in Section 9.9.2.1 propensity scores based on the likelihood of receiving 2 doses of RZV (versus no RZV vaccination) will be calculated using logistic regression models with RZV vaccination as the dependent variable and independent variables as outlined in Sections 9.5.4 and 9.9.2.1. Propensity scores will be used to balance measured confounders (e.g., through inverse probability weighting) among patients receiving RZV Dose 2 and unvaccinated comparators. Covariate balance will be assessed before and after applying propensity scores using standardized mean differences, with ***absolute*** standardized differences >0.1 suggestive of important imbalance [Austin, 2009a; Austin, 2009b]. ***If any*** covariate ***demonstrates*** imbalance after weighting, suggesting residual confounding, ***adjustments to the propensity score model or alternative modeling strategies*** will be ***considered***. Similarly, in secondary analyses assessing the effectiveness of a single RZV dose, the same approach will be used, noting that propensity scores will be estimated at Dose 1 and receipt of RZV Dose 2 will be a censoring event.

9.9.3.1. Analysis of primary effectiveness objectives 1 and 2

IPTW Cox proportional hazards models will be used for time-to-event analyses assessing risk of HZ, with follow-up beginning 30 days after the index date (to allow the development of immunity), assessing for violations of the proportional hazards assumptions ***based on a visual assessment of Kaplan-Meier plots and other diagnostics. Vaccine effectiveness is calculated as VE = (1 - HR)*100.***

- Patients will be followed from the index date (Dose 2) +31 days until the earliest of one of the following events:
- Occurrence of HZ
- End of enrollment
- Death
- End of data availability or end of defined study period
- RZV dose (***receipt of a third*** dose for vaccinated patients or first RZV dose in the case of ***unvaccinated comparators***)
- ZVL vaccination

9.9.3.1.1. Sensitivity analysis of primary effectiveness objectives 1 and 2

Similar methods as described in Section 9.9.3.1 will be implemented in these sensitivity analyses detailed below. In each case (unless otherwise noted) propensity scores will be re-estimated among the subset of patients being analysed.

- ***Estimating 2-dose VE in*** patients with SLE or MS who are currently treated with a non-glucocorticoid immunosuppressive/immunomodulatory therapy at the index date (expected to have even less misclassification of SLE or MS diagnoses).
- ***Estimating 2-dose VE after*** exclusion of time during the height of the COVID-19 pandemic.

9.9.3.1.2. Stratified analysis of primary effectiveness objectives 1 and 2

Pre-specified stratified analyses will be undertaken among patients receiving two doses of RZV to assess potential effect modifiers that could result in differential VE, ***if sufficient sample size is available***. Propensity scores will be recalculated within each ***strata*** to ensure covariate balance within ***the analysis. If any strata has inadequate sample size, exposure or outcome counts to allow for regression modelling, descriptive results will be shared instead of inferential results***.

Specific ***strata*** for the final analyses are as follows:

- SLE disease severity variables, which may affect HZ risk:
  - SLE disease severity (mild, moderate, severe)
  - Lupus nephritis ***(yes/no)***
- MS disease severity variable, which may affect HZ risk:
  - MS relapse in the 91-365 days prior to the index date ***(yes/no)***

9.9.3.2. Analysis of secondary effectiveness objectives 1 to 8

Similar methods as described in Section 9.9.3.1 will be implemented for the analysis of secondary objectives 1-8, with specific deviations as described below.

9.9.3.2.1. Secondary effectiveness objectives 1 and 2:

- ***For secondary VE objectives 1 and 2, the effectiveness of 1 RZV dose will be evaluated using Cox proportional hazards models, with IPTW to balance covariates as described above. However, in these analyses, propensity scores will be estimated at Dose 1 and receipt of RZV Dose 2 will be a censoring event.***

9.9.3.2.2. Secondary effectiveness objectives 3 and 4:

- ***For secondary VE objectives 3 and 4, the effectiveness of 2 doses of RZV within key strata will be evaluated using Cox proportional hazards models, using data handling and analytic methods detailed in Sections 9.9.3.1.2.***
- ***The results will be stratified by:***
  - ***Age (18-49 years; ≥50 years)***
  - ***Sex (male; female)***
  - ***Race/ethnicity (where adequate race/ethnicity data are available)***

9.9.3.2.3. Secondary effectiveness objectives 5 and 6:

- ***For secondary VE objectives 5 and 6, the effectiveness of 2 doses of RZV will be evaluated using Cox proportional hazards models, with IPTW to balance covariates. Specific modelling changes will allow VE to be modelled by:***
  - Time since vaccination, in 1-year blocks, to assess waning immunity
  - Time between RZV doses, categorized depending on distribution of dosing in the cohort (e.g., 28-56 days, 57-183 days, >183 days), to determine the effects of vaccine spacing on VE

9.9.3.2.4. Secondary effectiveness objectives 7 and 8:

- Assessment of the incidence of PHN will be conducted using the same methods as those in ***Section 9.9.3.1***, except the outcome being evaluated will be PHN ***and only incidence will be estimated***.

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9.10. Quality control

The distributed network utilizes a common data model that enables data standardization across Research Partners. 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 quality assurance procedures as the Sentinel System and the same curated datasets used by FDA to conduct Sentinel analyses. The quality assurance 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 quality assurance processes and details on the Sentinel data curation approach are documented on the Sentinel website [Sentinel Initiative , 2021]. The data curation approach is consistent with guidance set forth by the FDA in its current recommendations for data quality assurance, 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].

In addition to quality assurance of data elements, HPHCI adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check SAS programs and deliverables. 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.

9.11. Limitations of the research methods *(Amended 12 Dec 2025)*

Confounding, bias, and misclassification are concerns in any observational study.

1. Definition of the cohorts: The algorithms for SLE have not been validated and some misclassification is also expected using the validated MS algorithm. In addition, some patients with well controlled MS may not be captured, with algorithms biasing towards a higher risk group. However, to increase confidence in the definitions, neurologists and rheumatologist were consulted to provide expert opinion on the definitions for SLE and MS, these algorithms have been used in prior studies as described in detail above and additional subgroup analyses are planned examining patients with lupus nephritis (which has been validated) and a more restrictive subgroup of patients on immunosuppressive therapy.
2. Definitions of outcomes:
   - This study implements a definition of mild, moderate, or severe SLE flares based on previously published algorithm by Garris et al 2013 ***for interim analyses***. It is expected that misclassification may be more substantial for mild/moderate flares, as such severe flares will be used as a primary definition in this study. Algorithms for MS relapses are not validated, and do not

differentiate by types or severity. However, neurologists and rheumatologist provided consultations on these algorithms, and this study will evaluate 5 separate definitions of MS relapses. Further chart review will be conducted to further validate the flare and relapse event [Mozaffarian, 2016; Katz, 2020].

- ***Updated outcome algorithms were developed based on findings of the chart review and with clinical input to increase algorithm specificity for final analyses. This is expected to reduce the outcome rate for final analyses, but improves validity of the study findings.***
  - ***The updated SLE flare algorithm represents a component of the SLE flare algorithm used for interim analyses. The PPV of this component of the algorithm was >70% among the subgroup of adjudicated cases that met this definition. However, this PPV estimate is based on a small sample of cases.***
  - CCI [redacted]
- Use of glucocorticoids as a part of the flare definition: As with any analysis of claims data, there is a possibility of misclassification of medication use and dosage, as prescribed/filled medication or dose does not equate to actual consumption.

3. Exposure misclassification: Some patients thought to be unvaccinated may have received RZV prior to entering the dataset, leading to an underestimate of VE. Noting that among those vaccinated earlier in the study period, the likelihood of this occurrence is minimal given that the study accrual period starts 01 January 2018, and RZV was not available in the US prior to October 2017.
4. Outcome misclassification: As with any claims-based data source, outcome identification is dependent on patients presenting to health care providers. Outcomes asseses in this study will be unobserved if a patient does not seek health care services resulting in outcome misclassification.
5. ***The mean follow-up time for effectiveness analyses is expected to be at least 1.32 years, based on interim analyses. The ability to assess durability of VE at later time points is limited.***
6. Secular or seasonal trends in RZV use: Shingrix was not approved for use in people under the age of 50 until July 2021, and thus use in younger immunosuppressed patients was limited. Additionally, RZV vaccination patterns may have also changed during the COVID-19 pandemic. As described above, the methods will ensure similar distributions by calendar year and season among vaccinated and unvaccinated patients and impact of the COVID-19 pandemic will be assessed in sensitivity analyses.
7. Secular trends in medication use for SLE and MS: Newly approved therapies are available for both conditions and may primarily be used for those with more severe disease initially and then after a few years on the market, may be used in less severe disease or disease subsets. Some medications, such as belimumab, have been

approved for new indications over time (e.g., lupus nephritis). These trends may impact differences in patient populations and differences in the classification of disease severity. As described above, the methods will ensure similar distributions by calendar year and season among vaccinated and unvaccinated patients.

8. Alternative reasons for SLE flare or MS relapses and/or HZ: We have not incorporated alternative reasons for flare in this protocol such as COVID vaccination, which has been reported to be associated with flares of inflammatory conditions, and VZV reactivation [Fan, 2012; Rotondo, 2021; Zavala-Flores, 2021; Heshin-Bekenstein, 2022; Fragoso, 2022; Michelena, 2022]. This is beyond the scope of the current protocol but may be considered descriptively in sensitivity analyses. COVID vaccination is likely to be under-captured in administrative datasets because they can be obtained from numerous different sites and do not require a prescription nor an insurance claim. Additionally, propensity score methods are implemented to address measured confounders of interest likely to be associated with flares, relapses or HZ.

9. Medication initiations following RZV vaccination: Some patients may receive vaccination preferentially around the time of a new therapy initiation (e.g., SP1 receptor modulators), and the therapy initiated may increase the risk of HZ. A descriptive characteristic is included to define immunosuppressive therapy additions ***in the 3 months*** after vaccination.

10. Unmeasured confounding: Disease severity, disease activity, and disease duration may be associated with receipt of the vaccine and/or subsequent risk of flare, relapses and of HZ. However, these factors are challenging to measure in administrative claims data or can be unmeasured. To address this, this study assesses proxies for disease severity or activity (such as medication use and healthcare use). Also, medications used over-the-counter may not be captured and are unmeasured.

11. Healthy-user bias: Patients receiving vaccinations, such as RZV, may be healthier or have other behaviors leading to improved health compared to unvaccinated patients. This bias may lead vaccinated patients to have lower rates of relapse/flares as well as HZ/PHN in the cohort study designs. The study will capture and adjust for variables related to healthy users, such as use of other vaccinations, to minimize this bias.

12. Missing data: Missingness is a challenge in studies using claims-based data. In general, we assume that if a condition or procedure is not recorded in the health plan data, it was not diagnosed or did not happen. We recognize that some fields, such as race/ethnicity, can be especially challenging in analyses of claims data due to missing values. SLE disproportionately affects racial/ethnic minorities in the USs making the need for studies that include these populations even more critical. Race/ethnicity will be evaluated in Medicare and in other ***Research*** Partners with race/ethnicity data available, but this information is missing or partly missing in multiple ***Research*** Partners. While participating ***Research*** Partners have populations that reflect the general insured population and include racial/ethnic minorities, we will have limited ability to evaluate race/ethnicity in these data sets and overall assessments of race/ethnicity subgroups may be underpowered. Additionally, the available data is for the insured population.

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 de-identified data and 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 [ENCePP, 2010], Guidelines for Good Pharmacoepidemiology Practices [GPP, 2022] issued by the International Society for Pharmacoepidemiology [ISPE, 2015], 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, published in May 2013 [FDA, 2013].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional observational, retrospective, post-authorization safety study, based on data extracted from database(s). Participants will not be administered any vaccine as part of the study. Individual case adverse event/adverse reaction reports will not be generated from this study.

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e., the overall association between an exposure and an outcome. Relevant findings from the study report may be included in the periodic aggregated regulatory reports submitted to Health Authorities.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A protocol summary of this study will be registered on GSK clinical study register prior to start of data collection. Study protocol summary and results summary will be submitted within 12 months of statistical analysis completion. The study will also be registered on the European Union electronic Register of Post-Authorization Studies register prior to start of data collection. Study report(s) will be submitted to GSK and findings will be submitted for presentation at scientific conference(s) and in peer-reviewed journal(s) for publication. Any conference abstracts and or manuscript publications resulting from this study will be developed in collaboration with GSK and will be in accordance with the International Committee of Medical Journal Editors guidelines [ICMJE, 2021].

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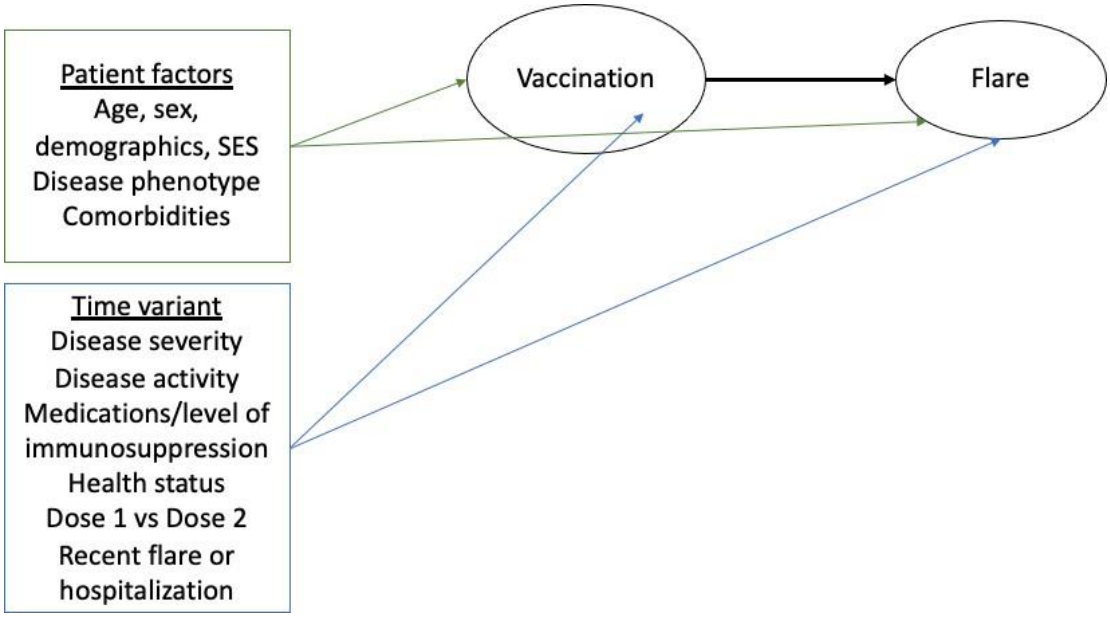
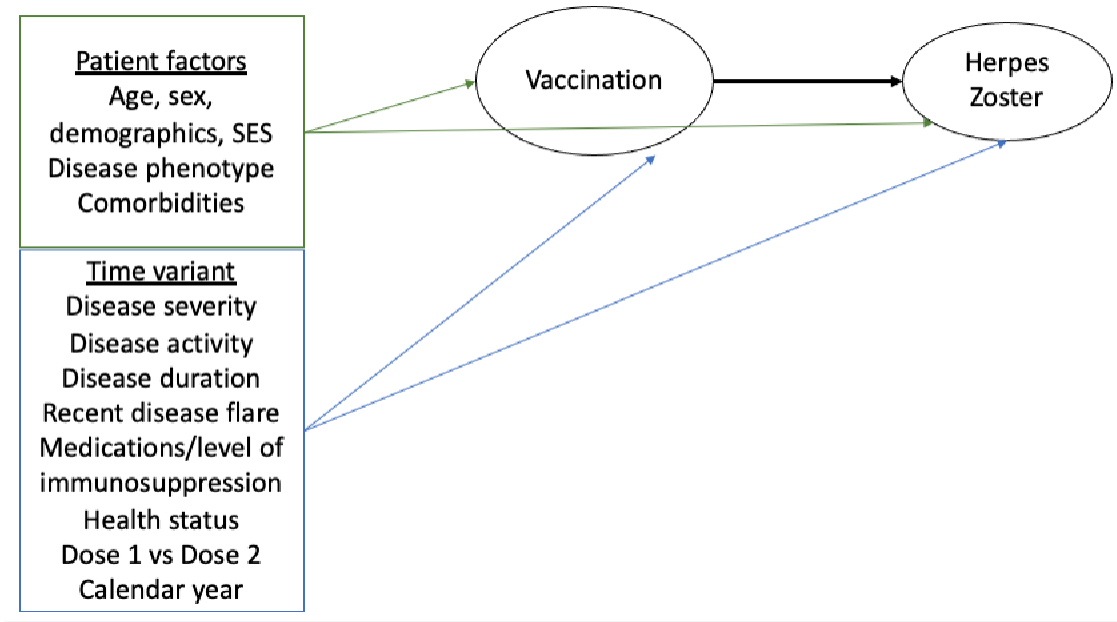
14. APPENDIX

14.1. Appendix 1 Directed Acyclic Graph for association between vaccination and disease flare



14.2. Appendix 2 Directed Acyclic Graph for association between vaccination and herpes zoster



ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1	TMF-14730954	02 June 2022	Final Protocol
2	TMF-14828731	07 September 2022	Descriptive query technical specifications
3	TMF-15216844	15 November 2022	Descriptive query report
4	TMF-15174013	29 November 2022	Final SAP
5	TMF-15196304	02 December 2022	Protocol Amendment 1
6	TMF-15256784	06 December 2022	Protocol Amendment 1 – Investigator signature
7	TMF-16435396	10 August 2023	Protocol Amendment 2
8	TMF-16720351	22 August 2023	Protocol Amendment 2 – Investigator signature
9	TMF-15174013	01 September 2023	SAP amendment 1
10	TMF-17008602	14 September 2023	SAP amendment 1 – investigator approval
11	TMF-16735270	05 September 2023	Medical Record Review Plan
12	TMF-16103108	14 March 2024	Interim analysis technical specification
13	TMF-22134939	21 April 2025	Monitoring query technical specifications
14	TMF-14841020	02 June 2022	Original code list
15	TMF-16103129	13 October 2023	Interim analysis code list
16	TMF-22607563	11 July 2025	Monitoring query code list
17	TMF-15216844	09 November 2023	Descriptive query report
18	TMF-19599826	08 July 2024	Interim analysis report
19	TMF-19501323	06 June 2024	Interim analysis tables - Commercial
20	TMF-19501335	30 May 2024	Interim analysis tables - Medicare
21	TMF-23301705	10 October 2025	Monitoring Query report

ANNEX 2 GLOSSARY OF TERMS

Adverse event: Any untoward medical occurrence in a study participant, 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.

Cohort study: A form of epidemiological study where participants in a study population are classified according to their exposure status/disease and followed over time (prospective/retrospective) to ascertain the outcome(s).

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 enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

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 studies.

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.

Participant:	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. Synonym: subject
Participant number:	A unique number identifying a participant, assigned to each participant consenting to participate in the study.
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.).
Primary completion date:	Primary completion date is defined as the date of final collection of data for all primary outcomes/endpoints.
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 participants, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
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 participants, scope of the investigation, study design, or scientific integrity of the study.
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.

Self-controlled case series (SCCS):	Statistical method for assessing the association between a transient exposure and an adverse event. The method was developed to study adverse reactions to vaccines. The method uses only cases; no controls are required as the cases act as their own controls. Each case's given observation time is divided into control and risk periods. Risk periods are defined during or after the exposure. The method estimates a relative incidence rate, that is, the incidence in risk periods relative to the incidence in control periods. An advantage of the method is that confounding factors that do not vary with time, such as genetics, location, socio-economic status are controlled for, implicitly.
Study population:	Sample of population of interest.
Sub-set:	A subgroup of the total cohort of study participants for whom the planned study procedures are different from those planned for the other study participants.
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

Investigator's name	Investigational site (institution /hospital)	Location (complete address)	Phone number Fax number
Kimberly Daniels, PhD, MS	Carelon Research, Inc.	123 Justison Street Suite 200 Wilmington, DE 19801	PPD
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Audrey Djibo	CVS Healthspire Payor & Life Sciences LLC	1425 Union Meeting Road –U21n Blue Bell, PA 19422	
Kristin K Palmsten	HealthPartners Institute	8170 33rd Ave South Bloomington, MN 55425	
Michael J. Miller, RPh, DrPH, FAPhA	Mid- Atlantic Permanente Research Institute	700-B 2nd St NE, 5th Floor Washington, DC 20002	
Sheryl Kluberg	Harvard Pilgrim Health Care Institute	401 Park Drive Suite 401 East Boston, MA 02215	
Michael George	University of Pennsylvania	523 White Building, 3400 Spruce St, Philadelphia, PA 19104	
Alexis Ogdie	University of Pennsylvania	524 White Building, 3400 Spruce St, Philadelphia, PA 19104	
Richard Platt, MD, MSc	Harvard Pilgrim Health Care Institute	401 Park Drive, Suite 401 East Boston, MA 02215	

* GSK assigned center number

ANNEX 4 SPONSOR INFORMATION

Sponsor:

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ANNEX 5 AMENDMENTS TO THE PROTOCOL

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

GlaxoSmithKline Biologicals SA Vaccines R & D Protocol Amendment *3*	
eTrack study number and Abbreviated Title:	215104 (EPI-ZOSTER-041 VS US DB)
Amendment number:	Amendment 3
Amendment date:	12 Dec 2025
Protocol Approved	Final: 02 June 2022 Amendment 1: 02 December 2022 Amendment 2: 10 August 2023

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

PASS INFORMATION

Research question and objectives	The primary safety objective is to assess the risk of ***hospitalized*** ~~severe~~ SLE flare ~~or any MS relapse~~ within 90 days following any RZV dose in adults ≥18 YOA with pre-existing SLE ~~or~~ MS, CCI [redacted] ~~separately~~. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]
Contributing Authors	**Harvard Pilgrim Health Care Institute** ~~Aaron Mendelsohn, PhD, MPH~~ PPD **GSK** • PPD ~~Supreeth Srinivasmurthy~~

LIST OF ABBREVIATIONS

FFS ***Fee-for-Service Medicare (excludes Part C plans)***

HR ***Hazard ratio***

ICD-10-CM ***International Classification of Diseases, Tenth Revision, Clinical Modification***

IPTW ***Inverse-probability-of-treatment weight***

RESPONSIBLE PARTIES

Study Teams ***(Amended 12 Dec 2025)***	**Harvard Pilgrim Health Care Institute** PPD • ***Biostatistics Consultant*** PPD ~~**Prime Insights, LLC**~~ PPD **GSK** PPD

ABSTRACT

Research question and objectives	The primary safety objective is to assess the risk of ***hospitalized*** ~~severe~~ SLE flare ~~or any MS relapse~~ within 90 days following any RZV dose in adults ≥18 YOA with

	pre-existing SLE ~~or~~ MS, ***as an exploratory objective*** ~~espectively~~. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]
Population	US adults ≥18 YOA who are diagnosed with SLE or MS and are members of ~~eight~~ participating ***Research*** ~~Data~~ Partners in the US FDA Sentinel System or ***enrolled in FFS*** Medicare
Variables	Primary safety outcome~~s~~***: Hospitalized Severe*** SLE flare ~~or any MS relapse~~ within 90 days of RZV vaccination CCI [redacted] CCI [redacted] CCI [redacted]
Data sources	This study will be conducted using health plan data held by ***up to 6 Research*** ~~Data~~ Partners that participate in the FDA's Sentinel System and ***FFS*** Medicare. The ***Sentinel Research Partners*** ~~data partners~~ participating in the study include CVS Health***/Aetna***, ***Point32Health*** ~~(CTS)~~, Harvard Pilgrim Health Care ***and Tufts Health Plan), Carelon Research (formerly*** HealthCore), Health Partners, Humana, and ~~Kaiser Permanente Hawaii~~, Kaiser Permanente Mid-Atlantic~~, and Optum~~. The study will use curated data ***from all sites*** that are formatted to the FDA ~~Sentinel Common Data Model (~~SCDM~~)~~ specifications, which permits the use of publicly available Sentinel analytic tools.~~Health plan claims data included in the SCDM will be supplemented with medical records chart review.~~
Study size (*Amended 12 Dec 2025)*	***For the primary safety objective,*** the sample size needed to detect a ***50*** ~~40~~% increase in the risk of ***hospitalized***~~severe~~ SLE flares (HR=1.***51***~~44~~, absolute increase

	in risk of ***0.25***~~1.2~~% over 90 days) ~~or a 50% increase in any MS relapse (HR 1.53, absolute increase in risk of 1.0% over 90 days)~~ with 80% power is as follows: • ***10 864***~~SLE: ~3251~~ vaccinated ***with SLE (assuming baseline flare incidence of 3 per 100 person-years)*** • ***44 367***~~MS ~13 227~~ unvaccinated ***with SLE (assuming baseline incidence of 2 per 100 person-years)***~~patients~~ • SLE: ~~~912~~ ***1,001*** vaccinated patients and ***4, 225*** ~~~4474~~ unvaccinated patients (assuming baseline HZ incidence of 20 ***per***~~/~~1000 person-years) • MS: ~~~1727~~ ***2,001***vaccinated patients and ~~~8648~~ ***8,544*** unvaccinated patients (assuming baseline HZ incidence of 10 ***per***~~/~~1000 person-years)

AMENDMENTS AND UPDATES

~~Protocol Amendment 1 dated 02 December 2022 was amended to make administrative changes and updates to clarify the operational definitions of specific health care settings.~~

~~Amendment number~~	~~Date~~	~~Amendment or update~~	~~Section of study protocol~~	~~Reason~~
~~2~~	~~10 August 2023~~	~~Clarified HZ or PHN exclusion criteria that hospital, ED and AVs defines all care settings.~~	~~9.3.2~~	~~Revised to clarify operational implementation of care settings~~
		~~Revised SLE setting to clarify as inpatient, ambulatory, and ED, removing previous specification as "inpatient hospital", "physician visit" and "ambulatory visit " and clarified that hospital, ED and AVs are all care settings.~~	~~9.4.1~~	~~Physician visit and AV are captured as ambulatory. Aligned with technical specifications, AVs are operationalized to include OA and AVs as opposed to only AV to allow opportunity to capture telemedicine visits. This specification is also intended to capture all care settings.~~
		~~Revised Lupus Nephritis setting to remove "AV" and clarify as~~		~~Ambulatory visits are operationalized to include OA and AVs as opposed~~

		~~"ambulatory" and clarified that hospital, ED and AVs are all care settings.~~		~~to only AV to allow opportunity to capture telemedicine visits. This specification is also intended to capture all care settings.~~
		~~Revised MS setting to remove "AV" and clarify as "ambulatory" and clarified that hospital, ED and AVs are all care settings.~~		~~Ambulatory visits are operationalized to include OA and AVs as opposed to only AV to allow opportunity to capture telemedicine visits. This specification is also intended to capture all care settings.~~
		~~Added alternative definition 5 in Table 3~~	~~9.4.3.1~~	~~Adding alternative definition 5 allows chart review and estimation of PPV when glucocorticoids are defined as new prescriptions. This avoids capturing patients filling a routine glucocorticoid prescription rather than being treated for MS relapse.~~
		~~Clarified HZ care setting as any care setting (inpatient, ED, or ambulatory visit), and the HZ date is the date of the encounter with the HZ diagnosis code.~~	~~9.4.3.2~~	~~Revised to clarify operational implementation of care settings.~~
		~~Revised covariate for number of ambulatory visits to remove "AV"~~	~~9.4.4~~	~~Ambulatory visits are operationalized to include OA and AVs as opposed to only AV to allow opportunity to capture telemedicine visits.~~
		~~Added separate covariates for mild and moderate SLE flares during baseline.~~		~~Aligned with SAP table shells.~~
		~~Removed covariates for number of rheumatologist outpatient visits and number of neurologist outpatient visits.~~		~~Specialist visits are not able to be captured in the data.~~
		~~Added definitions of specific healthcare settings as defined in the HPHCI databases.~~	~~9.5~~	~~To clarify the definition of each setting and provided operational implementation.~~

~~AV: Ambulatory visits; ED: Emergency department; OA: Other Ambulatory; HPHCI: Harvard Pilgrim Health Care Institute; HZ: Herpes Zoster; MS: Multiple sclerosis; SAP: Statistical analysis plan; SLE: Systemic lupus erythematous.~~

Protocol Amendment 2 (dated 10 August 2023) was primarily updated to amend the study safety objectives and associated safety outcome definitions. A pre-planned chart review sub-validation of previously defined safety outcomes (severe SLE flare and any MS relapse) demonstrated PPVs for these outcomes <70%, below the pre-defined threshold that necessitated an alternative approach to identify outcomes in final safety analyses.

Following the completion of the chart review sub-validation in December 2024, the outcome algorithms were refined considering the results of the chart review and expert clinical guidance. Additionally, CCI [redacted] CCI [redacted] CCI [redacted]. ***Given these needed changes to the objectives and outcome definitions, subsequent updates to the study variables, sample size estimates, and analytic approach were made for alignment with the new objectives and outcome definitions. Additionally, two Sentinel Research Partners will not be participating in the final study.***

MILESTONES

Milestone	Planned date
Start of data collection[1]	~Q1 2023 (start of data extraction)
Interim study report in ≥18 YOA of VE in MS/SLE and safety in SLE ~~(if sample size allows)~~[2]	~Q1-2 2024
End of data collection[3]	~Q***3*** ~~Q1~~ 2026 (The date from which the analytical dataset is completely available.)
Final report of study results ~~including age stratification 18-49, ≥50~~	~Q1 2027

MS: Multiple sclerosis; Q: calendar quarter; RZV: recombinant zoster vaccine; SLE: Systemic lupus erythematous; VE: vaccine effectiveness; YOA: Years of age

~~Note: the above timelines are tentative and subject to change. Interim report will include cohort studies assessing effectiveness in the overall SLE cohort and overall MS cohort ≥18 years old and possibly safety in the SLE cohort assuming adequate available sample size. Safety in the MS cohort will not be included in interim analyses but instead chart review to validate the MS relapse algorithm will be prioritized and initiated during this time. Final analyses will also be conducted in the overall cohort but will include analyses stratified by age 18-49 and ≥50.~~

d. Start of study activities including the start of data extraction.

e. Date analytic dataset available for analysis (***using*** last RZV vaccination ***accrued through September*** ~~entering the cohort approximately March~~ 2023). ***The interim report included cohort studies assessing effectiveness in the overall SLE cohort***, ~~allowing for 3 months of follow-up and~~ ***overall MS cohort ≥18 years old and*** ~~6 months of data lag.). If safety~~ in the SLE cohort. ***Safety in the MS cohort was not*** ~~is~~ included in ~~the~~ interim ***analyses but instead*** ~~report~~ chart review ***to validate the MS relapse*** ~~will not be conducted given that severe flare has an established claims based~~ algorithm ***was prioritized and initiated during this time***.

f. Date analytic dataset available for analysis (***the date of*** last RZV vaccination entering the cohort ***varies by Research Partner*** ~~approximately March 2025, allowing for 3 months of follow-up~~ and ***is based on most recent data available*** ~~6 months~~ ***at the*** **time of analytic** data ~~lag.~~ ***extract*** (***anticipated to be April 2025 or later for Sentinel Research Partners and end 2023 for FFS Medicare***)

RATIONALE AND BACKGROUND

~~Herpes Zoster~~ ***HZ***
~~Recombinant zoster vaccine~~ ***RZV***

RESEARCH OBJECTIVES

The study will address the question of whether adults ≥18 YOA with SLE ~~or MS~~ are at increased risk of ***hospitalized*** ~~severe~~ SLE flares ***and describe the occurrence of hospitalized or treatment/MRI-based*** ~~or any~~ CCI [redacted] CCI [redacted] ***The study*** ~~and~~ will also assess the real-world effectiveness of RZV in preventing HZ in these populations. The specific objectives are as follows:

8.1 Primary safety objectives~~~~

- To assess the risk of ***hospitalized*** ~~severe~~ flare within 90 days following any RZV dose in adults ≥18 years with pre-existing SLE
- ~~To assess the risk of any relapse within 90 days following any RZV dose in adults ≥18 years with pre-existing MS~~

8.2 Secondary safety objective

- To assess the risk of ***hospitalized*** ~~any relapse within 90 days following any RZV dose in adults ≥18 years with pre-existing MS~~ flare within 90 days following ~~any dose of~~ RZV in adults ≥18 years with pre-existing SLE, stratified by RZV dose.
- ~~To assess the risk of any relapse within 90 days following any dose of RZV in adults ≥18 years with pre-existing MS, stratified by RZV dose~~

CCI [redacted]

- CCI [redacted]
  CCI [redacted]
  CCI [redacted]

8.5 Secondary effectiveness objectives[1]

~~**Further stratification by race/ethnicity will be conducted with available race/ethnicity data. While the populations of participating research partners represent the general insured population, race/ethnicity data is not available in all datasets.*~~

- [1] ***Secondary VE objectives will be conducted only if sample size allows. In the event of small sample sizes, the study team may instead choose to report descriptive incidence rates. For secondary VE objectives 3 and 4, further stratification by race/ethnicity will be conducted if adequate race/ethnicity data are available. While the populations of participating Research Partners***

represent the general insured population, race/ethnicity data is not available for all participants.

CCI

[redacted]

RESEARCH METHODS

9.1 Study Preparation ~~Descriptive~~ Queries

We ***conducted*** ~~will conduct~~ several queries ***(called descriptive and monitoring)*** prior to the interim and final analyses. These queries ***involved*** ~~will involve~~ obtaining and aggregating ***descriptive*** data from all sources in Section 9.5 except for the CMS ***FFS*** Medicare data~~. which will be included in the interim analysis if available and will be included in the final analysis but not in the initial queries.~~ The queries ***were*** ~~will be~~ descriptive in nature and ~~will be~~ used to identify the number of persons with SLE and MS vaccinated with RZV, overall and by patient demographic and clinical characteristics of interest, as well as unvaccinated individuals with SLE and MS, ***and the frequency of planned and investigational outcome definitions***. The information from the queries ***informed*** ~~will inform~~ the finalization of the ***study methodology*** ~~SAP~~, specifically to refine and tailor the ~~study's methodology and~~ analytical approaches to be most appropriate with the expected final sample size (extrapolated from the descriptive queries results)***, select final outcome algorithms and assess study power, and assess***~~) and~~ the distribution of patients across meaningful subgroups (e.g., selection of variables for propensity score analyses).

9.2 Overview of study design

- A retrospective cohort study will be ***implemented*** ~~used~~ to evaluate ***all objectives*** ~~the primary objective of risk of severe SLE flares or any MS relapses within 90 days following any RZV exposure.~~
- ~~The effectiveness of RZV for the prevention of HZ will also be evaluated using a retrospective cohort study.~~
- ~~The incidence of PHN will also be evaluated using a retrospective cohort study.~~
- The study population will be comprised of US adults ≥18 YOA who are diagnosed with SLE or MS and who are commercially insured and enrolled in 1 of ***the*** ~~8~~

participating ***Sentinel Research Partners*** ~~data partners~~, or who are enrolled in ***FFS*** Medicare.

- Vaccinated patients will include adults who received at least 1 dose of RZV on or after 01 January 2018 ***until the most recent data available at each Research Partner***. Unvaccinated patients with SLE or MS will be included as ***comparators*** ~~controls~~.
- To evaluate safety ***of RZV***, RZV exposure will be defined as receipt of at least 1 dose of vaccine. The primary analysis will evaluate the risk of ***hospitalized*** ~~severe~~ SLE flares or ~~any MS relapse~~ after any RZV dose. Secondary analyses will be conducted to assess the risk of ***hospitalized*** ~~severe~~ SLE flares ~~or any MS relapse~~ separately after Dose 1 and Dose 2 of RZV. CCI [redacted] CCI [redacted] CCI [redacted]
- Data sources include ***6*** ~~8~~ selected ***Research*** ~~Data~~ Partners that participate in the FDA's Sentinel System ***and FFS*** ~~or~~ Medicare. Patients enrolled in Medicare will be analyzed separately from patients enrolled in Sentinel ***Research*** ~~Data~~ Partners.

~~9.2.1~~ 9.3 Rationale for retrospective cohort study design

Assessment of safety objectives~~:~~

A retrospective cohort study will be conducted to compare the hazard of ***hospitalized*** ~~severe~~ SLE flares ***using Cox proportional hazard models*** or ***describe the occurrence of hospitalized or treatment/MRI-based*** ~~any~~ MS relapses in patients receiving RZV versus unvaccinated patients ***within*** ~~using Cox proportional hazard models with~~ a 90-day follow-up period (Figure 1). Two base cohorts will be identified consisting of patients diagnosed with SLE and separately of patients diagnosed with MS***;*** ~~and~~ the safety analyses will be conducted separately among patients diagnosed with SLE and MS. A 90-day follow-up period was defined based on input from subject matter experts (board certified neurologists and rheumatologists) who recommended that ***hospitalized*** ~~severe~~ SLE flares or ***hospitalized or treatment/MRI-based*** ~~any~~ MS relapses might be expected to occur within 4-8 weeks of a trigger but that these events may not come to medical attention immediately, with 90 days a more appropriate window to capture outcomes.

Assessment of effectiveness objectives

To assess VE, a retrospective cohort design will be used to compare the hazard of HZ in patients with SLE or MS who received 2 doses of RZV relative to unvaccinated ***comparators*** ~~controls~~ using Cox proportional hazards models (Figure 2).~~Figure 4).~~

~~9.3~~ 9.4 Study population

The study population will be selected from adults enrolled in participating Sentinel ***Research*** ~~Data~~ Partners or ***FFS*** Medicare (Section 9.5~~9.4)~~ who are diagnosed with SLE or MS. Starting on 01 January 2018, the cohort will accrue commercially insured and Medicare beneficiaries in the US diagnosed with SLE or MS who are ≥18 YOA at

their index date (i.e., RZV vaccination date for RZV recipients or assigned index date for unvaccinated ***comparators*** ~~controls~~, see Sections 9.3.1 and 9.3.2).

~~9.3.1~~ 9.4.1 Study population to evaluate the safety of RZV

A retrospective cohort study will be used to assess the safety of RZV in patients with SLE ***with respect to hospitalized SLE flare*** and ***to describe the occurrence of relapse following RZV among patients with*** ~~and~~ MS (Figure 1). Vaccinated patients will include adults who received at least 1 dose of RZV. Unvaccinated ***individuals with SLE or MS*** ~~controls~~ will serve as comparators.

~~Inclusion/exclusion criteria for a cohort study to assess the risk of severe SLE flares or any MS relapses after RZV~~

Inclusion:

- Received at least 1 dose of RZV (for vaccinated individuals) on or after 01 January 2018 ***until the most recent data available at each Research Partner***.
- For ***Sentinel Research Partners***: 365 days of continuous enrollment with medical and prescription coverage (allowing ≤45-day administrative gaps in coverage) prior to the index date (baseline period).
- For ***FFS*** Medicare: continuous enrollment in Medicare part A/B/D (with no part C) 1 year prior to the index date (allowing 1 month gap in enrollment***).***

Exclusion:

- ***Treatment-based or hospitalized*** ~~Severe SLE~~ flares ***in patients with SLE*** or ***hospitalized or treatment/MRI-based*** ~~or any MS~~ relapses in ***patients with MS, in*** the 90 days prior to the index date (to ensure capture of incident ~~severe~~ SLE flares or MS relapses, as defined in Section 9.4.3.1). ***Regardless of the evaluated outcome definition for the particular objective, all flare/relapse definitions will be used for washout.*** ~~9.4).~~
- ~~*Note: The frequency of receiving RZV doses <28 days apart will be assessed and will be an exclusion criterion if frequency is <5%.*~~
- Additional RZV doses after the first 2 ~~(e.g., patients receiving 2 doses 1-28 days apart followed by a third dose)~~ will not be included and ***will*** serve as censoring events as detailed below.
- Unvaccinated patients will be matched to vaccinated patients by ***Research*** Partner ~~data partner~~, sex, and age ***(within 5 years)***, and assigned the same index date as the vaccinated patients, to ensure calendar year and seasonality is balanced across groups.

Definition of the index date:

- Unvaccinated patients will be matched to vaccinated patients by ***Research*** Partner, sex, and age ***(within 5 years)***, and assigned the same index date as the vaccinated patients, to ensure calendar year and seasonality is balanced across groups.

End of follow-up/censoring:

- Occurrence of the ***outcome of interest*** ~~severe SLE flare or any MS relapse~~
- End of data availability and/or end of study period ~~(based on data partner but latest end date will be approximately March 2025)~~
- RZV dose (any subsequent dose for vaccinated patients or first RZV dose for ***comparators***) ~~controls).~~
- End of 90-day ~~days~~ follow-up ***period***

Selection of unvaccinated *comparators* ~~controls~~:

Unvaccinated patients will be matched to each vaccinated patient by data partner, sex, and age to ensure an overall sample size of ~~approximately~~ 4 times unvaccinated to vaccinated (i.e., sample size ratio of ~~approximately~~ 4:1).

The same unvaccinated patients can serve as ***comparators*** ~~controls~~ for both cohorts, although index dates will differ.

~~9.3.2~~ 9.4.2 Study population to evaluate the effectiveness of RZV

Specific inclusion/exclusion criteria for the cohort analyses assessing RZV effectiveness are similar to the safety analyses except that ~~severe~~ SLE flares or ~~any~~ MS relapses in the 90 days prior to the index date are not exclusions (since HZ is the outcome for VE).

Inclusion:

- For ***Sentinel Research Partners*** ~~sentinel data partners~~: 365 days of continuous enrollment (allowing administrative gaps ≤45 days) prior to the index date (baseline period) to 30 days after the index date.
- For ***FFS*** Medicare: continuous enrollment in Medicare part A/B/D (with no part C) one-year prior to the index date (allowing 1 month gap in enrollment) ***to 30 days after the index date***.~~).~~
  - In secondary analysis evaluation 1 dose VE of RZV, the inclusion requirement is for at least 1 dose of RZV on or after 01 January 2018 (Figure 3). As such the 1 dose VE cohort will include patients who received only 1 RZV dose, as well as those who ***ultimately*** received 2 doses (***but*** ~~for those who receive 2 doses follow-up~~ will ~~also~~ be censored upon receipt of Dose 2).

Exclusion:

- This exclusion refers to diagnoses of HZ or PHN from hospital, emergency department, or ambulatory visits ***(all care settings)*** even if not accompanied by an anti-viral dispensing.

Definition of the index date:

- ***For*** ~~In the~~ primary ***VE objectives 1 and 2, secondary VE objectives 3-8 and*** CCI ~~analysis~~ which ***evaluate*** ~~evaluates~~ 2-dose VE, the index date is the date of the second RZV dose.
- ***For*** ~~In the~~ secondary ***objectives 1 and 2*** ~~analysis~~ evaluating 1-dose VE, the index date is the date of the first RZV dose.
- **Follow-up/censoring:**
  - ***Outcome of interest (i.e.,*** HZ ***or PHN)***
  - ~~HZ event date~~
  - End of data availability~~/study period (date will differ depending on the dataset but the latest end date will be approximately March 2025)~~
  - RZV dose
    - ~~(additional dose for vaccinated patients or first RZV dose in controls).~~ For 2-dose VE, vaccinated patients will be censored upon receipt of a third dose.
    - ***For all VE analyses, unvaccinated patients will be censored upon receipt of any RZV dose.***

Selection of unvaccinated comparators:

Unvaccinated patients will be matched to each vaccinated patient by data partner, sex, and age to ensure an overall sample size of ~~approximately~~ 4 times unvaccinated to vaccinated (i.e., sample size ratio of ~~approximately~~ 4:1), matched on data partner, sex, and age ***(±5 years)***.

Figure 2 Cohort design to assess vaccine effectiveness - ~~primary analysis assessing~~ 2 dose VE

Figure 3 Cohort design to assess vaccine effectiveness - ~~secondary analyses assessing~~ 1-dose VE

~~9.4~~ 9.5 Variables

~~9.4.1~~ 9.5.1 Definitions of SLE and MS

Table 1 ICD-9-CM and ICD-10-CM diagnosis codes for SLE and MS diagnoses

Diagnosis	*Diagnosis code(s)*
Systemic lupus erythematosus (SLE)	*M32.1*, M32.8, M32.9, 710.0*
Multiple sclerosis (MS)	*G35*

ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, 9th revision, Clinical Modification

Systemic Lupus Erythematosus:

~~Notes: The algorithm for SLE has been commonly used in studies published in high profile journals as noted in the citations above.~~ One validation study using electronic health record data found a PPV of 75% for ≥3 SLE encounters [Barnado, 2017]. This definition has also been used as part of the validated lupus nephritis algorithms which provides a sub-population that can be identified with high confidence.

~~Lupus Nephritis:~~

- ~~Among patients meeting the above definition for SLE, the presence of ≥3 ICD-9 diagnoses for renal disease (acute or chronic glomerulonephritis, acute or chronic renal failure, nephritis or nephrotic syndrome, renal failure or proteinuria,Annex 9) has shown a positive predictive value (PPV) of 80% for the identification of lupus nephritis [Chibnik, 2010]. A study of the lupus nephritis ICD-10 code M32.14 showed high PPV for lupus nephritis of 94% although low sensitivity of 33% (Li, 2021). Based on these studies lupus nephritis will be defined among the SLE cohort as:~~

- ~~≥1 visits/encounters with ICD-10 diagnoses of lupus nephritis (M32.14) from inpatient, ***ambulatory***, or ED visits ***(all care settings)*** in the year prior to the index date (any diagnosis position) [Li, 2021].~~

- ~~OR ≥3 visits/encounters with ICD-10 diagnoses of acute or chronic glomerulonephritis, acute or chronic renal failure, nephritis or nephrotic syndrome, renal failure or proteinuria from inpatient, ***ambulatory***, or ED visits ***(all care settings),*** any position, (correlates of the ICD-9 codes in Annex 9) in the year prior to the index date [Chibnik, 2010].~~

Multiple Sclerosis:

- ≥3 MS-related claims ~~(ICD-10 G35)~~ of any combination of ***encounters with ICD-10-CM diagnosis codes (see Table 1) from any care setting (***inpatient [any position], ***ambulatory***, ED), or MS-specific disease-modifying therapy (DMT) fills/infusions (see Table 8 for medication list) during the 1-year baseline period, requiring at least 1 of these to be an ***encounter with a*** diagnosis of MS

Table 1 ICD-9-CM and ICD-10-CM diagnosis codes for SLE and MS

Diagnosis	***Diagnosis code(s)***
Systemic lupus erythematosus (SLE)	***ICD-10: M32.1*, M32.8, M32.9, ICD-9: 710.0***
Multiple sclerosis (MS)	***ICD-10: G35***

ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, 9th revision, Clinical Modification

~~9.4.2~~ 9.5.2 Exposures

~~RZV exposure:~~

- For the secondary safety objective ***1 and*** CCI [redacted] to evaluate safety stratified by RZV dose, RZV exposure is defined as receipt of Dose 1 and receipt of Dose 2, separately.
- For the primary ***VE objectives 1 and 2***, ***secondary VE objective 3-8 and*** CCI [redacted] ~~analysis~~ to evaluate 2-dose VE, RZV exposure is defined as receipt of 2 doses of RZV occurring ≥28 days apart.
- For secondary ***VE***~~and exploratory~~ objectives ***1 and 2*** evaluating 1-dose VE, RZV exposure is defined as receipt of 1 dose of RZV. The 1 dose VE cohort will include patients who received only 1 RZV dose, as well as those who received 2 doses (for those who ***ultimately*** receive 2 doses, follow-up will be censored upon receipt of Dose 2).
- RZV vaccination will be identified using Current Procedural Terminology (CPT) code 90750 or National Drug ***Codes (NDCs) provided in a separate code list (and refreshed prior to each analysis) (see Annex 1).*** ~~Code (NDC) codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11.~~

~~9.4.3~~ 9.5.3 Outcomes of interest

Table 2 1 Overview of outcomes

Objectives	**Outcome of interest**	**Sensitivity ~~Alternative/sensitivity~~ outcome definitions**
Safety		
Primary safety objective	SLE: ***Hospitalized*** flare	N/A
Secondary ~~Primary~~ safety objective ~~objectives~~	SLE: ***Hospitalized*** ~~Severe~~ flare ~~MS: Any MS relapse~~	***SLE: Treatment-based flare, and hospitalized or treatment-based flare, respectively*** ~~SLE: Any SLE flare (i.e., mild, moderate, severe as defined in Table 2)~~ ~~MS: Alternative definitions 1-4 as defined in Table 3~~
CCI [redacted]		
Effectiveness		
Primary VE objective	Herpes Zoster	N/A
Secondary VE objectives	Herpes Zoster PHN	N/A
CCI [redacted]		

N/A: not applicable

~~9.4.3.1~~ 9.5.3.1 Outcomes to evaluate safety objectives

Safety outcomes for SLE

The primary outcome in all safety analysis among patients diagnosed with SLE is *hospitalized SLE flare as defined in Table 3 using a claims-based algorithm. Treatment-based flares and hospitalized or treatment-based flares will be assessed as sensitivity outcome definitions for safety secondary objective 1 (risk of flare, stratified by RZV dose). All relevant codes are provided in a standalone code list (see Annex 1).* ~~**severe SLE flare as defined in** Table 2 **using claims-based algorithms.**~~

~~Administrative claims-based algorithms for SLE flares have been developed with definitions shown in Table 2 [Garris, 2013]. While these algorithms have not been formally validated, they were developed based on the Lupus Foundation Second International Lupus Flare Conference definition of SLE flares (categorized as mild, moderate or severe), the consensus of expert clinical opinion, and incorporate additional criteria of ambulatory visits, hospitalizations, and emergency department visits supported by a qualifying SLE diagnosis or SLE-related condition. Studies using these algorithms have demonstrated associations between baseline SLE severity and frequency of flares as well as associations between flare severity and health-care costs, further supporting their validity [Lokhandwala, 2021; Hammond, 2021]. Severe lupus flares are the most clinically meaningful events, are likely to have the highest accuracy for identification (given requirements for high dose glucocorticoids, cyclophosphamide, or hospitalization) and will serve as the primary outcome measure. Given changes in SLE treatment since this algorithm was developed, new initiation of rituximab (used off-label for severe disease manifestations) [Rydén-Aulin, 2016] will also be included in the definition of severe flares.~~

~~**Severe SLE flares** (Table 2) will be defined as:~~

13. ~~Dispensing of an oral glucocorticoid prescription with prednisone-equivalent dose >40 mg/day, cyclophosphamide or rituximab, OR~~
14. ~~Inpatient hospitalization with a primary diagnosis of SLE (M32.1*) OR~~
15. ~~Inpatient hospitalization with a primary diagnosis of an SLE-related condition (ICD-10 codes for SLE-related conditions are to be determined based on mapping from previously used ICD-9 codes).~~

~~– The date of the severe flare is that date of the flare-defining prescription fill or infusion or inpatient hospitalization admission date~~

- ~~Alternative definition: Any type of SLE flare (i.e., mild, moderate, or severe as shown in Table 2).~~
- ~~Updated definitions: Flare algorithms may be modified if new algorithms or modifications of this algorithm are developed and validated prior to the start of analysis.~~

Revised algorithms for final analyses were informed by results from the chart-based sub-validation of the Garris severe flare algorithm [Garris, 2013] ***used for interim analyses, which had an overall PPV <70% but suggested acceptable performance of***

a hospitalized SLE flare algorithm. Treatment-based SLE flares will also be assessed as a clinically meaningful and more frequent outcome for sensitivity analyses, after modifications based on the observation from the chart review suggested more specific treatment criteria were needed.

The revised outcomes will not be separately adjudicated.

Table 2 Algorithm for determining SLE flare severity (adapted from Garris et al. 2013 with rituximab added as a criterion for severe flare)

Algorithm ~~Mild flare~~	**Criteria**	**Objective**
~~Initiation of any of the following:~~		
~~hydroxychloroquine or chloroquine~~		
~~an oral corticosteroid with prednisone-equivalent dose of ≤7.5 mg/day~~		
~~Treatment will be considered newly initiated if there is at least a 60-day gap between the end of any prior dispensing for that class of medication (based on days' supply) and the new medication fill. For example, if a 90-day supply of hydroxychloroquine was filled 120 days prior to the current dispensing, this would represent only a 30-day gap and so would not be considered new hydroxychloroquine initiation~~		
~~**Moderate flare**~~		
~~a. Initiation of any of the following:~~		
~~an oral corticosteroid with prednisone-equivalent dose >7.5 mg/day but ≤40 mg/day,~~		
~~immunosuppressive therapy, with the exception of cyclophosphamide or rituximab~~		
~~Treatment will be considered to be newly initiated if there is at least a 60-day gap between the end of any prior dispensing for that class of medication (based on days' supply) and the new medication fill. For oral corticosteroids, if the patient had an active prescription in the prior 60 days, treatment will be considered newly initiated if the prior fill is for a prednisone-equivalent dose ≤7.5 mg/day.~~		
~~OR~~		
~~b. A claim for an emergency department visit with a diagnosis of SLE with no inpatient admission within 1 day~~		
~~OR~~		
Hospitalized SLE flare	***Inpatient admission with SLE in primary diagnosis position*** ***OR*** ***Inpatient admission with a SLE-related condition[a] in the primary diagnosis position with an inpatient SLE diagnosis code during the same hospitalization*** ***OR***	• ***Safety primary objective 1*** • ***Safety secondary objective 1***

		Inpatient incident ESRD[b] in the primary diagnosis position with an inpatient SLE diagnosis code during the same hospitalization ***Flare date = date of inpatient admission, or date of emergency department admission if the patient was admitted to the emergency department, with any diagnosis, during the previous day.*** ~~c. A claim from an emergency department or ambulatory visit with a diagnosis for a specified SLE-related condition (Annex 10). If the diagnosis occurred during an office visit, the condition would be required to be new, defined as no claims with this diagnosis during the previous 60 days. If the condition occurred in an emergency department visit, no inpatient admission within 1 day following the emergency department visit will be allowed.~~	
~~**Severe flare (Primary Outcome)**~~			
~~a. Initiation of any of the following:~~			
~~an oral corticosteroid with prednisone-equivalent dose >40 mg/day,~~			
~~cyclophosphamide or rituximab~~			

Treatment-based SLE flare	***New initiation (no use in prior 183 days) of rituximab, cyclophosphamide, or mycophenolate[c]*** ***OR*** ***Initiation[d] of glucocorticoids with average daily prednisone equivalent dose (PED) ≥40mg for >14 days.*** ***Flare date = date of medication dispensing***~~For corticosteroids, if the patient had a prior active prescription within 60 days, treatment will be considered newly initiated if the prior fill was for a dose ≤40 mg/day. Other treatments will be considered to be newly initiated if there is at least a 60 day gap between the end of any prior prescriptions/infusion for that class of medication and the new medication fill/infusion, based on days' supply for prescription fills and based on a treatment duration of 30 days for cyclophosphamide infusions and 183 days for rituximab infusions.~~	***Sensitivity outcome definition for safety secondary objective 1***
~~OR~~		
~~b. Admission for an inpatient hospital stay with a primary diagnosis of SLE~~		
~~OR~~		
~~c. Admission for an inpatient hospital stay with a primary diagnosis for a specified SLE-related condition (Annex 11)~~		

Hospitalized or treatment-based SLE flare	***Either of the above.*** ***Flare date = earliest observed flare of either type.*** ~~For flares based upon a hospitalization, the start date of the flare is the date that the patient was admitted to the hospital, unless the patient was admitted to the emergency department (with any diagnosis) during the previous day, in which case the date of the emergency department admission would be considered the start date of the flare.~~	***Sensitivity outcome definition for safety secondary objective 1***

ESRD = end-stage renal disease; SLE = systemic lupus erythematosus

[a] SLE-related conditions for primary outcome definition: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, optic neuritis, pulmonary hemorrhage, stroke/TIA, acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, ischemic necrosis of bone, nephritis, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis, vasculitis (excluding aortitis).

[b] Incident ESRD defined based on no evidence of ESRD in the prior 365 days (any care setting).

[c] For the treatment-based SLE flare outcome, the washout for prior use will be based on days' supply for dispensings; when procedure codes are used to identify treatments, fixed treatment durations of 30 days for cyclophosphamide infusions and of 183 days for rituximab infusions will be used for washout.

[d] New glucocorticoid initiation excludes events with evidence of glucocorticoids within prior 60 days or if prior active glucocorticoid prescription within 60 days, prior fill was for a daily dose <40 mg PED. Further information on glucocorticoid dose conversion factors is provided in the SAP.

9.5.3.1.2 Safety outcomes for MS

The primary outcome in all safety analysis among patients diagnosed with MS is *hospitalized or treatment/MRI-based* ~~any~~ MS *relapse* ~~flare~~ as defined using claims-based algorithms in *Table 4*.~~Table 3~~.

Its components, hospitalized relapse and treatment/MRI-based relapse, will be assessed as a sensitivity outcome definition for CCI [redacted] CCI [redacted].

Revised algorithms for final analyses were informed by results from the chart-based sub-validation of algorithms for MS relapse used for Sentinel projects [Sentinel

Multiple Sclerosis Protocol, 2021] and reviewed by neurology subject matter experts. The chart review was completed in December 2024 and results indicated poor performance of the previously defined algorithms for identifying MS relapse (PPV <70%). Further, chart review did not provide sufficient data to definitively inform performance of an alternative algorithm. For this reason, assessment of MS relapse in final analyses will be descriptive and CCI [redacted] ***Based on chart review results and further input from subject matter experts, modified algorithms were created, which will be assessed descriptively, as detailed in Table 4, with codes provided in a standalone code list algorithms were created, which will be assessed descriptively, as detailed in Table 3, with codes provided in a standalone code list.***

The revised outcomes will not be separately adjudicated.

~~A prior FDA Sentinel report used a set of 5 potential definitions for MS relapse [Sentinel Multiple Sclerosis Protocol, 2021]. While not validated, these definitions have face validity for MS relapse based on input from MS/neurology subject matter experts. These experts noted that receipt of a corticosteroid prescription or infusion is most consistent with relapse and a 30 day window after an outpatient visit was considered preferable to a 7 day window. Modifications of the 5 FDA Sentinel-defined algorithms suggested by the consulting subject matter experts include:~~

- ~~Capturing glucocorticoids before or after an MS-related encounter. The experts suggested receipt of a glucocorticoid in the 7 days prior to an outpatient visit as well as either 7 or 30 days after an outpatient visit, given that glucocorticoids may be initiated before a visit.~~
- ~~Including hospitalizations with primary diagnoses of transverse myelitis or optic neuritis, as these would be indicative of a major flare in a patient with MS.~~
- ~~***Requiring glucocorticoid prescriptions to be new prescriptions (no prior fills for oral glucocorticoids in the preceding 90 days) to avoid capturing patients filling a routine glucocorticoid prescription rather than being treated for MS relapse.***~~
- ~~Incorporating the modifications listed above, the ***6*** algorithms of relapse that will be assessed are detailed in Table 3. Diagnosis codes are detailed in Annex 12) [Ollendorf, 2002; Sentinel Multiple Sclerosis Protocol, 2021].~~
- ~~MS relapse algorithms may be modified if new algorithms or modifications of this algorithm are developed and validated prior to the start of analysis.~~

Table 4-~~3~~ Algorithms to define MS relapse

Algorithm	Criteria	Objective
CCI [redacted]		
~~Alternative definition 1~~	~~MS diagnosis (or diagnoses of optic neuritis or transverse myelitis) in the inpatient care setting in the primary diagnosis position~~ ~~• Relapse date is the inpatient admission date.~~	
~~Alternative definition 2~~	~~MS diagnosis from an ambulatory visit with evidence of a glucocorticoid dispensing (or infusion) within 7 days before or after MS diagnosis~~ ~~• Relapse date is the earliest of glucocorticoid dispensing/infusion or ambulatory visit.~~	
~~CCI~~ [redacted]		
~~Alternative definition 4~~	~~MS diagnosis from an ambulatory visit with evidence of glucocorticoid dispensing (or infusion) within 7 days before or 30 days after the MS diagnosis.~~ ~~• Relapse date is the earliest of glucocorticoid dispensing/infusion or ambulatory visit.~~	
~~CCI~~ [redacted]		

~~***Note that if requiring new glucocorticoid dispensing is found to have improved performance, then incorporating this requirement into other alternative algorithms involving glucocorticoid dispensing may also be considered.***~~

IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis.

9.5.3.2 ~~9.4.3.2~~ Outcomes to evaluate effectiveness objectives

9.5.3.2.1 Primary effectiveness outcome

- The HZ date is the date of the ***encounter with the HZ diagnosis code***. ***HZ diagnosis codes and medications are provided in a standalone code list***.~~HZ diagnosis codes and medications are shown in Annex 13.~~

9.5.3.2.2 ~~Definition of PHN outcome for~~ sSecondary effectiveness outcome

A secondary VE objective is to evaluate the incidence of ~~post herpetic neuralgia~~ ***PHN***. An algorithm based on these studies modified by [Izurieta, 2021], will be used (codes and medications ***provided in a standalone code list***)~~in Annex 13~~) [Izurieta, 2021].

ICD-10-***CM***

~~9.4.5~~ 9.5.4 Covariates

Variables described in Table 5 ***may be redefined, combined, or excluded as needed due to sample size or to facilitate analysis. All codes to identify covariates are provided in a separate standalone code list (see Annex 1).***

Table 5 Covariates of interest

	Analyses in which covariates will be included			
Covariates	**Cohort study evaluating *safety*~~Severe flares/ any MS relapses~~**		**Cohort study evaluating RZV effectiveness**	
	SLE	**MS[a]**	**SLE**	**MS**
Demographics				
Age in categories: 18~~–29, 30-39, 40-~~49, 50-59, 60-69, ≥70~~79, ≥80~~	x	x	x	x
Sex	x	x	x	x
Race/Ethnicity (***where available***) ~~in Medicare and other datasets with adequate capture)~~	x	x	x	x
Data partner (de-identified in the final report)	x	x	x	x
Calendar year of the index date	x	x	x	
~~Disability as the original reason for entitlement (Medicare only)~~	~~x~~	~~x~~	~~x~~	~~x~~
Month of the index date (to capture seasonality)	x	x	x	x
Region of residence within USU~~.S. (as defined by either Department of Health and Human Services (11 regions)~~ or Census Bureau (4 regions)	x	x	x	x
Proxies of disease severity in SLE (other than medication use) measured during the baseline period				
Lupus nephritis (as defined in **Section 9.5.4.1.** ~~above~~)	x		x	
SLE disease severity (mild, moderate, or severe – see ***Table 6)*** ~~based on a validated algorithm in Garris et al. 2013 that has been shown to predict~~	x		x	

~~subsequent disease flares (Annex 10) [Garris, 2013; Speyer, 2022; Lokhandwala, 2021]~~				
~~***Number of mild SLE flares in 365 days prior the index date (as defined above***~~	~~x~~		~~x~~	
~~***Number of moderate SLE flares in 365 days prior the index date (as defined above***~~	~~x~~		~~x~~	
Number of ***hospitalized*** ~~mild or moderate~~ SLE flares in ***90-***365 days prior the index date (as defined above)[b]	x		x	
~~Number of severe SLE flares in the 0-90 days prior to the index date – an exclusion in safety analyses~~			~~x~~	
Number of ***treatment-based*** ~~severe~~ SLE flares in ~~the~~ **0-**365 days prior ~~to~~ the index date (as defined above)[b]	x		x	
~~Proxies of disease severity in MS (other than medication use)~~				
~~Number of MS relapses in 0-90 days prior to the index date (based on the primary algorithm described above) – an exclusion in safety analyses~~				x
Number of ***treatment/MRI-based or hospitalized*** MS relapses in 91-365 days prior to the index date (based on the primary algorithm described above)[b]		x		x
Other health characteristics				
Average glucocorticoid dose (oral and IV) in prednisone equivalents ~~(see Table 6)~~ in the 90 days prior to the index date ***(categorical)***[c]	x	x	x	x
Immunosuppressive/immunomodulatory therapies (each medication will be an individual covariate – see Section 9.5.4.2 and ~~see~~ Table 7and Table 8 for specific medications and time frame for measurement)	x	x	x	x
Opioid prescription fill in the 90 days prior to the index date~~(Annex 13)~~	x	x	x	x
~~Number of ED visits in the 365 days prior to the index date (categorized 0, 1, 2 3, ≥4)~~	~~x~~	~~x~~	~~x~~	~~x~~
~~Number of hospitalizations in the 365 days prior to the index date (categorized 0, 1, ≥2)~~	~~x~~	~~x~~	~~x~~	~~x~~
~~Number of ambulatory visits in the 365 days prior to the index date (continuous)~~	~~x~~	~~x~~	~~x~~	~~x~~
Comorbidities – diabetes mellitus, congestive heart failure ***or cardiomyopathy***, chronic kidney disease, chronic obstructive pulmonary disease, stroke, depression, ***hypertension, hyperlipidemia, fibromyalgia, obesity, smoking status***, rheumatoid arthritis, inflammatory bowel disease, Combined Comorbidity Index [Gagne, 2011; Sun, 2017]	x	x	x	x
Prior pneumococcal vaccination using all data prior to the index date, as a proxy for health behaviors	x	x	x	x
Influenza vaccination in the 365 days prior to the index date (vaccines administered outside of office visits or pharmacies, for example in workplace settings, will not be captured)	x	x	x	x
Prior HZ infection >365 days prior to the index date (all available data)			x	x
Prior ZVL (Zoster Vaccine Live, Zostavax) >365 days prior to the index date using all available data			x	x
Durable medical equipment codes (wheelchair, walker, oxygen, hospital bed, lift) in the 365 days prior to the index date ***(in commercial data only)***	x	x	x	x
COVID-19 infection in the 90 days prior to the index date	x	x	x	x
COVID-19 vaccination in the 90 days prior to the index date	x	x	x	x
New immunosuppressive therapy/immunomodulatory therapy[d] within 3 months following index (descriptive only)	x	x	x	x

Healthcare utilization				
Number of ED visits in the 365 days prior to the index date (categorized 0, 1, 2-3, ≥4)	x	x	x	x
Number of hospitalizations in the 365 days prior to the index date (categorized 0, 1, ≥2)	x	x	x	x
Number of ambulatory visits in the 365 days prior to the index date (continuous, quartiles)	x	x	x	x

Codes for ~~select~~ covariates ***are provided in a standalone code list.***

[a] ***Covariates to*** be ***used for descriptive purposes for MS safety analyses.***

[b] ***Individuals with hospitalized*** and ***treatment-based flares/relapses in 90 days prior to the index date are excluded from the safety cohort. For these analyses, the covariates for prior flares or relapses will identify those events in the 91-365 days pre-index.***

[c] ***Further information on glucocorticoid dose conversion factors is provided in the SAP.***

[d] ***Medications may be grouped in descriptive tables as needed for modelling or masking of small cells.***

9.5.4.1 Proxies for SLE disease severity

Lupus nephritis

Among patients meeting the definition for SLE, the presence lupus nephritis will be assessed as a proxy for severe disease, as:

- ≥1 visits/encounters with ICD-10-CM diagnoses of lupus nephritis (M32.14) from inpatient, ambulatory, or ED visits (all care settings) in the year prior to the index date (any diagnosis position) [Li, 2021].

  OR

- ≥3 visits/encounters with ICD-10-CM diagnoses of acute or chronic glomerulonephritis, acute or chronic renal failure, nephritis or nephrotic syndrome, renal failure or proteinuria from inpatient, ambulatory, or ED visits (all care settings), any position, in the year prior to the index date [Chibnik, 2010].

The presence of ≥3 ICD-9-CM diagnoses for renal disease (acute or chronic glomerulonephritis, acute or chronic renal failure, nephritis or nephrotic syndrome, renal failure or proteinuria) has shown a positive predictive value (PPV) of 80% for the identification of lupus nephritis [Chibnik, 2010]. A study of the lupus nephritis ICD-10-CM code M32.14 showed high PPV for lupus nephritis of 94% although low sensitivity of 33% [Li, 2021].

SLE disease severity

A validated algorithm by Garris et al. for SLE severity has been shown to predict subsequent ~~disease flares and correlated severity with~~ healthcare costs and correlates with clinical disease activity measures [Garris, 2013; Speyer, 2020; Hammond, 2021; Lokhandwala, 2021]. Given changes in ***SLE treatment since this algorithm was developed, use of rituximab (currently used off-label for severe disease manifestations) is included to define severe disease [Rydén-Aulin, 2016]. Further***

information on the algorithms used to define SLE disease severity are provided in Table 6.

Table ~~5~~ 6 Algorithm for defining SLE disease severity

Mild disease
Does not meet the criteria for moderate or severe disease.
Moderate disease
Had no filled prescriptions for cyclophosphamide or rituximab or ***mycophenolate/mycophenolic acid or*** oral corticosteroid with ≥60 mg/day of prednisone equivalent dose[a] and no claims with a diagnosis of a 'severe' condition
AND
Met 1 or both of the following any time during the follow-up period:
Had ≥1 non-laboratory claims with a diagnosis of a condition listed as 'moderate', where the diagnosis occurs in any position on the claim
OR
Had ≥1 filled prescription for an oral corticosteroid with a prednisone-equivalent dose of ≥7.5 mg/day and <60 mg/day[a] or for an immunosuppressive agent (other than cyclophosphamide or rituximab) ***or mycophenolate/mycophenolic acid***).
Moderate conditions: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, hepatitis (non-viral), ischemic necrosis of bone, nephritis, renal impairment other than nephritis or end stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis, vasculitis (excluding aortitis) – codes ***are provided in a standalone code list***.
Severe disease
a) Had ≥1 filled prescriptions for cyclophosphamide or rituximab or ***mycophenolate/mycophenolic acid or*** oral corticosteroid with a prednisone equivalent dose of ≥60 mg/day[a]
OR
b) Had ≥1 non-laboratory claims with a diagnosis listed as 'severe', where the diagnosis occurs in any position on the claim.
Severe conditions: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end stage renal disease, optic neuritis, pulmonary hemorrhage, stroke/TIA – codes ~~in Annex 14~~ ***are provided in a standalone code list***.

[a] Further information on glucocorticoid dose conversion factors is provided in the SAP.

9.5.4.2 Therapies for SLE and MS

Therapies to treat SLE and MS are described in Tables X and Y, below, including by medication class. Procedure codes and NDCs to assess these therapies are provided in a standalone code list. Further information on assessment of baseline glucocorticoid dose is provided in the SAP.

Table 6 Glucocorticoids with conversion factors [Liu, 2013]

~~Glucocorticoids (generic names)~~	~~Conversion factors (multiply mg by the following factor)~~
~~Dexamethasone~~	~~6.67~~
~~Hydrocortisone~~	~~0.25~~
~~Prednisolone~~	~~1.0~~
~~Prednisone~~	~~1.0~~
~~Methylprednisolone IV or PO~~	~~1.25~~

~~IV: Intravenous; PO: By Mouth~~

Table 7 SLE immunosuppressive/immunomodulatory therapies

Immunosuppression category	Medications (generic name)	Time frame for measurement prior to the index date indicating active use
Anti-malarial (non-immunosuppressing)	Hydroxychloroquine, chloroquine	90 days
Less immunosuppressive	Methotrexate	90 days
	Azathioprine	90 days
	Mycophenolate mofetil, mycophenolic acid	90 days
	Tacrolimus, cyclosporine, voclosporin	90 days
	Belimumab SQ	90 days
~~Immunosuppression category~~	~~Medications (generic name)~~	~~Time frame for measurement prior to the index date indicating active use~~
	Belimumab IV	90 days
	Anifrolumab IV	90 days
Highly immunosuppressive	Rituximab IV	183 days
	Cyclophosphamide PO	90 days
	Cyclophosphamide IV	90 days

Note: infusion therapies dosed monthly are considered an active treatment if they have been received in the past 90 days to account for interruptions in infusion treatments. ~~NDC codes and HCPCS/J-codes to be determined at a later date.~~, IV = intravenous, PO = by mouth; SQ = subcutaneous

Table 8 MS Immunosuppressive/immunomodulatory therapies (i.e., DMT)

Effectiveness/Immunosuppression category	Medications (generic name)	Time frame for measurement prior to the index date indicating active use
Highly effective and immunosuppressive	Alemtuzumab IV	365 days
	Cladribine PO	365 days
	Mitoxantrone IV	90 days (dosed every 1-3 months)
Highly effective and immunosuppressive, anti-CD20	Rituximab IV	183 days
	Ocrelizumab IV	183 days
	Ofatumumab SQ	90 days
	Ublituximab IV	***183 days***
Highly effective and immunosuppressing, SP1 receptor modulators	Fingolimod, Siponimod, ozanimod, ponesimod	90 days
Highly effective and less immunosuppressive therapies	Natalizumab IV	90 days (dosed every 4-6 weeks)
Less effective and less immunosuppressive therapies	Fumarates: dimethyl fumarate, diroximel fumarate, monomethyl fumarate	90 days
	Glatiramer acetate SQ or IM	90 days
	IVIG	90 days
	Interferon beta SQ or IM: recombinant human interferon beta- 1b, recombinant human interferon-1a, Pegylated recombinant interferon beta-1a	90 days
	Teriflunomide	90 days
	Azathioprine, methotrexate, mycophenolate mofetil/***mycophenolic acid*** (all uncommonly used)	90 days

Note: infusion therapies dosed monthly are still considered an active treatment if they have been received in the past 90 days to account for interruptions in treatment. ~~NDC codes and HCPCS/J-codes to be determined at a later date.~~

9.6.1 Research Partners

This study will be conducted using health plan data held by ***six Research***~~8 Data~~ Partners that participate in the FDA's Sentinel System. ***Three*** ~~Six~~ are national insurers that update their curated Sentinel database 3 to 4 times per year (CVS Health ~~Clinical Trial Services~~/Aetna, ***Carelon [formerly*** HealthCore***], and*** /~~Anthem, Health Partners,~~ Humana***; Point32Health (***, ~~and Optum);~~ Harvard Pilgrim Health Care ***and Tufts Health Plan), HealthPartners,***~~, Kaiser Permanente Hawaii~~ and Kaiser Permanente Mid-Atlantic States are regional insurers. This study will use the most recently available approved SCDM of the research portion of the population at each ***Research*** ~~Data~~ Partner at the time of analysis. In addition to providing claims data, the ***Research*** ~~Data~~ Partners will provide scientific input and feedback to support this study.

In the event that a Research Partner has inadequate sample size to perform any of the specified analyses for this study, the study team may choose to exclude this Partner from the respective analysis.

To ensure greater capture of persons with SLE and MS exposed to RZV beyond those covered by commercial insurers, we will also use data from CMS to examine ***FFS*** Medicare ***beneficiaries,*** ~~patients, evaluating patients with Medicare Parts A, B, and D and~~ including older patients ≥65 as well as patients <65, given the substantial number of younger patients with SLE and MS who have Medicare due to disability [Garris, 2015].

~~In 2010-2019, there were approximately 33 million Medicare beneficiaries meeting the full FFS criterion in the RIF data, [Medicare Tables and Reports] including approximately 76% with prescription drug benefit coverage (Part D), [CMS, 2016]. There are over 64 million beneficiaries enrolled in the Medicare program as of 2019, allowing for detailed sub-group analyses with reduced concerns about loss of statistical power [Medicare Tables and Reports].~~

~~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 US, established under the Sentinel Initiative [Sentinel Initiative].~~

- Aetna, a CVS Health company, is one of the ~~nation's~~ leading healthcare benefits companies ***in the US, currently*** serving ***39*** ~~38~~ million people***.*** ~~nation-wide with information and resources to help them make better-informed decisions about their healthcare.~~ Aetna became ***part of the Sentinel System in 2008. Aetna's SCDM captures longitudinal information on dispensed prescriptions, inpatient and outpatient diagnoses, inpatient and outpatient treatments and procedures, and outpatient laboratory results. The healthcare experience for over 41 million individuals is available for research, covering all ages. As of January 2025,*** ~~an FDA Sentinel DP in 2010 and continues to be one of the largest contributors of~~

~~data for public health purposes~~ CVS Health ***includes approximately 4.2 million members aged 18 years and older actively enrolled with ≥365 days of medical and prescription coverage who are research eligible. Among them, approximately 1.7 million are 18-59 years of age.*** ~~CTS, an affiliate of Aetna, conducts real-world evidence research, safety surveillance, chart validation studies, and clinical trials.~~

- ***Point32Health is the second largest New England based health plan. It provides care to 2.2 million individuals under the names, Harvard Pilgrim Health Care and Tufts Health Plan. Harvard Pilgrim Health Care participated in the Sentinel System and HPHCI is currently a site for the CDCs Vaccine Safety Datalink. As of September 2023, there are approximately 248 000 current members with both medical and drug coverage, who are ≥50 years of age, and are research eligible. Although Point32Health is smaller than the other RPs, it has the important advantages of being the institutional home of HPHCI. Designated HPHCI personnel have direct access to certain Point32Health data, providing the ability to work directly with source data to understand apparent anomalies in any analyses performed within this distributed data network.***

- ~~Harvard Pilgrim Health Care (HPHC) is 1 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.~~

- ***Carelon Research (formerly*** HealthCore***)*** ~~, Inc.,~~ a wholly owned***, independently operating*** subsidiary of ***Elevance Health,*** ~~Anthem, Inc.,~~ uses real-world data to conduct outcomes, health economics, pharmacoepidemiologic, and late phase research. ***Carelon Research curates the Healthcare*** ~~The HealthCore~~ Integrated Research Database ***(HIRD®),*** ~~is~~ a proprietary, fully integrated, longitudinal claims database that combines medical, pharmacy, and laboratory information drawn from ***approximately 88*** million unique individuals with medical coverage and more than ***67*** ~~51~~ million ***individuals with medical*** ~~lives with medical~~ and pharmacy claims information since 2006. In addition, ***Carelon*** Research ***can*** ~~Environment has the ability to~~ link ~~the~~ claims data in the ***HIRD®*** ~~HealthCore Integrated Research Database~~ 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. ***Carelon Research has been a partner within the Sentinel Initiative since 2008. As of January 2025, Carelon Research includes approximately 94 million members aged 18 years and older years actively enrolled with ≥365 days of medical and prescription coverage who are research eligible. Among them, approximately 14.9 million are 18-59 years of age.*** ~~Using these resources, HealthCore 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.~~

- **HealthPartners** ***is an active collaborator and RP in the FDA Sentinel System.*** HealthPartners is the largest consumer-governed ***non-profit health care*** ~~nonprofit~~ healthcare organization in the ***country*** ~~US~~, providing care, ~~insurance~~ coverage, research, and education to ***improve health and well-being in partnership with*** its

members***,*** and patients ***and community. Included under HealthPartners' umbrella are Regions Hospital, HealthPartners Care Group, HealthPartners Center for Memory & Aging, Park Nicollet Methodist Hospital and HealthPartners Institute. HealthPartners has formal relationships with hospitals and clinics throughout Minnesota and western Wisconsin, including Westfields Hospital (New Richmond, WI), Lakeview Hospital (Stillwater, MN), Hudson Hospitals and Clinics (Hudson, WI), Amery Hospital and Clinic (Amery, WI), St Francis Regional Medical Center (Shakopee, MN), Hutchinson Health (Hutchinson, MN), TRIA Orthopedic Center, and Physicians Neck and Back Clinic. Founded in 1957, the HealthPartners family of care*** ~~. HealthPartners operates primarily in the Midwest and~~ serves more than 1.8 million medical and dental health plan members***. As of September 2023, there are approximately 247 000 current members with both medical and drug coverage, who are ≥50*** ~~and more than 1.2 million patients, covering all ages, with median (range) age of 39 (0-110)~~ years ***of age,***~~. HealthPartners~~ and ***are*** ~~its associated~~ research ***eligible.*** ~~team~~, HealthPartners ***is one*** ~~Institute, became a member of the Sentinel System in 2008.~~ ***of the highest rated plans in the nation, according to National Committee for Quality Assurance's Health insurance Plans Rankings 2021-2022.***

- Kaiser Permanente Mid-Atlantic States (KPMAS) is an integrated healthcare delivery system providing comprehensive medical services, and currently serving ~~over~~ ***between 750 000 and*** 800 000 members at 32 Kaiser Permanente Medical Centers in the District of Columbia (DC), Maryland, and northern Virginia. Based in Rockville, Maryland, KPMAS is composed of the Kaiser Foundation Health Plan of the Mid-Atlantic States, a non-profit health care organization with more than ***8,000*** ~~6,000~~ employees, and the Mid-Atlantic Permanente Medical Group (MAPMG), a multi-specialty group practice of over ~~1,250~~ **1,700** physicians (including internal medicine/family practice, obstetricians/gynecologists, pediatricians, and specialists) and support personnel who provide or arrange health care for members of the health plan.
- Humana Healthcare Research (HHR) ~~is~~ a subsidiary of Humana Inc.,~~ which is headquartered in Louisville, KY, is a leading health plan and well-being company focused on making it easy for people to achieve their best health with clinical excellence through coordinated care. The research team conducts health economics and outcomes research focused on treatment effectiveness, drug & patient safety, patient centered research, adherence, medical and pharmacy benefit design, disease management programs, and other healthcare services. The research team also helps conduct internal research for the company. Team expertise includes areas of Distributed research networks, multisite research, adherence, clinical outcomes, overall health costs, pragmatic trials Medicare benefit designs & coverage gaps, Medication Therapy Management services, survey data linking to claims, impact of clinical programs and prescription formulary design. The team is/has been a core part of several Distributed Research Networks including the FDA Sentinel, PCORnet, NIH Collaboratory, OMOP and IMEDS. This involves experience in creating systems that have used a variety of common data models (Sentinel, OMOP & PCORnet) and utilizing external facing platforms such as PopMedNet to allow for query receipt, review and execution. These databases represent geographic*** ***is an active collaborator 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 for vaccine safety. Humana includes members throughout the US, with the highest concentration of members in the South. As of October 2024, Humana includes approximately 4.2 million members aged 18 years and older actively enrolled with ≥365 days of medical and prescription coverage who are research eligible. Among them, approximately 0.3 million are 18-59 years of age.

- Medicare provides health insurance to US residents aged 65 and over, as well as to younger individuals in special populations. It is estimated that over 98% of adults aged 65 years and over are enrolled in Medicare, making Medicare data one of the richest sources of utilization information in the country. Furthermore, over 99% of deaths in the US among persons aged 65 and older are accounted for by the Medicare program. ***There are over 66 million beneficiaries enrolled in the Medicare program as of December 2023, allowing for detailed sub-group analyses with reduced concerns about loss of statistical power [Medicare Tables and Reports].***

9.6.2 Sentinel System and Common Data Model

Research ~~Data~~ Partners

~~9.6~~ 9.7 Study Sample Size

All power calculations below evaluate necessary sample sizes for different effect sizes ***(minimum detectable HRs)*** with a power of 80% and alpha of 0.05. The primary method for the sample size calculation ***uses*** ~~and power analysis is a simulation-based grid search method, with the sample size from~~ the Schoenfeld formula [Schoenfeld, 1983] for log rank test to calculate the needed number ~~as the initial value. This method ensures adequate power of~~ events per group ~~80%. Details of the methods used~~ in the cohort study, and uses the observed or literature-based incidence rate of outcomes, observed average length of follow-up, and assumed attrition rate to calculate the required numbers of vaccinated and unvaccinated subjects. The specific steps are described below. ***All power*** calculations ***are performed using R open-source statistical software.*** ~~can be found in the Appendix 3.~~

a. To calculate the sample size for comparing two survival functions based on log-rank test, the Schoenfeld formula [Schoenfeld, 1983] for the needed total number of events is

$$N.events = \frac{(z_{1-\alpha/2}+z_{\beta})^2}{p_1 * p_2 (log\ HR)^2}$$

where:

- $z_{1-\alpha/2}$ ***and*** z_{β} ***are standard normal percentiles (here,*** α ***=0.05,*** β***=0.80,*** $z_{1-\alpha/2}$***=1.96,*** z_{β}***=0.84),***
- p_1 ***and*** p_2 ***are the proportions to be allocated to groups 1 and 2 (here, p1=0.2 and p2=0.8 to reflect the targeted 1:4 ratio for the sample sizes of the vaccinated and unvaccinated groups), and***

- ***HR is calculated as log(1-incidence.Vac)/log(1-incidence.unVac), where:***
  - ***incidence.Vac =1−(1−incidence.unVac)^HR [Schoenfeld, 1983].***

b. Now we need to calculate the proportion of patients in the cohort study who will have flare, as:

$$d = incidence.Vac * (p_1) + incidence.unVac * (1 - p_1)$$

c. Number of needed person-year is then:

$$N.person.years = N.events/d$$

d. Numbers of events for vaccinated and unvaccinated groups are:

$$N.event.Vac = N.person.years * p_1 * incidence.Vac$$

$$N.event.unVac = N.person.years * p_2 * incidence.unVac$$

e. Number of needed person-years per group is:

$$n.vaccine.grp = N.event.Vac/incidence.Vac$$

$$n.unvaccine.grp = N.event.unVac/incidence.unVac$$

f. Number of needed subjects per group is calculated by dividing follow-up time in years by a function of attrition rate, as follows:

$$nsubj.vaccine.grp = \frac{ceiling((n.vaccine.grp/avg.followup.time)}{(1-attrition.vaccinated)\text{^}avg.followup.time}$$

$$nsubj.unvaccine.grp = \frac{ceiling((n.unvaccine.grp/avg.followup.time)}{(1-attrition.unvaccinated)\text{^}avg.followup.time}$$

where attrition rate is assumed to be 7% among the vaccinated and 15% among the unvaccinated (due to the receipt of RZV among the unvaccinated).

Follow-up for safety is 0.25 years, based on the 90-day follow-up period used in this analysis. Follow-up for effectiveness is 1.32 years, based on the shortest observed follow-up time of any cohort observed during the interim analysis, though the follow-up may be longer for the final analysis.

9.7.1 Power calculations for safety analyses

~~Power calculations for ***the primary*** safety ***objective 1*** analyses assessing the risk of ***hospitalized***severe SLE flares or any MS relapses include the following assumptions:~~

- ~~A ***hospitalized***severe flare rate in ***unvaccinated*** SLE ***comparators*** of ***between 6***approximately 10-12 per 100 person-years ***was assumed based on the results of monitoring analyses completed in October 2025 among commercially insured patients. The results***(previous studies showed a 1-year rate of severe flares of ***this monitoring analyses revealed a background***13.2% or and a 2-year rate of ***hospitalized flare among unvaccinated adults***severe flares of ***1.97***19.9% or approximately 10% per year). [Garris, 2013; Lokhandwala, 2021]. A relapse rate in MS of approximately 6-10 per 100 person-years***, with rates for sensitivity flare outcome definitions ranging from 5.00 to 6.64 per 100 person-years.*** [Marrie, 2015].~~

~~A ***50%*** 40% increase in the risk of ***hospitalized*** severe SLE flares (***target HR=1.51, 0.25***1.2% absolute increase in risk over 90 days) or at 50% increased risk of any MS relapse (1% absolute increase in risk over 90 days) would be important to detect, although sample size needs for other effect sizes ***were*** will be assessed. Assume an average follow-up time of 90 days.~~

~~Assume an average follow up time of 90 days~~

- ~~The maximum amount of follow-up time after each vaccine dose is 90 days. The actual amount of follow-up time is likely to be less than 90 days for many patients, especially after RZV dose 1 (because of censoring at RZV Dose 2). Because patients can contribute follow-up time after both vaccine doses ***to the primary safety objective***, however, the total amount of follow-up time will be more than 90 days in most patients – the 90 day estimates below are conservative. ***They do not otherwise account for the combining of information from the Dose 1 and Dose 2 analyses.***~~
- ~~For secondary analyses that separately evaluate risk after each RZV dose, average follow-up time is expected to be closer to 60 days.~~
- ~~A cohort of patients without vaccination will be identified to achieve a ratio of at least 4:1 (unvaccinated to vaccinated).~~
- ~~Censoring rate of 7% per year in the RZV vaccinated group (due to death, ***flare***HZ occurrence, or end of enrollment) and 15% in the RZV unvaccinated group (due to death, ***flare***HZ occurrence, end of enrollment, or RZV vaccination), based on estimates from prior studies.~~

- ~~***Power calculations are not provided for analyses of MS relapse, since it is an exploratory objective.***~~

Table 9: Sample size calculation for *final SLE* safety analyses under a range of assumed incidence rates for unvaccinated and vaccinated group and assumed *minimal detectable* effect sizes (in hazard ratio) under *a 4:1 matched* cohort design

~~Incidence rate of flare in unvaccinated (in person-year, py)~~	~~Incidence rate in vaccinated (in person-year, py)~~	~~Effect size (percent increase in risk)~~	~~Hazard Ratio~~	~~Required person-years for vaccinated patients~~	~~Required person-years for unvaccinated patients~~	~~Required number of vaccinated patients (after adjusting for attrition)~~	~~Required number of unvaccinated patients (after adjusting for attrition)~~	~~Empirical power (and its 95% CI) from 1,000 replications of simulated data~~
~~12/100 py~~	~~24/100 py~~	~~100%~~	~~2.15~~	~~146~~	~~575~~	~~595~~	~~2396~~	~~81.4% (79.0 – 83.8%)~~
~~10/100 py~~	~~20/100 py~~	~~100%~~	~~2.12~~	~~180~~	~~710~~	~~734~~	~~2958~~	~~81.2% (78.8 – 83.6%)~~
~~8/100 py~~	~~16/100 py~~	~~100%~~	~~2.09~~	~~225~~	~~888~~	~~917~~	~~3700~~	~~81.2% (78.8 – 83.6%)~~
~~12/100 py 1~~	~~21/100~~	~~75%~~	~~1.84~~	~~243~~	~~959~~	~~990~~	~~3996~~	~~80.1%~~

	~~py~~							~~(77.6 – 82.6%)~~
~~10/100 py~~	~~17.5/100 py~~	~~75%~~	~~1.83~~	~~292~~	~~1170~~	~~1190~~	~~4875~~	~~80.3% (77.8 – 82.8%)~~
~~8/100 py~~	~~14/100 py~~	~~75%~~	~~1.81~~	~~365~~	~~1463~~	~~1487~~	~~6095~~	~~80.3% (77.8 – 82.8%)~~
~~12/100 py~~	~~18/100 py~~	~~50%~~	~~1.55~~	~~484~~	~~1934~~	~~2072~~	~~8057~~	~~80.6% (78.1 – 83.1%)~~
~~10/100 py~~	~~15/100 py~~	~~50%~~	~~1.54~~	~~627~~	~~2480~~	~~2554~~	~~10332~~	~~83.4% (81.1 – 85.7%)~~
~~8/100 py 2~~	~~12/100 py~~	~~50%~~	~~1.53~~	~~792~~	~~3175~~	~~3227~~	~~13227~~	~~81.9% (80.1 – 83.5%)~~
~~12/100 py 3~~	~~16.8/100 py~~	~~40%~~	~~1.44~~	~~798~~	~~3175~~	~~3251~~	~~13227~~	~~81.8% (79.4 – 84.2%)~~
~~10/100 py~~	~~14/100 py~~	~~40%~~	~~1.43~~	~~951~~	~~3780~~	~~3874~~	~~15747~~	~~81.8% (79.4 – 84.2%)~~
~~8/100 py~~	~~11.2/100 py~~	~~40%~~	~~1.42~~	~~1152~~	~~4575~~	~~4693~~	~~19059~~	~~81.0% (78.6 – 83.4%)~~
~~12/100 py~~	~~15.6/100 py~~	~~30%~~	~~1.33~~	~~1289~~	~~5159~~	~~5251~~	~~21492~~	~~80.9% (78.5 – 83.3%)~~
~~10/100 py~~	~~13/100 py~~	~~30%~~	~~1.32~~	~~1608~~	~~6440~~	~~6550~~	~~26829~~	~~80.1% (77.6 – 82.6%)~~
~~8/100 py~~	~~10.4/100 py~~	~~30%~~	~~1.32~~	~~2058~~	~~8225~~	~~8383~~	~~34265~~	~~83.2% (80.9 – 85.5%)~~

Incidence rate of *hospitalized* flare in unvaccinated (in person-year, py)	Incidence rate *of hospitalized flare* in vaccinated(in person-year, py)	Effect size (percent increase in risk)	*Minimum Detectable* Hazard Ratio	Required number of unvaccinated patients (after adjusting for attrition)	Required number of vaccinated patients (after adjusting for attrition)
1	*2*	*100%*	*2.01*	*28,328*	*6,925*
1	*1.75*	*75%*	*1.76*	*44,992*	*11,173*
1	*1.5*	*50%*	*1.50*	*89,567*	*21,996*
1	*1.4*	*40%*	*1.40*	*132,475*	*32,586*
1	*1.3*	*30%*	*1.30*	*222,041*	*54,207*
2	*4*	*100%*	*2.02*	*13,956*	*3,463*
2	*3.5*	*75%*	*1.76*	*22,288*	*5,471*
2	*3*	*50%*	*1.51*	*44,367*	*10,864*
2	*2.8*	*40%*	*1.41*	*65,405*	*16,004*
2	*2.6*	*30%*	*1.30*	*109,771*	*26,790*
3	*6*	*100%*	*2.03*	*9,165*	*2,241*
3	*5.25*	*75%*	*1.77*	*14,723*	*3,573*
3	*4.5*	*50%*	*1.51*	*29,162*	*7,153*
3	*4.2*	*40%*	*1.41*	*43,051*	*10,575*
3	*3.9*	*30%*	*1.31*	*72,349*	*17,756*
4	*8*	*100%*	*2.04*	*6,770*	*1,683*
4	*7*	*75%*	*1.78*	*10,832*	*2,681*
4	*6*	*50%*	*1.52*	*21,559*	*5,296*
4	*5.6*	*40%*	*1.41*	*31,869*	*7,858*
4	*5.2*	*30%*	*1.31*	*53,532*	*13,084*
5	*10*	*100%*	*2.05*	*5,333*	*1,304*
5	*8.75*	*75%*	*1.79*	*8,582*	*2,098*
5	*7.5*	*50%*	*1.52*	*16,997*	*4,184*
5	*7*	*40%*	*1.41*	*25,246*	*6,171*
5	*6.5*	*30%*	*1.31*	*42,326*	*10,342*
6	*12*	*100%*	*2.07*	*4,375*	*1,088*
6	*10.5*	*75%*	*1.79*	*7,016*	*1,711*
6	*9*	*50%*	*1.52*	*14,027*	*3,442*
6	*8.4*	*40%*	*1.42*	*20,763*	*5,092*
6	*7.8*	*30%*	*1.31*	*34,856*	*8,514*

Note: effect sizes reflect differences in risk and differ slightly from hazard ratios which reflect differences in hazard. Incidence rates are given per ***100*** person-year**s** (yearalthough absolute rates are lower given a 90-day follow-up period). . [1] represents estimates for SLE 18+ YOA interim analysis. [2] represents estimates for MS 18+ YOA final analysis. [3] represents estimates for SLE 18+ YOA in final analysis.

- ***Results of the monitoring queries conducted in October 2025 indicate a sample of 9544 dose 1 vaccinated, 7456 dose 2 vaccinated and 110893 unvaccinated individuals with pre-existing SLE are available among commercial Research Partners with data through April 2025. As such, it is expected that the primary safety objective will reach appropriate 80% power to detect a HR=1.51, assuming an incidence rate of 2 per 100 person years among unvaccinated and 3 per 100 person years among vaccinated (in line with observed rates among the unvaccinated). Notably, as we expect similar rates among the commercially insured and Medicare populations, the same sample size target is applied to both populations. Further, it is expected the sample would increase at the time the final analysis is completed given that a longer duration of data will be available at that time.***

~~See Appendix 3 for details on methods used for sample size calculations.~~

~~**Power calculations for final analysis in patients 18+ YOA:**~~

- ~~SLE : Based on these results, assuming a baseline severe flare rate of 12/100 person- years, approximately 3251 vaccinated patients with SLE with 13 227 unvaccinated patients are needed to detect a 40% (Hazard Ratio=1.44) increase in severe flares with 80% power. Over a 90-day period, this corresponds to a clinically meaningful increase in the rate of severe flares from 3% to 4.2% (1.2% absolute increase).~~
- ~~MS : With a baseline relapse rate of 8/100 person-years 3227 vaccinated patients with MS with 13 227 unvaccinated patients are needed to detect a 50% (Hazard Ratio= 1.53) increase in relapses with 80% power. Over a 90-day period, this corresponds to a clinically meaningful increase in the rate of relapse from 2% to 1% (1% absolute increase).~~
- ~~As noted above, these estimates are conservative as total follow-up time contributed per patient may be more than 90 days because patients can contribute follow-up time after both vaccine doses. Additionally, it is possible that more patients will be accrued in the database who meet the eligibility criteria at the time of analysis, and therefore the study might be powered to detect a lower effect size as shown in Table 9. Alternatively, if fewer patients are accrued, a decision can be made regarding whether accrual should be extended.~~

Power calculations for interim safety analysis (patients 18+ YOA with SLE):

~~Interim safety analyses are planned in adults 18+ YOA with SLE. Sample size will be lower in the interim analyses due to the shortened study period. Assuming a baseline severe flare rate of 12/100 person-years, it is expected that it would only be feasible for interim analyses to be 80% powered to detect a 75% (Hazard ratio = 1.84) increase in the risk of severe SLE flare. Detecting this risk would require 990 vaccinated patients with SLE with 3996 unvaccinated patients. It is possible that real-world uptake of RZV could results in a larger sample accrued in the database, in which case the interim analysis might be powered to detect a lower effect size. If sample size is not sufficient to detect at least a 100% increase in the risk of severe SLE flares (based on number of vaccinated and unvaccinated patients and number of outcomes), then interim safety analyses may not be conducted. Interim safety analyses are not planned in MS given the need to perform chart review to further evaluate the validity of the MS relapse algorithms prior to conducting safety analyses.~~

~~***Power calculations for effectiveness analyses***~~

- ~~The incidence of HZ in unvaccinated adults >65 YOA in the general population is approximately 10 ***per*** 1000 person-years [Izurieta, 2021], but a meta-analysis showed an approximately 2-fold higher risk in patients with SLE [Kawai, 2017]. Studies in SLE have shown rates of HZ of approximate 15-20 per 1000 person-years even among younger patients [Chakravarty, 2013; Chen, 2014; Yun, 2016]. Rates of HZ in MS are lower than in SLE, although are similar to that seen in the >65 YOA general population even among younger patients with MS, with an~~

~~expected overall rate of HZ in the MS population of approximately 10 ***per*** 1000 person-years and a rate of approximately 8 ***per*** 1000 person-years in patients 18-49 YOA [Chen, 2014].~~

- ~~Greater number of unvaccinated than vaccinated patients (at least a 4:1 ratio).~~
- ~~Average follow-up time of ***1.32***2.5 years based on ***the shortest observed follow-up in any cohort during the interim analysis. This is expected to be a conservative approach.***prior Sentinel data.~~

~~***Based on these results, with a baseline incidence of HZ of 20/1000 person-years in SLE in the overall population and VE of 50% (HR=0.5), sample size requirements are 912 vaccinated patients with SLE with 4,474 unvaccinated patients to provide 80% power. Results of the monitoring queries conducted in October 2025 indicate a sample of 9544 dose 1 vaccinated, 7456 dose 2 vaccinated and 110893 unvaccinated individuals with pre-existing SLE are available among commercial Research Partners with data through April 2025, therefore this sample size target is feasible.***~~

~~***With a baseline incidence of HZ of 10 per 1,000 person-years in MS and VE of 50% (HR=0.5), sample size requirements are 1,727 vaccinated patients with MS with 8,648 unvaccinated patients to provide 80% power. Among patients with MS, 11689 dose 1 vaccinated, 9284 dose 2 vaccinated and 123 761 unvaccinated individuals were identified in monitoring queries conducted in October 2025 among commercial Research Partners with data through April 2025, therefore this sample size target is feasible.***~~

~~***It is expected that sample size will be sufficient to detect an even smaller effect size (e.g., VE of 40%) as shown in Table 10.***~~

Table 10 Sample size calculation for effectiveness analyses under a range of assumed incidence rates for unvaccinated and vaccinated group and assumed *minimal detectable hazard ratio under a 4:1 matched cohort design* effect sizes (in hazard ratio)

~~Incidence rate in unvaccinated (in person-year, py)~~	~~Incidence rate in vaccinated (in person-year, py)~~	~~Effect size (percent reduction)~~	~~Hazard Ratio~~	~~Required person-years for vaccinated patients~~	~~Required person-years for unvaccinated patients~~	~~Required number of vaccinated patients (after adjusting for attrition)~~	~~Required number of unvaccinated patients (after adjusting for attrition)~~	~~Empirical power (and its 95% CI) from 1,000 replications of simulated data~~
~~20/1000 py~~	~~6/1000 py~~	~~70%~~	~~0.3~~	~~834~~	~~2700~~	~~400~~	~~1622~~	~~81.6% (79.2 – 84.0%)~~
~~15/1000 py~~	~~4.5/1000 py~~	~~70%~~	~~0.3~~	~~1112~~	~~3600~~	~~534~~	~~2162~~	~~82.1% (79.7 – 84.5%)~~
~~10/1000 py~~	~~3/1000 py~~	~~70%~~	~~0.3~~	~~1667~~	~~5900~~	~~800~~	~~3543~~	~~81.4% (79.0 – 83.8%)~~
~~8/1000 py~~	~~2.4/1000~~	~~70%~~	~~0.3~~	~~2084~~	~~6750~~	~~1000~~	~~4050~~	~~81.2%~~

	py							(78.8 – 83.6%)
20/1000 py	8/1000 py	60%	0.4	1250	4550	600	2733	82.4% (80.0 – 84.8%)
15/1000 py	6/1000 py	60%	0.4	1667	6067	800	3644	80.5% (78.0 – 83.0%)
10/1000 py	4/1000 py	60%	0.4	2500	9500	1199	5705	82.5% (80.1 – 84.9%)
8/1000 py	3.2/1000 py	60%	0.4	3125	11375	1499	6831	80.2% (77.7 – 82.7%)
20/1000 py 1	10/1000 py	50%	0.5	1900	7450	912	4474	81.2% (78.8 – 83.6%)
15/1000 py	7.5/1000 py	50%	0.5	2534	10067	1216	6046	79.5% (77.0 – 82.0%)
10/1000 py 2	5/1000 py	50%	0.5	3600	14400	1727	8648	79.9% (77.4 – 82.4%)
8/1000 py	4/1000 py	50%	0.5	4750	18125	2278	10885	81.0% c (78.6 – 83.4%)
20/1000 py	12/1000 py	40%	0.6	3084	12150	1472	7297	79.9% (77.4 – 82.4%)
15/1000 py	9/1000 py	40%	0.6	4223	16467	2026	9889	80.6% (78.1 – 83.1%)
10/1000 py	6/1000 py	40%	0.6	6167	24300	2958	14593	80.9% (78.5 – 83.3%)
8/1000 py	4.8/1000 py	40%	0.6	7709	30750	3698	18466	80.5% (78.0 – 83.0%)

[1] represents estimates for SLE 18+ YOA in final analysis; [2] represents estimates for MS 18+ YOA final analysis

See Appendix 3 for details on methods used for sample size calculations.

Incidence rate in unvaccinated (in person-year, py)	**Incidence rate in vaccinated (in person-year, py)**	**Effect size (percent reduction)**	**Hazard Ratio**	**Required person-years for vaccinated patients**	**Required person-years for unvaccinated patients**	**Required number of vaccinated patients (after adjusting for attrition)**	**Required number of unvaccinated patients (after adjusting for attrition)**
20	***6***	***70%***	***0.30***	***500***	***1,600***	***417***	***1,503***
15	***4.5***	***70%***	***0.30***	***667***	***2,134***	***557***	***2,004***
10	***3***	***70%***	***0.30***	***1,000***	***3,200***	***834***	***3,005***
8	***2.4***	***70%***	***0.30***	***1,250***	***4,000***	***1,043***	***3,756***
20	***8***	***60%***	***0.40***	***750***	***2,650***	***626***	***2,488***

~~15~~	~~6~~	~~60%~~	~~0.40~~	~~1,000~~	~~3,534~~	~~834~~	~~3,318~~
~~10~~	~~4~~	~~60%~~	~~0.40~~	~~1,500~~	~~5,400~~	~~1,251~~	~~5,070~~
~~8~~	~~3.2~~	~~60%~~	~~0.40~~	~~1,875~~	~~6,750~~	~~1,564~~	~~6,338~~
~~20~~	~~10~~	~~50%~~	~~0.50~~	~~1,200~~	~~4,500~~	~~1,001~~	~~4,225~~
~~15~~	~~7.5~~	~~50%~~	~~0.50~~	~~1,600~~	~~6,000~~	~~1,334~~	~~5,634~~
~~10~~	~~5~~	~~50%~~	~~0.50~~	~~2,400~~	~~9,100~~	~~2,001~~	~~8,544~~
~~8~~	~~4~~	~~50%~~	~~0.50~~	~~3,000~~	~~11,375~~	~~2,502~~	~~10,680~~
~~20~~	~~12~~	~~40%~~	~~0.60~~	~~2,084~~	~~8,100~~	~~1,738~~	~~7,605~~
~~15~~	~~9~~	~~40%~~	~~0.60~~	~~2,778~~	~~10,800~~	~~2,317~~	~~10,140~~
~~10~~	~~6~~	~~40%~~	~~0.60~~	~~4,167~~	~~16,300~~	~~3,475~~	~~15,304~~
~~8~~	~~4.8~~	~~40%~~	~~0.60~~	~~5,209~~	~~20,375~~	~~4,343~~	~~19,129~~

~~*Note: Incidence rates are given per 1,000 person-years. All power calculations performed using R statistical software.*~~

9.6.2 Power calculations for final analysis in patients 18+ YOA

~~Based on these results, with a baseline incidence of HZ of 20/1000 person-years in SLE in the overall population and VE of 50% (Hazard Ratio=0.5), sample size requirements are 912 vaccinated patients with SLE with 4474 unvaccinated patients to provide 80% power. With a baseline incidence of HZ of 10/1000 person-years in MS and VE of 50% (Hazard Ratio=0.5), sample size requirements are 1727 vaccinated patients with MS with 8648 unvaccinated patients to provide 80% power. It is expected that sample size will be sufficient to detect an even smaller effect size (e.g., VE of 40%) as shown in Table 10.~~

- ~~Age stratification in effectiveness analyses of 18+ YOA (final analyses): Subgroup analyses by age are of particular interest, given recent authorization of~~

  ~~RZV in patients ≥18 years old who are immunocompromised. VE is expected to be similar in the younger and older populations.~~

  ~~18-49 YOA subgroup: For VE of 50% (HR=0.5) and assuming a lower baseline incidence of HZ of 15/1000 person-years among patients 18-49 YOA with SLE, sample size requirements are 1216 vaccinated patients with SLE and 6046 unvaccinated controls. In MS assuming a baseline risk of 8/1000 person-years, sample size requirements are 2278 vaccinated patients and 10 885 unvaccinated patients to provide 80% power.~~

  ~~50+ YOA subgroup: With a VE of 50% (HR=0.5) and assuming a baseline incidence of HZ of 20/1000 person-years in patients ≥50 YOA with SLE, a sample of approximately 912 vaccinated patients with SLE with 4474 unvaccinated patients is expected to provide 80% power. In MS assuming a baseline risk of 10/1000 person- years sample size requirements are 1727 vaccinated patients and 8648 unvaccinated patients to provide 80% power.~~

9.6.3 Power calculations for interim effectiveness analysis in adults 18+ YOA

~~Interim analyses conducted among patients ≥18 YOA are expected to achieve the required sample size shown above for the final analysis of the 18+ YOA population (912 vaccinated and 4474 unvaccinated patients with SLE and 1727 vaccinated with~~

~~8648 unvaccinated patients with MS) to provide 80% power to detect an effect size of 50% reduction in HZ (HR=0.5). However, given that the population of 18-49 YOA is expected to be small in the interim analysis, accrual will continue for the full study.~~

~~9.7~~ 9.8 Data management

~~9.7.1~~ 9.8.1 Data handling conventions

~~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).~~

~~9.7.2~~ 9.8.2 Resourcing needs

Research ~~Data~~ Partners

9.7.3 Chart Reviews

- ~~A separate plan will be developed to detail the procedures for chart reviews.~~
- ~~Charts are not available for Medicare beneficiaries and are not available for 100% of patients in other data sources.~~
- ~~Chart review will only be conducted for the analysis of safety outcomes.~~
- ~~As detailed in Section 9.4, severe SLE flare for the potential interim safety analyses will only include the established administrative claims algorithms. Because algorithms for MS relapse have not been validated, MS relapse will not be assessed interim analyses. Chart review of possible MS relapses will be prioritized and will be initiated during the interim analyses, followed by severe SLE flare chart review prior to final safety analyses.~~
- ~~For final safety analyses, chart review will be undertaken using a random sample of approximately 100 cases [Pavlou, 2021] identified as having a severe SLE flare based on the claims-based algorithm among patients with chart review available (Table 1) and a random sample of approximately 100 cases identified as having any MS relapse based on the primary outcome definition as per Section 9.4 with chart review available. A stratified random sampling by vaccine status may be considered to ensure a balanced distribution of selected cases between vaccinated and unvaccinated groups. The random sample of approximately 100 charts, may be selected from one nationally representative data partner, or more than one if needed. The results of descriptive queries will facilitate this decision. Further details on the sampling approach and data partner selection will be provided in a separate plan for chart reviews.~~

- The PPV of the algorithms will be estimated. If the PPV of a claims algorithm is ≥70% then this algorithm will serve as the outcome definition for the final analysis. If PPV of claims algorithms are <70%, then the feasibility of alternative approaches will be evaluated, including refining administrative algorithms to achieve a PPV of >70% or using chart-adjudicated outcomes in the subset of patients with chart-review available.

Role of chart review for Severe Lupus Flare:

Potential interim safety analysis for ≥18 YOA: Administrative claims-based algorithms of severe flare (Table 2) will be the only outcome definition in the interim safety analyses. Although this analysis will be conducted prior to formal validation of the administrative algorithm, the algorithm is well established and has been used in multiple prior studies.

Final full study analysis for ≥18 YOA: Chart review will be conducted using a random sample of approximately 100 cases [Pavlou, 2021] of severe SLE flare identified using the claims-based algorithm to assess the PPV of the severe SLE flare algorithm. If the PPV of the severe flare algorithm is ≥70%, then all analysis will be conducted using the administrative claims-based algorithm to define the outcome of severe SLE flare. If the PPV is <70%, then the feasibility of alternative approaches will be evaluated, including refining administrative algorithms to achieve a PPV of >70% or using chart-adjudicated outcomes in the subset of patients with chart-review available.

- Mild and moderate flares are part of an alternative definition of any flare, but these flares are less clinically meaningful than severe flares. Also based on subject matter expert input mild and moderate flares are expected to be more difficult to accurately identify even with detailed chart review – for these reasons chart review will not be used to evaluate mild or moderate flares. If the PPV for the severe flare algorithm is < 70% then mild and moderate flares will not be assessed.

Role of chart review for any MS relapse:

Interim analyses: Given more limited data on the validity of administrative algorithms for MS relapse, MS relapse will not be assessed in interim analyses. Instead, chart review of MS outcomes will be prioritized in preparation for final analyses.

Final full study analysis in ≥18 YOA: Chart review of a random sample of approximately 100 subjects [Pavlou, 2021] meeting the primary relapse claims- based algorithm definition will be used to assess the PPV of the primary relapse definition and of the ***5*** alternative definitions detailed in Section 9.4. If the PPV of at least 1 of the administrative claims relapse algorithms is ≥70%, then the administrative algorithm with the highest PPV will be used for analyses. If the PPV is <70%, then the feasibility of alternative approaches will be evaluated, including refining administrative algorithms to achieve a PPV of >70% or using chart-adjudicated outcomes in the subset of patients with chart-review available.

- ~~Specific criteria for confirming severe SLE flares and MS relapses based on chart review will be determined as the project proceeds and will be detailed in a separate chart review plan.~~
- ~~Chart review criteria for defining severe SLE flare may be based on new major organ involvement as guided by the SLEDAI; although this index will not be formally recorded in clinical practice its elements can be used as a guide in creating a chart review tool [Mikdashi, 2015].~~
- ~~Chart review criteria for MS, based on input for subject matter experts, review may include having either new symptom attributable to MS lasting more than 24 hours and/or new demyelinating lesions on MRI.~~
- ~~If PPV of the claims algorithms are <70% and a secondary analysis is planned using chart-adjudicated outcomes, the study team may consider whether chart review should be undertaken among patients not meeting claims-based algorithms for SLE flares or MS relapses, but who may have outcomes of interest, including:~~
  - ~~Patients with SLE newly initiating mycophenolate, belimumab, anifrolumab, azathioprine, or glucocorticoid doses 20-40 mg/day (a minority of whom might be found on chart review to have a severe SLE flare)~~
  - ~~Patients with MS receiving a new DMT or receiving a new glucocorticoid prescription or infusion that is not accompanied by an outpatient diagnosis of MS~~

~~9.8~~ 9.9 Data analysis

~~Interim analyses for effectiveness will be conducted in patients ≥18 YOA following the same methods as outlined below. Additionally, interim analyses for safety will be conducted in patients ≥18 YOA with SLE if sample size permits. Interim safety analyses will not be conducted in MS given the need for chart review prior to using administrative algorithms. Interim analyses will include evaluation of HZ risk and evaluation of severe SLE flare using administrative claims algorithms. Secondary outcome such as any SLE flare will not be assessed in interim analyses. The final analyses will include an assessment of the entire ≥18 YOA population, but evaluation of age subgroups 18-49 and 50+ will be a key subgroup of interest in final analyses, recognizing that the 50+ group is expected to disproportionately contribute to interim analyses.~~

~~*Assessing and accounting for the impacts of COVID-19*~~

~~The COVID-19 pandemic could potentially impact results by affecting not only the rates of vaccination, but more importantly the capture of outcomes, with patients avoiding interactions with the healthcare system early in the pandemic beginning March 2020. [George, 2020; Moynihan, 2021; George, 2021]. Vaccination rates will be examined descriptively to evaluate the trend in RZV vaccination and to determine when RZV vaccination rates begin to rebound after 01 March 2020. This examination will inform what time period is the most likely to be potentially affected by the pandemic in the planned analyses. Analyses will be conducted that compare the frequency of outcomes during the height of the COVID-19 pandemic versus time prior~~

~~to 01 March 2020, and sensitivity analyses will be conducted excluding the time period most likely to be affected by the pandemic (e.g., right censoring patients with earlier index dates at 01 March 2020 and excluding patients with index dates during the time period found to be most affected by the COVID-19 pandemic).~~

~~9.8.1~~ 9.9.1 Descriptive analyses

All analyses will be conducted separately in SLE and MS populations. First, descriptive analyses of the study populations will be conducted comparing the baseline characteristics in the vaccinated and unvaccinated groups. ~~Prior to conducting the safety analysis of severe SLE flares or any MS relapses, kernel density plots and tree-scan analysis will be used to assess the temporal distribution of severe SLE flares or any MS relapses to assess for evidence that the choice of 90 days follow-up time is appropriate. If there is a peak of SLE flares or any MS relapses after vaccination that extends beyond 90 days (particularly among patients without flares/relapses during the baseline period), or which is shorter than expected (e.g., ends within 60 days) this information will be used to inform sensitivity analyses with different follow-up durations.~~

Additionally, temporal patterns of vaccination will be evaluated using histograms of the number of RZV vaccinations ***and outcomes*** by year-month.

The COVID-19 pandemic could potentially impact results by affecting not only the rates of vaccination, but more importantly the capture of outcomes, with patients avoiding interactions with the healthcare system early in the pandemic beginning March 2020 [George, 2020; Moynihan, 2021; George, 2021]. Vaccination rates will be examined descriptively to evaluate the trend in RZV vaccination and to determine when RZV vaccination rates begin to rebound after 01 March 2020. This examination will inform what time period is the most likely to be potentially affected by the pandemic in the planned analyses. Sensitivity analyses will be conducted excluding the time period most likely to be affected by the pandemic (see Sections 9.9.2.2.1 and 9.9.3.1.1).

Descriptive information on ~~and~~ the number of days between the 2 doses for 2 dose recipients, with the frequency of shorter intervals <2 months between doses of particular interest in this population. Additionally, the frequency of receiving RZV doses <28 days apart will be ***described***.~~assessed, with consideration of whether this should be an exclusion for safety analyses~~. Distributions of ***study outcomes*** ~~severe SLE flares or any MS relapses as well as HZ and post-herpetic neuralgia,~~ by vaccination status, will be collected through the follow-up period and graphed ***using Kaplan Meier curves***.

~~9.8.2~~ 9.9.2 Analysis for ~~primary and secondary~~ safety objectives

9.9.2.1 **Primary safety ~~objectives~~ *objective 1***

To evaluate ***risk of hospitalized SLE flare*** ~~safety outcomes~~ after any dose of RZV, separate cohorts will be created for RZV dose 1 and RZV Dose 2, each with matched unvaccinated comparators. This approach allows potential confounders to be balanced separately at RZV Dose 1 and RZV Dose 2, which is particularly important given that

doses may at times be separately significantly in time, while important confounders such as medications may also change over this timeframe. In addition, this approach simplifies the key secondary analysis that separately assesses RZV Dose 1 and RZV Dose 2 ***(see Section 9.8.2.2).*** ~~Details of how RZV Dose 1 and RZV Dose 2 cohorts will be analyzed to obtain a risk estimate after any RZV dose while also accounting for correlations within patients will be provided in the SAP. Different analytical approaches will be considered including combining the risk estimates analytically, a partly conditional Cox model, or other modeling methods as appropriate. If additional models are selected, the SAP will be adapted to reflect these changes, with~~ final

Propensity scores will be used to balance measured confounders, ~~(e.g., through inverse probability weighting, details to be provided in the SAP)~~ among patients receiving RZV Dose 1 and comparator patients with no prior RZV vaccination.

Covariate balance will be assessed before and after applying propensity scores using standardized mean differences, with ***absolute*** standardized differences >0.1 suggestive of important imbalance [Austin, 2009a; Austin, 2009b]. Any imbalanced factors after weighting suggests residual confounding, therefore ***adjustments to the propensity score model or alternative modeling strategies will be considered.*** ~~these variables will be included as additional covariates in the Cox proportional hazard models.~~

The risk of hospitalized ~~Severe~~ SLE flares ~~and any MS relapses~~ will be assessed ~~separately~~ in each cohort (Dose ***1 or Dose 2)*** ~~1 and Dose 2) first descriptively (e.g., incidence in each group), and~~ using time-to-event analysis with Cox proportional hazard models, assessing ~~for~~ violations of the proportional ***hazard*** ~~hazards~~ assumptions (***based on visual assessment of Kaplan-Meier plots and additional diagnostics [e.g., Schoenfeld residual or log(−log) plots]).***

To assess the risk of ***hospitalized*** SLE ~~flares~~ after any dose of RZV, risk assessments after RZV Dose 1 and Dose 2 will be combined to provide a single risk estimate using the ***bootstrapping method outlined*** ~~(details~~ in the SAP; ~~with additional~~ ***specialized*** methods ***are required to properly*** account for the correlation ~~within patient such as partly conditional Cox models or other modeling methods as appropriate).~~ ***between two estimated risks given the expected overlap in the two cohorts.***

- Occurrence of ***hospitalized*** ~~the severe~~ SLE flare ~~or any MS relapse~~
- End of data availability or study period ~~(approximately March 2023 for interim analysis or March 2025 for full study however date may differ depending on dataset)~~
- RZV dose (***any subsequent*** ~~second~~ dose for vaccinated patients or first RZV dose in the case of ***unvaccinated comparators*** ~~controls~~)

9.9.2.2 **Subgroup/stratified secondary analyses Secondary safety objective 1**

This analyses will use the same methods (IPTW Cox proportional hazards models) as the primary analyses, except risk assessments after RZV Dose 1 and Dose 2 ***will be reported separately; they will not*** be combined to provide a single risk estimate; ***thus***

no bootstrapping will be performed. ***This analysis will also inform whether there is evidence for different effects by dose***.

9.9.2.2.1 Sensitivity analysis for secondary safety objective 1

~~Pre-specified subgroup/stratified analyses will be undertaken to assess potential effect modifiers that could result in differential risks of disease SLE flares or MS relapses after any RZV dose. Propensity scores will be recalculated within each subgroup to ensure covariate balance within subgroups. Sub-group analyses are not planned for interim analyses given sample size limitations. Specific subgroups for the final analyses are as follows:~~

- ~~MS disease severity variables, which affect relapse risk~~
  - ~~Current use and absence of use of highly effective therapy (in patients with MS) (see Table 8)~~
  - ~~Presence and absence of MS relapse in the 91-365 days prior to the index date~~

~~Other secondary analyses:~~

- ~~Secondary objectives: Separate assessment of severe SLE flare or any MS relapse risk after RZV Dose 1 and after RZV Dose 2 to assess risk after each dose separately and evaluate whether there is evidence for different effects after Dose 1 and Dose 2 (as could conceivably occur if severe SLE flares or any MS relapse after Dose 1 led some patients not to receive Dose 2, although this situation is expected to be uncommon).~~
- ~~Assessment of any SLE flare (as opposed to only severe flares), noting limitations that the accuracy of identifying mild or moderate flares is expected to be lower than for severe flares, and that severe flares are of the most clinical importance~~
- ~~Assessment of an alternative follow-up period other than 90 days (either 60 days or an alternative follow-up time informed by tree scan analyses described in Section 9.8.1). Assessment of a longer follow-up period (e.g., 120 days) will also be considered based on the results of descriptive analyses.~~
- ~~If PPV of claims algorithms is <70%, using chart-confirmed adjudicated SLE flares or MS relapses as the outcome of interest, restricted to datasets/patients with chart- review available~~

~~Sensitivity analyses~~:

The following sensitivity analysis detailed below will be conducted for secondary safety objective 1. These analyses will use the same methods (i.e. IPTW Cox proportional hazards regression) as described in Section 9.8.2.2.

- ***Repeating analyses using sensitivity outcome definitions of treatment-based SLE flare, and hospitalized or treatment-based SLE flare (as defined in Table 2)***
- Repeating the ~~dose-specific~~ analyses restricted to patients with SLE who are currently treated with a non-glucocorticoid

immunosuppressive/immunomodulatory therapy at the index date (expected to have even less misclassification of SLE or MS diagnoses)

- Repeating the ~~dose-specific~~ ***analyses*** after excluding patients who also have administration of other ***influenza, pneumococcal or COVID-19*** vaccinations within 7 days before or after receipt of RZV to avoid flare/relapse outcomes that could be related to a different vaccine
- Repeating the ~~dose-specific~~ analyses after excluding time during the height of the COVID-19 pandemic as outlined ***in Section 9.8***
- ***9.9.2.2.2 Stratified analyses for secondary safety objective 1***

Pre-specified stratified analyses will be undertaken to assess potential effect modifiers that could result in differential risks of ***hospitalized*** SLE flares after RZV. ***Stratified analyses will use the same methods (i.e., Cox proportional hazards regression) as described in Section 9.8.2.2 , except strata will be treated as separate cohorts and*** propensity scores will be recalculated within each ***strata*** to ensure covariate balance ***in each analysis***. ***If any strata has inadequate*** sample size***, exposure or outcome counts to allow for regression modelling, descriptive results will be shared instead of inferential results.***

Specific strata for the final analyses are as follows:

CCI [redacted]

- ***Sensitivity analysis will be conducted with the MS relapse outcome defined using sensitivity outcomes defined as defined in Table 3. Additionally, subgroup analysis will also be conducted among individuals using an immunosuppressive/immunomodulatory therapy at index.***

~~9.8.3~~ 9.9.3 Analysis of effectiveness objectives

Covariate balance will be assessed before and after applying propensity scores using standardized mean differences, with ***absolute*** standardized differences >0.1 suggestive of important imbalance [Austin, 2009a; Austin, 2009b]. ***If any*** covariate ***demonstrates*** imbalance after weighting, suggesting residual confounding, ***adjustments to the propensity score model or alternative modeling strategies*** will be ***considered***. Similarly, in secondary analyses assessing the effectiveness of a single RZV dose, the same approach will be used, noting that propensity scores will be estimated at Dose 1 and receipt of RZV Dose 2 will be a censoring event.

9.9.3.1* ~~Primary~~ *Analysis* of primary effectiveness objectives *1 and 2

IPTW Cox proportional hazards models will be used for time-to-event analyses assessing risk of HZ, with follow-up beginning 30 days after the index date (to allow the development of immunity), assessing for violations of the proportional hazards assumptions ***based on a visual assessment of Kaplan-Meier plots and other diagnostics. Vaccine effectiveness is calculated as VE = (1 - HR)*100.***

- RZV dose (***receipt of a third*** dose for vaccinated patients or first RZV dose in the case of ***unvaccinated comparators***)
- ***9.9.3.1.1 Sensitivity analysis of primary effectiveness objectives 1 and 2***

Similar methods as described in Section 9.8.3.1 will be implemented in these sensitivity analyses detailed below ~~of the 2-dose VE objectives~~. In each case (unless otherwise noted) propensity scores will be re-estimated among the subset of patients being analysed.

- ***Estimating 2-dose VE in*** patients with SLE or MS who are currently treated with a non-glucocorticoid immunosuppressive/immunomodulatory therapy at the index date (expected to have even less misclassification of SLE or MS diagnoses).
- ***Estimating 2-dose VE after*** exclusion of time during the height of the COVID-19 pandemic. ~~as outlined in Section 9.8~~

- ~~**Subgroup/stratified secondary analyses for HZ:**~~

9.9.3.1.2 Stratified analysis of primary effectiveness objectives 1 and 2

Pre-specified stratified analyses will be undertaken among patients receiving two doses of RZV to assess potential effect modifiers that could result in differential VE, ***if sufficient sample size is available***. Propensity scores will be recalculated within each ***strata*** to ensure covariate balance within ***the analysis. If any strata has inadequate sample size, exposure or outcome counts to allow for regression modelling, descriptive results will be shared instead of inferential results***.

Specific ~~subgroups~~ ***strata*** for the final analyses are as follows:

- ~~Secondary objective: Age (18-49, ≥50 – key subgroups of interest given differences in HZ risk by age and recent extension of approval of RZV to high-risk younger populations)~~
- ~~Secondary objective: Sex (male, female)~~
- ~~Secondary objective: Race/ethnicity (in Medicare and in any other data sources where race/ethnicity data is available in sufficient numbers)~~
- SLE disease severity variables, which may affect HZ risk:
  - SLE disease severity (mild, moderate, severe)
  - Lupus nephritis ***(yes/no)***
- MS disease severity variable, which may affect HZ risk:

- ~~Presence and absence of~~ MS relapse in the 91-365 days prior to the index date ***(yes/no)***

- ~~Assessment of therapies that may impact VE or are specifically associated with HZ risk (note that some medication categories may be combined or excluded if the size of individual categories is insufficient)~~
  - ~~SLE medication categories (mutually exclusive) based on current use at the index date (Table 7):~~
    - ~~Highly immunosuppressive therapy (cyclophosphamide or rituximab)~~
    - ~~Less immunosuppressive therapy without use of highly immunosuppressive therapy,~~
    - ~~Anti-malarial therapy alone~~
    - ~~None of the above~~
  - ~~MS medication categories (mutually exclusive) based on current use at the index date (Table 8)~~
    - ~~Anti-CD20 therapy (particular effects on VE)~~
    - ~~SP1 receptor modulator therapies (associated with HZ risk)~~
    - ~~Other highly effective and immunosuppressive therapies~~
    - ~~Highly effective and less immunosuppressive therapies,~~
    - ~~Less effective and less~~ immunosuppressive therapies
    - ~~None of the above~~

~~Other secondary analyses aligned with secondary objectives (for HZ and PHN)~~:

- ~~VE after a 1 dose of RZV as described above, censoring at the time of RZV Dose 2~~
- ~~Assessment of VE after two doses of RZV by time since vaccination, in 1 year blocks, to assess waning immunity~~
- ~~Time between RZV doses, categorized depending on distribution of dosing in the cohort (e.g., 28-56 days, 57-183 days, >183 days), to determine the effects of vaccine spacing on VE~~
- ~~Assessment of the incidence of PHN in vaccinated (2 doses) and unvaccinated~~

~~Sensitivity analyses for HZ:~~

- ~~Exclusion of patients with medication changes around the time of vaccination~~
  - ~~Therapy may be switched or added around the time of vaccination (e.g., vaccination may occur prior to a therapy start). The frequency of new initiations in the 3 months after RZV Dose 2 will be assessed, with a particular interest in SP1 receptor modulator therapy in MS (since plans to start an SP1 receptor modulator may be the reason for RZV dosing).~~

- ~~A sensitivity analysis will be conducted assessing VE among patients who did not switch therapy in the 3 months after RZV Dose 2. This will help address the concern regarding the impact of highly immunosuppressive therapies on VE given that patients receiving a vaccine might be more likely to switch to a therapy that increases the risk of HZ after vaccination (which will not be accounted for in the propensity scores).~~

- ~~Including SLE and MS medication categories outlined in the subgroup analyses above as time-varying covariates in the primary analyses of VE after two doses of RZV.~~

- ~~Repeating the primary and subgroup analyses restricted to patients with SLE or MS who are currently treated with a non-glucocorticoid immunosuppressive/immunomodulatory therapy at the index date (expected to have even less misclassification of SLE or MS diagnoses)~~

- ~~Restricting to patients with at least 2 years of data available prior to the index date (instead of just 1 year) to address concerns that some patients thought to be unvaccinated could have received RZV prior to entry in the dataset~~

- ~~Exclusion of time during the height of the COVID-19 pandemic as outlined above~~

9.9.3.2. Analysis of secondary effectiveness objectives 1 to 8

Similar methods as described in Section 9.8.3.1 will be implemented for the analysis of secondary objectives 1-8, with specific deviations as described below.

9.9.3.2.1. Secondary effectiveness objectives 1 and 2:

For secondary VE objectives 1 and 2, the effectiveness of 1 RZV dose will be evaluated using Cox proportional hazards models, with IPTW to balance covariates as described above. However, in these analyses, propensity scores will be estimated at Dose 1 and receipt of RZV Dose 2 will be a censoring event.

9.9.3.2.2. Secondary effectiveness objectives 3 and 4:

For secondary VE objectives 3 and 4, the effectiveness of 2 doses of RZV within key strata will be evaluated using Cox proportional hazards models, using data handling and analytic methods detailed in Sections 9.8.3.1.2.

The results will be stratified by:

- ***Age (18-49 years; ≥50 years)***
- ***Sex (male; female)***
- ***Race/ethnicity (where adequate race/ethnicity data are available)***

9.9.3.2.3. Secondary effectiveness objectives 5 and 6:

For secondary VE objectives 5 and 6, the effectiveness of 2 doses of RZV will be evaluated using Cox proportional hazards models, with IPTW to balance covariates. Specific modelling changes will allow VE to be modelled by:

- ~~Assessment of VE after two doses of RZV by Time~~ since vaccination, in 1-year blocks, to assess waning immunity
- Time between RZV doses, categorized depending on distribution of dosing in the cohort (e.g., 28-56 days, 57-183 days, >183 days), to determine the effects of vaccine spacing on VE

9.9.3.2.4. Secondary effectiveness objectives 7 and 8:

Assessment of the incidence of PHN ~~in vaccinated (2 doses) and unvaccinated~~ will be conducted using the same methods as those ~~in the primary effectiveness analyses~~ ***section 9.8.3.1***, except the outcome being evaluated will be PHN ***and only incidence will be estimated***.

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[redacted]

~~9.9~~ 9.10 Quality control

Research **~~Data~~ Partners**

~~9.10~~ 9.11 Limitations of research methods

- This study implements a definition of mild, moderate, or severe SLE flares based on previously published algorithm by Garris et al 2013 ***for interim analyses***.
- ***Updated outcome algorithms were developed based on findings of the chart review and with clinical input to increase algorithm specificity for final analyses. This is expected to reduce the outcome rate for final analyses, but improves validity of the study findings.***
    - ***The updated SLE flare algorithm represents a component of the SLE flare algorithm used for interim analyses. The PPV of this component of the algorithm was >70% among the subgroup of adjudicated cases that met this definition. However, this PPV estimate is based on a small sample of cases.***
    - ***The updated MS relapse algorithm was developed based on clinical input. Because this algorithm has not been validated, outcome misclassification is possible and the magnitude is unknown; therefore it will be evaluated only as an*** CCI [redacted]

5. ***The mean follow-up time for effectiveness analyses is expected to be at least 1.32 years, based on interim analyses. The ability to assess durability of VE at later time points is limited.***

8. Alternative reasons for ~~severe~~ SLE flare or ~~any~~ MS relapses and/or HZ: We have not incorporated alternative reasons for flare in this protocol such as COVID vaccination, which has been reported to be associated with flares of inflammatory conditions, and VZV reactivation [Fan, 2012; Rotondo, 2021; Zavala-Flores, 2021; Heshin-Bekenstein, 2022; Fragoso, 2022; Michelena, 2022]. This is beyond the scope of the current protocol but may be considered descriptively in sensitivity analyses.

9**.** Medication initiations following RZV vaccination: Some patients may receive vaccination preferentially around the time of a new therapy initiation (e.g., SP1 receptor modulators), and the therapy initiated may increase the risk of HZ.- ~~Sensitivity analyses are planned to examine the impact of treatment switches or~~ ***A descriptive characteristic is included to define immunosuppressive*** therapy additions ***in the 3 months*** after vaccination.

Research ~~Data~~ Partners

PROTECTION OF HUMAN SUBJECTS

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

Research **~~Data~~ Partners**

GlaxoSmithKline Biologicals SA

Vaccines R & D

Protocol Amendment *2*

eTrack study number and Abbreviated Title:	215104 (EPI-ZOSTER-041 VS US DB)
Amendment number:	Amendment 2
Amendment date:	10 August 2023
Protocol Approved	Final: 02 June 2022 Amendment 1: 02 December 2022

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

PASS INFORMATION

Contributing Authors (*Amended 10 August 2023*):	PPD ***GSK***

MARKETING AUTHORIZATION HOLDER

MAH contact person (*Amended 21 July 2023*):	PPD PPD ~~(interim)~~, Viral Non-Respiratory Epidemiology, GSK

Responsible parties

Sponsor contact (*Amended 10 August 2023*)	PPD PPD ~~(interim)~~, Viral Non-Respiratory Epidemiology, GSK
Study Teams (*Amended 10 August 2023*)	Harvard Pilgrim Health Care Institute PPD

GSK

PPD

Section 9.3.2

- Diagnoses of HZ or PHN during the baseline period (see codes in Annex 13).
  - This exclusion refers to diagnoses of HZ or PHN from hospital, emergency department, or ambulatory visits ***(all care settings)*** even if not accompanied by an anti-viral dispensing.

Section 9.4.1

- Systemic Lupus Erythematosus:

≥3 visits/encounters for SLE (ICD-10 M32.1*, ICD-9 710.0), each at least 30 days apart from each other, including inpatient, ***ambulatory, and emergency department (ED)*** ~~hospital discharge~~ diagnoses (***all care setting***, any position) ~~or physician visit claims (ambulatory visit [AV] or emergency department [ED] visit)~~ in the entire enrollment history prior to the index date

  - In addition, the following will be required to ensure that the diagnosis of SLE is a current diagnosis (rather than a historical or rule-out diagnosis that was later considered to be incorrect): 1 inpatient, 1 ED or 2 ~~AV~~ ***ambulatory*** diagnoses for SLE ≥30 days apart during the 365-day baseline period (Lokhandwala, 2021).

- Lupus Nephritis:

≥1 visits/encounters with ICD-10 diagnoses of lupus nephritis (M32.14) from inpatient, ~~AV~~ ***ambulatory*** or ED visits ***(all care settings)*** in the year prior to the index date (any diagnosis position)

OR ≥3 visits/encounters with ICD-10 diagnoses of acute or chronic glomerulonephritis, acute or chronic renal failure, nephritis or nephrotic syndrome, renal failure or proteinuria from inpatient, ~~AV~~ ***ambulatory***, or ED visits ***(all care settings),*** ~~(~~any position~~),~~

- Multiple Sclerosis:

≥3 MS-related claims (ICD-10 G35) of any combination of ***encounters from any care setting (***inpatient ~~visit/encounter~~ (any position), ~~AV~~ ***ambulatory*** ~~visit/encounter~~, ED ~~visit/encounter~~, or MS-specific disease- modifying therapy (DMT) fills/infusions (see Table 8) for medication list) during the one-year baseline period, requiring at least one of these to be an ***encounter with*** ~~inpatient, AV, or ED~~ diagnosis of MS. Of note, because a combination of visit diagnoses and DMT will meet the definition of MS, a look-back

period >1 year is not needed to identify patients with MS, unlike in SLE where more time is needed to allow 3 SLE diagnoses to occur.

Section 9.4.3.1

- ***Requiring glucocorticoid prescriptions to be new prescriptions (no prior fills for oral glucocorticoids in the preceding 90 days) to avoid capturing patients filling a routine glucocorticoid prescription rather than being treated for MS relapse.***
- Incorporating the modifications listed above, the ~~5~~ ***6*** algorithms of relapse that will be assessed are detailed in Table 3.
- ***Alternative definition 5: MS diagnosis (or diagnoses of optic neuritis or transverse myelitis) in the inpatient care setting in the primary diagnostic position***

  OR

MS diagnosis from an ambulatory visit with evidence of glucocorticoid infusion or new glucocorticoid dispensing (no preceding glucocorticoid dispensing in the preceding 90 days, Table 6) within 7 days before or 30 days after the MS diagnosis.*

The relapse date is the date of inpatient admission, or the earliest of glucocorticoid dispensing/infusion or ambulatory visit date.

***** Note that if requiring new glucocorticoid dispensing is found to have improved performance, then incorporating this requirement into other alternative algorithms involving glucocorticoid dispensing may also be considered.***

Section 9.4.3.2

- An ICD-10 diagnosis code for HZ (B02.xx) ***from any care setting*** ~~hospital~~ ***(inpatient***, emergency department, or ambulatory visit) ~~diagnoses~~

  AND
- Dispensing for an oral antiviral (acyclovir, valacyclovir, or famciclovir) within 7 days before or after the HZ diagnosis
- The HZ date is the date of the ~~hospital, emergency department, or ambulatory visit~~ ***encounter with the HZ diagnosis code***

Section 9.4.4

- Number of ambulatory visits ~~(AV)~~ in the 365 days prior to the index date (continuous)
- ***Number of mild SLE flares in 365 days prior the index date***
- ***Number of moderate SLE flares in 365 days prior the index date***
- ~~Number of rheumatologist outpatient visits in the 365 days prior to the index date (for SLE)~~

• ~~Number of neurologist outpatient visits in the 365 days prior to the index date (for MS)~~
Section 9.5
The data are organized as: o ***Ambulatory Visits (AV): includes visits at outpatient clinics, same day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes Emergency Department encounters. Transfer from AV facility to an ED facility starts a new encounter at the new facility*** o ***Emergency Department (ED): includes ED encounters that become inpatient stays through hospital admission. In this scenario, ED is one encounter, Inpatient Hospital Stay after admission from the ED is a second encounter. ED data should be identified before hospitalization data to ensure that ED with subsequent admission won't be rolled up in the hospital event. Transfer from one ED facility to another ED facility starts a new encounter at the new facility. Excludes urgent care visits.*** o ***Inpatient Hospital Stay (IP): includes all inpatient stays, same-day hospital discharges, and other acute hospital care where the discharge is after the admission date. Transfer from one facility to another starts a new encounter at the new facility.*** o ***Non-Acute Institutional Stay (IS): includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays. Transfer from one facility to another starts a new encounter at the new facility.*** o ***Other Ambulatory Visit (OA): includes other non-overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.*** ***When capturing ambulatory visits, OA and AV settings will be used. IP will be used when capturing only inpatient settings (IS will only be used when all settings is specified). ED will be used when capturing only ED settings. All setting will be used when capturing "any care settings". Any revisions to this implementation will be reflected in the technical specifications.***
Section 9.7.3
Final full study analysis in ≥18 YOA: Chart review of a random sample of approximately 100 subjects (Pavlou, 2021) meeting the primary relapse claims- based algorithm definition will be used to assess the PPV of the primary relapse definition and of the ~~4~~***5*** alternative definitions detailed in Section 9.4

GlaxoSmithKline Biologicals SA

Vaccines R & D

Protocol Amendment *1*

eTrack study number and Abbreviated Title:	215104 (EPI-ZOSTER-041 VS US DB)
Amendment number:	Amendment 1
Amendment date:	02 December 2022
Protocol Approved	Final: 02 June 2022

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

MAH contact person (*Amended 02 December 2022*):	PPD ~~Clinical and Epidemiology Project Lead~~ PPD ***, MD, PhD*** PPD ***(interim), Viral Non-Respiratory Epidemiology, GSK***

Responsible parties

Sponsor contact (*Amended 02 December 2022*)	PPD ~~, PhD Clinical and Epidemiology Project Lead~~ PPD PPD ***(interim), Viral Non-Respiratory Epidemiology, GSK***
Study Teams	University of Pennsylvania • ***Prime Insights, LLC***

Section 7. RATIONALE AND BACKGROUND

- One study, which evaluated the effectiveness of RZV in a subgroup of patients ≥***50***~~65~~ YOA

Section 8. RESEARCH OBJECTIVES

Primary effectiveness objectives:

- To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥≥18 years with pre-existing SLE
- To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥≥18 years with pre-existing MS

Secondary effectiveness objectives

- To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥≥18 years with pre-existing SLE To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥≥18 years with pre-existing MS
- To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥≥18 years with SLE, stratified by age (18-49; ≥50 years) and sex*
- To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥≥18 years with MS, stratified by age (18- 49; ≥50 years) and sex*
- To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥≥18 years with SLE, by time since vaccination and time interval between 2 doses
- To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥≥18 years with MS, by time since vaccination and time interval between 2 doses

Exploratory effectiveness objectives

CCI [redacted]

Section 9.2. Overview of study design

- Data sources include eight selected Data Partners that participate in the FDA's Sentinel System or Medicare. ***Patients enrolled in Medicare will be analyzed separately from patients enrolled in Sentinel Data Partners.***

Section 9.3.1. Study population to evaluate the safety of RZV

- ***For sentinel Research Partners:*** 365 days of continuous enrollment with medical and prescription coverage (allowing ≤45-day administrative gaps in coverage) prior to the index date (baseline period). ***For Medicare: continuous enrollment in Medicare part A/B/D (with no part C) one-year prior to the index date (allowing 1 months gap in enrollment***
- Met criteria for SLE or MS prior to the index date ~~using all available data, with healthcare encounters for SLE or MS present during the baseline period to indicate that diagnoses of SLE or MS are current at the time of RZV vaccination. This requirement avoids historical or rule-out diagnoses of SLE or MS that were later considered by treating physicians to be incorrect, identifying a population at risk for severe SLE flares or any MS relapses~~
- ***Note: The frequency of receiving RZV doses <28 days apart will be assessed and will be an exclusion criterion if frequency is <5%. Sex is required for matching and in rare cases in which sex is missing or classified as "Other," this will also be an exclusion.***
- Unvaccinated patients will be matched to vaccinated patients by data partner, sex, and age ~~deciles~~, and assigned the same index date as the vaccinated patients, to ensure calendar year and seasonality is balanced across groups.
- Unvaccinated patients will be matched to each vaccinated patient by data partner, sex, and age ~~deciles~~ to ensure an overall ***sample size*** ~~unvaccinated: vaccinated ratio~~ of approximately 4 ***times unvaccinated to vaccinated*** ~~:1~~**(i.e., sample size ratio of approximately 4 :1).**
- Added ***unvaccinated controls for each dose*** to Figure 1: Cohort design to assess vaccine safety

Section 9.3.2. Study population to evaluate the effectiveness of RZV

- ***For sentinel data partners:*** 365 days of continuous enrollment with medical and prescription coverage (allowing ≤45-day administrative gaps in coverage) prior to the index date (baseline period). ***For Medicare: continuous enrollment in Medicare part A/B/D (with no part C) one-year prior to the index date (allowing 1 months gap in enrollment***
- The same selection process described in the safety analysis Section 9.3.1 above will be used to select ***an overall sample size of unvaccinated that is 4 times the*** ~~approximately 4 unvaccinated patients for each~~ vaccinated **(i.e., sample size ratio of approximately 4 :1),** ~~patient~~ matched on data partner, sex, and age~~ deciles and assign~~. Unvaccinated patients ***will be assigned*** the same index date as the matched vaccinated patient.
- ***Note: Sex is required for matching and in rare cases in which sex is missing or classified as "Other,"this will also be an exclusion.***

9.4.4. Covariates

Table 4:

- ***COVID-19 infection in the 90 days prior to the index date***
- ***COVID-19 vaccination in the 90 days prior to the index date***

9.7.1. Chart Reviews

- ***The random sample of approximately 100 charts, may be selected from one nationally representative data partner, or more than one if needed. The results of descriptive queries will facilitate this decision***. Further details on the sampling approach ***and data partner selection*** will be provided in a separate plan for chart reviews.

ANNEX 6 PROTOCOL AMENDMENT 3 SPONSOR SIGNATORY APPROVAL

eTrack study number and Abbreviated Title	215104 (EPI-ZOSTER-041 VS US DB)
Date of protocol	Amendment 3 Final 12 Dec 2025
Title	Safety and effectiveness of Recombinant Zoster Vaccine (RZV) in adults ≥18 years of age with Systemic lupus erythematosus (SLE) or Multiple sclerosis (MS)
Sponsor signatory	***Huifeng Yun, MD, PhD*** ***Head, Viral Non-Respiratory Epidemiology***
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 7 PROTOCOL AMENDMENT 3 PHARMACOVIGILANCE SIGNATORY APPROVAL

eTrack study number and Abbreviated Title	215104 (EPI-ZOSTER-041 VS US DB)
Date of protocol	Amendment 3 Final 12 Dec 2025
Title	Safety and effectiveness of Recombinant Zoster Vaccine (RZV) in adults ≥18 years of age with Systemic lupus erythematosus (SLE) or Multiple sclerosis (MS)
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.

ANNEX 8 PROTOCOL AMENDMENT 3 INVESTIGATOR AGREEMENT

I agree:

- To conduct the study in compliance with this protocol, any 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 GlaxoSmithKline Biologicals SA (GSK).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the marketed product *Shingrix* and 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.
- To co-operate with a representative of GSK in the monitoring process of the study and in resolution of queries about the data.
- 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 1 year following completion of the study.
- Agree that GSK may disclose any information 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.

Title	Safety and effectiveness of Recombinant Zoster Vaccine (RZV) in adults ≥18 years of age with Systemic lupus erythematosus (SLE) or Multiple sclerosis (MS)
Investigator name	Richard Platt, Harvard Medical School & Harvard Pilgrim Health Care Institute
Signature	_____
Date	_____

ANNEX 9 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[3]	☒	☐	☐	6
1.1.2 End of data collection[4]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	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:	☒	☐	☐	4, 7, 8, 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)	☒	☐	☐	4, 7, 8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	4, 7, 8, 9.2, 9.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7, 8
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

[3] 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.

[4] 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)	☒	☐	☐	9.2
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2, 9.4, 9.6
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	4, 8, 9.9.2, 9.9.3
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))	☒	☐	☐	9.7, 9.9.2, 9.9.3
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)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2, 9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	***6, 9.2,*** 9.4
4.2.2 Age and sex	☒	☐	☐	9.2, ***9.4,*** 9.5.3.2.2
4.2.3 Country of origin	☐	☐	☒	
4.2.4 Disease/indication	☒	☐	☐	***9.5.1,*** 9.2, ***9.3,***
4.2.5 Duration of follow-up	☒	☐	☐	9.4.1, 9.4.2, 9.7, 9.9.2, ***9.9.3***
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.4.1, 9.4.2

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)	☒	☐	☐	9.2, 9.4, 9.5.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.11
5.3 Is exposure categorized according to time windows?	☒	☐	☐	9.2, 9.4, 9.9.1, 9.9.2.2.1, 8.5, 9.8.3.2.3
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2, 9.4, 9.5.2, 8.5, 9.9.3.2.1
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.5.2, 8.5 9.8.3.2.1, 9.8.3.2.3
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2, 9.4

Comments:

5.3: Exposure is described by calendar time (9.8.1). Safety is described among those with 2 doses 2-6 months apart (9.8.2.2.1) and effectiveness is assessed with respect to time since vaccination and time between doses in sensitivity analyses (8.5, 9.8.3.2.3).

5.4: Receipt of doses is described (9.4.2). 1-dose VE is a secondary effectiveness objective (8.5, 9.8.3.2.1).

5.5: See above.

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?	☒	☐	☐	9.5.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.5.3
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)	☒	☐	☐	9.5.3, 9.11
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)	☒	☐	☐	9.5.3.1, 9.5.4, 9.9.2.2.1, 9.9.2.3, 9.9.3.1.1, 9.9.3.3

Comments:

6.4: Safety outcomes are considered indicative of disease activity (9.4.3.1), and effects are estimated among those on treatment at index (9.8.2.2.1, 9.8.3.1.1) CCI [redacted] CCI [redacted] (9.8.2.3, 9.8.3.3). Treatment, disease severity, and healthcare utilization are also described as covariates (9.4.4).

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.2, 9.9.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.11
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.11

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, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.9.2, 9.9.3

Comments:

A number of stratified secondary, sensitivity and CCI [redacted] are conducted for safety and effectiveness (see Section 9.9.2.2.1, 9.9.2.2.2, 9.9.3.1.1, 9.9.3.1.2, 9.9.3.2 and 9.9.3.3 for details).

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)	☒	☐	☐	9.5.2, 9.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.5.3, 9.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.5.3.2.2, 9.6
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)	☒	☐	☐	9.5.2, 9.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.5.3, 9.6
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.5.3.2.2, 9.6

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.5.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.5.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.5.3.2.2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.9.1
10.4 Are stratified analyses included?	☒	☐	☐	Safety: • 9.9.2.2.1 (on-treatment), • 9.9.2.2.2 (demographics, disease severity), • 9.9.2.3 (on-treatment) Effectiveness: • 9.9.3.1.1 (on treatment), • 9.9.3.1.2 (disease severity), • 9.9.3.2.2 (demographics), • 9.9.3.3 (by level of immunosuppression
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	***9.9.2.1, 9.9.3.1***
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.11
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	***9.9.2.2.1, 9.9.3.1.1***

Comments:

10.6: No analytic control for outcome misclassification is conducted. However, updates to safety outcome definitions are expected to increase specificity. Analyses of

on-treatment subgroups and by disease severity are also expected to result in less outcome misclassification.

10.7*: *All Research Partners currently provide some data on race/ethnicity; a missing category will be included for individuals for whom this information is not available. For other variables, given the nature of the claims data we are using, we make the assumption that if a code is not provided for a given treatment or condition, it did not happen/was not present. We acknowledge that this is a limitation of these analyses in Section 8.10.

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)	☒	☐	☐	9.6.2, 0, 9.10
11.2 Are methods of quality assurance described?	☒	☐	☐	0, 9.10
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.

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?	☒	☐	☐	9.11
12.1.2 Information bias?	☒	☐	☐	9.11
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	9.11
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
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)	☒	☐	☐	9.7

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	0, 10.1, 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?	☒	☐	☐	5, Annex 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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Signature Page for 215104 TMF-23083212 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 10-Dec-2025 18:51:54 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 12-Dec-2025 13:16:13 GMT+0000

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