NON-INTERVENTIONAL STUDY REPORT

TITLE PAGE

Division: Research and Development

Information Type: Non-Interventional Study Report - Post-Authorization Safety Study

Title:	A retrospective matched cohort database study in the United States to evaluate the effectiveness of Recombinant Zoster Vaccine (RZV) in patients with autoimmune diseases (AIDs)
Compound Number:	GSK1437173A
Effective Date:	29 October 2024
Subject:	Retrospective matched cohort database study to evaluate the RZV effectiveness in US patients with AIDs.
Author(s):	• PPD (Epidemiologist) • PPD (Epidemiology Lead) • PPD (Study Delivery Lead) • PPD (VET PM) • PPD (Oversight Data Manager) • PPD (Safety Lead) • PPD (Global Medical Affairs) • PPD (Asset Lead) • PPD (RWA Analyst) • PPD (RWA, PPD Scientific Lead) • PPD (RWDMP Programmer) • PPD (US MA LOC) • PPD (GRA) • PPD (GRA) <u>Coordinating authors:</u> • PPD (Medical Writing Asset Lead) • PPD (Medical Writer)
Indication Studied:	Herpes Zoster

STUDY INFORMATION

Title	A retrospective matched cohort database study in the United States to evaluate the effectiveness of Recombinant Zoster Vaccine (RZV) in patients with autoimmune diseases (AIDs)
Protocol version identifier	219111
Date of last version of protocol	Final: 28 February 2024
EU PAS (ENCEPP) register number	EUPAS49294
Active substance	Varicella Zoster Virus (VZV) glycoprotein E (gE)
Medicinal product	*Shingrix*
Product reference	EU/1/18/1272/001-1 Vial and 1 vial; EU/1/18/1272/002-10 vials and 10 vials
Procedure number	EMEA/H/C/004336
Marketing authorisation holder(s)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89, B-1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	Primary objectives: • To estimate the VE of 2 RZV doses in preventing HZ in adults aged ≥50 YOA with systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis (PsO), or psoriatic arthritis (PsA), respectively. Secondary objectives: • To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD). • To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA. • To estimate the VE of 2 RZV doses in preventing HZ in adults aged ≥50 YOA with SLE, MS, RA, IBD by condition (UC, CD), PsO, or PsA

	stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date. • To estimate the VE of 1 RZV dose in preventing HZ in adults aged ≥50 YOA with SLE, MS, RA, IBD by condition (UC, CD), PsO, or PsA. • To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date. • To estimate overall VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with selected AIDs by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
Country of study	United States
Author	PPD , PPD , Epidemiology GSK Rockville Center for Vaccines Research 14200 Shady Grove Rd, Rockville, MD 20850

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	GlaxoSmithKline Biologicals SA Rue de l'Institut 89, B-1330 Rixensart, Belgium
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SPONSOR SIGNATORY

Title: A retrospective matched cohort database study in the United States to evaluate the effectiveness of Recombinant Zoster Vaccine (RZV) in patients with autoimmune diseases (AIDs)

Compound Number: GSK1437173A

Hannah Alsdurf
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Note: Not applicable if an eSignature process is used to get the sponsor approval.

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AID	Autoimmune Disease
AuHSCT	Autologous Hematopoietic Stem Cell Transplants
BIC	Bayesian Information Criteria
CD	Crohn's Disease
CDM	Optum's de-identified Clinformatics® Data Mart Database
CI	Confidence Interval
CPT	Current Procedural Terminology
DMARD	Disease-Modifying Antirheumatic Drugs
ED	Emergency Department
EHR	Electronic Health Record
FDA	Food and Drug Administration, United States of America
FISMA	Federal Information Security Management Act
GSK	GlaxoSmithKline
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HM	Hematological Malignancies
HR	Hazard Ratio
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
IC	Immunocompromised
ICD	International Classification of Diseases

IDNs	Integrated Delivery Networks
IQR	Interquartile Range
IR	Incidence Rate
MS	Multiple Sclerosis
NDC	National Drug Code
NIST	National Institute of Standards and Technology
NSAID	Non-Steroidal Anti-Inflammatory Drug
PHN	Post Herpetic Neuralgia
PPV	Positive Predictive Value
PsA	Psoriatic Arthritis
PsO	Psoriasis
PY	Person-Years
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RDQ	Rapid Data Query
RWA	Real World Analytics
RZV	Recombinant Zoster Vaccine
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrom-Coronavirus-2
SAS	Statistical Analysis Software
SLE	Systemic Lupus Erythematosus
UC	Ulcerative Colitis
US	United States
VE	Vaccine Effectiveness
VZV	Varicella Zoster Virus

YOA	Years of Age
ZVL	Zoster Vaccine Live

TRADEMARK INFORMATION

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None

1. RESPONSIBLE PARTIES

GSK has the overall responsibility for the conduct of the study.

Responsible Party	Details
Epidemiological Lead	PPD MD, PhD. PPD Non-Respiratory Viral Vaccine Epidemiology, Vaccine Epidemiology, Value Evidence and Outcomes. Address: GlaxoSmithKline Research & Development Limited, 14200 Shady Grove Rd, Rockville, MD 20850, USA

1.1. STUDY ADVISORY COMMITTEE

Not applicable

2. SYNOPSIS

Title

A retrospective matched cohort database study in the United States to evaluate the effectiveness of Recombinant Zoster Vaccine (RZV) in patients with autoimmune diseases (AIDs)

Keywords

Retrospective matched cohort database study, Post-authorization Safety Study, Herpes Zoster, Shingrix vaccine, United States adults (adults ≥50 years of age), autoimmune disease, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, psoriasis, psoriatic arthritis.

Rationale and background

Individuals with autoimmune disease (AID) are at higher risk of Herpes Zoster (HZ) compared to immunocompetent individuals. Information on the effectiveness of RZV in AID populations is limited. One study from the Veterans Affairs Healthcare System among individuals diagnosed with inflammatory bowel disease (IBD) showed that the RZV group, when compared with the unvaccinated group, was associated with a decreased risk of HZ infection among both the 50-60 years of age (YOA) participants (0.00 vs 3.93 per 1000 person-years (PY)) and the >60 YOA participants (1.80 vs 4.57 per 1000 PY). A study evaluating the overall vaccine effectiveness (VE) of RZV in a subgroup of Medicare enrolled patients aged ≥65 YOA with AIDs reported a 1- and 2-dose VE of 57.7% (95% CI: 50.9, 63.6) and 68.0% (95% CI: 62.3, 72.8), respectively.

The current retrospective matched cohort database study used the Optum's de-identified Clinformatics® Data Mart Database (CDM) to provide early real-world evidence of the effectiveness of RZV in participants aged ≥50 YOA with AIDs.

Research questions and objectives

The primary objective was to estimate the VE of 2 RZV doses in preventing HZ in adults aged ≥50 YOA with systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis (PsO), or psoriatic arthritis (PsA). The primary outcome was the occurrence of HZ for all objectives.

Primary Objectives

- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS.

- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA.

Secondary Objectives

1. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (ulcerative colitis [UC], Crohn's disease [CD]).
2. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
3. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
4. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
5. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
6. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD), age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
7. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
8. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
9. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.

10. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with SLE.
11. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with MS.
12. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with RA.
13. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC and CD).
14. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsO.
15. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsA.
16. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
17. To estimate overall VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with selected AIDs by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.

Study design

- Type of design: A retrospective matched cohort database study.
- Study population: The study population included adults aged ≥50 YOA who are registered as a beneficiary in the CDM, diagnosed with an AID (defined as SLE, MS RA, IBD [UC or CD], PsO, and PsA), and who received RZV vaccination (along with their unvaccinated matches) anytime between 01 January 2018 to 31 December 2021.
- Vaccination schedule: Participants who received dose 2 of RZV at least 28 days after dose 1.
- Data source: Optum's de-identified Clinformatics® Data Mart Database data sets.
- Period of observation: January 2018 to December 2021.

Setting

This was a retrospective matched cohort database study which included adults aged ≥50 YOA who were beneficiaries in the CDM, diagnosed with an AID (defined as SLE, MS, RA, IBD [UC or CD], PsO and PsA), and who received RZV vaccination (along with their unvaccinated matches) anytime between 01 January 2018 to 31 December 2021. Co-existence of more than one AID can occur – while it was not required that each AID cohort be mutually exclusive, overlap was expected to be minimal except for PsO and PsA.

Participants and study size

A total of 36 645 participants who received 2 doses of RZV and 109 229 of the matched counterparts who did not receive RZV were identified in the 2-dose cohort analysis. The number of available participants with RZV vaccination for each AID condition exceeded the sample size requirements based on 80% power and a detectable VE of 50% during the accrual period of January 2018 to December 2021. This demonstrated that the study was sufficiently powered to assess the primary VE objectives.

Variables and data sources

Exposure

The exposure of interest was the receipt of RZV (1-dose or 2 RZV doses at least 28 days apart). The primary exposure of interest was receipt of 2 RZV doses with at least 28 days apart.

Outcomes

The primary outcome was the HZ event which can be identified with a high Positive Predictive Value (PPV) $\geq$80% based on ICD-10 diagnosis codes.An HZ event was to be defined by the occurrence of either:

- At least 1 inpatient claim with a HZ diagnosis (identified by pre-defined ICD-10 codes); OR
- At least 2 outpatient claims with HZ diagnosis which are no more than 30 days apart; OR
- At least 1 outpatient claim with HZ diagnosis with a pharmacy claim for anti-viral treatment within 7 days before or after the claim with HZ diagnosis.

Covariates of interest

- Age in 5-year increments: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, $\geq$80.
- Sex: female/male.
- Race/ethnicity: Asian, Black, Hispanic, White, Multiple/Other/Unknown.
- Use of AID-related medications.
- Medical encounters: number of inpatient admissions in the 365 days prior to the index date, number of ambulatory visits/ emergency department visits in the 365 days prior to the index date, number of rheumatologist outpatient visits (for SLE, RA, PsA) in the 365 days prior to the index date, number of dermatologists outpatient visits (for SLE, PsO) in the 365 days prior to the index date, number of neurologist outpatient visits (for MS) in the 365 days prior to the index date.
- Logarithm of the healthcare cost in the 365 days prior to the index date.
- Presence of co-morbidities in the 365 days prior to the index date.

- Concomitant vaccinations in the 365 days prior to the index date.
- Region of residence within US (West, Midwest, South, Northeast) most recently prior to the index date.
- Use of preventative services: screening, preventative visits in the 365 days prior to the index date.

Statistical Analysis

All analyses, including descriptive, were conducted separately for SLE, MS, RA, IBD, PsO, and PsA populations. Patients with AIDs who received 2 RZV doses were 1:3 matched to their unvaccinated counterparts (non-RZV cohort) by age, medication Category and other confounders (propensity score). For the primary objectives the number of incident HZ cases and the number of person-years of follow-up for participants were assessed for the 2-dose (≥ 28 days apart) RZV cohort and the matched unvaccinated cohort.

Adjusted HRs and 95% confidence intervals (CIs) comparing HZ incidence rates in the 2-dose (≥28 days apart) RZV cohort, and the matched unvaccinated cohort were estimated by Cox proportional hazards regression models. Estimates of VE (%) were calculated as (1 – adjusted HR) × 100%.

Analyses for the secondary objectives employed similar methods as primary analyses.

Data sources

CDM is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans description.

All the claims were linked to an individual participant, to obtain a complete picture of the healthcare claims submitted during the enrollment period.

Results

Participants and baseline characteristics

A total of 36 645 participants who received 2 doses of RZV and 109 229 of the matched counterparts who did not receive RZV were identified in the 2-dose cohort analysis. The median duration of follow-up was 1.29 years (interquartile range [IQR]: 0.73–2.12) for those RZV vaccinated and 1.07 (IQR: 0.59–1.95) years for those not vaccinated.

Study participants were predominantly female participants making up 64.95% of the RZV group and 64.88% of the non-RZV group. Over one third of both groups, 37.02% of RZV and 37.05% of non-RZV participants, were between the ages of 70 and 79 years during the study.

Among all participants, 58.62% of those in the RZV group and 58.63% of the non-RZV group had comorbidities such as asplenia/ hyposplenia, pneumonia due to COVID-19, COVID-19, cardiovascular disease, diabetes mellitus, kidney disease, lymphoma/leukaemia, liver disease and pulmonary disease.

Regarding treatment, the most commonly used medication for RA and PsA participants was from Category 4 (e.g., high-dose steroids). For other conditions such as IBD, SLE, MS, and PsO, Category 1 medications (e.g., Nonsteroidal anti-inflammatory drugs, low-dose steroids, anti-malarial, as well as no medication) were the most frequently administered.

For the single-dose cohort, 44 865 participants were administered one dose of RZV, while 130 458 matched participants did not receive the vaccine. The median follow-up period was 0.19 years (IQR: 0.11–0.38) for the RZV vaccinated cohort, and 0.50 years (IQR: 0.50-0.50) for the unvaccinated cohort, due to the censoring after 6 months of follow-up.

The majority of the study participants in the single-dose cohort were also female, with women constituting 65.73% of the RZV vaccinated group and 65.39% of the unvaccinated group. Most participants, 71.47% of the RZV vaccinated and 71.53% of the unvaccinated, were aged 60 to 79 years. Over half of the participants in both single-dose cohorts reported at least one comorbidity.

Primary analysis

For participants with selected AIDs who received 2 doses of RZV, the overall VE was 66.3% (95% CI: 61.4, 70.7). The specific VE for each AID is as follows:

- SLE: 60.5% (95% CI: 30.8, 77.5)
- MS: 48.1% (95% CI: 12.7, 69.1)
- RA: 62.8% (95% CI: 55.3, 69.1)
- IBD: 73.4% (95% CI: 60.8, 82.0)
- PsO: 77.2% (95% CI: 66.4, 84.5)
- PsA: 65.6% (95% CI: 37.3, 81.2)

The 66.3% VE observed for all selected AIDs aligns with previous studies [Izurieta, 2021], which reported a VE of 68.0%. This is consistent across each AIDs where sufficient data for follow-up time, as measured in person-years, are available to detect HZ cases. RZV vaccination is effective in preventing HZ in patients ≥50 YOA with selected AIDs.

Secondary analyses

For participants with selected AIDs who received a single dose of RZV, the overall VE was 58.4% (95% CI: 45.9, 68.0). The adjusted VE for each AID is as follows:

- SLE: 42.6% (95% CI: -45.5, 77.4)
- MS: 100.0% (The 95% CI could not be estimated due to the absence of HZ events)
- RA: 53.8% (95% CI: 34.5, 67.4)
- IBD: 64.5% (95% CI: 27.0, 82.7)
- PsO: 61.6% (95% CI: 26.8, 79.9).
- PsA: 63.2% (95% CI: -20.7, 88.7)

For all subgroup analyses by each AID condition, the VE against HZ varied with age following two vaccine doses, with no distinct age-related trend in VE shown. Further, the confidence intervals of these estimates were largely overlapping which prohibits definitive interpretations since the study was not powered for these comparisons. The VE remained consistent across both male and female participants. Nonetheless, the low number of PY of the data for specific subgroups, such as those defined by dose intervals, medication types, and the period after vaccination, made it difficult to fully interpret the VE for these conditions.

Similarly, the interpretation of VE for SLE, MS, and PsA subgroup analyses was hampered by limited PY data, particularly when stratified by age, gender, dose intervals, medication types, and duration post-vaccination.

Post-hoc analyses

Post-hoc analyses reinforced the robustness and clarity of the study findings, which are summarized as follows:

- A small fraction (under 5%) of the participants had overlapping conditions, predominantly PsO and PsA.
- The follow-up for most participants (70%) ended with the study's conclusion, minimizing the potential for selection bias due to participants dropping out for reasons associated with the measured outcome.
- Less than 7% of the study participants with RA, IBD or PsA received low-dose steroids (< 5 mg), which meant that the risk of not accurately reporting steroid potency level was low since there were few of the study participants who received low-dose steroid. As a result, the study's cut-off value for steroids (<5 mg for low-dose and ≥5 mg for high-dose) did not have a large impact on the study's matching process or its conclusions.
- Follow-up duration was similar among AID participants and consistent throughout the study cohort.

- Pooling categories within stratification variables like age, time since vaccination, dose intervals, and medication use enhanced the accuracy of VE calculations for certain diseases (RA, IBD, and PsO) where sufficient PY data were available. However, for other diseases (SLE, MS, and PsA), with fewer PY data, this pooling approach was still not sufficient to obtain precise VE estimates, leaving interpretation of the results for these conditions challenging.

Discussion

The estimate of overall VE against HZ following 2 doses of RZV for all selected AIDs (66.3%, 95% CI: 61.4, 70.7) was consistent with the VE in the available literature (68%) on RZV effectiveness in participants with selected AIDs. The VE ranged from 48.1% to 77.2% in MS and PsO participants, respectively, which was consistent with the overall VE across all AIDs.

The overall VE against HZ following a single dose of RZV for all selected AIDs was 58.4% (95% CI: 45.9, 68.0), is also consistent with the literature in which the VE was reported as 57.7%.The VE ranged from 42.6% to 100.0% in SLE and MS, respectively, however the 95% CI could not be estimated for MS since no HZ events were reported in the RZV cohort.

The estimated VE stratified by factors such as age, gender, time since vaccination, time interval between 2 doses and medication Category were only interpretable for RA, IBD and PsO. In contrast, the stratified VE estimates for SLE, MS and PsA were not interpretable. While distinct trends were observed in the stratified analyses upon aggregating relevant categories of variables, the importance of these trends remained unclear. The insufficient number of PY in certain stratified analyses hindered a meaningful interpretation of the results stratified by Category, particularly for the SLE, MS and PsA cohorts.

Conclusions

Our analysis provides real-world evidence that RZV vaccination is effective in preventing HZ in individuals ≥50 YOA with selected AIDs. Vaccination with RZV can reduce the burden of HZ in this population, underscoring its health benefits for specific patient groups.

Additional research to ascertain RZV's effectiveness in subgroups (i.e., age group) of patients with selected AID conditions is needed.

Marketing authorization holder

GlaxoSmithKline Biologicals SA

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B-1330 Rixensart, Belgium

Names and affiliations of principal investigators

Not applicable

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study report	Amendment or update	Reason
Protocol Amendment 2	28 February 2024	Section 2, Section 6 and Section 9.4	Revised secondary objective 17 to include analysis by stratified variables.	The analysis corresponding to secondary objective 17 included an estimation of the overall vaccine effectiveness by age, gender, time since vaccination, time interval between two doses, and medication Category. This revised analysis provided additional information about the overall analyses by stratified variables. This was consistent with the analyses by AID (secondary objectives 3-9), which estimated vaccine effectiveness by age, gender, time since vaccination, time interval between two doses, and medication Category.
		Section 7.6.7 and Section 9.4	Updated information about the secondary objective 17 as is indicated above	The rationale for this update is described above.
		Section 7.6.7.2 and Section 9.5	Additional sensitivity analyses to evaluate the impact of adding medication Category as a covariate on the vaccine effectiveness values.	Sensitivity analyses was performed to evaluate the impact of adding medication Category as a covariate on the primary analyses (primary objectives 1-6) and subgroup analyses (secondary objective 17).
		Section 7.6.8.1 and Section 9.6.1	The additional analyses section has been added to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses.	Additional tables listed below was created to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses: Distribution tables of participants associated with multiple AIDs for 1-dose and 2-dose cohorts to assess the proportion of participants diagnosed with overlapping AID conditions. Distribution tables of participants whose end of follow-up reason is either disenrollment or end of study for 2-dose cohort to identify risk of potential selection bias.

Amendment or update no	Date	Section of study report	Amendment or update	Reason
				Distribution tables of medication class within each medication Category to assess the frequency of medication class by age and by AID. Distribution tables of steroids to check the frequency of participants who receive low- versus high-dose steroids in the RZV vaccinated and unvaccinated groups. Baseline characteristics/ demographic tables for populations with different length of follow-up (0<1 years, 1<2 years, 2<3 years, 3+ years) to check if trends of HZ events can be observed in different follow-up periods. Cross tables between age categories and comorbidities to check the number of participants by age and comorbidity in the RZV vaccinated and unvaccinated groups.
		Section 7.6.8.2 and Section 9.6.2	Subgroup analyses corresponding to secondary objectives 3-9 and 17 will be modified to address potential study limitations.	This study was not powered for analyses of secondary objectives. This may not allow meaningful interpretation of some of the results of the subgroup analyses. Certain categories from the following variables were therefore be combined to address this issue: age, dose interval between two doses, time since vaccination, and medication Category. Combining these categories added additional statistical power and made the results more interpretable.

4. MILESTONES

Milestone	Planned date	Actual Date	Comments
Start of data collection	14 October 2022	14 October 2022	NA
End of data collection	15 December 2023	15 December 2023	NA
Registration in the EU PAS register	13 October 2022	13 October 2022	EU PAS register number - EUPAS49294
Statistical Analysis complete (SAC)	15 December 2023	15 December 2023	NA
Statistical Analysis complete (SAC) V2	20 March 2024	20 March 2024	Post-hoc analysis
Statistical Analysis complete (SAC) V3	17 April 2024	17 April 2024	Post-hoc analysis
Statistical Analysis complete (SAC) V4	03 May 2024	03 May 2024	Post-hoc analysis
Statistical Analysis complete (SAC) V5	31 May 2024	31 May 2024	Post-hoc analysis
Statistical Analysis complete (SAC) V6	09 August 2024	09 August 2023	Post-hoc analysis
Statistical Analysis complete (SAC) V7	11 September 2024	11 September 2024	Post-hoc analysis
Final report of study results	10 January 2024	29 October 2024	NA

5. RATIONALE AND BACKGROUND

Herpes Zoster, or shingles, results from the reactivation of Varicella Zoster Virus (VZV) and causes a painful, pruritic rash that usually resolves on its own within 1-2 weeks. HZ affects at least 1 million people in the US each year. An estimated 32% of persons in the US will experience HZ during their lifetime [Harpaz, 2008]. Furthermore, over 95% of adults ≥50 YOA are seropositive for VZV and susceptible to HZ [Johnson, 2015].

Individuals with AIDs are at higher risk of HZ than immunocompetent individuals [Gupta, 2006; Khan, 2018; Long, 2013; Smitten, 2007; Yun, 2016]. The incidence rate of HZ among adults with RA is almost double that among immunocompetent (non-RA) adults [Smitten, 2007; Yun, 2016], and it is higher among adults with IBD (e.g., UC or CD) than those without IBD [Gupta, 2006; Khan, 2018; Long, 2013; Yun, 2016]. The risk of HZ in individuals with SLE is also twice as high as in the general population [Kawai, 2017a]. Individuals with PsO have a higher HZ risk than the general population [Baumrin, 2019; Chen, 2014; Tsai, 2017].

Systemic therapies also play a major role in the risk of HZ. For example, immuno-suppressive therapy renders individuals with SLE and MS more susceptible to VZV reactivation [Borba, 2010; Manouchehrinia, 2017]. In a recent systematic literature review, patients with PsO or PsA treated with systemic corticosteroids and combination systemic therapy were reported to have increased HZ risk [Baumrin, 2019]. Patients with PsO and PsA had variable HZ risk, depending on disease severity and type of systematic therapy.

The US FDA approved RZV, a 2-dose subunit Zoster vaccine containing recombinant glycoprotein E in combination with the novel adjuvant $AS01_B$, in October 2017 for immunocompetent adults aged ≥50 YOA [FDA, 2017] and in July 2021 for adults aged ≥18 YOA who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy [FDA, 2021]. The FDA approvals were followed by the recommendations of the ACIP of RZV for use in immunocompetent adults aged ≥50 YOA [Dooling, 2018] and in immunocompromised adults aged ≥19 YOA [Anderson, 2022].

The GSK 2-dose RZV vaccine demonstrated efficacy in preventing HZ in two phase III randomized controlled trials (RCTs): ZOE-50 and ZOE-70 [Lal, 2015; Dagnew, 2019]. RZV efficacy in these trials was 97.2% (95% CI, 93.7, 99.0) in adults aged ≥50 YOA (ZOE-50) and 91.3% (95% CI, 86.8, 94.5) in adults ≥70 YOA (ZOE-70). Myalgia, injection site pain, and erythema were the most common adverse events (AEs) reported in these trials.

Vaccine efficacy of RZV in immunocompromised adults aged ≥18 YOA was evaluated in a clinical trial that included autologous hematopoietic stem cell transplant (auHSCT) recipients [Bastidas, 2019]. Among auHSCT recipients, RZV efficacy in preventing HZ was 68.2% (95% CI, 55.6, 77.5). Post-hoc vaccine efficacy among adults with hematological malignancies (HM) was 87.2% (95% CI, 44.3, 98.6) [Dagnew, 2019].

Data on RZV effectiveness in AID populations is limited. A recent cohort study evaluated the overall VE of RZV in a subgroup of Medicare enrolled participants aged ≥65 YOA with various immunocompromised (IC) conditions and AIDs and reported overall 1- and 2-dose VE of 57.7% (95% CI, 50.9, 63.6) and 68.0% (95% CI, 62.3, 72.8), respectively [Izurieta, 2021]. Another recent study from the Veterans Affairs Healthcare System among individuals diagnosed with IBD showed that RZV was associated with decreased risk of HZ infection among both the 50-60 years and >60 YOA participants [Khan, 2022]. More research is needed to evaluate the effectiveness of RZV in specific AID populations (SLE, MS, RA, IBD, PsO, and PsA).

This study aimed to critically inform participant and physician decision-making about vaccinating against HZ in these at-risk populations and support evidence-based AID recommendations and guidelines.

6. RESEARCH QUESTION AND OBJECTIVE(S)

This study assessed VE among participants enrolled in the CDM with SLE, MS, RA, IBD (UC, CD), PsO, or PsA who received RZV (vaccinated) compared to participants who did not receive RZV (unvaccinated). Occurrence of HZ was the outcome for all objectives.

Primary Objectives

- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA.

Secondary Objectives

- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD).
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.

- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD), age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
- To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.
- To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with SLE.
- To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with MS.
- To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with RA.
- To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC and CD).
- To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsO.
- To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsA.
- To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
- To estimate overall VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with selected AIDs by age, gender, time since vaccination, time interval between two doses, and medication Category (mutually exclusive) based on current use at the index date.

7. RESEARCH METHODS

7.1. Study Design

A retrospective matched cohort study with Cox proportional hazards modeling was performed to assess the risk of HZ after RZV in adults aged ≥50 YOA with SLE, MS, RA, IBD, PsO, or PsA. In the primary analysis, participants receiving a second dose of RZV (separated by >28 days after dose 1) on or after 01 January 2018 were compared to participants with no prior RZV vaccination (i.e., unvaccinated). For the primary objective, matching was done involving exact matching and a propensity score matching performed consecutively. Once cohorts for each AID were identified, participants meeting inclusion criteria who received 2 doses of RZV at least 28 days apart (2-dose cohort) at the index date were matched exactly with unvaccinated participants on age Category of 5-year increments (i.e., 50-54 age grouping) and by AID-related medication Category (mutually exclusive) based on current use at the index date. Following exact matching as described above, a matching with propensity scores was performed. The propensity score matching was based on the likelihood of receiving RZV dose 2 versus no RZV vaccination (2-dose cohort) and RZV dose 1 versus no RZV vaccination (1-dose cohort) which was calculated using logistic regression models. RZV vaccination exposure status was the dependent variable, and the independent variables were age, medication use, gender, comorbidities, use of preventative visits, concomitant vaccination, healthcare cost, race, number of inpatient and outpatient visits and region. A 3:1 matching ratio was applied with the propensity score matching. Matching was used to better control for the confounding effects and reduce bias in this observational study. The matching ratio of 3:1 of unvaccinated to RZV vaccinated participants. For IBD, a RZV vaccinated participant with UC was matched to an unvaccinated participant with UC. The same approach was used to match participants with CD. Matching was done with replacement. Several papers indicate that the use of replacement provides the most reliable treatment effect estimates [Bottigliengo, 2021]. This strategy can create better balance and yield estimates that are closer to the truth, on average. To address additional potential confounding due to differences between RZV vaccinated and unvaccinated cohorts, multiple covariates (Section 7.3.3) were assessed and balanced across the exposure groups using propensity score matching. Unvaccinated participants were assigned the same index date as their RZV vaccinated counterparts.

The study was conducted using health care encounters/claims of the CDM (Section 7.4). The primary outcome was a HZ event, and the primary exposure of interest was the receipt of 2 doses of RZV separated by ≥28 days after dose 1. The index date was defined as the date of receipt of the second dose for RZV (at least 28 days after first dose) for RZV vaccinated participants and their unvaccinated matches.

Additional secondary objectives examined 1-dose (with the index date as the date of receipt of RZV dose 1) and 2-dose VE by age, gender, time since vaccination, time interval between 2 doses, and medication Category, respectively. Secondary analyses also stratified 2-dose VE by UC and CD. Analyses were conducted separately among participants diagnosed with SLE, MS, RA, IBD, PsO, and PsA. The study period from identification of RZV vaccinated cases to study completion was 01 January 2018 to the first occurrence of HZ, termination of membership, death, receipt of RZV for

unvaccinated participants, receipt of second dose of RZV for 1-dose cohort, receipt of ZVL, or 31 December 2021 (i.e., end of the study period).

Figure 7.1 describes the cohort design to assess two-dose vaccine effectiveness.

Figure 7.1 Matched 2- dose cohort study design

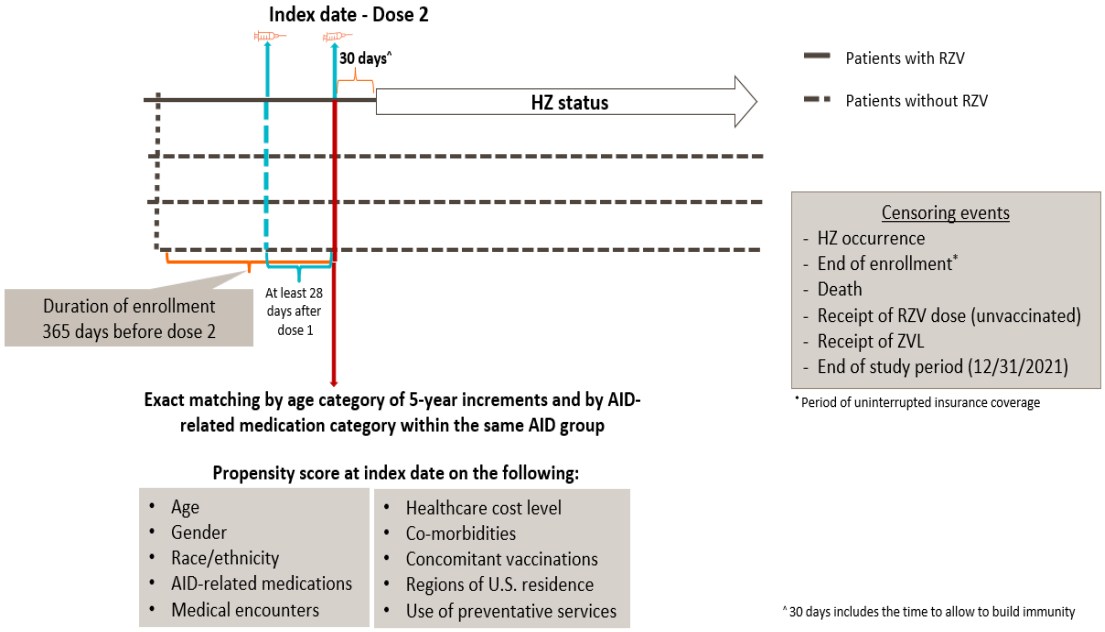
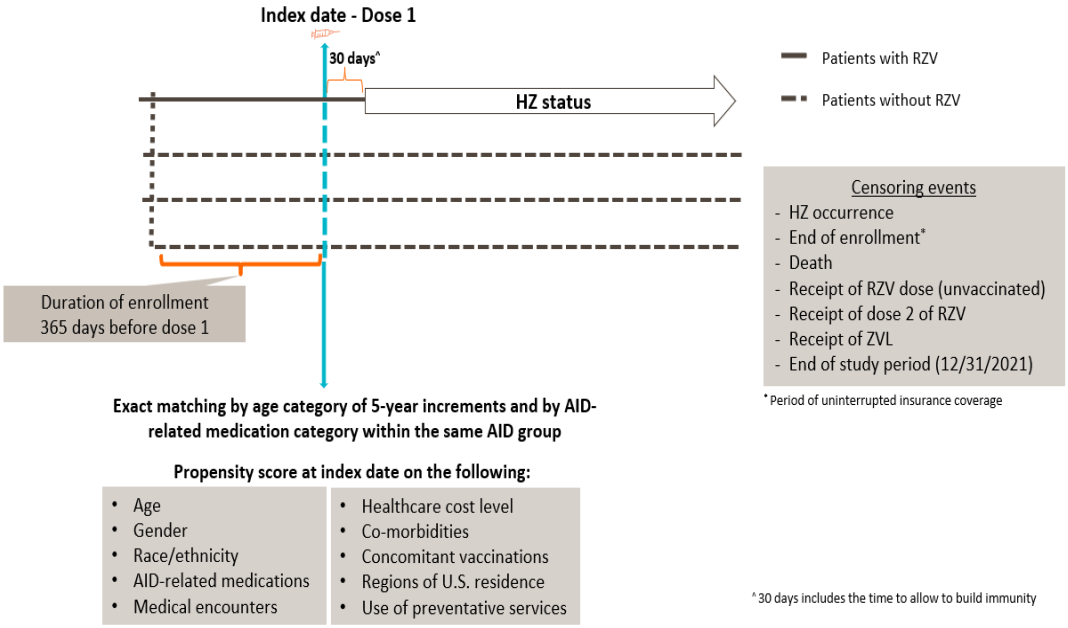


Figure 7.2 describes the cohort design to assess one-dose vaccine effectiveness.

Figure 7.2 Matched 1- dose cohort study design



7.1.1. Rationale for retrospective matched cohort design

To assess VE, a retrospective matched cohort design was used to compare the hazard of HZ in RZV vaccinated participants with SLE, MS, RA, IBD (UC, CD), PsO, or PsA, respectively, who received 2 doses of RZV relative to unvaccinated participants who received no RZV, using Cox proportional hazards models. A cohort design was used to evaluate the effectiveness of vaccination over time. Moreover, the potential for healthy-user bias (where RZV vaccinated populations may more frequently have healthy behaviors) and differing characteristics among RZV vaccinated and unvaccinated participants related to comorbidities, health status, disease activity, medications, and other factors necessitated a matching procedure to account for confounding due to these imbalances (e.g., propensity score methods described in Section 7.2.4).

7.2. Study Population/Participants and Setting

The study population included adults aged ≥50 YOA who are beneficiaries in the CDM, diagnosed with an AID (defined as SLE, MS, RA, IBD [UC or CD], PsO and PsA), and who received RZV vaccination (along with their unvaccinated matches) anytime between 01 January 2018 to 31 December 2021 (Section 7.2.3 describes the algorithms for identification of AIDs). Co-existence of more than one AID can occur – while it was not required that each AID cohort be mutually exclusive, overlap was expected to be minimal. Details of inclusion and exclusion criteria are defined in Section 7.2.1 and Section 7.2.2, respectively.

Table 7.1 shows results from a feasibility analysis presenting the demographic characteristics of beneficiaries in the CDM diagnosed with SLE, MS, RA, IBD, PsO and PsA during the study period (2018-2021). Most of the beneficiaries with SLE (38.6%), PsA (38.9%), and MS (47.3%) were 50-59 YOA, while most of the participants with IBD (39.4%), RA (42.8%), and PsO (36.9%) were >70 YOA. Most of these beneficiaries were female while over 60% were White in all AID groups.

Table 7.1 Demographic characteristics of beneficiaries by AID condition* during the study period (2018^-2021).

	SLE		IBD		RA		PsO		PsA		MS	
	N	%	N	%	N	%	N	%	N	%	N	%
Age at AID diagnosis (years)												
50-59	7740	38.6	11254	34.4	32130	30.5	22794	35.5	6194	38.9	10150	47.3
60-69	6086	30.4	8577	26.2	28028	26.6	17668	27.5	4968	31.2	6828	31.8
≥70	6224	31	12875	39.4	45029	42.8	23680	36.9	4747	29.8	4463	20.8
Sex												
Female	17665	88.1	18690	57.1	79127	75.2	34772	54.2	9314	58.5	16431	76.6
Male	2385	11.9	14016	42.9	26060	24.8	29370	45.8	6595	41.5	5010	23.4
Race /Ethnicity												
Asian	446	2.2	593	1.8	2331	2.2	1853	2.9	342	2.1	208	1.0
Black	3824	19.1	2796	8.5	13609	12.9	4440	6.9	930	5.8	2290	10.7
Hispanic	2492	12.4	2296	7	13491	12.8	5530	8.6	1505	9.5	1262	5.9
Multiple /Other/ Unknown	1076	5.4	1529	4.7	5299	5	2944	4.6	760	4.8	972	4.5
White	12212	60.9	25492	77.9	70457	67	49375	77.0	12372	77.8	16709	77.9
Total	20050	-	32706	-	105187	-	64142	-	15909	-	21441	-

* Table presents overall distribution of beneficiaries' characteristics by AID; no information on vaccination status (see Table 7.3).
^ Beneficiaries in 2017 were included if they were vaccinated in early 2018. Random index dates for unvaccinated beneficiaries were defined; some AID diagnoses were selected in 2017.

7.2.1. Inclusion Criteria

Participants were included in the study if the following inclusion criteria were met:

- Age ≥50 YOA at the index date for all study objectives and registered as beneficiary in the CDM.
- Met criteria for SLE, MS, RA, IBD, PsO or PsA prior to the index date (Section 7.2.3).
- Receipt of first dose of RZV on or after 01 January 2018.
- 365 days of continuous enrolment (allowing administrative gaps 30 days) prior to the index date (baseline period) and continuous enrolment in the 30 days after the index date.

7.2.2. Exclusion Criteria

Participants were excluded from the study if the following exclusion criterions were met:

- Any previous RZV doses before index date (for unvaccinated participants only) using all available data.
- Receipt of second dose of RZV less than 28 days apart since ACIP guidelines state that these participants must repeat the second dose [Dooling, 2018].
- Receipt of ZVL any time during the baseline as this may affect rates of HZ.

- HZ diagnosis or prescription fills for oral acyclovir, valacyclovir or famciclovir given specifically for HZ and within 30 days of index date since it is unclear if the HZ episode began before or after the index date and whether the length of time since vaccination (for RZV vaccinated participants) is long enough to allow for sufficient development of immunity.
- HZ diagnosis or prescription fills for oral acyclovir, valacyclovir or famciclovir in the 12 months before the index date to ensure that HZ diagnoses after the index date are new, rather than carried over from HZ episodes prior to the index date.
- PHN diagnosis in the 12 months before the index date.
- Censoring events within 30 days after the index date (before the start of follow-up) (Section 7.2.5).

7.2.3. Definitions of AIDs

Claims based algorithms obtained from the published literature defining AID conditions and validated with demonstrated PPV were used to identify AIDs. If participants met >1 definitions, they were included in multiple cohorts; AIDs were analyzed separately.

SLE:

≥1 inpatient claim with a diagnosis code for SLE (ICD-10 M32.1, M32.8, M32.9) OR ≥2 physician outpatient claims with SLE diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date OR >1 rheumatologist visit/encounter/claim for SLE.

- The algorithm that includes ≥1 rheumatologist visit/encounter/claim has demonstrated a PPV of 95% and sensitivity of 83% [Hanly, 2014].

MS:

≥3 of any combination of inpatient diagnoses (any position) of MS (ICD-10 G35), ambulatory visit diagnoses of MS, ED diagnoses of MS, or MS-specific disease-modifying therapy fills/infusions (refer to Appendix 6 of Protocol for medication categories) during the 365-day baseline period. At least one of these must be an inpatient, AV, or ED diagnosis of MS.

- This algorithm has demonstrated a PPV of 95-97% and sensitivity of 85-93% [Wallin, 2019].

IBD (CD and UC):

≥1 inpatient claim with a diagnosis code for CD (ICD-10 K50) and UC (ICD-10 K51) OR ≥2 physician outpatient claims with CD (ICD-10 K50) and UC (ICD-10 K51) diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 physician outpatient claims with CD and UC diagnoses during an office visit and/or emergency visit has been used extensively in the literature though no PPV has been reported [Weng, 2007].

- Algorithms that have been published to classify mutually exclusive groups of UC and CD participants will be considered to differentiate between the two conditions [Pilon, 2020]. Participants will be identified as having UC if (i) they had more UC-related patient admissions than CD-related inpatient admissions; (ii) they had an equal number of UC- and CD-related inpatient admissions but more UC-related outpatient visits than CD-related outpatient visits; (iii) they had an equal number of UC- and CD-related inpatient admissions and outpatient visits. [Bernstein, 1999; Shaw, 2011].

RA:

≥1 inpatient claim with a diagnosis code for RA (ICD-10 M05, M06) OR ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit has been used extensively in the literature though no PPV has been reported [MacLean, 2000].

PsO:

≥1 inpatient claim with a diagnosis code for PsO (ICD-10 L40) OR ≥2 physician outpatient claims with PsO diagnosis during an office visit and/or emergency visit that were at least 30 days apart OR ≥1 dermatologist visit/encounter/claim for PsO in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥1 dermatologist visit/encounter/claim has demonstrated a PPV of 90% and sensitivity of 88% [Asgari, 2013]. These algorithms assume PsO without PsA. Based on the RDQs, 9% of participants diagnosed with PsO had PsA. In practice, rheumatologists tend to assess PsO and PsA by criteria which are unique to each. Then, they assess the 2 AIDs together in participants with symptoms of both. Sensitivity analyses were performed on participants who have either PsO or PSA, participants who have PsO only, participants who have PsA only, and participants who have both PsO and PsA to address the potential overlap between PsO and PsA.

PsA:

≥1 inpatient claim with a diagnosis code for PsA (ICD-10 L40.5) OR ≥2 physician outpatient claims with PsA diagnosis during an office visit and/or emergency visit that were at least 30 days apart OR ≥2 rheumatologist visit/encounter/claim for PsA OR ≥1 rheumatologist diagnosis code for PsA together with ≥1 dermatologist diagnosis code for PsA in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 rheumatologist visit/encounter/claim for PsA has demonstrated a PPV of 81% and sensitivity of 77% [Asgari, 2013]. These algorithms assume PsA without PsO. Based on the RDQs, 37% of participants diagnosed with PsA had PsO. Sensitivity analyses was conducted to address the potential overlap between PsO and PsA as described above.

7.2.4. Matching

For the primary objectives, a unique matching was done involving an exact matching and a propensity score matching performed consecutively.

- Exact matching: once cohorts for each AID condition were identified, participants meeting inclusion criteria who received 2 doses of RZV at least 28 days apart (2-dose cohort) at the index date were matched exactly with unvaccinated participants on age Category by 5-year increments (50-54, 55-59, 60-64, 65-69, 70-74, 75-79, ≥80) and AID-related medication Category (mutually exclusive) based on current use at the index date within the same AID group. Medication categories were based on the medication windows described in Section 13.6 of the protocol amendment 2. The same exact matching approach was done for 1-dose cohort.
- Propensity score matching: Following matching as described above, a matching with propensity scores based on the likelihood of receiving RZV dose 2 versus no RZV vaccination (2-dose cohort) and RZV dose 1 versus no RZV vaccination (1-dose cohort) was calculated using logistic regression models with RZV vaccination as the dependent variable and independent variables as outlined in Section 7.3.3.

RZV vaccinated and unvaccinated participants were matched at a ratio of RZV vaccinated to RZV unvaccinated of 1:3.

- The matching was done by replacement, meaning that the same unvaccinated participant was matched to several RZV vaccinated participants.
- Note: within the same index date, a propensity score based on a greedy matching algorithm was applied where distinct unvaccinated participants were chosen to be matched to a RZV vaccinated participant.
- This strategy helped to create better balance, which yielded estimates that were closer to the truth on average.

An unvaccinated participant served as a comparator for both the dose 1 and dose 2 cohorts, although separate index dates were applied.

The difference in terms of propensity score were considered as minimal if it was lower or equal to a caliper of 0.1 [Austin, 2014]. In case a significant number of the RZV vaccinated participants were not matched with at least one control, alternative methods such as Inverse Probability Weighting would be considered.

Covariate balance was assessed before and after matching using standardized mean differences, with standardized differences of 0.1 [Austin, 2009a], [Austin, 2009b] suggestive of important imbalance. Any covariate demonstrating imbalance after weighting, suggesting residual confounding, were considered as an additional covariate in the Cox proportional hazard models. The same approach was used for the secondary analyses for 1-dose cohorts.

7.2.5. Follow-up/censoring

The follow-up period was from 30 days after the index date (to allow development of immunity after vaccination) and ended at the earliest occurrence of the following events:

- HZ occurrence.
- End of continuous enrollment (period of uninterrupted insurance coverage with gap allowance of 30 days).
- Death (date of death including the year and month of death).
- End of data availability/study period (31 December 2021).
- Receipt of RZV (additional dose for RZV vaccinated participants or first RZV dose in the case of unvaccinated participants):
  - For 2-dose VE, RZV vaccinated participants were censored upon receipt of a dose 3.
  - For 1-dose VE, RZV vaccinated participants were censored upon receipt of dose 2.
- Receipt of ZVL vaccination.

7.3. Variables

7.3.1. Exposure

The details on ICD-10 codes are described in Section 13.4 of the protocol amendment 2. The codes to identify the use of Zoster vaccine, CPT/HCPCS codes used to identify influenza vaccinations and NDC codes used to identify HZ antivirals are detailed in Section 13.4.3, Section 13.4.4 and Section 13.4.5 of protocol amendment 2, respectively.

For primary objectives 1 to 6 and secondary objectives 1 to 9 and 17, the exposure of interest was the receipt of 2-dose-RZV at least 28 days apart.

Only vaccinations that were less or equal to 1 year apart were considered for defining the 2-dose cohort.

RZV vaccination was identified from administrative and claims data by means of CPT code 90750 and NDC codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11.

For secondary objectives 10 to 16, the exposure of interest was the receipt of 1-dose-RZV.

The exposure was during the study period: 01 January 2018– 01 November 2021.

7.3.2. Outcomes

The primary outcome was the occurrence of HZ event which was identified with a high PPV ≥ 80% based on diagnosis codes, with additional accuracy established through the requirement for use of an antiviral medication if only one outpatient claim was considered [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]. An HZ event defined by the occurrence of either:

- At least 1 inpatient claim with a HZ diagnosis (identified by pre-defined ICD-10 codes); OR
- At least 2 outpatient claims with HZ diagnosis which are no more than 30 days apart OR
- At least 1 outpatient claim with HZ diagnosis with a pharmacy claim for anti-viral treatment within 7 days before or after the claim with HZ diagnosis.

HZ diagnosis codes and medications are shown in Section 13.4.2 of protocol amendment 2.

7.3.3. Covariates of interest

- Age in 5-year increments: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, ≥80 [Harpaz, 2019; Hayter, 2012; Johnston, 2009; Kawai, 2016; Marra, 2020; Tsai, 2017; Yun, 2016; Wallin, 2019; Weng, 2007; Yamaguchi, 2021].
- Sex: female/male [Hayter, 2012; Johnson, 2015; Kawai, 2016; Marra, 2020; Tsai, 2017; Yamaguchi, 2021]
- Race/ethnicity: Asian, Black, Hispanic, White, Multiple/Other/Unknown [Kawai, 2017a].
- Use of AID-related medications: included but not limited to: tofacitinib, biologics and conventional synthetic DMARD combination therapy, biologics (tumor necrosis factor-alpha blockers), and disease-modifying antirheumatic drugs [Baumrin, 2019; Chakravarty, 2013; Khan, 2018; Lai, 2021; Marra, 2016; Yamaguchi, 2021]. Details of how medication categories for AIDs were determined at index date are described in Section 13.6 of the protocol amendment 2.
- Medical encounters: number of inpatient admissions in the 365 days prior to the index date (continuous), number of ambulatory visits in the 365 days prior to the index date (continuous), number of Emergency Department visits in the 365 days prior to the index date (categorized 0, 1, 2-3, ≥4), number of rheumatologist outpatient visits (for SLE, RA, PsA) in the 365 days prior to the index date (categorized 0-11, 12-23, 24+), number of dermatologists outpatient visits (for SLE, PsO) in the 365 days prior to the index date (categorized 0-11, 12-23, 24+), number of neurologist outpatient visits (for MS) in the 365 days prior to the index date (categorized 0-11, 12-23, 24+).

- Logarithm of the healthcare cost: calculated as LN(Cost+1), with LN the Napierian logarithm and cost the continuous healthcare cost. Participants followed during the observation period without any claims reported were considered as having a cost of $0; if a participant had a negative estimated cost, the cost was set to missing and the cost of all the unvaccinated matched participants was set to missing also.
- Presence of co-morbidities: kidney disease, cardiovascular disease, pulmonary disease [i.e., chronic obstructive pulmonary disease or chronic bronchitis, asthma], liver disease, diabetes mellitus, other autoimmune diseases, cancer, immunocompromising conditions [i.e., human immunodeficiency virus, cancer, transplant, immune-suppressive medications], SARS-CoV-2 infection/COVID-19 diagnosis with an index date after 2020) in the 365 days prior to the index date [Kawai, 2017a; Marra, 2020; Tsai, 2017; Yun, 2016].
- Concomitant vaccinations at the time of index date: Influenza vaccine, tetanus, diphtheria and pertussis vaccine, pneumococcal vaccine in the 365 days prior to the index date, as a proxy for health behaviours.
- Region of residence within U.S. as defined by the Census Bureau (4 regions: West, Midwest, South, Northeast) most recently prior to the index date [Izurieta, 2021; Sun, 2021].
- Use of preventative services: screening, preventative visits in the 365 days prior to the index date [Izurieta, 2021].

7.4. Data sources

This study was conducted using data from the health care administrative encounters/claims (United Healthcare enrollees) of the CDM. The detail on the database is described in detail in Section 13.3 of the protocol amendment 2. CDM is a quarterly updated database for members of a large national managed care company affiliated with CDM. It includes both commercial and Medicare Advantage health plan enrollees from all 50 states in the US. The database includes proprietary, de-identified health claims data from a geographically diverse US population (16% West, 20% Midwest, 36% South, and 27% Northeast). In addition to medical claims, pharmacy claims, and outpatient laboratory tests, CDM includes data tables related to member inpatient confinements and eligibility data. CDM includes data with service dates from 2007 to present and approximately 15 – 18 million annually insured lives. The CDM system contains more than 80 million lives, of which more than 40% have more than 4 years of clinical history. Clinical history data are sourced from the EHR of the large IDNs, with more than 60% of participants having both outpatient and hospital information. Remaining patients come from large multispecialty physician practices. The age and sex distribution of the beneficiaries of CDM is similar to that reported by the US Census Bureau for the commercially insured and the Medicare Advantage managed care populations. This study used IDN lives to provide information on healthcare use from both an inpatient and outpatient perspective.

Providers and pharmacies submit administrative claims for payment. These claims are then verified, adjudicated, adjusted, and de-identified prior to inclusion. The de-identified data are fully compliant with the HIPAA. Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within 6 weeks of dispensing.

Medical claims or encounter data are collected from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, for example, physicians, use the Health Care Financing Agency 1500 format. Claims for facility services submitted by institutions, for example, hospitals, use the UB-82 or UB-92 format. Medical claims include multiple diagnosis codes recorded with the ICD-10-CM diagnosis codes; procedures recorded with ICD-10-CM procedure codes, CPT codes, or HCPCS codes; site-of-service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include any drugs administered in a hospital.

Specific information in the CDM included, but not limited to, the following types of data:

- Enrollment: Beneficiaries were assigned a unique identifier by their insurer, which is linkable to all other data. They may be enrolled multiple times with the same insurer, and the length of each given enrollment "span" may vary substantially.
- Demographic: Included birth date, sex, race/ethnicity, and ZIP code of the most recently recorded primary residence.
- Pharmacy dispensing: Included 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. Over-the-counter medications were not captured in the databases.
- Medical encounter: Included the healthcare provider, facility of the encounter, admission and discharge dates, encounter type (ambulatory visit, emergency visit, inpatient hospital stay).
- Diagnosis: Included the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type, diagnoses with ICD-9-CM and ICD-10-CM codes.
- Procedure: Included the date of the procedure, 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.

7.5. Handling of study bias

Outcome misclassification

- To accurately diagnose HZ occurrence, specific algorithms using an ICD-10 diagnosis code for HZ (B02.xx) from hospital, ED, or ambulatory visit diagnoses, and dispensing for an oral antiviral (acyclovir, valacyclovir, or famciclovir) within 7 days before or after the HZ diagnosis were used.

Exposure misclassification

- Receipt of RZV dose 1 or 2 was identified from administrative and claims data by means of CPT codes and NDC codes to minimize the risk of exposure misclassification.

Secular or seasonal trends of RZV use

- To address secular trends or seasonal patterns of RZV use, sensitivity analyses were performed to assess if the occurrence of the COVID-19 pandemic caused changes in secular or seasonal trends in vaccine use.

Unmeasured confounding

- Proxies for disease activity, including medication consumption and healthcare utilization for assessing disease severity, were evaluated to measure confounding factors. Furthermore, to mitigate confounding by indication, participants who received treatment with JAK inhibitors one month after index date were considered. Propensity score matching was employed to adjust for all known confounders. Additionally, a thorough review of the literature was conducted to pinpoint all possible confounders and consider to add them or their proxies if available in the CDM.

Healthy-user bias

- The study captured and adjusted for variables related to healthy users, such as use of other vaccines and screening programs, to minimize healthy-user bias.

Limited follow-up period

- This study was an open cohort study that allowed RZV vaccinated and unvaccinated participants to come in late or die during the follow-up period; participants entering the cohort in early 2018 could have 4 years of follow-up.

Potential of overlapping/coexisting AIDs

- Distribution tables of participants associated with multiple AIDs for 1-dose and 2-dose cohorts were created to determine if there was a significant rate of participants with overlapping or coexisting AIDs.

Selection bias

- The study utilized a healthcare claims database reflective of the U.S. demographic distribution across age, gender, and geographical regions to maintain the study's external validity. Moreover, tables were created to evaluate the participant distribution in the 2-dose cohort based on the reason for concluding follow-up, which mainly included either disenrollment or the end of the study. These tables served to confirm that the percentage of participants citing the study's end as the reason for completing follow-up was similar between the RZV vaccinated and unvaccinated groups within the studied population.

7.6. Study size

Preliminary descriptive queries in the CDM were performed to identify, obtain, and aggregate the number of ≥50 YOA US participants with AID using the algorithm definition presented in Section 7.2.3. The outputs of these queries were used to define the AID populations in the study and inform the study design and SAP by refining the study methodology and analytical approaches most appropriate for the expected sample size. The outputs of these queries were used to estimate:

- The incidence rate of HZ in the unvaccinated group (Table 7.2).
- The sample size and average follow-up duration of RZV vaccinated group (Table 7.3).

Table 7.2 Incidence rate of HZ in unvaccinated group by AID, CDM database 01/2018-12/2021*

AID	Number of participants with HZ in unvaccinated group	Number of participants in unvaccinated group	Person-years (PY)	Incidence rate (1000 PY)
IBD	693	24234	51090	13.56
RA	2781	81639	179079	15.53
SLE	565	15644	33195	17.02
PsO	1533	60533	134443	11.40
PsA	499	14942	34023	14.67
MS	677	20407	48656	13.91

HZ= Herpes zoster; SLE: systemic lupus erythematosus; MS: multiple sclerosis; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; PsO: psoriasis; PsA: psoriatic arthritis.
* This represents the actual study population.

Table 7.3 Sample size and average follow up time among 2-dose recipients, CDM database 01/2018-12/2021*

Year of receipt of dose 2 RZV	Category	SLE	IBD	RA	PsO	PsA	MS
2018	Average FU (years)	2.7	2.5	2.6	2.6	2.5	2.7
	N	269	640	1761	1280	277	299
2019	Average FU (years)	1.9	1.9	2.0	2.0	2.0	1.9
	N	831	1700	4787	3372	772	877
2020	Average FU (years)	1.2	1.3	1.2	1.2	1.2	1.2
	N	935	1906	5113	3996	967	997
2021	Average FU (years)	0.5	0.5	0.5	0.5	0.5	0.5
	N	875	1619	4267	3468	839	948
Overall	Average FU (years)	1.3	1.4	1.4	1.4	1.3	1.4
	N	2910	5865	15928	12086	2845	3121
Average follow-up time (weighted): 1.4 year							

RZV= recombinant zoster vaccine, FU = follow-up, N: number of participants with 2 doses RZV.
* This represents the actual study population.

A two-sided log rank test with an alpha of 5% was used for the sample size calculation of the primary VE objectives. Assumptions for sample size calculation are:

- Incidence of HZ in the RZV unvaccinated group: 12, 15, 20 /1,000 person-years [Baumrin, 2019; Izurieta, 2021; Kawai, 2017b], in accordance with the preliminary analysis performed in CDM (Table 7.2)
- Detectable HR (or VE): 0.3, 0.4, 0.5 or 0.6 (VE=70%, 60%, 50%, or 40%)
- Ratio of RZV unvaccinated to RZV vaccinated group: 3:1.
- Average follow-up period: 1 or 2 years after the second dose of RZV; the estimated average follow-up time in CDM was 1.4 year (Table 7.3)
- Censoring rate in the RZV vaccinated group: 20%
- Censoring rate in the RZV unvaccinated group: 15%

Results of the sample size calculation are presented in Table 7.4.

Table 7.4 Sample size calculation* for effectiveness analyses under a range of assumed incidence rates for unvaccinated group and different detectable VE

			Sample Size of RZV vaccinated group			
Power	**Follow up time**	**Incidence rate in RZV unvaccinated group (/1000 person-years)**	**VE (70%)**	**VE (60%)**	**VE (50%)**	**VE (40%)**
90%	1 year	12	1398	2197	3545	6089
		15	1120	1760	2840	4877
		20	841	1323	2134	3666
	2 years	12	765	1203	1941	3333
		15	614	965	1557	2673
		20	462	726	1172	2013
80%	1 year	12	1017	1599	2588	4463
		15	815	1281	2073	3575
		20	612	963	1558	2687
	2 years	12	558	876	1418	2444
		15	447	703	1137	1961
		20	337	529	856	1477

RZV= recombinant zoster vaccine, VE= vaccine effectiveness, % = Percentage.
Sample size has been calculated for each of the six cohorts.

The number of potential participants who received 2 doses of RZV during the accrual period between 1/2018 to 12/2021 was 5865 for IBD, 2910 for SLE, 15 928 for RA, 3121 for MS, 12 086 for PsO and 2845 for PsA, respectively (Table 7.3). This exceeded the required numbers for a power of 80% and detectable VE of 50% (Table 7.4). This demonstrated that the study was sufficiently powered to assess the primary VE objectives.

7.7. Data analysis

7.7.1. General Methodology

7.7.1.1. Vaccine Effectiveness

Vaccine effectiveness estimates were calculated using Cox regression models using the PHREG procedure of SAS v9.4 to assess each of the primary and secondary objectives.

For the primary objectives, the model was defined as follows:

$H(t) = \exp(\alpha + \beta 1\ (\text{vaccination status}) + \beta 2\ XX1 + \ldots\ \beta n\ (XX(n-1))$

with XX variables: any covariate demonstrating imbalance after weighting.

Where:

- H(t) is the hazard function, corresponding to the instantaneous risk of demise at time t, conditional on survival to that time.

- α is the baseline log-hazard, assuming all covariates are as their reference values
- β1 to βn are the regression coefficients, corresponding to the log-hazard of experiencing HZ for specific categories of the covariates adjusted on the other covariates.

From this model the Hazard ratio of experiencing HZ in the RZV vaccinated cohort compared to the unvaccinated cohort adjusted on the other covariates were calculated.

Then, the Hazard ratio of HZ and its confidence limits were transformed into vaccine effectiveness values.

An example of the code to be used to run the Cox regression modeling shown here:

PROC PHREG DATA=<input data set>;
CLASS <vaccination status> <age Category> <sex> <race>
<*logarithm healthcare cost* > <medication Category>
<presence of comorbidities> <concomitant vaccinations>
<number of encounters> <region> <use of preventive services>
;
model Time*case(0)= <vaccination status> <age Category> <sex> <race>
<number of encounters> <*logarithm healthcare cost* >
<medication Category> <presence of comorbidities>
<concomitant vaccinations> <number of encounters>
<region> <use of preventive services>
RUN;

With

- case =1 for HZ occurrence, 0 for no HZ,
- Time= follow-up time in days

Covariate's format defined in Section 7.3.3.

7.7.1.2. VE (%) Confidence intervals

VE (%) 95% CIs were computed using the following formula:

CI (95%) = 1 – [exp(ln(HR) ± Z x SE)].
Where Z is the Z-score statistics obtained with the Cox Regression model and SE is the standard error.

$$SE = \sqrt{\frac{1}{Expected\ (vaccinated)} + \frac{1}{Expected\ (unvaccinated)}}$$

With, expected (RZV vaccinated) and expected (unvaccinated) being the expected HZ rate at time t in the RZV vaccinated and unvaccinated groups, respectively.

7.7.2. Methods to Address Confounding and Effect Modification

The effect of confounding was addressed using a propensity score matching on all measured confounders.

The study was not powered for running interaction testing, therefore no analyses on effect modifiers were performed.

7.7.3. Statistical Software

Analyses was conducted using SAS version 9.4 (SAS Institute, Cary, NC).

7.7.4. Statistical Hypotheses

For all objectives, the same hypothesis was tested using an alpha risk of 5% and two-sided tests.

The null and alternative hypotheses are respectively:

H0: HR = 1 (i.e VE = 0%)

H1: HR $\neq$ 1 (i.e VE $\neq$ 0%)

7.7.5. Descriptive Analyses

The number and characteristics of RZV vaccinated versus unvaccinated participants in each AID cohort was described and compared. Categorical variables such as gender were presented as numbers and percentages with p-values for the Pearson χ^2 test or Fisher's exact test, as appropriate. Continuous variables such as the number of encounters were presented as the mean with standard deviation and/or median with interquartile ranges, with p-values for the two-sample t-test or Wilcoxon rank-sum test, as appropriate. Absolute standardized differences were calculated to assess the balance of covariates with a cut-off value of 0.1. Overall incidence rates of HZ for the 2-dose ($\geq$28 days apart) and the 1-dose RZV vaccinated cohort and the matched unvaccinated cohort were calculated by dividing the number of HZ cases by the total number of person-years.

7.7.6. Primary analysis

7.7.6.1. Main Analytical approach

For the primary objectives 1-6, the number of incident HZ cases and the number of person-years of follow-up for participants were assessed for the 2-dose (> 28 days apart) RZV cohort and the matched unvaccinated cohort. Overall incidence rates of HZ for the 2-dose (>28 days apart) RZV vaccinated cohort and the matched unvaccinated cohort was calculated by dividing the number of HZ cases by the total number of person-years.

The number of person-years were calculated as the sum of the duration of the risk periods of all participants included in the cohort (RZV vaccinated or Unvaccinated cohort). Crude VE (%) was estimated as (1 – [incidence rate of HZ among 2-dose (at least 28 days apart) RZV recipients / incidence rate of HZ among RZV unvaccinated participants]) × 100%.

Adjusted HRs and 95% CIs comparing HZ incidence rates in the 2-dose (>28 days apart) RZV cohort, and the matched unvaccinated cohort was estimated by Cox proportional hazards regression models. Estimates of VE (%) was calculated as (1 – adjusted HR)× 100%.

The model was built in selecting the vaccination status as well as the confounding variables (used for matching) that are minimizing the BIC.

In addition to that, to adjust for potential residual confounding after matching if some covariates distributions remained unbalanced between the RZV vaccinated and unvaccinated cohorts (Standardized Mean Difference > 0.1 or p-value of $\chi 2$ test or Fisher's exact test < 0.1), they were included in the model, regardless of their impact on the BIC.

7.7.6.2. Data handling conventions/data transformations

The system met all required State and Federal security guidelines for health data (e.g., FISMA, Health Insurance Portability and Accountability Act of 1996), specifically FISMA compliant for FISMA security controls as specified in the NIST Special Publication 800-53 (NIST and Joint Task Force Transformation Initiative 2017).

7.7.7. Secondary analysis

7.7.7.1. Main Analytical Approach

Secondary objective 1: Analyses for secondary objective 1 employed similar methods as for the primary analyses. Analyses for IBD (secondary objective 1) were stratified by UC and CD. A separate VE for UC and CD will be estimated. Descriptive analyses and Cox proportional hazards regression were conducted and estimates of VE (%) were calculated as (1 – adjusted HR) × 100.

Secondary objective 2: Analyses for secondary objective 2 employed similar methods as for the primary analyses. Analyses were performed in the matched 2-dose cohort of either PsO or PsA (secondary objective 2). Descriptive analyses and Cox proportional hazards regression was conducted and estimates of VE (%) was calculated as (1 – adjusted HR) × 100. Descriptive analyses and Cox proportional hazards regression were conducted and estimates of VE (%) were calculated as (1 – adjusted HR) × 100.

Secondary objectives 3-9: Analyses for secondary objectives 3-9 employed similar methods as for the primary analyses and was conducted among the matched 2-dose cohorts of participants with SLE (secondary objective 3), MS (secondary objective 4), RA (secondary objective 5), IBD (secondary objective 6), PsO (secondary objective 7),

PsA (secondary objective 8), either PsO or PsA (secondary objective 9) and their unvaccinated counterparts. Analyses were stratified by the following variables and related categories:

- Age group: 50-59 YOA, 60-69 YOA, 70-79 YOA, 80+ YOA
- Gender
- Time since vaccination: 0 to <1 year, 1-<2 years, 2-<3 years, 3+ years
- Time interval between 2 doses (>28 days apart): 29 – 59 days, 60 – 179 days, 180 – <365 days
- Medication Category during baseline.

Depending on the sample size in each stratum, some categories were pooled.

Analyses for IBD (secondary objective 6) were stratified by UC and CD. Descriptive analyses and Cox proportional hazards regression were conducted and estimates of VE (%) were calculated as (1 – adjusted HR) × 100. Two categories were considered to differentiate UC and CD. Analyses for either PsO or PsA (secondary objective 9) were performed. Descriptive analyses and Cox proportional hazards regression were conducted and estimates of VE (%) were calculated as (1 – adjusted HR) × 100.

Secondary objectives 10-16: Analyses for secondary objectives 10-16 employed similar methods as for the primary analyses and were conducted among the matched 1-dose cohorts of participants with SLE (secondary objective 10), MS (secondary objective 11), RA (secondary objective 12), IBD (secondary objective 13), PsO (secondary objective 14), PsA (secondary objective 15), and either PsO or PsA (secondary objective 16). Descriptive analyses and Cox proportional hazards regression were conducted and estimates of VE (%) were calculated as (1 – adjusted HR) × 100.

Secondary objective 17: Analyses for secondary objective 17 employed similar methods as for the primary analyses and were conducted among the matched 2-dose cohorts. In these analyses, participants were allowed to have multiple AIDs. Analyses were stratified by age group, gender, time since vaccination, time interval between 2 doses and medication Category during baseline. Descriptive analyses and Cox proportional hazards regression were conducted and overall estimates and stratified by age group, gender, time since vaccination, dose interval between 2 doses and medication categories of VE (%) were calculated for all selected AIDs as (1 – adjusted HR) × 100.

Note: This study was not powered to effectively interpret the results of secondary analyses. Therefore, for the assessments of the VE and incidence rates per stratification variable, it was challenging to precisely estimate the true value of the VE and HZ incidence rates. Therefore, for these analyses specifically, certain categories (e.g., 50 to 59 years and 60 to 69 years) were pooled together (see Section 7.7.8.2). This provided additional precision and made the results more interpretable.

7.7.7.2. Sensitivity analyses

Sensitivity analyses were performed to assess if the occurrence of the COVID-19 pandemic had an impact on the effectiveness of the vaccine in participants who tested positive for COVID-19 during the follow-up period. In case of significant differences, additional analyses were performed by AID.

Sensitivity analyses were performed on participants who either had PsO or PSA, PsO only, PsA only, and both PsO and PsA to address the potential overlap between PsO and PsA.

In addition, sensitivity analyses were also performed to assess if adding a medication Category as a covariate after propensity score matching had an impact on the results of the primary analyses (primary objectives 1-6) and subgroup analyses (secondary objective 17).

7.7.8. Additional/Modified Analyses

7.7.8.1. Additional analyses

Additional tables described below were created to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the initial analyses.

AID diagnosis

Study participants may have reported more than one AID diagnosis resulting in potential overlap between AIDs. Distribution tables of participants associated with multiple AIDs for 1-dose and 2-dose cohorts were created to assess the proportion of participants diagnosed with one or more AIDs in the RZV vaccinated and unvaccinated groups. The rationale for this analysis is to check whether there is not a significant rate of participants with overlapping conditions.

Time since vaccination

Baseline characteristics/demographic tables for the 2-dose cohort reporting different lengths of follow-up (0<1 years, 1<2 years, 2<3 years, 3+ years) were created to check the number of HZ events observed in the different follow-up periods for the analysed population and to check whether trends were observed in the different follow-up periods for the analyses corresponding to secondary objectives 3-9 and 17. More granular information about length of follow-up helped to explain varying VE values observed by time since vaccination.

End of follow-up

Distribution tables of participants in the 2-dose cohort whose end of follow-up reason was either disenrollment or study end date was created to estimate the number of participants that end follow-up for a reason other than study end. If many study participants end follow-up for a reason that was not the study end, it could introduce a selection bias, especially if the reason that a study participant disenrolled is linked to the

primary outcome (HZ). This assessment was done to check whether the number of such participants in the analysed population who reported study end as the reason to end follow-up was similar in the RZV vaccinated and the unvaccinated groups.

Medication class/categories

Distribution tables of medication class (type of medication) within each existing medication Category described in Section 13.6 of the protocol amendment 2 were created to assess the distribution of medications class by age and by AID. The purpose of these tables was to identify which medication class was observed in greater frequency by age and by AID. Information about the types of medications in each of the existing medication categories helped to explain when varying vaccine effectiveness values by medication Category were observed.

Additional distribution tables of steroids were created to check the frequency of participants who received low-dose (< 5 mg) versus high-dose (≥5 mg) steroids in the RZV vaccinated and unvaccinated groups. This included participants with RA, IBD and PsA. This assessment was done to check the impact of the cut-off assigned to low-dose and high-dose on the analyses of RA, IBD and PsA cohorts since the cut-off, while clinically acceptable, is considered arbitrary.

The following generic names for low-dose and high-dose steroids for RA, IBD and PsA were considered in the distribution tables:

AID	Generic names for steroids*
RA	Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol), prednisolone, prednisone hydrocortisone
IBD	Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone budesonide (Entocort/Uceris).
PsA	Methylprednisolone (Medrol), prednisolone, prednisone, hydrocortisone (IM/IV), methylprednisolone (Medrol [IM/IV], Solu-Medrol [IM/IV], Depo-Medrol [IM/IV]), prednisolone (IM/IV), triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte) [IM/IV]).

Note: *Section 13.6 of the protocol amendment 2 provides detailed information about the above steroids.

Comorbidities covariates

Cross tables between age categories and comorbidities (asplenia/hyposplenia, COVID-19, pneumonia due to COVID-19, cardiovascular disease, diabetes mellitus, kidney disease, lymphoma/leukemia, liver disease, pulmonary disease, congenital and other immunodeficiencies), described in Section 13.5 of the protocol amendment 2 were created to estimate the number of study participants by comorbidity and age in the RZV vaccinated and unvaccinated groups. This assessment was done for all AIDs separately for the 2-dose cohort to check the impact that co-morbidities had on the overall VE values.

7.7.8.2. Modifications to Subgroup Analyses

As previously mentioned, the study lacked the statistical power for detailed subgroup analyses for each of the AIDs. Person-year data from these subgroups may have been insufficient to yield insights about the subgroup analyses findings. To enhance the statistical robustness and interpretability of the results of these subgroup analyses, certain statistical and theoretical approaches were employed. These methods were applied to combine variables such as age, dose interval between 2 doses, time since vaccination, and medication Category, and are described below:

Age Category, dose interval between 2 doses Category, and time since vaccination Category

A PY threshold was established to determine the combination of categories within the stratification variables (age Category, time since vaccination and dose interval) for each AID. This threshold was based on the following rationale:

- Based on the sample size calculated in Table 7.5 below, within less than 200 person-years, there is less than 1/3 chance to find statistical significance for a true VE of 70% with an incidence of less than 15 per 1000 PY in the control group, indicating a low precision.
- Conversely, within at least 255 PY, for an incidence of at least 12 per 1000 PY in the control group, the likelihood of reaching statistical significance for a true VE of 70% is at least 1/3, equating to a power of 33%. Thus, for sample sizes <255 PY, the chance of proving VE is less than one third.

Based on the above, 255 person-years was used as the cut-off for pooling the analysis of age groups, dose intervals, and time since vaccination. The numerical outcomes of the logrank test, which support this decision, are detailed in Table 7.5:

Table 7.5 Number of PY needed to observe a true VE of 70% with a statistical power of 30% for incidence rate of 12 and 15 per 1000 PY

Solve For: Sample Size
Alternative Hypothesis: Two-Sided

Power	N1	N2	N	Haz Ratio HR	Ctrl Haz Rate h1	Trt Haz Rate h2	Acc-rual Pat'n	Acc-rual Time/ Total Time	Ctrl Loss	Trt Loss	Ctrl to Trt	Trt to Ctrl	Alpha	Beta
0,33342	763	255	1018	0,3	0,012	0,0036	Equal	0 / 1	0,15	0,2	0	0	0,05	0,66658
0,33343	611	204	815	0,3	0,015	0,0045	Equal	0 / 1	0,15	0,2	0	0	0,05	0,66657

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1|N2|N	The sample sizes of the control group, treatment group, and both groups, respectively.
HR	Hazard Ratio. The treatment group's hazard rate divided by the control group's hazard rate.
Hazard Rate	The instantaneous failure rate. Its scale is events per time period.
Accrual Time	The number of time periods (years or months) during which accrual takes place.
Total Time	The total number of time periods in the study. Follow-up time = (Total Time) - (Accrual Time).
Ctrl Loss	The proportion of the control group that is lost (drop out) during a single time period (year or month).
Trt Loss	The proportion of the treatment group that is lost (drop out) during a single time period (year or month).
Ctrl to Trt	Drop In. The proportion of the control group that switch to a group with a hazard rate equal to the treatment group.
Trt to Ctrl	Noncompliance. The proportion of the treatment group that switch to a group with a hazard rate equal to the control group.
Alpha	The probability of rejecting a true null hypothesis.
Beta	The probability of failing to reject the null hypothesis when the alternative hypothesis is true.

7.7.8.2.1. New Combination of Medication Category

Medication categories were recombined using the existing medication categories described in Section 13.6 of the protocol amendment 2. This theoretical approach to recombining the existing medication categories was based on the systemic action of the medications and was applied to the subgroup analyses (secondary objectives 3-9, 17). The approach was used to: (i) make the results of these subgroup analyses more comparable across AIDs as medications are AID-specific; and (ii) make the results more interpretable as low number of participants in these analyzed populations were expected across certain types of medications.

The new combination of these medications is described below:

- Category 1: non-immunosuppressive therapy (e.g., no treatment, NSAIDs, low dose (<5mg) steroids, anti-malarial, topical medications (corticosteroids, non-pharmacologic therapies).
- Category 2: mild-moderate immunosuppressive therapy (e.g., conventional DMARDs, aminosalicylate, psoralen and PUVA, PDT, NB-UVB, UV phototherapy, excimer laser).
- Category 3+4 (combined): highly immunosuppressive (e.g., biologics, high dose (>5 mg) steroids, thiopurines, SP1 receptor modulators, intralesional/IM corticosteroids).
- Category 5: JAK inhibitors, DMARDs (synthetic and targeted synthetic).

Note: For some categories (e.g., Category 5), due to a low number of PY, the results were difficult to interpret.

7.7.9. Amendments to statistical plan

The statistical analysis plan was amended on 02 October 2023 and on 29 February 2024. Amendments to the statistical plan are summarized below.

For SAP amendment 1:

- Update of the definition of concomitant vaccinations.
- Update of the definition of the healthcare cost to use the logarithm.
- Explanation of how to handle the outliers to limit their impact on the analysis results (set a maximum follow-up for six months for the 1-dose cohort and exclude subjects, whose interval between 2 doses is greater or equal to 365 days in the 2-dose cohort).
- Inclusion criterion related to follow-up time of at least 3 months after the follow up start date has been removed.
- Exclusion criterion related to follow-up time of at least 3 months after the follow up start date has been removed.
- Clarification of the methodology for matching vaccinated and unvaccinated subjects.
- Update exposure definition for 2-dose cohort.

- Update time interval between 2 doses.
- Revise definition of low dose and high dose steroids.
- Update of the timeframe for measurement of medication use prior to the index date to indicate active use of AID-related medications (RA, IBD).
- Addition of medication categories for PsO and PsA.

For SAP amendment 2:

- Revision of secondary objective 17 to include stratified analyses.
- Addition of sensitivity analysis to evaluate the impact of including medication Category as a covariate in the analyses.
- Additional analyses to provide more detailed information about the distribution of some of the incidence and VE values reported in the initial analyses.
- Subgroup analyses modifications to enhance the statistical robustness and interpretability of the results.

7.8. Quality control and Quality Assurance

The Project Analyst followed the appropriate GSK written standard to ensure that the study results were complete, internally consistent, and accurately reflected the source.

8. PROTECTION OF HUMAN PARTICIPANTS

8.1. Ethical approval and subject consent

This study was conducted in accordance with the protocol and:

- Ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines
- FDA Code of Federal Regulations Title 21 (21 CFR)
- All other applicable regulations and local laws

8.2. Subject confidentiality

The RWA team at GSK coordinated all data management aspects for the proposed study based on secondary data. RWA was responsible for writing and distributing SAS programs to use for evaluating data from the administrative claims CDM. RWA maintained a secure distributed querying web-based portal to enable secure distribution of analytic queries, data transfer, and document storage. CDM is compliant with the HIPAA of 1996. Data privacy was protected by using anonymized data.

9. RESULTS

Overall results for participants are presented below (Section 9.1), followed by descriptive data including baseline characteristics for all participants, as well as by AID condition (Section 9.2). Results of the primary analyses are presented in Section 9.3. In Section 9.4, results from the secondary analyses, including VE against HZ after 1 dose of RZV followed by stratified analyses for all AIDs, and then by each AID condition (RA, IBD [UC, CD], PsO, SLE, MS and PsA). Sensitivity analyses for PsO and/or PsA, as well as PsO and PsA combined, are found in Section 9.5. Lastly, the results for the post-hoc analyses are shown in Section 9.6 below.

9.1. Participants

The study analysis of the 2-dose cohort involved 36 645 individuals in the RZV group and 109 229 in the non-RZV group (Refer to Table 9.1). The distribution of conditions among those RZV vaccinated 2 dose cohort included 15 061 with RA, 6501 with IBD, 1775 with SLE, 2288 with MS, 8866 with PsO, and 2154 with PsA (Refer to Table 9.1). In contrast, the 2-dose unvaccinated cohort comprised 44 652 with RA, 19 962 with IBD, 5264 with SLE, 6760 with MS, 26 250 with PsO, and 6341 with PsA (Refer to Table 9.1). Participants in the 2-dose cohort were censored mainly due to disenrollment (29.85%) , with 70.15% of participants reaching the end of the study follow-up period (Refer to Source Table 66). Additional participant demographic details of 2-dose RZV vaccinated and unvaccinated cohort for SLE, MS, RA, IBD, UC, CD, PsO, PsA, either PsO or PsA, with PsO and PsA, with all selected AIDs, and with all selected AIDs not considering the COVID-19 period, are provided in Source Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 17, Table 19, Table 21 and Table 22, respectively.

In terms of the 1-dose cohort, 44 865 subjects received one dose of RZV, and 130 458 matched counterparts were not RZV vaccinated (Refer to Source Table 23). The breakdown for the 1-dose RZV vaccinated group was 19 016 with RA (Refer to Source Table 11), 7461 with IBD (Refer to Source Table 12), 2294 with SLE (Refer to Source Table 9), 2752 with MS (Refer to Source Table 10), 10 815 with PsO (Refer to Source Table 15), and 2527 with PsA (Refer to Source Table 16). For those not vaccinated, the numbers were 55 034 with RA (Refer to Source Table 11), 22 396 with IBD (Refer to Source Table 12), 6626 with SLE (Refer to Source Table 9), 7899 with MS (Refer to Source Table 10), 31 144 with PsO (Refer to Source Table 15), and 7359 with PsA (Refer to Source Table 16). Additional participant demographic details of 1-dose RZV vaccinated and unvaccinated cohort for SLE, MS, RA, IBD, UC, CD, PsO, PsA, either PsO or PsA, with PsO and PsA, and with all selected AIDs are provided in Source Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, Table 16, Table 18, Table 20 and Table 23, respectively.

Table 9.1 Number of subjects included by AID in the 2-dose cohort

	RZV cohort N= 36 645		**non-RZV cohort N=109 229**	
AID	n	%	n	%
RA	15 061	41.1	44 652	40.9
IBD	6501	17.7	19 962	18.3
SLE	1775	4.8	5264	4.8
MS	2288	6.2	6760	6.2
PsO	8866	24.2	26 250	24.0
PsA	2154	5.9	6341	5.8

N = number of total subjects
n/% = number / percentage of subjects for a given AID
*Note: Participants were allowed to be included in multiple AID categories, thus the number of participants in the RZV cohort overlap for some conditions (i.e. PsO, PsA)
Source: Table 0, Table 58, Table 59, Table 60, Table 61, Table 62 and Table 63.

Refer to Source Table 88, Table 89, Table 90 and Table 91 for details on demographic characteristics 2-dose (> 28 days apart) RZV vaccinated and unvaccinated cohorts with SLE and with <1 year follow-up, 1-<2 years follow-up, 2-<3 years follow-up and 3+ years follow-up, respectively.

Refer to Source Table 92, Table 93, Table 94 and Table 95 for details on demographic characteristics 2-dose (> 28 days apart) RZV vaccinated and unvaccinated cohorts with MS and with <1 year follow-up, 1-<2 years follow-up, 2-<3 years follow-up and 3+ years follow-up, respectively.

Refer to Source Table 96, Table 97, Table 98 and Table 99 for details on demographic characteristics 2-dose (> 28 days apart) RZV vaccinated and unvaccinated cohorts with RA and with <1 year follow-up, 1-<2 years follow-up, 2-<3 years follow-up and 3+ years follow-up, respectively.

Refer to Source Table 100, Table 101, Table 102 and Table 103 for details on demographic characteristics 2-dose (> 28 days apart) RZV vaccinated and unvaccinated cohorts with IBD and with <1 year follow-up, 1-<2 years follow-up, 2-<3 years follow-up and 3+ years follow-up, respectively.

Refer to Source Table 104, Table 105, Table 106 and Table 107 for details on demographic characteristics 2-dose (> 28 days apart) RZV vaccinated and unvaccinated cohorts with PsO and with <1 year follow-up, 1-<2 years follow-up, 2-<3 years follow-up and 3+ years follow-up, respectively.

Refer to Source Table 108, Table 109, Table 110 and Table 111 for details on demographic characteristics 2-dose (> 28 days apart) RZV vaccinated and unvaccinated cohorts with PsA and with <1 year follow-up, 1-<2 years follow-up, 2-<3 years follow-up and 3+ years follow-up, respectively.

Refer to Source Table 112, Table 113, Table 114 and Table 115 for details on demographic characteristics 2-dose (> 28 days apart) RZV vaccinated and unvaccinated cohorts with all AIDs and with <1 year follow-up, 1-<2 years follow-up, 2-<3 years follow-up and 3+ years follow-up, respectively.

Differences between the pre-matched and post-matched vaccination subjects was due to the removal of vaccinated subjects for whom there was not a match, as well as vaccinated subjects with a dose interval of more than one year (Refer to Source Table 58, Table 59, Table 60. Table 61, Table 62 and Table 63).

9.2. Descriptive data including baseline characteristics

2-dose cohort

Within the group of matched participants, both in the cohort that received 2 doses of the vaccine (N=36 645) and the cohort that did not (N=109 229) across all AIDs:

- Most participants were females in both RZV (64.95%) and non-RZV (64.88%) cohorts, and over a third in both cohorts, 37.02% in RZV and 37.05% in non-RZV, were aged between 70 to 79 years at index (Refer to Table 9.2).
- More than half of the participants, 58.62% in the RZV group and 58.63% in the non-RZV cohort, had at least one comorbidity, including asplenia/hyposplenia, pneumonia due to COVID-19, COVID-19, cardiovascular disease, diabetes mellitus, kidney disease, lymphoma/leukemia, liver disease, pulmonary disease (Refer to Table 9.2).
- The average follow-up period for all AIDs was 1.44 years, with a median of 1.29 years (IQR: 0.73–2.12) in the RZV group. In the non-RZV cohort, these figures were slightly lower, with an average follow-up period of 1.30 years and a median of 1.07 years (IQR: 0.59–1.95) (Refer to Source Table 129).
- Regarding medication usage among study participants, the most common treatment for RA participants was medication Category 4, with 36.60% of RZV and 36.58% of non-RZV participants being prescribed this Category. For those with IBD, SLE, MS and PsO, the most common medications were from Category 1, which included participants not taking any medications for certain AID conditions. Specifically, 31.21% of RZV vaccinated and 30.61% of unvaccinated participants with IBD, 76.90% for RZV vaccinated and 77.11% of unvaccinated participants with SLE, 87.11% for RZV vaccinated and 87.19% of unvaccinated participants with MS and 68.16% for both groups with PsO, respectively, were treated with Category 1 medications. The most common treatment for PsA participants was medication Category 4 with 35.05% for RZV vaccinated versus 35.23% for unvaccinated participants. Information about medication categories is available in Table 9.2.
- Detailed demographic data for the 2-dose RZV and non-RZV cohorts, categorized by specific AIDs, can be found in Table 9.2.

Table 9.2 The demographic characteristics of 2-dose RZV vaccinated and unvaccinated cohorts across AIDs.

	All		RA		IBD		SLE		MS		PsO		PsA	
	Vaccine	No Vaccine	Vaccine	No Vaccine	Vaccine	No Vaccine	Vaccine	No Vaccine	Vaccine	No Vaccine	Vaccine	No Vaccine	Vaccine	No Vaccine
N	36645	109229	15061	44652	6501	19962	1775	5264	2288	6760	8866	26250	2154	6341
Females (%)	64.95	64.88	73.31	73.44	54.73	54.73	88.9	89.19	75.66	75.19	53.24	53.15	54.46	53.92
Comor (%)	58.62	58.63	63.13	63.04	56.51	56.93	65.97	65.01	44.41	44.42	54.06	54.22	61.33	61
Follow-up (years)														
Average Follow-up	1.44	1.3	1.47	1.32	1.47	1.32	1.38	1.25	1.37	1.25	1.42	1.28	1.38	1.24
Median Follow-up	1.29	1.07	1.35	1.10	1.34	1.09	1.17	1.02	1.10	1.00	1.25	1.06	1.15	1.03
Age at index, %														
50-59 Y	15.98	15.94	12.91	12.82	16.32	16.44	20.28	20.44	27.58	27.5	15.88	15.76	20.98	20.93
60-69 Y	35.47	35.45	33.83	33.75	33.1	33.3	38.08	37.9	44.49	44.5	35.91	35.89	40.58	40.67
70-79 Y	37.02	37.05	38.88	38.96	38.58	38.34	33.69	33.74	24.3	24.36	37.74	37.83	32.54	32.53
≥80 Y	11.53	11.57	14.38	14.46	12	11.92	7.94	7.92	3.63	3.64	10.47	10.52	5.9	5.87
Medication Category, %														
Cat 1	--	--	21.07	21.1	31.21	30.61	76.9	77.11	87.11	87.19	68.16	68.16	25.95	26.1
Cat 2	--	--	29.47	29.43	27.76	27.64	22.31	22.36	2.1	2.09	1.5	1.47	10.82	10.68
Cat 3	--	--	9.12	9.17	15.77	16.17	0.79	0.53	3.45	3.4	16.13	16.2	25.07	25.31
Cat 4	--	--	36.6	36.58	24.93	25.36	.	.	7.12	7.13	13.91	13.92	35.05	35.23
Cat 5	--	--	3.72	3.73	0.32	0.22	.	.	0.22	0.19	0.3	0.24	3.11	2.68

Source: Table 0 and Table 129

1-dose cohort

In the 1-dose cohort involving 44 865 participants who received a single dose of the vaccine and 130 458 matched participants who did not, a few consistent trends were noted:

- Most participants were female, with 65.73% in the RZV vaccinated group and 65.39% in the unvaccinated group. The age Category with the most participants was the 70–79-year-olds, 36.40% of those were RZV vaccinated and 36.70% were unvaccinated (Refer to Source Table 23).
- More than half of the participants in each group reported having at least one comorbidity, with 59.38% in the RZV vaccinated group and 59.34% in the unvaccinated group indicating such conditions (Refer to Source Table 23).

Two specific observations were noted in the 1-dose cohort:

- The median duration of follow-up was 0.19 years (IQR: 0.11-0.38) for the RZV vaccinated participants, compared to 0.50 years (IQR: 0.50-0.50) for the unvaccinated participants (Refer to Source Table 128). This shorter follow-up period resulted from censoring of subjects that received a second dose of vaccine 2 to 3 months after the first dose. A six-month cut-off point was defined for both cohorts to keep follow-up lengths between the two cohorts similar.
- In terms of medication use, the most frequently prescribed treatment for RA and PsA were Category 4 medications. Among participants with RA, 38.62% and 38.59% in the RZV vaccinated and unvaccinated groups were prescribed Category 4 medication, respectively (Refer to Source Table 11). While medication Category 4 prescription among PsA participants was 34.23% and 34.26% among RZV vaccinated and unvaccinated, respectively (Refer to Source Table 16). For IBD, SLE, MS, and PsO, the most commonly used medications fell into Category 1 (non-suppressive medications). Detailed information on medication categories can be found in Source Table 9, Table 10, Table 12, Table 15, for SLE, MS, IBD, and PsO, respectively.

9.3. Results of primary analyses

9.3.1. Vaccine effectiveness against HZ after 2 doses of RZV in participants aged ≥50 YOA across AIDs

The primary objective of this study was to estimate the VE of 2 doses of RZV in preventing HZ among participants aged ≥50 YOA with various AIDs including SLE, MS, RA, IBD, PsO and PsA.

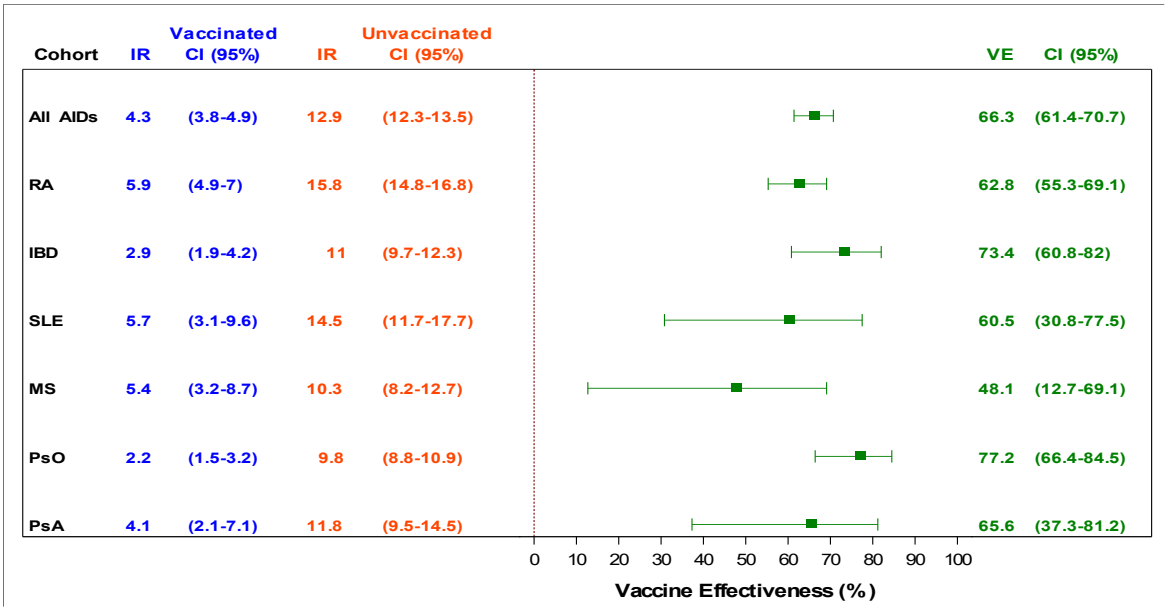
The VE following a second dose of RZV in participants aged ≥50 YOA overall and by various AIDs is summarized in Figure 9.1 as follows:

- Overall, VE against HZ was 66.3% (95% CI: 61.4, 70.7)
- For SLE, the VE was 60.5% (95% CI: 30.8, 77.5)
- For MS, the VE was 48.1% (95% CI: 12.7, 69.1)

- For RA, the VE was 62.8% (95% CI: 55.3, 69.1)
- For IBD, the VE was 73.4% (95% CI: 60.8, 82.0)
- For PsO, the VE was 77.2% (95% CI: 66.4, 84.5)
- For PsA, VE was 65.6% (95% CI: 37.3, 81.2)

The overall observed VE of 66.3% for all selected AIDs aligns with the VE reported in existing research [Izurieta, 2021] as 68.0%, and this consistency holds true for certain AIDs where there were sufficient PY to detect HZ cases.

Figure 9.1 Overall IR and VE (%) across AIDs – RZV 2-dose cohort



Refer to the source tables mentioned below for details on HR.
Source: Figure 1, Table 24, Table 27, Table 30, Table 33, Table 42, Table 45 and Table 54.

9.4. Results of secondary analyses

9.4.1. Vaccine effectiveness against HZ after 1 dose of RZV in participants aged ≥50 YOA across AIDs

The VE of a single dose of RZV in preventing HZ among participants aged ≥50 YOA with various AIDs (SLE, MS, RA, IBD, PsO, PsA and all AIDs) is summarized in Figure 9.2 as follows:

- The overall VE against HZ following 1 dose of RZV was 58.4% (95% CI: 45.9, 68.0)
- For SLE, the VE was 42.6% (95% CI: -45.5, 77.4)
- For MS, the VE was 100%. The 95% CI could not be estimated as no HZ events were reported in the RZV cohort.
- For RA, the VE was 53.8% (95% CI: 34.5, 67.4)

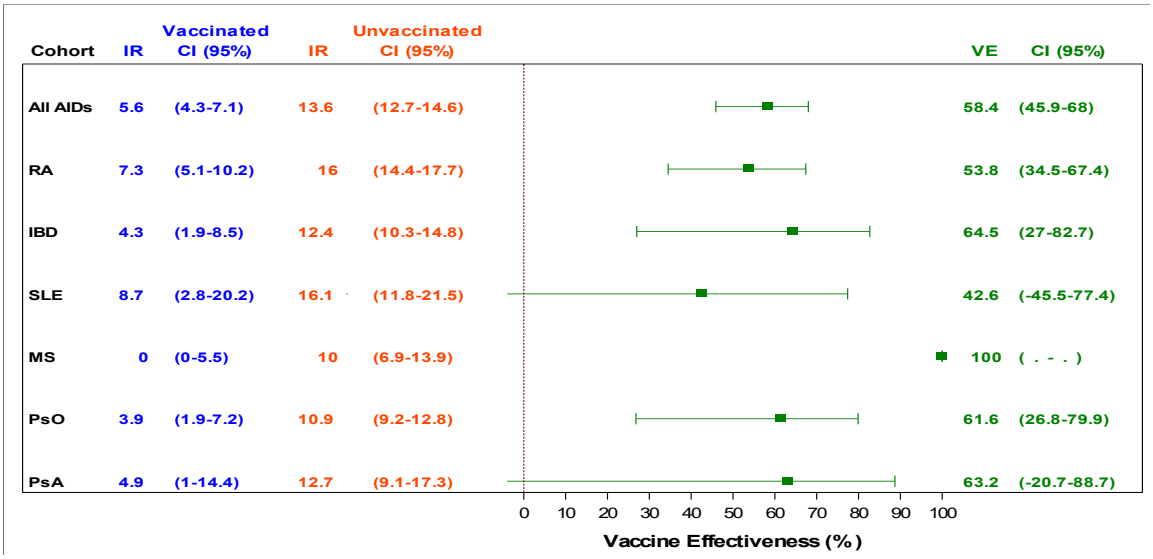
- For IBD, the VE was 64.5% (95% CI: 27.0, 82.7)
- For PsO, the VE was 61.6% (95% CI: 26.8, 79.9)
- For PsA, the VE was 63.2% (95% CI: -20.7, 88.7)

The overall VE of 58.4% across all AIDs aligns with previous research findings 57.7% [Izurieta, 2021] and is considered consistent where sufficient PY data are available to detect HZ cases.

Refer to Source Table 36 and Table 37 for IR, HZ and VE summary, HZ outcome for individuals with UC in 2-dose and 1-dose cohort, respectively.

Refer to Source Table 39 and Table 40 for IR, HZ and VE summary, HZ outcome for individuals with CD in 2-dose and 1-dose cohort, respectively.

Figure 9.2 Overall IR and VE (%) across AIDs – RZV 1-dose cohort



Refer to the source tables mentioned below for details on HR
Source: Figure 2, Table 25, Table 28, Table 31, Table 34, Table 43, Table 46 and Table 55.

9.4.2. Vaccine effectiveness against HZ after 2 doses of RZV in participants aged ≥50 YOA s across all AIDs stratified by age, gender, dose interval, and time since vaccination, and medication Category

The VE against HZ for participants aged ≥50 YOA with selected AIDs who received 2 doses of RZV, stratified by age, gender, dose interval, and time since vaccination are summarized below and presented in Figure 9.3.

- VE by age: When looking at age categories, the VE was highest for the oldest participants (over 80 years) and lowest for the youngest group (50-59 years) at 73.8% (95% CI: 60.2, 82.8) and 59.5% (95% CI, 41.6, 71.9), respectively. Details of the incidence rates for AIDS by age are available in Source Table 56.

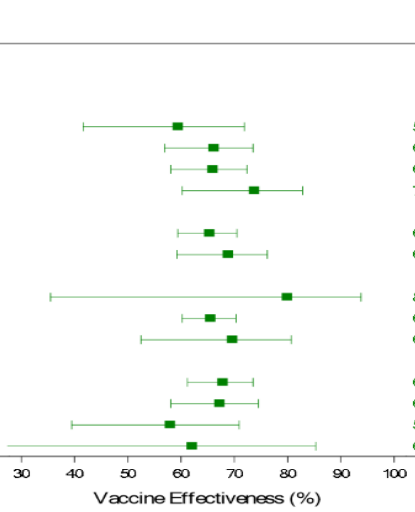
- VE by gender: VE was consistent across genders, with 68.9% (95% CI: 59.2, 76.2%) in males and 65.4% (95% CI: 59.4, 70.5%) in females (Refer to Source Table 56).
- VE by dose intervals: During the 28 to 59 day interval between 2 doses, the vaccine demonstrated an 80.0% (95% CI: 35.5, 93.8) effectiveness rate. During the 60 to 179 day and 180 to <365 day intervals, the vaccine demonstrated a 65.6% (95% CI: 60.2, 70.3) and 69.7% (95% CI: 52.5, 80.7) effectiveness rate, respectively (Refer to Source Table 56).
- VE by time since vaccination: Regarding the time since vaccination, VE was 67.9% (95% CI: 61.2, 73.5) within the first year, 67.3% (95% CI: 58.1, 74.5%) in the second year, 58.0% (95% CI: 39.5, 70.9%) in the third year, and 62.1% (95% CI: 2.1, 85.3) 3 years or longer after vaccination (Refer to Source Table 56).

The overall VE of 66.3% for all AIDs in the 2-dose cohort aligns with previous literature findings [Izurieta, 2021], 68%. Although the VE data, when categorized by age and gender, are comprehensible, the VE assessment relative to duration post vaccination and dose interval is constrained by the lack of adequate PY data (Refer to Source Table 54).

Note: Since medications are AID-specific, it was not meaningful to estimate the VE by medication Category in participants with selected AIDs (all 6 AIDs). Medication categories were recombined during the post-hoc analysis to ensure comparability of medication categories between AIDs and to estimate VE for all AIDs by medication Category, as detailed in Section 7.7.8.2.1 of the study report (Refer to Source Table 67, Table 68, Table 69, Table 70, Table 71 and Table 72).

Figure 9.3 IR and VE (%) of All AIDs 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use

Category	Strata	Vaccinated IR	Vaccinated CI(95%)	Unvaccinated IR	Unvaccinated CI(95%)	VE	CI(95%)
Age group	50-59 y	4.7	(3.3-6.6)	11.6	(10.1-13.2)	59.5	(41.6-71.9)
Age group	60-69 y	4.1	(3.2-5.2)	12.2	(11.2-13.2)	66.2	(56.9-73.5)
Age group	70-79 y	4.6	(3.7-5.6)	13.5	(12.6-14.5)	66	(58.1-72.4)
Age group	80+ y	3.6	(2.3-5.4)	13.9	(12.2-15.7)	73.8	(60.2-82.8)
Sex	Female	5	(4.2-5.8)	14.3	(13.5-15.1)	65.4	(59.4-70.5)
Sex	Male	3.2	(2.4-4.1)	10.2	(9.3-11.1)	68.9	(59.2-76.2)
Dose interval	28-59	2.6	(0.5-7.4)	12.6	(9-17)	80	(35.5-93.8)
Dose interval	60-179	4.4	(3.8-5)	12.8	(12.2-13.4)	65.6	(60.2-70.3)
Dose interval	180-<365	4.1	(2.5-6.3)	13.6	(11.7-15.6)	69.7	(52.5-80.7)
Time since Vx	0-<1	4.2	(3.4-5)	12.9	(12.2-13.7)	67.9	(61.2-73.5)
Time since Vx	1-<2	4.1	(3.2-5.2)	12.7	(11.7-13.8)	67.3	(58.1-74.5)
Time since Vx	2-<3	5.3	(3.7-7.4)	12.4	(10.7-14.3)	58	(39.5-70.9)
Time since Vx	3+	7.6	(2.8-16.6)	17.4	(11.7-24.8)	62.1	(2.1-85.3)



Refer to the source tables mentioned below for details on HR
Source: Figure 13, Table 56

9.4.3. Vaccine effectiveness against HZ after 2 doses of RZV in participants with RA aged ≥50 YOA stratified by age, gender, dose interval, time since vaccination, and medication Category

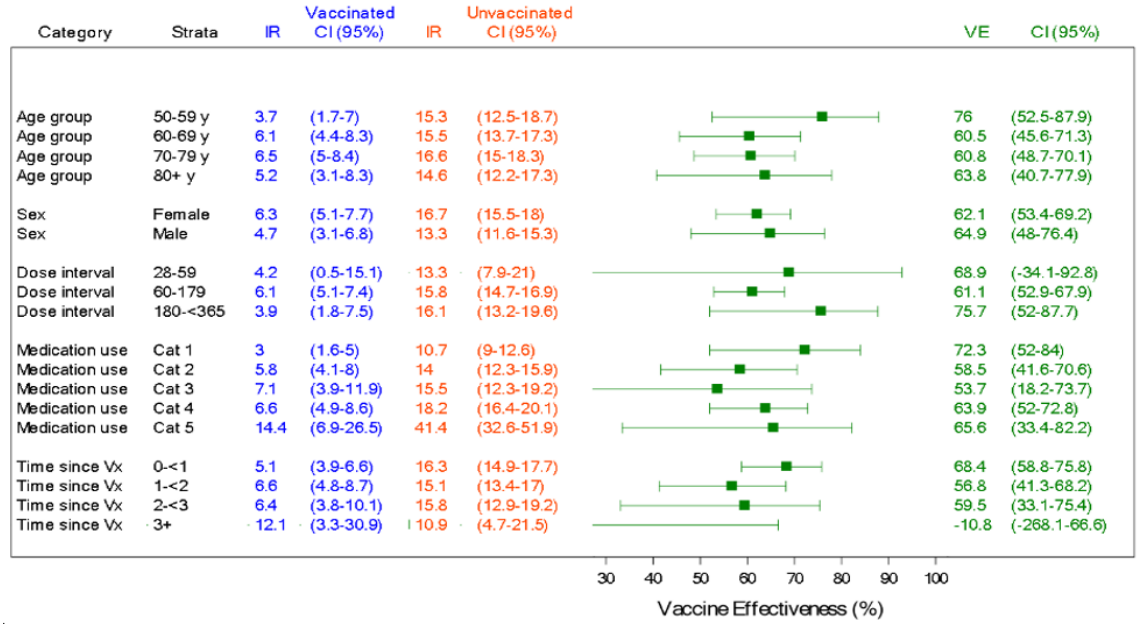
The VE against HZ following 2 doses of RZV in RA participants aged ≥50 YOA, stratified by age, gender, dose interval, time since vaccination and medication Category, are summarized below and presented in Figure 9.4.

- VE by age: VE in the younger age group of 50 to 59 years was 76.0% (95% CI: 52.5, 87.9). For older age groups, VE was 63.8% (95% CI: 40.7, 77.9) for those over 80 years, 60.8% (95% CI: 48.7, 70.1) for the ages 70 to 79 years, and 60.5% (95% CI: 45.6, 71.3) for ages 60-69 years (Refer to Source Table 32).
- VE by gender: VE was 64.9% (95% CI: 48.0, 76.4) in males and 62.1% (95% CI: 53.4, 69.2) in females (Refer to Source Table 32).
- VE for different dose intervals: During the 28 to59 day interval between 2 doses, VE was 68.9% (95% CI: -34.1, 92.8). For the 60 to 179 day and for 180 to <365 day, VE was 61.1% (95% CI: 52.9, 67.9) and 75.7% (95% CI: 52.0, 87.7), respectively (Refer to Source Table 32).
- VE for different medication categories: The VE across medication categories 1, 2, 3, 4 and 5 was 72.3% (95% CI: 52.0, 84.0), 58.5% (95% CI: 41.6, 70.6), 53.7% (95% CI: 18.2, 73.7), 63.9% (95% CI: 52.0, 72.8), and 65.6% (95% CI: 33.4, 82.2), respectively (Refer to Source Table 32).
- VE by time since vaccination: The VE was 68.4% (95% CI: 58.8, 75.8) for 0 to <1 year, 56.8% (95% CI: 41.3, 68.2) for 1 to <2 years, 59.5% (95% CI: 33.1, 75.4), for 2 to <3 years and -10.8 (95% CI: -268.1, 66.6) for 3+ years (Refer to Source Table 32).

The point estimate for the VE for 3+ years post vaccination is not informative given the wide confidence intervals. The incidence rates for this stratified analysis are provided in Source Table 32.

Although the VE data, when stratified by age and gender were clear for RA, interpreting the data for additional stratification variables (dose interval, medication categories, time since vaccination) proved to be challenging.

Figure 9.4 IR and VE (%) of RA 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 3, Table 32

9.4.4. Vaccine effectiveness against HZ after 2 doses of RZV in participants with IBD aged ≥50 YOA stratified by age, gender, dose interval, time since vaccination, and medication Category

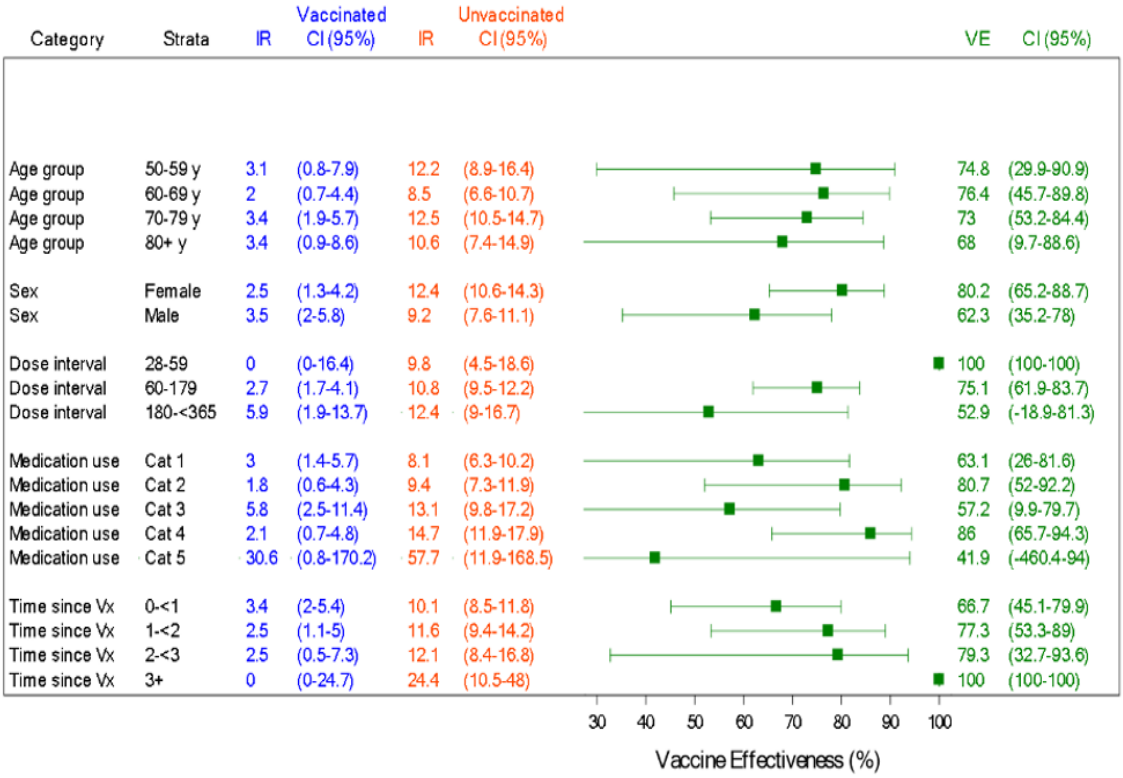
The VE of RZV in preventing HZ among participants aged ≥50 YOA with IBD, stratified by age, gender, time since vaccination, time interval between 2 doses and medication Category, are summarized in Figure 9.5 as follows:

- VE by age: Age-specific VE for ages 50 to 59 years was 74.8% (95% CI: 29.9, 90.9), 76.4% (95% CI: 45.7, 89.8) for ages 60-69 years, 73.0% (95% CI: 53.2, 84.4) for ages 70 to 79 years and 68.0% (95% CI: 9.7, 88.6) for 80+ years (Refer to Source Table 35).
- VE by gender: VE was 80.2% (95% CI: 65.2, 88.7) for females and 62.3% (95% CI: 35.2, 78.0%) for males (Refer to Source Table 35).
- VE by dose intervals: VE was 75.1% (95% CI: 61.9, 83.7) and 52.9% (95% CI: -18.9, 81.3) for 60 to 179-day and 180 to <365-days dose intervals, respectively. For the 28 to 59-day interval, VE was 100% but the 95% CI could not be estimated due to the fact that there was no HZ event in the RZV cohort (Refer to Source Table 35).
- VE by medication categories: VE across medication categories 1, 2, 3, 4 and 5 was 63.1% (95% CI: 26.0, 81.6), 80.7% (95% CI: 52.0, 92.2), 57.2% (95% CI: 9.9, 79.7), 86.0% (95% CI: 65.7, 94.3) and 41.9% (95% CI: -460.4, 94.0), respectively (Refer to Source Table 35).

- VE by time since vaccination: VE was 66.7% (95% CI: 45.1, 79.9) within the first year, 77.3% (95% CI: 53.3, 89.0) in the second year and 79.3% (95% CI: 32.7, 93.6) in the third year. The VE three years post vaccination was 100% (The 95% CI could not be estimated due to an absence of HZ events in the RZV). The incidence rates for this stratified analysis are detailed in Source Table 35.

While VE estimates stratified by age and gender were interpretable for IBD, the interpretation of results for other stratifications like dose interval, medication categories and time since vaccination, is limited due to insufficient PY data.

Figure 9.5 IR and VE (%) of IBD 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 4, Table 35

9.4.5. Vaccine effectiveness against HZ after 2 doses of RZV in participants with IBD by condition (UC, CD) aged ≥50 YOA stratified by age, gender, dose interval, time since vaccination, and medication Category

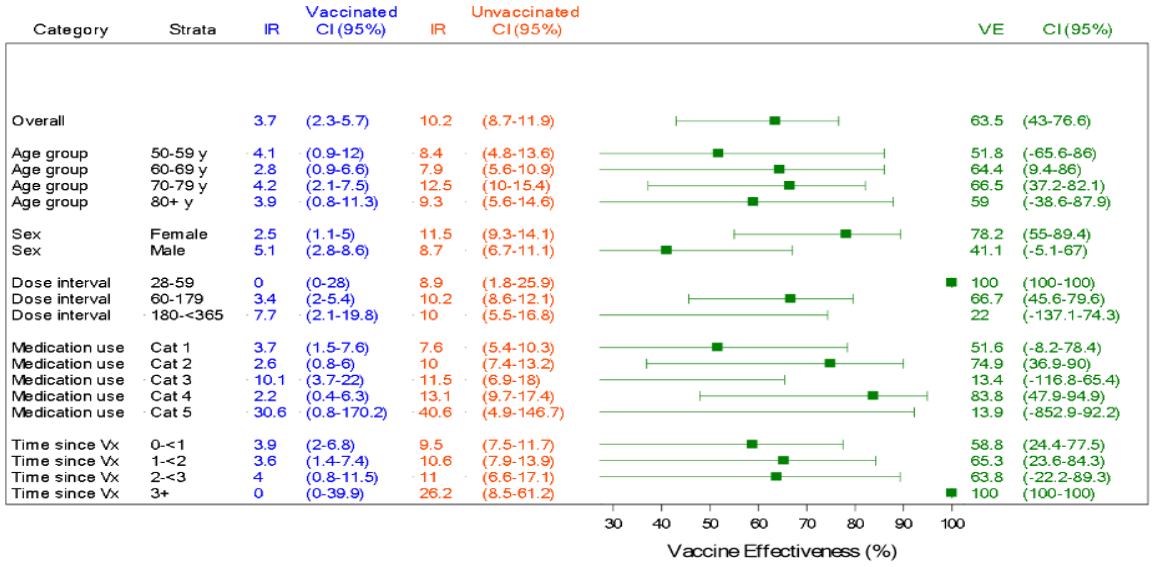
9.4.5.1. UC analysis

The VE against HZ in participants with UC aged ≥50 YOA who received 2 doses of RZV was assessed and stratified by age, gender, dose interval, time since vaccination and medication Category. The findings are summarized below and are presented in Figure 9.6

- VE by age: For UC participants aged over 80 years, the vaccine was 59.0% (95% CI: -38.6, 87.9) effective. VE for age groups70-79 years, 60-69 years, and 50 to 59 years was 66.5% (95% CI: 37.2, 82.1), 64.4% (95% CI: 9.4, 86) and 51.8% (95% CI: -65.6, 86.0), respectively (Refer to Source Table 38).
- VE by gender: VE was 78.2% (95% CI: 55.0-89.4) in females and 41.1% (95% CI: -5.1, 67.0) in males (Refer to Source Table 38).
- VE by dose intervals: During the 60-179-days and 180-<365-day dose intervals, VE was 66.7% (95% CI: 45.6, 79.6) and 22.0% (95% CI: -137.1, 74.3), respectively. The VE during the 28-59-day dose interval was 100.0%. The 95% CI could not be estimated due to the absence of HZ events in the RZV cohort (Refer to Source Table 38).
- VE by medication categories: VE across medication categories 1, 2, 3, 4 and 5 was 51.6% (95% CI: -8.2, 78.4), 74.9% (95% CI: 36.9, 90.0), 13.4% (95% CI: -116.8, 65.4), 83.8% (95% CI: 47.9, 94.9), and 13.9% (95% CI: -852.9, 92.2), respectively (Refer to Source Table 38).
- VE by time since vaccination: VE relative to time since vaccination was 58.8% (95% CI: 24.4, 77.5), 65.3% (95% CI: 23.6, 84.3), and 63.8% (95% CI: -22.2, 89.3) for the intervals of 0 to <1 year,1 to <2 years, and 2 to <3 years, respectively. VE for three years post vaccination was 100.0%. The 95% CI could not be estimated due to absence of HZ events in the RZV cohort and only 5 HZ events in the non-RZV cohort. The incidence rates for this stratified analysis are detailed in Source Table 38.

VE estimations stratified by age and gender were interpretable for UC. However, the interpretation of VE for dose interval, medication categories and time since vaccination was hindered by a lack of PY data.

Figure 9.6 IR and VE (%) of UC 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 5, Table 38

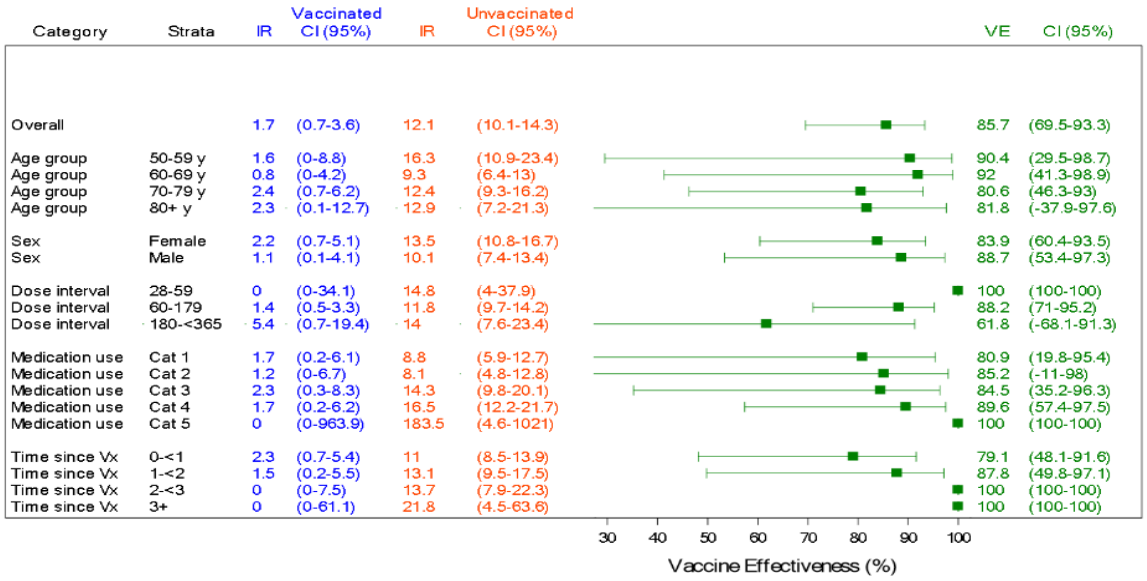
9.4.5.2. CD analysis

The VE against HZ in participants with CD aged ≥50 YOA who received 2 doses of RZV with the results stratified by age, gender, dose interval, time since vaccination and medication Category are presented in the Figure 9.7. The key results are:

- VE by age: The VE was highest among 60-69 age group at 92.0% (95% CI: 41.3, 98.9) and remained high in other age groups, with a VE of 90.4% (95% CI: 29.5, 98.7), 80.6% (95% CI: 46.3, 93.0), and 81.8% (95% CI: -37.9, 97.6) in the 50-59 YOA, 70-79 YOA, and the 80+ YOA, respectively (Refer to Source Table 41).
- VE by gender: The VE was similar in females and males with 83.9% (95% CI: 60.4, 93.5) and 88.7% (95% CI: 53.4, 97.3), respectively (Refer to Source Table 41).
- VE by dose intervals: During the 60 to 179-day and 180 to <365-day intervals, the VE was 88.2% (95% CI: 71.0, 95.2) and 61.8% (95% CI: -68.1, 91.3), respectively. VE for the shorter dose interval of 28 to 59 days was 100.0% but the 95% CI could not be estimated due to the absence of HZ events in the RZV cohort. Details of the incidence rates for this stratified analysis are provided in Source Table 41.
- VE by medication categories: The VE for different medication categories 1, 2, 3, and 4 was 80.9% (95% CI: 19.8, 95.4), 85.2% (95% CI: -11.0, 98.0), 84.5% (95% CI: 35.2, 96.3), and 89.6% (95% CI: 57.4, 97.5), respectively. For Category 5, VE was 100.0% but the 95% CI could not be determined due to the absence of HZ events in the RZV cohort. Details of the incidence rates for this stratified analysis are provided in Source Table 41.
- VE by time since vaccination: Within the first year (0 to <1 year), VE was 79.1% (95% CI: 48.1, 91.6) and between 1 to 2 years, VE was 87.8% (95% CI: 49.8, 97.1). VE for the periods of 2 to <3 years and 3+ years post vaccination was 100.0%. However, the 95% CIs for these two periods could not be estimated due to the absence of HZ events in the RZV cohort beyond two years. The incidence rates for this stratified analysis are detailed in Source Table 41.

VE estimation stratified by age and gender was interpretable for CD. However, insufficient data in terms of PY for certain stratified analyses, such as dose interval, medication categories and time since vaccination, made it challenging to interpret VE for some stratifications related to CD.

Figure 9.7 IR and VE (%) of CD 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 6, Table 41

9.4.6. Vaccine effectiveness against HZ after 2 doses of RZV in participants with PsO aged ≥50 YOA stratified by age, gender, dose interval, time since vaccination, and medication Category

For those aged ≥50 YOA with PsO, the vaccine's protection against HZ was assessed and stratified by age, gender, time since vaccination, time interval between 2 doses and medication Category. The findings are summarized below and presented in the Figure 9.8.

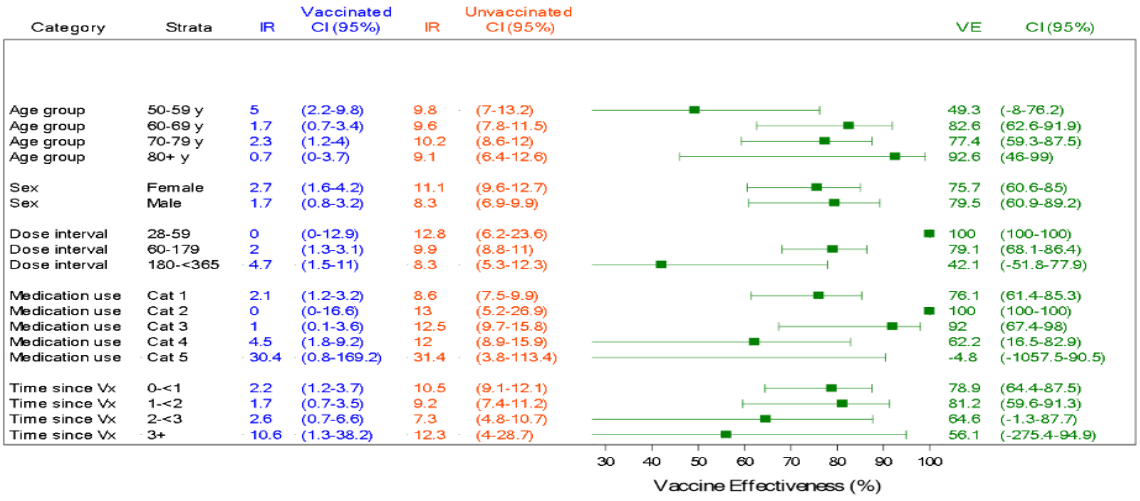
- VE by age: The VE was 92.6% (95% CI: 46.0, 99.0), 77.4% (95% CI: 59.3, 87.5), 82.6% (95% CI: 62.6, 91.9), and 49.3% (95% CI: -8.0, 76.2) for participants who were aged 80+ years, 70 to 79 years, 60 to 69 years, and 50 to 59 years, respectively (Refer to Source Table 44).
- VE by gender: The VE was consistent between genders, with 79.5% (95% CI: 60.9, 89.2) in males and 75.7% (95% CI: 60.6, 85.0%) in females (Refer to Source Table 44).
- VE by dose interval: A medium interval between 2 doses (60 to 179 days) resulted in a VE of 79.1% (95% CI: 68.1, 86.4), while a longer interval (180 to <365 days) showed a VE of 42.1% (95% CI: -51.8, 77.9). The VE for the shortest interval (28 to 59 days) was 100.0%. The 95% CI for this dose interval could not be estimated due to the absence of HZ events in the RZV cohort. Details of the incidence rates for this stratified analysis are available in Source Table 44.
- VE by medication categories: The VE for medication varied across medication categories, with 76.1% (95% CI: 61.4, 85.3) for Category 1, 92.0% (95% CI: 67.4, 98.0) for Category 3 and 62.2% (95% CI: 16.5, 82.9) for Category 4. The VE for

Category 2 could not be estimated due to the absence of HZ events in the RZV cohort. The point estimate of -4.8% (95% CI: -1057.5, 90.5) VE for Category 5 medications is not informative given the wide associated confidence interval. Details of the incidence rates for this stratified analysis are available in Source Table 44.

- VE by time since vaccination: The VE remained high within the first 2 years post-vaccination, with 78.9% (95% CI: 64.4, 87.5) in 0 to <1 year and 81.2% (95% CI: 59.6, 91.3) in 1 to <2 years. Beyond the second year, conclusions regarding VE by time since vaccination cannot be made due to very wide confidence intervals. Details of the incidence rates for this stratified analysis are available in Source Table 44.

While VE could be determined for age and gender, the lack of PY in certain subgroups, such as dose intervals, medication categories and time since vaccination, made it challenging to interpret the VE for PsO cohort.

Figure 9.8 IR and VE (%) of PsO 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 9, Table 44

9.4.7. Vaccine effectiveness against HZ after 2 doses of RZV in participants with SLE aged ≥50 YOA stratified by age, gender, dose interval, time since vaccination, and medication Category

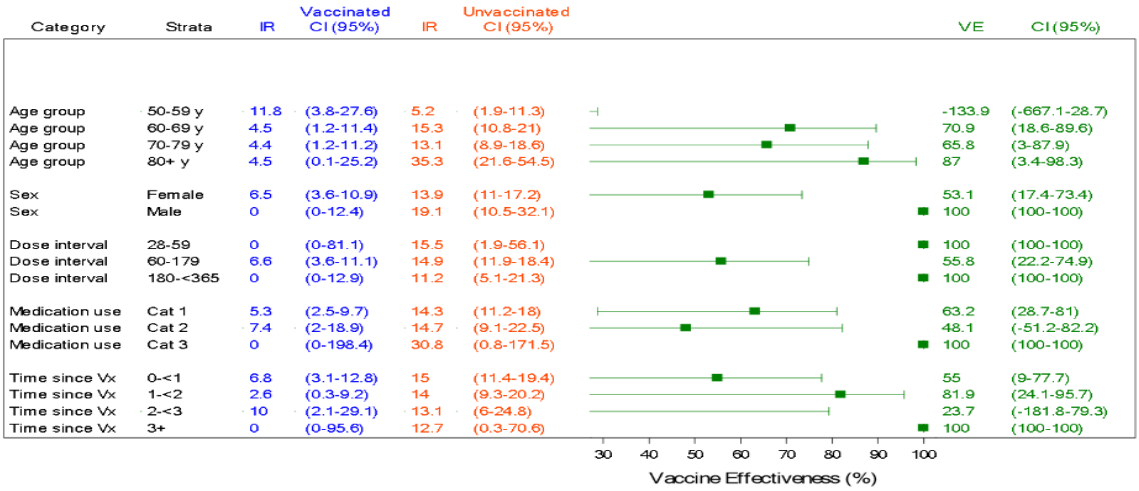
Figure 9.9 presents the VE for preventing HZ in participants aged ≥50 YOA with SLE, following 2 doses of RZV, stratified by age, gender, dose interval, time since vaccination and medication Category.

- VE by age: The VE was 87.0% (95% CI: 3.4, 98.3) for those aged over 80 years, 65.8% (95% CI: 3.0, 87.9) for the 70-79 age group, and 70.9% (95% CI: 18.6, 89.6), for the 60-69 age group. The VE was –133.9 (95% CI: -667.1, 28.7) for the 50-59 age group and was not informative given the wide confidence interval (Refer to Source Table 26).

- VE by gender: The VE was 53.1% (95% CI: 17.4, 73.4) in females and 100.0% in males. The 95% CI for males could not be estimated due to the absence of HZ events in the RZV cohort (Refer to Source Table 26).
- VE by dose interval: For the dose interval of 60 to 179 days, the VE was 55.8% (95% CI: 22.2, 74.9). The VE for dose intervals of 28 to 59 days and 180 to <365 days were both 100.0%. The 95% CI for these 2 dose intervals could not be estimated due to the absence of HZ events in the RZV cohort. Incidence rate details for this stratified analysis are provided in Source Table 26.
- VE by medication categories: The VE for medication categories 1 and 2 were 63.2% (95% CI: 28.7, 81.0) and 48.1% (95% CI: -51.2, 82.2), respectively. VE for medication Category 3 was 100.0% but 95% CI could not be estimated due to the absence of HZ events in the RZV cohort. Details of the incidence rates for this stratified analysis are available in Source Table 26.
- VE by time since vaccination: VE based on time since vaccination was 55.0% (95% CI: 9.0, 77.7), 81.9% (95% CI: 24.1, 95.7), 23.7% (95% CI: -181.8, 79.3) for 0 to <1 year post vaccination,1 to <2 years post vaccination and 2 to <3 years post vaccination, respectively. VE for more than 3 years post-vaccination was 100.0% but the 95% CI could not be estimated due to the absence of HZ events in the RZV cohort. Details of the incidence rates for this stratified analysis are provided in Source Table 26.

The limited number of PY based on factors such as age, gender, dose interval, medication categories and time since vaccination made it difficult to interpret the results of the stratified analyses for SLE cohort who received 2 doses of RZV.

Figure 9.9 IR and VE (%) of SLE 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 7, Table 26

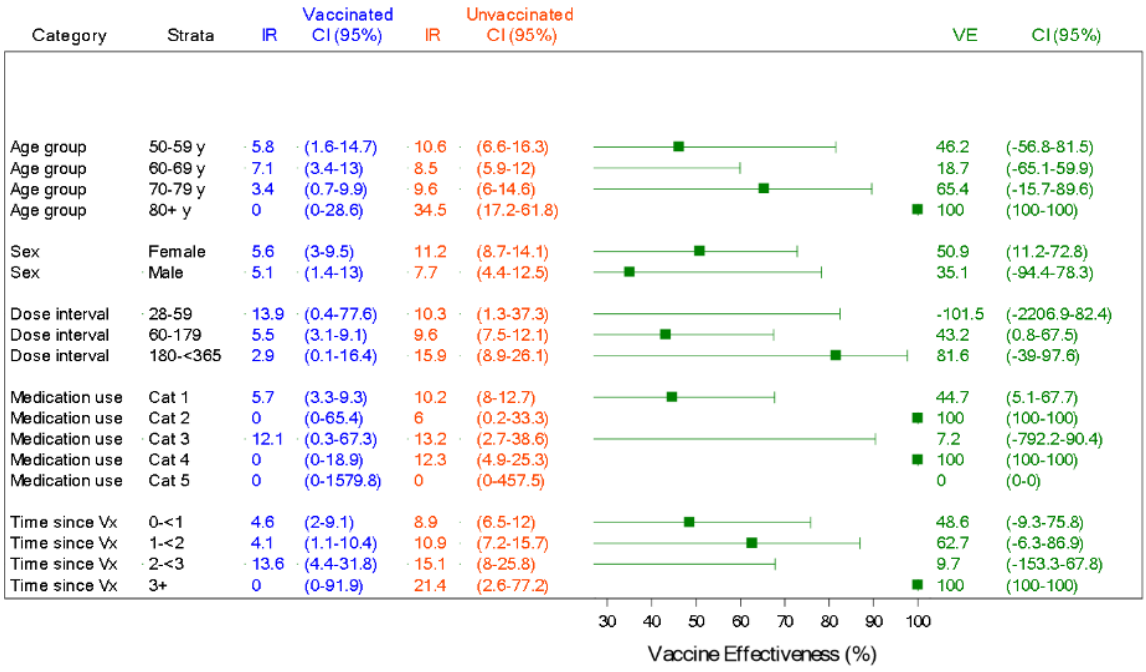
9.4.8. Vaccine effectiveness against HZ after 2 doses of RZV in participants with MS aged ≥50 YOA stratified by age, gender, dose interval, time since vaccination, and medication Category

Figure 9.10 outlines the VE of two RZV doses in preventing participants aged ≥50 YOA with MS from HZ, stratified by age, gender, dose interval, time since vaccination and medication Category.

- VE by age: The VE was 65.4% (95% CI: -15.7, 89.6) for those aged 70 to 79 years, 18.7% (95% CI: -65.1, 59.9) for the 60-69 age group, 46.2% (95% CI: -56.8, 81.5) for the 50 to 59 age group, and 100.0% for those 80+. The 95%CI for the oldest age group (80+) could not be estimated due to the absence of HZ cases in the RZV group. Incidence rates specifics for this stratified analysis are available in Source Table 29.
- VE by gender: The VE was 50.9% (95% CI: 11.2, 72.8) for females and 35.1% (95% CI, -94.4, 78.3%) for males (Refer to Source Table 29).

It was not possible to interpret the results of the stratified analysis of VE in participants with MS due to the insufficient number of PY available (Refer to Source Table 29).

Figure 9.10 IR and VE (%) of MS 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



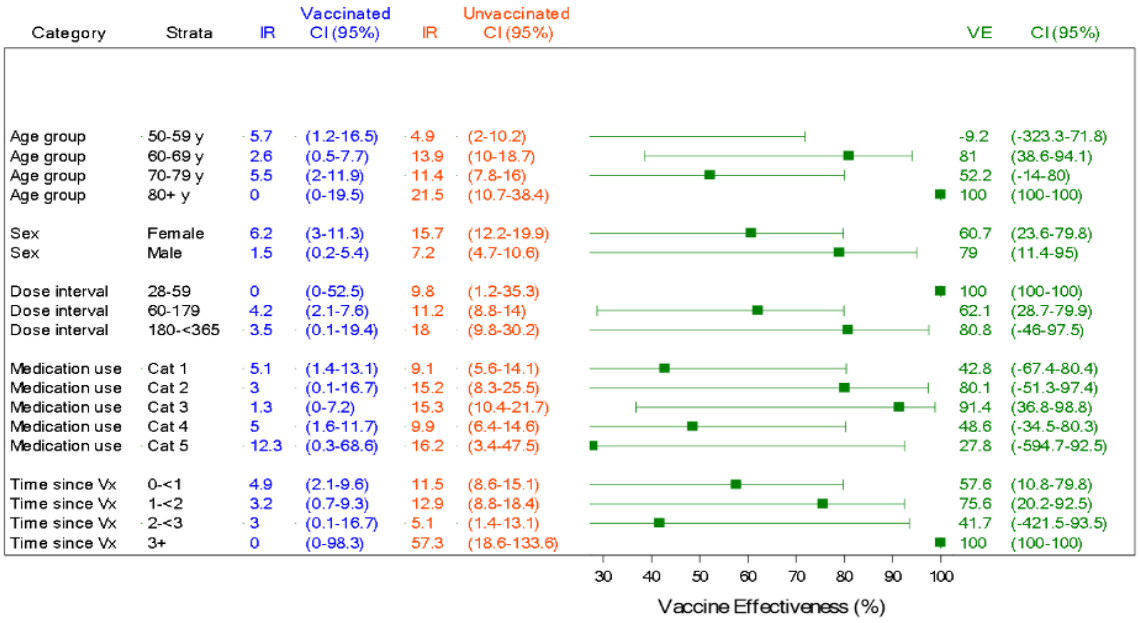
Refer to the source tables mentioned below for details on HR
Source: Figure 8, Table 29

9.4.9. Vaccine effectiveness against HZ after 2 doses of RZV in participants with PsA aged ≥50 YOA stratified by age, gender, dose interval, time since vaccination, and medication Category

Figure 9.11 presents the VE for the prevention of HZ in participants aged ≥50 YOA with PsA, following 2 doses of RZV, stratified by age, gender, dose interval, time since vaccination and medication Category.

- VE by gender: The VE was found to be 79.0% (95% CI: 11.4, 95.0) for male participants and 60.7% (95% CI: 23.6, 79.8%) for female participants (Refer to Source Table 47).
- The VEs, when stratified by variables such as age, time since vaccination, time interval between 2 doses and medication Category, had very wide confidence interval for the PsA group that received 2 doses of RZV, rendering the interpretation of the point estimates impossible Incidence rates details for these stratified analyses are available in Source Table 47.

Figure 9.11 IR and VE (%) of PsA 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 10, Table 47

9.5. Results of sensitivity analyses

9.5.1. PsO and/or PsA analyses

A sensitivity analysis was performed looking at the VE of participants diagnosed with either PsO or PsA, as well as PsO and PsA combined, in order to estimate the impact of overlaps between PsO and PsA diagnoses.

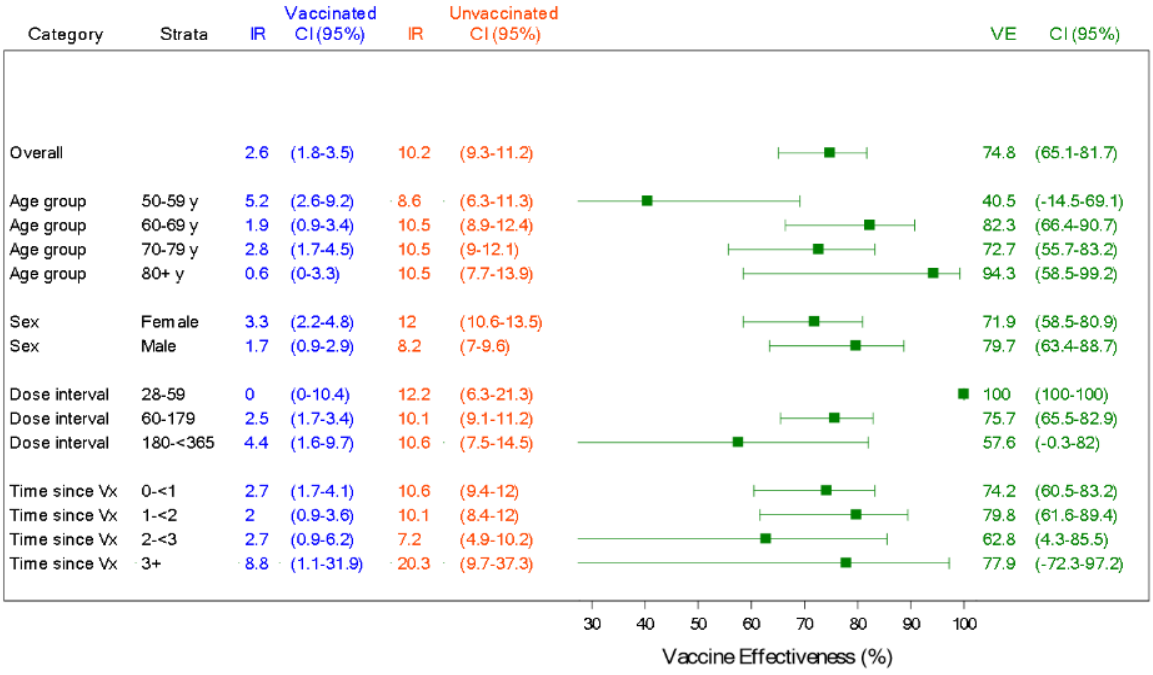
PsO or PsA analysis

Figure 9.12 shows the VE against HZ for participants aged ≥50 YOA who received 2 doses of RZV and were diagnosed with either PsO or PsA, stratified by age, gender, dose interval, time since vaccination and medication Category.

The overall VE for participants in the 2 dose cohort with a diagnosis of PsO or PSA was 74.8% (95% CI: 65.1, 81.7) (Refer to Source Table 48).

For those in the 1-dose cohort with PsO or PSA the VE was 62.0% (95% CI: 33.0, 78.4) (Refer to Source Table 49).

Figure 9.12 IR and VE (%) of either PsO or PsA 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 11, Table 50

- VE by age: The VE varied by age group, ranging from 40.5% (95% CI: -14.5, 69.1) in 50–59 YOA to 94.3% (95% CI: 58.5, 99.2) in 80+ YOA (Refer to Source Table 50).
- VE by gender: The VE was comparable by gender with 71.9% (95% CI: 58.5, 80.9) for females and 79.7% (95% CI: 63.4, 88.7) for males (Refer to Source Table 50).
- VE by dose intervals: VE could not be calculated for participants with a dose interval of 28-59 days as there were no HZ events in the vaccinated group. Additionally, VE estimates by dose intervals should be interpreted with caution due to the broad and overlapping 95% CIs. Details of the incidence rates for this stratified analysis are detailed in Source Table 50.

- VE by time since vaccination: The VE for the first-year post vaccination was 74.2% (95% CI: 60.5, 83.2), and during the second year, VE was 79.8% (95% CI: 61.6, 89.4). Interpretation for other time categories was impeded by insufficient person-year data (Refer to Source Table 50).

The VE figures for PsO or PsA were similar to those for PsO alone. Though some participants may have PsO and PsA diagnoses (refer to Section 9.6.1.1 for an assessment of overlapping conditions), the influence that this overlapping had on the PsO analysis was considered minimal.

PsO and PsA combined analysis

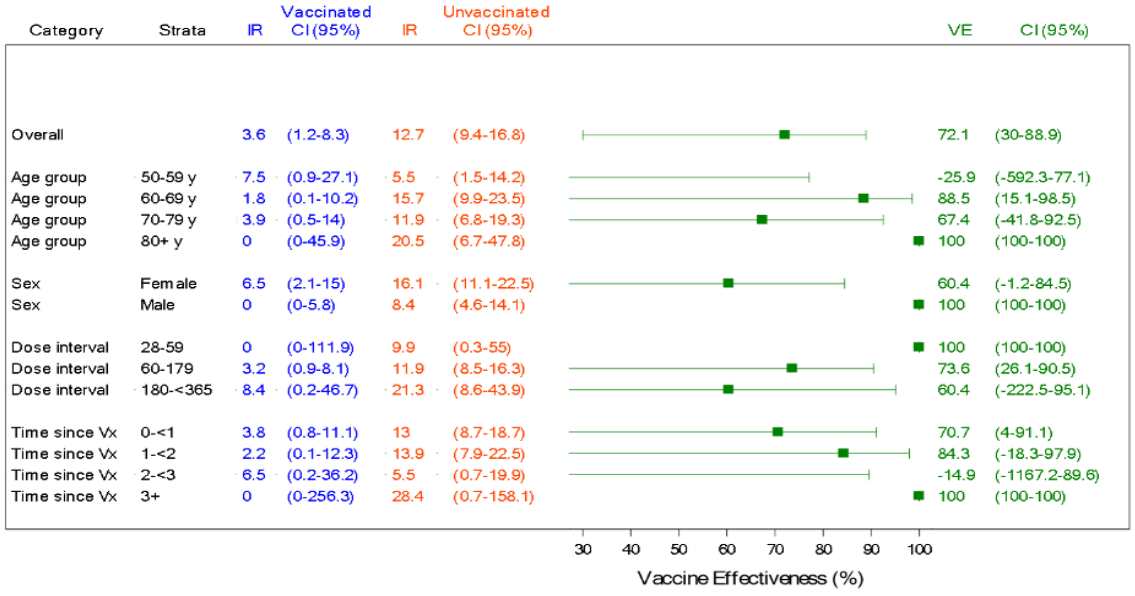
For participants who received 2 doses of RZV and were diagnosed with both PsO and PSA, the overall VE was 72.1% (95% CI: 30.0, 88.9) (Refer to Source Table 51).

For those in the 1-dose cohort with a combined diagnosis of PsO and PSA, the overall VE was found to be 25.3% (95% CI: -153.6, 78.0) (Refer to Source Table 52).

The VE for the prevention of HZ after 2 doses of RZV vaccine in participants aged ≥50 YOA with PsO and PsA, stratified by age, gender, dose interval, time since vaccination and medication Category is depicted in Figure 9.13.

Since the majority of the participants were diagnosed with PsO when selected for either PsO or PsA, VE was similar to the VE of the PsO analysis (Section 9.4.6). The VE for the combined conditions was higher at 72.1% (95% CI: 30.0, 88.9), compared to 65.6% (95% CI: 37.3, 81.2) for PsA alone (Refer to Source Table 45).

Figure 9.13 IR and VE (%) of PsO and PsA combined 2nd dose cohort by age Category, gender, dose interval, time since vaccination and medication use



Refer to the source tables mentioned below for details on HR
Source: Figure 12, Table 53

9.5.2. Analysis of the impact of the COVID-19 period

To gauge the effect of the pandemic on the VE calculations across all AID cohorts, a sensitivity analysis excluding the COVID-19 period (Mar 2020 - Dec 2020) was conducted.

The overall VE estimates in this sensitivity analysis were 64.8% (95% CI: 58.6, 70.0) which was in line with the primary analysis of an overall VE of 66.3% (95% CI: 61.4, 70.7). Thus, the exclusion of the COVID-19 period did not impact the analysis in terms of reducing PYs or the number of HZ events reported during the pandemic (Refer to Source Table 57).

Details of this sensitivity analysis can be found in Source Table 57.

9.5.3. Cox regression models adjusted on medication use

Supplementary Cox regression analyses were conducted to evaluate the effects of incorporating medication usage as a covariate in the model in the 2-dose cohort.

The resulting VE figures adjusted on medication use were consistent with those from the primary analysis as follows:

Table 9.3 Comparison of VE (%) with and without adjustment on medication usage in all AID cohorts (2-dose)

	Adjusted model (post-hoc analysis)			Unadjusted model (initial analysis)		
	VE	LL CI 95%	UL CI 95%	VE	LL CI 95%	UL CI 95%
All AIDs	66.5	61.5	70.8	66.3	61.4	70.7
SLE	60.6	30.9	77.5	60.5	30.8	77.5
MS	48.1	12.6	69.1	48.1	12.7	69.1
RA	63.0	55.5	69.2	62.8	55.3	69.1
IBD	73.5	60.9	82.0	73.4	60.8	82.0
PsO	77.2	66.5	84.5	77.2	66.4	84.5
PsA	65.7	37.5	81.2	65.6	37.3	81.2

Source: Table 24, Table 27, Table 30, Table 33, Table 42, Table 45, Table 54, Table 121, Table 122, Table 123, Table 124, Table 125, Table 126, Table 127

By incorporating medication use as a covariate in the exact matching process, comparable patterns of medication use were observed between the RZV and non-RZV cohorts. This reduced considerably the impact of a confounding bias on the effect of the vaccination exposure on the risk of HZ and explains the similarities in VE for the unadjusted model and the adjusted model on medication usage.

The detailed IR, HZ and VE summary adjusted on medication use, HZ outcome for individuals in 2-dose RZV vaccinated and unvaccinated cohorts for SLE, MS, RA, IBD, PsO, PsA and with all AIDs are presented in Source Table 121, Table 122, Table 123, Table 124, Table 125, Table 126 and Table 127, respectively.

9.6. Results of post-hoc analyses

Post-hoc analyses were conducted to increase interpretability of the study's findings. Additional tables were generated to provide a more detailed breakdown of the IRs and VE values from the subgroup analyses. The post-hoc analyses were done to enhance the study's scientific validity and reliability of the study, without deviating from the original goals and objectives.

9.6.1. Results of additional analyses

9.6.1.1. Participants with overlapping conditions

In both cohorts receiving either 1 or 2 doses, the rate of participants with concurrent conditions was minimal (<5%). Notably, 95.77% and 95.58% of the 2-dose and 1-dose group, respectively were identified with a distinct AID diagnosis (Refer to Source Table 65 and Table 64). As a result, the presence of overlapping conditions was not sufficient to have significant impact on the VE estimates.

Furthermore, the proportion of participants with 2 AID conditions stood at 3.97% for the 2-dose cohort and 4.12% for the 1-dose cohorts (Refer to Source Table 65 and Table 64). These percentages predominantly reflect the co-occurrence of PsO and PsA diagnoses. Section 9.5.1 provides details of the either PsO or PsA and PsO and PsA combined analyses.

The results of the analyses for participants with either PsO or PsA for the 2-dose and 1-dose cohorts, respectively in Source Table 48 and Table 49. Results for participants with PsO and PsA combined for the 2-dose and 1-dose cohorts, respectively, are found in Source Table 51 and 52.

9.6.1.2. Average and median follow-up time

The average and median duration of follow-up for the 2-dose and 1-dose cohorts were analyzed to assess the similarity in follow-up lengths between RZV and non-RZV groups.

Minor discrepancies were noted in the follow-up times when comparing the RZV and non-RZV participants. For all AID conditions, the duration of follow-up was consistently longer within the RZV cohort. The respective median follow-up times in years for the 2-dose RZV and non-RZV cohorts were as follows:

- RA: 1.35 versus 1.10
- IBD: 1.34 versus 1.09
- SLE: 1.17 versus 1.02
- MS: 1.10 versus 1.00
- PsO: 1.25 versus 1.06
- PsA: 1.15 versus 1.03

This observed difference in follow-up times among the RZV and non-RZV cohorts may be due to unmeasured confounders (e.g., education level), which were not considered during the matching process, or due to unvaccinated subjects switching groups once being vaccinated which automatically terminated their follow-up (due to censoring). Nonetheless, this difference was not substantial enough to impact the comparability of the RZV and non-RZV cohorts.

The results of this analysis for the 1-dose and 2-dose cohorts can be found in Source Table 128 and Table 129, respectively.

9.6.1.3. End of follow-up reason

For the majority of participants, the follow-up period concluded with the study's end date. This limited the potential for selection bias that typically arises when the participant exits the study early for reasons related to the outcome being measured. Specifically, for 70.15% of participants, the follow-up concluded with the study's end date, while for the remaining 29.85%, it concluded due to disenrollment resulting from any of the following censoring events:

- Occurrence of HZ
- Receipt of a dose of RZV
- Receipt of a ZVL vaccination
- Death

The results of this analysis can be found in Source Table 66.

The distribution of participants associated with 1, 2, 3 or 4 AID conditions for 1-dose and 2-dose cohort are provided in Source Table 64 and Table 65, respectively.

9.6.1.4. Use of high-dose versus low-dose steroids

Section 7.7.8.1 details the assessment done to determine the effects of the study's cut-off value for steroids (<5 mg for low-dose and ≥5 mg for high-dose steroids). This assessment also included an assessment of the potential misclassification of low-dose steroids within the RA, IBD and PsA groups. The reasons for this assessment were two-fold:

- The assigned cut-off value, while clinically acceptable, was considered arbitrary.
- The concern that the claims database may not accurately report the potency level of the steroid, leading to a misclassification of what constitutes a high-dose steroid

Within the 2-dose RZV cohort, the percentages of participants with RA, IBD and PsA who received low-dose steroids were 6.86%, 1.76% and 5.69%, respectively. Conversely, in the 2-dose non-RZV cohort, these figures were 0.66%, 0.56% and 4.54%, respectively (Refer to Source Table 116, Table 117 and Table 118).

For the same conditions in the 1-dose RZV vaccinated cohort, the usage rates of low-dose steroids were 6.19%, 1.77% and 4.73%, respectively. In comparison, the 1-dose unvaccinated cohort had rates of 6.54%, 1.91% and 5.25%, respectively (Refer to Source Table 116, Table 117 and Table 118).

With less than 7% of participants receiving low-dose steroids for every condition and treatment group, the subsequent risk of potential misclassification overall is low, as a result, this risk was not likely to affect the comparability of the group and the study's conclusions.

Details of this analysis can be found in Source Table 116, Table 117 and Table 118 for RA, IBD and PsA, respectively.

9.6.1.5. Distribution of comorbidities by age and vaccination status

The proportion of comorbidities stratified by age group was evenly distributed among both RZV vaccinated and unvaccinated cohorts across all AIDs.

The analysis revealed common trends across all AIDs:

- The most frequent comorbidities were related to cardiovascular, kidney, pulmonary and diabetes conditions.
- A higher proportion of cardiovascular and renal conditions were observed in the older participants compared to younger ones.
- A greater percentage of younger participants were free from any comorbidities.

Taking RA as an example (Refer to Source Table 84):

- In the 50-59 age range, 8.06% of RZV vaccinated and 8.55% of unvaccinated participants reported cardiovascular events whereas these figures rose to 21.98% and 22.69%, respectively in the oldest age group (80+ years).
- Kidney disease reports were at 4.67% for RZV vaccinated and 5.55% for unvaccinated participants aged 50-59 years, which increased to 19.37% and 19.74%, respectively among the oldest age group (80+ years).
- 37.35% of RZV vaccinated and 38.12% of unvaccinated participants in the 50-59 age group did not report any comorbidity, in contrast to 16.06% and 15.72%, respectively, reported in the oldest age group (80+ years).
- Conditions such as asplenia, COVID-19, lymphoma/leukemia and liver disease were reported at relatively low rates.

The results of this analysis can be found in Source Table 82, Table 83, Table 84, Table 85, Table 86 and Table 87 for SLE, MS, RA, IBD, PsO and PsA, respectively.

9.6.1.6. Distribution of medication use by age group and vaccination status

The distribution of medication use across different age groups showed a consistent pattern between those who were RZV vaccinated and those who were not across all AIDs.

The following findings were observed for each specific AIDs:

Medication Category distribution related to RA (Refer to Source Table 69):

- The most commonly used medications included conventional DMARDs, high-dose steroids and non-AID medications.
- There was less frequent use of low-dose steroids, NSAIDs and biologics agents.
- A higher percentage of older participants were prescribed non-AID medication compared to their younger counterparts, with 22.16% versus 10.69% in the RZV vaccinated group and 24.78% versus 10.95% in the unvaccinated group.
- Younger participants in the cohort were more likely to be on biologics medication, with 15.48% in the RZV vaccinated group and 15.64% in the unvaccinated group, as opposed to 4.47% and 4.50%, respectively in the oldest age group bracket (80+ years).
- Usage rates for conventional DMARDs and high-dose steroids remained relatively uniform across all age categories. For instance, the percentages of participants taking high-dose steroids in the RZV vaccinated group were 36.66%, 36.80%, 36.63% and 36.71% for 50-59 years, 60-69 years, 70-79 years and 80+ years, respectively. In the unvaccinated cohort, the percentages were: 36.28%, 36.79%, 36.57%, 36.67% for 50-59 years, 60-60 years, 70-79 years and 80+ years, respectively.

Medication Category distribution related to IBD (Refer to Source Table 70):

- The primary medication utilized were 5-ASA, high-dose steroids and non-AID medications.
- Less commonly used were low-dose steroids, conventional DMARDs and JAK inhibitors.
- Older participants (80+ years) had a higher proportion of non-AID medication use, with 33.84% versus 23.38% in the RZV vaccinated group and 34.12% versus 22.48% in the unvaccinated group for younger participants (50-59 years).
- Younger participants (50-59 years) showed a higher usage of biologics medications with 20.11% in the RZV vaccinated group and 20.04% in the unvaccinated group, compared to 4.34% and 5.83%, respectively, in the older cohorts (80+ years).
- The distribution of 5-ASA, thiopurines and high-dose steroids usage did not vary significantly with age. For instance, the percentages of participants taking high-dose steroids in the RZV vaccinated group were 24.75%, 22.58%, 24.10% and 25.80% for 50-59 years, 60-60 years, 70-79 years and 80+ years, respectively. In the unvaccinated cohort, the percentages were: 26.31%, 23.45%, 24.30%, 25.98%.

Medication Category distribution related to SLE (Refer to Source Table 67):

- Anti-malarial, less immunosuppressive and non-AID medications were the most frequently used.
- Highly immunosuppressive medications were less commonly used.
- A greater proportion of the older age group (80+ years) received non-AID medications, with 36.17% versus 27.22% in the RZV vaccinated group and 55.88% versus 35.50% in the unvaccinated groups.
- Younger participants (50-59 years) were more inclined to use less-immunosuppressive medications, with 30.28% in the RZV vaccinated group and 30.39% in the unvaccinated group, as opposed to 14.89% and 14.63%, respectively in the older age groups (80+ years).
- The use of anti-malarial treatments was consistent across age groups. The percentages of participants taking this medication in the RZV vaccinated group were 42.22%, 42.60%, 49.67.% and 48.94% for 50-59 years, 60-60 years, 70-79 years and 80+ years, respectively. In the unvaccinated cohort, the percentages were: 34.01%, 34.49%, 32.21% and 29.50%.

Medication Category distribution related to MS (Refer to Source Table 68):

- The majority of participants were treated with less effective and less immunosuppressive therapies, in addition to non-AID medications.
- A higher proportion of older participants (80+ years) were not prescribed any-AID medications compared to their younger counterparts (50-59 years), with 84.34% and 55.88% in the older age brackets of the RZV vaccinated and unvaccinated groups, respectively, versus 26.31% and 35.50% versus in the younger age groups. Which was the reverse of what was observed in the other AIDs.
- Conversely, the younger age group (50-59 years) reported less effective and less immunosuppressive treatments, with 49.60% in the RZV vaccinated group and 30.39% in the unvaccinated group, as opposed to 15.66% and 14.63%, respectively, in the older cohorts (80+ years).

Medication Category distribution related to PsO (Refer to Source Table 71):

- Topical medications and non-AID medications were the primary treatments used.
- Older participants (80+ years), particularly those unvaccinated, were more likely to be on non-AID medications, with 39.38% compared to 23.30% in the younger group.
- The use of topical medications was more common among the older age group (80+ years), especially in the RZV vaccinated cohort, with 49.41% versus 33.99% in younger age group (50-59 years).
- The use of TNF-alpha inhibitors was more common among the younger participants (50-59 years), with 13.07% in the RZV vaccinated group and 11.93% in the unvaccinated group, as opposed to 2.15% and 2.42% respectively in the older participants (80+ years).

Medication Category distribution related to PsA (Refer to Source Table 72):

- Cat 5 TNF-α inhibitors and non-AID medications were the primary treatments used.
- The use of non-AID medication was higher in the older age group, with 43.85% and 43.83%, for the RZV vaccinated and unvaccinated cohorts, respectively, compared to 13.59% and 13.84% in the younger age groups.
- A greater number of older participants reported using high-dose steroids, with 20.00% and 20.47% in the RZV vaccinated and unvaccinated cohorts, respectively, versus 8.92%. and 10.17% in the younger cohorts.
- Younger participants reported a higher use of TNF-alpha inhibitors, with 36.09% in the RZV vaccinated group and 34.10% in the unvaccinated group, compared to 11.54% and versus 9.97%, respectively in the older age groups.

The results of this analysis can be found in Source Table 67, Table 68, Table 69, Table 70, Table 71 and Table 72 for SLE, MS, RA, IBD, PsO and PsA, respectively.

9.6.2. Results of modified subgroup analyses

By pooling relevant categories across the stratification variables (age, time since vaccination, dose interval between 2 doses and medication use) per AID, the combined analyses enhanced the accuracy of the VE (%) estimates for conditions (RA, IBD and PsO) for which a sufficient number of person-years was already present in the initial subgroup analysis.

For the other conditions (SLE, MS and PsA), where enough person-year data was not available in the initial subgroup analysis, the combined analysis did not substantially enhance the accuracy of the estimated vaccine effectiveness for these conditions. Consequently, results for these conditions have to be interpreted with caution.

Presented below is a comparison of VE (%) with and without pooled categories using an example of an AID condition (RA) where the modified analysis was effective, as well as an example (MS) where the modified analysis proved to be ineffective.

Table 9.4 Comparison of VE (%) with and without pooled categories in the RA cohort (2-dose)

Characteristics	Without pooled categories (initial analysis)		With pooled categories (post-hoc analysis)	
	Strata	VE (95% CI)	Strata	VE (95% CI)
Age group	50-59 y (N=6699)	76.0 (52.5-87.9)	50-59 y (N=6699)	76.0 (52.5-87.9)
	60-69 y (N=16945)	60.5 (45.6-71.3)	60-69 y (N=16945)	60.5 (45.6-71.3)
	70-79 y (N=19250)	60.8 (48.7-70.1)	70+ y (N=26561)	61.6 (51.3-69.7)
	80+ y (N=7499)	63.8 (40.7-77.9)		
Sex	Female (N=36380)	62.1 (53.4-69.2)	Female (N=36380)	62.1 (53.4-69.2)
	Male (N=13264)	64.9 (48.0-76.4)	Male (N=13264)	64.9 (48.0-76.4)
Dose interval between 2 doses	28-59 (N=1332)	68.9 (-34.1-92.8)	28-179 (N=44688)	61.3 (53.1-68)
	60-179 (N=43707)	61.1 (52.9-67.9)		
	180-<365 (N=6631)	75.7 (52.0-87.7)	180-<365 (N=6631)	75.7 (52.0-87.7)
Medication use	Cat 1 (N=11737)	72.3 (52.0-84.0)	Cat 1 (N=11737)	72.3 (52.0-84.0)
	Cat 2 (N=14676)	58.5 (41.6-70.6)	Cat 2 (N=14676)	58.5 (41.6-70.6)

Characteristics	Without pooled categories (initial analysis)		With pooled categories (post-hoc analysis)	
	Strata	VE (95% CI)	Strata	VE (95% CI)
	Cat 3 (N=4572)	53.7 (18.2-73.7)	Cat 3-4 (N=23574)	62.2 (51.3-70.7)
	Cat 4 (N=19413)	63.9 (52.0-72.8)		
	Cat 5 (N=1781)	65.6 (33.4-82.2)	Cat 5 (N=1781)	65.6 (33.4-82.2)
Time since vaccination	0-<1 (N=49644)	68.4 (58.8-75.8)	0-<1 (N=49644)	68.4 (58.8-75.8)
	1-<2 (N=32304)	56.8 (41.3-68.2)	1-<2 (N=32304)	56.8 (41.3-68.2)
	2-<3 (N=15658)	59.5 (33.1-75.4)	2+ (N=15658)	54.2 (27.7-71)
	3+ (N=3760)	-10.8 (-268.1-66.6)		

Source table: Table 75 and Table 32.

Overall, the pooled analysis helped to bring more precision to the estimated VE for RA 2-dose cohort, as evident by the narrowed CI in the stratification variables (dose interval between 2 doses, medication use and time since vaccination).

In addition, some trends can be observed across categories. For example, a higher VE for the 50-59 age group or a higher VE for the longest dose interval Category. However, because of the overlapping of the CIs, it is not possible to conclude that these trends would be observed in the actual RA population (Refer to Source Table 75 and Table 32).

Table 9.5 Comparison of VE (%) with and without pooled categories in the MS cohort (2-dose)

Characteristics	**Without pooled categories (initial analysis)**		**With pooled categories (post-hoc analysis)**	
	Strata	VE (95% CI)	Strata	VE (95% CI)
Age group	50-59 y (N=2199)	46.2 (-56.8-81.5)	50-59 y (N=2199)	46.2 (-56.8-81.5)
	60-69 y (N=3385)	18.7 (-65.1-59.9)	60-69 y (N=3385)	18.7 (-65.1-59.9)
	70-79 y (N=1905)	65.4 (-15.7-89.6)	70+ y (N=2188)	77.4 (26.3-93.1)
	80+ y (N=296)	100		
Sex	Female (N=5784)	50.9 (11.2-72.8)	Female (N=5784)	50.9 (11.2-72.8)
	Male (N=1891)	35.1(-94.4-78.3)	Male (N=1891)	35.1 (-94.4-78.3)
Dose interval between 2 doses	28-59 (N=230)	-101.5 (-2206.9-82.4)	28-179 (N=6900)	41.2 (-1-65.8)
	60-179 (N=6722)	43.2 (0.8-67.5)	180-<365 (N=1031)	81.6 (-39-97.6)
	180-<365 (N=1031)	81.6 (-39-97.6)		
Medication use	Cat 1 (N=6744)	44.7 (5.1-67.7)	Cat 1 (N=6744)	44.7 (5.1-67.7)
	Cat 2 (N=163)	100	Cat 2 (N=163)	100 (. – 100)
	Cat 3 (N=256)	7.2 (-792.2-90.4)	Cat 3-4 (N=820)	71.8 (-120.8-96.4)
	Cat 4 (N=565)	100		
	Cat 5 (N=18)	0	Cat 5 (N=18)	100 (0-100)
Time since vaccination	0-<1 (N=7675)	48.6 (-9.3-75.8)	0-<1 (N=7675)	48.6 (-9.3-75.8)
	1-<2 (N=4670)	62.7(-6.3-86.9)	1-<2 (N=4670)	62.7 (-6.3-86.9)
	2-<3 (N=2224)	9.7 (-153.3-67.8)	2+ (N=2224)	21.8 (-115.2-71.6)
	3+ (N=471)	100		

Source table: Table 74 and Table 29

After pooling relevant categories for the MS 2-dose cohort it is not possible to effectively interpret the results of all stratified analyses due to still very wide confidence intervals for MS 2-dose cohort even for the pooled categories. Interpreting the results for this cohort by strata is still not possible.

The results of these analyses can be found in Source Table 73, Table 76, Table 77, Table 78, Table 79, Table 80, Table 81, Table 119 and Table 120 for SLE, IBD, UC, CD, PsO, PsA, with all AIDs, either PsO or PsA and with PsO and PsA combined, respectively.

10. DISCUSSION

10.1. Key results

Participants and baseline characteristics

A total of 36 645 RZV vaccinated and 109 229 matched non-RZV vaccinated participants with selected AIDs were identified in the 2-dose cohort analysis. Median follow-up was 1.29 (IQR: 0.73–2.12) and 1.07 (IQR: 0.59–1.95) years for RZV vaccinated and non-vaccinated participants, respectively.

Our study had slightly higher rates of female participants ~65% compared to 58% in the literature, but fewer participants 80+ years (12% vs. 18% in our study and literature, respectively) [Izurieta, 2021].

For the 1-dose cohort analysis, 44 865 participants with selected AIDs were identified in the RZV group, while 130 458 matched participants were identified in the non-RZV group. The median follow-up period was 0.19 years (IQR: 0.11–0.38) for the RZV cohort, and 0.50 years (IQR: 0.50-0.50) for the non-RZV cohort.

The majority of the study participants in the 1-dose cohort were also female, with women constituting 65.73% of the RZV vaccinated group and 65.39% of the unvaccinated group. Similar trends for the baseline characteristics in the 1-dose cohort were observed except for the follow-up duration which was truncated at 6 months.

Primary analysis

The results showed an overall VE of 66.3% for all selected AIDs which corresponds with the VE of 68% reported from prior research [Izurieta, 2021]. This consistency in VE persists among all AIDs individually where there was sufficient PY data to detect HZ cases, including all categories except MS.

Secondary analyses

The overall VE of 58.4% for participants with selected AIDs who received one dose of RZV corresponds with the VE findings of previous research 57.7% [Izurieta, 2021]. This consistency in VE is observed in specific AIDs with cohorts that have adequate PY data to detect HZ cases, including RA, IBD and PsO.

The estimated VE stratified by factors such as age, gender, time since vaccination, time interval between 2 doses and medication Category were only interpretable for RA, IBD and PsO. In contrast, the stratified VE estimates for SLE, MS and PsA were not interpretable.

For subjects who are immunodeficient, immunosuppressed or likely to become immunosuppressed due to known disease or therapy, and who would benefit from a shorter vaccination schedule, RZV dosing and administration has been approved such that the second dose can be given 1 to 2 months after the initial dose. Thus, additional

analyses are needed which are powered to assess the impact of dosing schedule on the VE of RZV in selected AID patients.

While distinct trends were observed in the stratified analyses upon aggregating relevant categories of variables, the importance of these trends remained unclear. The insufficient number of PY in certain stratified analyses hindered a meaningful interpretation of the results stratified by Category, particularly for the SLE, MS and PsA cohorts.

Precise conclusions about the vaccine's effectiveness concerning age or levels of immunosuppression are not possible due to a lack of statistical power to assess the effectiveness of the vaccine by age or medication categories, a proxy indicator for the participant's level of immunosuppression. No conclusions can be made about the vaccine's long-term effectiveness or its effectiveness across different dosing intervals.

Sensitivity analyses

Sensitivity analyses results examining the influence of concurrent diagnoses of PsO and PsA, as well as their combined analysis, revealed that the VE for participants with either PsO or PsA mirrored the VE observed in the PsO specific analysis. The presence of diagnosis overlap did not markedly affect the outcome of this study.

Additionally, sensitivity analyses assessing the impact of the COVID-19 pandemic on VE across all AIDs indicated that excluding the period affected by COVID-19 period did not result in a large change in VE estimates.

Post-hoc analyses

Post-hoc analyses helped underline the robustness of the primary analysis and interpretability of the study findings, detailed as follows:

- Less than 5% of study participants experienced concurrent conditions, with the majority of these cases involving PsO and PsA diagnoses.
- For the majority of study participants (70%), the follow-up period concluded with the study's end date, thereby reducing the likelihood of selection bias that might arise from participants being lost to follow-up for reasons related to the outcome being measured.
- With less than 7% of participants with RA, IBD, or PsA placed in the low-dose steroid group, the risk of potential misclassification of high potency steroid was minimal and, as a result, this risk did not affect the study's matching process or its conclusions.
- The use of medication and the presence of comorbidities were evenly distributed among the vaccinated and unvaccinated groups.
- The duration of follow-up was consistent among participants with AIDs and was relatively similar between vaccinated and unvaccinated groups. Pooling relevant categories within stratification variables (such as age, time since vaccination, dose interval between 2 doses and medication use), improved the precision of VE estimates for certain conditions (RA, IBD and PsO). However, for other conditions

(SLE, MS and PsA), where the initial analysis lacked sufficient person-year data, this combined approach did not substantially improve the level of confidence around the VE estimates. As a result, interpreting findings of stratified analyses for these conditions could not really be performed.

- Conclusive statements regarding the vaccine's long-term effectiveness or its effectiveness across varying dosing schedules cannot be made as the study was not powered to analyze VE by timing post-vaccination and the interval between 2 doses.
- Similarly, definitive assertions about the vaccine's effectiveness in relation to age or the degree of immunosuppression across AIDs was not feasible due to insufficient precision of the stratified VEs.

10.2. Limitations

Several limitations should be considered when interpreting study findings:

- Insufficient statistical power for subgroup analyses: The study was not powered for analysis of VE by stratification variables such as age, gender, time since vaccination, dose intervals and medication categories. This limitation impacted the precision and reliability of findings for the subgroup analyses. Subgroup analyses were modified to address this limitation, as described in Section 7.7.8.2 of this report but were not always interpretable.
- The retrospective nature of the study, coupled with the inherent limitations of the commercial claims database, means that despite efforts to adjust for these, confounding by indication, misclassification of exposures and outcomes, and selection bias may have still influenced the results of the study. Post-hoc analyses were conducted to address the inherent limitations of this observational study, as described in Section 7.7.8 of this report.

For a detailed discussion of how study biases were addressed, please refer to Section 7.5 of this report.

10.3. Generalisability

The external validity was ensured by considering the following:

- Database representativeness: CDM is a retrospective healthcare claim database representative of the U.S. workforce, their dependents and Medicare supplemental health insurance beneficiaries. It also reflects the broader U.S. population in terms of age, gender and geographic distribution.
- Algorithm validation for AID cohorts: The study employed well established algorithms with proven positive predictive value, as reported in the published literature, to accurately identify AIDs and represent the proportion of subjects with AIDs within the database, closely mirroring that in the overall U.S. population.
- Algorithm validation for HZ events: An algorithm stricter than validated ones was used to detect HZ events, incorporating ICD-10 diagnosis codes and related inpatient or outpatient claims, as well as the use of HZ antiviral medication use around the

time of diagnosis. This algorithm provided HZ incidence rates in the different AID groups comparable to those in the U.S. population with AIDs.

11. CONCLUSIONS

Our analysis provides real-world evidence that RZV vaccination is effective in preventing HZ in individuals ≥50 YOA with selected AIDs. Vaccination with RZV can reduce the burden of HZ in this population, underscoring its health benefits for specific patient groups.

Additional research to ascertain RZV's effectiveness in subgroups (i.e., age group) of patients with selected AID conditions is needed.

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13. TABLES AND FIGURES

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	TMF-18587403	28 February 2024	Protocol Amendment 2
2.	TMF-18872683	08 March 2024	Clinical Study Report Study Administrative Table
3.	TMF-19431395	31 May 2024	Clinical Study Report Important Publications Referenced in the Report
4.	TMF-18592485	17 June 2024	Statistical Analysis Plan Statistical Analysis Plan_EPI-Zoster-097_Amendment 2

EPIDEMIOLOGY STUDY PROTOCOL
SPONSOR:

GLAXOSMITHKLINE BIOLOGICALS SA (GSK)

eTrack study number and abbreviated title	219111 (EPI-ZOSTER-097 VE US DB)
Date of protocol:	Final: 18 August 2022
Date of protocol amendment	Amendment 2 Final: 28 Feb 2024 Amendment 1 Final: 11 August 2023
Title	A retrospective matched cohort database study in the United States to evaluate the effectiveness of recombinant zoster vaccine (RZV) in patients with autoimmune diseases (AIDs)
Brief title	A matched cohort study to evaluate RZV effectiveness in U.S. patients with autoimmune diseases.
Sponsor signatory	Huifeng Yun, PhD Viral Vaccines Epidemiology Head

Based on GlaxoSmithKline Biologicals SA protocol for epidemiology studies WS v 17.2

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and abbreviated title	219111 (EPI-ZOSTER-097 VE US DB)
Date of protocol amendment	Amendment 2 Final: 28 Feb 2024
Title	A retrospective matched cohort database study in the United States to evaluate the effectiveness of recombinant zoster vaccine (RZV) in patients with autoimmune diseases (AIDs)
Sponsor signatory	Huifeng Yun, PhD Viral Vaccines Epidemiology Head
Signature	_____
Date	_____

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

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 2 (28 Feb 2024)

Overall rationale for the current amendment:

This protocol amendment 2 was prepared in order to update a secondary objective, to modify the subgroup analyses for additional statistical power and make the results of these analyses more interpretable. Several additional tables will also be created to provide more granular information about the distribution of incidence rates and vaccine effectiveness values reported in the subgroup analyses.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Section 4.2 Secondary objective	Revise secondary objective 17 to include analysis by stratified variables.	The analysis corresponding to secondary objective 17 will include an estimation of the overall vaccine effectiveness by age, gender, time since vaccination, time interval between two doses, and medication category. This revised analysis will provide additional information about the overall analyses by stratified variables. This is consistent with the analyses by AID (secondary objectives 3-9), which estimate vaccine effectiveness by age, gender, time since vaccination, time interval between two doses, and medication category.
Section 11.3.4 Secondary analysis	Update information about the secondary objective 17 as is indicated above	The rationale for this update is described in Section 4.2 above.
Section 11.3.5 Sensitivity analyses	Additional sensitivity analyses to evaluate the impact of adding medication category as a covariate on the vaccine effectiveness values.	Sensitivity analyses will be performed to evaluate the impact of adding medication category as a covariate on the primary analyses (primary objectives 1-6) and subgroup analyses (secondary objective 17).
Section 11.3.6 Additional analyses	The additional analyses section has been added to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses.	Additional tables listed below will be created to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses: 1. Distribution tables of subjects associated with multiple AIDs for 1-dose and 2-dose cohorts to assess the proportion of subjects diagnosed with overlapping AID conditions. 2. Distribution tables of subjects whose end of follow-up reason is either disenrollment or end of study for 2-dose cohort to identify risk of potential selection bias. 3. Distribution tables of medication class within each medication category to assess the frequency of medication class by age and by AID.

Section # and title	Description of change	Brief rationale
		4. Distribution tables of steroids to check the frequency of subjects who receive low- versus high-dose steroids in the vaccinated and unvaccinated groups. 5. Baseline characteristics/ demographic tables for populations with different length of follow-up (0<1 years, 1<2 years, 2<3 years, 3+ years) to check if trends of HZ events can be observed in different follow-up periods. 6. Cross tables between age categories and comorbidities to check the number of participants by age and comorbidity in the vaccinated and unvaccinated groups.
Section 11.3.7 Modifications to subgroup analyses	Subgroup analyses corresponding to secondary objectives 3-9 and 17 will be modified to address potential study limitations.	This study is not powered for analyses of secondary objectives. This may not allow meaningful interpretation of some of the results of the subgroup analyses. Certain categories from the following variables will therefore be combined to address this issue: age, dose interval between two doses, time since vaccination, and medication category. Combining these categories will add additional statistical power and make the results more interpretable.

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1. SYNOPSIS

1.1. Rationale

Individuals with autoimmune disease (AID) are at higher risk of herpes zoster (HZ) compared to immunocompetent individuals [Gupta, 2006; Khan, 2018; Long, 2013; Smitten, 2007; Yun, 2016]. Information on the effectiveness of RZV in AID populations is limited. One study from the Veterans Affairs Healthcare System among individuals diagnosed with inflammatory bowel disease (IBD) showed that the recombinant zoster vaccine (RZV) group, when compared with the unvaccinated group, was associated with decreased risk of HZ infection among both the 50-60 years of age (YOA) (0.00 vs 3.93 per 1000 person years) and the >60 YOA (1.80 vs 4.57 per 1000 person-years) [Khan, 2022]. A study evaluating the overall vaccine effectiveness (VE) of RZV in a subgroup of Medicare enrolled patients aged ≥65 YOA with AID reported a 1- and 2-dose VE of 57.7% (95% CI, 50.9, 63.6) and 68.0% (95% CI, 62.3, 72.8), respectively [Izurieta, 2021].

The current retrospective matched cohort database study will use the Optum™ Clinformatics Data Mart database to provide early real-world evidence of the effectiveness of RZV in patients aged ≥50 YOA with AIDs. Section 3 provides further details of this study's rationale and background.

1.2. Objectives and outcomes

The primary objective is to estimate the VE of 2 RZV doses in preventing HZ in adults aged ≥50 YOA with systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis (PsO), or psoriatic arthritis (PsA). The primary and secondary objectives are listed in Section 4.2. The primary outcome is HZ (Section 4.2) for all objectives.

1.3. Overall design

Using the Optum™ Clinformatics Data Mart data sets from January 2018 to December 2021, a retrospective matched cohort study will be conducted to estimate the VE of 2 RZV doses in participants who are ≥50 YOA with SLE, MS, RA, IBD, PsO, or PsA, respectively. Separate cohorts will be considered: a 2-dose cohort (primary analysis) and a 1-dose cohort (secondary analysis). For the primary objective, a unique matching will be done involving an exact matching and a propensity score matching performed consecutively. Once cohorts for each AID are identified, participants meeting inclusion criteria who received dose 2 of RZV at least 28 days after dose 1 (2-dose cohort) will be exactly matched with participants who have not received any RZV dose by age category of 5-year increments (i.e., 50-54 age grouping) and by AID-related medication category (mutually exclusive) based on current use at the index date within the same AID group. Following matching as described above, a matching with propensity scores based on the likelihood of receiving RZV dose 2 versus no RZV vaccination (2-dose cohort) and RZV dose 1 versus no RZV vaccination (1-dose cohort) will be calculated using logistic regression models with RZV vaccination as the dependent variable and independent

variables. A 3:1 matching ratio will be applied with the propensity score matching. For the 2-dose cohort, the index date for the vaccinated will be defined as the date of receipt of the second dose. The same index date will be assigned to their unvaccinated matches. For the 1-dose cohort, the index date will be defined as the date of receipt of the first dose for vaccinated participants. The same index date will be used for their unvaccinated matches.

Twelve matched cohorts for a 1-dose and 2-dose for each AID condition (SLE, MS, RA, IBD [ulcerative colitis (UC), Crohn's disease (CD)], PsO, and PsA) will be considered. Participants will be followed through Optum™ database from index date + 30 days until the earliest date of the occurrence of HZ, termination of continuous enrolment (period of uninterrupted insurance coverage), date of death (described in detail in the statistical analysis plan [SAP]), receipt of a dose of RZV for unvaccinated participants, receipt of RZV dose 2 for 1-dose cohort, receipt of zoster vaccine live (ZVL), or end of the study period (December 31, 2021). To be eligible for the analysis, participants who are $\geq$50 YOA at the index date will be required to have at least 365 days of continuous medical and pharmaceutical coverage (allowing administrative gap of 30 days) immediately before index date and 30 days after index date. The 365 days before the index date is defined as the baseline period. Propensity scores based on the likelihood of receiving RZV versus no RZV vaccination will be calculated using logistic regression models to balance measured confounders among participants receiving RZV and comparator participants with no prior RZV vaccination. The overall incidence rates of HZ for the 2-dose RZV vaccinated cohort and the matched unvaccinated cohort will be estimated. VE will be calculated from the hazard ratio obtained from Cox regression models. Analyses will be conducted separately in RA, IBD (UC, CD), SLE, MS, PsO, and PsA populations. Section 5 provides further study design details.

2. SCHEDULE OF ACTIVITIES (SOA)

Below is a list of data extraction procedures that will be considered for this study.

List of data extraction procedures

Retrospective data collection
Define code lists and algorithms to extract variables of interest including AIDs, HZ events.
Identify eligible participants and variables of interest; use of algorithms needed to perform the extraction of the data from the Optum™ database.
Extract participant data from different sources within Optum™ database.
Extracted dataset undergoes: - Quality control and validation - Check for consistency with the required format.
Perform quality control and validation.
Perform specification of analysis dataset including derived variables.
Create analysis dataset.
Perform database freeze of the analysis dataset.
Archive programs and outputs of the analysis dataset.

3. RATIONALE AND BACKGROUND

HZ, or shingles, results from the reactivation of varicella zoster virus (VZV) and causes a painful, pruritic rash that usually resolves on its own within 1-2 weeks. HZ affects at least 1 million people in the United States each year. An estimated 32% of persons in the United States will experience HZ during their lifetime [Harpaz, 2008]. Furthermore, over 95% of adults ≥50 YOA are seropositive for VZV and susceptible to HZ [Johnson, 2015].

Individuals with AID are at higher risk of HZ than immunocompetent individuals [Gupta, 2006; Khan, 2018; Long, 2013; Smitten, 2007; Yun, 2016]. The incidence rate of HZ among adults with RA is about double than that among immunocompetent (non-RA) adults [Smitten, 2007; Yun, 2016], and it is higher among adults with IBD (e.g., UC or CD) than those without IBD [Gupta, 2006; Khan, 2018; Long, 2013; Yun, 2016]. The risk of HZ in patients with SLE is also twice as high than in the general population [Kawai, 2017a]. Patients with PsO have a higher HZ risk than the general population [Baumrin, 2019; Chen, 2014; Tsai, 2017].

Systemic therapies also play a major role in the risk of HZ. For example, immuno-suppressive therapy renders patients with SLE and MS more susceptible to VZV reactivation [Borba, 2010; Manouchehrinia, 2017]. In a recent systematic literature review, patients with PsO or PsA treated with systemic corticosteroids and combination systemic therapy were reported to have increased HZ risk [Baumrin, 2019]. Patients with PsO and PsA had variable HZ risk, depending on disease severity and type of systematic therapy.

The US Food and Drug Administration (FDA) approved RZV, a 2-dose subunit zoster vaccine containing recombinant glycoprotein E in combination with the novel adjuvant $AS01_B$, in October 2017 for immunocompetent adults aged ≥50 YOA [FDA, 2017] and in July 2021 for adults aged ≥18 YOA who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy [FDA, 2021]. The FDA approvals were followed by the recommendations of the Advisory Committee on Immunization Practices (ACIP) of RZV for use in immunocompetent adults aged ≥50 YOA [Dooling, 2018] and in immunocompromised adults aged ≥19 YOA [Anderson, 2022].

The GSK 2-dose RZV vaccine demonstrated efficacy in preventing HZ in two phase III randomized controlled trials (RCTs): ZOE-50 and ZOE-70 [Lal, 2015; Dagnew, 2019]. RZV efficacy in these trials was 97.2% (95% CI, 93.7, 99.0) in adults aged ≥50 YOA (ZOE-50) and 91.3% (95% CI, 86.8, 94.5) in adults ≥70 YOA (ZOE-70). Myalgia, injection site pain, and erythema were the most common adverse events (AEs) reported in these trials.

Vaccine efficacy of RZV in immunocompromised adults aged ≥18 YOA was evaluated in a clinical trial that included autologous hematopoietic stem cell transplant (auHSCT) recipients [Bastidas, 2019]. Among auHSCT recipients, RZV efficacy in preventing HZ was 68.2% (95% CI, 55.6, 77.5). Post-hoc vaccine efficacy among adults with hematological malignancies (HM) was 87.2% (95% CI, 44.3, 98.6) [Dagnew, 2019].

Data on RZV effectiveness in AID populations is limited. A recent cohort study evaluated the overall VE of RZV in a subgroup of Medicare enrolled patients aged ≥65 YOA with various immunocompromised (IC) conditions and AIDs and reported overall 1- and 2-dose VE of 57.7% (95% CI, 50.9, 63.6) and 68.0% (95% CI, 62.3, 72.8), respectively [Izurieta, 2021]. Another recent study from the Veterans Affairs Healthcare System among individuals diagnosed with IBD showed that RZV was associated with decreased risk of HZ infection among both the 50-60 years and >60 years of age (YOA) patients [Khan, 2022]. More research is needed to evaluate the effectiveness of RZV in specific AID populations (SLE, MS, RA, IBD, PsO, and PsA).

This study will help to critically inform patient and physician decision-making about vaccinating against HZ in these at-risk populations and support evidence-based AID recommendations and guidelines.

3.1. Description of the database

This study will be conducted using data from the health care administrative encounters/claims (United enrollees) of the Clinformatics Data Mart (CDM) Optum™. CDM Optum™ is a quarterly updated database for members of a large national managed care company affiliated with Optum™. It includes both commercial and Medicare Advantage health plan enrollees from all 50 states in the United States. The database includes proprietary, deidentified health claims data from a geographically diverse US population (16% West, 20% Midwest, 36% South, and 27% Northeast). In addition to medical claims, pharmacy claims, and outpatient laboratory tests, Optum™ includes data tables related to member inpatient confinements and eligibility data. Optum™ includes data with service dates from 2007 to present and approximately 15 – 18 million annually insured lives. The Optum™ database system contains more than 80 million lives, of which more than 40% have more than 4 years of clinical history. Clinical history data are sourced from the electronic health record (EHR) of the large integrated delivery networks (IDNs), with more than 60% of patients having both outpatient and hospital information. Remaining patients come from large multispecialty physician practices. The age and sex distribution of the beneficiaries of Optum™ is similar to that reported by the US Census Bureau for the commercially insured and the Medicare managed care populations. This study will use IDN lives to provide information on healthcare use from both an inpatient and outpatient perspective.

Providers and pharmacies submit administrative claims for payment. These claims are then verified, adjudicated, adjusted, and de-identified prior to inclusion. The deidentified data are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA). Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within 6 weeks of dispensing.

Medical claims or encounter data are collected from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, for example, physicians, use the Health Care Finance Administration 1500 format. Claims for facility services submitted by institutions, for example, hospitals, use the UB-82 or UB-92 format. Medical claims include multiple diagnosis codes recorded with the ICD-10-CM diagnosis codes; procedures recorded with ICD-10-CM procedure codes, Current Procedural Terminology (CPT) codes, or Healthcare Common Procedure Coding System codes; site-of-service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include any drugs administered in a hospital.

Specific information in the Optum™ database includes, but is not limited to, the following types of data:

- Enrolment: Beneficiaries are assigned a unique identifier by their insurer, which is linkable to all other data. They may be enrolled multiple times with the same insurer, and the length of each given enrolment "span" may vary substantially.
- Demographic: Includes birth date, sex, race/ethnicity, and ZIP code of the most recently recorded primary residence.
- Pharmacy dispensing: Includes the date of each prescription dispensing, the National Drug Code (NDC).
- Identifier associated with the dispensed product, the nominal days' supply, and the number of individual units (pills, tables, vials, etc.) dispensed. Over-the-counter medications are not captured in the databases.
- Medical encounter: Includes the healthcare provider, facility of the encounter, admission and discharge dates, encounter type (ambulatory visit, emergency visit, inpatient hospital stay).
- Diagnosis: Includes the date of diagnosis, its associated encounter identifier, admission date, provider identifier, and encounter type, diagnoses with ICD-9-CM and ICD-10-CM codes.
- Procedure: Includes the date of the procedure, 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.

4. OBJECTIVES AND OUTCOMES

4.1. Objectives

This study will assess VE among participants enrolled in the Optum™ database with SLE, MS, RA, IBD (UC, CD), PsO, or PsA who received RZV (vaccinated) compared to participants who did not receive RZV (unvaccinated), as per the objectives described in Section 4.2. HZ will define the outcome (Section 4.2) for all objectives in Section 4.2.

4.2. Study objectives

Primary Objectives

1. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE.
2. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS
3. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA.
4. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD
5. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO
6. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA

Secondary Objectives

1. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD)
2. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
3. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
4. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
5. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.

6. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD), age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
7. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
8. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
9. To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
10. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with SLE.
11. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with MS.
12. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with RA.
13. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC and CD).
14. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsO.
15. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsA.
16. To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
17. To estimate overall VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with selected AIDs ***by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.***

4.3. Outcomes

The primary outcome is the HZ event which can be identified with a high PPV ≥ 80% based on diagnosis codes, with additional accuracy established through the requirement for use of an antiviral medication if only one outpatient claim is considered [Zhang, 2012]. A recent study has shown a high PPV of 97.5% for an ICD-10 code for HZ accompanied by either a prescription or laboratory test results [Baxter, 2018]. An HZ event will be defined by the occurrence of either:

- At least 1 inpatient claim with a HZ diagnosis (identified by pre-defined ICD-10 codes); OR
- At least 2 outpatient claims with HZ diagnosis which are no more than 30 days apart: OR
- At least 1 outpatient claim with HZ diagnosis with a pharmacy claim for anti-viral treatment within 7 days before or after the claim with HZ diagnosis.

HZ diagnosis codes and medications are shown in Appendix 4.

5. STUDY DESIGN

5.1 Overall design

A retrospective matched cohort study with Cox proportional hazards modeling will be performed to assess the risk of HZ after RZV in adults aged ≥50 YOA with RA, IBD, SLE, MS, PsO, or PsA. In the primary analysis, participants receiving a second dose of RZV (separated by >28 days after dose 1) on or after 01 January 2018 will be compared to participants with no prior RZV vaccination (i.e., unvaccinated). For the primary objective, a unique matching will be done involving an exact matching and a propensity score matching performed consecutively. Once cohorts for each AID are identified, participants meeting inclusion criteria who receive 2 doses of RZV at least 28 days apart (2-dose cohort) at the index date will be matched exactly with unvaccinated participants on age category of 5-year increments (i.e., 50-54 age grouping) and by AID-related medication category (mutually exclusive) based on current use at the index date. Following matching as described above, a matching with propensity scores based on the likelihood of receiving RZV dose 2 versus no RZV vaccination (2-dose cohort) and RZV dose 1 versus no RZV vaccination (1-dose cohort) will be calculated using logistic regression models with RZV vaccination as the dependent variable and independent variables. A 3:1 matching ratio will be applied with the propensity score matching. Matching will be used to better control for the confounding effects and reduce bias in this observational study. The matching ratio of ***3:1*** is selected by optimizing the sample size and potential censoring for the unvaccinated participants due to receipt of RZV. For IBD, a vaccinated participant with UC will be matched to an unvaccinated participant with UC. The same approach will be used to match participants with CD. Matching will be done with replacement. Several papers indicate that the use of replacement provides the most reliable treatment effect estimates [Bottigliengo, 2021]. Details will be described in the SAP prior to the analysis. This strategy can create better balance, which should yield

estimates that are closer to the truth on average. To address additional potential confounding due to differences between vaccinated and unvaccinated cohorts, multiple covariates (Section 6.2) will be assessed and balanced across the exposure groups using propensity score matching. Unvaccinated participants will be assigned the same index date as their vaccinated counterparts.

The study will be conducted using health care encounters/claims of the Optum™ database (Section 3.1). The primary outcome is a HZ event and the primary exposure of interest is the receipt of 2 doses of RZV separated by ≥28 days after dose 1. The index date will be defined as the date of receipt of the second dose for RZV (at least 28 days after first dose) for vaccinated participants and their unvaccinated matches.

Additional secondary objectives will examine 1-dose (with the index date as the date of receipt of RZV dose 1) and 2-dose VE by age, gender, time since vaccination, time interval between two doses, and medication category, respectively. Secondary analyses will also stratify 2-dose VE by UC and CD. Analyses will be conducted separately among participants diagnosed with RA, IBD, SLE, MS, PsO, and PsA. The study period from identification of vaccinated cases to study completion will be 01 January 2018 to the first occurrence of HZ, termination of membership, death, receipt of RZV for unvaccinated participants, receipt of second dose of RZV for 1-dose cohort, receipt of ZVL, or 31 December 2021 (i.e., end of the study period).

Figure 1 describes the cohort design to assess two-dose vaccine effectiveness.

Figure 1 Matched 2-dose cohort study

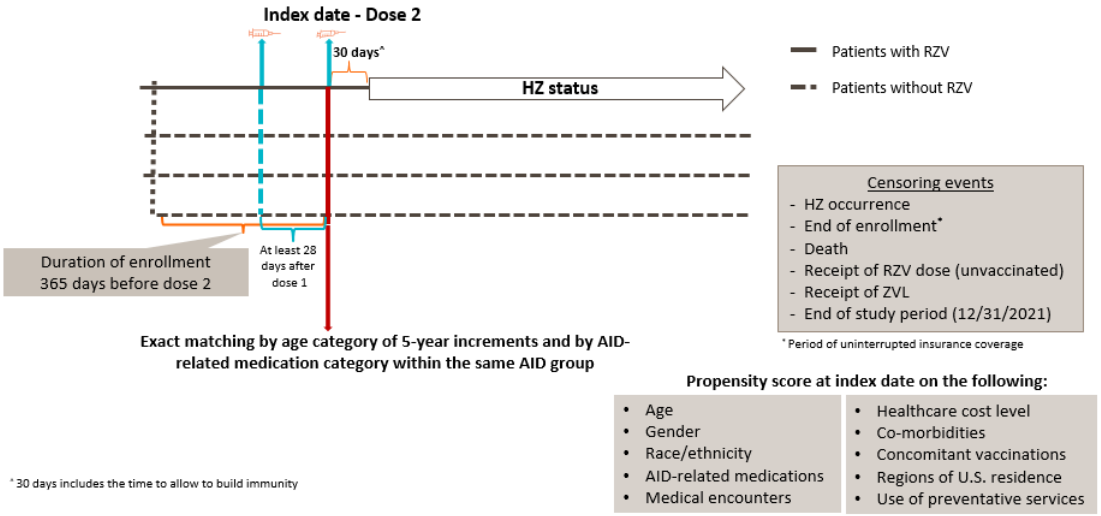
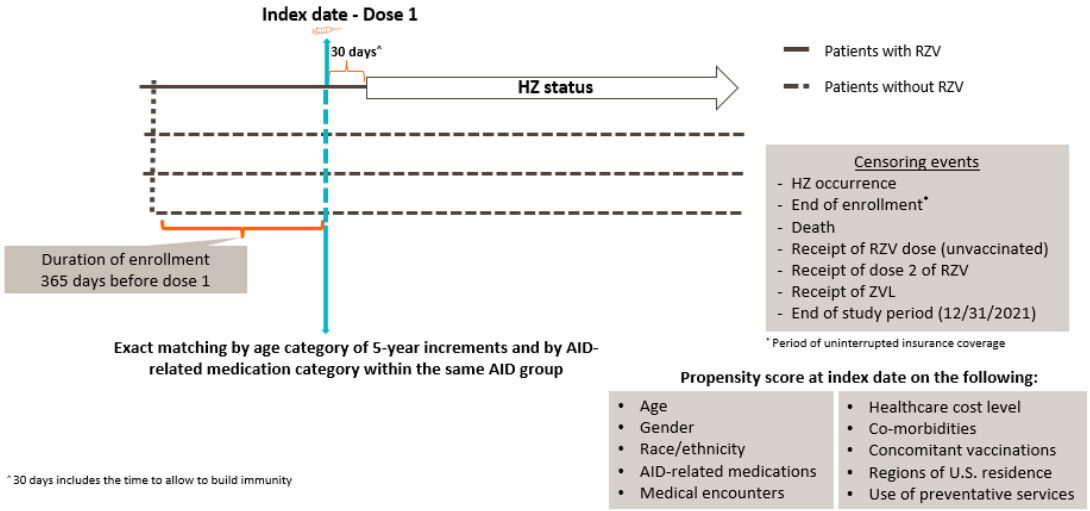


Figure 2 describes the cohort design to assess one-dose vaccine effectiveness.

Figure 2 Matched 1-dose cohort study



5.1.1. Rationale for retrospective matched cohort design

To assess VE, a retrospective matched cohort design will be used to compare the hazard of HZ in vaccinated participants with SLE, MS, RA, IBD (UC, CD), PsO, or PsA, respectively, who received two doses of RZV relative to unvaccinated participants who receive no RZV, using Cox proportional hazards models. A cohort design is used to evaluate the effectiveness of vaccination over time. Moreover, the potential for healthy-user bias (where vaccinated populations may more frequently have healthy behaviors) and differing characteristics among vaccinated and unvaccinated participants related to comorbidities, health status, disease activity, medications, and other factors necessitate rigorous methods to account for confounding (e.g., propensity score methods described in Section 7.6) that can be evaluated using a retrospective matched cohort design.

5.2 Limitations and strengths

5.2.1 Limitations

Various limitations must be considered in a retrospective matched cohort study design, including confounding, bias, and misclassification.

1. Definition of the cohorts: Though the majority of the algorithms that will be used to identify participants with AIDs have demonstrated a good positive predictive value (PPV) (Section 7.5), some misclassification is expected using the validated AID-specific algorithms given the difficulty in diagnosing some AIDs (e.g., SLE, MS). In addition, some participants with well controlled AIDs may not be captured, with algorithms biasing towards a higher risk group. To improve confidence in the definitions, similar algorithms that are being used in studies that are targeting AID populations [EPI-ZOSTER-041; EPI-ZOSTER-044] will be used. These studies rely

on specialists (e.g., neurologists, rheumatologists, dermatologists) consultation to provide expert opinion on the definitions of the AIDs.

2. Outcome misclassification: Some participants that are reported as having a HZ occurrence may not have an accurate diagnosis of HZ occurrence, which may result in a possible underestimation of VE. However, this is expected to be minimal as the detection of HZ using an ICD-10 diagnosis code for HZ (B02.xx) from hospital, 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 has been used to evaluate the HZ occurrence based on the available literature [Izurieta, 2021]. Systematic differences in HZ misclassification between vaccinated and unvaccinated are not expected.

3. Exposure misclassification: It is possible that some participants who are reportedly unvaccinated may have received RZV prior to entering the dataset, leading to an underestimation of VE. Receipt of RZV dose 1 or 2 will be identified from administrative and claims data by means of Current Procedural Terminology (CPT) code 90750 and National Drug Code (NDC) codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11 to minimize the risk of exposure misclassification. Additional codes for identification of RZV vaccination may be considered if relevant codes become available in the future.

4. Secular or seasonal trends in RZV use: RZV vaccination patterns may have changed during the COVID-19 pandemic. Receipt of RZV will be accurately captured in the Optum™ database, including dates of administration such that receipt of dose 1 and dose 2 are correctly ascertained. In addition, the study methods will ensure similar distributions by calendar year and season among vaccinated and unvaccinated participants and sensitivity analyses will be performed to assess if the occurrence of the COVID-19 pandemic resulted in an increase or decrease of VE. This will be further discussed in the SAP. Although in this study appropriate methodologies will be applied to statistically adjust for differences between RZV exposed participants versus RZV unexposed participants, not all potential confounders may be available in the database, and residual confounding may still be present.

5. Secular trends in medication use for AIDs: Newly approved therapies may be available for AIDs and may be used primarily for those with more severe disease initially. After a few years on the market, these therapies may be used in less severe disease or disease subsets. These trends may impact differences in populations and differences in the classification of disease occurrence. The study methods will ensure similar distributions by calendar year and season among vaccinated and unvaccinated participants.

6. Unmeasured confounding: Disease severity and disease duration may be associated with receipt of the vaccine and/or subsequent risk of HZ. However, these factors are challenging to measure in administrative claims data or may not be measured. This study assesses proxies for disease activity (such as medication use and healthcare use for disease severity) to measure confounding. Disease duration is difficult to measure as the entire medical history of a participant is not available. Confounding by indication is another potential limitation. Participants may receive RZV before initiating immunosuppressive (or more highly immunosuppressive) treatment in order to protect them from that planned treatment. This would bias the VE estimates.

To address this bias, participants receiving JAK inhibitor, for example, one month after index date in the JAK inhibitor medication category will be included to account for this.

7. Healthy-user bias: Participants receiving RZV, or other vaccines may be healthier or have other behaviors leading to improved health compared to their unvaccinated matches. This bias may lead vaccinated participants to have lower rates of HZ in the study. The study will capture and adjust for variables related to healthy users, such as use of other vaccinations, to minimize this bias.
8. Duplicate health care claims: A beneficiary of Optum™ may be a beneficiary of more than one insurance product at a time or switch to a new insurance product before departing from another, resulting in duplicate health care claims and multiple lines per participant. Also, when time periods overlap, a clean link between claims and the eligibility table may be absent because multiple rows may be returned in a match. While there is a risk of this happening, the number of multiple health care claims and their impact is expected to be negligible.
9. Limited follow-up period: While the ability to assess durability of VE at extended time points is limited, this is an open cohort study that will allow vaccinated and unvaccinated participants to come in late or die during the follow-up period; this is not expected to impact the overall incidence rate of HZ. In addition, participants entering the cohort in early 2018 could have 4 years of follow-up.
10. Generalizability: The population in Optum™ have racial/ethnic diversity, and the age distribution of participants with selected AIDs in this claims database are expected to reflect the distribution nationally. The practices of care for participants with selected AIDs are expected to be largely standardized across U.S. health care systems. However, this is a claims database and only the insured and beneficiaries who have Supplementary Medicare will be included in the database.

5.2.2 Strengths

1. Like other health claim databases, the high retention rate and stability of Optum™ membership provide an opportunity to follow participants over time and conduct long-term effectiveness studies and assess the impact of RZV vaccination in real life setting.
2. Optum™ is one of the largest a commercial insurance claims databases, covering inpatient, outpatient, and pharmacy claims. The database includes approximately 17-19 million annual covered lives, for a total of over 68 million unique lives over a 12-year period (1/2007 through 9/2019). Optum™ database, like other health claim databases, offers several distinct advantages over other types of data sources, including but not limited to:
   - Large sample size resulting in nationally representative sample populations covered by health insurance.
   - Complete episodes of care, including physician office visits, hospital stays, pharmacies, and other settings.
   - Standardized diagnosis and procedure coding.

- Quarterly updates making the data from the database readily available.
- Ability to link different patient data sources i.e., subject ID with claims data related to clinical history (diagnoses, procedures) and pharmacy services.

6. VARIABLES

6.1. Exposure

The exposure of interest is the receipt of RZV (1-dose or 2 RZV doses at least 28 days apart). RZV vaccination will be identified from administrative and claims data by means of Current Procedural Terminology (CPT) code 90750 and National Drug Code (NDC) codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11 (Appendix 3, Section 13.4.3, Section 13.4.4, Section 13.4.5). Additional codes may be included for identification of RZV vaccination if relevant codes become available in the future.

6.2. Other variables

Other variables will be identified from the Optum™ database and considered in the analyses when appropriate as covariates. A list of covariates to be included followed by a detailed description of covariates and sources is in Section 6.3.

6.3. Covariates of interest

Age in 5-year increments: 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, ≥80 [Harpaz, 2019; Hayter, 2012; Johnston, 2009; Kawai, 2016; Marra, 2020; Tsai, 2017; Yun, 2016; Wallin, 2019; Weng, 2007; Yamaguchi, 2021].

Sex: female/male [Hayter, 2012; Johnson, 2015; Kawai, 2016; Marra, 2020; Tsai, 2017; Yamaguchi, 2021]

Race/ethnicity: Asian, Black, Hispanic, White, Multiple/Other/Unknown [Kawai, 2017a]. The definition of race/ethnicity will be further discussed in the SAP.

Use of AID-related medications: includes but not limited to: tofacitinib, biologics and conventional synthetic DMARD combination therapy, biologics (tumor necrosis factor-alpha blockers), and disease-modifying antirheumatic drugs as detailed in Appendix 6 [Baumrin, 2019; Chakravarty, 2013; Khan, 2018; ILai, 2021; Marra, 2016; Yamaguchi, 2021]. Details of how medication categories for AIDs will be determined at index date are in Appendix 6.

Medical encounters: number of inpatient admissions in the 365 days prior to the index date (continuous), number of ambulatory visits in the 365 days prior to the index date (continuous), number of Emergency Department visits in the 365 days prior to the index date (categorized 0, 1, 2-3, ≥4), number of rheumatologist outpatient visits (for SLE, RA, PsA) in the 365 days prior to the index date, number of dermatologists outpatient visits (for SLE, PsO) in the 365 days prior to the index date, number of neurologist outpatient visits (for MS) in the 365 days prior to the index date.

Healthcare cost level: categorized according to specific i^{th} percentile in the 365 days prior to the index date. The definition of healthcare cost level will be further discussed in the SAP. Participants followed during the observation period without any claims reported will be considered as having a cost of $0; if a participant has a negative estimated cost, the cost will be set to missing and the cost of all the unvaccinated matched participants will be set to missing also.

Presence of co-morbidities: kidney disease, cardiovascular disease, pulmonary disease [i.e., chronic obstructive pulmonary disease or chronic bronchitis, asthma], liver disease, diabetes mellitus, other autoimmune diseases, cancer, immunocompromising conditions [i.e., human immunodeficiency virus, cancer, transplant, immune-suppressive medications], SARS-CoV-2 infection/COVID-19 diagnosis with an index date after 2020) in the 365 days prior to the index date [Kawai, 2017a; Marra, 2020; Tsai, 2017; Yun, 2016].

Concomitant vaccinations during baseline: Influenza vaccine, tetanus, diphtheria and pertussis vaccine, pneumococcal vaccine in the 365 days prior to the index date, as a proxy for health behaviors.

Region of residence within U.S. as defined by the Census Bureau (4 regions: West, Midwest, South, Northeast) most recently prior to the index date [Izurieta, 2021; Sun, 2021].

Use of preventative services: screening, preventative visits in the 365 days prior to the index date [Izurieta, 2021].

7. STUDY POPULATION

7.1. Description of population

The study population will include adults aged ≥50 YOA who are beneficiaries in the Optum™ database, diagnosed with an AID (defined as RA, IBD [UC or CD], SLE, PsO, PsA and MS), and who received RZV vaccination (along with their unvaccinated matches) anytime between 1 January 2018 to 31 December 2021 (Section 7.5 describes the algorithms for identification of AIDs). Co-existence of more than one AID can occur – while it is not required that each AID cohorts be mutually exclusive, overlap is expected to be minimal. Details of inclusion and exclusion criteria are defined in Section 7.2 and Section 7.3.

Table 1 shows the demographic characteristics of beneficiaries in the Optum™ database diagnosed with RA, IBD, SLE, PsO, PsA and MS during the study period (2018-2021) based on the inclusion criteria (Section 7.2) and exclusion criteria (Section 7.3). Most of the beneficiaries with SLE (38.6%), PsA (38.9%), and MS (47.3%) were 50-59 YOA, while most of the participants with IBD (39.4%), RA (42.8%), and PsO (36.9%) were >70 YOA. Most of these beneficiaries were female while over 60% were white in all AID groups.

Table 1 Demographic characteristics of beneficiaries by AID condition* during the study period (2018^-2021).

	SLE		IBD		RA		PsO		PsA		MS	
	N	%	N	%	N	%	N	%	N	%	N	%
Age at AID diagnosis (years)												
50-59	7740	38.6	11254	34.4	32130	30.5	22794	35.5	6194	38.9	10150	47.3
60-69	6086	30.4	8577	26.2	28028	26.6	17668	27.5	4968	31.2	6828	31.8
≥70	6224	31	12875	39.4	45029	42.8	23680	36.9	4747	29.8	4463	20.8
Sex												
Female	17665	88.1	18690	57.1	79127	75.2	34772	54.2	9314	58.5	16431	76.6
Male	2385	11.9	14016	42.9	26060	24.8	29370	45.8	6595	41.5	5010	23.4
Race /Ethnicity												
Asian	446	2.2	593	1.8	2331	2.2	1853	2.9	342	2.1	208	1
Black	3824	19.1	2796	8.5	13609	12.9	4440	6.9	930	5.8	2290	10.7
Hispanic	2492	12.4	2296	7	13491	12.8	5530	8.6	1505	9.5	1262	5.9
Multiple/Other/ Unknown	1076	5.4	1529	4.7	5299	5	2944	4.6	760	4.8	972	4.5
White	12212	60.9	25492	77.9	70457	67	49375	77	12372	77.8	16709	77.9
Total	20050	-	32706	-	105187	-	64142	-	15909	-	21441	-

* Table presents overall distribution of beneficiaries' characteristics by AID; no information on vaccination status (see Table 3).

^ Beneficiaries in 2017 were included if they were vaccinated in early 2018. Random index dates for unvaccinated beneficiaries were defined; some AID diagnoses were selected in 2017.

7.2. Inclusion criteria

Participants will be included in the study if the following inclusion criteria are met:

- Age >50 YOA at the index date for all study objectives and registered as beneficiary in the Optum™ database.
- Meet criteria for RA, IBD, SLE, MS, PsO or PsA prior to the index date (Section 7.5).
- Receipt of first dose of RZV on or after 1 January 2018.
- 365 days of continuous enrollment (allowing administrative gaps 30 days) prior to the index date (baseline period) and continuous enrollment in the 30 days after the index date.

7.3. Exclusion criteria

Participants will be excluded from the study if the following exclusion criteria are met:

- Any previous RZV doses before index date (for unvaccinated participants only) using all available data.
- Receipt of second dose of RZV less than 28 days apart since ACIP guidelines state that these participants must repeat the second dose [Dooling, 2018].
- Receipt of ZVL any time during the baseline as this may affect rates of HZ.
- HZ diagnosis or prescription fills for oral acyclovir, valacyclovir or famciclovir given specifically for HZ and within 30 days of index date since it is unclear if the HZ episode began before or after the index date and whether the length of time since vaccination (for RZV vaccinated participants) is long enough to allow for sufficient development of immunity.
- HZ diagnosis or prescription fills for oral acyclovir, valacyclovir or famciclovir in the 12 months before the index date to ensure that HZ diagnoses after the index date are new, rather than carried over from HZ episodes prior to the index date.
- Postherpetic neuralgia (PHN) diagnosis in the 12 months before the index date.
- Censoring events within 30 days after the index date (before the start of follow-up) (Section 7.7).

7.4. Number of participants

Not applicable.

7.5. Definitions of AIDs

Claims based algorithms obtained from the published literature defining AID conditions and are validated with demonstrated PPV will be used to identify AIDs. If participants meet >1 definitions, they will be included in multiple cohorts; AIDs will be analyzed separately.

SLE:

≥1 inpatient claim with a diagnosis code for SLE (ICD-10 M32.1, M32.8, M32.9) OR ≥2 physician outpatient claims with SLE diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date OR >1 rheumatologist visit/encounter/claim for SLE.

- The algorithm that includes ≥1 rheumatologist visit/encounter/claim has demonstrated a PPV of 95% and sensitivity of 83% [Hanly, 2014].

MS:

≥3 of any combination of inpatient diagnoses (any position) of MS (ICD-10 G35), ambulatory visit diagnoses of MS, emergency department (ED) diagnoses of MS, or MS-specific disease-modifying therapy fills/infusions (refer to Appendix 6 for medication categories) during the 365-day baseline period. At least one of these must be an inpatient, AV, or ED diagnosis of MS.

- This algorithm has demonstrated a PPV of 95-97% and sensitivity of 85-93% [Wallin, 2019].

IBD (CD and UC):

≥1 inpatient claim with a diagnosis code for CD (ICD-10 K50) and UC (ICD-10 K51) OR ≥2 physician outpatient claims with CD (ICD-10 K50) and UC (ICD-10 K51) diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 physician outpatient claims with CD and UC diagnoses during an office visit and/or emergency visit has been used extensively in the literature though no PPV has been reported [Weng, 2007].
- Algorithms that have been published to classify mutually exclusive groups of UC and CD participants will be considered to differentiate between the two conditions [Pilon, 2020]. Participants will be identified as having UC if (i) they had more UC-related patient admissions than CD-related inpatient admissions; (ii) they had an equal number of UC- and CD-related inpatient admissions but more UC-related outpatient visits than CD-related outpatient visits; (iii) they had an equal number of UC- and CD-related inpatient admissions and outpatient visits. [Bernstein, 1999; Shaw, 2011].

RA:

≥1 inpatient claim with a diagnosis code for RA (ICD-10 M05, M06) OR ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit has been used extensively in the literature though no PPV has been reported [MacLean, 2000].

PsO:

≥1 inpatient claim with a diagnosis code for PsO (ICD-10 L40) OR ≥2 physician outpatient claims with PsO diagnosis during an office visit and/or emergency visit that were at least 30 days apart OR ≥1 dermatologist visit/encounter/claim for PsO in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥1 dermatologist visit/encounter/claim has demonstrated a PPV of 90% and sensitivity of 88% [Asgari, 2013]. These algorithms assume PsO without PsA. Based on the rapid data queries (RDQs), 9% of participants diagnosed with PsO had PsA. In practice, rheumatologists tend to assess PsO and PsA by criteria which are unique to each. Then, they assess the 2 AIDs together in patients with symptoms of both. Sensitivity analyses will be performed on participants who

have either PsO or PSA, participants who have PsO only, participants who have PsA only, and participants who have both PsO and PsA to address the potential overlap between PsO and PsA. These analyses will be described in detail in the SAP.

PsA:

≥1 inpatient claim with a diagnosis code for PsA (ICD-10 L40.5) OR ≥2 physician outpatient claims with PsA diagnosis during an office visit and/or emergency visit that were at least 30 days apart OR ≥2 rheumatologist visit/encounter/claim for PsA OR ≥1 rheumatologist diagnosis code for PsA together with ≥1 dermatologist diagnosis code for PsA in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 rheumatologist visit/encounter/claim for PsA has demonstrated a PPV of 81% and sensitivity of 77% [Asgari, 2013]. These algorithms assume PsA without PsO. Based on the RDQs, 37% of participants diagnosed with PsA had PsO. Sensitivity analyses will be conducted to address the potential overlap between PsO and PsA as described above.

7.6. Matching

For the primary objectives, participants meeting inclusion criteria who receive 2 doses of RZV at least 28 days apart at the index date will be matched exactly with unvaccinated participants. Matching will be done by age category in 5-year increments (50-54, 55-59, 60-64, 65-69, 70-74, 75-79, ≥80) and AID-related medication category (mutually exclusive) based on current use at the index date within the same AID group. Medication categories will be based on the medication windows described in Section 13.6. The same exact matching approach will be done for the secondary objectives. Matching will be done with replacement.

In addition to the exact matching approach described above, a matching with propensity scores based on the likelihood of receiving RZV dose 2 versus no RZV vaccination (2-dose cohort) and RZV dose 1 versus no RZV vaccination (1-dose cohort) will be calculated using logistic regression models with RZV vaccination as the dependent variable and independent variables as outlined in Section 6.2. A 3:1 matching ratio will be applied with the propensity score matching. Propensity scores will be calculated within each cohort defined by AID to balance measured confounders (details to be provided in the SAP) among patients receiving RZV dose 2 and comparator patients with no prior RZV vaccination). A second cohort of patients will be created to compare patients receiving RZV dose 1 to patients with no prior vaccination, using the same approach to calculate propensity scores within each cohort defined by AID based on the likelihood of receiving RZV dose 1 versus no RZV vaccination. An unvaccinated patient may serve as a comparator for both the dose 1 and dose 2 cohorts, although separate index dates will be applied. Further details of the methodology used for matching vaccinated and unvaccinated groups is provided in Section 8.2.3 of the SAP.

Covariate balance will be assessed before and after applying propensity scores using standardized mean differences, with standardized differences of 0.2 suggestive of important imbalance [Austin, 2009a; Austin, 2009b]. Any covariate demonstrating imbalance after weighting, suggesting residual confounding, will be included as an additional covariate in the Cox proportional hazard models. The same approach will be used for the secondary analyses for 1-dose noting that propensity scores will be estimated at dose 1 and receipt of RZV dose 2 will be a censoring event.

7.7. Follow-up/censoring

The follow-up period will begin from 30 days after the index date (to allow development of immunity after vaccination) and will end at the earliest occurrence of the following events:

- HZ occurrence
- End of continuous enrolment (period of uninterrupted insurance coverage with gap allowance of 30 days).
- Death (date of death including the year and month of death).
- End of data availability/study period (December 31, 2021).
- Receipt of RZV (additional dose for vaccinated participants or first RZV dose in the case of unvaccinated participants):
    - For 2-dose VE, vaccinated participants will be censored upon receipt of a dose 3.
    - For 1-dose VE, vaccinated participants will be censored upon receipt of dose 2.
- Receipt of ZVL vaccination.

8. STUDY PROCEDURES

Not applicable.

9. SAFETY

Not applicable.

10. DISCONTINUATION/WITHDRAWAL CRITERIA

Not applicable.

11. STATISTICAL CONSIDERATIONS

11.1. Sample size determination

Descriptive queries in the Optum™ database were performed to identify, obtain, and aggregate the number of ≥50 YOA US patients with AID using the algorithm definition presented in Section 7.5. The outputs of these queries will be used to define the AID populations in the study and inform the study design and SAP by refining the study methodology and analytical approaches most appropriate for the expected sample size. The outputs of these queries will be used to estimate:

The incidence rate of HZ in the unvaccinated group (Table 2).

- The sample size and average follow-up duration of vaccinated group (Table 3).

Table 2 Incidence rate of HZ in unvaccinated group by AID, Optum™ database 01/2018-12/2021*

AID	Number of participants with HZ in unvaccinated group	Number of participants in unvaccinated group	Person-years (PY)	Incidence rate (1000 PY)
IBD	693	24234	51090	13.56
RA	2781	81639	179079	15.53
SLE	565	15644	33195	17.02
PsO	1533	60533	134443	11.40
PsA	499	14942	34023	14.67
MS	677	20407	48656	13.91

HZ= herpes zoster; SLE: systemic lupus erythematosus; MS: multiple sclerosis; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; PsO: psoriasis; PsA: psoriatic arthritis.
* This represents the actual study population.

Table 3 Sample size and average follow up time among 2-dose recipients, Optum database 01/2018-12/2021*

Year of receipt of dose 2 RZV	Category	SLE	IBD	RA	PsO	PsA	MS
2018	Average FU (years)	2.7	2.5	2.6	2.6	2.5	2.7
	N	269	640	1761	1280	277	299
2019	Average FU (years)	1.9	1.9	2.0	2.0	2.0	1.9
	N	831	1700	4787	3372	772	877
2020	Average FU (years)	1.2	1.3	1.2	1.2	1.2	1.2
	N	935	1906	5113	3996	967	997
2021	Average FU (years)	0.5	0.5	0.5	0.5	0.5	0.5
	N	875	1619	4267	3468	839	948
Overall	Average FU (years)	1.3	1.4	1.4	1.4	1.3	1.4
	N	2910	5865	15928	12086	2845	3121
Average follow-up time (weighted): 1.4 year							

RZV= recombinant zoster vaccine, FU = follow-up, N: number of participants with 2 doses RZV.

*This represents the actual study population.

A two-sided log rank test with an alpha of 5% is used for the sample size calculation of the primary VE objectives. Assumptions for sample size calculation are:

- Incidence of HZ in the RZV unvaccinated group: 12, 15, 20 /1,000 person-years [Baumrin, 2019; Izurieta, 2021; Kawai, 2017b], in accordance with the preliminary analysis performed in Optum™ database (Table 2)
- Detectable HR (or VE): 0.3, 0.4, 0.5 or 0.6 (VE=70%, 60%, 50%, or 40%)
- Ratio of RZV unvaccinated to RZV vaccinated group: 3:1
- Average follow-up period: 1 or 2 years after the second dose of RZV; the estimated average follow-up time in Optum database was 1.4 year (Table 3)
- Censoring rate in the RZV vaccinated group: 20%
- Censoring rate in the RZV unvaccinated group: 15%

Results of the sample size calculation are presented in Table 4:

Table 4 Sample size calculation* for effectiveness analyses under a range of assumed incidence rates for unvaccinated group and different detectable VE

			Sample Size of RZV vaccinated group			
Power	**Follow up time**	**Incidence rate in RZV unvaccinated group (/1000 person-years)**	**VE (70%)**	**VE (60%)**	**VE (50%)**	**VE (40%)**
90%	1 year	12	1398	2197	3545	6089
		15	1120	1760	2840	4877
		20	841	1323	2134	3666
	2 years	12	765	1203	1941	3333
		15	614	965	1557	2673
		20	462	726	1172	2013
80%	1 year	12	1017	1599	2588	4463
		15	815	1281	2073	3575
		20	612	963	1558	2687
	2 years	12	558	876	1418	2444
		15	447	703	1137	1961
		20	337	529	856	1477

RZV= recombinant zoster vaccine, VE= vaccine effectiveness, % = Percentage.
Sample size has been calculated for each of the six cohorts.

The number of potential participants who received 2 doses of RZV during the accrual period between 1/2018 to 12/2021 is 5865 for IBD, 2910 for SLE, 15928 for RA, 3121 for MS, 12086 for PsO, 2845 for PsA, respectively (Table 3). This exceeds the required numbers for a power of 80% and detectable VE of 50% (Table 4). This demonstrates that the study is sufficiently powered to assess the primary VE objectives. The sample size calculation is only for primary objectives.

11.2. Sets for analyses

Not applicable.

11.3. Statistical analysis

11.3.1. Sequence of analyses

All analyses, including descriptive, will be conducted separately for RA, IBD, SLE, MS, PsO, and PsA populations based on when information related to the medication categories for each AID becomes available. The analyses of RA and IBD will be performed first, followed by the analyses of SLE and MS and the analyses of PsO and PsA.

11.3.2. Primary analyses

For the primary objectives 1-6, the number of incident HZ cases and the number of person-years of follow-up for participants will be assessed for the 2-dose (≥ 28 days apart) RZV cohort and the matched unvaccinated cohort. Crude VE (%) will be estimated as (1 – [incidence rate of HZ among 2-dose (at least 28 days apart) RZV recipients / incidence rate of HZ among RZV unvaccinated participants]) x 100%.

Adjusted HRs and 95% confidence intervals (CIs) comparing HZ incidence rates in the 2-dose (≥28 days apart) RZV cohort, and the matched unvaccinated cohort will be estimated by Cox proportional hazards regression models. Estimates of VE (%) will be calculated as (1 – adjusted HR) × 100%.

11.3.3. Descriptive analyses

The number and characteristics of participants in each cohort will be described and compared. Categorical variables such as gender will be presented as absolute numbers and percentages with p-values for the Pearson χ^2 test or Fisher's exact test, as appropriate. Continuous variables such as age in years will be presented as the mean with standard deviation and/or median with interquartile ranges, with p-values for the two-sample t-test or Wilcoxon rank-sum test, as appropriate. Absolute standardized differences will be calculated to assess the balance of covariates with a cut-off value of 0.20. Overall incidence rates of HZ for the 2-dose (≥28 days apart) and the 1-dose RZV vaccinated cohort and the matched unvaccinated cohort will be calculated by dividing the number of HZ cases by the total number of person-years.

11.3.4. Secondary analysis

Secondary objective 1: Analyses for secondary objective 1 will employ similar methods as for the primary analyses. Analyses for IBD (secondary objective 1) will be stratified by UC and CD. A separate VE for UC and CD will be estimated. Descriptive analyses and Cox proportional hazards regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary objective 2: Analyses for secondary objective 2 will employ similar methods as for the primary analyses. Analyses for either PsO or PsA (secondary objective 2) will be performed. Descriptive analyses and Cox proportional hazards regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary objectives 3-9: Analyses for secondary objectives 3-9 will employ similar methods as for the primary analyses and will be conducted among the matched 2-dose cohorts of participants with SLE (secondary objective 3), MS (secondary objective 4), RA (secondary objective 5), IBD (secondary objective 6), PsO (secondary objective 7), PsA (secondary objective 8), either PsO or PsA (secondary objective 9) who receive 2 doses of RZV ≥28 days apart. Analyses will be stratified by age group, gender, time since vaccination, time interval between two doses (≥28 days apart), and medication category (as described in Appendix 6) during baseline. Analyses for IBD (secondary objective 6) will be stratified by UC and CD. Two categories will be considered to differentiate UC and CD: UC, and CD. Analyses for either PsO or PsA (secondary objective 9) will be performed. Descriptive analyses and Cox proportional hazards regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary objectives 10-16: Analyses for secondary objectives 10-16 will employ similar methods as for the primary analyses and will be conducted among the matched 1-dose cohorts of participants with SLE (secondary objective 10), MS (secondary objective 11), RA (secondary objective 12), IBD (secondary objective 13), PsO (secondary objective 14), PsA (secondary objective 15), and either PsO or PsA (secondary objective 16). Analyses for either PsO or PsA (secondary objective 16) will be performed. Descriptive analyses and Cox proportional hazards regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary objective 17: Analyses for secondary objective 17 will employ similar methods as for the primary analyses and will be conducted among the matched 2-dose cohorts. ***In these analyses, participants are allowed to have multiple AIDs. Analyses will be stratified by age group, gender, time since vaccination, time interval between two doses and medication category during baseline, as described in Appendix 6.*** Descriptive analyses and Cox proportional hazards regression will be conducted and overall estimates of VE (%) will be calculated for all selected AIDs as (1 – adjusted HR) × 100.

11.3.5. Sensitivity analyses

Sensitivity analyses will be performed to assess if the occurrence of the COVID-19 pandemic has an impact on the effectiveness of the vaccine in participants who test positive for COVID-19 during the follow-up period. Methods to identify the COVID test result (i.e., PCR) and analyses to assess the impact of the pandemic on the VE will be described in the SAP. Sensitivity analyses will also be performed on participants who have either PsO or PSA, participants who have PsO only, participants who have PsA only, and participants who have both PsO and PsA to address the potential overlap between PsO and PsA. ***In addition, sensitivity analyses will be performed to assess if adding medication category as a covariate after propensity score matching has an impact on the results of the primary analyses (primary objectives 1-6) and subgroup***

analyses (secondary objective 17). Further details of the sensitivity analyses will be described in ***Section 10.4.3 of*** the SAP ***amendment 2.***

11.3.6. Additional analyses

Additional tables described below will be created to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses. The additional tables will require further analyses described in detail in Section 10.6 of the SAP amendment 2.

11.3.6.1. AID diagnosis

Study participants may report more than one AID diagnosis resulting in potential overlap between AIDs. Distribution tables of participants associated with multiple AIDs for 1-dose and 2-dose cohorts will be created to assess the proportion of participants diagnosed with one or more AIDs in the vaccinated and unvaccinated groups. The rationale for this analysis is to check whether there is not a significant rate of participants with overlapping conditions, which would need to be documented as a study limitation in the final study report.

11.3.6.2. Time since vaccination

Baseline characteristics/demographic tables for the 2-dose cohort reporting different lengths of follow-up (0<1 years, 1<2 years, 2<3 years, 3+ years) will be created to check the number of HZ events observed in the different follow-up periods for the analyzed population and to check whether trends are observed in the different follow-up periods for the analyses corresponding to secondary objectives 3-9 and 17. More granular information about length of follow-up may help to explain varying vaccine effectiveness values observed by time since vaccination.

11.3.6.3. End of follow-up

Distribution tables of participants in the 2-dose cohort whose end of follow-up reason is either disenrollment or study end date will be created to estimate the number of participants that end follow-up for a reason other than study end. If many study participants end follow-up for a reason that is not the study end, it can introduce a selection bias, especially if the reason that a study participant disenrolled is linked to the primary outcome (HZ). This assessment will be done to check whether the number of such participants in the analyzed population who report study end as the reason to end follow-up is similar in the vaccinated and the unvaccinated groups.

11.3.6.4. Medication class/medication categories

Distribution tables of medication class (type of medication) within each existing medication category described in Appendix 6 of the current protocol amendment will be created to assess the distribution of medications class by age and by AID. The purpose of these tables is to identify which medication class is observed in greater frequency by age and by AID. Information about the types of medications in each of the existing medication categories may help to explain when varying vaccine effectiveness values by medication category are observed.

Additional distribution tables of steroids will be created to check the frequency of participants who receive low-dose (< 5mg) versus high-dose (≥5 mg) steroids in the vaccinated and unvaccinated groups. This includes patients with RA, IBD and PsA. This assessment will be done to check the impact of the cut-off assigned to low-dose and high-dose on the analyses of RA, IBD and PsA cohorts since the cut-off, while clinically acceptable, is considered arbitrary. The following generic names for low-dose and high-dose steroids for RA, IBD and PsA will be considered in the distribution tables:

AID	Generic names for steroids*
RA	Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol), prednisolone, prednisone hydrocortisone.
IBD	Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone budesonide (Entocort/Uceris).
PsA	Methylprednisolone (Medrol), prednisolone, prednisone, hydrocortisone (IM/IV), methylprednisolone (Medrol [IM/IV], Solu-Medrol [IM/IV], Depo-Medrol [IM/IV]), prednisolone (IM/IV), triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte) [IM/IV]).

*Appendix 6 of the current protocol amendment provides detailed information about the above steroids.

11.3.6.5. Comorbidities covariates

Cross tables between age categories and comorbidities (asplenia/hyposplenia, COVID-19, cardiovascular disease, diabetes mellitus, kidney disease, lymphoma/leukemia, liver disease, pulmonary disease), described in Appendix 5 of the current protocol amendment, will be created to estimate the number of study participants by comorbidity and age in the vaccinated and unvaccinated groups. This assessment will be done for all AIDs separately for the 2-dose cohort to check the impact that co-morbidities have on the overall vaccine effectiveness values.

11.3.7. Modifications to subgroup analyses

This study is not powered for analyses of the secondary objectives described in Section 4.2 of the current protocol amendment. For this reason, there may not be sufficient data from the subgroup analyses to allow meaningful interpretation of results. Statistical and theoretical approaches summarized below will be used to combine the following categories of variables to add additional statistical power and make the results of these analyses more interpretable: age, dose interval between two doses, time since vaccination, and medication category:

11.3.7.1. Age category, dose interval between two doses category, and time since vaccination category

A person-year cut-off value will be used to identify which categories will be combined across the stratification variables per AID. The cut-off value will be estimated using the following assumptions:

- ***Based on the sample size calculated in Table 9 of the SAP amendment 2, within less than 200 PY there is less than 1/3 chance to find a statistically significance for a true vaccine effectiveness of 70% with an incidence of less than 15 per 1000 PY in the control group, which would indicate a low precision.***
- ***Based on the sample size calculated in Table 9 of the SAP amendment, within at least 255 PY, for an incidence of at least 12 per 1000 PY in the control group, we have not less than 1/3 to find a statistical significance for a true VE of 70%. More specifically, for a power of 33%, for sample sizes <255 PY, there is less than one third of chance of proving vaccine effectiveness.***

Based on the above, <255 PY will be used as the threshold for the combined/pooled analysis of the following variables: age category, dose interval between two doses category, and time since vaccination. Further details of the modifications to subgroup analyses are described in Section 10.6.2 of the SAP amendment 2.

11.3.7.2. New combination of medication categories

Medication categories will be recombined using the existing medication categories described in Appendix 6 of the current protocol amendment. This theoretical approach to recombining the existing medication categories will be based on the systemic action of the medications and will apply to the subgroup analyses (secondary objectives 3-9, 17). The approach will be used to make the results of these subgroup analyses more interpretable as low number of participants in these analyzed populations are expected across certain types of medications.

The new combination of these medications is described below:

- ***Category 1: non-immunosuppressive therapy (e.g., no treatment, NSAIDs, low dose (<5mg) steroids, anti-malarial, topical medications (corticosteroids, non-pharmacologic therapies).***
- ***Category 2: mild-moderate immunosuppressive therapy (e.g., conventional DMARDs, aminosalicylate, psoralen and PUVA, PDT, NB-UVB, UV phototherapy, excimer laser).***
- ***Category 3+4 (combined): highly immunosuppressive (e.g., biologics, high dose (≥5 mg) steroids, thiopurines, SP1 receptor modulators, intralesional/IM corticosteroids).***
- ***Category 5: JAK inhibitors, DMARDs (synthetic and targeted synthetic).***

11.3.8. Missing data

Missing data will be handled differently depending on the data. For demographic variables, the rate of missing data is <5% and so it's negligible. For healthcare cost level, a cost of zero will be considered if a vaccinated participant does not have any cost reported in the baseline period (such participants will be matched with unvaccinated participants with no cost reported, so missing data would not impact the analysis). For the other variables, these are based on ICD codes and the variables will be defined as Y/N format. Handling missing data using more complex methods is being reviewed. More details of the approaches to address missing data will be included in the SAP.

11.4. Data management

11.4.1. Data handling conventions

The Real-World Analytics (RWA) Team at GSK will coordinate all data management aspects for the proposed study. RWA in collaboration with the biostatistician will be responsible for writing and distributing SAS programs to use for evaluating data from the administrative claims Optum™ database. RWA 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).

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13. APPENDICES

13.1 Appendix 1: Abbreviations and glossary of terms

13.1.1. List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AID	Autoimmune Disease
AuHSCT	Autologous Hematopoietic Stem Cell Transplants
CD	Crohn's Disease
CDM	Clinformatics Data Mart
COVID	Corona Virus Disease
CPT	Current Procedural Terminology
DMARDs	Disease modifying antirheumatic drugs
ED	Emergency Department
E H R	Electronic Health Record
FDA	Food and Drug Administration, United States of America
GSK	GlaxoSmithKline
HM	Hematological Malignancies
HR	Hazard ratio
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
IC	Immunocompromised
ICD	International Classification of Diseases
IDNs	Integrated Delivery Networks
IM	Intramuscular

IV	Intravenous
JAK	Janus kinases
MS	Multiple Sclerosis
NB-UVB	Narrow band ultraviolet B
NDC	National Drug Code
PDT	Photodynamic therapy
PHN	Post Herpetic Neuralgia
PPV	Positive Predictive Value
PsA	Psoriatic Arthritis
PsO	Psoriasis
PUVA	Psoralen and ultraviolet A radiation
PY	Person year
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RWA	Real World Analytics
RZV	Recombinant Zoster Vaccine
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome related Corona Virus 2
SLE	Systemic Lupus Erythematosus
UC	Ulcerative Colitis
VE	Vaccine effectiveness
VZV	Varicella Zoster Virus
YOA	Years of Age
ZVL	Zoster vaccine Live

13.1.2. Glossary of terms

Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.
Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.

13.2. Appendix 2: Study governance considerations

13.2.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and:
  - Ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Food and Drug Administration (FDA) Code of Federal Regulations Title 21 (21 CFR)
  - All other applicable regulations and local laws

13.2.2. Data protection

Data privacy is protected by using anonymized data.

13.2.3. Dissemination of study data

- The key design elements of this protocol and results summaries will be posted on GSK Clinical Study register in compliance with the applicable regulations/GSK policy according to the timelines described below
- Protocol summaries will be registered prior to study start.
- Results summaries will be posted within 12 months of analysis completion date.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.

13.2.4. Data quality assurance

The sponsor will permit audits and regulatory agency inspections.

13.2.5. Publication policy

GSK aims to submit the results of the study for publication in searchable, peer reviewed scientific literature and follow the guidance from the International Committee of Medical Journal Editors (ICMJE).

13.3. Appendix 3 Appendix Data types

Specific information in the Optum™ database includes, but is not limited to, the following types of data:

- Enrollment data.
  - A unique identifier received from the insurer, which is linkable to all other data.
  - Possible multiple enrolments with the same insurer; the length of each given enrollment "span" may vary substantially.
- Demographic data.
  - Birth date, sex, race/ethnicity, and ZIP code of their most recently recorded primary residence.
- Medical encounter data.
  - The healthcare provider, facility of the encounter, admission and discharge dates, encounter type (ambulatory visit, emergency visit, inpatient hospital stay).
- Pharmacy dispensing data.
  - Date of each dispensed prescription, the NDC identifier associated with the dispensed product, the nominal days' supply, and the number of dispensed individual units (pills, tables, vials, etc.). (Over the counter medications are not captured in the databases.)
- Diagnosis data.
  - Date of diagnosis with associated encounter identifier, admission date, provider identifier.
  - Encounter type, diagnoses with ICD-9-CM, and ICD-10-CM codes.
- Procedure data.
  - Date of procedure, associated encounter identifier, admission date, provider identifier, and encounter type.
  - Codes: ICD-9-CM and ICD-10-CM, CPT categories (II, III, or IV), revenue.

13.4. Appendix 4: ICD-10 codes

13.4.1. Codes to identify auto-immune diagnoses

The following ICD-10 codes will be used to define the auto-immune population:

ICD-10	**AID**	**Description**
M32.X	SLE	Systemic lupus erythematosus
G35.X	MS	Multiple sclerosis
M05.X	RA	Rheumatoid arthritis with rheumatoid factor
M06.X		Other rheumatoid arthritis
K50.X	IBD	Crohn's disease
K51.X		Ulcerative colitis
L40.X	PsO	Psoriasis
L40.5	PsA	Psoriatic arthritis

Codes will be updated as needed if additional codes are identified.

13.4.2. Codes and medications for the diagnosis of herpes zoster

	Diagnosis code or medication generic names
Codes/medications for herpes zoster diagnosis	
Herpes Zoster	B02.xx
Medications to treat herpes zoster	Acyclovir, valacyclovir, or famciclovir

Codes will be updated as needed if additional codes are identified.

13.4.3. Codes to identify the use of zoster vaccine

The following Current Procedural Terminology (CPT) code will be used to retrieve Shingrix vaccinations:

Code	Description	Vaccine type
90750	Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use	Shingrix

Codes will be updated as needed if additional codes are identified.

The following National Drug Codes (NDCs) codes will be used to retrieve Shingrix vaccinations:

Code	description	vaccine type
58160-082-311	Zoster vaccine recombinant, adjuvanted	Shingrix
58160-081-912	Zoster vaccine recombinant, adjuvanted	Shingrix
50090-514-700	Zoster vaccine recombinant, adjuvanted	Shingrix
58160-082-801	Varicella-zoster ge vac,2 of 2	Shingrix
50090-337-200	Zoster vaccine recombinant, adjuvanted	Shingrix
58160-082-803	Varicella-zoster ge vac,2 of 2	Shingrix

Codes will be updated as needed if additional codes are identified.

13.4.4. CPT/HCPCS codes used to identify influenza vaccinations

CPT/HCPCS Code	Description
90630	Vaccine for influenza for injection into skin, quadrivalent, preservative free
90653	Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted
90654	Vaccine for influenza injection into skin, trivalent, preservative free
90656	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free
90658	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent
90661	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, cell culture-based
90662	Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content
90673	Vaccine for influenza administered into muscle, preservative and antibiotic free, trivalent, recombinant DNA-derived
90674	Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based
90682	Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use)
90686	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free
90688	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent
90756	Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free, 0.5mL dosage, for intramuscular use)
G0008	Administration of influenza virus vaccine
Q2034	Influenza virus vaccine, split virus, for intramuscular use (agriflu)
Q2035	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria)
Q2036	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval)
Q2037	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin)
Q2038	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluzone)
Q2039	Influenza virus vaccine, not otherwise specified

13.4.5. dNDC Codes Used to identify herpes zoster antivirals

Drug	NDCs
Acyclovir	00093363020, 00093894001, 00093894005, 00093894019, 00093894093, 00093894301, 00093894305, 00093894319, 00093894393, 00093894701, 00093894705, 00093894719, 00093894793, 00168082515, 00168082530, 00172426660, 00172426670, 00172426760, 00172426770, 00172426860, 00172426870, 00182266600, 00182266689, 00182266700, 00182266789, 00182820000, 00182820089, 00228260511, 00228260550, 00228260611, 00228260650, 00228260711, 00228260750, 00364269201, 00378025301, 00378025305, 00378030201, 00378146801, 00378220001, 00378220005, 00378870006, 00378870049, 00378871273, 00395809719, 00395809762, 00440103030, 00440103130, 00440603001, 00440603005, 00440603030, 00440603060, 00440603081, 00440603101, 00440603105, 00440603125, 00440603130, 00440603181, 00440603301, 00440603305, 00440603310, 00440603320, 00440603381, 00440703005, 00440703025, 00440703030, 00440703050, 00440703060, 00440703081, 00440703083, 00440703085, 00440703089, 00440703125, 00440703130, 00440703181, 00440703185, 00440703189, 00440703310, 00440703320, 00440703350, 00440703381, 00440703385, 00440703389, 00472008216, 00591033501, 00591033505, 00591033601, 00591033605, 00591115930, 00591269201, 00591269205, 00713063015, 00713063031, 00904578961, 00904579061, 00904579961, 00904612161, 10544002640, 10544002725, 10544003925, 10544003940, 10544010125, 10544010225, 10544010240, 10544010340, 10544014625, 10544014630, 10544015124, 10544015130, 10544015160, 10544020435, 10544020440, 10544020450, 10544094214, 10544094260, 12634069771, 13411018201, 13411018203, 13411018206, 13411018209, 13411018210, 13411018301, 13411018303, 13411018306, 13411018309, 13411018310, 13668051501, 13668051502, 15455950001, 15455950002, 15455950003, 15455950005, 15455950008, 15455950009, 16590000325, 16590000330, 16590000335, 16590000350, 16590000360, 16590037020, 16590037030, 16590037040, 16590037090, 16714066801, 16714066802, 16714088501, 16714088502, 17236085301, 17236085401, 17856008205, 21695000925, 21695000930, 21695001015, 21695001020, 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Drug	NDCs
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Acyclovir Sodium	00074199010, 00074442701, 00074442749, 00074445201, 00074445249, 55150015410, 55150015411, 55150015520, 55150015521, 55390061210, 55390061320, 61703031121, 61703031143, 63323010510, 63323032510, 63323032514, 63323032520, 63323032524, 00173095201, 00173099501, 70004000533
Acyclovir Susp 200 Mg/5Ml	50962045360, 60346085434, 60346085471

Drug	NDCs
Acyclovir, Micronized	28595059277
Acyclovir/ Hydrocortisone	00037050105, 00187510401
Acyclovir/ Lidocaine Hcl	28595097362
Famciclovir	00054019613, 00054019713, 00054019813, 00093811756, 00093811856, 00093811956, 00378449093, 00378449193, 00378449293, 00440750002, 00440750010, 00440750121, 00440750160, 00440750202, 00440753121, 00591327130, 00591327230, 00591327330, 00781562031, 00781562131, 00781562231, 16714030001, 16714030401, 16714030501, 16714061401, 16714061501, 16714061601, 31722070630, 31722070730, 31722070830, 33342002407, 33342002507, 33342002607, 42291027530, 42291027630, 42291027730, 50090306600, 50090333700, 50268030511, 50268030513, 50268030611, 50268030613, 50268030711, 50268030713, 52959094604, 52959094621, 54569604600, 54569604601, 54868590500, 54868590501, 54868590503, 54868590504, 55289016803, 59762270001, 59762270102, 59762270301, 60429035930, 60429036030, 60429036130, 60505324503, 60505324603, 60505324703, 60687010325, 60687010395, 63187091921, 63187092021, 63187099821, 63187099830, 65862046530, 65862046630, 65862046730, 69097026902, 69097027102, 69097027202, 00078036615, 00078036715, 00078036815, 00078036861, 00078036864, 00440752802, 49999030821, 49999030830, 54348062310, 54569453300, 54569453400, 54569453401, 54569466000, 54868388200, 54868388201, 54868396900, 54868396901, 54868400900, 54868400901, 68115040730, 68115040760, 68115040830, 68115040860, 68115040921, 68115040930, 68115040960
Valacyclovir Hcl	00054011413, 00054011427, 00054011513, 00054011527, 00093725856, 00093725898, 00093725956, 00093725998, 00378427505, 00378427577, 00378427593, 00378427605, 00378427677, 00378427693, 00591324819, 00591324830, 00591324930, 00781520831, 00781520892, 00781520931, 00781520992, 00904656507, 00904656561, 10544093704, 16714069701, 16714069702, 16714069703, 16714069801, 16714069802, 16714069803, 21695083210, 21695083221, 21695083230, 21695096504, 21695096506, 21695096507, 21695096521, 31722070430, 31722070490, 31722070530, 31722070590, 42254044110, 42291088930, 43063020010, 43063049810, 43063049814, 43063053404, 43063053406, 43063053421, 43063073010, 43063073090, 43063076806, 43063077106, 43063077114, 43063077120, 43063077121, 43063077810, 43063077814, 43063077890, 43353075899, 43353080699, 43353088383, 43353088399, 45963055804, 45963055808, 45963055830, 45963055904, 45963055908, 45963055930, 50090117300, 50090117302, 50090222300, 50090251000, 50090251001, 50090251002, 50090257500, 50090257501, 50090257502, 50090257503, 50268078811, 50268078815, 50268078911, 50268078915, 51079009301, 51079009303, 51660090430, 51660090530, 52343005130, 52343005190, 52343005230, 52343005290, 52959030321, 54569617800, 54569617801, 54569617802, 54569617900, 54569617901, 54569617902, 54868608900, 54868608901, 54868608902, 54868608903, 54868608904, 54868608905, 54868608906, 54868608907, 54868609000, 54868609001, 54868609002, 54868609003, 54868609004, 55111055205, 55111055230, 55111055290, 55111055305, 55111055330, 55111055390, 55700004504, 55700034521, 57237004230, 57237004290, 57237004330, 57237004390, 59746032430, 59746032437, 59746032530, 59746032537, 59762839801, 59762839802, 59762839806, 59762839901, 59762839902, 59762839906, 61919051520, 61919091930, 63187077604, 63187077610, 63187077614, 63187077621, 63187077630, 63187083206, 63187083210, 63187083230, 63187095030, 63304090430, 63304090530, 63739052510, 63739055210, 64679015201, 64679015203, 64679015204, 64679015302, 64679015303, 64679015304, 65862044830, 65862044890, 65862044930, 65862044990, 66336039830, 68084021501, 68084021511, 68084030911, 68084030921, 68084040801, 68084040811, 68084040911, 68084040921, 68084063301, 68084063311, 68084063411, 68084063421, 69097015302, 69097015305, 69097015312, 69097015402, 69097015405, 69097015412, 70934010614, 72189003730, 72189003760, 72189003790, 00395810356, 00395810362, 00395810556, 23490704804, 23490704905, 23490704907, 33261076208, 33261076221, 33261076230, 38779255003, 38779255004, 38779255005, 38779255008, 50090117301, 52372079401, 53002000601, 53002000603, 53002000604, 53002000606, 53002000609, 53002000610, 53002000620, 53002000621, 54569617903, 54868609005, 55700034530, 58118520903, 58118520908, 61919091904, 61919091921, 63275992801, 63275992802, 63275992803, 63275992804, 63275992805, 63275992808, 63275992809, 66336039860, 66336039906, 66336039930, 68788634500, 68788634501, 68788634502, 68788634503, 68788634504, 68788634507, 68788955400, 71335012301, 71335012302, 71335012303, 71335012304, 71335012305, 71335012306, 71335012307, 71335012308, 71335063001, 72189005130, 43063073014, 50090222301, 50090222302, 50090222303, 50090251003, 53002078306, 53002078310, 53002078312, 53002078320, 53002078330, 53002078340, 53217005410, 53217005414, 53217005430, 53217005460, 53217005490, 54569617803, 58118090403, 58118090409, 61919006660, 68788637900, 68788637901, 68788637902, 68788637903, 68788637904, 68788637907, 71335002106, 71335070806, 72189003721, 00173056502, 00173056504, 00173056510, 00173093303, 00173093308, 00173093310, 00173093356, 00440860106, 00440860204, 00490005200, 00490005230, 00490005260, 00490005290, 23490704901, 23490704903, 33358035306, 33358035310, 33358035312, 33358035330, 49999048607, 49999048630, 49999086503, 49999086518, 49999086530, 52959038421, 52959064110, 52959064114, 52959064130, 52959064142, 54569428000, 54569428001, 54569428002, 54569428003, 54569428004, 54569428006, 54569428007, 54569532400, 54569532401, 54569532402, 54569532403, 54868380400, 54868380401, 54868380402, 54868380403, 54868380404, 54868380405, 54868380406, 54868399300, 54868399301, 54868399302, 54868399303, 54868399304, 54868399305, 54868399306, 54868399307, 54868399308, 55289092604, 55289092606, 55289092607, 55289092608, 55289092610, 55289092614, 57866126502, 58016085501, 58864068320, 58864068321, 62682101201, 62682101304, 63629398201, 67544006930, 67544006953, 68115047914, 68115047930

13.5. Appendix 5: Diagnosis codes for co-morbidities

Covariate	ICD-10 codes
Chronic diseases	
Kidney disease	I12.0, I12.9, I13.1*, N03.2-N03.7, N05.2-N05.7, N18.*, N19.*, N25.0, Z49.0*-Z49.2*, Z94.0, Z99.2
Cardiovascular disease	I21.*, I22.*, I25.2, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.*, I50.*, P29.0
Pulmonary disease	I27.8*, I27.9, J40.*-J47.*, J60.*-J67.*, J68.4, J70.1, J70.3
Liver disease	B18.*, I85.0*, I86.4, I98.2, K70.0, K70.1*-K70.4*, K70.9, K71.1*, K71.3, K71.4, K71.5*, K71.7, K72.1*, K72.9*, K73.*, K74.*, K76.0, K76.2-K76.7, K76.8*, K76.9, Z94.4
Diabetes mellitus	E10.*-E14.*
Autoimmune conditions	
Rheumatoid arthritis	M05.*, M06.*
Inflammatory bowel disease	K50.*, K51.*
Psoriasis/Psoriatic arthritis	L40.*, L40.5*
Multiple sclerosis	G35
Systemic lupus erythematosus	M32.1, M32.8, M32.9
Immunosuppressant conditions	
Lymphoma/leukemia	C81.*C86.*, C88.*, C90.*-C96.*, D45, D46.*
Congenital and other immunodeficiencies	D61.09, D61.3, D61.82, D61.9, D70.0, D71, D80.0, D80.1, D80.5, D80.8, D81.*, D82.*, D83.*, D84.0, D84.1, D84.89, D84.9, D89.81*, D89.82, D89.9, E31.0, E70.330, G11.3, Q82.4, Q89.0*
Asplenia/hyposplenia	D57.00, D57.01, D57.02, D57.1, D57.2, D57.20, D57.21, D57.211, D57.212, D57.219, D57.4, D57.40, D57.41, D57.411, D57.412, D57.419, D57.8, D57.80, D57.81, D57.811, D57.812, D57.819, D73.0, Q89.01, Q89.09, Z90.81

U07.1	COVID-19 virus identified (On February 11, 2020, the WHO announced the official name of COVID-19)
J12.82	Pneumonia due to coronavirus disease 2019

13.6. Appendix 6: Medication categories

13.6.1. RA medication category

Medication category for RA will be determined by the highest category of medication prescribed during the search periods specified below:

- Rituximab (Rituxan) or rituximab-abbs/rituximab-pvvr (Truxima): 6 months before index date[1]
- Biologics: 3 months before index date[2]
- JAK inhibitors: 3 months before index date to 1 month after index date[3]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), 5-aminosalicylate (5-ASA), aminosalicylate, sulfasalazine, thiopurines, steroids, and conventional DMARDs: Medication prescribed/refilled within 6 months prior to index date[4]
- Any medication that is active at the index date will be considered regardless of when it was prescribed/refilled.

[1] Rituximab (Category 3 biologics medication) is typically dosed every 6 months, so the search period for rituximab is 6 months before the index date.
[2] Some biologics are given as far apart as every ~8 weeks, so the search period for biologics is 3 months before the index date.
[3] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.
[4] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply.

Medication category for RA

Category 1	No treatment Or NSAID: ibuprofen (Motrin, Advil), naproxen (Aleve, Anaprox, Mediproxen), indomethacin (Indocin, Tivorbex), meloxicam (Vivlodex, Mobic, Comfort Pac Meloxicam), celecoxib (Celebrex), nabumetone (Relafen), etodolac (Lodine), diclofenac (Xrylix, Voltaren, Solaraze, Flector, Zorvolex, Zipsor, Cambia), sulindac (Clinoril), salsalate (Disalcid), ketorolac (Toradol, Acular) Or Low dose steroids: Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone (all <5 mg or equivalent)
Category 2	Conventional DMARDs: hydroxychloroquine (Plaquenil), leflunomide (Arava), Methotraxate (MTX) (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo), sulfasalazine (Azulfidine), minocycline (Minocin), azathioprine (Imuran, Azasan)
Category 3	Biologics: abatacept (Orencia), rituximab (Rituxan), rituximab-abbs (Truxima), rituximab-pvvr (Ruxience), rituximab-arrx (Riabni), tocilizumab (Actemra), sarilumab (Kevzara), adalimumab (Humira), etanercept (Enbrel), etanercept-szzs (Erelzi), etanercept-ykro (Eticovo), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), certolizumab pegol (Cimzia), golimumab (Simponi), anakinra (Kineret)
Category 4	High dose systemic steroids (any ≥***5*** mg prednisone or equivalent): hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone
Category 5	JAK inhibitors: tofacitinib (Xeljanz, Xeljanz XR), baricitinib (Olumiant), upadicitinib (Rinvoq)

DMARDs = disease-modifying antirheumatic drugs; JAK = Janus Kinase; MTX = methotrexate; NSAID = Nonsteroidal Anti-Inflammatory Drug; RA = Rheumatoid arthritis

Source: Treatment category from EPI-ZOSTER-044

13.6.2. IBD medication category

Medication category for IBD will be determined by the highest category of medication prescribed during the search periods specified below:

- Rituximab (Rituxan) or rituximab-abbs/rituximab-pvvr (Truxima): 6 months before index date[1]
- Biologics: 3 months before index date[2]
- JAK inhibitors: 3 months before index date to 1 month after index date[3]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), 5-aminosalicylate (5-ASA), aminosalicylate, sulfasalazine, thiopurines, steroids, and conventional DMARDs: Medication prescribed/refilled within 6 months prior to index date[4]
- Any medication that is active at the index date will be considered regardless of when it was prescribed/refilled.

[1] Rituximab is typically dosed every 6 months, so the search period for rituximab is 6 months before the index date.
[2] Some biologics are given as far apart as every ~8 weeks, so the search period for biologics is 3 months before the index date.
[3] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.
[4] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply.

Medication category for IBD

Category 1	No treatment
Category 2	Aminosalicylate (5-ASA): aminosalicylate (5-ASA), sulfasalazine (Azulfidine), olsalazine (Dipentum), mesalamine (Canasa, Asacol, mesalamine (Canasa, Asacol, Pentasa, Apriso, Lialda, Rowasa, Delzicol), balsalazide (Giazo, Colazal) Or Low dose steroids (all <***5*** mg or equivalent): Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone budesonide (Entocort/Uceris)
Category 3	Biologics: infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), adalimumab (Humira), adalimumab-adaz (Hyrimoz), adalimumab-adbm (Cyltezo), adalimumab-atto (Amjevita), adalimumab-bwwd (Hadlima), vedolizumab (Entyvio), ustekinumab (Stelara), golimumab (Simponi), certolizumab (Cimzia), natalizumab (Tysabri) Or Conventional DMARD: MTX (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo) Or Thiopurines: azathioprine (Imuran, Azasan), mercaptopurine (Perinethol), and thioguanine (6-TG, Tabloid or Lanvis)
Category 4	High dose systemic steroids (any ≥***5*** mg prednisone or equivalent): hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone
Category 5	JAK inhibitors: tofacitinib (Xeljanz), baricitinib (Olumiant) Cyclosporine (Gengraf, Neoral, Sandimmune)

DMARD: = Disease-Modifying Antirheumatic Drugs; IBD = Inflammatory bowel disease; JAK = Janus kinase; MTX = methotrexate

Source: Treatment category from EPI-ZOSTER-044

13.6.3. 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.
SQ = subcutaneous, IV = intravenous, PO = by mouth
Source:EPI-ZOSTER-041

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

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
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
	Intravenous IgG (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 (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.
SQ = subcutaneous, IV = intravenous, IM = intramuscular, PO = by mouth
Source: EPI-ZOSTER-041

13.6.5. PsO Immunosuppressive/immunomodulatory therapies

Medication category for PsO will be determined by the highest category of medication prescribed during the search periods specified below:

- Biologic disease-modifying anti-rheumatic drugs (DMARDs), intralesional/Intramuscular corticosteroids, psoralen and ultraviolet A (PUVA), photodynamic therapy (PDT), narrowband ultraviolet B (NB-UVB) (with or without tar), UV phototherapy (with or without tar), and excimer laser: 3 months before index date[1]
- Targeted synthetic DMARDs (JAK inhibitors): 3 months before index date to 1 month after index date[2]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), topical medications, steroids, and conventional synthetic DMARDs: Medication prescribed/refilled within 6 months prior to index date[3]

[1] Some biologics are given as far apart as approximately every 8 weeks, thus the search period for biologics is 3 months before the index date.

[2] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.

[3] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply. Medications prescribed/refilled within 6 months prior to the index date will be searched to identify those medications.

Individuals who meet the criteria for both PsO and PsA will be included in both the PsO and PsA cohorts. The most advanced medication category used for treatment of either condition will be used for both cohorts. For example, if an individual identified as having both PsO and PsA is using a Category 2 medication for PsO (e.g., UV phototherapy) and a Category 4 medication for PsA (e.g., Orencia), then Category 4 will be used for both PsO and PsA analyses.

Medication category for PsO

Category 1 (least severe)	Topical medications (topical corticosteroids, calcineurin inhibitors, vitamin D analogues, tazarotene, salicylic acid, anthralin [dithranol], coal tar/liquor carbonis detergens [LCD], roflumilast [Zoryve], tapinarof [Vtama]), or no treatment from Category 2 to Category 5
Category 2	Psoralen and ultraviolet A (PUVA), photodynamic therapy (PDT), narrowband ultraviolet B (NB-UVB) (with or without tar), UV phototherapy (with or without tar), and excimer laser.
Category 3	Conventional synthetic DMARDs: Traditional DMARD: methotrexate (MTX) (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo), cyclosporine, acitretin, apremilast (Otezla), azathioprine (Imuran, Azasan), hydroxyurea, mycophenolate mofetil (MMF), tacrolimus, leflunomide (Arava), thioguanine (6-TG, Tabloid, Lanvis) Intralesional/IM corticosteroids: triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte)
Category 4	Biologic DMARDs[1]: TNF-α inhibitors: etanercept (Enbrel), infliximab and biosimilars (Avsola, Inflectra, Remicade, Renflexis), adalimumab and biosimilars (Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Humira, Hyrimoz, Idacio, Yusimry), certolizumab pegol (Cimzia), golimumab (Simponi, Simponi Aria) IL-12/IL-23 inhibitors: ustekinumab (Stelara) IL-17 inhibitors: secukinumab (Cosentyx), ixekizumab (Taltz), brodalumab (Siliq), bimekizumab (Bimzelx) IL-23 inhibitors: guselkumab (Tremfya), tildrakizumab-asmn (Ilumya), risankizumab-rzaa (Skyrizi)
Category 5 (most severe)	Targeted synthetic DMARDs: JAK inhibitors: tofacitinib (Xeljanz, Xeljanz XR), upadacitinib (Rinvoq), deucravacitinib (Sotyktu)

[1] Biologics are administered as either SC or IV. Both SC or IV forms are available for golimumab (SC [Simponi] or IV [Simponi Aria]) and ustekinumab (Stelara). Infliximab and biosimilars are administered as IV only. All others are administered as SC.

IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous

13.6.6. PsA Immunosuppressive/immunomodulatory therapies

Medication category for PsA will be determined by the highest category of medication prescribed during the search periods specified below:

- Biologic disease-modifying anti-rheumatic drugs (DMARDs), intralesional/Intramuscular corticosteroids, psoralen and ultraviolet A (PUVA), photodynamic therapy (PDT), narrowband ultraviolet B (NB-UVB) (with or without tar), UV phototherapy (with or without tar), and excimer laser: 3 months before index date[1]
- Targeted synthetic DMARDs (JAK inhibitors): 3 months before index date to 1 month after index date[2]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), topical medications, steroids, and conventional synthetic DMARDs: Medication prescribed/refilled within 6 months prior to index date[3]

[1] Some biologics are given as far apart as approximately every 8 weeks, thus the search period for biologics is 3 months before the index date.
[2] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.
[3] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply. Medications prescribed/refilled within 6 months prior to the index date will be searched to identify those medications.

Individuals who meet the criteria for both PsO and PsA will be included in both the PsO and PsA cohorts. The most advanced medication category used for treatment of either condition will be used for both cohorts. For example, if an individual identified as having both PsO and PsA is using a Category 2 medication for PsO (e.g., UV phototherapy) and a Category 4 medication for PsA (e.g., Orencia), then Category 4 will be used for both PsO and PsA analyses.

Medication category for PsA

Category 1 (least severe)	Non-pharmacologic therapies, or no treatment from Category 2 to Category 5
Category 2	Nonsteroidal anti-inflammatory drugs (NSAIDs): ibuprofen (Motrin, Advil), naproxen (Aleve, Anaprox, Mediproxen), indomethacin (Indocin, Tivorbex), meloxicam (Vivlodex, Mobic, Comfort Pac Meloxicam), celecoxib (Celebrex), nabumetone (Relafen), etodolac (Lodine), diclofenac (Xrylix, Voltaren, Solaraze, Flector, Zorvolex, Zipsor, Cambia), sulindac (Clinoril), salsalate (Disalcid), ketorolac (Toradol, Acular) Low dose steroids (PO): methylprednisolone (Medrol), prednisolone, prednisone (<5mg prednisone or equivalent)
Category 3	Conventional synthetic DMARDs: Oral small molecules (OSMs): MTX (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo), sulfasalazine (Azulfidine), leflunomide (Arava), apremilast (Otezla) High-dose systemic steroids: hydrocortisone (IM/IV), methylprednisolone (Medrol [IM/IV], Solu-Medrol [IM/IV], Depo-Medrol [IM/IV]), prednisolone (IM/IV), triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte) [IM/IV]), prednisone (PO) (≥5 mg prednisone or equivalent)
Category 4[1]	Biologic DMARDs[2]: TNF-α inhibitors: etanercept (Enbrel), infliximab and biosimilars (Avsola, Inflectra, Remicade, Renflexis), adalimumab and biosimilars (Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Humira, Hyrimoz, Idacio, Yusimry), certolizumab pegol (Cimzia), golimumab (Simponi, Simponi Aria) IL-12/IL-23 inhibitors: ustekinumab (Stelara) IL-17 inhibitors: secukinumab (Cosentyx), ixekizumab (Taltz) CTLA4-immunoglobulin: abatacept (Orencia) IL-23 inhibitors: guselkumab (Tremfya), risankizumab-rzaa (Skyrizi) and biosimilars (risankizumab-AbbVie, risankizumab-rzza)
Category 5[1]	Targeted synthetic DMARDs: JAK inhibitors: tofacitinib (Xeljanz, Xeljanz XR), upadacitinib (Rinvoq) and biosimilars (upadacitinib-AbbVie)

[1] Categories 1 – 5 will be used as listed, as the risk of HZ is greater in those treated with JAK inhibitors compared to the risk in those treated with medications in Category 4.

[2] Biologics are administered either as SC or IV. Both SC or IV forms are available for abatacept (Orencia), ustekinumab (Stelara) and golimumab (SC [Simponi] or IV [Simponi Aria]). Infliximab and biosimilars are administered as IV only. All others are administered as SC.

IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous

13.7. Appendix 7: Protocol Amendment history

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

DOCUMENT HISTORY	
Document	**Date of Issue**
Protocol Amendment 2	28 Feb 2024
Protocol Amendment 1	11 August 2023
Original protocol	18 August 2022

Amendment summary of changes table:

Document	Date of issue	Section # and title	Description of change	Brief rationale
Protocol amendment 1	11 August 2023	Section 1. Synopsis; Section 1.3. Overall design. Section 5. Study design; Section 5.1. Overall design. Section 7. Study Population; Section 7.6. Matching.	The section has been updated to clarify that there are two unique types of matching performed consecutively (exact matching and propensity score matching).	The matching approach that is employed in the SAP was clarified in the protocol.
		Section 5. Study design; Section 5.1. Overall design.	Exclusion criterion related to the follow up time of at least 3 months before the end of study has been removed.	Sentence no longer needed as exclusion criterion related to follow-up time of at least 3 months after follow-up start date was removed (see Section 7. Study Population; Section 7.3. Exclusion criteria below).

Document	Date of issue	Section # and title	Description of change	Brief rationale
		Section 6. Variables; Section 6.3. Covariates of interest.	Reference to Appendix 6 (AID- related medications) has been added.	This information was not available at the time the protocol was approved.
		Section 7. Study Population; Section 7.2. Inclusion criteria.	Inclusion criterion related to follow-up time of at least 3 months after the follow up start date has been removed.	Inclusion criterion related to the follow-up time of at least 3 months after the follow-up start date was removed because exclusion criterion of the same follow-up time was removed (see Section 7. Study Population; Section 7.3. Exclusion criteria below).
		Section 7. Study Population; Section 7.3. Exclusion criteria.	Exclusion criterion related to follow-up time of at least 3 months after the follow up start date has been removed.	This exclusion criterion was added because of a comment made by a PRB member at the time the protocol was reviewed. As this study was designed as an open cohort study to allow all subjects to come in late and some to come in as early as 2018, there is no need to have a minimum follow-up duration as an exclusion criterion. In this way, all subjects

Document	Date of issue	Section # and title	Description of change	Brief rationale
				with lesser than 3 months follow-up duration are allowed and subjects that have received 2 doses at least 28 days apart will not be lost. This is not expected to impact the overall incidence rate of HZ. This has been performed to increase the sample size and the follow up time. As the analysis is taking into account the follow-up time, the impact of adding subjects that would have less than 3 months follow-up for the analysis will not be disproportionally high.
		Section 7. Study population; Section 7.7. Follow-up/censoring	The latest date of patient enrollment to ensure 3 months follow up has been removed.	Sentence no longer needed as exclusion criterion related to follow-up time of at least 3 months after follow-up start date was removed.
		Section 13.6. Appendix 6: Medication category	Update of the timeframe for measurement of medication use prior to the index date to	This information was not available at the time the protocol was approved.

Document	Date of issue	Section # and title	Description of change	Brief rationale
		Section 13.6.1. RA medication category	indicate active use of RA medication.	
		Section 13.6. Appendix 6: Medication category Section 13.6.2. IBD medication category	Update of the timeframe for measurement of medication use prior to the index date to indicate active use of IBD medication.	This information was not available at the time the protocol was approved.
		Section 13.6. Appendix 6: Medication category Section 13.6.5. PsO Immunosuppressive/immunomodulatory therapies	Medication category and timeframe for measurement of medication use prior to the index date to indicate active use of Pso has been added.	Information about the medication category for PsO was not available at the time the protocol was approved.
		Section 13.6. Appendix 6: Medication category Section 13.6.6. PsA Immunosuppressive/immunomodulatory therapies	Medication category and timeframe for measurement of medication use prior to the index date to indicate active use of PsA has been added.	Information about the medication category for PsA was not available at the time the protocol was approved.

Detailed description of Protocol amendment 2:

4.2 Study objectives

Primary Objectives

1. […]

Secondary Objectives

1. […]

17. To estimate overall VE after 2 doses of RZV for preventing HZ in participants >50 YOA with selected AIDs ***by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.***

11.3.4 Secondary analysis

[…]

Secondary objective 17: Analyses for secondary objective 17 will employ similar methods as for the primary analyses and will be conducted among the matched 2-dose cohorts. ***In these analyses, participants are allowed to have multiple AIDs. Analyses will be stratified by age group, gender, time since vaccination, time interval between two doses and medication category during baseline, as described in Appendix 6.*** Descriptive analyses and Cox proportional hazards regression will be conducted and overall estimates of VE (%) will be calculated for all selected AIDs as (1 – adjusted HR) × 100.

11.3.5 Sensitivity analyses

Sensitivity analyses will be performed to assess if the occurrence of the COVID-19 pandemic has an impact on the effectiveness of the vaccine in participants who test positive for COVID-19 during the follow-up period. Methods to identify the COVID test result (i.e., PCR) and analyses to assess the impact of the pandemic on the VE will be described in the SAP. Sensitivity analyses will also be performed on participants who have either PsO or PSA, participants who have PsO only, participants who have PsA only, and participants who have both PsO and PsA to address the potential overlap between PsO and PsA. ***In addition, sensitivity analyses will be performed to assess if adding medication category as a covariate after propensity score matching has an impact on the results of the primary analyses (primary objectives 1-6) and subgroup analyses (secondary objective 17). Further*** details of the sensitivity analyses will be described in ***Section 10.4.3 of*** the SAP ***amendment 2.***

11.3.6 Additional analyses

Additional tables described below will be created to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses. The additional tables will require further analyses described in detail in Section 10.6 of the SAP amendment 2.

11.3.6.1 AID diagnosis

Study participants may report more than one AID diagnosis resulting in potential overlap between AIDs. Distribution tables of participants associated with multiple AIDs for 1-dose and 2-dose cohorts will be created to assess the proportion of participants

diagnosed with one or more AIDs in the vaccinated and unvaccinated groups. The rationale for this analysis is to check whether there is not a significant rate of participants with overlapping conditions, which would need to be documented as a study limitation in the final study report.

11.3.6.2 Time since vaccination

Baseline characteristics/demographic tables for the 2-dose cohort reporting different lengths of follow-up (0<1 years, 1<2 years, 2<3 years, 3+ years) will be created to check the number of HZ events observed in the different follow-up periods for the analyzed population and to check whether trends are observed in the different follow-up periods for the analyses corresponding to secondary objectives 3-9 and 17. More granular information about length of follow-up may help to explain varying vaccine effectiveness values observed by time since vaccination.

11.3.6.3 End of follow-up

Distribution tables of participants in the 2-dose cohort whose end of follow-up reason is either disenrollment or study end date will be created to estimate the number of participants that end follow-up for a reason other than study end. If many study participants end follow-up for a reason that is not the study end, it can introduce a selection bias, especially if the reason that a study participant disenrolled is linked to the primary outcome (HZ). This assessment will be done to check whether the number of such participants in the analyzed population who report study end as the reason to end follow-up is similar in the vaccinated and the unvaccinated groups.

11.3.6.4 Medication class/medication categories

Distribution tables of medication class (type of medication) within each existing medication category described in Appendix 6 of the current protocol amendment will be created to assess the distribution of medications class by age and by AID. The purpose of these tables is to identify which medication class is observed in greater frequency by age and by AID. Information about the types of medications in each of the existing medication categories may help to explain when varying vaccine effectiveness values by medication category are observed.

Additional distribution tables of steroids will be created to check the frequency of participants who receive low-dose (< 5mg) versus high-dose (≥5 mg) steroids in the vaccinated and unvaccinated groups. This includes patients with RA, IBD and PsA. This assessment will be done to check the impact of the cut-off assigned to low-dose and high-dose on the analyses of RA, IBD and PsA cohorts since the cut-off, while clinically acceptable, is considered arbitrary. The following generic names for low-dose and high-dose steroids for RA, IBD and PsA will be considered in the distribution tables:

AID	***Generic names for steroids****
RA	***Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol), prednisolone, prednisone hydrocortisone.***
IBD	***Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone budesonide (Entocort/Uceris).***
PsA	***Methylprednisolone (Medrol), prednisolone, prednisone, hydrocortisone (IM/IV), methylprednisolone (Medrol [IM/IV], Solu-Medrol [IM/IV], Depo-Medrol [IM/IV]), prednisolone (IM/IV), triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte) [IM/IV]).***

****Appendix 6** of the current protocol amendment provides detailed information about the above steroids.*

11.3.6.5 Comorbidities covariates

Cross tables between age categories and comorbidities (asplenia/hyposplenia, COVID-19, cardiovascular disease, diabetes mellitus, kidney disease, lymphoma/leukemia, liver disease, pulmonary disease), described in Appendix 5 of the current protocol amendment, will be created to estimate the number of study participants by comorbidity and age in the vaccinated and unvaccinated groups. This assessment will be done for all AIDs separately for the 2-dose cohort to check the impact that co-morbidities have on the overall vaccine effectiveness values.

11.3.7 Modifications to subgroup analyses

This study is not powered for analyses of the secondary objectives described in Section 4.2 of the current protocol amendment. For this reason, there may not be sufficient data from the subgroup analyses to allow meaningful interpretation of results. Statistical and theoretical approaches summarized below will be used to combine the following categories of variables to add additional statistical power and make the results of these analyses more interpretable: age, dose interval between two doses, time since vaccination, and medication category:

11.3.7.1 Age category, dose interval between two doses category, and time since vaccination category

A person-year cut-off value will be used to identify which categories will be combined across the stratification variables per AID. The cut-off value will be estimated using the following assumptions:

- ***Based on the sample size calculated in Table 9 of the SAP amendment 2, within less than 200 PY there is less than 1/3 chance to find a statistically significance for a true vaccine effectiveness of 70% with an incidence of less than 15 per 1000 PY in the control group, which would indicate a low precision.***
- ***Based on the sample size calculated in Table 9 of the SAP amendment, within at least 255 PY, for an incidence of at least 12 per 1000 PY in the control group, we have not less than 1/3 to find a statistical significance for a true VE of 70%. More***

specifically, for a power of 33%, for sample sizes <255 PY, there is less than one third of chance of proving vaccine effectiveness.

Based on the above, <255 PY will be used as the threshold for the combined/pooled analysis of the following variables: age category, dose interval between two doses category, and time since vaccination. Further details of the modifications to subgroup analyses are described in Section 10.6.2 of the SAP amendment 2.

11.3.7.2 New combination of medication categories

Medication categories will be recombined using the existing medication categories described in Appendix 6 of the current protocol amendment. This theoretical approach to recombining the existing medication categories will be based on the systemic action of the medications and will apply to the subgroup analyses (secondary objectives 3-9, 17). The approach will be used to make the results of these subgroup analyses more interpretable as low number of participants in these analyzed populations are expected across certain types of medications.

The new combination of these medications is described below:

- ***Category 1: non-immunosuppressive therapy (e.g., no treatment, NSAIDs, low dose (<5mg) steroids, anti-malarial, topical medications (corticosteroids, non-pharmacologic therapies).***
- ***Category 2: mild-moderate immunosuppressive therapy (e.g., conventional DMARDs, aminosalicylate, psoralen and PUVA, PDT, NB-UVB, UV phototherapy, excimer laser).***
- ***Category 3+4 (combined): highly immunosuppressive (e.g., biologics, high dose (≥5 mg) steroids, thiopurines, SP1 receptor modulators, intralesional/IM corticosteroids).***
- ***Category 5: JAK inhibitors, DMARDs (synthetic and targeted synthetic).***

Signature Page for 219111 TMF-18587403 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 28-Feb-2024 04:59:32 GMT+0000

Signature Page for TMF-18587403 v1.0

Information Type: Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A retrospective matched cohort database study in the United States to evaluate the effectiveness of recombinant zoster vaccine (RZV) in patients with autoimmune diseases (AIDs)

Study Number: 219111

Abbreviated Title: A matched cohort study to evaluate RZV effectiveness in U.S. patients with AID

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Registry	**ID**
Disclosure registry name	Registry ID
Clintrials.gov	NCT01234567

Statistical Analysis Plan (SAP) for Non-Interventional Studies (NIS) Template v01 27 July 2023

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1. VERSION HISTORY

SAP Version	Approval Date	Protocol Version [Date] on which SAP is Based	Change	Rationale*
SAP	19/09/2022	18/08/2022	Not Applicable	Original version
SAP Amendment 1	02/10/2023	26/07/2023	Amendment 1	Analysis already performed led to some of the amendments but new information about medication categories were made available after the analysis started.
SAP Amendment 2		***28/02/2024***	***Amendment 2***	In consultation with our Epi team and after rigorous internal discussions, we have decided to modify the subgroup analyses to add additional statistical power and make the results of these analyses more interpretable. Several additional tables will also be created to provide more granular information about the distribution of incidence rates and vaccine effectiveness values reported in the subgroup analyses. The subgroup

SAP Version	Approval Date	Protocol Version [Date] on which SAP is Based	Change	Rationale*
				analyses of one of the secondary objectives will also be revised by stratified variables and additional sensitivity analyses will be performed to assess the impact of including one additional covariate in some of the analyses. The changes to the SAP amendment 2 are being made solely to enhance the study's scientific integrity and robustness and does not alter the fundamental concept and objectives of the research.

* If the analysis was started prior to the amendment, describe whether the analyses already preformed led to an amendment.

2. SAP AMENDMENT SUMMARY OF CHANGES TABLE

Overall rationale for the current amendment:

SAP amendment 2 was prepared to revise one of the secondary objectives, to add the variable medication category as a covariate in the analyses by AID and AID overall, and to perform sensitivity analyses to assess the impact of including this covariate in the above analyses. Several additional tables were also created to provide more granular information about the distribution of incidence rates and vaccine effectiveness values reported in the preliminary analyses. Modifications to the sub-analyses were also done to allow certain categories of variables to be combined for additional statistical power and to make the results of secondary objectives which are not powered to be more interpretable.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale	Amendment or update no.
Section 9.3.3 Covariates Table 5: Definition of covariates in matching and their associated reference period	Update of the definition of concomitant vaccinations	Influenza vaccine, tetanus, diphtheria and pertussis vaccine, pneumococcal vaccine occurring on the same day of the index date instead of the 365 days prior to the index date proposed at the time the SAP was approved.	1
	Update of the definition of the healthcare cost logarithm	Logarithm of the Healthcare cost will be assessed during the baseline period and calculated as follows: Log(cost) = LN(Cost + 1)	1
Section 9.2.2 Study Timeframes	Explanation of how to handle the outliers to limit their impact on the analysis results.	For 2-dose cohort: participants who had a dose interval greater than 1 year apart will be considered as outliers and remove from the 2-dose analysis. For 1-dose cohort: the maximum follow-up duration will be restricted to 6 months to ensure comparability between vaccinated and unvaccinated participants.	1
Section 9.2.1 Eligibility Criteria – Inclusion Criteria	Inclusion criterion related to follow-up time of at least 3 months after the follow up start date has been removed.	Inclusion criterion related to the follow-up time of at least 3 months after the follow-up start date no longer applies since the exclusion criterion of the same follow-up time was removed.	1
Section 9.2.1 Eligibility Criteria – Exclusion Criteria Section 9.3.1 Exposure Definitions	Exclusion criterion related to follow-up time of at least 3 months after the follow up start date has been removed.	Exclusion criterion added because of a comment made by a PRB member at the time the protocol was reviewed. As this study was designed as an open cohort study to allow all subjects to come in late and some to come in as early as 2018, there is no need to have a minimum follow-up duration as an	1

Section # and title	Description of change	Brief rationale	Amendment or update no.
		exclusion criterion. In this way, all subjects with lesser than 3 months follow-up duration are allowed and subjects that have received 2 doses at least 28 days apart will not be lost. This is not expected to impact the overall incidence rate of HZ.	
Section 9.2.3 Methodology for matching vaccinated and unvaccinated	Clarification of the methodology for matching vaccinated and unvaccinated subjects.	Detailed information about applying greedy matching at the index date provided.	1
Section 9.3.1 Exposure Definitions	Update exposure definition for 2-dose cohort	Only vaccinations that <= 1 year apart will be considered for 2-dose cohort.	1
Section 10.5 Secondary analyses – 10.5.1 Main Analytical Approach	Update time interval between two doses	Limit time interval between two doses to 1 year (365 days).	1
Section 14.1.7 Medication categories Table 9 RA Medication Category Table 10 IBD Medication Category	Revise definition of low dose and high dose steroids.	The low dose will be defined as a daily dose lower than 5 mg. The high dose will be defined as a daily dose greater or equal to 5 mg. Formula was added in the programming to calculate the daily dose of steroids	1
	Update of the timeframe for measurement of medication use prior to the index date to indicate active use of AID-related medications (RA, IBD).	This information was not available at the time the SAP was approved	1
Section 14.1.7 Medication categories Table 13: PsO Medication Category Table 14: PsA Medication Category	Addition of medication categories for PsO and PsA.	This information was not available at the time the SAP was approved	1
Section 8 Secondary objective	***Revise secondary objective 17 to include analysis by stratified variables.***	***The analysis corresponding to secondary objective 17 will include an estimation of the overall vaccine effectiveness by age, gender, time since vaccination, time interval between two doses, and medication category. This revised***	***2***

Section # and title	Description of change	Brief rationale	Amendment or update no.
		analysis will provide additional information about the overall analyses by stratified variables. This is consistent with the analyses by AID which estimated vaccine effectiveness by age, gender, time since vaccination, time interval between two doses, and medication category, based on secondary objectives 3-9.	
Section 10.4.3: Sensitivity Analyses	***Additional sensitivity analyses to assess the impact of including medication category as a covariate on the vaccine effectiveness values***	***Sensitivity analyses will be performed to assess the impact of including medication category as a covariate in vaccine effectiveness values by AID and AIDs overall.***	***2***
Section 10.5.1 Main Analytical Approach	***Update information about the secondary objective 17 as is indicated above***	***The rationale for this update is described in Section above.***	***2***
Section 10.6.1: Additional Analyses	***The additional analyses section has been added to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the initial analyses.***	***Additional tables listed below will be created to understand the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses:*** ***1. Distribution tables of subjects associated with 1, 2, 3 or 4 AIDs for 1-dose and 2-dose cohorts to assess the proportion of subjects diagnosed with overlapping AID conditions.*** ***2. Distribution tables of subjects whose end of follow-up reason is either disenrollment or end of study for***	***2***

Section # and title	Description of change	Brief rationale	Amendment or update no.
		2-dose cohort to identify risk of potential selection bias. *3. Distribution tables of medication class within each medication category to assess the frequency of medication class by age and by AID.* *4. Distribution tables of steroids to check the frequency of subjects who receive low- versus high-dose steroids in the vaccinated and unvaccinated groups.* *5. Baseline characteristics/ demographic tables for populations with different length of follow-up (0<1 years, 1<2 years, 2<3 years, 3+ years) to check if trends of HZ events can be observed in different follow-up periods.* *Cross tables between age categories and comorbidities to check the proportion of comorbidities by age and comorbidity in the vaccinated and unvaccinated groups.*	
Section 10.6.2 Modified Analysis	*Subgroup analyses corresponding to secondary objectives 3-9 and 17 will be modified to address potential study limitations.*	*Modifications to the sub-analyses (secondary objectives 3-9, 17) were done to allow certain*	*2*

Section # and title	Description of change	Brief rationale	Amendment or update no.
		categories from the following variables to be combined: age, dose interval between two doses, time since vaccination, and medication category. Combining these categories will add statistical power and make the results of secondary objectives which are not powered to be more interpretable.	

3. LIST OF ABBREVIATIONS

ACIP	Advisory Committee of Immunization Practices
AID	Autoimmune Disease
auHSCT	autologous hematopoietic stem cell transplant
CD	Crohn's Disease
CDM	Clinformatics Data Mart
CI	Confidence Interval
CPT	Current Procedural Terminology
EHR	Electronic Health Records
ER	Emergency Room
FDA	Food and Drug Administration, United States of America
FISMA	Federal Information Security Management Act
GSK	GlaxoSmithKline
HCFA	Health Care Financing Agency
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act

HM	Hematological malignancies
HR	Hazard Ratio
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
ICD-10	International Classification of Diseases, Clinical Modification, 10th version
IDNs	Integrated Delivery Networks
JAK	Janus Kinase
LL	Lower limit of the confidence interval
MS	Multiple Sclerosis
NA	Not Applicable
NDC	National Drug Code
NIST	National Institute of Standards and Technology
P10	10^{th} Percentile
P20	20^{th} Percentile
P30	30^{th} Percentile
P40	40^{th} Percentile
P50	50^{th} Percentile
P60	60^{th} Percentile
P70	70^{th} Percentile
P80	80^{th} Percentile
P90	90^{th} Percentile
PHN	Post-Herpetic Neuralgia
PsA	Psoriatic Arthritis
PsO	Psoriasis

PY	Person-years
Q1	First Quartile
Q3	Third Quartile
RA	Rheumatoid Arthritis
RWA	Real-World Analytics
RZV	Recombinant Zoster Vaccine
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrom-Coronavirus-2
SAS	Statistical Analysis Software
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SMD	Standardized Mean Difference
UC	Ulcerative Colitis
UL	Upper limit of the confidence interval
VE	Vaccine Effectiveness
VZV	Varicella Zoster Virus
YOA	Year Of Age
ZVL	Zoster Vaccine Live

4. TRADEMARK INFORMATION

Trademarks of the [GSK\ViiV] group of companies
N/A

Trademarks not owned by the [GSK\ViiV] group of companies
N/A

5. RESPONSIBLE PARTIES (Amended: 28 February 2024)

Role	Name, affiliation, contact information
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SAP Author	PPD, RWA, PPD
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6. APPROVALS

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Director Biostatistics

Date

7. RATIONALE AND BACKGROUND

HZ, or shingles, results from the reactivation of varicella zoster virus (VZV) and causes a painful, pruritic rash that usually resolves on its own within 1-2 weeks. HZ affects at least 1 million people in the United States each year. An estimated 32% of persons in the United States will experience HZ during their lifetime [Harpaz, 2008]. Furthermore, over 95% of adults ≥50 YOA are seropositive for VZV and susceptible to HZ [Johnson, 2015].

Individuals with AID are at higher risk of HZ than immunocompetent individuals [Gupta, 2006; Khan, 2018; Long, 2013; Smitten, 2007; Yun, 2016]. The incidence rate of HZ among adults with RA is about double than that among immunocompetent (non-RA)

adults [Smitten, 2007; Yun, 2016], and it is higher among adults with IBD (e.g., UC or CD) than those without IBD [Gupta, 2006; Khan, 2018; Long, 2013; Yun, 2016]. The risk of HZ in patients with SLE is also twice as high than in the general population [Kawai, 2017]. Patients with PsO have a higher HZ risk than the general population [Baumrin, 2019; Chen, 2014; Tsai, 2017].

Systemic therapies also play a major role in the risk of HZ. For example, immuno-suppressive therapy renders patients with SLE and MS more susceptible to VZV reactivation [Borba, 2010; Manouchehrinia, 2017]. In a recent systematic literature review, patients with PsO or PsA treated with systemic corticosteroids and combination systemic therapy were reported to have increased HZ risk [Baumrin, 2019]. Patients with PsO and PsA had variable HZ risk, depending on disease severity and type of systematic therapy.

The US Food and Drug Administration (FDA) approved RZV, a 2-dose subunit zoster vaccine containing recombinant glycoprotein E in combination with the novel adjuvant $AS01_B$, in October 2017 for immunocompetent adults aged ≥50 YOA [FDA, 2017] and in July 2021 for adults aged ≥18 YOA who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy [FDA, 2021]. The FDA approvals were followed by the recommendations of the Advisory Committee on Immunization Practices (ACIP) of RZV for use in immunocompetent adults aged ≥50 YOA [Dooling, 2018] and in immunocompromised adults aged ≥19 YOA [Anderson, 2022].

The GSK 2-dose RZV vaccine demonstrated efficacy in preventing HZ in two phase III randomized controlled trials (RCTs): ZOE-50 and ZOE-70 [Lal, 2015; Dagnew, 2019]. RZV efficacy in these trials was 97.2% (95% CI, 93.7, 99.0) in adults aged ≥50 YOA (ZOE-50) and 91.3% (95% CI, 86.8, 94.5) in adults ≥70 YOA (ZOE-70). Myalgia, injection site pain, and erythema were the most common adverse events (AEs) reported in these trials.

Vaccine efficacy of RZV in immunocompromised adults aged ≥18 YOA was evaluated in a clinical trial that included autologous hematopoietic stem cell transplant (auHSCT) recipients [Bastidas, 2019]. Among auHSCT recipients, RZV efficacy in preventing HZ was 68.2% (95% CI, 55.6, 77.5). Post-hoc vaccine efficacy among adults with hematological malignancies (HM) was 87.2% (95% CI, 44.3, 98.6) [Dagnew, 2019].

Data on RZV effectiveness in AID populations is limited. A recent cohort study evaluated the overall VE of RZV in a subgroup of Medicare enrolled patients aged ≥65 YOA with AID and reported overall 1- and 2-dose VE of 57.7% (95% CI, 50.9, 63.6) and 68.0% (95% CI, 62.3, 72.8), respectively [Izurieta, 2021]. Another recent study from the Veterans Affairs Healthcare System among individuals diagnosed with IBD showed that RZV was associated with decreased risk of HZ infection among both the 50-60 years and >60 years of age (YOA) patients [Khan, 2021]. More research is needed to evaluate the effectiveness of RZV in specific AID populations (SLE, MS, RA, IBD, PsO, and PsA).

This study will help to critically inform patient and physician decision-making about vaccinating against HZ in these at-risk populations and support evidence-based AID recommendations and guidelines.

8. RESEARCH QUESTION(S) AND OBJECTIVE(S) (Amended: 28 February 2024)

This study will assess VE among participants enrolled in the Optum™ database with SLE, MS, RA, IBD (UC, CD), PsO, or PsA who received RZV (vaccinated) compared to participants who did not receive RZV (unvaccinated), as per the objectives described in **Table 1**. HZ will define the outcome (Section 9.3.2) for all objectives.

Table 1 Study Objectives

Primary Objectives	
1.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE.
2.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS
3.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA.
4.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD
5.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO
6.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA
Secondary Objectives	
1.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD)
2.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
3.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with SLE stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
4.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with MS stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
5.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with RA stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
6.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC, CD), age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.

Secondary Objectives	
7.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsO stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
8.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
9.	To estimate VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA stratified by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.
10.	To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with SLE.
11.	To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with MS.
12.	To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with RA.
13.	To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with IBD stratified by condition (UC and CD).
14.	To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsO.
15.	To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with PsA.
16.	To estimate VE after 1 dose of RZV for preventing HZ in participants ≥50 YOA with either PsO or PsA.
17.	To estimate overall VE after 2 doses of RZV for preventing HZ in participants ≥50 YOA with selected AIDs by age, gender, time since vaccination, time interval between two doses, and medication category (mutually exclusive) based on current use at the index date.

9. RESEARCH METHODS

9.1. Study Design

The study will be conducted using health care encounters/claims of the Optum™ database (Section 9.4).

A retrospective matched cohort study with Cox proportional hazards modeling will be performed to assess the risk of HZ after RZV in adults aged □50 YOA with RA, IBD, SLE, MS, PsO, or PsA, respectively. In the primary analysis, participants receiving a second dose of RZV (separated by ≥28 days after dose 1) on or after 01 January 2018 will be compared to participants with no prior RZV vaccination (i.e., unvaccinated).

In the secondary analysis, participants receiving at least one dose on or after 01 January 2018 will be compared to participants with no prior RZV vaccination. An index date will be defined for all vaccinated subjects and will correspond to the date of receipt of the 1st dose for the one-dose cohort and the date of receipt of the 2nd dose for the second-dose cohort.

A baseline period will be defined in the 365 days before the index date. Values of covariates (e.g., logarithm of the healthcare cost) described in Section 9.3.3 will be measured during this period and will be balanced using matching.

Matching between vaccinated and unvaccinated will be done by condition. Vaccinated patients will be matched exactly to unvaccinated patients on a ratio of 1:3. Matching will be done by age category of 5-year increments (i.e., 50-54 age grouping) and by AID-related medication category (mutually exclusive) based on current use at the index date. In addition, vaccinated and unvaccinated participants within exact matched categories will be balanced against multiple covariates (Section 9.3.3) using propensity score matching.

For IBD, a vaccinated participant with UC will be matched to an unvaccinated participant with UC. The same approach will be used to match participants with CD. Matching will be done with replacement. Unvaccinated participants will be assigned the same index date as their vaccinated counterparts.

To address the potential overlap between PsO and PsA and the pathogenesis of these two AIDs, vaccinated participants with either PsO or PsA will be matched to unvaccinated participants with either PsO or PsA.

Figure 1 describes the cohort design to assess vaccine effectiveness.

Figure 1 Matched 2-dose cohort study

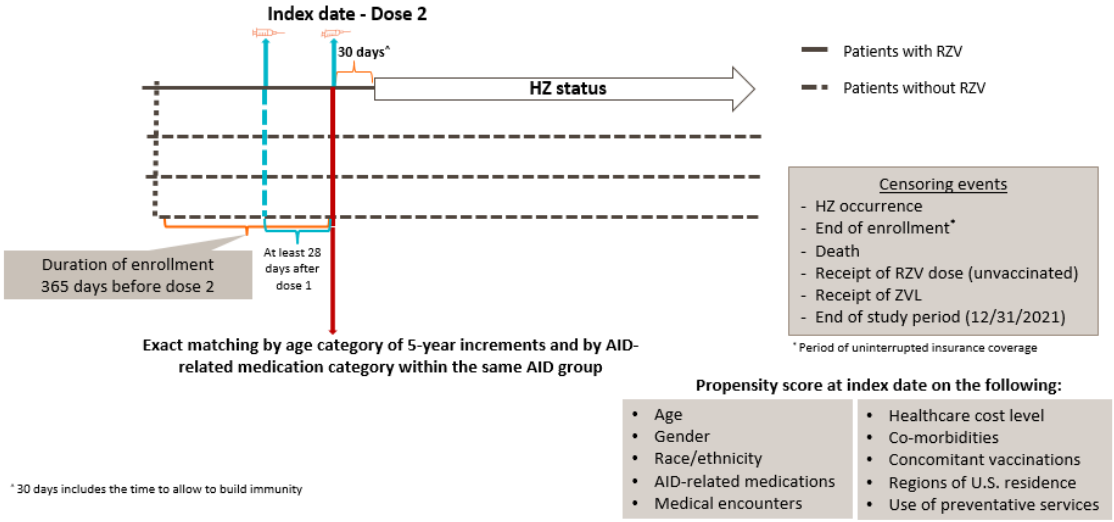
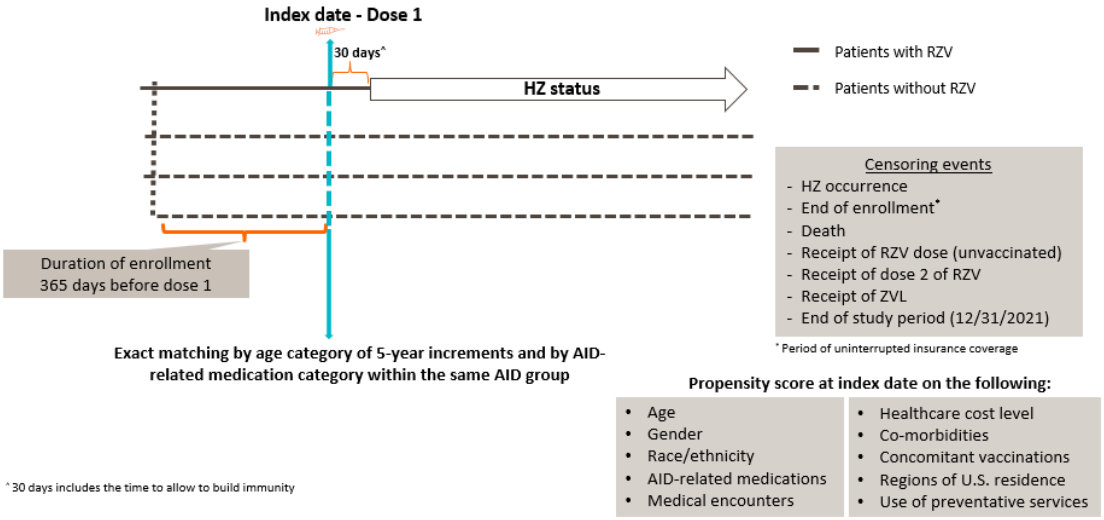


Figure 2 describes the cohort design to assess one-dose vaccine effectiveness.

Figure 2 Matched 1-dose cohort study



9.2. Study population and setting

The study population will include adults aged ≥50 YOA who are beneficiaries in the Optum™ database, diagnosed with an AID (defined as RA, IBD [UC or CD], SLE, PsO, PsA and MS), and who received RZV vaccination (along with their unvaccinated matches) anytime between 01 January 2018 to 31st December 2021 (Section 14.1.8 describes the algorithms for identification of AIDs). Details of inclusion and exclusion criteria are defined in Section 9.2.1.

Based on the number of doses of RZV received by the vaccinated participants and the type of AID, twenty-six sets of matched cohorts will be defined:

Table 2 Definition of analysis cohorts

Objective	AID condition	Name of the matched cohort
Primary objective 1	SLE	cohort SLE – 2 doses
Primary objective 2	MS	cohort MS – 2 doses
Primary objective 3	RA	cohort RA – 2 doses
Primary objective 4	IBD	cohort IBD – 2 doses
Primary objective 5	PsA	cohort PsA – 2 doses
Primary objective 6	PsO	cohort PsO – 2 doses
Secondary objective 1	UC	cohort UC – 2 doses
Secondary objective 1	CD	cohort CD – 2 doses
Secondary objective 2	Either PsO or PsA	cohort PsO or PsA – 2 doses

Objective	AID condition	Name of the matched cohort
Secondary objective 3	SLE	cohort SLE –2 doses
Secondary objective 4	MS	cohort MS – 2 doses
Secondary objective 5	RA	cohort RA – 2 doses
Secondary objective 6	UC	cohort UC – 2 doses
Secondary objective 6	CD	cohort CD – 2 doses
Secondary objective 7	PsO	cohort PsO – 2 doses
Secondary objective 8	PsA	cohort PsA – 2 doses
Secondary objective 9	Either PsA or PsO	cohort PsA or PsO – 2 doses
Secondary objective 10	SLE	cohort SLE – 1 dose
Secondary objective 11	MS	cohort MS – 1 dose
Secondary objective 12	RA	cohort RA – 1 dose
Secondary objective 13	UC	cohort UC – 1 dose
Secondary objective 13	CD	cohort CD – 1 dose
Secondary objective 14	PsA	cohort PsA – 1 dose
Secondary objective 15	PsO	cohort PsO – 1 dose
Secondary objective 16	Either PsO or PsA	cohort PsA or PsO – 1 dose
Secondary objective 17	All AID	All AIDs cohort – 2 doses

The diagnosis codes used to define the AID events are presented in Appendix section 14.1.1: Codes to identify auto-immune diagnoses.

The algorithm used to retrieve the AID diagnosis from the database is defined in Appendix section 14.1.8 Algorithm to define AID conditions.

9.2.1. Eligibility Criteria

INCLUSION CRITERIA

Participants will be included in the vaccinated cohort if the following inclusion criteria are met:

- Age ≥50 YOA at the index date for all study objectives and registered as beneficiary in the Optum™ database.
- Diagnosis of RA, IBD, SLE, MS, PsO or PsA prior to the index date
- Receipt of first dose of RZV on or after 1 January 2018

- At least 365 days of continuous enrolment (allowing administrative gaps 30 days) prior to the index date (baseline period) and continuous enrolment in the 30 days after the index date.

Participants will be included in the unvaccinated cohort if the following inclusion criteria are met:

- Age ≥50 YOA at the index date for all study objectives and registered as beneficiary in the Optum™ database.
- Diagnosis for RA, IBD, SLE, MS, PsO or PsA prior to the index date
- No RZV received before 1 January 2018
- At least 365 days of continuous enrolment (allowing administrative gaps 30 days) prior to the index date (baseline period) and continuous enrolment in the 30 days after the index date.

Note:

- Unvaccinated participants will be matched with vaccinated participants, as long as they don't receive vaccination between the start of the study period and the index date of the vaccinated participants they are matched with.
- The condition on the 365 days of continuous enrolment prior to the index date and in the 30 days after the index date will be assessed at the time of the matching.

EXCLUSION CRITERIA

Participants will be excluded from the study if the following exclusion criteria are met:

- Any previous RZV doses before index date (for unvaccinated participants only) using all available data.
- Receipt of second dose of RZV less than 28 days apart since ACIP guidelines state that these participants must repeat the second dose [Dooling, 2018].
- Receipt of ZVL any time during the baseline as this may affect rates of HZ.
- HZ diagnosis or prescription fills for oral acyclovir, valacyclovir or famciclovir within 30 days of index date since it is unclear if the HZ episode began before or after the index date and whether the length of time since vaccination (for RZV vaccinated participants) is long enough to allow for sufficient development of immunity.
- HZ diagnosis or prescription fills for oral acyclovir, valacyclovir or famciclovir in the 12 months before the index date to ensure that HZ diagnoses after the index date are new, rather than carried over from HZ episodes prior to the index date.
- Postherpetic neuralgia (PHN) diagnosis in the 12 months before the index date for reasons described above.
- Censoring events within 30 days after the index date (before the start of the study period).

9.2.2. Study Timeframes

- Study initiation date: index date of Shingrix (date of first dose for 1-dose cohort and date of second dose for 2-doses cohort)
- Baseline period: defined as the period occurring 365 days before the index date
- Follow-up period: the follow-up period will begin from 30 days after the index date (to allow for development of immunity after vaccination) and will end at the earliest occurrence of the following events:
    - HZ occurrence
    - End of continuous enrolment (period of uninterrupted insurance coverage with gap allowance of 30 days).
    - Death (date of death including the year and month of death, see Appendix section 14.1.9 Derivation of the date of death for more information on the algorithm used to define the death dates).
    - End of data availability/study period (December 31, 2021)
    - Receipt of RZV (additional dose for vaccinated participants or first RZV dose in the case of unvaccinated participants):
        - For 2-dose VE, vaccinated participants will be censored upon receipt of a dose 3.
        - For 1-dose VE, vaccinated participants will be censored upon receipt of dose 2.
    - Receipt of ZVL vaccination
    - The latest date a patient can be enrolled to ensure minimum duration of follow up is 1st November 2021 to allow for at least 1 month follow-up after the index date.
- For the 1-dose cohort only, the maximum follow-up duration will be restricted to 6 months, to ensure comparability between vaccinated and unvaccinated participants. Indeed, vaccinated participants in the 1-dose cohort will be censored upon receipt of their second dose and hence couldn't be followed-up more than 6 months.
- For the 2-dose cohort, participants who had a dose interval greater than 1 year, will be considered as outliers and remove from the 2-dose analysis.

9.2.3. Methodology for matching vaccinated and unvaccinated participants

For the primary objectives, a unique matching will be done involving an exact matching and a propensity score matching performed consecutively.

- Exact matching: once cohorts for each AID condition are identified, participants meeting inclusion criteria who receive 2 doses of RZV at least 28 days apart (2-dose cohort) at the index date will be matched exactly with unvaccinated participants on age category by 5-year increments (50-54, 55-59, 60-64, 65-69, 70-74, 75-79, ≥80)

and AID-related medication category (mutually exclusive) based on current use at the index date within the same AID group. Medication categories will be based on the medication windows described in Medication categories section 14.1.7 Medication categories. The same exact matching approach will be done for 1-dose cohort.

- Propensity score matching: Following matching as described above, a matching with propensity scores based on the likelihood of receiving RZV dose 2 versus no RZV vaccination (2-dose cohort) and RZV dose 1 versus no RZV vaccination (1-dose cohort) will be calculated using logistic regression models with RZV vaccination as the dependent variable and independent variables as outlined in Section 9.3.3.

Vaccinated and unvaccinated participants will be matched at a ratio of RZV vaccinated to RZV unvaccinated of 1:3.

The matching will be done by replacement, meaning that the same unvaccinated participant may be matched to several vaccinated participants.

Note: within the same index date, a greedy matching will be applied. This means that distinct unvaccinated participants will be chosen to be matched to a vaccinated participant as long as these participants have the same index date.

This strategy can create better balance, which should yield estimates that are closer to the truth on average.

An unvaccinated patient may serve as a comparator for both the dose 1 and dose 2 cohorts, although separate index dates will be applied.

The difference in terms of propensity score will be considered as minimal if it is lower of equal to a caliper of e.g., 0.1 [Austin,2014]. In case a significant number of the vaccinated subjects (e.g., more than 5%) cannot be matched with at least one control, alternative methods such as Inverse Probability Weighting, will be considered.

Covariate balance will be assessed before and after matching using standardized mean differences, with standardized differences of 0.1 [Austin, 2009a/b] suggestive of important imbalance. Any covariate demonstrating imbalance after weighting, suggesting residual confounding, will be considered as an additional covariate in the Cox proportional hazard models. The same approach will be used for the secondary analyses for 1-dose cohorts.

The matching will be done using the PROC PSMATCH procedure with the following parameters:

- The matching will be done with replacement using the optimal method, with a ratio 1:3 between vaccinated and matched unvaccinated participants (METHOD=REPLACEMENT (K=3)).
- The distance will be considered as the absolute difference between the Propensity score a vaccinated individual and the one associated to his matched unvaccinated individual (DISTANCE=PS)

A caliper value will be set to 0.01 (CALIPER=0.01) (Austin PC 2014)

- Participants will be exactly matched on age category and AID-related medication category (EXACT = (age category medication category))
- The logistic regression model used to calculate the propensity score will use the vaccination status as the dependent variable and the covariates will be the ones specified in section 9.3.3 (excepted age and medication category)

  (PS MODEL statement)
- Covariates will be assessed before and after matching using Standardized mean differences for continuous variables and Chi-Square tests for categorical variables (ASSESS statement)

Below is PROC PSMATCH code:

PROC PSMATCH data=<SAS input dataset>;

ASSESS PS VAR(<vaccination status> <sex> <race> <logarithm healthcare cost>

<presence of comorbidities>

<concomitant vaccinations> <number of consultations> <region>

<use of preventive services>);

CLASS <age category> <sex> <race> <logarithm healthcare cost>

<medication category> <presence of comorbidities>

<concomitant vaccinations> <number of consultations> <region>

<use of preventive services>

MATCH CALIPER = 0.1 DISTANCE = PS EXACT = (<age category> <medication category>)

METHOD = GREEDY (K=3 ORDER=RANDOM)

OUTPUT OUT (OBS=MATCH) = <output SAS dataset>;

PSMODEL <vaccination status> (TREATED = "Vaccinated") = <sex> + <race> + <logarithm healthcare cost> + <presence of comorbidities> + <concomitant vaccinations> + <number of consultations> + <region> + <use of preventive services>;

run;

9.3. Variables

9.3.1. Exposure Definitions

The exposure of interest is the receipt of RZV (1-dose or 2 RZV doses at least 28 days apart). RZV vaccination will be identified from administrative and claims data by means of Current Procedural Terminology (CPT) and National Drug Code (NDC) codes **(Table 3)**

For primary objectives 1 to 6 and secondary objectives 1 to 9 and 17, the exposure of interest is the receipt of 2-dose-RZV at least 28 days apart.

Only vaccinations that are less or equal to 1 year apart will be considered for defining the 2-dose cohort.

For secondary objectives 10 to 16, the exposure of interest is the receipt of 1-dose-RZV.

The exposure will be during the study period: 1st January 2018 – 1st November 2021.

Table 3 Definition of the exposure

Exposure Variables	Definition
RZV vaccination	Any claim associated with a CPT code = 90750 or NDC codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11 (Appendix 14.1.3)

9.3.2. Outcome Definitions

The primary outcome is the HZ event which can be identified using the following algorithm including at least:

- an inpatient claim with a HZ diagnosis
- two outpatient claims with HZ diagnosis which are no more than 30 days apart,
- one outpatient claim with HZ diagnosis with a pharmacy claim for anti-viral treatment within 7 days before or after the claim with HZ diagnosis.

HZ diagnosis codes and medications are shown in Appendix section 14.1.2: Codes and medications for the diagnosis of herpes zoster.

For each of the study objective VE for preventing HZ in participants ≥50 YOA with an AID will be calculated. The definition of this outcome is presented in the table below:

Table 4 Definition of the outcome

	Outcome	*Population Level Summary Measure*
Primary Objective: Primary 1 -6	HZ	VE (%) and its CI (95%) based on the Hazard ratio obtained from Cox regression models (see section 10.1.1.1 for model specification). The risk period will be defined as starting from 30 days after index date and will end at the study end date as defined in section 9.2.2. The VE will be computed from the HR using the following formula: VE (%) = 1 – HR = 1 – $\frac{Hazard\ (Vaccinated)}{Hazard\ (unvaccinated)}$ * 100.
Secondary Objectives Secondary 1-17	HZ	Same as above

9.3.3. Covariates

The list of covariates that will be used for matching followed by a detailed description and sources is presented in the table below.

Any of the following covariates demonstrating imbalance after weighting in matching will be included as a covariate in the Cox proportional hazard models.

Table 5 Definition of the covariates in matching and their associated reference period

Covariate	Collection Timeframe	Definition
Age group	Index date	The age groups will correspond to the following categories in years: "50-54", "55-59", "60-64", "65-69", "70-74", "75-79", "≥80".
Sex: female/male	Index date	Directly retrieved from the database: "Male" / "Female".
Race/ethnicity	Index date	Directly retrieved from the database: "Asian", "Black", "Hispanic", "White", "/Unknown" corresponding to subjects having a missing value for the race.
Use of AID-related medications:	Baseline period	Exposure to the medications, as detailed in Appendix section 14.1.7: Medication categories during the relevant timeframe before the index date. Each participant will have a unique medication category assigned from 1 to 5.

Covariate	Collection Timeframe	Definition
Medical encounters	Baseline period	Number of visits occurring in the 365 days before index date and summarized for each of the following categories: • Inpatient admission • Ambulatory/ER visits • Number of rheumatologist outpatient visits (for SLE, RA, PsA) • Number of Dermatologists outpatient visits (for SLE, PsO) • Number of Neurologist outpatient visits (for MS) The number of visits will be categorized as follows: "0", "1", "2", "3", or "4+".
Logarithm of the healthcare cost:	Baseline period	Logarithm of the Healthcare cost will be assessed during the baseline period and calculated as follows: Log(cost) = LN(Cost + 1) With LN, the Napierian Logarithm function and Cost, the continuous healthcare cost. Notes: • individuals followed up during this period without any claims reported will be considered as having a cost of 0$. • if an RZV-vaccinated individual has a negative estimated cost, his cost will be set to missing, and the cost of all his unvaccinated matched individuals will also be set to missing. In addition, if a control has a negative cost, his cost will be set as missing.
Presence of co-morbidities:	Baseline period	Presence of comorbidities in the 365 days before the index date: kidney disease, cardiovascular disease, pulmonary disease [i.e., chronic obstructive pulmonary disease or chronic bronchitis, asthma], liver disease, diabetes mellitus, other autoimmune diseases, cancer, immunocompromising conditions [i.e., human immunodeficiency virus, cancer, transplant, immune-suppressive medications], SARS-CoV-2 infection/COVID-19 diagnosis with an index date after 2020) in the 365 days prior to the index date. Diagnoses of these comorbidities will be retrieved using ICD10 diagnosis codes. Definitions are presented in section 14.1.6 Diagnosis codes for co-morbidities.

Covariate	Collection Timeframe	Definition
		"Y" for presence of comorbidities reported during the baseline period, "N" otherwise.
Concomitant vaccinations	Baseline period	Influenza vaccine, tetanus, diphtheria and pertussis vaccine, pneumococcal vaccine occurring on the same day of the index date. See appendix section 14.1.4: CPT/HCPCS codes used to identify influenza vaccinations. "Y" for concomitant vaccinations reported during the baseline period, "N" otherwise.
Region of residence within U.S.	Baseline period	As defined by the Census Bureau most recently prior to the index date. The region will be categorized as: "West", "Midwest", "South", "Northeast".
Use of preventative services:	Baseline period	Screening, preventative visits in the 365 days prior to the index date. "Y" for use of preventative services, "N" otherwise.

9.4. Data Sources

This study will be conducted using data from the health care administrative encounters/claims (United enrollees) of the Clinformatics Data Mart (CDM) Optum™. CDM Optum™ is a quarterly updated database for members of a large national managed care company affiliated with Optum™. It includes both commercial and Medicare Advantage health plan enrollees from all 50 states in the United States. The database includes proprietary, deidentified health claims data from a geographically diverse US population (16% West, 20% Midwest, 36% South, and 27% Northeast). In addition to medical claims, pharmacy claims, and outpatient laboratory tests, Optum™ includes data tables related to member inpatient confinements and eligibility data. Optum™ includes data with service dates from 2007 to present and approximately 15 – 18 million annually insured lives. The Optum™ database system contains more than 80 million lives, of which more than 40% have more than 4 years of clinical history. Clinical history data are sourced from the electronic health record (EHR) of the large integrated delivery networks (IDNs), with more than 60% of patients having both outpatient and hospital information. Remaining patients come from large multispecialty physician practices. The age and sex distribution of the beneficiaries of Optum™ is similar to that reported by the US Census Bureau for the commercially insured and the Medicare managed care populations. This study will use IDN lives to provide information on healthcare use from both an inpatient and outpatient perspective.

Providers and pharmacies submit administrative claims for payment. These claims are then verified, adjudicated, adjusted, and de-identified prior to inclusion. The deidentified data are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA). Claims for pharmacy services are typically submitted electronically by the

pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within 6 weeks of dispensing.

Medical claims or encounter data are collected from all available healthcare sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, for example, physicians, use the Health Care Financing Agency (HCFA) 1500 format. Claims for facility services submitted by institutions, for example, hospitals, use the UB-82 or UB-92 format. Medical claims include multiple diagnosis codes recorded with the ICD-10-CM diagnosis codes; procedures recorded with ICD-10-CM procedure codes, Current Procedural Terminology (CPT) codes, or Healthcare Common Procedure Coding System (HCPCS) codes; site-of-service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include any drugs administered in a hospital.

Note: all the claims can be linked to an individual subject, which allow to obtain a complete picture of the healthcare claims submitted for every subject during the enrolment period of their health care insurance.

9.5. Study Size

Descriptive queries in the Optum™ database were performed to identify, obtain, and aggregate the number of ≥50 YOA US patients with AID using the algorithm definition presented in Section 14.1.8. The outputs of these queries have been used to estimate:

- The incidence rate of HZ in the unvaccinated group (**Table 6**)
- The sample size and average follow-up duration of vaccinated group (**Table 7**).

Table 6 Incidence rate of HZ in unvaccinated group by AID, Optum™ database 01/2018-12/2021

AID	Number of participants with HZ in unvaccinated group	Number of participants in unvaccinated group	Person-years (PY)	Incidence rate (1000 PY)
IBD	693	24234	51090	13.56
RA	2781	81639	179079	15.53
SLE	565	15644	33195	17.02
PsO	1533	60533	134443	11.40
PsA	499	14942	34023	14.67
MS	677	20407	48656	13.91

HZ= herpes zoster; SLE: systemic lupus erythematosus; MS: multiple sclerosis; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; PsO: psoriasis; PsA: psoriatric arthritis.

Table 7 Sample size and average follow up time among 2-dose recipients, Optum database 01/2018-12/2021

Year of receipt of dose 2 RZV	Category	SLE	IBD	RA	PsO	PsA	MS
2018	Average FU (years)	2.7	2.5	2.6	2.6	2.5	2.7
	N	269	640	1761	1280	277	299
2019	Average FU (years)	1.9	1.9	2.0	2.0	2.0	1.9
	N	831	1700	4787	3372	772	877
2020	Average FU (years)	1.2	1.3	1.2	1.2	1.2	1.2
	N	935	1906	5113	3996	967	997
2021	Average FU (years)	0.5	0.5	0.5	0.5	0.5	0.5
	N	875	1619	4267	3468	839	948
Overall	Average FU (years)	1.3	1.4	1.4	1.4	1.3	1.4
	N	2910	5865	15928	12086	2845	3121
Average follow-up time (weighted): 1.4 year							

RZV= recombinant zoster vaccine, FU = follow-up, N: number of participants with 2 doses RZV.

A two-sided log rank test with an alpha of 5% was used for the estimation of the sample size needed to achieve the primary VE objective in the different AID cohorts. Assumptions for sample size calculation are:

- Incidence of HZ in the RZV unvaccinated group: 12, 15, 20 /1,000 person-years, in accordance with the preliminary analysis performed in Optum™ database (Table 6**)**
- HR: 0.3, 0.4, 0.5 or 0.6 (corresponding to VE=70%, 60%, 50%, or 40%)
- Ratio of RZV unvaccinated to RZV vaccinated group: 3:1
- Average follow-up period: 1 or 2 years after the second dose of RZV; the estimated average follow-up time in Optum database was 1.4 year **(**Table 7)
- Censoring rate in the RZV vaccinated group: 20%
- Censoring rate in the RZV unvaccinated group: 15%

Results of the sample size calculation are presented in Table 8 (below):

Table 8 Sample size calculation for effectiveness analyses under a range of assumed incidence rates for unvaccinated group and different detectable VE

			Sample Size of RZV vaccinated group			
Power	Follow up time	Incidence rate in RZV unvaccinated group (/1000 person-years)	VE (70%)	VE (60%)	VE (50%)	VE (40%)
90%	1 year	12	1398	2197	3545	6089
		15	1120	1760	2840	4877
		20	841	1323	2134	3666
	2 years	12	765	1203	1941	3333
		15	614	965	1557	2673
		20	462	726	1172	2013
80%	1 year	12	1017	1599	2588	4463
		15	815	1281	2073	3575
		20	612	963	1558	2687
	2 years	12	558	876	1418	2444
		15	447	703	1137	1961
		20	337	529	856	1477

RZV= recombinant zoster vaccine, VE= vaccine effectiveness, % = Percentage.

The number of potential participants who received 2 doses of RZV during the accrual period between 1/2018 to 12/2021 is 5865 for IBD, 2910 for SLE, 15928 for RA, 3121 for MS, 12086 for PsO, 2845 for PsA, respectively (Table 7). This exceeds the required numbers for a power of 80% and detectable VE of 50% (Table 8). This demonstrates that the study is sufficiently powered to assess the primary VE objectives.

10. STATISTICAL ANALYSES

10.1. General Considerations

10.1.1. General Methodology

10.1.1.1. Vaccine Effectiveness

Vaccine effectiveness estimates will be calculated using Cox regression models using the PHREG procedure of SAS v9.4 to assess each of the primary and secondary objectives.

For the primary objectives, the model will be defined as follows:

$H(t) = \exp(\alpha + \beta 1\ (\text{vaccination status}) + \beta 2\ XX1 + \ldots \beta n\ (XX(n-1))$

XX variables : any covariate demonstrating imbalance after weighting

Where:

- H(t) is the hazard function, corresponding to the instantaneous risk of demise at time t, conditional on survival to that time.
- α is the baseline log-hazard, assuming all covariates are as their reference values
- $\beta 1$ to βn are the regression coefficients, corresponding to the log-hazard of experiencing HZ for specific categories of the covariates adjusted on the other covariates.

From this model the Hazard ratio of experiencing HZ in the vaccinated cohort compared to the unvaccinated cohort adjusted on the other covariates will be calculated.

Then, the Hazard ratio of HZ and its confidence limits will be transformed into vaccine effectiveness values as detailed in section 9.3.2.

An example of the code to be used to run the Cox regression modeling shown here:

PROC PHREG DATA=<input data set>;

CLASS <vaccination status> <age category> <sex> <race>

<logarithm healthcare cost >

<medication category> <presence of comorbidities>

<concomitant vaccinations> <number of encounters> <region>

<use of preventive services>

;

model Time*case(0)= <vaccination status> <age category> <sex> <race>

<number of encounters> <logarithm healthcare cost >

<medication category>

<presence of comorbidities>

<concomitant vaccinations>

<number of encounters> <region>

<use of preventive services>

RUN;

With

- case =1 for vaccinated, 0 for unvaccinated,
- Time= 1 for vaccinated and 2 for unvaccinated

Covariate's format defined in section 9.3.3

10.1.1.2. VE (%) Confidence intervals:

VE(%) 95% Confidence intervals will be computed using the following formula:

CI(95%) = 1 – [exp(ln(HR) ± Z x SE)].

Where Z is the Z-score statistics obtained with the Cox Regression model and SE is the standard error.

$$SE = \sqrt{\frac{1}{Expected\ (vaccinated)} + \frac{1}{Expected\ (unvaccinated)}}$$

With, Expected(vaccinated) and Expected(unvaccinated) being the expected HZ rate at time t in the vaccinated and unvaccinated groups, respectively.

10.1.2. Methods to Address Confounding and Effect Modification

The effect of confounding will be addressed using a propensity score matching on all measured confounders.

The study was not powered for running interaction testing, therefore no analyses on effect modifiers will be performed.

10.1.3. Statistical Software

Analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC).

10.2. Statistical Hypotheses

For all objectives, the same hypothesis will be tested using an alpha risk of 5% and two-sided tests.

The null and alternative hypotheses are respectively:

H0: HR = 1 (i.e VE = 0%)

H1: HR ≠ 1 (i.e VE ≠ 0%)

10.3. Descriptive Analyses

The number and characteristics of vaccinated versus unvaccinated participants in each AID cohort will be described and compared. Categorical variables such as gender will be presented as numbers and percentages with p-values for the Pearson χ^2 test or Fisher's exact test, as appropriate. Continuous variables such as the number of encounters will be presented as the mean with standard deviation and/or median with interquartile ranges, with p-values for the two-sample t-test or Wilcoxon rank-sum test, as appropriate.

Absolute standardized differences will be calculated to assess the balance of covariates with a cut-off value of 0.1.

Distribution of time between first dose and second dose for the 2-dose cohort

10.4. Primary Analyses

10.4.1. Main Analytical Approach

For the primary objectives 1-6, the number of incident HZ cases and the number of person-years of follow-up for participants will be assessed for the 2-dose (≥ 28 days apart) RZV cohort and the matched unvaccinated cohort. Overall incidence rates of HZ for the 2-dose (≥28 days apart) RZV vaccinated cohort and the matched unvaccinated cohort will be calculated by dividing the number of HZ cases by the total number of person-years.

The number of person-years will be calculated as the sum of the duration of the risk periods of all participants included in the cohort (Vaccinated or Unvaccinated cohort). (See Table 4 for more information about the definition of the risk periods). Crude VE (%) will be estimated as (1 – [incidence rate of HZ among 2-dose (at least 28 days apart) RZV recipients / incidence rate of HZ among RZV unvaccinated participants]) x 100%.

Adjusted HRs and 95% confidence intervals (CIs) comparing HZ incidence rates in the 2-dose (≥28 days apart) RZV cohort, and the matched unvaccinated cohort will be estimated by Cox proportional hazards regression models. Estimates of VE (%) will be calculated as (1 – adjusted HR) × 100%.

The model will be built in selecting the vaccination status as well as the confounding variables (used for matching) that are minimizing the Bayesian information criteria (BIC).

In addition to that, to adjust for potential residual confounding after matching if some covariates distributions remained unbalanced between the vaccinated and unvaccinated cohorts (SMD > 0.1 or p-value of χ^2 test or Fisher's exact test < 0.1), they will be included in the model, regardless of their impact on the BIC.

10.4.2. Data Handling Convention

Information about Data Handling convention will be defined in the Data Management plan.

10.4.3. Sensitivity Analyses (Amended: 28 February 2024)

A sensitivity analysis will be performed to assess if adding medication category as a covariate after propensity score matching in the Cox proportional hazard models has an impact on the results of the primary analyses (primary objectives 1-6) and subgroup analyses (secondary objective 17 (overall analysis only).

An example of the code to be used to run the Cox regression modeling is shown below:

PROC PHREG DATA=<input data set>;

CLASS <vaccination status> <medication category> ;

MODEL Time*case(0)= <vaccination status> <medication category> ;

RUN;

With

- ***case =1 for vaccinated, 0 for unvaccinated,***
- ***Time= 1 for vaccinated and 2 for unvaccinated***

Covariate's format defined in section 9.3.3

See tables shells in Appendix section 14.1.12

10.5. Secondary Analyses

MAIN ANALYTICAL APPROACH (AMENDED: 28 FEBRUARY 2024)

Secondary objective 1: Analyses for secondary objectives 1 will employ similar methods as for the primary analyses. Analyses for IBD (secondary objective 1) will be stratified by UC and CD.

Secondary objective 2: Analyses for secondary objective 2 will employ similar methods as for the primary analyses. Analyses will be performed in the matched 2-dose cohort of either PsO or PsA (secondary objective 2). Descriptive analyses and Cox proportional hazards regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary objectives 3-9: Analyses for secondary objectives 3-9 will employ similar methods as for the primary analyses and will be conducted among the matched 2-dose cohorts of participants with SLE (secondary objective 3), MS (secondary objective 4), RA (secondary objective 5), IBD (secondary objective 6), PsO (secondary objective 7), PsA (secondary objective 8), either PsO or PsA (secondary objective 9) and their unvaccinated counterparts. Analyses will be stratified by the following variables and related categories:

- Age group: 50-59 years, 60-69 years, 70-79 years, 80+ years
- Gender
- Time since vaccination: 0-<1 year, 1-<2 years, 2-<3 years, 3+ years
- Time interval between two doses (>28 days apart): 29 – 59 days, 60 – 179 days, 180 –<365 days
- Medication category (as described in section 14.1.7) during baseline.

Depending on the sample size in each stratum, some categories may be pooled.

Analyses for IBD (secondary objective 6) will be stratified by UC and CD. Descriptive analyses and Cox proportional hazards regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary objectives 10-16: Analyses for secondary objectives 10-16 will employ similar methods as for the primary analyses and will be conducted among the matched 1-dose cohorts of participants with SLE (secondary objective 10), MS (secondary objective 11), RA (secondary objective 12), IBD (secondary objective 13), PsO (secondary objective 14), PsA (secondary objective 15), and either PsO or PsA (secondary objective 16). Descriptive analyses and Cox proportional hazards regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary objective 17: Analyses for secondary objective 17 will employ similar methods as for the primary analyses and will be conducted among the matched 2-dose cohorts. Descriptive analyses and Cox proportional hazards regression will be conducted and overall estimates ***and stratified by age group, gender, time since vaccination, dose interval between two doses and medication categories*** of VE (%) will be calculated for all selected AIDs as (1 – adjusted HR) × 100.

Note: This study was not powered to effectively interpret the results of secondary analyses. Therefore, for the assessments of the vaccine effectiveness and incidence rates per stratification variable, it may be challenging to precisely estimate the true value of the vaccine effectiveness and HZ incidence rates. Therefore, for these analyses specifically, certain categories (e.g 50-59 y and 60-69 y) will be pooled together. This will add additional statistical power and make the results more interpretable.

10.5.1. Sensitivity analyses

A sensitivity analysis will be conducted excluding the COVID-19 period (Mar 2020 – Dec 2020) in the analysis, to estimate the impact that the pandemic will have on the increase or decrease of the VE among all AIDs cohort (1-dose recipients). In case of significant difference, additional analyses will be carried out by AID condition.

Another sensitivity analysis will be done looking at the VE (%) on participants, who received one dose of RZV and having PsO and PsA combined to estimate the impact of overlaps between PsO and PsA diagnoses.

10.6. Additional/Modified Analyses (Amended: 28 February 2024)

10.6.1. Additional analyses

Additional tables described below will be created to evaluate the distribution of some of the incidence and vaccine effectiveness values generated in the preliminary analyses.

AID diagnosis

Study participants may report more than one AID diagnosis resulting in potential overlap between AIDs. Distribution tables of participants associated with multiple AIDs for 1-dose and 2-dose cohorts will be created to assess the proportion of participants diagnosed with one or more AIDs in the vaccinated and unvaccinated groups. The rationale for this analysis is to check whether there is not a significant rate of participants with overlapping conditions, which would need to be documented as a study limitation in the final report.

Time since vaccination

Baseline characteristics/demographic tables for the 2-dose cohort reporting different lengths of follow-up (0<1 years, 1<2 years, 2<3 years, 3+ years) will be created to check the number of HZ events observed in the different follow-up periods for the analyzed population and to check whether trends are observed in the different follow-up periods for the analyses corresponding to secondary objectives 3-9 and 17. More granular information about length of follow-up may help to explain varying vaccine effectiveness values observed by time since vaccination.

End of follow-up

Distribution tables of participants in the 2-dose cohort whose end of follow-up reason is either disenrollment or study end date will be created to estimate the number of participants that end follow-up for a reason other than study end. If many study participants end follow-up for a reason that is not the study end, it can introduce a selection bias, especially if the reason that a study participant disenrolled is linked to the primary outcome (HZ). This assessment will be done to check whether the number of such participants in the analyzed population who report study end as the reason to end follow-up is similar in the vaccinated and the unvaccinated groups.

Medication class/categories

Distribution tables of medication class (type of medication) within each existing medication category described in Appendix 6 of the Protocol Amendment 2 will be created to assess the distribution of medications class by age and by AID. The purpose of these tables is to identify which medication class is observed in greater frequency by age and by AID. Information about the types of medications in each of the existing medication categories may help to explain when varying vaccine effectiveness values by medication category are observed.

Additional distribution tables of steroids will be created to check the frequency of participants who receive low-dose (< 5mg) versus high-dose (≥5 mg) steroids in the vaccinated and unvaccinated groups. This includes patients with RA, IBD and PsA. This assessment will be done to check the impact of the cut-off assigned to low-dose and high-dose on the analyses of RA, IBD and PsA cohorts since the cut-off, while clinically acceptable, is considered arbitrary. The following generic names for low-dose and high-dose

The denominator in these tables will correspond to the number of subjects for specific medication classes within category. In these tables, we assume 100% for each class (type of medication) across all medication categories. "Missing" will correspond to the use of medication data not found in any of the medication categories.

steroids for RA, IBD and PsA will be considered in the distribution tables:

AID	***Generic names for steroids****
RA	***Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol), prednisolone, prednisone hydrocortisone***
IBD	***Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone budesonide (Entocort/Uceris).***
PsA	***Methylprednisolone (Medrol), prednisolone, prednisone, hydrocortisone (IM/IV), methylprednisolone (Medrol [IM/IV], Solu-Medrol [IM/IV], Depo-Medrol [IM/IV]), prednisolone (IM/IV), triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte) [IM/IV]).***

****Appendix 6 of the Protocol Amendment 2 provides detailed information about the above steroids.***

Comorbidities covariates

Cross tables between age categories and comorbidities (asplenia/hyposplenia, COVID-19, pneumonia due to COVID-19, cardiovascular disease, diabetes mellitus, kidney disease, lymphoma/leukemia, liver disease, pulmonary disease, congenital and other immunodeficiencies), described in Appendix 5 of the Protocol Amendment 2, will be created to estimate the number of study participants by comorbidity and age in the vaccinated and unvaccinated groups. This assessment will be done for all AIDs separately for the 2-dose cohort to check the impact that co-morbidities have on the overall vaccine effectiveness values.

The denominator in these tables will correspond to the number of subjects for each comorbidity (e.g Diabetes mellitus).

10.6.2. Modifications to Subgroup Analyses

This study is not powered for analyses of secondary objectives described in Section 4.2 of the Protocol Amendment 2. For this reason, there may not be sufficient data from the subgroup analyses to allow meaningful interpretation of results. **Statistical and theoretical approaches summarized below will be used to combine the following categories of variables** ***to add additional statistical power and make the results of these analyses more interpretable*****: a*****ge, dose interval between two doses, time since vaccination, and medication category*****:**

10.6.2.1. Age category, dose interval between two doses category, and time since vaccination category

A person-year cut-off value will be used to identify which categories will be combined across the stratification variables (age category, time since vaccination and dose interval) per AID. The cut-off value will be estimated using the following assumptions:

- ***Based on the sample size calculated in Table 9, within less than 200 person-year (PY) we have less than 1/3 chance to find a statistically significance for a true VE of 70% with an incidence of less than 15 per 1000 PY, which would indicate a low precision.***
- ***Based on the sample size calculated in Table 9, within at least 255 PY, for an incidence of at least 12 per 1000PY in the control group, we have not less than 1/3 to find a statistical significance for a true VE of 70%. In other words, for a power of 33%, for sample sizes <255 PY, there is less than one third of chance of proving VE.***

Based on the above, we will use 255 PY as the threshold for the combined/pooled analysis of the following variables: age category, dose interval between two doses category, and time since vaccination. The details of the numeric results for the logrank test are as follows

Table 9 Number of PY needed to observe a true VE of 70% with a statistical power of 30% for incidence rate of 12 and 15 per 1000 PY

Solve For: Sample Size
Alternative Hypothesis: Two-Sided

Power	N1	N2	N	Haz Ratio HR	Ctrl Haz Rate h1	Trt Haz Rate h2	Acc-rual Pat'n	Acc-rual Time/ Total Time	Ctrl Loss	Trt Loss	Ctrl to Trt	Trt to Ctrl	Alpha	Beta
0,33342	763	255	1018	0,3	0,012	0,0036	Equal	0 / 1	0,15	0,2	0	0	0,05	0,66658
0,33343	611	204	815	0,3	0,015	0,0045	Equal	0 / 1	0,15	0,2	0	0	0,05	0,66657

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1|N2|N	The sample sizes of the control group, treatment group, and both groups, respectively.
HR	Hazard Ratio. The treatment group's hazard rate divided by the control group's hazard rate.
Hazard Rate	The instantaneous failure rate. Its scale is events per time period.
Accrual Time	The number of time periods (years or months) during which accrual takes place.
Total Time	The total number of time periods in the study. Follow-up time = (Total Time) - (Accrual Time).
Ctrl Loss	The proportion of the control group that is lost (drop out) during a single time period (year or month).
Trt Loss	The proportion of the treatment group that is lost (drop out) during a single time period (year or month).
Ctrl to Trt	Drop In. The proportion of the control group that switch to a group with a hazard rate equal to the treatment group.
Trt to Ctrl	Noncompliance. The proportion of the treatment group that switch to a group with a hazard rate equal to the control group.
Alpha	The probability of rejecting a true null hypothesis.
Beta	The probability of failing to reject the null hypothesis when the alternative hypothesis is true.

10.6.2.2. New Combination of Medication Category

Medication categories will be recombined using the existing medication categories described in Appendix 6 of the Protocol Amendment 2. This theoretical approach to recombining the existing medication categories will be based on the systemic action of the medications and will apply to the subgroup analyses (secondary objectives 3-9, 17). The approach will be used to make the results of these subgroup analyses more interpretable as low number of participants in these analyzed populations are expected across certain types of medications.

The new combination of these medications is described below:

- ***Category 1: non-immunosuppressive therapy (e.g., no treatment, NSAIDs, low dose (<5mg) steroids, anti-malarial, topical medications (corticosteroids, non-pharmacologic therapies).***
- ***Category 2: mild-moderate immunosuppressive therapy (e.g., conventional DMARDs, aminosalicylate, psoralen and PUVA, PDT, NB-UVB, UV phototherapy, excimer laser).***
- ***Category 3+4 (combined): highly immunosuppressive (e.g., biologics, high dose (≥5 mg) steroids, thiopurines, SP1 receptor modulators, intralesional/IM corticosteroids).***
- ***Category 5: JAK inhibitors, DMARDs (synthetic and targeted synthetic).***

Note: It is possible that for some categories (e.g Category 5), due to a low number of patient-years, the results may be difficult to interpret.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The Project Analyst will follow the appropriate GSK written standard to ensure that the study results are complete, internally consistent, and accurately reflect the source.

12. LIMITATIONS OF THE RESEARCH METHODS

Various limitations must be considered in a retrospective matched cohort study design, including confounding, bias, and misclassification.

1. Definition of the cohorts: Though the majority of the algorithms that will be used to identify participants with AIDs have demonstrated a good positive predictive value (PPV) (refer to section 14.1.8)[Zhang, 2012; Baxter, 2018], some misclassification is expected using the validated AID-specific algorithms given the difficulty in diagnosing some AIDs (e.g., SLE, MS). In addition, some participants with well controlled AIDs may not be captured, with algorithms biasing towards a higher risk group. To improve confidence in the definitions, similar algorithms that are being used in studies that are targeting AID populations (E-Z-041, E-Z-044) will be used. These studies rely on specialists (e.g., neurologists, rheumatologists, dermatologists) consultation to provide expert opinion on the definitions of the AIDs.

2. Outcome misclassification: Some participants that are reported as having a HZ occurrence may not have an accurate diagnosis of HZ occurrence, which may result in a possible underestimation of VE. However, this is expected to be minimal as the detection of HZ using an ICD-10 diagnosis code for HZ (B02.xx) from hospital, 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 has been used to evaluate the HZ occurrence based on the available literature [Izurieta, 2021]. Systematic differences in HZ misclassification between vaccinated and unvaccinated are not expected.

3 Exposure misclassification: It is possible though unlikely that some participants who are reportedly unvaccinated may have received RZV prior to entering the dataset, leading to an underestimation of VE. Receipt of RZV dose 1 or 2 will be identified from administrative and claims data by means of Current Procedural Terminology (CPT) code 90750 and National Drug Code (NDC) codes 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11 to minimize the risk of exposure misclassification. Additional codes for identification of RZV vaccination may be considered if relevant codes become available in the future.

4 Secular or seasonal trends in RZV use: RZV vaccination patterns may have changed during the COVID-19 pandemic. Receipt of RZV will be accurately captured in the Optum™ database, including dates of administration such that receipt of dose 1 and dose 2 are correctly ascertained. In addition, the study methods will ensure similar distributions by calendar year and season among vaccinated and unvaccinated participants and sensitivity analyses will be performed to assess if the occurrence of the COVID-19 pandemic caused the secular or seasonal trends in RZV use to change. This will be further discussed in the statistical analysis plan. Although in this study appropriate methodologies will be applied to statistically adjust for differences between RZV exposed participants versus RZV unexposed participants, not all potential confounders may be available in the database, and residual confounding may still be present.

5 Secular trends in medication use for AIDs: Newly approved therapies may be available for AIDs and may be used primarily for those with more severe disease initially. After a few years on the market, these therapies may be used in less severe disease or disease subsets. These trends may impact differences in populations and differences in the classification of disease occurrence. The study methods will ensure similar distributions by calendar year and season among vaccinated and unvaccinated participants.

6 Unmeasured confounding: Disease severity and disease duration may be associated with receipt of the vaccine and/or subsequent risk of HZ. However, these factors are challenging to measure in administrative claims data or may not be measured. This study assesses proxies for disease activity (such as medication use and healthcare use) to address this. Confounding by indication is another potential limitation. Participants may receive RZV before initiating immunosuppressive (or more highly immunosuppressive) treatment in order to protect them from that planned treatment. This would bias the VE estimates. To address this bias, participants receiving JAK inhibitor, for example, one month after index date in the JAK inhibitor medication category will be included to account for this. This will be addressed by matching on

condition (SLE, MS, IBD [UC, CD], RA, PsO, PsA), age, and AID-related medication category, which may impact the development of the outcome and likelihood of RZV vaccination.

7 Healthy-user bias: Participants receiving RZV, or other vaccines may be healthier or have other behaviors leading to improved health compared to their unvaccinated matches. This bias may lead vaccinated participants to have lower rates of HZ in the study. The study will capture and adjust for variables related to healthy users, such as use of other vaccinations, to minimize this bias.

8 Duplicate health care claims: A beneficiary of Optum™ may be a beneficiary of more than one insurance product at a time or switch to a new insurance product before departing from another, resulting in duplicate health care claims and multiple lines per participant. Also, when time periods overlap, a clean link between claims and the eligibility table may be absent because multiple rows may be returned in a match. While there is a risk of this happening, the number of multiple health care claims and their impact is expected to be negligible.

9 Limited follow-up period: While the ability to assess durability of VE at extended time points is limited, this is an open cohort study that will allow vaccinated and unvaccinated participants to come in late or die during the follow-up period; this is not expected to impact the overall incidence rate of HZ. In addition, participants entering the cohort in early 2018 could have 4 years of follow-up.

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14. APPENDIX

14.1.1. Codes to identify auto-immune diagnoses

The following ICD-10 codes will be used to define the auto-immune population:

ICD-10	AID	Description
M32.X	SLE	Systemic lupus erythematosus
G35.X	MS	Multiple sclerosis
M05.X	RA	Rheumatoid arthritis with rheumatoid factor
M06.X	RA	Other rheumatoid arthritis
K50.X	IBD	Crohn's disease
K51.X	IBD	Ulcerative colitis
L40.X	PsO	Psoriasis
L40.5	PsA	Psoriatic arthritis

Codes will be updated as needed if additional codes are identified.

14.1.2. Codes and medications for the diagnosis of herpes zoster

	Diagnosis code or medication generic names
Codes/medications for herpes zoster diagnosis	
Herpes Zoster	B02.xx
Medications to treat herpes zoster	Acyclovir, valacyclovir, or famciclovir

Codes will be updated as needed if additional codes are identified.

14.1.3. Codes to identify the use of zoster vaccine

The following Current Procedural Terminology (CPT) code will be used to retrieve Shingrix vaccinations:

Code	Description	Vaccine type
90750	Zoster (shingles) vaccine (HZV), recombinant, subunit, adjuvanted, for intramuscular use	Shingrix

Codes will be updated as needed if additional codes are identified.

The following National Drug Codes (NDCs) codes will be used to retrieve Shingrix vaccinations:

Code	Description	Vaccine type
58160-082-311	Zoster vaccine recombinant, adjuvanted	Shingrix
58160-081-912	Zoster vaccine recombinant, adjuvanted	Shingrix
50090-514-700	Zoster vaccine recombinant, adjuvanted	Shingrix
58160-082-801	Varicella-zoster ge vac,2 of 2	Shingrix
50090-337-200	Zoster vaccine recombinant, adjuvanted	Shingrix
58160-082-803	Varicella-zoster ge vac,2 of 2	Shingrix

Codes will be updated as needed if additional codes are identified.

14.1.4. CPT/HCPCS codes used to identify influenza vaccinations

CPT/HCPCS Code	Description
90630	Vaccine for influenza for injection into skin, quadrivalent, preservative free
90653	Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted
90654	Vaccine for influenza injection into skin, trivalent, preservative free
90656	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free
90658	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent
90661	Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, cell culture-based
90662	Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content
90673	Vaccine for influenza administered into muscle, preservative and antibiotic free, trivalent, recombinant DNA-derived
90674	Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based
90682	Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use)
90686	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free
90688	Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent

CPT/HCPCS Code	Description
90756	Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free, 0.5mL dosage, for intramuscular use)
G0008	Administration of influenza virus vaccine
Q2034	Influenza virus vaccine, split virus, for intramuscular use (agriflu)
Q2035	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria)
Q2036	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval)
Q2037	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin)
Q2038	Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluzone)
Q2039	Influenza virus vaccine, not otherwise specified

14.1.5. NDC Codes Used to identify herpes zoster antivirals

Drug	NDCs
Acyclovir	00093363020, 00093894001, 00093894005, 00093894019, 00093894093, 00093894301, 00093894305, 00093894319, 00093894393, 00093894701, 00093894705, 00093894719, 00093894793, 00168082515, 00168082530, 00172426660, 00172426670, 00172426760, 00172426770, 00172426860, 00172426870, 00182266600, 00182266689, 00182266700, 00182266789, 00182820000, 00182820089, 00228260511, 00228260550, 00228260611, 00228260650, 00228260711, 00228260750, 00364269201, 00378025301, 00378025305, 00378030201, 00378146801, 00378220001, 00378220005, 00378870006, 00378870049, 00378871273, 00395809719, 00395809762, 00440103030, 00440103130, 00440603001, 00440603005, 00440603030, 00440603060, 00440603081, 00440603101, 00440603105, 00440603125, 00440603130, 00440603181, 00440603301, 00440603305, 00440603310, 00440603320, 00440603381, 00440703005, 00440703025, 00440703030, 00440703050, 00440703060, 00440703081, 00440703083, 00440703085, 00440703089, 00440703125, 00440703130, 00440703181, 00440703185, 00440703189, 00440703310, 00440703320, 00440703350, 00440703381, 00440703385, 00440703389, 00472008216, 00591033501, 00591033505, 00591033601, 00591033605, 00591115930, 00591269201, 00591269205, 00713063015, 00713063031, 00904578961, 00904579061, 00904579961, 00904612161, 10544002640, 10544002725, 10544003925, 10544003940, 10544010125, 10544010225, 10544010240, 10544010340, 10544014625, 10544014630, 10544015124, 10544015130, 10544015160, 10544020435, 10544020440, 10544020450, 10544094214, 10544094260, 12634069771, 13411018201, 13411018203, 13411018206, 13411018209, 13411018210, 13411018301, 13411018303, 13411018306, 13411018309, 13411018310, 13668051501, 13668051502, 15455950001, 15455950002, 15455950003, 15455950005, 15455950008, 15455950009, 16590000325, 16590000330, 16590000335, 16590000350, 16590000360, 16590037020, 16590037030, 16590037040, 16590037090, 16714066801, 16714066802, 16714088501, 16714088502, 17236085301, 17236085401, 17856008205, 21695000925, 21695000930, 21695001015, 21695001020, 21695001021, 21695001025, 21695001030, 21695001060, 21695001090, 21695001121, 21695001125, 21695001130, 21695001135, 21695001140, 23155014601, 23155022701, 23155022705, 23155022801, 23155022805, 23155022901, 23155022905, 23490501101, 23490501201, 23490501202, 23490501203, 23490501204, 23490501301, 23490501302, 23490501303, 23490501304, 23490501501, 23490501502, 23490501503, 23490501504, 23490501505, 23490501508, 31722077701,

Drug	NDCs
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Drug	NDCs
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Acyclovir Susp 200 Mg/5Ml	50962045360, 60346085434, 60346085471
Acyclovir, Micronized	28595059277
Acyclovir/Hydrocortisone	00037050105, 00187510401
Acyclovir/Lidocaine Hcl	28595097362
Famciclovir	00054019613, 00054019713, 00054019813, 00093811756, 00093811856, 00093811956, 00378449093, 00378449193, 00378449293, 00440750002, 00440750010, 00440750121, 00440750160, 00440750202, 00440753121, 00591327130, 00591327230, 00591327330, 00781562031, 00781562131, 00781562231, 16714030001, 16714030401, 16714030501, 16714061401, 16714061501, 16714061601, 31722070630, 31722070730, 31722070830, 33342002407, 33342002507, 33342002607, 42291027530, 42291027630, 42291027730, 50090306600, 50090333700, 50268030511, 50268030513, 50268030611, 50268030613, 50268030711, 50268030713, 52959094604, 52959094621, 54569604600, 54569604601, 54868590500, 54868590501, 54868590503, 54868590504, 55289016803, 59762270001, 59762270102, 59762270301, 60429035930, 60429036030, 60429036130, 60505324503, 60505324603, 60505324703, 60687010325, 60687010395, 63187091921, 63187092021, 63187099821, 63187099830, 65862046530, 65862046630, 65862046730, 69097026902, 69097027102, 69097027202, 00078036615, 00078036715, 00078036815, 00078036861, 00078036864, 00440752802, 49999030821, 49999030830, 54348062310, 54569453300, 54569453400, 54569453401, 54569466000, 54868388200, 54868388201, 54868396900, 54868396901, 54868400900, 54868400901, 68115040730, 68115040760, 68115040830, 68115040860, 68115040921, 68115040930, 68115040960
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Drug	NDCs
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14.1.6. Diagnosis codes for co-morbidities

Co-morbidities	**ICD-10 codes**
COVID-19 virus identified (On February 11, 2020, the WHO announced the official name of COVID-19)	U07.1
Pneumonia due to coronavirus disease 2019	J12.82
Kidney disease	I12.0, I12.9, I13.1*, N03.2-N03.7, N05.2-N05.7, N18.*, N19.*, N25.0, Z49.0*-Z49.2*, Z94.0, Z99.2
Cardiovascular disease	I21. *, I22.*, I25*, 125.2, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.*, I50.*, P29.0
Pulmonary disease	I27.8*, I27.9, J40.* - J47.*, J60.* - J67.*, J68.4, J70.1, J70.3
Liver disease	B18. *, I85.0*, I86.4, I98.2, K70.0, K70.1* - K70.4*, K70.9, K71.1*, K71.3, K71.4, K71.5*, K71.7, K72.1*, K72.9*, K73. *, K74. *, K76.0, K76.2-K76.-7, K76.-8*, K76.9, Z94.4
Diabetes mellitus	E10. * - E14.*
Lymphoma/leukemia	C81. *C86., C88. *, C90. *-C96. *, D45, D46*
Congenital and other immunodeficiencies	D61.09, D61.3, D61.82, D61.9, D70.0, D71, D80.0, D80.1, D80.5, D80.8, D81.*, D82.*, D83.*, D84.0, D84.1, D84.89, D84.,9, D89.81, D89.82, D89.9, E31.0, E70.330, G11.3, Q82.4, Q89.0*
Asplenia/hyposplenia	D57.00, D57.01, D57.02, D57.1, D57.2, D57.20, D57.21, D57.211, D57.212, D57.219, D57.4, D57.40, D57.41, D57.411, D57.412, D57.419, D57.8, D57.80, D57.81, D57.811, D57.812, D57.819, D73.0, Q89.01, Q89.09, Z90.81

14.1.7. Medication categories

Table 10 RA medication category

Category 1	No treatment
	NSAID: ibuprofen (Motrin, Advil), naproxen (Aleve, Anaprox, Mediproxen), indomethacin (Indocin, Tivorbex), meloxicam (Vivlodex, Mobic, Comfort Pac Meloxicam), celecoxib (Celebrex), nabumetone (Relafen), etodolac (Lodine), diclofenac (Xrylix, Voltaren, Solaraze, Flector, Zorvolex, Zipsor, Cambia), sulindac (Clinoril), salsalate (Disalcid), ketorolac (Toradol, Acular, ReadySharp, Ketorolac Kit)
	Low dose steroids (all <5 mg prednisone or equivalent): Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol), prednisolone, prednisone
Category 2	Conventional DMARDs: hydroxychloroquine (Plaquenil), leflunomide (Arava), Methotraxate (MTX) (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo), sulfasalazine (Azulfidine), minocycline (Minocin), azathioprine (Imuran, Azasan)
Category 3	Biologics: abatacept (Orencia), rituximab (Rituxan), rituximab-abbs (Truxima), rituximab-pvvr (Ruxience), rituximab-arrx (Riabni), tocilizumab (Actemra), sarilumab (Kevzara), adalimumab (Humira), etanercept (Enbrel), etanercept-szzs (Erelzi), etanercept-ykro (Eticovo), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), certolizumab pegol (Cimzia), golimumab (Simponi), anakinra (Kineret)
Category 4	High dose systemic steroids (any ≥5 mg prednisone or equivalent): hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone
Category 5	JAK inhibitors: tofacitinib (Xeljanz, Xeljanz XR), baricitinib (Olumiant), upadicitinib (Rinvoq)

DMARDs = disease-modifying antirheumatic drugs; JAK = Janus Kinase; MTX = methotrexate; NSAID = Nonsteroidal Anti-Inflammatory Drug; RA = Rheumatoid arthritis

Medication category for RA will be determined by the highest category of medication prescribed during the search periods specified below:

- Rituximab (Rituxan) or rituximab-abbs/rituximab-pvvr (Truxima): 6 months before index date1
- Biologics: 3 months before index date2
- JAK inhibitors: 3 months before index date to 1 month after index date3
- Nonsteroidal anti-inflammatory drugs (NSAIDs), 5-aminosalicylate (5-ASA), aminosalicylate, sulfasalazine, thiopurines, steroids, and conventional DMARDs: Medication prescribed/refilled within 6 months prior to index date4.
- Any medication that is active at the index date will be considered regardless of when it was prescribed/refilled.

[1] Rituximab (Category 3 biologics medication) is typically dosed every 6 months, so the search period for rituximab is 6 months before the index date.

[2] Some biologics are given as far apart as every ~8 weeks, so the search period for biologics is 3 months before the index date.

[3] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.

[4] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply.

Source: Treatment category from Epi-Z-044

Table 11 IBD medication category

Category 1	No treatment
Category 2	Aminosalicylate (5-ASA): aminosalicylate (5-ASA), sulfasalazine (Azulfidine), olsalazine (Dipentum), mesalamine (Canasa, Asacol, mesalamine (Canasa, Asacol, Pentasa, Apriso, Lialda, Rowasa, Delzicol), balsalazide (Giazo, Colazal)
	Low dose steroids (all <5 mg or equivalent): Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone budesonide (Entocort/Uceris)
Category 3	Biologics: infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), adalimumab (Humira), adalimumab-adaz (Hyrimoz), adalimumab-adbm (Cyltezo), adalimumab-atto (Amjevita), adalimumab-bwwd (Hadlima), vedolizumab (Entyvio), ustekinumab (Stelara), golimumab (Simponi), certolizumab (Cimzia), natalizumab (Tysabri)
	Conventional DMARD: MTX (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo)
	Thiopurines: azathioprine (Imuran, Azasan), mercaptopurine (Perinethol), and thioguanine (6-TG, Tabloid or Lanvis)
Category 4	High dose systemic steroids (any ≥5 mg prednisone or equivalent): hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Dep-Medrol), prednisolone, prednisone
Category 5	JAK inhibitors: tofacitinib (Xeljanz), baricitinib (Olumiant) Cyclosporine (Gengraf, Neoral, Sandimmune)

DMARD: = Disease-Modifying Antirheumatic Drugs; IBD = Inflammatory bowel disease; JAK = Janus kinase; MTX = methotrexate

Medication category for IBD will be determined by the highest category of medication prescribed during the search periods specified below:

- Rituximab (Rituxan) or rituximab-abbs/rituximab-pvvr (Truxima): 6 months before index date[1]
- Biologics: 3 months before index date[2]
- JAK inhibitors: 3 months before index date to 1 month after index date[3]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), 5-aminosalicylate (5-ASA), aminosalicylate, sulfasalazine, thiopurines, steroids, and conventional DMARDs: Medication prescribed/refilled within 6 months prior to index date[4]
- Any medication that is active at the index date will be considered regardless of when it was prescribed/refilled.

[1] Rituximab is typically dosed every 6 months, so the search period for rituximab is 6 months before the index date.

[2] Some biologics are given as far apart as every ~8 weeks, so the search period for biologics is 3 months before the index date.

[3] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.

[4] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply.

Source: Treatment category from Epi-Z-044

Table 12 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. NDC codes and HCPCS/J-codes to be determined at a later date.

SQ = subcutaneous, IV = intravenous, PO = by mouth

Source: E-Z-041

Table 13 MS Immunosuppressive/immunomodulatory therapies (i.e., DMT)

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
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
	Intravenous IgG (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 (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.

SQ = subcutaneous, IV = intravenous, IM = intramuscular, PO = by mouth

Source: E-Z-041

Table 14 PsO Immunosuppressive/immunomodulatory therapies

Category 1 (least severe)	Topical medications (topical corticosteroids, calcineurin inhibitors, vitamin D analogues, tazarotene, salicylic acid, anthralin [dithranol], coal tar/liquor carbonis detergens [LCD], roflumilast [Zoryve], tapinarof [Vtama]), or no treatment from Category 2 to Category 5
Category 2	Psoralen and ultraviolet A (PUVA), photodynamic therapy (PDT), narrowband ultraviolet B (NB-UVB) (with or without tar), UV phototherapy (with or without tar), and excimer laser.
Category 3	Conventional synthetic DMARDs: Traditional DMARD: methotrexate (MTX) (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo), cyclosporine, acitretin, apremilast (Otezla), azathioprine (Imuran, Azasan), hydroxyurea, mycophenolate mofetil (MMF), tacrolimus, leflunomide (Arava), thioguanine (6-TG, Tabloid, Lanvis) Intralesional/IM corticosteroids: triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte)
Category 4	Biologic DMARDs[1]: TNF-α inhibitors: etanercept (Enbrel), infliximab and biosimilars (Avsola, Inflectra, Remicade, Renflexis), adalimumab and biosimilars (Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Humira, Hyrimoz, Idacio, Yusimry), certolizumab pegol (Cimzia), golimumab (Simponi, Simponi Aria) IL-12/IL-23 inhibitors: ustekinumab (Stelara) IL-17 inhibitors: secukinumab (Cosentyx), ixekizumab (Taltz), brodalumab (Siliq), bimekizumab (Bimzelx) IL-23 inhibitors: guselkumab (Tremfya), tildrakizumab-asmn (Ilumya), risankizumab-rzaa (Skyrizi)
Category 5 (most severe)	Targeted synthetic DMARDs: JAK inhibitors: tofacitinib (Xeljanz, Xeljanz XR), upadacitinib (Rinvoq), deucravacitinib (Sotyktu)

[1] Biologics are administered as either SC or IV. Both SC or IV forms are available for golimumab (SC [Simponi] or IV [Simponi Aria]) and ustekinumab (Stelara). Infliximab and biosimilars are administered as IV only. All others are administered as SC.

IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous

Medication category for PsO will be determined by the highest category of medication prescribed during the search periods specified below:

- Biologic disease-modifying anti-rheumatic drugs (DMARDs), intralesional/Intramuscular corticosteroids, psoralen and ultraviolet A (PUVA), photodynamic therapy (PDT), narrowband ultraviolet B (NB-UVB) (with or without tar), UV phototherapy (with or without tar), and excimer laser: 3 months before index date[1]
- Targeted synthetic DMARDs (JAK inhibitors): 3 months before index date to 1 month after index date[2]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), topical medications, steroids, and conventional synthetic DMARDs: Medication prescribed/refilled within 6 months prior to index date[3]

[1] Some biologics are given as far apart as approximately every 8 weeks, thus the search period for biologics is 3 months before the index date.

[2] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.

[3] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply. Medications prescribed/refilled within 6 months prior to the index date will be searched to identify those medications.

Individuals who meet the criteria for both PsO and PsA will be included in both the PsO and PsA cohorts. The most advanced medication category used for treatment of either condition will be used for both cohorts. For example, if an individual identified as having both PsO and PsA is using a Category 2 medication for PsO (e.g., UV phototherapy) and a Category 4 medication for PsA (e.g., Orencia), then Category 4 will be used for both PsO and PsA analyses.

Table 15 PsA Immunosuppressive/immunomodulatory therapies

Category 1 (least severe)	Non-pharmacologic therapies, or no treatment from Category 2 to Category 5
Category 2	Nonsteroidal anti-inflammatory drugs (NSAIDs): ibuprofen (Motrin, Advil), naproxen (Aleve, Anaprox, Mediproxen), indomethacin (Indocin, Tivorbex), meloxicam (Vivlodex, Mobic, Comfort Pac Meloxicam), celecoxib (Celebrex), nabumetone (Relafen), etodolac (Lodine), diclofenac (Xrylix, Voltaren, Solaraze, Flector, Zorvolex, Zipsor, Cambia), sulindac (Clinoril), salsalate (Disalcid), ketorolac (Toradol, Acular) Low dose steroids (PO): methylprednisolone (Medrol), prednisolone, prednisone (<5mg prednisone or equivalent)
Category 3	Conventional synthetic DMARDs: Oral small molecules (OSMs): MTX (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo), sulfasalazine (Azulfidine), leflunomide (Arava), apremilast (Otezla) High-dose systemic steroids: hydrocortisone (IM/IV), methylprednisolone (Medrol [IM/IV], Solu-Medrol [IM/IV], Depo-Medrol [IM/IV]), prednisolone (IM/IV), triamcinolone (Kenalog, Aristocort-Forte, Aristospan, Cinacort Span, Triamcort, Triam-Forte) [IM/IV]), prednisone (PO) (≥5 mg prednisone or equivalent)
Category 41	Biologic DMARDs2: TNF-α inhibitors: etanercept (Enbrel), infliximab and biosimilars (Avsola, Inflectra, Remicade, Renflexis), adalimumab and biosimilars (Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Humira, Hyrimoz, Idacio, Yusimry), certolizumab pegol (Cimzia), golimumab (Simponi, Simponi Aria) IL-12/IL-23 inhibitors: ustekinumab (Stelara) IL-17 inhibitors: secukinumab (Cosentyx), ixekizumab (Taltz) CTLA4-immunoglobulin: abatacept (Orencia) IL-23 inhibitors: guselkumab (Tremfya), risankizumab-rzaa (Skyrizi) and biosimilars (risankizumab-AbbVie, risankizumab-rzza)
Category 51	Targeted synthetic DMARDs: JAK inhibitors: tofacitinib (Xeljanz, Xeljanz XR), upadacitinib (Rinvoq) and biosimilars (upadacitinib-AbbVie)

1 For safety objectives, Categories 4 and 5 will be combined into Category 4, indicating most severe disease, as use of JAK inhibitors (Category 5) is not indicative of more severe disease than use of Category 4 medications. For VE objectives, Categories 1 – 5 will be used as listed, as the risk of HZ is greater in those treated with JAK inhibitors compared to the risk in those treated with medications in Category 4.
2 Biologics are administered either as SC or IV. Both SC or IV forms are available for abatacept (Orencia), ustekinumab (Stelara) and golimumab (SC [Simponi] or IV [Simponi Aria]). Infliximab and biosimilars are administered as IV only. All others are administered as SC.
IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous

Medication category for PsA will be determined by the highest category of medication prescribed during the search periods specified below:

- Biologic disease-modifying anti-rheumatic drugs (DMARDs), intralesional/Intramuscular corticosteroids, psoralen and ultraviolet A (PUVA), photodynamic therapy (PDT), narrowband ultraviolet B (NB-UVB) (with or without tar), UV phototherapy (with or without tar), and excimer laser: 3 months before index date[1]
- Targeted synthetic DMARDs (JAK inhibitors): 3 months before index date to 1 month after index date[2]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), topical medications, steroids, and conventional synthetic DMARDs: Medication prescribed/refilled within 6 months prior to index date[3]

[1] Some biologics are given as far apart as approximately every 8 weeks, thus the search period for biologics is 3 months before the index date.
[2] The search period for JAK inhibitors (a type of biologic) is extended to 1 month after the index date; because JAK inhibitors are associated with a significantly increased risk of HZ, providers may administer RZV prior to initiating treatment with a JAK inhibitor.
[3] While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply. To ensure identification of prescriptions covering the index date, medications prescribed/refilled within 6 months prior to the index date will be searched to identify those medications with a duration covering the index date.

Individuals who meet the criteria for both PsO and PsA will be included in both the PsO and PsA cohorts. The most advanced medication category used for treatment of either condition will be used for both cohorts. For example, if an individual identified as having both PsO and PsA is using a Category 2 medication for PsO (e.g., UV phototherapy) and a Category 4 medication for PsA (e.g., Orencia), then Category 4 will be used for both PsO and PsA analyses.

14.1.8. Algorithm to define AID conditions

SLE:

≥1 inpatient claim with a diagnosis code for SLE (ICD-10 M32.1, M32.8, M32.9) OR ≥2 physician outpatient claims with SLE diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date OR >1 rheumatologist visit/encounter/claim for SLE.

- The algorithm that includes ≥1 rheumatologist visit/encounter/claim has demonstrated a PPV of 95% and sensitivity of 83% [Hanly, 2014].

MS:

≥3 of any combination of inpatient diagnoses (any position) of MS (ICD-10 G35), ambulatory visit (AV) diagnoses of MS, emergency department (ED) diagnoses of MS, or MS-specific disease-modifying therapy (DMT) fills/infusions (refer to section 14.1.7 for medication categories) during the 365-day baseline period. At least one of these must be an inpatient, AV, or ED diagnosis of MS.

- This algorithm has demonstrated a PPV of 95-97% and sensitivity of 85-93% [Wallin, 2019].

IBD (CD and UC):

≥1 inpatient claim with a diagnosis code for CD (ICD-10 K50) and UC (ICD-10 K51) OR ≥2 physician outpatient claims with CD (ICD-10 K50) and UC (ICD-10 K51) diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 physician outpatient claims with CD and UC diagnoses during an office visit and/or emergency visit has been used extensively in the literature though no PPV has been reported [Weng, 2007].
- Algorithms that have been published to classify mutually exclusive groups of UC and CD participants will be considered to differentiate between the two conditions [Pilon, 2020]. Participants will be identified as having UC if (i) they had more UC-related patient admissions than CD-related inpatient admissions; (ii) they had an equal number of UC- and CD-related inpatient admissions but more UC-related outpatient visits than CD-related outpatient visits; (iii) they had an equal number of UC- and CD-related inpatient admissions and outpatient visits. [Bernstein, 1999; Shaw, 2011].

RA:

≥1 inpatient claim with a diagnosis code for RA (ICD-10 M05, M06) OR ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit that were at least 30 days apart in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥2 physician outpatient claims with RA diagnosis during an office visit and/or emergency visit has been used extensively in the literature though no PPV has been reported [MacLean, 2000].

PsO:

≥1 inpatient claim with a diagnosis code for PsO (ICD-10 L40) OR ≥2 physician outpatient claims with PsO diagnosis during an office visit and/or emergency visit that were at least 30 days apart OR ≥1 dermatologist visit/encounter/claim for PsO in the 365-day baseline period prior to the index date.

- The algorithm that includes ≥1 dermatologist visit/encounter/claim has demonstrated a PPV of 90% and sensitivity of 88% [Asgari, 2013]. Based on the rapid data queries

(RDQs), 9% of participants diagnosed with PsO had PsA. In practice, rheumatologists tend to assess PsO and PsA by criteria which are unique to each. Then, they assess the 2 AIDs together in patients with symptoms of both. Sensitivity analyses will be performed on participants who have either PsO or PSA, participants who have PsO only, participants who have PsA only, and participants who have both PsO and PsA to address the potential overlap between PsO and PsA.

PsA:

≥1 inpatient claim with a diagnosis code for PsA (ICD-10 L40.5) OR ≥2 physician outpatient claims with PsA diagnosis during an office visit and/or emergency visit that were at least 30 days apart OR ≥2 rheumatologist visit/encounter/claim for PsA OR ≥1 rheumatologist diagnosis code for PsA together with ≥1 dermatologist diagnosis code for PsA in the 365-day baseline period prior to the index date.

The algorithm that includes ≥2 rheumatologist visit/encounter/claim for PsA has demonstrated a PPV of 81% and sensitivity of 77% [Asgari, 2013]. These algorithms assume PsA without PsO. Based on the RDQs, 37% of participants diagnosed with PsA had PsO.

14.1.9. Derivation of the date of death

In *Optum* database, a dataset including the year and month of death is provided, therefore we will use this file to define the potential death date of a subject. The day of death will be derived by the day of the last claim with a selected ICD-10 death code if this code is occurring during the month and year of death reported in the death dataset. Otherwise, if the month of death is not consistent or there is not death claim, the day of death will be assigned as the 15th day of the month provided by the death dataset, or the index date, whichever comes last.

In case ICD10 death codes are reported in the database but a death date is not present in the death file, and that there are no other claim occurring in the database more than 7 days after these death codes, the date of death will be considered to be the maximum date between the date of the last claim with a selected death code and the index date.

The ICD-10 codes related to a death event are listed in the table below:

Table 16 ICD10 code list related to Death diagnoses

ICD-10	Description
R99	Ill-defined and unknown cause of mortality
R96	Other sudden death, cause unknown
R96.0	Instantaneous death
R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained
I46.1	Sudden cardiac death, so described
S06347	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06337S	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06347D	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S069X8	Unspecified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S064X7D	Epidural hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06328S	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S066X8A	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S065X8S	Traumatic subdural hemorrhage with loss of consciousness of any duration with death due to other cause before regaining consciousness, sequela
S06347S	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S061X8S	Traumatic cerebral edema with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S060X7S	Concussion with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S065X7A	Traumatic subdural hemorrhage with loss of consciousness of any duration with death due to brain injury before regaining consciousness, initial encounter
S06338D	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06898S	Other specified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06898D	Other specified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06358S	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06307D	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06377	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S069X7A	Unspecified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S069X7D	Unspecified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S065X7S	Traumatic subdural hemorrhage with loss of consciousness of any duration with death due to brain injury before regaining consciousness, sequela

ICD-10	Description
S06367A	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S062X8D	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S061X7D	Traumatic cerebral edema with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S060X7D	Concussion with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06367D	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S062X7	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06337	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06378D	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06348D	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06368A	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S06377S	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06368D	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S069X8D	Unspecified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06387S	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06897	Other specified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S066X8	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06827D	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06828	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06348S	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06388S	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S062X7S	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06327	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06337D	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06357D	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06387D	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter

ICD-10	Description
S06367	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06317S	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06357S	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S066X8D	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06328D	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06387	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S064X7S	Epidural hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S066X8S	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S069X8S	Unspecified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06358A	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S066X7S	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06818D	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06897A	Other specified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06827	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06818S	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S066X7	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06338A	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S061X7S	Traumatic cerebral edema with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06317	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06308S	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S064X8D	Epidural hemorrhage with loss of consciousness of any duration with death due to other causes prior to regaining consciousness, subsequent encounter
S06348A	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S06348	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06818A	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter

ICD-10	Description
S06897S	Other specified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06828D	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06817S	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S065X8D	Traumatic subdural hemorrhage with loss of consciousness of any duration with death due to other cause before regaining consciousness, subsequent encounter
S06328A	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S06368	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S065X8	Traumatic subdural hemorrhage with loss of consciousness of any duration with death due to other cause before regaining consciousness
S06318S	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06368S	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06387A	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06827A	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06327A	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S062X8	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06338S	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S069X7S	Unspecified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S069X7	Unspecified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06318A	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S062X7D	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06377D	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S060X8D	Concussion with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06817	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06328	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06318	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06308A	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter

ICD-10	Description
S06817D	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06327S	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S060X8A	Concussion with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S06308	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06367S	Traumatic hemorrhage of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06338	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06898	Other specified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S061X7	Traumatic cerebral edema with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06317D	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06307A	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06828A	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S06388D	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06898A	Other specified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S06817A	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06388A	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S061X8A	Traumatic cerebral edema with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S06337A	Contusion and laceration of cerebrum, unspecified, with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S060X8S	Concussion with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06307S	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S06358	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S062X8A	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
G9382	Brain death
S06318D	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S069X8A	Unspecified intracranial injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter

ICD-10	Description
S060X7A	Concussion with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06358D	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06357	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S064X7A	Epidural hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06378S	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S062X7A	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06327D	Contusion and laceration of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S061X8	Traumatic cerebral edema with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S066X7A	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06317A	Contusion and laceration of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06828S	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06308D	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter
S06347A	Traumatic hemorrhage of right cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06307	Unspecified focal traumatic brain injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S06357A	Traumatic hemorrhage of left cerebrum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06897D	Other specified intracranial injury with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S06377A	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S065X8A	Traumatic subdural hemorrhage with loss of consciousness of any duration with death due to other cause before regaining consciousness, initial encounter
S062X8S	Diffuse traumatic brain injury with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, sequela
S06827S	Injury of left internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, sequela
S065X7	Traumatic subdural hemorrhage with loss of consciousness of any duration with death due to brain injury before regaining consciousness
S06388	Contusion, laceration, and hemorrhage of brainstem with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S064X8S	Epidural hemorrhage with loss of consciousness of any duration with death due to other causes prior to regaining consciousness, sequela
S06378A	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, initial encounter
S061X8D	Traumatic cerebral edema with loss of consciousness of any duration with death due to other cause prior to regaining consciousness, subsequent encounter

ICD-10	Description
S064X7	Epidural hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness
S064X8A	Epidural hemorrhage with loss of consciousness of any duration with death due to other causes prior to regaining consciousness, initial encounter
S061X7A	Traumatic cerebral edema with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06818	Injury of right internal carotid artery, intracranial portion, not elsewhere classified with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S064X8	Epidural hemorrhage with loss of consciousness of any duration with death due to other causes prior to regaining consciousness
S066X7D	Traumatic subarachnoid hemorrhage with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, subsequent encounter
S060X8	Concussion with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
S06378	Contusion, laceration, and hemorrhage of cerebellum with loss of consciousness of any duration with death due to other cause prior to regaining consciousness
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14.1.12. Tables, listing and figures

The Tables and figures document is attached with the additional study material in Veeva Vault.

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