Epidemiology Study Protocol
Sponsor:

GlaxoSmithKline Biologicals SA (GSK)

eTrack study number and abbreviated title	219111 (EPI-ZOSTER-097 VE US DB)
Date of protocol	18 August 2022
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	Agnes Mwakingwe-Omari, M.D. PhD Clinical & Epidemiology Project Lead

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

Protocol Sponsor Signatory Approval

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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

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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 2-dose cohort, participants aged ≥50 YOA who received dose 2 of RZV at least 28 days after dose 1 (as per prescribing information, as patients who are immunocompromised qualify for a shorter vaccination schedule) will be exactly matched with participants who have not received any RZV dose by condition as of the index date. After identifying the sub-cohorts for each AID condition, vaccinated and unvaccinated participants will be matched exactly on a ratio of 1:3 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. 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. Matching will occur separately in each cohort (2-dose cohort, 1-dose cohort).

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. Following matching, 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 **s**pecific 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.

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). After identifying the sub-cohorts for each AID condition, vaccinated patients will be matched exactly to unvaccinated patients on a ratio of 1:3 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. Matching will be used to better control for the confounding effects and reduce bias in this observational study. The matching ratio of 1:3 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).

All participants are required to have at least 3 months of follow-up time, which means the latest follow-up start date for all cohorts will be 30 September 2021, 3 months before the end of the study period (31 December 2021).

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

Figure 1 Matched 2-dose cohort study

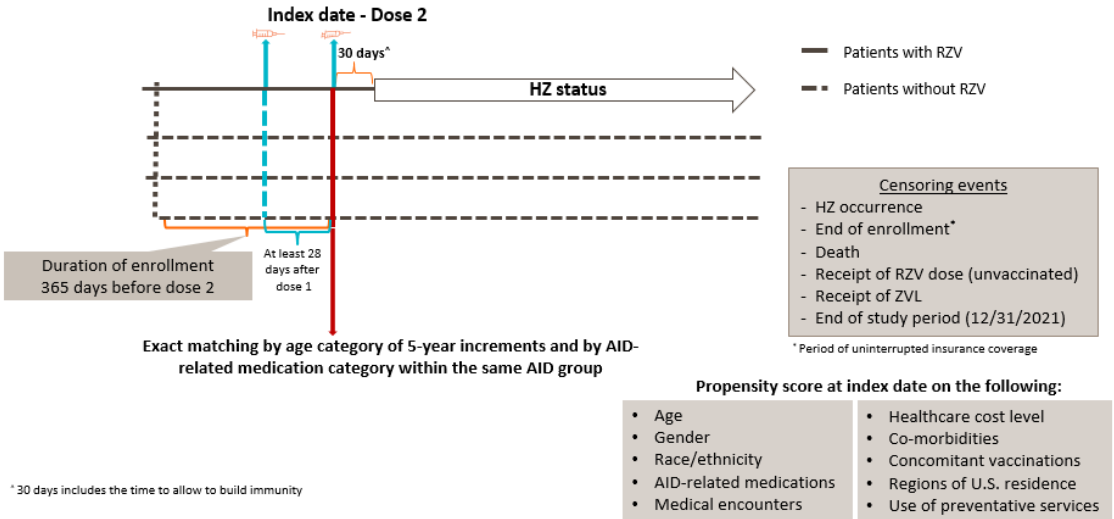
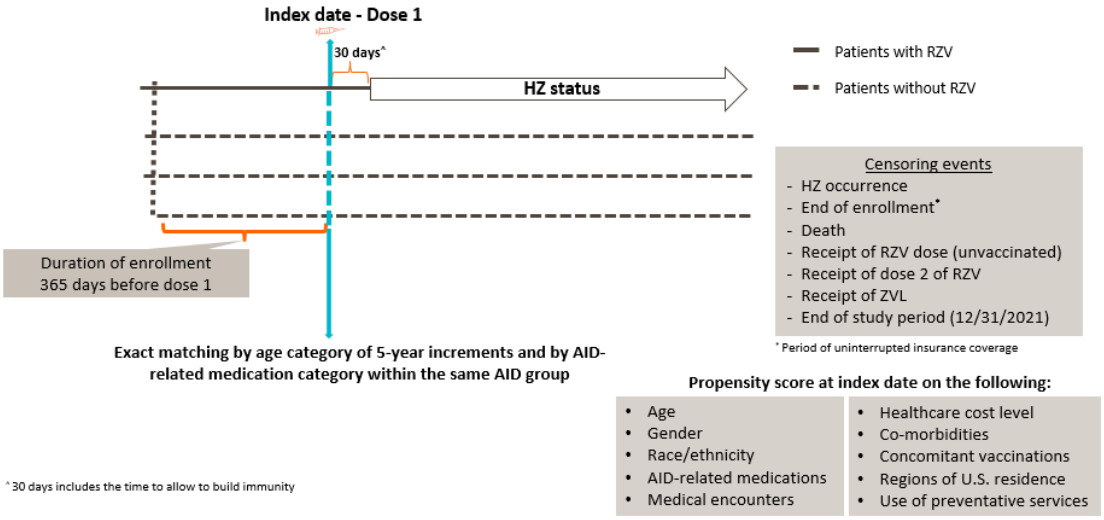


Figure 2 describes the cohort design to assess one-dose vaccine effectiveness.

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 4, Sections 13.4.3, 13.4.4, 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 in the 365 days prior to the index date, as detailed in Appendix 4[Baumrin, 2019; Chakravarty, 2013; Khan, 2018; ILai, 2021; Marra, 2016; Yamaguchi, 2021].

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 SLE, MS) in the 365 days prior to the index date.

Healthcare cost level: categorized according to specific ith 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 Sections 7.2 and 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.
- At least 3 months of follow-up time.

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).
- Follow up time is less than 3 months after the follow up start date.

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, once sub-cohorts for each AID condition are identified, 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 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 13.6. For the secondary objectives, participants meeting inclusion criteria who receive 1 dose of RZV at the index date will be matched with unvaccinated participants by 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. Matching will be done with replacement.

Following matching as described above, propensity scores based on the likelihood of receiving RZV dose 2 versus no RZV vaccination will be calculated using logistic regression models with RZV vaccination as the dependent variable and independent variables as outlined in Section 6.2 to select the 3 unvaccinated participants which are the closest to each vaccinated participant, to reach a ratio of RZV vaccinated to RZV unvaccinated of 1:3. 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.

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.

The latest date a patient can be enrolled to ensure minimum duration of follow up is 30 September 2021 to allow for at least 3 months follow-up to observe HZ.

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. 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. Further details of the sensitivity analyses will be described in the SAP.

11.3.6. 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
CPT	Current Procedural Terminology
E H R	Electronic Health Record
ED	Emergency Department
FDA	Food and Drug Administration, United States of America
GSK	GlaxoSmithKline
HM	Hematological Malignancies
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
IC	Immunocompromised
ICD	International Classification of Diseases
IDNs	Integrated Delivery Networks
MS	Multiple Sclerosis
NDC	National Drug Code
PHN	Post Herpetic Neuralgia
PPV	Positive Predictive Value

PsA	Psoriatic Arthritis
PsO	Psoriasis
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RWA	Real World Analytics
RZV	Recombinant Zoster Vaccine
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. 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, 31722077705, 31722077801, 31722077805, 33261022716, 33261022725, 33261022730, 33261022735, 33261022740, 33261022750, 33261022760, 33261022790, 33261041930, 33261041960, 33261041990, 33261049128, 33261049130, 33261049160, 33261049190, 33358000925, 33358001015, 33358001028, 33358001030, 33358001060, 33358001125, 33358001130, 33358001135, 35356090315, 35356090330, 35356090335, 35356090340, 35356090360, 35573040315, 35573040331, 38779017301, 38779017304, 38779017305, 38779017308, 40085084296, 42254013315, 42254013320, 42254013321, 42254013325, 42254013330, 42254013360, 42254013390, 42254019821, 42254019825, 42254019830, 42254019835, 42254019840, 42254019850, 42254031325, 42254031330, 42254031390, 42291001701, 42291001750, 42291010701, 42291010750, 42291010850, 42291010890, 42291010950, 42291010990, 43063000101, 43063020405, 43063034001, 43063034004, 43063034005, 43063034015, 43063034025, 43063034030, 43063034040, 43063034060, 43063058910, 43063058930, 43063058935, 43063058950, 43063070135, 43063070150, 43063082605, 43063082650, 43063088801, 43063088882, 43063092815, 43063092825, 43063092830, 43063092840, 43063092860, 43353093318, 45802004475, 47463000325, 47463000330, 47463000335, 47463000430, 49452000101, 49452000102, 49452000103, 49452000108, 49884056501, 49884056505, 49884056601, 49884056605, 49884056701, 49884056705, 49999008600, 49999008621, 49999008625, 49999008630, 49999008690, 49999023100, 49999023115, 49999023130, 49999023135, 49999023140, 49999038510, 49999038515, 49999038525, 49999038540, 50090059500, 50090059501, 50090059507, 50090059600, 50090059601, 50090059607, 50090063800, 50090063802, 50090064402, 50090064403, 50090064404, 50090064405, 50090064406, 50090064409, 50090064500, 50090064501, 50090156702, 50090156705, 50090156706, 50090162400, 50090162402, 50090325002, 50090325003, 50090325004, 50090325005, 50090325006, 50090325009, 50090325400, 50090325401, 50268006011, 50268006015, 50268006111, 50268006115, 50268006211, 50268006215, 50383081016, 51079044701, 51079044720, 51079044801, 51079044820, 51079044901, 51079044920, 51079055067, 51079055068, 51079087601, 51079087620, 51079087701, 51079087720, 51079087801, 51079087820, 51407014501, 51407014505, 51407014601, 51407014605, 51552067101, 51552067102, 51552067103, 51552067104, 51552067105, 51552067106, 51672136001, 51672136002, 51927299400, 52372081101, 52372081102, 52372081103, 52372081104, 52544033501, 52544033601, 52959051725, 52959051730, 52959051735, 52959051750, 52959054401, 52959054410, 52959054412, 52959054415, 52959054421, 52959054425, 52959054430, 52959054440, 52959054450, 52959054460, 52959067830, 52959067840, 52959067850, 53002000815, 53002000821, 53002000830, 53002000860, 53002002710, 53002002715, 53002002720, 53002002725, 53002002730, 53002002735, 53002002750, 53002002760, 53002024525, 53002024530, 53002024535, 53002024550, 53002024560, 53217018815, 53217018821, 53217018825, 53217018828, 53217018830, 53217018850, 53217018860, 53217031325, 53217031330, 53217031335, 53217031340, 53217031350, 54348062025, 54348062030, 54348062035, 54348062050, 54348062625, 54348062630, 54348062650, 54348062710, 54348062715, 54348062730, 54569448200, 54569448201, 54569448202, 54569448203, 54569448204, 54569448206, 54569448207, 54569472400, 54569472402, 54569476500, 54569476501, 54569476502, 54569476503, 54569476504, 54569476505, 54569476506, 54569476509, 54569652700, 54569652701, 54569888000, 54569888001, 54569888100, 54569888101, 54569888200, 54569888201, 54868399600, 54868399601, 54868399602, 54868399603, 54868399604, 54868399605, 54868399700, 54868399701, 54868399702, 54868399703, 54868399704, 54868399705, 54868399800, 54868399801, 54868399802, 54868399803, 54868399804, 54868399805, 54868399806, 54868399807, 54868399808, 54868568700, 55045256504, 55045257100, 55045257104, 55045257106, 55045257108, 55045264802, 55045264803, 55045264806, 55048000325, 55048000330, 55048000335, 55048000430, 55048000470, 55289027305, 55289027310, 55289027325, 55289027330, 55289027335, 55289027350, 55289027412, 55289027415, 55289027425, 55289027605, 55289046201, 55289046205, 55289046212, 55289046215, 55289046221, 55289046225, 55289046230, 55289046235, 55289046240, 55289046260, 55289062910, 55289062920, 55289062930, 55289062935, 55289062940, 55289062950, 55370055507, 55370055509, 55370055607, 55370055608, 55370055707, 55370055709,

Drug	NDCs
	55700053930, 55700065130, 55700066335, 55700066415, 55700066435, 55700066440, 55700066460, 55700078635, 55812038401, 55812038402, 55812038403, 55887024615, 55887024621, 55887024625, 55887024630, 55887024640, 55887024650, 55887085325, 55887085330, 55887085350, 55887085360, 55887085390, 55887097730, 55887097740, 57866695002, 57866695003, 57866695004, 57866695005, 57866695103, 58016011100, 58016011115, 58016011120, 58016011125, 58016011130, 58016011160, 58016011190, 58016011200, 58016011220, 58016011230, 58016011260, 58016011290, 58016062700, 58016062720, 58016062730, 58016062760, 58016062790, 58118894303, 58118894304, 58118894308, 58118894703, 58118894705, 58597806703, 58597806704, 58597806706, 58597806707, 58597806708, 58864019125, 58864019135, 58864060201, 58864060230, 58864087635, 59911316305, 60429001201, 60429001205, 60429030901, 60429030905, 60429030910, 60429031001, 60429031005, 60429071101, 60429071105, 60429071150, 60429071201, 60429071205, 60429071301, 60429071305, 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71335022502, 71335022503, 71335022504, 71335022505, 71335022506, 71335022507, 71335022508, 71335022509, 71335024800, 71335024801, 71335024802, 71335024803, 71335024804, 71335024805, 71335024806, 71335024807, 71335024808, 71335024809, 71335028000, 71335028001, 71335028002, 71335028003, 71335028004, 71335028005, 71335028006, 71335028007, 71335028008, 71335028009, 71335031901, 71335031902, 71335031903, 71335031904, 71335031905, 71335031906, 71335031907, 71335031908, 71335031909, 71335032300, 71335032301, 71335032302, 71335032303, 71335032304, 71335032305, 71335032306, 71335032307, 71335032308, 71335032309, 71335047000, 71335047001, 71335047002, 71335047003, 71335047004, 71335047005, 71335047006, 71335047007, 71335047008, 71335047009, 71335069502, 71335069508, 75834012201, 75834012205, 75834012301, 75834012305, 75834012401, 68712004901, 68712004902, 71403004901, 71403004902, 00173094555, 00173094556, 00173094955, 00173095396, 00173099155, 00173099156, 00173099341, 00187099395, 00187099445, 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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

Drug	NDCs
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
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,

Drug	NDCs
	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

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 <20 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 ≥20 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 window pending.
Source: Treatment category from EPI-ZOSTER-044

13.6.2. 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 <20 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 ≥20 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 window pending.
Source: Treatment category from Epi-Z-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. NDC codes and HCPCS/J-codes to be determined at a later date.
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. NDC codes and HCPCS/J-codes to be determined at a later date.
SQ = subcutaneous, IV = intravenous, IM = intramuscular, PO = by mouth
Source: EPI-ZOSTER-041

13.6.4.1. PsO Immunosuppressive/immunomodulatory therapies

A list of medication categories and medication window for PsO will be generated during the study using a template similar to Appendix section 13.6.1 and section 13.6.2.

13.6.4.2. PsA Immunosuppressive/immunomodulatory therapies

A list of medication categories and medication window for PsA will be generated during the study using a template similar to Appendix section 13.6.1 and section 13.6.2.

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Reason for signing: Approved	Name: Agnes Mwakingwe-Omari Role: Approver Date of signature: 22-Aug-2022 14:46:20 GMT+0000

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