EPIDEMIOLOGY STUDY PROTOCOL
SPONSOR:
GLAXOSMITHKLINE BIOLOGICALS SA (GSK)

PASS INFORMATION

eTrack study number and abbreviated title	213825 (EPI-ZOSTER-044 VE US)
Date of protocol	Final: 2 March 2022
Date of protocol amendment 1	Final: 01 Feb 2024
Date of protocol amendment 2	Final: 09 Jan 2025
Title	Non-interventional (observational) post-licensure study to assess the vaccine effectiveness and safety of recombinant zoster vaccine (RZV) in the rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) patient populations in adults 18 years of age and older
Brief title	RZV effectiveness and safety in patients with RA or IBD
EU PAS Register No:	EUPAS48157
Active substance:	VZV glycoprotein E (gE)
Medicinal product(s):	*Shingrix* (Recombinant Zoster Vaccine, RZV)
Product reference:	For EMA: EU/1/18/1272/001-1 Vial and 1 vial; EU/1/18/1272/002-10 vials and 10 vials For FDA: IND #013879
Procedure number:	EMEA/H/C/004336
Marketing Authorisation Holder(s) (MAH):	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89, 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	Provide data on VE and safety of RZV among individuals with RA or IBD. The primary VE objectives are to estimate the 2-dose VE of RZV in preventing HZ in adults ≥18 years of age with RA or IBD, respectively. The primary safety objectives are to assess the incidence rate and relative risk of flares within 30 days following any RZV vaccination as compared to the risk in self-controlled comparison periods, in adults ≥18 years of age with RA or IBD, respectively.
Country(-ies) of study:	United States

Author:

KPSC authors

Hung-Fu Tseng, Principal Investigator
PPD, Co-Investigator
PPD, Co-Investigator
PPD, Co-Investigator
PPD, Co-Investigator
PPD Co-Investigator
PPD, Co-Investigator/Biostatistician

GSK authors

PPD
PPD, Epidemiology
PPD, Real World Analytics
PPD, Study Delivery Lead
PPD, Regulatory
PPD, Global Medical Affairs
PPD, Medical Affairs
PPD, Global Safety
PPD, Vaccines Safety;
PPD
PPD
Global Safety; PPD

MARKETING AUTHORISATION HOLDER

MAH(s):	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89, 1330 Rixensart, Belgium
MAH contact person:	PPD

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

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and abbreviated title	213825 (EPI-ZOSTER-044 VE US)
Date of protocol	Final: 2 March 2022
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Title	Non-interventional (observational) post-licensure study to assess the vaccine effectiveness and safety of recombinant zoster vaccine (RZV) in the rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) patient populations in adults 18 years of age and older
Sponsor signatory	Huifeng Yun, Viral Vaccines Epidemiology Head, GSK
Signature	_____
Date	_____
QPPV signatory or delegate	Jens-Ulrich Stegmann Senior Vice President, Clinical Safety and Pharmacovigilance, GSK
Signature	_____
Date	_____

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

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol and with the terms of the study agreement.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, "Good Pharmacoepidemiology Practice" (GPP) and "Good Epidemiologic Practices" as well as all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	213825 (EPI-ZOSTER-044 VE US)
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Investigator name	Hung-Fu Tseng
Signature	
Date	

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Sponsor study contact for reporting of Serious Adverse Events (SAEs)

GSK central back up study contact for reporting SAEs: Not applicable to this study

Study contact for reporting SAEs: refer to the local study contact information document.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 2: (09 Jan 2025)

Overall rationale for the current amendment 2:

The protocol has been amended to clarify the study design, accrual, analysis, and medication list..

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
1.3 Overall design	Added "31 days after."	Clarified that the follow-up period starts 31 days after the index date.
4.0 Objectives and outcomes	Added "31 days after."	Clarified that the follow-up period starts 31 days after the index date.
5.1 Overall design	Added "however, the accrual for individuals ≥50 years of age may end earlier than 08/2023 once the target sample size is met." Added "31 days after."	Clarified the accrual end date for individuals aged ≥50 years. Clarified that the follow-up period starts 31 days after the index date.
6.1.2 Safety	Clarified Figure 1 (SCCS Design Overview for Safety Analysis) and updated the text description of Figure 1.	Clarified the risk window, comparison window, and washout window for various scenarios for the SCCS design.
7.2.1. Inclusion criteria	Clarified the inclusion criteria.	As part of the inclusion criteria for individuals with at least 2 health care encounters with assigned ICD-10 codes for RA or IBD, clarified that the lookback period spans the year prior to and including the index date.

Section # and title	**Description of change**	**Brief rationale**
11.1.1. VE	Updated the sample size calculation using an incidence rate of 12 cases per 1,000 person years (Table 6). Updated sample size calculation with follow-up beginning 31 days after index date and a censoring rate in the unvaccinated group of 25% (Tables 5 and 6).	Provided the estimated sample size required given a lower incidence rate of HZ. Revised estimated sample size since follow-up will not begin until 31 days after index date. Updated censoring rate in unvaccinated group to account for more loss to follow up from unvaccinated individuals receiving RZV.
11.2.2. Primary analyses	Clarified calculation of unadjusted HR and VE. Added "The VE of 2 doses of RZV by time since vaccination will also be evaluated."	Clarified that unadjusted VE will be estimated based on HR from Cox stratified proportional hazards regression. Clarified that an analysis will be conducted of VE of 2 doses of RZV by time since vaccination.
11.2.3. Secondary analyses	Added, "For secondary and exploratory analyses, subgroups may be recategorized in post-hoc analyses if sample size in any subgroup is small." Added "31 days after."	Clarified that subgroups may be reclassified if needed after final analysis. Clarified that the follow-up period starts 31 days after the index date.
13.3. Appendix 3. Medication categories	Replaced "aqvh" with "aaty" for Yuflyma.	Corrected the medication extension for Yuflyma.

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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. Studies have shown that the incidence rate of HZ among adults with rheumatoid arthritis (RA) is approximately twice the incidence rate of HZ among immunocompetent adults [Smitten, 2007; Yun, 2016]. Similarly, the incidence rate of HZ is higher among adults with inflammatory bowel disease (IBD), including ulcerative colitis (UC) or Crohn's disease (CD), than among immunocompetent adults [Gupta, 2006; Khan, 2018; Long, 2013; Yun, 2016]. In July 2021, the Food and Drug Administration (FDA) expanded the indication for use of recombinant zoster vaccine (RZV) to include immunodeficient or immunosuppressed adults. In October 2021, the Advisory Committee on Immunization Practices (ACIP) recommended 2 doses of RZV for the prevention of HZ and related complications in immunodeficient or immunosuppressed adults [Anderson, 2022]. RZV may provide a substantial benefit in preventing HZ in these populations, although more data are needed on vaccine effectiveness (VE) in adults with RA and IBD. Demonstrating the safety of RZV among adults with RA or IBD is also of critical importance, as these data have also been extremely limited. Given the ACIP's latest recommendation, this study aims to generate more evidence on VE and safety of RZV in adults with RA and IBD.

1.2. Objective(s) and outcome(s)

The primary VE objectives are to estimate the 2-dose VE of RZV in preventing HZ in adults ≥18 years of age with RA or IBD, respectively. The primary safety objectives are to assess the number of incident flare cases within 30 days following any RZV vaccination as compared to the risk in self-controlled comparison periods, in adults ≥18 years of age with RA or IBD, respectively.

1.3. Overall design

This study will examine the effectiveness and safety of RZV in adults with RA or IBD (UC or CD) at Kaiser Permanente Southern California (KPSC). The vaccine accrual period for the full study will extend from 04/2018 to 08/2023 with follow-up through 08/2024.

For the VE objectives, an observational matched cohort design will be used. For the primary analyses, the index date will be defined as the date of receipt of the second dose of RZV (given 4 weeks to 6 months after the first dose) for vaccinated individuals; the same index date will be used for their unvaccinated matches. Individuals ≥18 years of age who receive a second dose of RZV will be matched to RZV unvaccinated individuals by condition (RA, UC, CD), age, sex, race/ethnicity (if sample size allows), and medication category. Individuals will be followed through the KPSC electronic health record (EHR) from 31 days after the index date until occurrence of HZ, termination of membership, death, receipt of a subsequent dose of zoster vaccine, or end of the study period, whichever comes first. VE will be calculated from the hazard ratio (HR) obtained from

Cox regression analysis. Secondary analyses will stratify 2-dose VE (second dose given at least 4 weeks after the first dose) by UC and CD, and by age group (18-49 years and ≥50 years [≥50 years, 50-59 years, 60-69 years, and ≥70 years]). The 2-dose VE will also be estimated by timing of the second dose of RZV (second dose given >6 months after first dose, and second dose given at least 4 weeks after first dose). The VE of 1 dose of RZV in preventing HZ in adults ≥18 years of age with RA or IBD will also be estimated. The index date for these secondary 1-dose objectives will be date of receipt of the first RZV dose. Additional exploratory analyses will also be conducted.

For the safety objectives, a self-controlled case series (SCCS) analysis will be conducted among individuals aged ≥18 years with RA or IBD who receive at least one dose of RZV. The date of vaccination with the first dose of RZV will be defined as Day 0. Given the complexity of accurately ascertaining disease flare, the EHR will be reviewed for these individuals for occurrence of flare rather than relying on administrative data. For primary analyses, for individuals receiving only 1 dose of RZV, the relative risk (RR) of flare in the pre-defined risk period (+1 to +30 days) compared to comparison periods (defined as -90 to -61 days and +31 to +60 days) will be assessed for RA and IBD. For individuals who receive a second dose of RZV, risk and comparison periods will be defined depending on timing of receipt of the second dose. Secondary analyses will stratify the risk of flares by UC and CD. Exploratory analyses will stratify the risk of flares by medication category at baseline.

2. SCHEDULE OF ACTIVITIES (SOA)

Not applicable.

3. RATIONALE AND BACKGROUND

HZ, or shingles, is an often painful vesicular rash caused by reactivation of varicella zoster virus (VZV) persisting latently in dorsal root ganglia [Dworkin, 2007; Gnann, 2002]. The pain from acute HZ can be disabling, and if complicated by the development of post-herpetic neuralgia (PHN), can last for months or years. Before a vaccine was introduced, about one million episodes of HZ occurred in the United States (U.S.) annually [Harpaz, 2008]. Aside from increasing age and immunosuppression, other risk factors for this condition are not well known [Thomas, 2004], but some evidence suggests that sex, race/ethnicity, family history, and comorbidities may be associated with the occurrence of HZ [Lasa, 2021; Kawai, 2017].

Recombinant zoster vaccine (SHINGRIX, RZV), a 2-dose subunit zoster vaccine containing recombinant glycoprotein E in combination with a novel adjuvant, was approved by the FDA in October 2017 for the prevention of HZ in adults ≥50 years of age, and by the European Medicines Agency (EMA) in March 2018 for the prevention of HZ and PHN in adults ≥50 years of age. The ACIP recommends RZV vaccination for the prevention of HZ in immunocompetent adults ≥50 years of age [Dooling, 2018]. On July 23, 2021, the FDA approved the expansion of the indication to include the prevention of HZ in adults ≥18 years of age who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy [U.S.

Food & Drug Administration, 2021]. On October 20, 2021, the ACIP recommended 2 doses of RZV for the prevention of HZ and its complications in adults ≥19 years of age who are or will be immunodeficient or immunosuppressed due to disease or therapy [Anderson, 2022]. Expansion of RZV recommendations to these at-risk populations (i.e., those patient populations for whom zoster vaccine live [ZVL] was largely contraindicated) will help address an unmet medical need for HZ prevention. Data on the use of RZV in these complex patient populations, including in individuals with AID, are critical in assessing the effectiveness and safety of the vaccine in real-world settings.

Individuals with AID are at higher risk of HZ compared to immunocompetent individuals, including adults aged ≥50 years as well as adults aged <50 years. Studies have shown that the incidence rate of HZ among adults with RA is approximately twice the incidence rate of HZ among immunocompetent adults [Smitten, 2007; Yun, 2016]. Similarly, the incidence rate of HZ is higher among adults with IBD, including UC or CD, than among immunocompetent adults [Gupta, 2006; Khan, 2018; Long, 2013; Yun, 2016]. The risk of HZ may also be increased by some medications commonly prescribed for RA and IBD, such as corticosteroids, Janus kinase (JAK)-inhibitors, and some biologic disease-modifying antirheumatic drugs (DMARDs) [Bechman, 2019; Choden, 2022; Colombel, 2018; Curtis, 2019; Marra, 2016; Sandborn, 2019; Winthrop, 2017; Yun, 2015]. RZV, as recommended by the ACIP, may provide a substantial benefit in preventing HZ in these populations [Anderson, 2022]. One study from the Veterans Affairs Healthcare System among individuals diagnosed with IBD showed that RZV vaccination was associated with decreased risk of HZ infection among both the 50-60-year and >60-year age groups [Khan, 2021]. Nevertheless, more evidence is needed on VE of RZV in adults with RA and IBD.

Demonstrating the safety of RZV among individuals with RA or IBD is also of critical importance, as data have been extremely limited and solely descriptive. While no safety signal has been detected in these populations, there is a theoretical concern for disease flare with administration of an adjuvanted vaccine. New or worsening signs and/or symptoms suggestive of a flare include joint swelling, joint pain/tenderness, and joint stiffness for RA, and abdominal pain/tenderness, diarrhea (increased stool frequency and/or soft or liquid stool), urgency, rectal bleeding, blood in stool, nausea/vomiting, and unintentional weight loss for IBD. In a descriptive study of 403 individuals (239 patients with RA and 164 patients with other systemic rheumatic diseases) who received at least 1 dose of RZV, 6.7% experienced a flare within 12 weeks of a dose of RZV; the percentage experiencing a flare was lower than expected based on a previous study conducted at the same institution [Bykerk, 2014; Stevens, 2020]. In a cohort of 67 individuals with IBD who received at least 1 dose of RZV, only one individual experienced a flare within 2 weeks following any dose [Satyam, 2020]. Larger and more robust comparative studies are needed in these populations to assess the safety of RZV.

This real-world observational study utilizing EHR data from a large integrated health care delivery network will evaluate the effectiveness and safety of RZV in preventing HZ in adults ≥18 years of age with RA or IBD (UC or CD). This study provides a valuable opportunity to rigorously evaluate the real-world effectiveness and safety of RZV in patients with RA or IBD and will help critically inform patient and physician decision-making regarding vaccination against HZ in these at-risk populations. In particular, with

the expanded indications from FDA and recommendations from ACIP on the use of RZV in immunocompromised adults ≥18 years of age, this study provides a timely response to the need for more real-world evidence on VE and safety of RZV in patients with RA or IBD.

3.1. Research institution overview (Study setting)

KPSC is one of the largest not-for-profit health plans and integrated health care systems in the U.S., providing an ideal environment for population-based research. KPSC's population includes more than 4.6 million members, of which 2,044,338 are ages 18-49 years, and 1,577,812 are ages ≥50 years (as of May 1, 2020). The diverse demographic makeup, including 260 different ethnicities and more than 150 different languages, closely mirrors the Southern California population [Koebnick, 2012]. Compared to the racial/ethnic distribution of the U.S. population, KPSC membership is composed of twice as many individuals of Asian/Pacific Islander descent and 3 times as many Hispanic individuals.

KPSC facilities include hospitals and medical offices, all linked by an information infrastructure that supports both clinical practice and business needs. Health information from this infrastructure can be leveraged for research purposes. More than 90% of members remain in the health plan after one year; more than three-quarters remain after 3 years. The large, diverse, and stable population permits the rapid accrual of a representative sample size and offers the ability to evaluate long-term implications of immunization.

KPSC began administering ZVL in late 2006 when it was first recommended by the ACIP and KPSC Regional Immunization Practice Committee. In 2017, the ACIP recommended RZV preferentially over ZVL. Since April 2018, RZV has been the preferred HZ vaccine for routine use and the standard of care for the prevention of HZ in adults aged 50 years and older at KPSC.

3.2. Description of the database (Electronic health records)

Kaiser Permanente Health Connect is the largest and most advanced civilian EHR system available in the U.S. In addition to supporting patient care, this robust system facilitates research, providing access to the EHR for the KPSC vaccine research team. Up-to-date details of patient care are available and accessible to researchers. Data regarding demographics, services, and diagnoses are tracked from the outpatient, Emergency Department, and hospital settings.

Pharmacy and vaccination utilization are linked through patients' unique medical record numbers. As KPSC is a pre-paid health care system, recommended vaccines such as RZV are provided to KPSC members at no charge and can be obtained at no-cost nurse visits or on a walk-in basis without appointment, which is an incentive for members to receive immunizations within the system. Vaccinations received outside of the health plan with appropriate documentation are also recorded in KPSC databases.

KPSC members have very strong motivation to use services internally. For outside providers to be reimbursed by the health plan for covered emergent or contract care, claims must be submitted with documentation of the episode of care, which is integrated into KPSC databases. Thus, the capture of care is considered to be very comprehensive. Care received at KPSC is updated and available to researchers in near real time. Claims data are over 90% complete after 3 months.

4. OBJECTIVES AND OUTCOMES

This study will assess VE and safety among individuals at KPSC with RA or IBD who received RZV ("vaccinated") compared to individuals who did not receive RZV ("RZV unvaccinated"), addressing the objectives listed in Table 1. The table lists the primary, secondary and exploratory VE objectives as well as the primary, secondary, and exploratory safety objectives.

VE objectives refer to 2 doses of RZV given at least 4 weeks apart, except where otherwise indicated (Primary VE Objectives 1-2, Secondary VE Objectives 4 and 6-7, and the Safety Objectives). VE outcomes will be ascertained during the follow-up period from the 31 days after the index date until termination of membership, death, receipt of a dose of RZV for unvaccinated individuals, or end of the study period, whichever comes first. Safety outcomes will be ascertained during pre-specified risk and comparison periods (Section 6.1.2). The outcomes are further detailed in Section 6.2 and Section 11.2.

Table 1 Study objectives and outcomes

Objectives	Outcomes
Primary VE Objectives	
1. To estimate the VE of 2 doses of RZV, given 4 weeks to 6 months apart, in preventing HZ in adults ≥18 years of age with RA	• Number of incident HZ cases • Incidence rate of HZ
2. To estimate the VE of 2 doses of RZV, given 4 weeks to 6 months apart, in preventing HZ in adults ≥18 years of age with IBD	• Number of incident HZ cases • Incidence rate of HZ
Secondary VE Objectives	
1. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years of age with IBD, stratified by condition (UC and CD)	• Number of incident HZ cases • Incidence rate of HZ
2. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years with RA, stratified by age (18-49 years, ≥50 years)	• Number of incident HZ cases • Incidence rate of HZ
3. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years of age with IBD, stratified by age (18-49 years, ≥50 years)	• Number of incident HZ cases • Incidence rate of HZ
4. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years of age with RA or IBD, stratified by condition, with second dose administered >6 months after the first dose	• Number of incident HZ cases • Incidence rate of HZ
5. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years of age with RA or IBD, stratified by condition	• Number of incident HZ cases • Incidence rate of HZ
6. To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥18 years of age with RA	• Number of incident HZ cases • Incidence rate of HZ
7. To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥18 years of age with IBD	• Number of incident HZ cases • Incidence rate of HZ

Objectives	Outcomes
Exploratory VE Objectives	
1. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years of age with RA, stratified by medication category at baseline	• Number of incident HZ cases • Incidence rate of HZ
2. To estimate the VE of 2 doses of RZV in preventing HZ in adults ≥18 years of age with IBD, stratified by medication category at baseline	• Number of incident HZ cases • Incidence rate of HZ
3. To estimate the incidence of PHN, disseminated HZ, HZ-related meningoencephalitis, and hospitalized HZ in 2-dose RZV vaccinated and unvaccinated adults ≥18 years of age with RA	• Number of incident PHN, disseminated HZ, HZ-related meningoencephalitis, and hospitalized HZ cases • Proportion of HZ cases with PHN, disseminated HZ, HZ-related meningoencephalitis, and hospitalized HZ
4. To estimate the incidence of PHN, disseminated HZ, HZ-related meningoencephalitis, and hospitalized HZ in 2-dose RZV vaccinated and unvaccinated adults ≥18 years of age with IBD	• Number of incident PHN, disseminated HZ, HZ-related meningoencephalitis, and hospitalized HZ cases • Proportion of HZ cases with PHN, disseminated HZ, HZ-related meningoencephalitis, and hospitalized HZ
Primary Safety Objectives	
1. To assess the risk of RA flares within 30 days following any RZV vaccination as compared to the risk in self-controlled comparison periods, in adults ≥18 years of age with RA	• Number of incident RA flare cases
2. To assess the risk of IBD flares within 30 days following any RZV vaccination as compared to the risk in self-controlled comparison periods, in adults ≥18 years of age with IBD	• Number of incident IBD flare cases
Secondary Safety Objectives	
1. To assess the risk of flares within 30 days following any RZV vaccination as compared to the risk in self-controlled comparison periods, in adults ≥18 years of age with IBD, stratified by condition (UC and CD)	• Number of incident IBD flare cases
Exploratory Safety Objectives	
1. To assess the risk of flares within 30 days following RZV vaccination as compared to the risk in self-controlled comparison periods, in adults ≥18 years of age with RA, stratified by medication category at baseline	• Number of incident RA flare cases
2. To assess the risk of flares within 30 days following RZV vaccination as compared to the risk in self-controlled comparison periods, in adults ≥18 years of age with IBD, stratified by medication category at baseline	• Number of incident IBD flare cases

5. STUDY DESIGN

5.1. Overall design

This study will examine the effectiveness and safety of RZV in adults with RA or IBD (UC or CD) at KPSC in the U.S. Given that some individuals ≥50 years of age are currently being vaccinated with RZV (Table 2, Section 7), an earlier analysis is planned on primary VE and primary safety in this age group; the analysis will also include VE stratified by age group and time between doses (≤6 months and >6 months). The vaccine accrual period for this age group will extend from 04/2018 to 12/2021 with follow-up through 12/2022. These results will be important to help address a current data gap and inform physician and patient decision-making regarding RZV vaccination in patients ≥50 years of age with RA or IBD. Full results for all VE and safety objectives for individuals ≥18 years of age will then be targeted for completion at the end of this study. The vaccine accrual period for the full study will extend from 04/2018 to 08/2023 with follow-up through 08/2024; however, the accrual for individuals ≥50 years of age may end earlier than 08/2023 once the target sample size is met. This study period will include accrual of patients after approval of the expanded ≥18 years of age at-risk indication for RZV. Due to the COVID-19 pandemic indirectly impacting health care delivery and vaccine seeking behaviors, subjects will not be accrued in the study from March through December 2020. HZ outcomes will continue to be assessed during this period.

For the VE objectives, an observational matched cohort design will be used. For primary analyses, the index date will be defined as the date of receipt of the second dose of RZV (4 weeks to 6 months apart) for vaccinated individuals and their unvaccinated matches. Individuals ≥18 years of age who receive a second dose of RZV will be matched to RZV unvaccinated individuals on the following variables: medical condition (RA, UC, or CD); sex; age strata; and disease medication category. Further matching will be done on race/ethnicity if sample size allows.

Individuals will be followed through the KPSC EHR from 31 days after the index date until occurrence of HZ, termination of membership (allowing for a 31-day gap in membership), death, receipt of a dose of zoster vaccine (receipt of a third dose of RZV for 2-dose vaccinated individuals, receipt of a second dose of RZV for 1-dose vaccinated individuals, receipt of a first dose of RZV for unvaccinated individuals, or receipt of ZVL), or end of the study period, whichever comes first. Individuals are followed from 31 days after index date to allow sufficient time for development of immunity in the vaccinated cohort and to avoid capture of pre-existing HZ episodes. Cox proportional hazards regression will be used to assess the HR for HZ comparing RZV vaccinated and unvaccinated individuals with RA or with IBD (UC and CD). VE will be calculated from the HR. Secondary analyses will stratify VE by UC and CD, by age group (18-49 years and ≥50 years [≥50 years, 50-59 years, 60-69 years, and ≥70 years]), and by timing of the second dose of RZV (second dose given >6 months after first dose, second dose given at least 4 weeks after first dose). Additional secondary analyses will examine VE after one dose of RZV with the index date as the date of receipt of the first RZV dose. Additional exploratory analyses will also be conducted.

For the safety objectives, an SCCS analysis will be conducted among individuals aged ≥18 years with RA or IBD who receive at least one dose of RZV. The date of vaccination with the first dose of RZV will be defined as Day 0. Given the complexity of accurately ascertaining disease flares, the EHR will be reviewed for these individuals for occurrence of flares rather than relying on administrative data. A flare will be identified by documented contact with a health care provider, and new or worsening signs and/or symptoms suggestive of a flare, and a change in medication for flare (Appendix 2). For primary analyses, the RR of flare in pre-defined risk periods compared to comparison periods will be assessed for RA and IBD (details in Section 6.1.2). Secondary analyses will stratify the risk of flares by UC and CD. Exploratory analyses will stratify the risk of flares by medication category at baseline.

The study will be conducted in accordance with regulations and guidelines from the International Society for Pharmacoepidemiology Guidelines for GPP, International Epidemiological Association Guidance on Good Epidemiological Practices, and the Council for International Organizations of Medical Sciences International Ethical Guidelines for Epidemiological Studies.

5.2. Strengths and limitations

5.2.1. Strengths

First, the high retention rate and stability of KPSC membership provide a unique opportunity to follow patients over time and conduct long-term effectiveness studies. More than 90% of members remain in the KPSC health plan after one year; more than three-quarters remain after 3 years. The large, diverse, and stable population makes rapid accrual of a large, representative sample size possible to evaluate long-term implications of vaccination.

Second, Kaiser Permanente Health Connect, KPSC's comprehensive EHR system, is one of the largest private EHR systems in the world. Kaiser Permanente Health Connect and KPSC's integrated model securely connect medical offices and hospitals across the region, providing members, physicians, and other authorized health care providers with online access to clinical information. The system integrates all aspects of care, including pharmacy and lab services, as well as appointments, registration, and billing. This robust system facilitates research by providing comprehensive EHR data for the research team. Care received in the outpatient, inpatient, and emergency settings is documented in the EHR and captured in research databases. Care received outside the KPSC system is captured through claims. Up-to-date details of patient care are available and accessible to researchers near real-time.

Third, chart reviews will be performed to identify and confirm PHN cases, rather than identifying them by diagnosis codes only. Given the expected low positive predictive value and negative predictive value of diagnosis codes for PHN, all HZ cases with encounters during ≥3 to 6-month period after HZ diagnosis will be chart reviewed for the occurrence of PHN.

Fourth, for the safety objectives, SCCS analysis will be conducted among individuals with RA or IBD who receive at least one dose of RZV. The SCCS design is a case-only method, in which each case serves as their own control. A major advantage of this design is that the potential confounding by characteristics that vary between individuals and may have an impact on disease outcomes, such as comorbidities and genetic and socioeconomic factors are removed [Farrington, 1995; Wilson, 2011]. Additionally, with comparison periods within close proximity to the risk period (before and after the risk period), the design also controls for time-varying covariates such as age and seasonality. Furthermore, chart review will be performed to ascertain RA and IBD flares.

5.2.2. Limitations

First, confounding by indication is a potential limitation. For the VE objectives, this will be addressed by matching on condition (RA, UC, CD), age, sex, race/ethnicity (if sample size allows), and medication category, which may impact the development of the outcome and likelihood of RZV vaccination. For the safety objectives, the SCCS design mitigates bias through implicit control for time-fixed confounders. While the short risk window minimizes changes in confounders during follow-up, potential confounders will be assessed and adjusted for in final analysis.

Second, a potential limitation is misclassification of exposures and outcomes. However, receipt of RZV should be accurately captured in the EHR system, including dates of administration such that receipt of dose 1 and dose 2 are correctly ascertained. The effectiveness outcome of incident HZ is expected to be accurately captured using an algorithm based on a combination of an International Classification of Diseases (ICD)-10 code and prescription for an antiviral. This algorithm has been used in previous studies and was found to have high accuracy in identifying incident HZ [Capistran, 2021; Langan, 2013; Tseng, 2020; Zhang, 2012]. Given the complexity and significant potential for misclassification of the safety outcome of disease flare, medical record review using standardized criteria will be performed to ascertain this outcome. Since this study uses EHR data, the effectiveness and safety outcomes being captured are those for which medical attention is sought. Mild outcomes may be missed.

Third, there is a potential concern for missing patient data during the course of follow-up, particularly for the longer follow-up duration required for the primary effectiveness outcome. However, patients within KPSC are incentivized to use care inside the health care system, so it is expected that the majority of care, including rheumatologist and gastroenterologist visits, will occur within network, and that there will be comprehensive longitudinal capture of a patient's baseline disease activity, medication regimens, and flares so long as they remain KPSC members.

Fourth, a potential limitation is generalizability. However, the patient population within KPSC exhibits significant racial/ethnic diversity, and the age distribution of patients with RA or IBD in this health care network are expected to reflect the distribution nationally. In addition, although the practices of care for patients with RA and IBD (e.g., treatment regimens) are expected to be largely standardized across U.S. health care systems, the results of this study may not be generalizable to patients who receive care in very different health systems in the U.S.

Finally, the coronavirus disease 2019 (COVID-19) pandemic has significantly affected vaccine uptake in general and in the study patient populations specifically. The pandemic has also indirectly impacted behaviors and policies such as health care delivery, insurance eligibility, and health care-seeking behaviors, and ascertainment of and control for these known and unknown variables may not be fully possible. Thus, subjects will not be accrued in the study from March through December 2020. KPSC will continue to monitor RZV uptake in these patient populations in the KPSC system on a regular basis during study conduct.

6. VARIABLES

The RA and IBD cohorts are detailed in Section 7.2.

6.1. Exposures (VE and Safety)

RZV vaccine doses will be identified using CVX code 187: Zoster vaccine recombinant.

6.1.1. VE

Although RZV should be administered as 2 doses separated by 2-6 months, ACIP guidance followed at KPSC specifies that a second dose administered <4 weeks after the first dose should be repeated, but a second dose administered ≥4 weeks after the first dose does not need to be repeated [Anderson, 2022]. Furthermore, due to variation in real-world practice, the second dose may be given earlier than 2 months after the first dose or later than 6 months after the first dose. Additionally, as of January 21, 2022, ACIP guidelines indicate that the second dose of RZV can be administered 1–2 months after the first dose for individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule [Anderson, 2022]. Therefore, VE objectives refer to 2 doses of RZV given at least 4 weeks apart through the end of the study accrual, except where indicated otherwise.

The exposure for primary VE objectives 1-2 is 2 doses of RZV with the second dose received 4 weeks to 6 months after the first dose through the end of study accrual. The exposure for secondary VE objectives 1-3 and 5 and exploratory VE objectives 1-4 is 2 doses of RZV, with the second dose received at least 4 weeks after the first dose ("2-dose [≥4 weeks]"). The exposure for secondary VE objective 4 is 2 doses of RZV, with the second dose received >6 months after the first dose through the end of study accrual. The index date will be date of receipt of the second RZV dose.

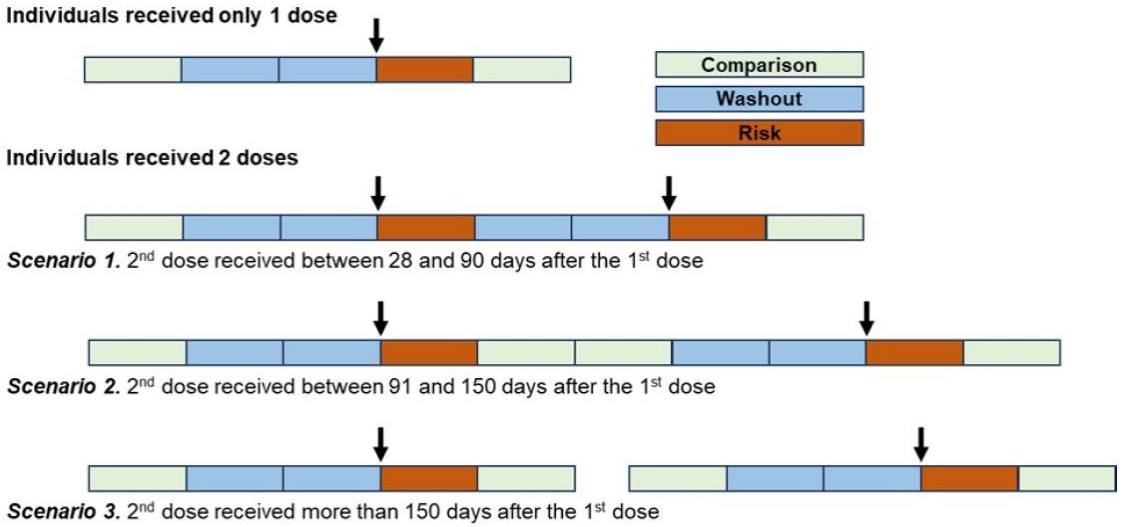
The exposure for secondary VE objectives 6-7 is 1 dose of RZV. The index date will be date of receipt of the first RZV dose. The 1-dose VE will be evaluated in individuals who receive 1 dose of RZV and do not receive a second dose within 6 months after the first dose.

6.1.2. Safety

An SCCS design (Figure 1) will be used. For patients receiving only 1 dose of RZV, the date of vaccination with the first dose of RZV will be defined as Day 0, the risk period will be defined as +1 to +30 days, and comparison periods will be defined as -90 to -61 days and +31 to +60 days (Figure 1, Individuals received only one dose). The washout period will be defined as -60 to -1 days. The 30-day risk period was determined based on prior literature, vaccine mode of action, and consultation with external physician experts (rheumatologists and gastroenterologists) [Basra, 2012; Didierlaurent, 2017].

For individuals who receive a second dose of RZV within 300 days of the first RZV dose, there are several scenarios for additional risk and comparison periods. If the second dose is received between +28 to +90 days after the first dose, the risk period after the first dose will be immediately followed by a washout period up to receipt of the second dose (Figure 1, Scenario 1). If the second dose is received between +91 to +150 days after the first dose, the risk and comparison periods following the first dose will be followed by a 60-day washout period immediately before the receipt of the second dose (Figure 1, Scenario 2). If the second dose is received between +151 days to +300 days after the first dose (expected to be less common), there will be a comparison period -90 to -61 days prior to the second dose and a washout period -60 to -1 days prior to the second dose (Figure 1, Scenario 3). In Scenario 1, the risk window after the first dose could be between 28 and 30 days and the subsequent washout window could be between 0 and 60 days. In Scenario 2, the comparison window between 2 doses could be between 1 and 60 days. The maximum follow-up period will be 360 days after the first dose. Scenarios 2-4 in Figure 1 represent the maximum time period between the first and second dose

Figure 1 SCCS Design Overview for Safety Analysis



6.2. Outcomes (VE and Safety)

6.2.1. VE

HZ

The primary outcome is HZ, identified by ICD-10 code B02.xx in any health care setting (outpatient [to include virtual visits], inpatient, Emergency Department) AND a prescription for a non-topical antiviral (acyclovir, valacyclovir, famciclovir) in the 7 days before or after the HZ diagnosis code date, without a non-topical antiviral (acyclovir, valacyclovir, famciclovir) prescribed in the 183 days to 8 days prior to the HZ diagnosis code date [Langan, 2013; Tseng, 2020]. The first eligible HZ diagnosis after the index date will be considered an incident HZ event.

PHN

PHN will be defined as HZ-related pain persisting ≥3 months after HZ diagnosis. HZ-related pain will be defined as pain consistent with the HZ episode which is not explained by other obvious causes. Targeted chart review will be used to identify PHN from encounters in the ≥3 to 6-month period after HZ diagnosis. Given the potential for poor positive predictive value and negative predictive value for PHN using only automated data (based on prior work by the KPSC research team), all HZ cases with encounters during ≥3 to 6-month period after HZ diagnosis will be chart reviewed for the occurrence of PHN.

Disseminated HZ

Disseminated HZ will be defined as an ICD-10 code for disseminated zoster (B02.7) on or within the 30 days following the incident HZ event date.

HZ-related meningoencephalitis

HZ-related meningoencephalitis will be defined based on ICD-10 codes and laboratory tests among individuals with HZ who are hospitalized during or within the 6 months after the incident HZ event date, based on any of the following criteria: (1) ICD-10 codes for zoster encephalitis (B02.0) or zoster meningitis (B02.1) in the hospital setting, (2) an HZ diagnosis with a cerebrospinal fluid (CSF) PCR or rapid culture test that is positive for VZV, or (3) a herpes viral infection diagnosis (B00.xx) in the hospital setting with a CSF test that is positive for VZV.

Hospitalized HZ

Hospitalized HZ will be identified among incident HZ events with ICD-10 codes for HZ from inpatient encounters or emergency department-to-inpatient transfers.

6.2.2. Safety

The outcome for primary safety objectives 1-2, secondary safety objective 1, and exploratory safety objectives 1-2 is flare, defined as new-onset flare or new-onset of disease worsening of RA (primary safety objective 1, exploratory safety objective 1) or IBD (UC or CD) (primary safety objective 2, secondary safety objective 1, exploratory safety objective 2). Flare will be identified through EHR review by trained research associates and RA or IBD specialists. Events are counted in the period in which earliest symptom onset occurs. Clinically relevant flare is described in Appendix 2.

6.3. Other variable definitions (VE and Safety)

6.3.1. VE

Other variables will be identified from the EHR and considered in analyses when appropriate as covariates, including:

- Demographic variables: age at index date, sex, race/ethnicity
- Health care utilization (number of outpatient [to include virtual visits]/Emergency Department/inpatient encounters) in the year prior to the index date
- Comorbidities (e.g., kidney disease, cardiovascular disease, pulmonary disease [i.e., chronic obstructive pulmonary disease or chronic bronchitis], liver disease, diabetes mellitus, other autoimmune diseases, cancer, immunocompromising conditions [i.e., human immunodeficiency virus, cancer, transplant, immunosuppressive medications], SARS-CoV-2 infection/COVID-19 diagnosis) in the year prior to the index date
- History of ZVL or varicella vaccination prior to the index date based on dates of vaccinations in the EHR
- History of HZ prior to the index date identified using ICD-10 codes (B02.xx) and ICD-9 codes (053.xx) from hospital, outpatient (to include virtual visits), and Emergency Department settings
- Concomitant vaccinations at time of exposure (e.g., receipt of influenza vaccine, pneumococcal vaccine, Tetanus, diphtheria and pertussis vaccine, COVID-19 vaccine)
- Medication category as detailed in Appendix 3.
- Membership history: length of continuous membership (allowing 31 days gap) prior to the index date.

6.3.2. Safety

The SCCS design inherently controls for fixed individual-level confounders. With comparison periods before and after the risk period, the design also controls for time-varying covariates such as age and seasonality.

7. STUDY POPULATION

7.1. Demographics

Table 2 shows the characteristics of individuals with RA and IBD by RZV vaccination status as of 1/1/2020, thus is not indicative of the entire study population. Most of the individuals with RA who were unvaccinated were 50 years or older (80.3%), female (80.7%), and Hispanic or White (78.5%), while most individuals with RA who were vaccinated were 50 years or older (98.8%), female (80.7%), and White or Hispanic (74.5%). In those with IBD for both the vaccinated and unvaccinated, approximately half of the group was female and half male, while over 50% were White in both groups. Due to the expanded indication in July 2021 and new recommendations in October 2021 for RZV vaccination in those ≥18 years of age who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy, the number of vaccinated individuals 18-49 years of age is expected to increase after 2021.

Table 2 Demographic characteristics of RZV unvaccinated and vaccinated individuals with RA and IBD at KPSC as of 1/1/2020

	Rheumatoid arthritis				Inflammatory bowel disease[1]			
	Unvaccinated[2]		Vaccinated[3]		Unvaccinated[2]		Vaccinated[3]	
	N	Percent	N	Percent	N	Percent	N	Percent
Age at index date (years)								
18-49	2831	19.7	15	1.2	3923	44.4	30	3.9
50-69	6758	47.0	611	49.6	3166	35.9	401	52.5
≥70	4797	33.3	607	49.2	1742	19.7	333	43.6
Sex								
Female	11616	80.7	995	80.7	4475	50.7	412	53.9
Male	2770	19.3	238	19.3	4356	49.3	352	46.1
Race/ethnicity								
Asian	1104	7.7	182	14.8	555	6.3	58	7.6
Black	1570	10.9	107	8.7	840	9.5	38	5.0
Hispanic	6265	43.6	340	27.6	2167	24.5	97	12.7
Multiple/Other/ Unknown	432	3.0	26	2.1	351	4.0	12	1.6
White	5015	34.9	578	46.9	4918	55.7	559	73.2
Charlson comorbidity index[4]								
0	0	0.0	0	0.0	4157	47.1	199	26.1
1-2	8645	60.1	649	52.6	3175	36.0	331	43.3
3-4	3645	25.3	361	29.3	999	11.3	165	21.6
5 or higher	2096	14.6	223	18.1	500	5.7	69	9.0
Total	14386	100	1233	100	8831	100	764	100

CD = Crohn's disease; IBD = inflammatory bowel disease; KPSC = Kaiser Permanente Southern California; N = number; RA = Rheumatoid arthritis; RZV = Recombinant Zoster Vaccine; UC = ulcerative colitis

[1]IBD includes UC and CD.

[2]Index date was 1/1/2020. Individuals had ≥1 year of KPSC membership prior to index date, had ≥2 diagnoses of the autoimmune condition in the year prior to index date, and never received RZV prior to 2020.

[3]Index date was date of the first RZV dose from 4/2018-12/2019. Individuals had ≥1 year of KPSC membership prior to index date and had ≥2 diagnoses of the autoimmune condition in the year prior to index date.

[4]Charlson comorbidity index is based on data in the 1 year prior to index date. It includes connective tissue disease-rheumatic disease, and all RA patients had 2 or more rheumatic disease codes in the 1 year prior to index date.

As of January 1, 2018, KPSC membership consisted of 1,495,838 KPSC members aged 50 years and older, 899,592 members aged 60 years and older, and more than 130,000 members aged 80 years and older (Table 3). Approximately 53% of KPSC members were female, and the racial/ethnic composition included White (43%), Hispanic (30%), Asian/Pacific Islander (11%), and African American (9%). Geographically, KPSC covers the entire Southern California region from Bakersfield to San Diego.

Table 3 Demographic distribution of KPSC members 50 years and older on January 1, 2018

Age on January 1, 2018 (years)	Frequency	Percent
50-59	596,246	39.86
60-69	493,190	32.97
70-79	275,722	18.43
80+	130,680	8.74
Sex		
Female	793,381	53.04
Male	702,457	46.96
Race/Ethnicity[1]		
White	636,438	42.55
Hispanic	452,243	30.23
Asian and Pacific Islander	167,298	11.18
African American	138,879	9.28
Multiple/other/unknown	100,980	6.75
Total	1,495,838	100

[1]All categories other than Hispanic are non-Hispanic ethnicity.

Table 4 shows the length of retention of KPSC membership by age group beginning January 1, 2008. Approximately 52% of members aged 50-59, 61% of members aged 60-69 years, and 57% of members aged 70-79 years had completed 10 years of membership at KPSC. For members aged 80 years and older, the percentage of members who completed 10 years of membership at KPSC decreased to 24%. The stability of KPSC membership allows the unique opportunity to follow patients over time and conduct long-term effectiveness studies.

Table 4 Prospective length of KPSC membership among individuals aged ≥50 years on January 1, 2008

		Membership length (years)			Total
		0-5	>5-10	>10	
Age on January 1, 2008 (years)					
50-59	N	145,613	77,164	239,563	462,340
	Row %	31.49	16.69	51.82	
60-69	N	76,378	37,055	176,036	289,469
	Row %	26.39	12.8	60.81	
70-79	N	33,640	34,072	88,441	156,153
	Row %	21.54	21.82	56.64	
80+	N	34,335	23,808	18309	76,452
	Row %	44.91	31.14	23.95	
Total	Frequency	289,966	172,099	522,349	984,414

7.2. Inclusion and exclusion criteria (Eligibility criteria)

7.2.1. Inclusion criteria

Individuals with at least 2 health care encounters with assigned ICD-10 codes for RA or IBD (UC or CD) in the year prior to and including the index date will be identified from the EHR, as specified below. This algorithm was selected based on the literature [MacLean, 2000; Weng, 2007] and KPSC chart review indicated a high positive predictive value of this approach.

Rheumatoid arthritis ICD-10 Codes

- M05.* - Rheumatoid arthritis with rheumatoid factor
- M06.* - Other rheumatoid arthritis

Crohn's disease ICD-10 Codes

- K50.* - Crohn's disease

Ulcerative colitis ICD-10 Codes

- K51.* - Ulcerative colitis

The population for primary VE objective 1, secondary VE objectives 2 and 4-6, and exploratory VE objectives 1 and 3 will be drawn from individuals with RA, and the population for primary VE objective 2, secondary VE objectives 1, 3-5, and 7, and exploratory VE objectives 2 and 4 will be drawn from individuals with IBD (UC or CD).

Similarly, the population for primary safety objective 1 and exploratory safety objective 1 will be drawn from individuals with RA, and the population for primary safety objective 2, secondary safety objective 1, and exploratory safety objective 2 will be drawn from individuals with IBD (UC or CD).

While co-occurrence of both conditions in the same individual is expected to be rare, individuals with both RA and IBD will be included in analyses for both conditions.

Individuals will be included in the study if they meet the following criteria:

VE

- Aged ≥18 years at index date
- At least 1-year of continuous KPSC membership prior to the index date and until 31 days after index date (allowing for a 31-day gap in membership)

Safety

- Received ≥1 dose of RZV
- Aged ≥18 years at date of first RZV dose
- At least 1-year continuous KPSC membership prior to date of first RZV dose (allowing for a 31-day gap in membership)

7.2.2. Exclusion criteria

For both VE and safety objectives, individuals who receive a second dose less than 4 weeks (i.e., 28 days) after the first dose will be excluded, since ACIP guidelines state that these individuals must repeat the second dose [Dooling, 2018].

For the VE objectives, individuals with an HZ diagnosis in the 6 months prior to the index date will be excluded to ensure that HZ diagnoses after the index date are new, rather than carried over from HZ episodes prior to the index date. Individuals with HZ occurring within 30 days after the index date for both vaccinated and unvaccinated groups will also be excluded 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 individuals) is long enough to allow for sufficient development of immunity. Individuals with receipt of zoster vaccine within 30 days after index date will be excluded. Individuals with a death date within 30 days after index date will be excluded.

7.3. Number of participants

Detailed in Section 11.

7.4. Matching for VE analyses

For secondary VE objectives 1-3, secondary VE objective 5, and exploratory VE objectives 1-4, individuals meeting inclusion criteria who receive 2 doses of RZV at least 4 weeks apart through the end of the accrual period will be matched with unvaccinated individuals who have not received any doses of RZV as of the index date at a ratio of 1 to up to 3. For secondary VE objective 4, individuals meeting inclusion criteria who receive 2 doses of RZV >6 months apart through the end of the accrual period, and for primary VE objectives 1-2, individuals meeting inclusion criteria who receive 2 doses of RZV 4 weeks to 6 months apart, and their respective matched unvaccinated comparators will be included. No separate matching is needed.

Matching variables will comprise the following:

- Condition (RA, UC, CD)
- Age (by decade) at index date
- Sex
- Race/ethnicity, if sample size allows
- Medication category at index date (detailed in Appendix 3).

For secondary VE objectives 6-7, individuals who receive 1 dose of RZV but do not receive a second dose 4 weeks to 6 months after the first dose will be matched with unvaccinated individuals who have not received any doses of RZV as of the index date at a ratio of 1 to up to 3. The 1-dose person-time will be censored upon receipt of the second RZV dose received >6 months after the first dose. Matching variables will comprise condition (RA, UC, CD), age (by decade) at index date, sex, race/ethnicity (if sample size allows), and medication category at index date.

The 2-dose (4 weeks to 6 months) RZV cohort and 1-dose RZV cohort will be mutually exclusive. Unvaccinated individuals who are matched to RZV vaccinated individuals can contribute person-time to a vaccinated cohort if they receive RZV; their unvaccinated person-time is censored upon receipt of the first dose of RZV.

8. STUDY PROCEDURES

Not applicable.

9. SAFETY

Regarding management and reporting of adverse events/adverse reactions:

This study is an observational, retrospective, post-authorization safety study, based on data extracted from KPSC databases. Safety as an endpoint will be reported in aggregate; individual case adverse event/adverse reaction reports will not be generated from this study.

Spontaneous reports of serious adverse events (SAEs) received by GSK are processed according to standard pharmacovigilance procedures, which include reporting of adverse events, adverse reactions, and SAEs, to regulatory authorities.

10. DISCONTINUATION/WITHDRAWAL CRITERIA

Not applicable.

11. STATISTICAL CONSIDERATIONS

11.1. Sample size determination and power estimation

Table 5 describes the expected number of individuals ages ≥18 years at KPSC that will be available for full analyses for VE and safety objectives.

Appendix 4: Sample size for early analyses of primary objectives among individuals ≥50 years of age shows similar tables with expected sample size and timelines for early analyses in individuals ages ≥50 years.

Table 5 Sample size and average follow-up time per person (ages ≥18 years) for full analyses

	Sample size for eligible 2-dose RZV recipients[1] (regardless of RA or IBD)	Average follow-up time (years) by 8/2024	RA cohort[2]	IBD cohort[3]
2018	12100	5.8	118	96
2019	53400	5.1	505	386
1/2020-2/2020[4]	12000	4.5	112	58
2021 (estimate)	40000	3.1	364	220
2022 (estimate)[5]	40000	2.1	444	373
1/2023-8/2023 (estimate)	27000	1.2	300	252
Average follow-up time (weighted)		3.5		
Total sample size of 2-dose RZV recipients			1843	1385
Total sample size of at least 1-dose RZV recipients			3071	2308

ACIP = Advisory Committee on Immunization Practices; COVID-19 = Coronavirus Virus Disease 2019; IBD = Inflammatory bowel disease; KPSC = Kaiser Permanente Southern California; RA = rheumatoid arthritis; RZV = Recombinant zoster vaccine; ZVL = Zoster vaccine live

[1]Based on May 2020 uptake and historical ZVL uptake, accounting for 1-year membership prior to index date.

[2]Based on May 2020 uptake, 0.91% of vaccinees age 50+ are RA patients (2 diagnosis codes in year prior to index), and 18% RA patients are age 18-49, accounting for 1-year membership prior to index date.

[3]Based on May 2020 uptake, 0.55% of vaccinees age 50+ are IBD patients (2 diagnosis codes in year prior to index), and 41% IBD patients are age 18-49, accounting for 1-year membership prior to index date.

[4]Vaccine accrual period in 2020 shortened due to impact of COVID-19 on vaccination and health care-seeking behaviors.

[5]Assuming ACIP recommendation of 18+ for immunocompromised individuals in Oct 2021, with KPSC use beginning Jan 2022.

11.1.1. VE

The sample size calculation for the primary VE objectives was conducted using a two-sided log rank test with alpha=0.05, to achieve 80% statistical power, assuming a range of HZ incidence rates in the RZV unvaccinated group (12, 15, 18, 20 per 1000 person-years) [Yun, 2016], a detectable HR of 0.1 to 0.4 (VE of 60% to 90%), a ratio of RZV vaccinated to RZV unvaccinated of 1:3, and a censoring rate of 7% in the RZV vaccinated group (due to termination of membership, or death) and 25% in the RZV unvaccinated group (due to termination of membership, death, or receipt of zoster vaccine). The calculation was performed using SAS software package (version 9.3) PROC POWER procedure.

Table 6 shows that in a cohort study with 1:3 matching ratio and an average 3.5 years of follow-up, the number of vaccinated subjects needed to detect a VE of 60, 70, 80, 90% with 80% power and a type 1 error rate of 5% is 564, 397, 291, and 219, respectively, assuming the incidence of HZ in the unvaccinated population is 15/1000 person-years.

The expected number of RA and IBD patients who will receive 2 doses of RZV (4 weeks to 6 months apart) during the assumed accrual period between 5/2018 to 8/2023 is 1843 and 1385 (Table 5), respectively, substantially exceeding the required numbers illustrated in Table 6. This demonstrates that the study is sufficiently powered to assess the primary VE objectives.

The power for analyses of secondary or exploratory objectives could vary and may not reach 80% depending on available sample size.

Table 6 VE sample size required for individuals ages ≥18 years to achieve 80% power, given alpha=0.05, and different detectable HR (or VE)

Average length of follow-up (years)	Incidence rate in RZV unvaccinated group (cases/1000 person-years)[1]	HR	VE (%)	Total sample size	Sample size of RZV vaccinated group[2]
3.5	12	0.1	90	1096	274
		0.2	80	1452	363
		0.3	70	1984	496
		0.4	60	2816	704
	15	0.1	90	876	219
		0.2	80	1164	291
		0.3	70	1588	397
		0.4	60	2256	564
	18	0.1	90	732	183
		0.2	80	968	242
		0.3	70	1324	331
		0.4	60	1880	470
	20	0.1	90	656	164
		0.2	80	872	218
		0.3	70	1192	298
		0.4	60	1696	424

HR = Hazard ratio; VE = Vaccine effectiveness; RZV = Recombinant zoster vaccine; % = Percentage
[1][Yun, 2016]
[2]The number can be compared with the numbers in Table 5, demonstrating that the study is powered to assess the primary VE objectives.

11.1.2. Safety

The power calculation for the SCCS design is based on the signed root likelihood ratio method [Musonda, 2006]. Let k be the ratio of the length of comparison window vs. length of risk window. The number of flares that need to be observed in the risk window and comparison window to achieve 80% power is shown in Table 7 for different values of detectable RR.

Vaccination (first dose)*: Day 0

Risk period: +1 to +30 days

Comparison period: (-90 to -61 days) AND (+31 to +60 days)

Washout period: -60 to -1 days

**The current sample size calculations are based on the first RZV dose only. The design can be extended to include second RZV dose exposure. The total length of the risk windows and comparison windows will depend on the timing of receipt of the second dose.*

Table 7 Sample size required for individuals ages ≥18 years to achieve 80% power, given alpha=0.05, k=2 and different detectable RR for safety

k	RR	No. of events in the risk period	No. of events in the comparison period
2	1.2	386	643
2	1.5	87	115
2	2	34	34
2	3	16	10

No = Number; RR = Relative risk

Our SCCS design requires at least 115 events in the comparison window to achieve 80% power of detecting an increased risk of flare of RR=1.5 with a type 1 error rate of 5%.

Table 8 Estimated flares and detectable RR for safety among RA cohort ages ≥18 years who receive at least one dose of RZV

Sample size of RA cohort[1]	RA flare rate (per 30 days)[2]	Number of flares in comparison window (60 days)	Detectable RR[3]
3071	1.5%	92	2
3071	2.5%	154	1.5
3071	3%	184	1.5
3071	3.5%	215	1.5
3071	5%	307	1.5
3071	7%	430	1.5

RA = Rheumatoid arthritis; RR = Relative risk; RZV = Recombinant zoster vaccine
[1]Sample size from Table 5 (total sample size of at least 1-dose recipients).
[2][Bechman, 2018 ; Bykerk, 2014 ; Markusse, 2015; Stevens, 2020].
[3]Compare with Table 7.

With 3071 RA patients expected to receive at least one dose of RZV during the accrual period (Table 5), there will be 154 flares in the 60 days comparison period, assuming the flare rate in RA patients is 2.5% in 30 days. This would allow us to detect an increased risk of flare of RR=1.5 (risk of flare in the risk window vs. risk of flare in the comparison window) with 80% power and 5% type 1 error rate (Table 8).

With 2308 IBD patients expected to receive at least one dose of RZV during the accrual period (Table 5), there will be 138 flares in the 60 days comparison period, assuming the flare rate in IBD patients is 3% in 30 days. This would allow us to detect an increased risk of flare of RR=1.5 (risk of flare in the risk window vs. risk of flare in the comparison window) with 80% power and 5% type 1 error rate (Table 9). The power for analysis of the secondary objective may not reach 80% if the number of events is less than the desired size due to smaller sample size in IBD subgroups.

Table 9 Estimated flares and detectable RR for safety among IBD cohort ages ≥18 years who receive at least one dose of RZV

Sample size of IBD cohort[1]	IBD flare rate (per 30 days)[2]	Number of flares in comparison window (60 days)	Detectable RR[3]
2308	1%	46	2
2308	1.5%	69	2
2308	2%	92	2
2308	3%	138	1.5
2308	4%	185	1.5

IBD = Inflammatory bowel disease; RR = Relative risk; RZV = Recombinant zoster vaccine
[1]Sample size from Table 5 (total sample size of at least 1-dose recipients).
[2][Bolge, 2010 ; Satyam, 2020 ; Rahier, 2011].
[3]Compare with Table 7

11.2. Statistical analyses

11.2.1. Descriptive

For the VE analyses, the number and characteristics of individuals in each cohort will be described and compared. Categorical variables such as those listed above 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. Overall incidence rates of HZ for the 2-dose (4 weeks to 6 months) 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.

11.2.2. Primary analyses

For primary VE objectives 1-2, the number of incident HZ cases and the number of person-years of follow-up for subjects will be assessed for the 2-dose (4 weeks to 6 months) RZV cohort and the matched unvaccinated cohort.

Unadjusted and adjusted HRs and 95% confidence intervals (CIs) comparing HZ incidence rates in the 2-dose (4 weeks to 6 months) RZV cohort and the matched

unvaccinated cohort will be estimated by Cox stratified proportional hazards regression models without and with adjusting for potential confounders described above. Estimates of VE (%) will be calculated as (1 –HR) × 100 when the HR is less than or equal to 1, and ([1/HR] – 1) × 100 when the hazard ratio is greater than 1.

The VE of 2 doses of RZV by time since vaccination will also be evaluated.

For the primary safety analyses, characteristics of individuals with RA or IBD who meet inclusion criteria will be described. Incidence rates for RA or IBD (UC or CD) flare for risk periods and comparison periods will be calculated by dividing the number of flares by person-time. Relative risks (95% CI) for flare comparing risk and comparison periods overall and by first dose and second dose will be estimated using conditional Poisson regression.

11.2.3. Secondary analyses

For secondary and exploratory analyses, subgroups may be recategorized in post-hoc analyses if sample size in a subgroup is small

Secondary VE objectives 1-3: Analyses for secondary VE objectives 1-3 (2 doses of RZV given at least 4 weeks apart) will employ similar methods as for the primary VE analyses. In secondary VE objective 1, analyses for IBD (primary VE objective 2) will be stratified by UC and CD. In secondary VE objective 2, analyses for RA (primary VE objective 1) will be stratified by age group (18-49 years and ≥50 years [≥50 years, 50-59 years, 60-69 years, and ≥70 years]). In secondary VE objective 3, analyses for IBD (primary VE objective 2) will be stratified by age group (18-49 years and ≥50 years [≥50 years, 50-59 years, 60-69 years, and ≥70 years]). Descriptive analyses and multivariable Cox proportional hazards regression will be conducted by strata and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Secondary VE objectives 4-5: Analyses for secondary VE objectives 4-5 will employ similar methods as for the primary VE analyses. For secondary VE objective 4, the 2-dose RZV cohort will include individuals who receive their second dose >6 months after the first dose during the accrual period. For secondary VE objective 5, the 2-dose RZV cohort will include individuals who receive their second dose at least 4 weeks after the first dose during the accrual period. Analyses will be stratified by condition (RA or IBD). The VE of 2 doses (≥4 weeks apart) of RZV by time since vaccination will also be evaluated.

Secondary VE objectives 6-7: Analyses for secondary VE objectives 6-7 will be conducted among the matched cohorts of individuals with RA (secondary VE objective 6) or with IBD (secondary VE objective 7) who receive 1 dose of RZV and do not receive a second dose within 6 months after the first dose. Individuals will be followed from 31 days after the index date until occurrence of HZ, termination of membership, receipt of a dose of RZV for unvaccinated individuals, receipt of a second dose of RZV >6 months after the first dose among vaccinated individuals, or end of study period, whichever comes first. Descriptive analyses and multivariable Cox proportional hazards

regression will be conducted and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100. The VE of 1 dose of RZV by time since vaccination will also be evaluated.

Secondary safety objective 1: Analyses for IBD will be stratified by UC or CD.

11.2.4. Exploratory analyses

Exploratory VE objectives 1-2: Analyses for exploratory VE objectives 1-2 (2 doses of RZV given at least 4 weeks apart) will employ similar methods as for the primary VE objectives. In exploratory VE objective 1, analyses for RA (primary VE objective 1) will be stratified by medication category at index date (Appendix 3). In exploratory VE objective 2, analyses for IBD (primary VE objective 2) will be stratified by medication category at index date (Appendix 3). Descriptive analyses and multivariable Cox proportional hazards regression will be conducted by strata and estimates of VE (%) will be calculated as (1 – adjusted HR) × 100.

Exploratory VE objectives 3-4: For exploratory VE objectives 3-4, the incidence of PHN, disseminated HZ, HZ-related meningoencephalitis, and hospitalized HZ will be described in 2-dose (2 doses of RZV given at least 4 weeks apart) RZV vaccinated and unvaccinated adults ≥18 years with RA (exploratory VE objective 3) and IBD (exploratory VE objective 4). The proportion of HZ cases with PHN, disseminated VZV, VZV-related meningoencephalitis, and hospitalized HZ will also be described among RZV vaccinated and unvaccinated adults ≥18 years with RA and IBD. Hospitalized HZ will be evaluated in the final analysis only (i.e., not in the interim analysis).

Exploratory safety objectives 1-2: In exploratory safety objective 1, analyses for RA (primary safety objective 1) will be stratified by medication category at index date (Appendix 3) if sample size allows. In exploratory safety objective 2, analyses for IBD (primary safety objective 2) will be stratified by medication category at index date (Appendix 3) if sample size allows.

11.3. Sequence of analyses and projected study timelines

The effectiveness and safety of RZV in adults with RA or IBD (UC or CD) at KPSC will be examined, with primary VE, select secondary VE, and primary safety results for individuals ages ≥50 years estimated first during the first half of 2024, and full results for individuals ages ≥18 years to be available to GSK at the end of the study (late 2025) Appendix 4.

Appendix 4: Sample size for early analyses of primary objectives among individuals ≥50 years of age shows sample size estimations for early analyses in individuals ages ≥50 years.

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13. APPENDICES

13.1. Appendix 1: Abbreviations and glossary of terms

13.1.1. List of abbreviations

5-ASA	5-aminosalicylate
ACIP	Advisory Committee on Immunization Practices
AID	Autoimmune Disease
CD	Crohn's Disease
CI	Confidence Interval
COVID-19	Coronavirus Virus Disease 2019
CSF	Cerebrospinal Fluid
DMARD	Disease-Modifying Antirheumatic Drug
EnCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EHR	Electronic Health Record
EMA	European Medicines Agency
EU PAS	European Union electronic Register of Post-Authorisation Studies
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline Biologicals SA
HR	Hazard Ratio
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
IRB	Institutional Review Board
JAK	Janus Kinase
KPSC	Kaiser Permanente Southern California
MTX	Methotrexate
NSAID	Nonsteroidal Anti-Inflammatory Drug
PHN	Post-Herpetic Neuralgia
RA	Rheumatoid Arthritis
RR	Relative Risk
RZV	Recombinant Zoster Vaccine

SAEs	Serious Adverse Events
SAS	Statistical Analysis System
SCCS	Self-Controlled Case Series
TNF	Tumor Necrosis Factor
U.S.	United States
UC	Ulcerative Colitis
VE	Vaccine Effectiveness
VZV	Varicella Zoster Virus
ZVL	Zoster Vaccine Live

13.1.2. Glossary of terms

Day 0	For safety objectives, the date of vaccination with the first dose of RZV
Flare	Clinically relevant new-onset flare or new-onset disease worsening of RA or IBD (UC or CD) (Appendix 2)
HZ	Herpes zoster (shingles), an often painful vesicular rash caused by reactivation of VZV persisting latently in dorsal root ganglia
Index date	For 2-dose RZV VE objectives, the index date is the date of receipt of the second dose of RZV for vaccinated individuals and their unvaccinated matches. For 1-dose RZV VE objectives, the index date is the date of receipt of the first dose of RZV for vaccinated individuals and their unvaccinated matches.
PHN	Neuropathic pain that arises from sensory (dorsal root or trigeminal ganglion cells). HZ-related pain persisting ≥3 months after HZ diagnosis.
RZV	A 2-dose subunit zoster vaccine containing recombinant glycoprotein E in combination with a novel adjuvant

13.2. Appendix 2: Definition of clinically relevant flare

Definition of "clinically relevant" flare

For this study, flare is defined as clinically relevant new-onset flare or new-onset disease worsening of RA (primary safety objective 1, exploratory safety objective 1) or IBD (UC or CD) (primary safety objective 2, secondary safety objective 1, exploratory safety objective 2). This definition was selected in consultation with rheumatologist and gastroenterologist experts, recognizing that new-onset disease worsening can be difficult to differentiate from flare. Trained research associates and RA or IBD specialists will review all potential flare events, according to the following case definition:

1. Contact with health care provider via documented phone call, email, telehealth visit, or in-person office, Emergency Department, or inpatient visit, AND
2. New or worsening signs and/or symptoms suggestive of a flare (at least one of the signs or symptoms below):
    a. RA – joint swelling, joint pain/tenderness, joint stiffness.
    b. IBD – abdominal pain/tenderness, diarrhea (increased stool frequency and/or soft or liquid stool), urgency, rectal bleeding, blood in stool, nausea/vomiting, unintentional weight loss.
    c. Provider mention of flare, worsening of disease, recurrence, or relapse

AND

1. Change in medication for flare*:

    Proposed medication regimen change/escalation algorithm for flare

    a. Intra-articular corticosteroid joint(s) injection (for RA), or
    b. Initiation of systemic corticosteroid (e.g., prednisone), or
    c. Increase in dose of baseline systemic corticosteroid (e.g., prednisone 5 mg daily to prednisone 40 mg daily with taper), or
    d. Switch in methotrexate (MTX) from oral route to subcutaneous (for RA), or
    e. Increase in dose and/or frequency of administration of any medication in current baseline regimen, or
    f. Addition of another medication to current medication regimen (e.g., MTX to current regimen of hydroxychloroquine [(Plaquenil),], biologic to current regimen of MTX), or
    g. Switch of a current medication to another medication, in the same or different category (e.g., MTX + tumor necrosis factor [TNF]-alpha inhibitor to MTX + tofacitinib; MTX + TNF-alpha inhibitor to MTX + a different TNF-alpha inhibitor)

    *Exclude medication changes for any reasons other than for flare, such as acute kidney injury or other adverse effects from prior medication.

Chart review will be performed among individuals eligible for the safety analysis. Trained research associates will review medical records from health care encounters during risk windows, comparison windows, and the 30 days after a risk or comparison window (while masked to the precise window) for evidence of flare. They will identify new or worsening signs and/or symptoms suggestive of a flare and capture the date of onset of new or worsening signs and/or symptoms. They will determine whether a change in medication was made for flare by a provider. Cases with unclear sign and/or symptoms, date of onset, or change in medication for flare will be reviewed by an RA or IBD specialist.

13.3. Appendix 3: Medication categories

a. Vaccinated and unvaccinated subjects will be matched on age, sex, race/ethnicity (if sample size allows), autoimmune disease (RA, CD, UC), and medication category (as a proxy for disease severity and risk of HZ) at the beginning of follow-up (index date). The medication categories were developed based on consultation with KPSC and external experts (rheumatologists and gastroenterologists) to ensure matching based on differences in disease severity and risk of HZ.

b. Search period

- Rituximab (Rituxan) or rituximab-abbs/rituximab-pvvr (Truxima): 6 months before index date[1]
- Biologics: 3 months before index date[2]
- JAK inhibitors, sphingosine-1 phosphate (S1P) receptor modulators, cyclosporine: 3 months before index date to 1 month after index date[3]
- Nonsteroidal anti-inflammatory drugs (NSAIDs), 5-aminosalicylate (5-ASA), aminosalicylate, sulfasalazine, thiopurines, steroids, and conventional DMARDs: Medication prescribed/refilled within 6 months prior to index date AND medication duration covers the index date[4]

c. Medication category will be determined by the highest category of medication during the search period.

d. Medication categories may be consolidated to ensure at least 1:1 matching.

[1]Rituximab is typically dosed every 6 months, so the search period for rituximab is 6 months before the index date.

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

[3]The search period for JAK inhibitors and S1P modulators is extended to 1 month after the index date; because JAK inhibitors and S1P modulators are associated with a significantly increased risk of HZ, [Bechman, 2019; Choden, 2022; Colombel, 2018; Curtis, 2019; Lasa, 2021; Marra, 2016; Sandborn, 2019; Winthrop, 2017; Yun, 2015] providers may administer RZV prior to initiating treatment with a JAK inhibitor or S1P modulator. Since cyclosporine is included in the same IBD medication category as JAK inhibitors and S1P modulators, the same search period will be used.

[4]While medications are typically dispensed as a ≤90-day supply, some medications are occasionally dispensed as a ≥100-day supply. To ensure identification of prescriptions covering the index date, medications prescribed/refilled within 6 months prior to the index date will be searched to identify those medications with a duration covering the index date.

Appendix Table 1 RA medication category

Category 1	No treatment Or NSAID: ibuprofen (Motrin, Advil), naproxen (Aleve, Anaprox, Mediproxen), indomethacin (Indocin, Tivorbex), meloxicam (Vivlodex, Mobic, Comfort Pac Meloxicam), celecoxib (Celebrex), nabumetone (Relafen), etodolac (Lodine), diclofenac (Xrylix, Voltaren, Solaraze, Flector, Zorvolex, Zipsor, Cambia), sulindac (Clinoril), salsalate (Disalcid), ketorolac (Toradol, Acular, ReadySharp Ketorolac Kit) Or 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), tocilizumab-bavi (Tofidence)*, sarilumab (Kevzara), adalimumab (Humira), adalimumab-atto (Amjevita)*, adalimumab-afzb (Abrilada)*, adalimumab-adbm (Cyltezo)*, adalimumab-bwwd (Hadlima)*, adalimumab-fkjp (Hulio)*, adalimumab-adaz (Hyrimoz)*, adalimumab-aqvh (Yusimry)*, adalimumab-aacf (Idacio)*, adalimumab-aaty (Yuflyma)*, 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, Depo-Medrol), prednisolone, prednisone
Category 5	JAK inhibitors: tofacitinib (Xeljanz, Xeljanz XR), baricitinib (Olumiant), upadacitinib (Rinvoq)

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

*Medication will be explicitly searched for in the final analysis only, mainly reflecting newly licensed medications. These medications may have been captured for the interim analysis since the search for biosimilars was based on the root name (reference product, e.g., adalimumab) and not limited to the brand names or 4-letter suffix.

Appendix Table 2 IBD medication category

Category 1	No treatment
Category 2	Aminosalicylate (*5-ASA*): aminosalicylate (5-ASA), sulfasalazine (Azulfidine), olsalazine (Dipentum), mesalamine (Canasa, Asacol, Pentasa, Apriso, Lialda, Rowasa, Delzicol), balsalazide (Giazo, Colazal) Or Low dose steroids (all <20 mg prednisone or equivalent): Hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol), prednisolone, prednisone, budesonide (Entocort/Uceris)
Category 3	Biologics: infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra, Zymfentra*), adalimumab (Humira), adalimumab-adaz (Hyrimoz), adalimumab-adbm (Cyltezo), adalimumab-atto (Amjevita), adalimumab-afzb (Abrilada)*, adalimumab-fkjp (Hulio)*, adalimumab-aqvh (Yusimry)*, adalimumab-aacf (Idacio)*, adalimumab-aaty (Yuflyma)*, adalimumab-bwwd (Hadlima), vedolizumab (Entyvio), ustekinumab (Stelara), ustekinumab-auub (Wezlana)*, golimumab (Simponi), certolizumab (Cimzia), natalizumab (Tysabri), mirikizumab-mrkz (Omvoh)*, risankizumab-rzaa (Skyrizi)* Or Conventional DMARD: MTX (Trexall, Xatmep, Otrexup, Rheumatrex, Rasuvo) Or Thiopurines: azathioprine (Imuran, Azasan), mercaptopurine (Purinethol), and thioguanine (6-TG, Tabloid or Lanvis)

Category 4	High dose systemic steroids (any ≥20 mg prednisone or equivalent): hydrocortisone, methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol), prednisolone, prednisone, budesonide (Entocort)
Category 5	JAK inhibitors: tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq)* Or S1P modulator: etrasimod (Velsipity)*, ozanimod (Zeposia)* Or Cyclosporine (Gengraf, Neoral, Sandimmune)

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

*Medication will be explicitly searched for in the final analysis only, mainly reflecting newly licensed medications. These medications may have been captured for the interim analysis since the search for biosimilars was based on the root name (reference product, e.g., adalimumab) and not limited to the brand names or 4-letter suffix.

13.4. Appendix 4: Sample size for early analyses of primary objectives among individuals ≥50 years of age

Appendix Table 3 Sample size and average follow-up time per person (ages ≥50 years) for early analyses

	Sample size for eligible 2-dose RZV recipients[1] (regardless of RA or IBD)	**Average follow-up time (years) by 12/2022**	**RA cohort[2]**	**IBD cohort[3]**
2018	12100	4.25	118	96
2019	53400	3.5	505	386
1/2020-2/2020[4]	12000	2.9	112	58
2021 (estimate)	40000	1.5	364	220
Average follow-up time (weighted)		2.8		
Total sample size of 2-dose RZV recipients			1099	760
Total sample size of at least 1-dose RZV recipients			1832	1267

IBD = Inflammatory bowel disease; RA = Rheumatoid arthritis; RZV = Recombinant zoster vaccine; ZVL = Zoster vaccine live

[1]Based on May 2020 uptake and historical ZVL uptake, accounting for 1-year membership prior to index.
[2]Based on May 2020 uptake, 0.91% of vaccinees age 50+ are RA patients (2 diagnosis codes in year prior to index).
[3]Based on May 2020 uptake, 0.55% of vaccinees age 50+ are IBD patients (2 diagnosis codes in year prior to index).
[4]Vaccine accrual period in 2020 shortened due to impact of COVID-19 on vaccination and health care-seeking.

Appendix Table 4 Sample size required for individuals ages ≥50 years to achieve 80% power, given alpha 0.05, and different detectable HR (or VE)

Average length of follow-up (years)	Incidence rate in RZV unvaccinated group (cases/1000 person-years)[1]	HR	VE (%)	Total Sample Size	Sample size of RZV vaccinated group[2]
2.8	15	0.1	90	1068	267
		0.2	80	1404	351
		0.3	70	1904	476
		0.4	60	2684	671
	18	0.1	90	892	223
		0.2	80	1172	293
		0.3	70	1588	397
		0.4	60	2236	559
	20	0.1	90	800	200
		0.2	80	1052	263
		0.3	70	1428	357
		0.4	60	2012	503

HR = Hazard ratio; RZV = Recombinant zoster vaccine; VE = Vaccine effectiveness; % = percentage

[1][Yun, 2016]

[2]The number can be compared with the numbers in Appendix Table 3, demonstrating that the study is powered to assess the primary VE objectives for the early analyses.

Appendix Table 5 Sample size required for individuals ages ≥50 years to achieve 80% power, given alpha=0.05, k=2 and different detectable RR for safety

k	RR	No. of events in the risk period	No. of events in the comparison period
2	1.2	386	643
2	1.5	87	115
2	2	34	34
2	3	16	10

No = Number; RR = Relative risk

Appendix Table 6 Estimated flares and detectable RR for safety among RA cohort ages ≥50 years who receive at least one dose of RZV

Sample size of RA cohort[1]	RA flare rate (per 30 days)[2]	Number of flares in comparison window (60 days)	Detectable RR[3]
1832	1.5%	55	2.0
1832	2.5%	92	2.0
1832	3%	110	2.0
1832	3.5%	128	1.5
1832	5%	183	1.5
1832	7%	256	1.5

RA = Rheumatoid arthritis; RR = Relative risk; RZV = Recombinant zoster vaccine
[1]Sample size from Appendix Table 3 (total sample size of at least 1-dose recipients).
[2][Bechman, 2018; Bykerk, 2014 ; Markusse, 2015; Stevens, 2020].
[3]Compare with Appendix Table 5.

Appendix Table 7 Estimated flares and detectable RR for safety among IBD cohort ages ≥50 years who receive at least one dose of RZV

Sample size of IBD cohort[1]	IBD flare rate (per 30 days)[2]	Number of flares in comparison window (60 days)	Detectable RR[3]
1267	1%	25	3.0
1267	1.5%	38	2.0
1267	2%	51	2.0
1267	3%	76	2.0
1267	4%	101	2.0

IBD = Inflammatory bowel disease; RR = Relative risk; RZV = Recombinant zoster vaccine
[1]Sample size from Appendix Table 3 (total sample size of at least 1-dose recipients).
[2][Bolge, 2010 ; Satyam, 2020 ; Rahier, 2011].
[3]Compare with Appendix Table 5.

13.5. Appendix 5: Study governance considerations

13.5.1. 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 International Ethical Guidelines
  - FDA Code of Federal Regulations Title 21 (21 CFR)
  - GPP
  - All other applicable regulations and local laws
- The protocol, protocol amendments, and other relevant documents must be submitted to an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Providing oversight of the conduct of the study at the site and adherence to all applicable regulations and local laws.

The protocol will be reviewed and approved by the KPSC IRB. All study staff with access to protected health information are trained in procedures to protect the confidentiality of subject data. As this is a data-only study, a waiver for individual written Health Insurance Portability and Accountability Act (HIPAA) authorizations prior to initiating data collection using EHR will be obtained. Adverse event reporting is not required as part of this study, as this is a non-interventional study based on secondary use of KPSC EHR.

13.5.2. Legal requirements and data protection

Federal Policy for the Protection of Human Subjects is codified by the Department of Health and Human Services 45 Code of Federal Regulations Part 46 which outlines the basic regulations governing the protection of human subjects in research, including requirements for assuring compliance by research institutions, requirements for obtaining and documenting informed consent, and requirements for IRB membership, function, operations, review of research, and record keeping.

The HIPAA Privacy Rule governs the use and disclosure of protected health information (PHI) from covered entities. Throughout the course of the study, no human subjects will be contacted or enrolled, and no PHI will be disclosed; however, PHI will be accessed through the EHR. This information will only be accessed by those authorized to do so and will not be shared with GSK or anyone outside of the KPSC study team. Electronic study data will be stored in files on the KPSC secure network. The KPSC team will obtain institutional approval to use PHI for research activities. Since this access to PHI presents no more than minimal risk to individuals, and the research could not be practically done if required to obtain written authorization for usage, a waiver for written HIPAA authorization for research involving use of the EHR to conduct the study will be obtained.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

Additionally, all investigators and project managers are trained in the protection of human research participants, GPP, and HIPAA. The KPSC Department of Research and Evaluation has policies in place to govern the conduct and administration of research at KPSC. These policies support compliance with federal and state regulatory requirements. Policies include conflict of interest, misconduct, sensitive data, and system access control. Policies are in place to ensure compliance with the Sunshine Act. All KPSC staff undergo annual compliance training and certification. The Principles of Responsibility is KPSC's code of conduct that addresses such issues as protection of confidential information and anti-bribery and corruption.

13.5.3. Data management

Data management activities will be performed by KPSC. The KPSC EHR will be the data source for extracting information on exposures, outcomes, and covariates. KPSC will develop the study datasets, maintain documentation, and perform data quality checks.

Programmers will extract data per protocol and reference documentation for KPSC EHR databases. They will conduct data quality checks which include data integrity control, double programming, and program review. Data integrity control will include checks such as sample size, duplications, formatting, etc. Double programming (i.e., programming independently conducted by 2 people) will be performed on the cohort extraction as well as outcome variables. The results of the original and validation programming will be compared, discrepancies will be investigated, and action will be taken to resolve discrepancies. Program review (i.e., a second person reviews the code of the lead programmer) will be performed on covariate extraction and statistical analyses. All decisions made during data extraction and data quality checks will be documented in a programming decision log.

13.5.4. Committee structure

Not applicable.

13.5.5. Dissemination of study data

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

13.5.6. Data quality assurance

Data quality details are provided above in Section 13.5.3.

13.5.7. Publication policy

Results of the study will be submitted for publication in accordance with International Committee of Medical Journal Editors (ICMJE) guidelines.

13.5.8. EnCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	1.3 and 5.1
1.1.2 End of data collection[2]	☒	☐	☐	1.3 and 5.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	11.3
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Page 1
1.1.6 Final report of study results.	☒	☐	☐	11.3

Comments:

1.1.1 and 1.1.2: This is an observational retrospective study and existing data sources will be used. 1.1.3: No formal progress reports will be done for this study.

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	3
2.1.2 The objective(s) of the study?	☒	☐	☐	4
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

2.1.4 and 2.1.5: Sponsor and study site have decided to remove the hypothesis section from the protocol template (not applicable for this study design).

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

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	5.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	3.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	4
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	11.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

Nil

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	3.1 and 7.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	5.1
4.2.2 Age and sex	☒	☐	☐	5.1
4.2.3 Country of origin	☒	☐	☐	5.1
4.2.4 Disease/indication	☒	☐	☐	5.1
4.2.5 Duration of follow-up	☒	☐	☐	5.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2

Comments:

Nil

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	5.1 and 6.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	3.2
5.3 Is exposure categorised according to time windows?	☒	☐	☐	5.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	5.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	5.1 and 7.4

Comments:

5.5: Biological mechanism of action is not applicable.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4 and 6.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	6.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	5.2 and 6.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

6.4: Health Technology Assessment is not applicable.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	6.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	5.2.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	5.2.2 and 6.2

Comments:

Nil

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	4

Comments:

Nil

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	3.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	3.2
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	Yes	No	N/A	Section Number
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	6.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	6.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	6.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	6.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	6.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	6.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	3.2

Comments:

Nil

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	11
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	11
10.3 Are descriptive analyses included?	☒	☐	☐	11
10.4 Are stratified analyses included?	☒	☐	☐	11
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	11
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

10.6: Outcome misclassification will be accounted for in non-analytic ways; it will be controlled by chart confirmation of PHN and flare outcomes as well as an algorithm for HZ detailed in Section 6.2.1. 10.7: Methods for handling missing data will be addressed in the SAP. 10.8: No sensitivity analyses are planned for this study.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	13.5.2
11.2 Are methods of quality assurance described?	☒	☐	☐	13.5.3
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.3: There is no independent data monitoring committee for this observational study.

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	5.2.2
12.1.2 Information bias?	☒	☐	☐	5.2.2
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	5.2.1 and 5.2.2
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	5.1, 7.1, and 11.1

Comments:

Nil

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13.5.1 and 13.5.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	13.5.2

Comments:

13.2: The study has not yet been submitted to the IRB for approval.

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

Comments:

14.1: Future amendments will be documented as protocol amendments.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13.5.5 and 13.5.7
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13.5.5 and 13.5.7

Comments:

Nil

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

13.6. Appendix 6: Protocol Amendment history

The Protocol Amendment Summary of Changes Table for the current amendment (Amendment 2) is located directly before the Table of Contents

DOCUMENT HISTORY	
Document	**Date of Issue**
Protocol Amendment 2	09 Jan 2025
Protocol Amendment 1	01 Feb 2024
Original protocol	2 March 2022

Overall rationale for the current amendment 2:

The protocol has been amended to clarify the study design, accrual, analysis, and medication list.

Overall rationale for protocol amendment 1:

The protocol has been amended to document changes prior to conduct of interim analysis (i.e., early analysis in individuals ages ≥50 years). Other administrative updates and typographical corrections were made throughout the document for better clarity.

List of main changes in the protocol and their rationale:

Section # and title	**Description of change**	**Brief rationale**
1.3 Overall design	Replaced "receipt of a dose of RZV for unvaccinated individuals" with "receipt of a subsequent dose of zoster vaccine". Added age groups by decade of age for individuals in the age group of ≥50 years.	Clarify censoring events. Clarify age stratification for secondary analyses.
4. Objectives and outcomes (Table 1)	Added hospitalized HZ as an exploratory VE outcome.	Evaluate incidence of hospitalized HZ as an exploratory VE objective.

Section # and title	Description of change	Brief rationale
5.1 Overall design	Edited description of censoring events. Added age groups by decade of age for individuals in the age group of ≥50 years.	Clarify censoring events. Clarify age stratification for secondary analyses.
6.2.1 VE (Outcomes)	Clarified type of CSF testing required for diagnosis of HZ-related meningoencephalitis. Added definition of hospitalized HZ outcome.	Clarify outcome definition. Evaluate incidence of hospitalized HZ as an exploratory VE objective.
6.3.1 VE (Other variable definitions)	Added membership history as a variable.	Characterize membership history and adjust as covariate when appropriate.
7.2.1 Inclusion criteria	For VE inclusion criteria, required membership “until 31 days after index date”.	Clarify inclusion criteria for VE.
7.2.2 Exclusion criteria	Edited exclusion criteria for VE to exclude those with receipt of zoster vaccine or death within 30 days after index date.	Clarify exclusion criteria for VE.
11.1.1 VE	Edited description of censoring events.	Clarify censoring events.
11.2.3 Secondary analyses	Added age groups by decade of age for individuals in the age group of ≥50 years. Added VE analyses by time since vaccination.	Clarify age stratification for secondary analyses. Evaluate VE by time since vaccination.
11.2.4 Exploratory analyses	Added hospitalized HZ as an exploratory VE outcome.	Evaluate incidence of hospitalized HZ as an exploratory VE objective.

Section # and title	Description of change	Brief rationale
13.2 Appendix 2: Definition of clinically relevant flare	Added email as a type of contact with health care provider.	Clarify health care provider contact types.
13.3 Appendix 3: Medication categories	Edited RA and IBD medications.	Clarify and update RA and IBD medications.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 28-Dec-2024 05:43:27 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 09-Jan-2025 15:22:19 GMT+0000

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