

NON-INTERVENTIONAL STUDY REPORT**TITLE PAGE****Division:** Research and Development**Information Type:** Non-Interventional Study Report

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

Compound Number: GSK1437173A

Effective Date: 10 Dec 2025

Subject: Vaccine effectiveness and safety of RZV in the rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) patient populations ≥ 18 years of age

Author(s):

PPD

PPD

PPD

PPD

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Indication Studied: Prevention of herpes zoster in RA and IBD adult patient populations

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STUDY INFORMATION

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
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Date of last version of report	10 Dec 2025
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Active substance	VZV glycoprotein E (gE)
Medicinal product	Shingrix (Recombinant Zoster Vaccine, RZV)
Product reference	<u>For EMA:</u> EU/1/18/1272/001-1 Vial and 1 vial; EU/1/18/1272/002-10 vials and 10 vials <u>For FDA:</u> IND #013879
Procedure number	EMA/H/C/004336
Marketing authorisation holder(s)	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 were to estimate the 2-dose VE of RZV in preventing HZ in adults ≥ 18 years of age with RA or IBD. The primary safety objectives were 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	PPD
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MARKETING AUTHORISATION HOLDER(S)

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

STUDY DETAILS

UNIQUE IDENTIFIER	213825
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
STUDY ACCOUNTABLE PERSON	PPD NIS & Planning Study Delivery Lead
CONTRIBUTING AUTHORS	Kaiser Permanente Southern California
ASSET ID	GSK1437173A
GSK ASSET	Recombinant Zoster Vaccine (Shingrix)
EFFECTIVE DATE	10 Dec 2025
INDICATION	Shingrix is indicated for the prevention of herpes zoster (HZ) and HZ-related complications, such as postherpetic neuralgia (PHN), in: - Adults 50 years of age or older; - Adults 18 years of age or older at increased risk of HZ (in the EU); and - Adults 18 years of age or older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy (in the US)

REPORT REVISION HISTORY

Date	Version	Change(s) since last version
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SPONSOR SIGNATORY

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

Compound Number: GSK1437173A

Elizabeth Chmielewski-Yee
Primary Author/NI Scientific Lead

Date (DD Month YYYY)

Huifeng Yun
Therapy Area Leader/+1 Manager

Date (DD Month YYYY)

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

INVESTIGATOR REPORT AGREEMENT PAGE

- I have read this report and confirm that to the best of my knowledge the study was carried out as described in this GSK report
- I acknowledge that I was responsible for overall study conduct. I personally conducted or supervised the described clinical study.
- I ensured that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations. Mechanisms were in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name:

Hung-Fu Tseng

Investigator Signature

Date (DD Month YYYY)

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LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylate
ACIP	Advisory Committee on Immunization Practices
AID	Autoimmune Disease
AIDS	Acquired Immunodeficiency Syndrome
aOR	Adjusted Odds Ratio
ASD	Absolute Standardized Difference
CD	Crohn's Disease
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CSF	Cerebrospinal Fluid
DMARD	Disease-Modifying Antirheumatic Drug
ED	Emergency Department
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
GSK	GlaxoSmithKline Biologicals SA
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
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
PCV	Pneumococcal Conjugate Vaccine
PHI	Protected Health Information
CCI	CCI
PPSV	Pneumococcal Polysaccharide Vaccine
RA	Rheumatoid Arthritis
RR	Relative Risk
RZV	Recombinant Zoster Vaccine
SAEs	Serious Adverse Events
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SCCS	Self-Controlled Case Series
SD	Standard Deviation
Tdap	Tetanus, Diphtheria, and Acellular Pertussis Vaccine
TNF	Tumor Necrosis Factor
U.S.	United States
UC	Ulcerative Colitis
VAHS	Veterans Affairs Healthcare System
VE	Vaccine Effectiveness
VZV	Varicella Zoster Virus
ZVL	Zoster Vaccine Live

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1. RESPONSIBLE PARTIES

Kaiser Permanente Southern California

Hung-Fu Tseng, Principal Investigator

Department of Research & Evaluation

Kaiser Permanente Southern California
100 S. Los Robles Ave, 2nd Floor
Pasadena, CA 91101

PPD

PPD

GSK

Responsible Party	Details
Epidemiology Lead	PPD
Epidemiology Head	PPD
Study Delivery Lead	PPD

2. SYNOPSIS

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

Keywords: Herpes zoster, vaccine effectiveness, vaccine safety, recombinant zoster vaccine, rheumatoid arthritis, inflammatory bowel disease

Rationale and background

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; Long, 2013; Yun, 2016; Khan, 2018]. Given the increased risk of HZ among those with AID, RZV may provide a substantial benefit to this at-risk population, but further studies are needed to examine its effectiveness and safety. In July 2021, the Food and Drug Administration (FDA) expanded the indication for RZV to include adults who are immunodeficient or immunosuppressed due to known disease or therapy [U.S. Food & Drug Administration, 2017]. This study aimed to provide vaccine effectiveness (VE) and safety data (risk of flare) in adult patients with RA and IBD, including UC or CD. The study was conducted at Kaiser Permanente Southern California (KPSC), an integrated health care system in the United States.

Research questions and objectives

The primary VE objectives were to estimate the 2-dose (4 weeks to 6 months apart) VE of RZV in preventing HZ in adults ≥ 18 years of age with RA or IBD, respectively. The primary safety objectives were 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 RA or IBD, respectively. Secondary and exploratory objectives are detailed in Section 6.

Study design

This study examined the effectiveness and safety of RZV in adults with RA or IBD (UC or CD) at KPSC. The vaccine accrual period for the study extended from 04/2018 to 08/2023 with follow-up through 08/2024. For the primary VE objectives, an observational matched cohort design was used. Individuals ≥ 18 years of age who received 2 doses of RZV were up to 1:3 matched to RZV unvaccinated individuals by condition (RA, UC, CD), age, sex, race/ethnicity, and medication category. For the safety objectives, a self-controlled case series (SCCS) analysis was conducted among individuals aged ≥ 18 years with RA or IBD who received at least one dose of RZV.

Setting

Kaiser Permanente Southern California includes more than 4.6 million members. The demographic makeup of the KPSC membership closely mirrors the Southern California population.

To address primary VE objectives, 2-dose RZV cohorts were constructed for each autoimmune condition (RA and IBD). The primary VE analysis included eligible individuals who received 2 doses of RZV separated by 4 weeks to 6 months by the end of the accrual period and their unvaccinated matched counterparts.

To address the safety objectives, separate safety cohorts were constructed for RA and IBD and included individuals who received at least 1 dose of RZV.

Subjects and study size

The primary VE analyses included 7,565 RA (1,900 vaccinated and 5,665 unvaccinated) and 5,558 IBD (1,509 vaccinated and 4,049 unvaccinated) individuals. The RA safety cohort included 3,211 vaccinated individuals and the IBD safety cohort included 2,600 vaccinated individuals.

Variables and data sources

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 (date vaccine was received; same date was used for unvaccinated matched individuals) were identified from electronic health records (EHR). The primary exposure for VE analysis was 2 doses of RZV administered between 4 weeks and 6 months apart, identified from EHR codes. The primary outcome for VE analysis was HZ, identified by ICD-10 code and antiviral prescription. The primary outcome for safety analysis was clinically relevant flares identified from EHR by trained staff.

Results

The adjusted VE of 2 doses of RZV administered 4 weeks to 6 months apart against HZ in adults (≥ 18 years) was 57.2% (95% confidence interval [CI]: 39.0%, 69.9%) and 62.9% (95% CI: 34.3%, 79.1%) for RA and IBD patients, respectively. The risk of flares was comparable across the risk and comparison windows for recipients of RZV with RA (relative risk [RR]= 0.92, 95% CI: 0.70, 1.20) and IBD (RR= 0.80, 95% CI: 0.58, 1.12).

Discussion

Previous studies assessing the effectiveness and safety of RZV largely focused on older and immunocompetent adults. This study addressed an important gap in literature by expanding the inclusion criteria to include ≥ 18 -year-olds with RA and IBD using real-world data from a large integrated health care delivery network.

Conclusions

For adults with RA and IBD, 2 doses of RZV (4 weeks to 6 months apart) conferred protection against HZ with no elevated risk of flares observed following vaccination. Our findings support the recommendation to vaccinate adults with RA and IBD with 2 doses of RZV.

Marketing authorization holder

GlaxoSmithKline Biologicals S.A.

Names and affiliations of principal investigators

Hung-Fu Tseng, Kaiser Permanente Southern California

3. AMENDMENTS AND UPDATES

None

4. MILESTONES

Milestone	Planned date	Actual Date	Comments
Start of data collection	16 July 2022	16 July 2022	
End of data collection	31 March 2025	02 April 2025	The actual soft data lock (data collection freeze) date was 02 April 2025. However, ad-hoc chart review (additional data collection) was done during the finalization of the final tables which was completed on 15 July 2025
Registration in the EU PAS register	21 July 2022	21 July 2022	
Interim report	31 May 2025	05 June 2025	An additional review cycle was added to the interim report to complete additional requests pertaining to dose-specific safety analysis, and additional clarifications were added to the report as requested by GSK.
Final report of study results	26 November 2025	10 Dec 2025	

5. 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 [Gnann, 2002; Dworkin, 2007]. 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 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 [Kawai, 2017; Lasa, 2021].

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 U.S. Food and Drug Administration (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 Advisory Committee on Immunization Practices (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) helped address an unmet medical need for HZ prevention. Data on the use of RZV in these complex patient populations, including 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; Long, 2013; Yun, 2016; Khan, 2018]. 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) [Yun, 2015; Marra, 2016; Winthrop, 2017; Colombel, 2018; Bechman, 2019; Curtis, 2019; Sandborn, 2019; Choden, 2022]. 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 among both the 50-60-year and > 60 -year age groups [Khan, 2022]. 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 limited and predominantly 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. Leung et al studied the risk of flares after RZV among ≥ 50 -year-old individuals with immune-mediated inflammatory diseases including RA and IBD using a self-controlled risk interval study design [Leung, 2022]. The study relied on administrative data to identify flares and did not have access to medical records to confirm occurrence of flares. Another study looked at the risk of flares associated with RZV among ≥ 50 -year-old individuals with IBD using a matched cohort design [Khan, 2022]. Potential flares identified through an algorithm-based approach were manually reviewed for confirmation. Both studies did not find an increased risk of flares associated with RZV. Studies that more comprehensively capture occurrence of flares from medical records are needed to evaluate the safety of RZV among >18 -year-old RA and IBD populations.

This real-world observational study utilizing EHR data from a large integrated health care delivery network evaluated 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. 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 adult patients with RA or IBD.

6. RESEARCH QUESTION AND OBJECTIVE(S)

This study assessed 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 below. The table below 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 were 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 came first. Safety outcomes were ascertained during pre-specified risk and comparison periods (Section 7.3.1.2). The outcomes are further detailed in Section 7.3.2.

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
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

Objectives		Outcomes
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

7. RESEARCH METHODS

7.1. Study design

This study examined the effectiveness and safety of RZV in adults with RA or IBD (UC or CD) at KPSC in the U.S. The vaccine accrual period for the full study extended from 04/2018 to 08/2023 with follow-up through 08/2024; however, the accrual for individuals ≥ 50 years of age ended earlier than 08/2023 as the target sample size was met sooner. For individuals ≥ 50 years of age, the vaccine accrual extended till 05/2022 for VE and safety RA cohorts, till 11/2022 for VE IBD cohort and 09/2022 for safety IBD cohort. This study period included accrual of patients after approval of the expanded ≥ 18 years of age at-risk indication for RZV. Due to the coronavirus disease 2019 (COVID-19) pandemic indirectly impacting health care delivery and vaccine seeking behaviors, subjects were not accrued in the study from March through December 2020. HZ outcomes were assessed during this period.

For the VE objectives, an observational matched cohort design was used. For primary analyses, the index date was defined as the date of receipt of the 2nd dose of RZV (4 weeks to 6 months apart) for vaccinated individuals and their unvaccinated matches. Individuals ≥ 18 years of age who received a 2nd dose of RZV were matched up to 1:3 to RZV unvaccinated individuals on the following variables: medical condition (RA, UC, or CD), sex, age strata, race/ethnicity, and disease medication category.

Individuals were 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 2nd dose of RZV for 1-dose vaccinated individuals, receipt of a 1st dose of RZV for unvaccinated individuals, or receipt of ZVL), or end of the study period, whichever came first. Individuals were 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 was used to assess the hazard ratio (HR) for HZ comparing RZV vaccinated and unvaccinated individuals with RA or with IBD (UC and CD). VE was calculated from the HR. Secondary analyses included stratification of 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 2nd dose of RZV (2nd dose given >6 months after 1st dose, 2nd dose given at least 4 weeks after 1st dose). Additional secondary analyses examined VE after one dose of RZV with the index date as the date of receipt of the first RZV dose. Additional exploratory analyses were also conducted.

For the safety objectives, an SCCS analysis was conducted among individuals aged ≥ 18 years with RA or IBD who received at least one dose of RZV. The date of vaccination with the 1st dose of RZV was defined as Day 0. Given the complexity of accurately ascertaining disease flares, the EHR was reviewed for these individuals for occurrence of flares rather than relying on administrative data. A flare was 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 C](#)). For primary analyses, the RR of flare in pre-defined risk periods compared to comparison periods was assessed for RA and IBD (details in Section [7.3.1.2](#)). Secondary analyses included stratification of the risk of flares by UC and CD. Exploratory analyses stratified the risk of flares by medication category at baseline.

7.2. Study population/subjects and setting

7.2.1. 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.

7.2.2. Study population

To address VE related study objectives, two study cohorts were constructed, the 2-dose RZV cohort and 1-dose RZV cohort, for each autoimmune condition (RA and IBD). Individuals were eligible for the VE study cohort if the eligibility criteria detailed below were met.

The 2-dose RZV cohort included eligible individuals who received 2 doses of RZV separated by at least 4 weeks by the end of the accrual period. The index date was the vaccination date of the second RZV dose. RZV unvaccinated individuals who met the inclusion/exclusion criteria and were unvaccinated on the index date were randomly selected and up to 3:1 matched to the 2-dose RZV vaccinated individuals by age group (18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, and 80+ years), sex, race/ethnicity (White, Black, Hispanic, Asian, and Other), condition (RA, IBD [UC, CD]), and medication category at index date. Individuals with both RA and IBD were included in both the RA group and the IBD group for matching. Matching for the RA group and the IBD group was conducted separately. Vaccinated individuals with both UC and CD were matched to unvaccinated individuals with both conditions if sufficient matches were found. Otherwise, they were matched to unvaccinated individuals with CD (which had a smaller sample size) and were included only in the CD analysis. The index date for the 2-dose RZV unvaccinated match was the same as his/her matched 2-dose RZV vaccinated counterpart. Flow charts with inclusion/exclusion criteria applied for the 2-dose RZV cohort with RA and the 2-dose RZV cohort with IBD are provided. See [Appendix A Figure 1](#) and [Appendix A Figure 2](#)

Individuals were followed from the 31st day after the index date until the end of study follow-up, occurrence of a censoring event (i.e., death, termination of KPSC membership, receipt of a dose of zoster vaccine among the RZV unvaccinated individuals, receipt of the third dose of zoster vaccine among RZV vaccinated individuals), or occurrence of event of interest (for event-specific analyses), whichever came first.

The 1-dose RZV cohort included eligible individuals who received 1 dose of RZV but did not receive a 2nd dose within 6 months after the 1st dose during the vaccine accrual period. Such individuals may have received a 2nd RZV dose more than 6 months after the 1st RZV dose or no subsequent RZV doses by the end of the accrual period. The index date was the vaccination date of the 1st dose of RZV.

RZV unvaccinated individuals who met the eligibility criteria and were unvaccinated on the index date were randomly selected and up to 3:1 matched to the 1-dose RZV vaccinated individuals using the same matching algorithm described for the 2-dose RZV cohort above. An unvaccinated individual was allowed to be matched to both a

vaccinated individual in the 2-dose RZV cohort and a vaccinated individual in the 1-dose RZV cohort. The index date for the 1-dose RZV unvaccinated match was the same as his/her matched 1-dose RZV vaccinated counterpart. Flow charts with inclusion/exclusion criteria applied for the 1-dose RZV cohort with RA and the 1-dose RZV cohort with IBD are provided. See [Appendix A Figure 3](#) and [Appendix A Figure 4](#).

Individuals were followed from the 31st day after the index date until the end of study follow-up, occurrence of a censoring event (i.e., death, termination of KPSC membership, receipt of a dose of zoster vaccine among the RZV unvaccinated individuals, receipt of 2nd dose of RZV or receipt of another zoster vaccine among the RZV vaccinated individuals), or occurrence of event of interest (for event-specific analyses), whichever came first. Unvaccinated individuals stopped contributing person-time upon their matched vaccinated individuals' receipt of the second RZV dose.

To address the safety objectives, individuals who received at least 1 dose of RZV were eligible for the safety cohort if the following eligibility criteria were met. The index date was the vaccination date of the 1st RZV dose.

Flow charts with inclusion/exclusion criteria applied for RZV recipients with RA and RZV recipients with IBD are provided. See [Appendix B Figure 1](#) and [Appendix B Figure 2](#)

Eligibility criteria

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 were 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 was 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 was drawn from individuals with IBD (UC or CD).

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

Individuals with both RA and IBD were included in analyses for both conditions.

Individuals were 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 of continuous KPSC membership prior to date of first RZV dose (allowing for a 31-day gap in membership)

Exclusion criteria

For both VE and safety objectives, individuals who received a 2nd dose less than 4 weeks (i.e., 28 days) after the 1st dose were excluded, since ACIP guidelines state that these individuals must repeat the 2nd dose [[Dooling, 2018](#)].

For the VE objectives, individuals with an HZ diagnosis in the 6 months prior to the index date were excluded to ensure that HZ diagnoses after the index date were 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 were also excluded since it was unclear if the HZ episode began before or after the index date and whether the length of time since vaccination (for RZV vaccinated individuals) was long enough to allow for sufficient development of immunity. Individuals with receipt of zoster vaccine within 30 days after index date were excluded. Individuals with a death date within 30 days after index date were also excluded.

7.3. Variables

7.3.1. Exposures (VE and safety)

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

7.3.1.1. VE

Although RZV should be administered as 2 doses separated by 2-6 months, ACIP guidance followed at KPSC specifies that a 2nd dose administered <4 weeks after the 1st dose should be repeated, but a 2nd dose administered ≥ 4 weeks after the 1st dose does not need to be repeated [Anderson, 2022]. Furthermore, due to variation in real-world practice, the 2nd dose may be given earlier than 2 months after the 1st dose or later than 6 months after the 1st dose. Additionally, as of January 21, 2022, ACIP guidelines indicate that the 2nd dose of RZV can be administered 1–2 months after the 1st 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 was 2 doses of RZV with the 2nd dose received 4 weeks to 6 months after the 1st dose through the end of study accrual. The exposure for secondary VE objectives 1-3 and 5 and CCI was 2 doses of RZV, with the 2nd dose received at least 4 weeks after the 1st dose (“2-dose [≥ 4 weeks]”). The exposure for secondary VE objective 4 was 2 doses of RZV, with the 2nd dose received >6 months after the 1st dose through the end of study accrual. The index date was the date of receipt of the 2nd RZV dose.

The exposure for secondary VE objectives 6-7 was 1 dose of RZV. The index date was the date of receipt of the 1st RZV dose. The 1-dose VE was evaluated in individuals who received 1 dose of RZV and did not receive a 2nd dose within 6 months after the 1st dose.

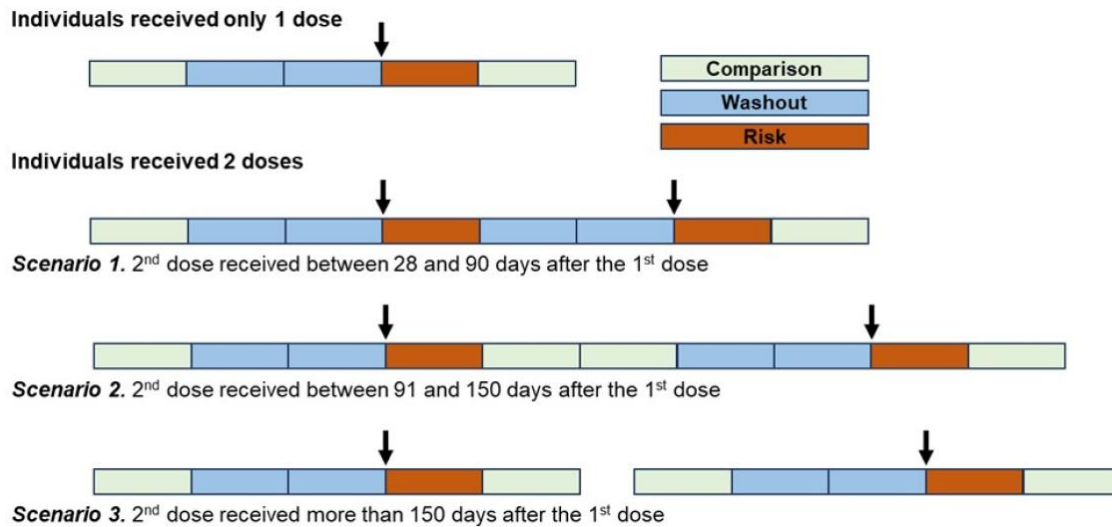
7.3.1.2. Safety

An SCCS design (Figure 1 below) was used. For patients receiving only 1 dose of RZV, the date of vaccination with the 1st dose of RZV was defined as Day 0, the risk period was defined as +1 to +30 days, and comparison periods were defined as -90 to -61 days and +31 to +60 days (Figure 1 below, Individuals received only 1 dose). The washout period was 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 received a 2nd dose of RZV within 300 days of the 1st RZV dose, there were several scenarios for additional risk and comparison periods. If the 2nd dose was received between +28 to +90 days after the 1st dose, the risk period after the 1st dose was immediately followed by a washout period up to receipt of the 2nd dose (Figure 1 below, Scenario 1). If the 2nd dose was received between +91 to +150 days after the 1st dose, the risk and comparison periods following the 1st dose were followed by a 60-day washout period immediately before the receipt of the 2nd dose (Figure 1 below, Scenario 2). If the 2nd dose was received between +151 days to +300 days after the 1st dose, the comparison period was -90 to -61 days prior to the 2nd dose and the washout period was -60 to -1 days prior to the 2nd dose (Figure 1 below, Scenario 3). In Scenario 1, the risk window after the 1st dose was between 28 and 30 days and the subsequent washout window was between 0 and 60 days. In Scenario 2, the comparison window between 2

doses was between 1 and 60 days. The maximum follow-up period was set to 360 days after the 1st dose. Scenarios 2-4 in Figure 1 below represent the maximum time period between the 1st and 2nd dose.

Figure 1 **SCCS Design Overview for Safety Analysis**

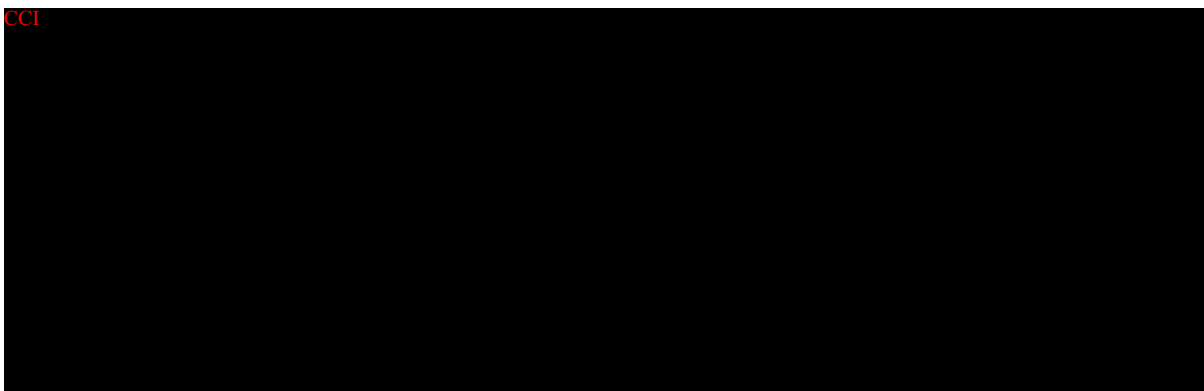


7.3.2. Outcomes (VE and safety)

7.3.2.1. VE

HZ

The primary outcome was HZ, identified by ICD-10 code B02.xx in any health care setting (outpatient [to include virtual visits], inpatient, Emergency Department [ED]) 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 was considered an incident HZ event.



CCI

7.3.2.2. Safety

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

7.4. Other variable definitions (VE and safety)

7.4.1. VE

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

- Demographic variables: age at index date, sex, race/ethnicity
- Health care utilization (number of outpatient [to include virtual visits]/ED/inpatient encounters) in the year prior to the index date
- Comorbidities (kidney disease, heart disease, lung disease, liver disease, diabetes, other autoimmune diseases, severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2 infection]/COVID-19 diagnosis) in the year prior to the index date
- Immunocompromised status (human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS], leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell transplant/solid

organ transplant, and receipt of immunosuppressive medications) assessed at 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 ED settings
- Concomitant vaccinations defined as receipt of vaccines such as influenza vaccine, pneumococcal conjugate vaccine (PCV)/pneumococcal polysaccharide vaccine (PPSV), Tetanus, diphtheria, and acellular pertussis (Tdap) vaccine, or COVID-19 vaccine at the time (same date) of either the 1st or 2nd dose of RZV
- Medication category as detailed in [Appendix D](#).
- Membership history: length of continuous membership (allowing 31 days gap) prior to the index date.

7.4.2. Safety

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

7.5. Data sources

The KPSC electronic health record (EHR) system was the data source for extracting information on exposures, outcomes, and covariates. Kaiser Permanente Health Connect is the largest 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 were available and accessible to researchers. Data regarding demographics, services, and diagnoses were tracked from the outpatient, ED, and hospital settings.

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

KPSC members had 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 was integrated into administrative data systems. Thus, the capture of care should have been very comprehensive. Care received at KPSC was updated and available to researchers in near real time. Claims data are typically over 90% complete after 3 months.

7.6. Bias

Some of the potential limitations of this study included residual confounding, misclassification, and misdiagnosis of HZ. These limitations are discussed in detail in Section [10.2](#).

7.7. Study size

Based on our power calculation for primary VE objectives, in a cohort study with a 1:3 matching ratio and an average 3.5 years of follow-up, 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 number of vaccinated subjects needed to detect a VE of 60% with 80% power and a type 1 error rate of 5% was 564 and 704, assuming that the incidence of HZ in the unvaccinated population was 15/1000 person-years and 12/1000 person-years, respectively.

Our SCCS design required 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%, assuming the length of comparison window was twice of the length of risk window. To detect an increased risk of flare of $RR=2$, at least 34 events were required in the comparison window.

The 2 dose (4 weeks to 6 months apart) RZV cohorts for RA and IBD had 1900 and 1509 vaccinated patients, exceeding the target numbers for achieving 80% power to detect a VE of 60%. For the primary safety objectives, 135 and 95 events were recorded in the comparison windows for RA and IBD, respectively.

7.8. Data analysis

7.8.1. Primary analysis

7.8.1.1. Main analytical approach

For the VE analyses, the number and characteristics of vaccinated and unvaccinated individuals in each cohort were described and compared. Categorical variables were presented as absolute numbers and percentages with p-values for the Pearson χ^2 test or Fisher's exact test, as appropriate. For continuous variables such as age in years, mean with standard deviation (SD) and median with interquartile range were calculated, with p-values for the two-sample t-test or Wilcoxon rank-sum test, as appropriate. Absolute standardized differences (ASD) were calculated to assess the balance of covariates [[Austin, 2011](#)]. Potential confounders were determined by scientific relevance and association with exposure ($ASD > 0.1$). Immunocompromised status and history of HZ, which were considered important risk factors, were kept in the adjusted model regardless of their association with exposure.

For primary VE objectives 1-2, the number of incident HZ cases and the number of person-years of follow-up for subjects were assessed for the 2-dose (4 weeks to 6 months) RZV cohort and the matched unvaccinated cohort. The incidence rates of HZ were calculated by dividing the number of HZ cases by the number of person-years. 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 were estimated by Cox stratified proportional hazards regression models without and with adjusting for potential confounders described above. Death was considered as a competing risk, handled using cause-specific hazards models [Prentice, 1978; So, 2015]. Estimates of VE (%) were calculated as $(1 - \text{HR}) \times 100$ when the HR was less than or equal to 1, and $([1/\text{HR}] - 1) \times 100$ when the HR was greater than 1.

For the primary safety analyses, characteristics of individuals with RA or IBD who met inclusion criteria were described. Incidence rates for RA or IBD (UC or CD) flare for risk periods and comparison periods were calculated by dividing the number of flares by person-time. Relative risks (95% CI) for flare comparing risk and comparison periods overall and by 1st dose and 2nd dose were estimated using conditional Poisson regression [Whitaker, 2006].

7.8.1.2. Data handling conventions/data transformations

Coding for exposures and outcomes is described in Section 7.3.

7.8.1.3. Sensitivity analyses

In addition to assessing the VE of 2 doses of RZV administered 4 weeks to 6 months apart (primary VE objectives 1 and 2), the cumulative incidence of HZ was estimated by the Kaplan–Meier method. Vaccinated and the unvaccinated cumulative incidence estimates were plotted and the difference between the two curves was tested by the log-rank test. This analysis was performed for both RA and IBD cohorts (4 weeks to 6 months apart) separately. Additionally, the VE of 2 doses (4 weeks to 6 months apart) of RZV by time since vaccination was evaluated.

7.8.2. Secondary analysis/exploratory analysis

For secondary and exploratory analyses, subgroups were recategorized in post-hoc analyses if sample size in a subgroup was small.

Secondary VE objectives 1-3: Analyses for secondary VE objectives 1-3 (2 doses of RZV given at least 4 weeks apart) used similar methods as for the primary VE analyses. In secondary VE objective 1, analyses for IBD (primary VE objective 2) were stratified by UC and CD. In secondary VE objective 2, analyses for RA (primary VE objective 1) were 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) were 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 was conducted by strata and estimates of VE (%) were

calculated as $(1 - \text{HR}) \times 100$ when the HR was less than or equal to 1, and $([1/\text{HR}] - 1) \times 100$ when the HR was greater than 1.

Secondary VE objectives 4-5: Analyses for secondary VE objectives 4-5 used similar methods as for the primary VE analyses. For secondary VE objective 4, the 2-dose RZV cohort included individuals who received their 2nd dose >6 months after the 1st dose during the accrual period. For secondary VE objective 5, the 2-dose RZV cohort included individuals who received their 2nd dose at least 4 weeks after the 1st dose during the accrual period. Analyses were stratified by condition (RA or IBD). The VE of 2 doses (≥ 4 weeks apart) of RZV by time since vaccination was also evaluated. The cumulative incidence of HZ was estimated by the Kaplan–Meier method and plotted for the vaccinated and unvaccinated groups. The difference between two curves was tested by the log-rank test.

Secondary VE objectives 6-7: Analyses for secondary VE objectives 6-7 were conducted among the matched cohorts of individuals with RA (secondary VE objective 6) or with IBD (secondary VE objective 7) who received 1 dose of RZV and did not receive a 2nd dose within 6 months after the 1st dose. Individuals were 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 2nd dose of RZV >6 months after the 1st dose among vaccinated individuals, or end of study period, whichever came first. Descriptive analyses and multivariable Cox proportional hazards regression was conducted and estimates of VE (%) were calculated as $(1 - \text{HR}) \times 100$ when the HR was less than or equal to 1, and $([1/\text{HR}] - 1) \times 100$ when the HR was greater than 1. The VE of 1 dose of RZV by time since vaccination was also evaluated.

Secondary safety objective 1: Analyses for IBD was stratified by UC and CD.

CCI



CCI

7.8.3. Amendments to statistical plan

Some of the major amendments are listed below:

1. CCI
2. The description of censoring events was updated to reflect that the accrual for individuals ≥ 50 years of age could end earlier than August 2023 once the target sample size was met.
3. The exclusion criterion was reworded to clearly communicate that those receiving the 2nd dose of RZV less than 4 weeks after the first RZV dose would be excluded.
4. The criterion for matching on race/ethnicity was updated to “if $\geq 95\%$ of vaccinated individuals can be matched to at least 1 unvaccinated individual” from “if 95% of exposed individuals can be fully matched to 3 unexposed individuals” to allow for matching on race/ethnicity.
5. Censoring criterion for 2-dose RZV vaccinated individuals was revised to “upon receipt of the third dose of RZV or receipt of another zoster vaccine” from “upon receipt of the third dose of RZV”. Similar wording was added for the 1-dose RZV cohort.
6. History of HZ was added as a covariate for the adjusted model regardless of its association with exposure as it is considered an important risk factor.
7. The sample size calculation was updated using an incidence rate of 12 cases per 1,000 person years, an average follow-up time of 3.5 years, and a censoring rate of 25% in the unvaccinated group for the primary VE full analysis.
8. The possibility of recategorizing subgroups in post-hoc analysis due to small sample size for safety and VE secondary/exploratory objectives was added.
9. For accuracy, it was clarified that a “matched set” with both UC and CD conditions were included in both the UC and CD analyses. Previously, it was stated as “an individual with both UC and CD...”.
10. For the analysis related to VE secondary objectives 2 and 3, a 50+ years age group was added in addition to the previously considered groups (18-49 years, 50-59 years, 60-69 years, and 70+ years).
11. CCI
CCI
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12. Comparison of baseline characteristics between 18-49 years and 50+ age groups was added for the RA and IBD safety cohorts.

7.9. Quality control and quality assurance

KPSC followed the Department of Research and Evaluation's Analytical Research Project Standard Operating Procedures (SOP), including data extraction, data analysis, communication, and documentation. The program for identifying the study cohorts as well as the program for identifying all outcomes were validated by double programming. Other programs developed for study purposes, including programs for data lock and programs for identifying covariates were reviewed by a second programmer. SAS programs used for the analysis were reviewed by a second statistician. Statistical analyses (results tables) were discussed in the multisite meetings with GSK prior to study report finalization. KPSC provided a quality control (QC) checklist of data management and statistical analysis validation signed and dated by programmers and statisticians.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

This study complied with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data occurred. Study results were in tabular form and presented as aggregate analyses that omitted subject identification. Any publications and reports did not include subject identifiers. The study was IRB-approved and the requirement for informed consent was waived due to minimal risk to study subjects.

8.2. Subject confidentiality

In the U.S., 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 Health Insurance Portability and Accountability Act (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 were contacted or enrolled, and no PHI was disclosed; however, PHI was accessed through the EHR. This information was only accessed by those authorized to do so and was not shared with GSK or anyone outside of the KPSC study team. The KPSC team obtained IRB approval to use PHI for research activities. Since this access to PHI presented no more than minimal risk to individuals, and the research could not be practically done if required to obtain written authorization for usage, KPSC obtained a waiver for written HIPAA authorization for research involving use of the EHR to conduct the study.

Additionally, all investigators and project managers were trained in the protection of human research participants, Good Pharmacoepidemiology Practices, and HIPAA. The KPSC Department of Research and Evaluation had policies in place to govern the conduct and administration of research at KPSC. These policies supported compliance with federal and state regulatory requirements. Policies included conflict of interest, misconduct, sensitive data, and system access control. Policies were in place to ensure compliance with the Sunshine Act. All KPSC staff underwent annual compliance training and certification. The Principles of Responsibility was KPSC's code of conduct that addressed such issues as protection of confidential information and anti-bribery and corruption.

9. RESULTS

9.1. Participants

The 2-dose RZV cohort with RA ([Appendix A Figure 1](#)) contributed person-time to the analyses pertaining to primary VE objective 1, secondary objectives 2, 4, 5 and CCI. For primary VE objective 1, 1,900 vaccinated (2nd dose administered between 4 weeks to 6 months after the 1st dose) and 5,665 unvaccinated matched individuals were assessed for HZ during the study period ([Appendix A Table 5](#)). For secondary VE objective 2, secondary VE objective 5, CCI CCI 2,460 vaccinated (2nd dose administered at least 4 weeks after the 1st dose) and 7,326 matched unvaccinated individuals contributed to the person-time. For secondary VE objective 4, 560 vaccinated (2nd dose administered >6 months after the 1st dose) and 1,661 unvaccinated matched individuals were assessed for HZ. The 1-dose RZV cohort with RA comprised 1,012 vaccinated and 3,023 unvaccinated individuals which contributed person-time to the secondary VE objective 6 ([Appendix A Figure 3](#)).

The 2-dose RZV cohort with IBD ([Appendix A Figure 2](#)) contributed person-time to the analyses pertaining to primary VE objective 2, secondary objectives 1, 3, 4, 5 and CCI. For primary VE objective 2, 1,509 vaccinated individuals (2nd dose administered between 4 weeks to 6 months after the 1st dose) and 4,049 unvaccinated matched individuals were assessed for HZ during the study period ([Appendix A Table 7](#)). For secondary VE objective 1, 3,739 individuals with UC (989 vaccinated, 2,750 unvaccinated) and 2,962 with CD (827 vaccinated, 2,135 unvaccinated) contributed to the person-time ([Appendix A Table 7](#)). There were 14 vaccinated individuals with both UC and CD who were matched to unvaccinated CD individuals only. For secondary VE objective 3, secondary VE objective 5, CCI CCI 1,811 vaccinated individuals (2nd dose administered at least 4 weeks after the 1st dose) and 4,880 matched unvaccinated individuals contributed to the person-time. For secondary VE objective 4, 302 vaccinated individuals (2nd dose administered >6 months after the 1st dose) and 831 unvaccinated matched individuals were assessed for HZ. The 1-dose RZV cohort with IBD comprised 801 vaccinated and 2,340 unvaccinated individuals which contributed person-time to the secondary objective 7 ([Appendix A Figure 4](#)).

The RA safety cohort described in [Appendix B Figure 1](#) comprised 3,211 vaccinated individuals who contributed person-time to the analyses pertaining to primary safety objective 1 and CCI [REDACTED]. The IBD safety cohort described in [Appendix B Figure 2](#) comprised 2,600 vaccinated individuals who contributed person-time to the analyses pertaining to primary safety objective 2, secondary safety objective 1 and CCI [REDACTED]. The two cohorts were assessed for the occurrence of flares during the risk and comparison periods.

9.2. Descriptive data including baseline characteristics

RA VE cohorts

In the 2-dose (2nd dose administered at least 4 weeks after the 1st dose) RZV cohort of RA patients (vaccinated and unvaccinated), the mean age was 68.4 years (standard deviation [SD] 10.1), 79.2% were female and 45.2% were non-Hispanic White ([Appendix A Table 1](#)). Compared to unvaccinated individuals, vaccinated individuals had more outpatient visits (≥ 11 visits, 91.1% vs. 86.0%, ASD 0.178), less ED visits (≥ 2 visits, 10.5% vs. 14.1%, ASD 0.120), and less hospitalizations (≥ 2 hospitalizations, 2.7% vs. 4.6% ASD 0.119) in the year prior to the index date. Apart from heart disease (8.4% vaccinated vs. 11.7% unvaccinated, ASD 0.111), the frequency of all other baseline comorbidities was similar (ASD < 0.1) across vaccinated and unvaccinated individuals. Vaccinated individuals had a higher frequency of previous ZVL/varicella vaccination (34.8% vs. 23.0%, ASD 0.299), compared to unvaccinated individuals. Continuous KPSC membership was longer for vaccinated individuals (≥ 11 years, 63.8% vs. 59.8%, ASD 0.104).

The majority (77.2%) of the 2-dose vaccinated RA patients received the 2nd dose between 4 weeks to 6 months after the 1st dose. Those who received the 2nd dose > 6 months after the 1st dose (mean age: 70.55 years) were older than those who received the 2nd dose between 4 weeks to 6 months after the 1st dose (mean age: 67.98 years) (ASD 0.265) ([Appendix A Table 17](#)). The distribution of race/ethnicity among those who received the 2nd dose between 4 weeks to 6 months after the 1st dose was different from those who received the 2nd dose > 6 months after the 1st dose (ASD 0.162). Some of the baseline comorbidities including kidney disease (14.6% vs. 18.6%, ASD 0.106), heart disease (7.2% vs. 12.7%, ASD 0.185), and diabetes (22.4% vs. 29.5%, ASD 0.161) were less prevalent among those who received the 2nd dose between 4 weeks to 6 months after the 1st dose. Those who received the 2nd dose between 4 weeks to 6 months had less ED visits (≥ 2 visits, 9.4% vs. 14.3%, ASD 0.188) and hospitalizations (≥ 2 hospitalizations, 1.8% vs. 5.7%, ASD 0.216) compared to those who received the 2nd dose > 6 months after the 1st dose. Frequency of concomitant vaccination (34.4% vs. 45.7%, ASD 0.232) was lower for those who received the 2nd dose between 4 weeks to 6 months after the 1st dose.

In the 1-dose RZV cohort of RA patients (vaccinated and unvaccinated), the mean age was 67.71 years (SD 10.7), 76.7% were female and 41.5% were non-Hispanic White ([Appendix A Table 3](#)). Compared to unvaccinated individuals, vaccinated individuals had less hospitalizations (≥ 2 hospitalizations, 3.3% vs. 5.1% ASD 0.107) in the year prior to the index date. The frequency of all baseline comorbidities and length of continuous KPSC membership was similar across vaccinated and unvaccinated individuals (ASD

<0.1). Vaccinated individuals had a higher frequency of previous ZVL/varicella vaccination (31.7% vs. 22.7%, ASD 0.221), compared to unvaccinated individuals.

IBD VE cohorts

In the 2-dose (2nd dose administered at least 4 weeks after the 1st dose) RZV cohort of IBD patients (vaccinated and unvaccinated), the mean age was 65.95 years (SD 11.9), 54.0% were female and 65.6% were non-Hispanic White ([Appendix A Table 2](#)). Compared to unvaccinated individuals, vaccinated individuals had more outpatient visits (≥ 11 visits, 88.6% vs. 80.8%, ASD 0.227) and less ED visits (≥ 2 visits, 13.3% vs. 16.6%, ASD 0.102) in the year prior to the index date. The frequency of all baseline comorbidities was similar across vaccinated and unvaccinated individuals (ASD <0.1). Vaccinated individuals had a higher frequency of previous ZVL/varicella vaccination (36.2% vs. 25.7%, ASD 0.275), compared to unvaccinated individuals. Continuous KPSC membership was longer for vaccinated individuals (≥ 11 years, 63.4% vs. 57.2%, ASD 0.142).

The majority (83.3%) of the 2-dose vaccinated IBD patients received the 2nd dose between 4 weeks to 6 months after the 1st dose. Those who received the 2nd dose >6 months after the 1st dose (mean age: 67.68 years) were older than those who received the 2nd dose between 4 weeks to 6 months (mean age: 66.27 years) ([Appendix A Table 18](#)). The distributions of race/ethnicity (ASD 0.126), sex (ASD 0.158), and medication category (ASD 0.154) among those who received the 2nd dose between 4 weeks to 6 months after the 1st dose were different from those who received the 2nd dose >6 months after the 1st dose. The frequency of liver disease was higher (9.7% vs. 6.6%, ASD 0.112) among those who received the 2nd dose between 4 weeks to 6 months after the 1st dose. Those who received the 2nd dose between 4 weeks to 6 months had more outpatient visits (≥ 11 visits, 89.3% vs. 85.1%, ASD 0.153), ED visits (≥ 2 visits, 14.0% vs. 9.6%, ASD 0.159) and hospitalizations (≥ 2 hospitalizations, 5.2% vs. 2.6%, ASD 0.158) compared to those who received the 2nd dose >6 months after the 1st dose. Frequency of HZ history (14.4% vs. 18.5%, ASD 0.112) and concomitant vaccination (41.5% vs. 52.6%, ASD 0.225) was lower for those who received the 2nd dose between 4 weeks to 6 months after the 1st dose.

In the 1-dose RZV cohort of IBD patients (vaccinated and unvaccinated), the mean age was 63.84 years (SD 14.4), 52.2% were female and 61.1% were non-Hispanic White ([Appendix A Table 4](#)). Compared to unvaccinated individuals, vaccinated individuals had less outpatient visits (≥ 11 visits, 79.9% vs. 80.6%, ASD 0.119) in the year prior to the index date. The frequency of all baseline comorbidities and length of continuous KPSC membership was similar across vaccinated and unvaccinated individuals (ASD <0.1). Vaccinated individuals had a higher frequency of previous ZVL/varicella vaccination (32.5% vs. 25.7%, ASD 0.178), compared to unvaccinated individuals.

RA safety cohort

In the RA safety cohort, the mean age was 67.74 years (SD 10.16), 79.2% were female, 42.9% were non-Hispanic White, and 54.0% were on category 2 medication ([Appendix B Table 1](#)). The majority (77.0%) of the cohort received 2 doses of RZV. The distribution of race/ethnicity among 18–49-year-old RZV recipients was different from ≥ 50 -year-old

RZV recipients (p-value: 0.039, [Appendix B Table 7](#)). Compared to the 18-49-year RZV recipients in this cohort, the ≥ 50 -year RZV recipients had a higher frequency of individuals who were on category 2 medication and a lower frequency of individuals on Category 3-5 medications (Category 2: 54.9% vs. 24.4%, Category 3-5: 22.2% vs. 56.6%, p-value <0.001, [Appendix B Table 7](#)).

IBD safety cohort

In the IBD safety cohort, the mean age was 65.66 years (SD 12.91), 53.4% were female, 61.0% were non-Hispanic White, 56.0% had UC, and 33.1% were on category 2 medication ([Appendix B Table 2](#)). The majority (78.5%) of the cohort had received 2 doses of RZV. The distributions of race/ethnicity and IBD condition (UC, CD, UC+CD) among 18-49-year-old RZV recipients were different from ≥ 50 -year-old RZV recipients (p-value: <0.001, [Appendix B Table 8](#)). Compared to the 18-49-year RZV recipients in this cohort, the ≥ 50 -year RZV recipients had a higher frequency of individuals who were on category 2 medication and a lower frequency of individuals on Category 3-5 medications (Category 2: 34.3% vs. 17.9%, Category 3-5: 25.9% vs. 61.2%, p-value <0.001, [Appendix B Table 8](#)).

9.3. Outcome data

VE

Among RA patients who received 2 doses of RZV (4 weeks to 6 months), 57 HZ cases were identified during the study period with an incidence of 9.0 (95% CI: 6.9, 11.6) per 1,000 person-years compared to 222 HZ cases among unvaccinated RA patients with an incidence of 18.6 (95% CI: 16.3, 21.2) per 1,000 person-years (primary VE objective 1; [Appendix A Table 5](#)). Among IBD patients who received 2 doses of RZV (4 weeks to 6 months), 23 HZ cases were identified during the study period with an incidence of 5.5 (95% CI: 3.6, 8.2) per 1,000 person-years compared to 87 HZ cases among unvaccinated IBD patients with an incidence of 12.0 (95% CI: 9.7, 14.8) per 1,000 person-years (primary VE objective 2; [Appendix A Table 7](#)).

To address secondary VE objectives 1-5, the number of incident HZ cases and incidence of HZ by condition, age group, and timing of 2nd dose are provided in [Appendix A Table 5](#) and [Appendix A Table 7](#). For secondary VE objectives (6,7) related to 1-dose RZV VE, the number of incident HZ cases and incidence of HZ are provided in [Appendix A Table 9](#) and [Appendix A Table 11](#). The years after index date were collapsed in [Appendix A Table 10](#) and [Appendix A Table 12](#) in a post-hoc analysis. CCI

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In the RA safety cohort, 88 flare cases were identified in the risk window with an incidence of 188.74 (95% CI: 153.15, 232.60) per 1,000 person-years compared to 135 flare cases in the comparison window with an incidence of 208.30 (95% CI: 175.97, 246.58) per 1,000 person-years (primary safety objective 1; [Appendix B Table 3](#)). In the IBD safety cohort, 57 flare cases were identified in the risk window with an incidence of 149.82 (95% CI: 115.57, 194.23) per 1,000 person-years compared to 95 flare cases in the comparison window with an incidence of 181.29 (95% CI: 148.26, 221.66) per 1,000 person-years (primary safety objective 2; [Appendix B Table 5](#)).

To address secondary safety objective 1 and CCI, the number of incident flare cases and incidence of flare by condition and medication category are provided in [Appendix B Table 3](#) and [Appendix B Table 5](#). In post-hoc analyses, medication categories were combined in [Appendix B Table 4](#) and [Appendix B Table 6](#).

9.4. Results of primary analyses

For **primary VE objective 1** evaluating the VE of 2 doses of RZV administered 4 weeks to 6 months apart against HZ in adults (≥ 18 years) with RA, the unadjusted HR was 0.425 (95% CI: 0.306, 0.590) and adjusted HR was 0.428 (95% CI: 0.301, 0.610). The associated unadjusted and adjusted VE was 57.5% (95% CI: 41.0%, 69.4%) and 57.2% (95% CI: 39.0%, 69.9%), respectively ([Appendix A Table 5](#)). The cumulative incidence of HZ was higher in unvaccinated individuals compared to those vaccinated with 2 doses of RZV administered 4 weeks to 6 months apart (p-value < 0.0001 ; [Appendix A Figure 11](#)). In the sensitivity analysis, adjusted 2-dose RZV (4 weeks to 6 months) VE against HZ was 64.0% (95% CI: 27.9%, 82.0%) in the 1st year after the index date ([Appendix A Table 19](#), [Appendix A Figure 13](#)). The adjusted VE dropped to 43.8% (95% CI: 1.3%, 67.9%) in the 2nd year and increased to 89.3% (95% CI: 58.7%, 97.2%) in the 3rd year (2- < 3). The adjusted VE for 1- < 3 years after index date (post-hoc analysis) was 60.0% (95% CI: 34.4%, 75.5%; [Appendix A Table 20](#), [Appendix A Figure 14](#)). The confidence interval was wide for subsequent years due to smaller sample size.

For **primary VE objective 2** evaluating the VE of 2 doses of RZV administered 4 weeks to 6 months apart against HZ in adults (≥ 18 years) with IBD, the unadjusted HR was 0.370 (95% CI: 0.212, 0.645) and adjusted HR was 0.371 (95% CI: 0.209, 0.657). The associated unadjusted and adjusted VE was 63.0% (95% CI: 35.5%, 78.8%) and 62.9% (95% CI: 34.3%, 79.1%), respectively ([Appendix A Table 7](#)). The cumulative incidence of HZ was higher in unvaccinated individuals compared to those vaccinated with 2 doses of RZV administered 4 weeks to 6 months apart (p-value < 0.0004 ; [Appendix A Figure 12](#)). In the sensitivity analysis, adjusted 2-dose RZV (4 weeks to 6 months) VE against HZ was 76.6% (95% CI: 34.6%, 91.6%) in the 1st year after the index date ([Appendix A Table 21](#), [Appendix A Figure 15](#)). The adjusted VE for 1-3 years after index date (post-hoc analysis) was 94.8% (95% CI: 60.3%, 99.3%; [Appendix A Table 22](#), [Appendix A Figure 16](#)). The confidence interval was wide for subsequent years due to smaller sample size.

For **primary safety objective 1**, the risk of flares was comparable across the risk and comparison windows (RR= 0.92, 95% CI: 0.70,1.20) for recipients of RZV with RA ([Appendix B Table 3](#)). The risks of flares within the risk periods following the 1st dose (RR=0.94, 95% CI: 0.68, 1.30) and 2nd dose (RR= 0.88, 95% CI: 0.61, 1.29) were comparable to the risks of flares in their respective comparison windows. A combined comparison period was used for RR calculations, but incidence of flares for the pre- and post-comparison windows are provided in [Appendix B Figure 3](#) and [Appendix B Figure 4](#).

For **primary safety objective 2**, the risk of flares was comparable across the risk and comparison windows (RR= 0.80, 95% CI: 0.58, 1.12) for recipients of RZV with IBD ([Appendix B Table 5](#)). The risk of flares in the risk period following the 1st dose (RR=1.03, 95% CI: 0.72, 1.47) was comparable to the comparison period. The risk of flares in the risk window following the 2nd dose (RR= 0.45, 95% CI: 0.25, 0.81) was lower compared to the risk of flares in the comparison window. A combined comparison period was used for RR calculations, but incidence of flares for the pre- and post-comparison windows are provided in [Appendix B Figure 5](#) and [Appendix B Figure 6](#).

9.5. Results of secondary analyses/CCI

VE among RA cohorts

In adults (≥ 18 years) with RA, the cumulative incidence of HZ was higher in unvaccinated individuals compared to those vaccinated with 2 doses of RZV administered at least 4 weeks apart (p-value <0.0001; [Appendix A Figure 5](#)). The adjusted VE of 2 doses of RZV (at least 4 weeks after the 1st dose) in prevention of HZ in adults (≥ 18 years) with RA was 58.7% (95% CI: 43.6%, 69.7%; [Appendix A Table 5](#); **secondary VE objective 5**). Adjusted VE against HZ was 61.0% (95% CI: 30.6%, 78.1%) in the 1st year following the index date and peaked at 89.2% (95% CI: 68.7%, 96.3%) in the 3rd year (2-<3) ([Appendix A Table 5](#), [Appendix A Figure 7](#)). The adjusted VE for 1-3 years after index date (post-hoc analysis) was 63.2% (95% CI: 42.8%, 76.3%; [Appendix A Table 6](#), [Appendix A Figure 8](#)). The confidence interval was wide for subsequent years due to smaller sample size. Due to small sample size for adults 18-49 years, the confidence interval was wide for an adjusted VE of -67.7% (95% CI: -93.5%, 38.0%) compared to 61.8% (95% CI: 47.2%, 72.3%) for ≥ 50 years (**secondary VE objective 2**) ([Appendix A Table 5](#)). Adjusted VE estimates for 50-59, 60-69 and ≥ 70 years are presented in [Appendix A Table 5](#). CCI

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([Appendix A Table 5](#)). Several categories had wide confidence intervals given the small sample size. When category 1 and 2 were collapsed (post-hoc analysis), the adjusted VE was 56.1% (95% CI: 36.8%, 69.5%; [Appendix A Table 6](#)). The adjusted VE for adults (≥ 18 years) with RA who received the 2nd dose >6 months after receiving the 1st dose was 70.1% (95% CI: 38.3%, 85.5%; **secondary VE objective 4**) ([Appendix A Table 5](#)).

The adjusted VE of 1 dose of RZV in preventing HZ among adults (≥ 18 years) with RA was 45.5% (95% CI: 5.5%, 68.6%). VE (1 dose) estimates by time elapsed since index date are provided in [Appendix A Table 9](#) and [Appendix A Table 10](#) (**secondary VE objective 6**).

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VE among IBD cohorts

In adults (≥ 18 years) with IBD, the cumulative incidence of HZ was higher in unvaccinated individuals compared to those vaccinated with 2 doses of RZV administered at least 4 weeks apart (p-value < 0.0001 ; [Appendix A Figure 6](#)). The adjusted VE of 2 doses of RZV (at least 4 weeks after the 1st dose) in prevention of HZ in adults (≥ 18 years) with IBD was 65.4% (95% CI: 40.6%, 79.9%, [Appendix A Table 7](#); **secondary VE objective 5**). Adjusted VE against HZ was 73.1% (95% CI: 32.5%, 89.3%) in the 1st year following the index date ([Appendix A Table 7](#), [Appendix A Figure 9](#)). The adjusted VE for 1-3 years after index date (post-hoc analysis) was 92.2% (95% CI: 61.5%, 98.4%; [Appendix A Table 8](#), [Appendix A Figure 10](#)). The confidence interval was wide for subsequent years due to smaller sample size. Due to small sample size for adults 18-49 years, only unadjusted VE was calculated at 53.2% (95% CI: -74.4%, 94.4%) with a wide confidence interval. The adjusted VE estimate for ≥ 50 years was 67.0% (95% CI: 42.2%, 81.2%; **secondary VE objective 3**) ([Appendix A Table 7](#)). Adjusted VE estimates for 50-59, 60-69 and ≥ 70 years are presented in [Appendix A Table 7](#). The adjusted VE for UC was 62.7% (95% CI: 17.2%, 83.2%) and 70.2% (95% CI: 34.5%, 86.4%) for CD (**secondary VE objective 1**) ([Appendix A Table 7](#)). CCI

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Several categories had wide confidence intervals given the small sample size. When category 1 and 2 were collapsed (post-hoc analysis), the adjusted VE was 73.1% (95% CI: 44.5%, 87.0%) ([Appendix A Table 8](#)). The adjusted VE for adults (≥ 18 years) with IBD who received the 2nd dose > 6 months after receiving the 1st dose was 72.7% (95% CI: -30.4%, 94.8%) with a wide confidence interval (**secondary VE objective 4**) ([Appendix A Table 7](#)).

The adjusted VE of 1-dose of RZV in preventing HZ among adults (≥ 18 years) with IBD was 28.9% (95% CI: -41.5%, 70.4%). VE (1 dose) estimates by time elapsed since index date are provided in [Appendix A Table 11](#) and [Appendix A Table 12](#) (**secondary VE objective 7**).

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Appendix B Table 3, Appendix B Table 4). When stratified by IBD condition, the risks of flares continued to be comparable across the risk and comparison windows in both UC (RR= 0.91; 95% CI: 0.59, 1.40) and CD (RR= 0.69; 95% CI: 0.41, 1.14) patients (secondary safety objective 1; Appendix B Table 5). CCI
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9.6. Adverse events/adverse reactions

This study was based on retrospective, observational data previously collected for other purposes e.g., routine healthcare encounters. As such, there was no requirement for the collection and reporting of Individual Case Safety Reports. Although the study was based on human review of unstructured data, the nature of the secondary data protocol driven data collection and analysis did not allow for reporting of serious and non-serious adverse events, pregnancy exposures, or incidents related to any GSK product during the conduct of this research.

10. DISCUSSION

10.1. Key results

This study provides real world data to assess the VE and safety of RZV among adults aged ≥ 18 years with RA or IBD. For adults with RA, 2 doses of RZV administered 4 weeks to 6 months apart conferred protection against HZ with a VE of 57.2% and no elevated risk of flares observed during the 30-day risk period following vaccination. Similarly, for adults with IBD, 2 doses of RZV administered 4 weeks to 6 months apart conferred protection against HZ with a VE of 62.9% and no elevated risk of flares observed during the 30-day risk period following vaccination.

Previous studies assessing the effectiveness of RZV largely focused on older individuals, mostly ≥ 50 years, with AID [Zeevaert, 2023; Constenla, 2025]. Hence, this study addressed an important gap in literature by expanding the inclusion criteria to include

≥18-year-olds with RA and IBD. The overall 2-dose RZV (4 weeks to 6 months) VE for the RA population was 57.2% in our study, lower than the vaccine efficacy in randomized controlled trials and VE in observational studies reported for immunocompetent older adults but similar to the VE estimate (62.8%) reported for ≥50-year-old RA patients [Zeevaert, 2023; Constenla, 2025].

The adjusted 2-dose RZV (≥4 weeks) VE for ≥50-year-old RA patients was 61.8%, similar to previously reported estimates for this age group. Based on the recently published interim results of our study, the adjusted VE of 2 doses of RZV administered between 4 weeks to 6 months after the 1st dose was 57.9% against HZ among RA patients aged ≥50 years [Rayens, 2025]. Another recently published KPSC study reported VE to be 61.7% for ≥50-year-old immunocompromised individuals, including those on immunosuppressive medication [Tseng, 2025]. A large retrospective study of ≥50-year-old RA patients found a significantly lower risk of HZ in the propensity score matched RZV vaccinated cohort compared to the unvaccinated cohort; however, this study had major limitations in the choice of the database and methodology [Lin, 2025]. The 18–49-year-old group in our study was small (n=192) and the 2-dose RZV (≥4 weeks) VE estimate (-67.7%) for this group had a wide confidence interval.

Results from the RA cohort showed that 2 doses of RZV were effective even if given more than 6 months apart (70.1%). Among individuals who received the 2nd dose more than 6 months after the 1st dose, the median time between the 1st and 2nd dose was 11 months and the time between the doses ranged from 6–48 months. A prospective cohort study of the Medicare population showed that VE against outpatient HZ was similar for those who received the 2nd dose within 180 days of the 1st dose (median= 90 days) and those who received the 2nd dose after 180 days (median=230 days) [Izurieta, 2021]. In our study, the VE (2 doses at least 4 weeks apart) for the 1st year after vaccination was 61.0% followed by 48.6% in the 2nd year and 89.2% in the 3rd year. A previous study found that VE (2 doses given at least 4 weeks apart) in the 1st year was 68.4%, followed by 56.8% in the 2nd and 59.5% in the 3rd year for ≥50-year-old RA patients, suggesting a different trend than what we observed [Constenla, 2025]. Our VE estimates by year were likely unstable due to small numbers of individuals. A single dose of RZV was not as effective with an adjusted VE of 45.5%. In our study, the 95% CI for 2-dose RZV (≥4 weeks) VE included the null for RA patients on medication categories 1, 4, and 5; however, the study was not powered for subgroup analyses. Another study that similarly defined medication categories found RZV to be effective for RA patients (≥50 years) across all medication categories [Constenla, 2025].

The risk of disease flare after RZV has not been well-documented especially for ≥18-year-old RA patients. Our study found that RZV was not associated with an increased risk of flares among RA patients during the 30-day risk period following vaccination. In another SCCS study, the authors did not find an elevated risk of flares during a 42-day risk window post-RZV among ≥50-year-old RA patients, compared to the 42-day comparison window pre-RZV [Leung, 2022].

In this study, the adjusted VE (2 doses administered 4 weeks to 6 months apart) against HZ for adults (≥18 years) with IBD was 62.9%. The adjusted 2-dose RZV (≥4 weeks) VE against HZ for adults with UC and CD was 62.7% and 70.2%, respectively. In a

previously published study of ≥ 50 -year-old IBD patients, the risks of HZ were lower among 2-dose RZV vaccinated IBD (adjusted odds ratio [aOR]=0.44), UC (aOR=0.41) and CD (aOR=0.44) patients, compared to their unvaccinated counterparts [Desai, 2024]. Another previously published analysis indicated higher VE estimates (2 doses administered ≥ 4 weeks apart) in the ≥ 50 -year-old IBD population (73.4% for all IBD, 63.5% for UC and 85.7% for CD), compared to the estimates provided in our study for the ≥ 18 -year-old IBD population [Constenla, 2025]. 2-dose RZV (≥ 4 weeks) VE for the ≥ 50 -year-old IBD patients in our study was 67.0%. VE could not be estimated in the 18–49-year group due to a small sample size.

The 2-dose RZV (>6 months) VE against HZ for IBD patients had a wide CI and included the null; however, sample size in this subgroup was small. The 95% CI for 1-dose RZV VE included the null for IBD patients. A retrospective study conducted among patients with IBD in the Veterans Affairs Healthcare System (VAHS) found that a single dose of RZV did not yield a significantly lower risk of HZ when compared to the unvaccinated in the 50-60-year-old and >60 -year-old groups [Khan, 2022].

The VE for 2 doses administered at least 4 weeks apart was 73.1% in the 1st year of vaccination followed by 92.2% during 1-3 years after vaccination among IBD patients. Constenla et al. found that VE (2 doses given at least 4 weeks apart) in the 1st year was 66.7%, followed by 77.3% in the 2nd and 79.3% in the 3rd year for ≥ 50 -year-old IBD patients [Constenla, 2025].

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For the IBD cohort, RZV did not contribute to a higher risk of flares post vaccination in our study. A study of 67 IBD patients conducted at the Boston Medical Center prospectively followed RZV recipients and found the rate of flares to be 1.5% during a median follow up of 207 days following vaccination [Satyam, 2020]. In a VAHS based study of ≥ 50 -year-olds, the 90-day cumulative incidence of IBD-flares was similar for RZV-vaccinated (1.2%) and unvaccinated (1.0%) IBD patients [Khan, 2022]. Consistent with our findings, another study that used a SCCS design also found that the risk of flares was similar pre- and post-RZV in ≥ 50 -year-old IBD patients [Leung, 2022].

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CCI. Recently published interim results of this study for the ≥ 50 -year-old RA patients found VE against PHN to be 88.7% [Rayens, 2025]. In a study of ≥ 50 -year-old IBD patients, the odds of developing PHN among HZ patients were similar for vaccinated and unvaccinated cohorts [Desai, 2024].

10.2. Limitations

A potential limitation of this study was that there could be differences between vaccinated and unvaccinated individuals that were difficult to control and measure despite matching on key variables and adjusting for several covariates including demographic characteristics, health care utilization, and comorbidities. The effect of residual confounding may have impacted VE or safety estimates. Proxy measures may not completely and accurately capture disease severity (medication category) and healthcare utilization (captured from one year prior to index date).

During the initial months of the vaccine accrual period, RZV vaccination at KPSC was prioritized for individuals ages 60 years and older. However, this should not have biased results since individuals were matched on age.

Despite high validity of diagnostic algorithms, misclassification of HZ status could occur inherently in EHR studies using automated data, but we do not expect differential misclassification between exposure groups.

It was unknown if RZV vaccination led to modified or atypical HZ presentations that were more likely to be underdiagnosed or misdiagnosed. If these cases were never diagnosed or were diagnosed as other conditions, they would not be identified through ICD-10 codes for HZ. This would lead to a potential overestimation of VE. It was also possible that there was differential misclassification of HZ due to differential health care seeking behaviors, but to address this, prior health care utilization was included as a covariate.

Some of the secondary and exploratory objective analyses, including subgroup analyses, yielded wide confidence intervals potentially due to small sample size, limiting our ability to draw robust conclusions. This was true especially for the 18–49-year age group. For several VE estimates, we could not adjust for all potential confounders due to model convergence issues.

10.3. Interpretation of results

Our findings suggest that vaccination with 2 doses of RZV is protective against HZ for individuals with RA and IBD aged 18 years and over. CCI [REDACTED] CCI [REDACTED]. For both RA and IBD patients, RZV is not associated with increased risk of disease flare within 30 days after vaccination.

10.4. Generalisability

This was a large study, composed of a diverse population that is representative of the Southern California region. Study results should be generalizable to similar clinical practice and care settings. Results may not be generalizable to individuals who receive care in different types of health systems in the U.S., for example, uninsured populations, or in other countries.

11. OTHER INFORMATION

Not applicable

12. CONCLUSIONS

For adults with RA, 2 doses of RZV administered ≥ 4 weeks apart conferred protection against HZ and CCI. For adults with IBD, 2 doses of RZV administered ≥ 4 weeks apart conferred protection against HZ. RZV vaccination was not associated with elevated risk of flares following vaccination in either the RA or IBD cohorts. For both UC and CD, 2 doses of RZV administered ≥ 4 weeks apart was protective against HZ with no flare safety concerns. Despite a delay in the receipt of the 2nd dose (> 6 months), RZV remained effective against HZ for RA patients. A single dose of RZV was not as effective as 2 doses against HZ in both RA and IBD cohorts. VE estimates were robust for the ≥ 50 -year-old RA and IBD patients. For the 18–49-year age group, the sample size was too small to draw a definite conclusion. For the first 3 years after 2-dose vaccination, RZV continued to offer substantial protection against HZ for IBD and RA patients.

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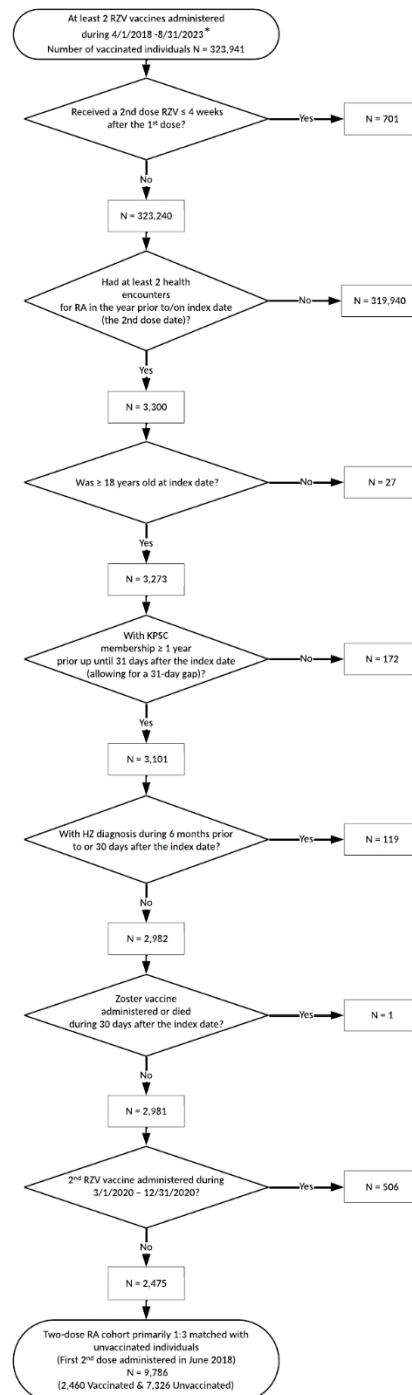
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14. TABLES AND FIGURES

14.1. Appendix A - Vaccine Effectiveness

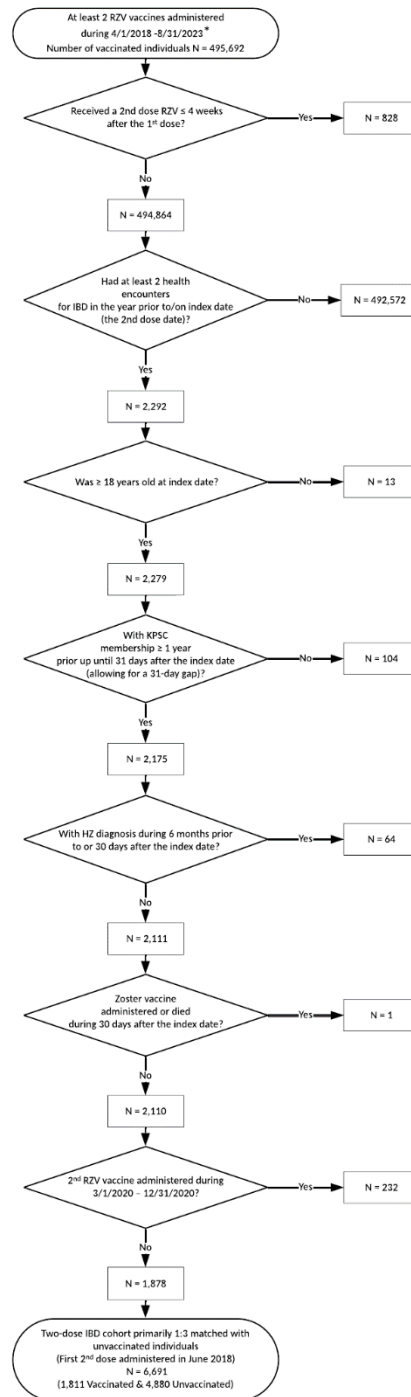
Appendix A Figure 1 Flow chart for 2-dose RZV cohort with RA



* Accrual period for age 50+ individuals was 4/1/2018 - 5/31/2022.

Appendix A Figure 2

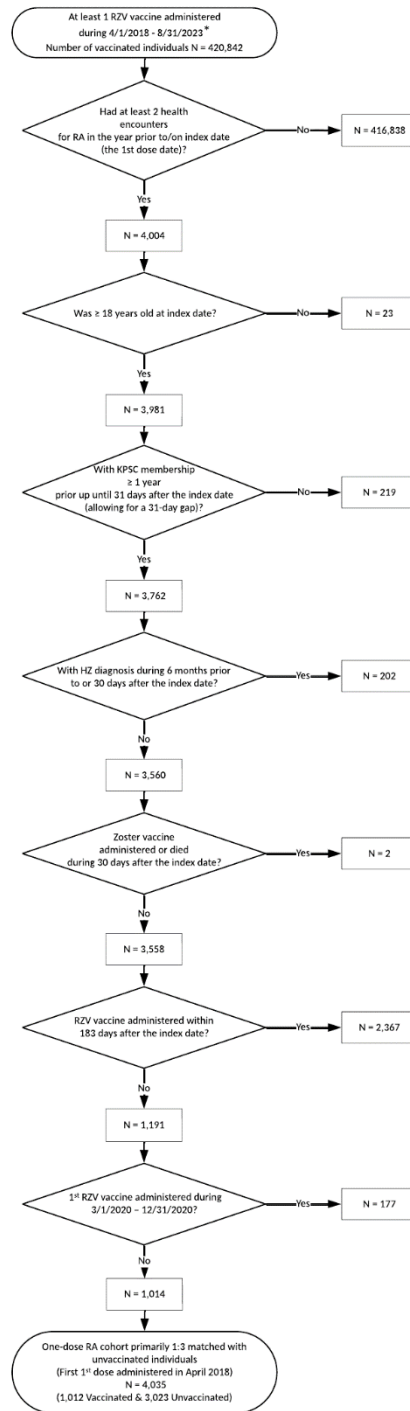
Flow chart for 2-dose RZV cohort with IBD



*Accrual period for age 50+ individuals was 4/1/2018 - 11/30/2022.

Appendix A Figure 3

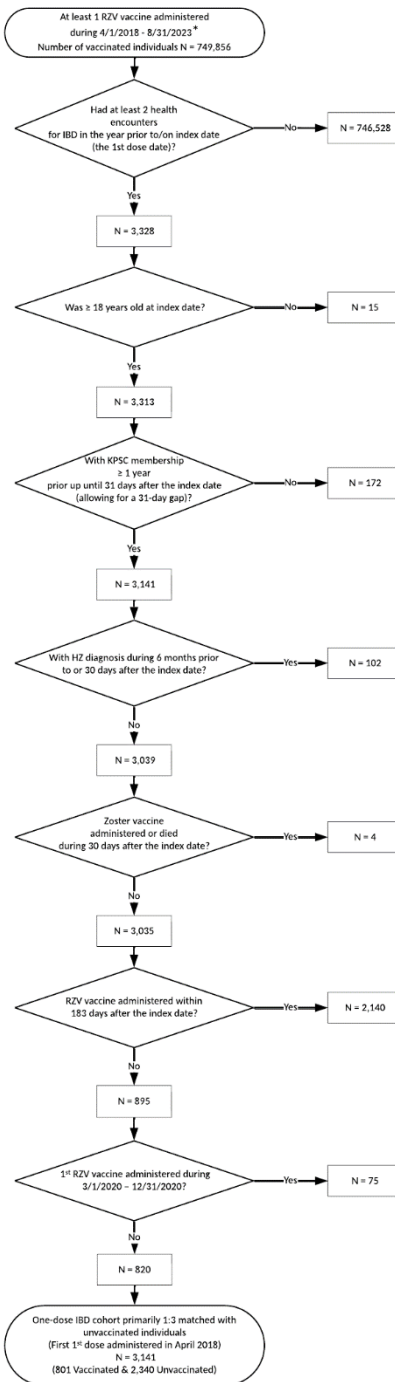
Flow chart for 1-dose RZV cohort with RA



* Accrual period for age 50+ individuals was 4/1/2018 - 5/31/2022.

Appendix A Figure 4

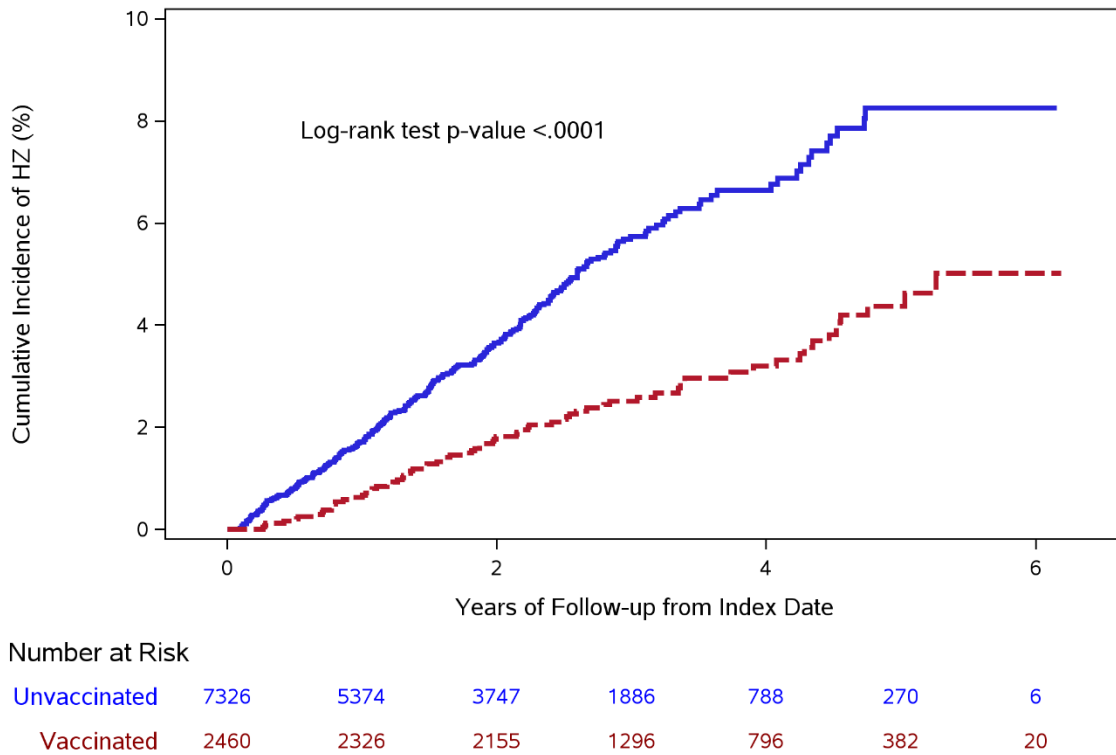
Flow chart for 1-dose RZV cohort with IBD



*Accrual period for age 50+ individuals was 4/1/2018 - 11/30/2022.

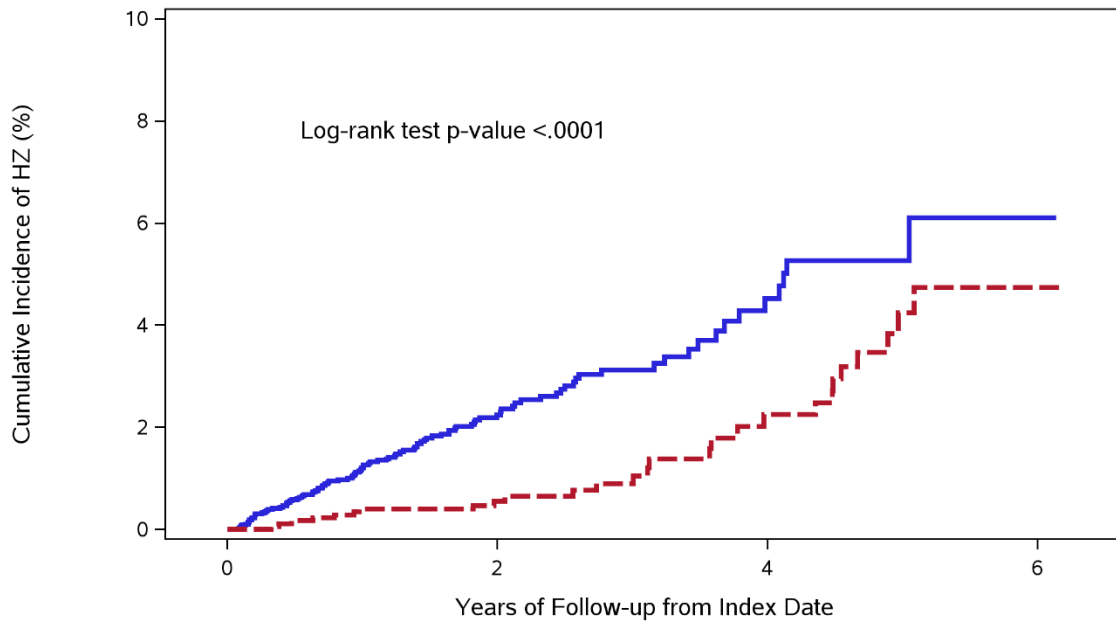
Appendix A Figure 5

Cumulative incidence estimates of HZ by RZV
vaccination status in 2-dose RZV cohort with RA



Appendix A Figure 6

Cumulative incidence estimates of HZ by RZV vaccination status in 2-dose RZV cohort with IBD

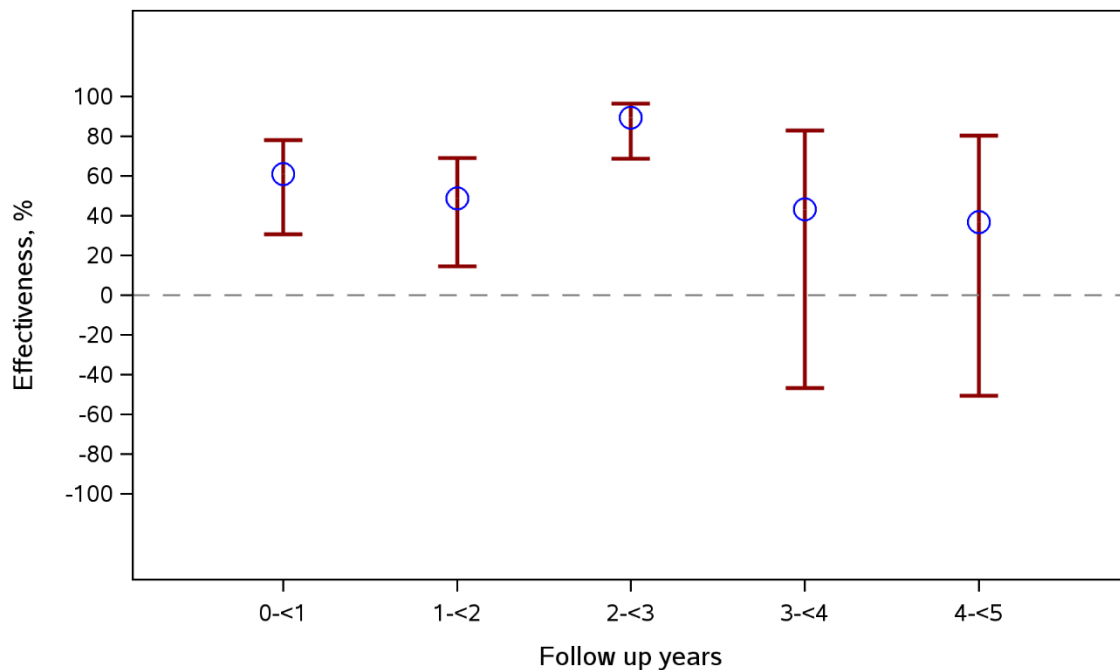


Number at Risk

Unvaccinated	4880	3377	1798	944	405	124	6
Vaccinated	1811	1700	1148	647	428	218	13

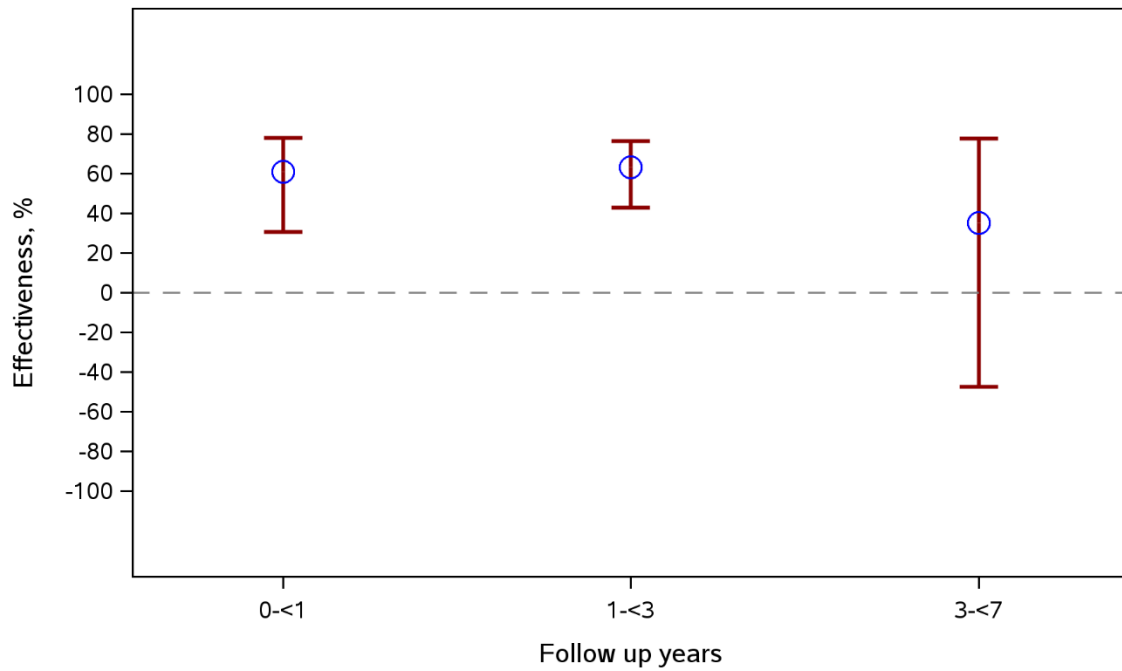
Appendix A Figure 7

Effectiveness of 2 doses of RZV in preventing HZ by year after vaccination among individuals with RA



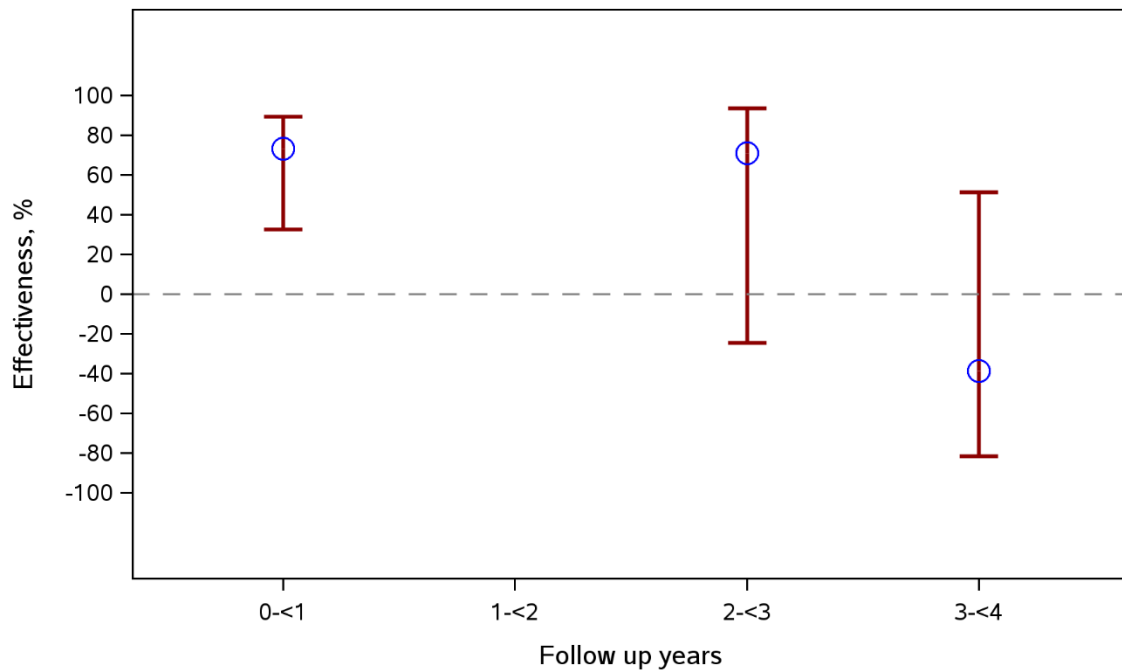
Appendix A Figure 8

Effectiveness of 2 doses of RZV in preventing HZ by year after vaccination among individuals with RA (combined follow-up years)



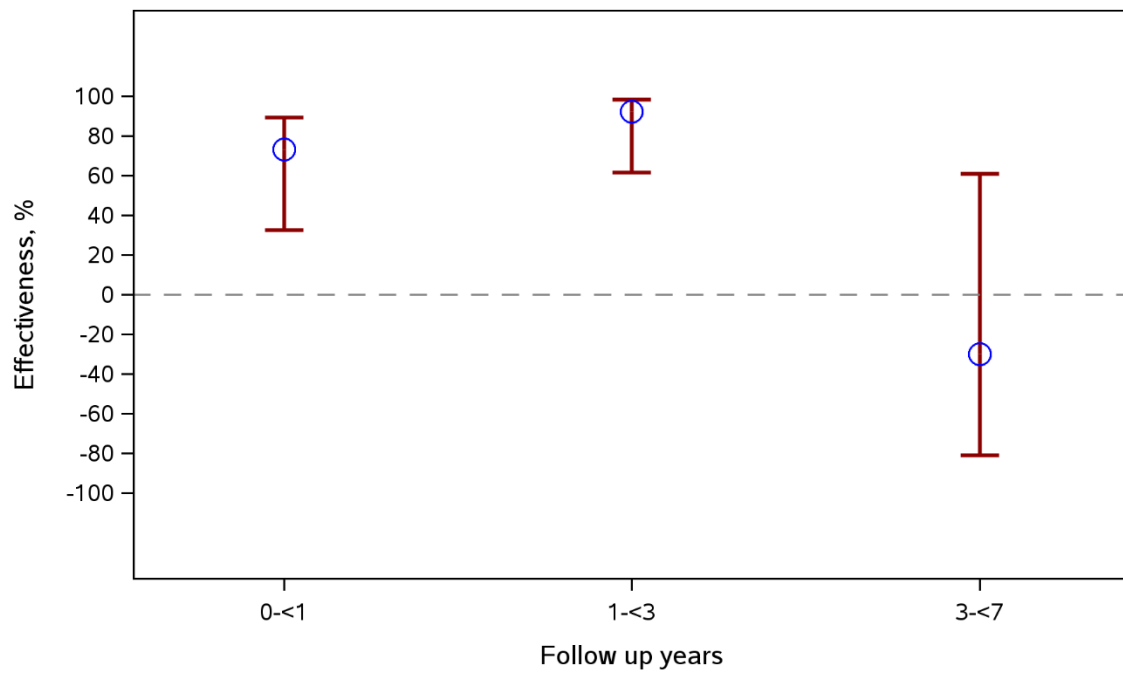
Appendix A Figure 9

Effectiveness of 2 doses of RZV in preventing HZ by year after vaccination among individuals with IBD

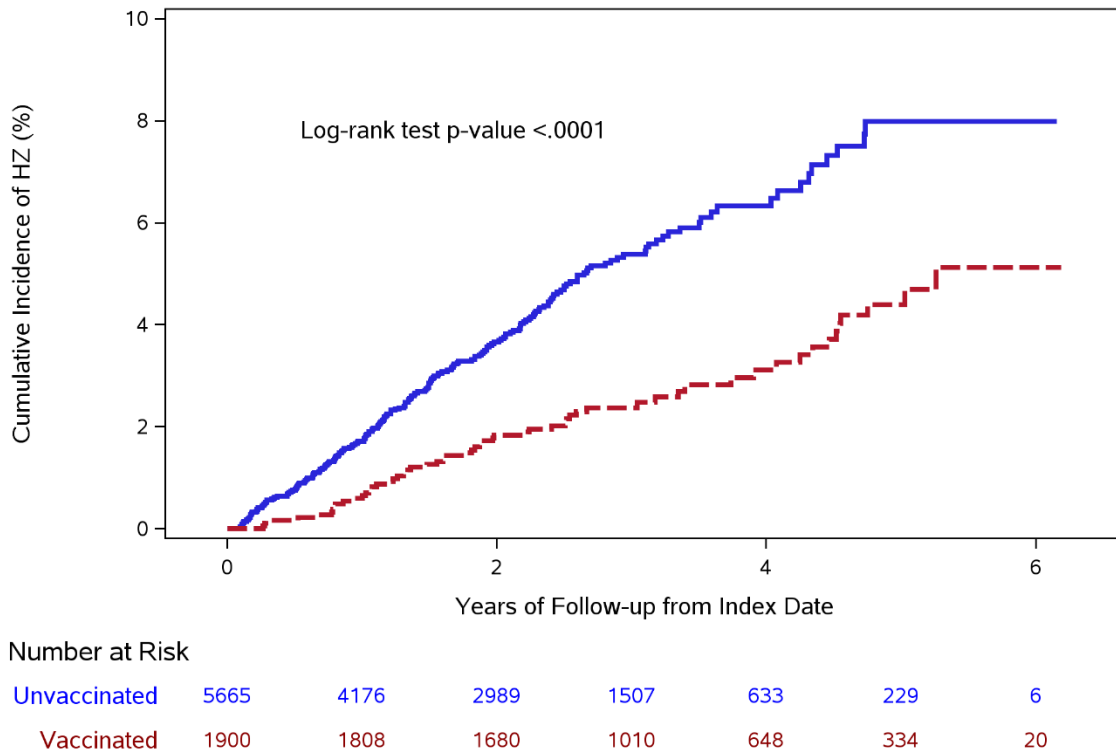


Appendix A Figure 10

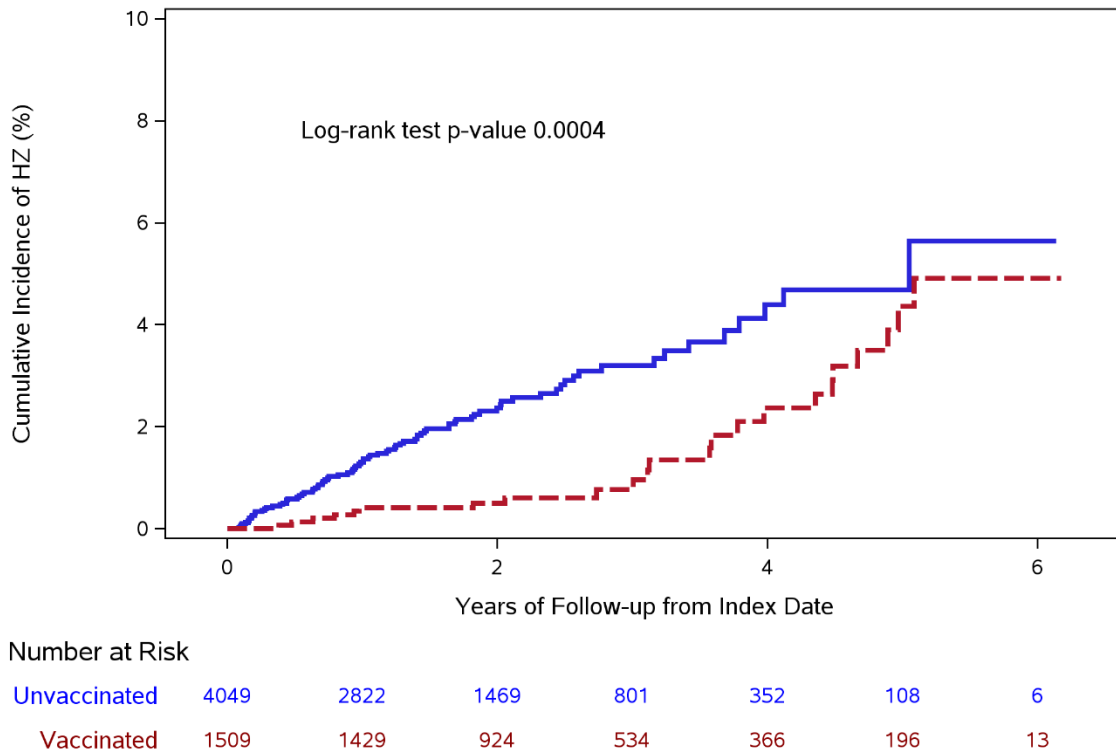
Effectiveness of 2 doses of RZV in preventing HZ by year after vaccination among individuals with IBD (combined follow-up years)



Appendix A Figure 11 Cumulative incidence estimates of HZ by RZV vaccination status in 2-dose RZV cohort (4 weeks - 6 months) with RA

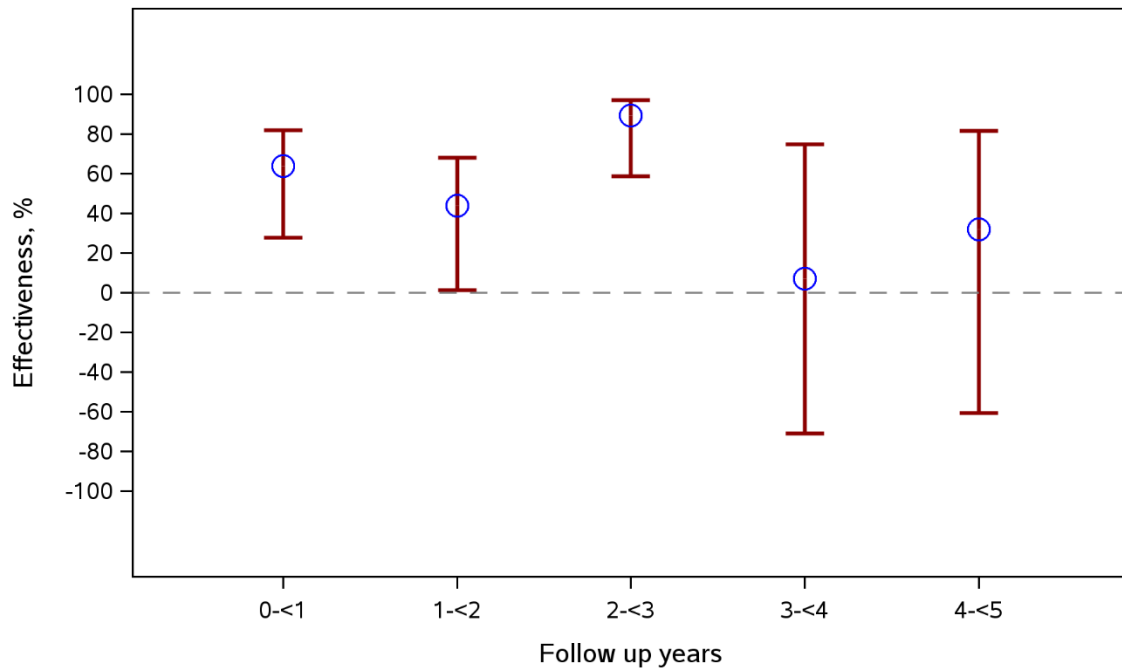


Appendix A Figure 12 Cumulative incidence estimates of HZ by RZV vaccination status in 2-dose RZV cohort (4 weeks - 6 months) with IBD



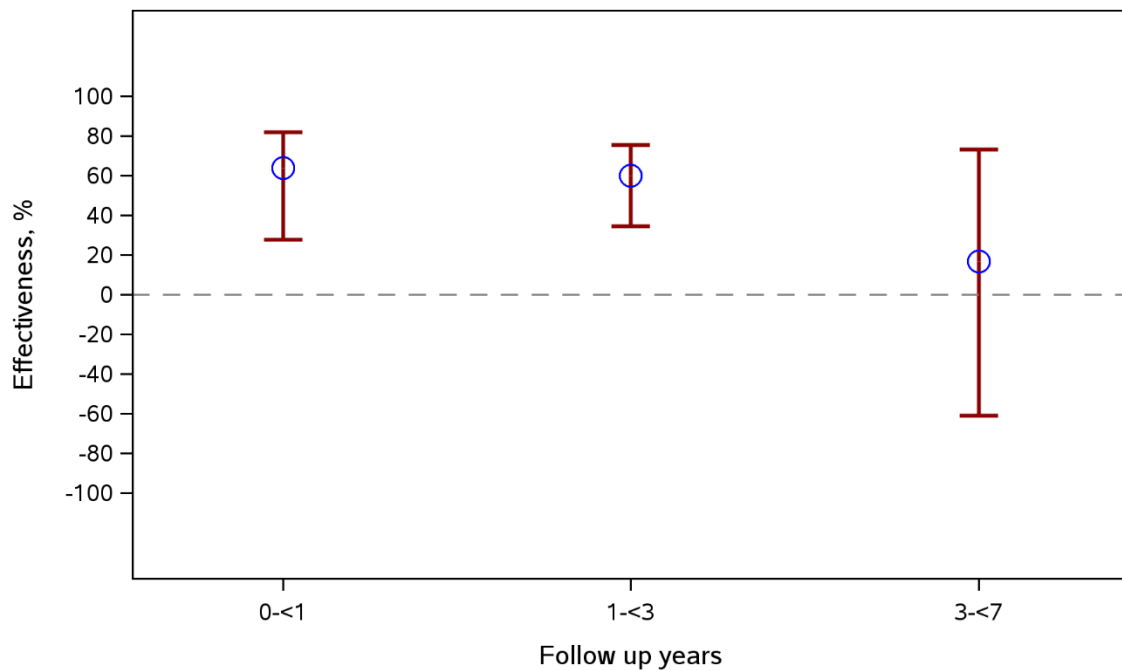
Appendix A Figure 13

Effectiveness of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with RA



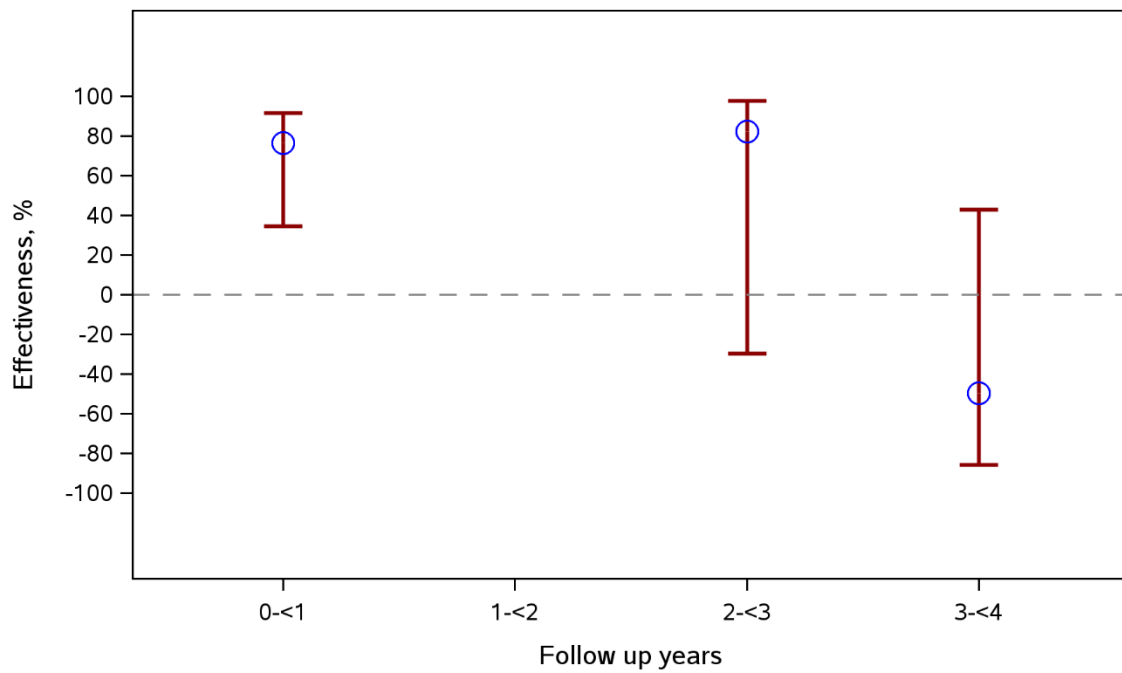
Appendix A Figure 14

Effectiveness of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with RA (combined follow-up years)



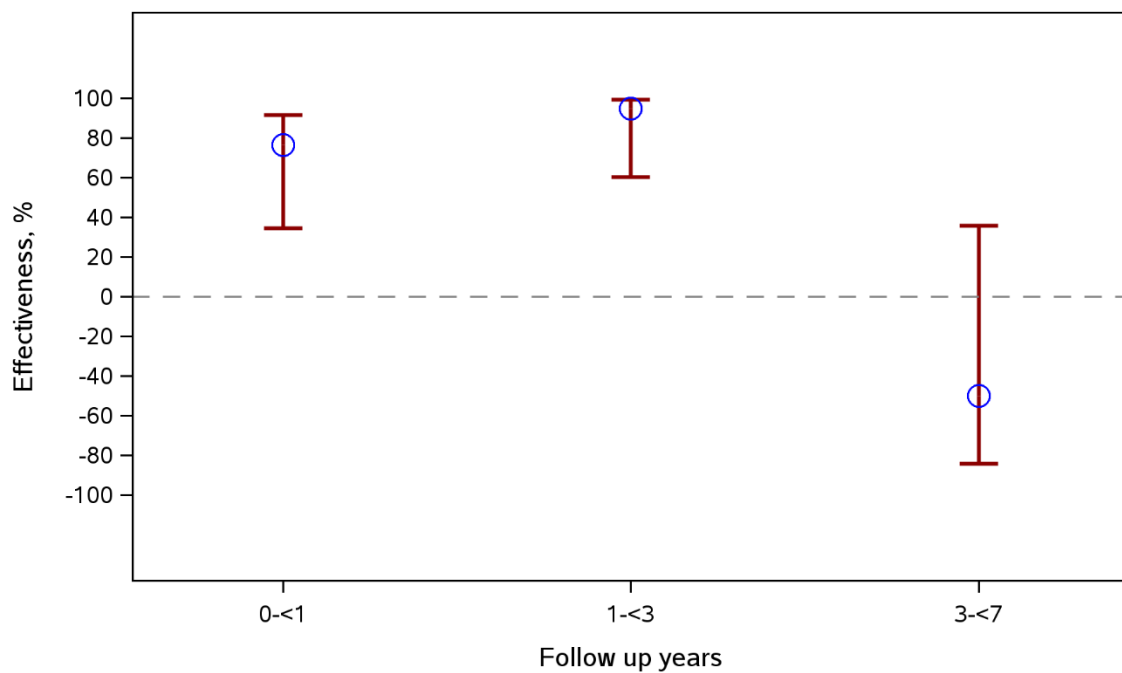
Appendix A Figure 15

Effectiveness of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with IBD



Appendix A Figure 16

Effectiveness of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with IBD (combined follow-up years)



Appendix A Table 1 Baseline characteristics of 2-dose RZV vaccinated and unvaccinated cohort with RA

	Vaccinate d N=2460	Unvaccina ted N=7326	Total N=9786	p value	ASD
Age at index date, years				0.323	0.016
mean (sd)	68.56 (9.82)	68.40 (10.14)	68.44 (10.06)		
median	69	69	69		
Q1, Q3	62, 75	62, 75	62, 75		
range	27, 96	20, 101	20, 101		
Age at index date, years, n (%)				1.000	0.005
18-49	49 (2.0%) 392	143 (2.0%) 1171	192 (2.0%) 1563		
50-59	(15.9%) 848	(16.0%) 2531	(16.0%) 3379		
60-69	(34.5%) 844	(34.5%) 2518	(34.5%) 3362		
70-79	(34.3%) 327	(34.4%) 963	(34.4%) 1290		
≥80	(13.3%)	(13.1%)	(13.2%)		
Sex, n (%)				0.900	0.003
Female	1947 (79.1%) 513	5807 (79.3%) 1519	7754 (79.2%) 2032		
Male	(20.9%)	(20.7%)	(20.8%)		
Race/Ethnicity, n (%)				0.985	0.014
White	1109 (45.1%) 227	3319 (45.3%)	4428 (45.2%)		
Black	(9.2%) 763	679 (9.3%) 2283	906 (9.3%) 3046		
Hispanic	(31.0%) 309	(31.2%) 902	(31.1%) 1211		
Asian	(12.6%)	(12.3%)	(12.4%)		
Other	52 (2.1%)	143 (2.0%)	195 (2.0%)		
Medication category, n (%)				0.971	0.017
Category 1	569 (23.1%) 1318	1705 (23.3%) 3953	2274 (23.2%) 5271		
Category 2	(53.6%) 318	(54.0%) 943	(53.9%) 1261		
Category 3	(12.9%) 112	(12.9%)	(12.9%)		
Category 4	(4.6%)	324 (4.4%)	436 (4.5%)		

	Vaccinated N=2460	Unvaccinated N=7326	Total N=9786	p value	ASD
Category 5	143 (5.8%)	401 (5.5%)	544 (5.6%)		
Number of outpatient visits ^a , n (%)				<0.001	0.178
0-4	6 (0.2%)	87 (1.2%)	93 (1.0%)		
5-10	214 (8.7%)	941 (12.8%)	1155 (11.8%)		
≥11	2240 (91.1%)	6298 (86.0%)	8538 (87.2%)		
Number of ED visits ^a , n (%)				<0.001	0.120
0	1778 (72.3%)	4958 (67.7%)	6736 (68.8%)		
1	424 (17.2%)	1332 (18.2%)	1756 (17.9%)		
≥2	258 (10.5%)	1036 (14.1%)	1294 (13.2%)		
Number of hospitalizations ^a , n (%)				<0.001	0.119
0	2219 (90.2%)	6360 (86.8%)	8579 (87.7%)		
1	175 (7.1%)	629 (8.6%)	804 (8.2%)		
≥2	66 (2.7%)	337 (4.6%)	403 (4.1%)		
Baseline comorbidities ^a , n (%)					
Kidney disease	382 (15.5%)	1299 (17.7%)	1681 (17.2%)	0.012	0.059
Heart disease	207 (8.4%)	860 (11.7%)	1067 (10.9%)	<0.001	0.111
Lung disease	592 (24.1%)	1738 (23.7%)	2330 (23.8%)	0.731	0.008
Liver disease	163 (6.6%)	493 (6.7%)	656 (6.7%)	0.859	0.004
Diabetes	591 (24.0%)	1884 (25.7%)	2475 (25.3%)	0.095	0.039
Other autoimmune diseases ^b	159 (6.5%)	448 (6.1%)	607 (6.2%)	0.536	0.014
SARS-CoV-2 infection/COVID-19 diagnosis	136 (5.5%)	477 (6.5%)	613 (6.3%)	0.082	0.041
Immunocompromised status ^c at index date, n (%)				0.001	0.078
Yes	1589 (64.6%)	4456 (60.8%)	6045 (61.8%)		
No	871 (35.4%)	2870 (39.2%)	3741 (38.2%)		

	Vaccinate d N=2460	Unvaccina ted N=7326	Total N=9786	p value	ASD
History of ZVL/varicella vaccination ^d , n (%)				<0.00 1	0.299
No	1605 (65.2%)	5641 (77.0%)	7246 (74.0%)		
Yes, ≤ 5 years	83 (3.4%)	321 (4.4%)	404 (4.1%)		
Yes, > 5 years	772 (31.4%)	1364 (18.6%)	2136 (21.8%)		
History of HZ ^d , n (%)				0.809	0.006
Yes	429 (17.4%)	1262 (17.2%)	1691 (17.3%)		
No	2031 (82.6%)	6064 (82.8%)	8095 (82.7%)		
Length of continuous KPSC membership ^d , years, n (%)				<0.00 1	0.104
0-5	461 (18.7%)	1676 (22.9%)	2137 (21.8%)		
6-10	430 (17.5%)	1271 (17.3%)	1701 (17.4%)		
≥11	1569 (63.8%)	4379 (59.8%)	5948 (60.8%)		
Concomitant vaccination ^e , n (%)				N/A ^f	N/A
Yes	910 (37.0%)	N/A	N/A		
No	1550 (63.0%)	N/A	N/A		
Time between first and second doses, n (%)				N/A	N/A
4 weeks - 6 months	1900 (77.2%)	N/A	N/A		
>6 months ^g	560 (22.8%)	N/A	N/A		

a. Defined in the one year prior to index date

b. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease.

c. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

d. Defined based on all available medical records prior to index date.

e. Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (47%), COVID-19 vaccine (4%), PCV13/PCV20/PPSV23 (24%), Tdap (34%), and other (10%); 73% concomitant with 1st dose and 40% concomitant with 2nd dose.

f. N/A= not applicable.

g. Among individuals who received the 2nd dose more than 6 months after the 1st dose, the range of time between two doses was from 6 to 48 months with a median of 11 months.

AIDS, acquired immunodeficiency syndrome; ASD, absolute standard difference; ED, emergency department; HIV, human immunodeficiency virus; HZ, herpes zoster; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; RA, rheumatoid arthritis; RZV, recombinant zoster vaccine; sd, standard deviation; Q, quartile; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; ZVL, zoster vaccine live.

Appendix A Table 2 Baseline characteristics of 2-dose RZV vaccinated and unvaccinated cohort with IBD

	Vaccinated N=1811	Unvaccinated N=4880	Total N=6691	p value	ASD
Age at index date, years				0.004	0.065
mean (sd)	66.51 (11.59)	65.74 (11.99)	65.95 (11.88)		
median	67	66	67		
Q1, Q3	60, 74	60, 73	60, 74		
range	18, 98	19, 99	18, 99		
Age at index date, years, n (%)				0.723	0.040
18-49	85 (4.7%)	251 (5.1%)	336 (5.0%)		
50-59	330 (18.2%)	941 (19.3%)	1271 (19.0%)		
60-69	656 (36.2%)	1767 (36.2%)	2423 (36.2%)		
70-79	548 (30.3%)	1419 (29.1%)	1967 (29.4%)		
≥80	192 (10.6%)	502 (10.3%)	694 (10.4%)		
Sex, n (%)				0.928	0.002
Female	976 (53.9%)	2636 (54.0%)	3612 (54.0%)		
Male	835 (46.1%)	2244 (46.0%)	3079 (46.0%)		
Race/Ethnicity, n (%)				0.255	0.062
White	1167 (64.4%)	3223 (66.0%)	4390 (65.6%)		
Black	122 (6.7%)	304 (6.2%)	426 (6.4%)		
Hispanic	365 (20.2%)	1002 (20.5%)	1367 (20.4%)		
Asian	122 (6.7%)	281 (5.8%)	403 (6.0%)		
Other	35 (1.9%)	70 (1.4%)	105 (1.6%)		
IBD ^a , n (%)				0.108	0.054
UC	984 (54.3%)	2745 (56.3%)	3729 (55.7%)		
CD ^b	822 (45.4%)	2130 (43.6%)	2952 (44.1%)		
UC+CD	5 (0.3%)	5 (0.1%)	10 (0.1%)		
Medication category, n (%)				0.150	0.075
Category 1	719 (39.7%)	2006 (41.1%)	2725 (40.7%)		
Category 2	622 (34.3%)	1690 (34.6%)	2312 (34.6%)		

	Vaccinated N=1811	Unvaccinat ed N=4880	Total N=6691	p value	ASD
Category 3	316 (17.4%)	811 (16.6%)	1127 (16.8%)		
Category 4	152 (8.4%)	354 (7.3%)	506 (7.6%)		
Category 5	2 (0.1%)	19 (0.4%)	21 (0.3%)		
Number of outpatient visits ^a , n (%)				<0.001	0.227
0-4	12 (0.7%)	97 (2.0%)	109 (1.6%)		
5-10	194 (10.7%)	841 (17.2%)	1035 (15.5%)		
≥11	1605 (88.6%)	3942 (80.8%)	5547 (82.9%)		
Number of ED visits ^a , n (%)				0.001	0.102
0	1250 (69.0%)	3165 (64.9%)	4415 (66.0%)		
1	321 (17.7%)	905 (18.5%)	1226 (18.3%)		
≥2	240 (13.3%)	810 (16.6%)	1050 (15.7%)		
Number of hospitalizations ^a , n (%)				0.048	0.069
0	1540 (85.0%)	4032 (82.6%)	5572 (83.3%)		
1	185 (10.2%)	557 (11.4%)	742 (11.1%)		
≥2	86 (4.7%)	291 (6.0%)	377 (5.6%)		
Baseline comorbidities ^a , n (%)					
Kidney disease	329 (18.2%)	779 (16.0%)	1108 (16.6%)	0.031	0.059
Heart disease	175 (9.7%)	489 (10.0%)	664 (9.9%)	0.664	0.012
Lung disease	403 (22.3%)	1044 (21.4%)	1447 (21.6%)	0.448	0.021
Liver disease	166 (9.2%)	427 (8.8%)	593 (8.9%)	0.595	0.015
Diabetes	439 (24.2%)	1111 (22.8%)	1550 (23.2%)	0.204	0.035
Other autoimmune diseases ^c	133 (7.3%)	350 (7.2%)	483 (7.2%)	0.809	0.007
SARS-CoV-2 infection/ COVID-19 diagnosis	205 (11.3%)	514 (10.5%)	719 (10.7%)	0.356	0.025
Immunocompromised status ^d at index date, n (%)				0.006	0.074
Yes	481 (26.6%)	1139 (23.3%)	1620 (24.2%)		
No	1330 (73.4%)	3741 (76.7%)	5071 (75.8%)		

	Vaccinated N=1811	Unvaccinat ed N=4880	Total N=6691	p value	ASD
History of ZVL/varicella vaccination ^e , n (%)				<0.001	0.275
No	1155 (63.8%)	3627 (74.3%)	4782 (71.5%)		
Yes, ≤ 5 years	63 (3.5%)	238 (4.9%)	301 (4.5%)		
Yes, > 5 years	593 (32.7%)	1015 (20.8%)	1608 (24.0%)		
History of HZ ^e , n (%)				0.027	0.060
Yes	273 (15.1%)	634 (13.0%)	907 (13.6%)		
No	1538 (84.9%)	4246 (87.0%)	5784 (86.4%)		
Length of continuous KPSC membership ^e , years, n (%)				<0.001	0.142
0-5	335 (18.5%)	1160 (23.8%)	1495 (22.3%)		
6-10	327 (18.1%)	927 (19.0%)	1254 (18.7%)		
≥11	1149 (63.4%)	2793 (57.2%)	3942 (58.9%)		
Concomitant vaccination ^f , n (%)				N/A ^g	N/A
Yes	785 (43.3%)	N/A	N/A		
No	1026 (56.7%)	N/A	N/A		
Time between first and second doses, n (%)				N/A	N/A
4 weeks - 6 months	1509 (83.3%)	N/A	N/A		
>6 months ^h	302 (16.7%)	N/A	N/A		

a. Defined in the one year prior to index date

b. 14 of the vaccinated individuals in the CD category also had UC but could only be matched to other unvaccinated individuals with CD.

c. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis.

d. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

e. Defined based on all available medical records prior to index date

f. Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (47%), COVID-19 vaccine (10%), PCV13/PCV20/PPSV23 (30%), Tdap (26%), and other (14%); 70% concomitant with 1st dose and 47% concomitant with 2nd dose.

g. N/A= not applicable

h. Among individuals who received the 2nd dose more than 6 months after the 1st dose, the range of time between two doses was from 6 to 58 months with a median of 11 months

AIDS, acquired immunodeficiency syndrome; ASD, absolute standard difference; ED, emergency department; HIV, human immunodeficiency virus; HZ, herpes zoster; IBD, inflammatory bowel disease; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; sd, standard deviation; Q, quartile; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; ZVL, zoster vaccine live.

Appendix A Table 3 Baseline characteristics of 1-dose RZV vaccinated and unvaccinated cohort with RA^a

	Vaccinated N=1012	Unvaccinated N=3023	Total N=4035	p value	AS D
Age at index date, years				0.727	0.00 6
mean (sd)	67.76 (10.46)	67.69 (10.81)	67.71 (10.72)		
median	68	68	68		
Q1, Q3	61, 75	61, 75	61, 75		
range	22, 98	22, 100	22, 100		
Age at index date, years, n (%)				1.000	0.00 3
18-49	42 (4.2%)	125 (4.1%)	167 (4.1%)		
50-59	170 (16.8%)	508 (16.8%)	678 (16.8%)		
60-69	332 (32.8%)	991 (32.8%)	1323 (32.8%)		
70-79	337 (33.3%)	1010 (33.4%)	1347 (33.4%)		
≥80	131 (12.9%)	389 (12.9%)	520 (12.9%)		
Sex, n (%)				0.881	0.00 5
Female	774 (76.5%)	2319 (76.7%)	3093 (76.7%)		
Male	238 (23.5%)	704 (23.3%)	942 (23.3%)		
Race/Ethnicity, n (%)				1.000	0.00 5
White	420 (41.5%)	1254 (41.5%)	1674 (41.5%)		
Black	110 (10.9%)	328 (10.9%)	438 (10.9%)		
Hispanic	346 (34.2%)	1038 (34.3%)	1384 (34.3%)		
Asian	116 (11.5%)	345 (11.4%)	461 (11.4%)		
Other	20 (2.0%)	58 (1.9%)	78 (1.9%)		
Medication category, n (%)				0.998	0.01 4
Category 1	240 (23.7%)	720 (23.8%)	960 (23.8%)		
Category 2	535 (52.9%)	1605 (53.1%)	2140 (53.0%)		
Category 3	113 (11.2%)	339 (11.2%)	452 (11.2%)		
Category 4	55 (5.4%)	163 (5.4%)	218 (5.4%)		
Category 5	69 (6.8%)	196 (6.5%)	265 (6.6%)		
Number of outpatient visits ^b , n (%)				0.269	0.05 6
0-4	17 (1.7%)	33 (1.1%)	50 (1.2%)		
5-10	124 (12.3%)	348 (11.5%)	472 (11.7%)		
≥11	871 (86.1%)	2642 (87.4%)	3513 (87.1%)		
Number of ED visits ^b , n (%)				0.068	0.08 5
0	714 (70.6%)	2014 (66.6%)	2728 (67.6%)		
1	164 (16.2%)	562 (18.6%)	726 (18.0%)		

	Vaccinated N=1012	Unvaccinated N=3023	Total N=4035	p value	AS D
≥2	134 (13.2%)	447 (14.8%)	581 (14.4%)		
Number of hospitalizations ^b , n (%)				0.018	0.10 7
0	906 (89.5%)	2609 (86.3%)	3515 (87.1%)		
1	73 (7.2%)	261 (8.6%)	334 (8.3%)		
≥2	33 (3.3%)	153 (5.1%)	186 (4.6%)		
Baseline comorbidities ^b , n (%)					
Kidney disease	175 (17.3%)	553 (18.3%)	728 (18.0%)	0.474	0.02 6
Heart disease	108 (10.7%)	352 (11.6%)	460 (11.4%)	0.400	0.03 1
Lung disease	228 (22.5%)	717 (23.7%)	945 (23.4%)	0.440	0.02 8
Liver disease	73 (7.2%)	207 (6.8%)	280 (6.9%)	0.692	0.01 4
Diabetes	250 (24.7%)	797 (26.4%)	1047 (25.9%)	0.297	0.03 8
Other autoimmune diseases ^c	63 (6.2%)	172 (5.7%)	235 (5.8%)	0.529	0.02 3
SARS-CoV-2 infection/ COVID-19 diagnosis	40 (4.0%)	114 (3.8%)	154 (3.8%)	0.794	0.00 9
Immunocompromised status ^d at index date, n (%)				0.125	0.05 6
Yes	654 (64.6%)	1872 (61.9%)	2526 (62.6%)		
No	358 (35.4%)	1151 (38.1%)	1509 (37.4%)		
History of ZVL/varicella vaccination ^e , n (%)				<0.001	0.22 1
No	691 (68.3%)	2336 (77.3%)	3027 (75.0%)		
Yes, ≤ 5 years	63 (6.2%)	184 (6.1%)	247 (6.1%)		
Yes, > 5 years	258 (25.5%)	503 (16.6%)	761 (18.9%)		
History of HZ ^e , n (%)				0.862	0.00 6
Yes	170 (16.8%)	515 (17.0%)	685 (17.0%)		
No	842 (83.2%)	2508 (83.0%)	3350 (83.0%)		
Length of continuous KPSC membership ^e , years, n (%)				0.480	0.04 4
0-5	235 (23.2%)	673 (22.3%)	908 (22.5%)		
6-10	163 (16.1%)	535 (17.7%)	698 (17.3%)		
≥11	614 (60.7%)	1815 (60.0%)	2429 (60.2%)		

	Vaccinated N=1012	Unvaccinate d N=3023	Total N=4035	p value	AS D
Concomitant vaccination ^f , n (%)				N/A ^g	N/A
Yes	292 (28.9%)	N/A	N/A		
No	720 (71.1%)	N/A	N/A		

a. Eligible vaccinated individuals in 1-dose RZV cohort either received only 1 dose of RZV by the end of the accrual period or received a 2nd dose more than 6 months after the 1st dose.

b. Defined in the one year prior to index date

c. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease.

d. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenism, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

e. Defined based on all available medical records prior to index date

f. Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (44%), COVID-19 vaccine (2%), PCV13/PCV20/PPSV23 (28%), Tdap (24%), and other (12%)

g. N/A= not applicable

AIDS, acquired immunodeficiency syndrome; ASD, absolute standard difference; ED, emergency department; HIV, human immunodeficiency virus; HZ, herpes zoster; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; RA, rheumatoid arthritis; RZV, recombinant zoster vaccine; sd, standard deviation; Q, quartile; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; ZVL, zoster vaccine live.

Appendix A Table 4 Baseline characteristics of 1-dose RZV vaccinated and unvaccinated cohort with IBD^a

	Vaccinated N=801	Unvaccinate d N=2340	Total N=3141	p value	ASD
Age at index date, years				0.501	0.012
mean (sd)	63.98 (14.58)	63.80 (14.40)	63.84 (14.44)		
median	66	66	66		
Q1, Q3	57, 74	56, 73	57, 73		
range	18, 95	18, 98	18, 98		
Age at index date, years, n (%)				0.999	0.011
18-49	98 (12.2%)	281 (12.0%)	379 (12.1%)		
50-59	148 (18.5%)	440 (18.8%)	588 (18.7%)		
60-69	246 (30.7%)	721 (30.8%)	967 (30.8%)		
70-79	223 (27.8%)	650 (27.8%)	873 (27.8%)		
≥80	86 (10.7%)	248 (10.6%)	334 (10.6%)		
Sex, n (%)				0.792	0.011
Female	415 (51.8%)	1225 (52.4%)	1640 (52.2%)		
Male	386 (48.2%)	1115 (47.6%)	1501 (47.8%)		
Race/Ethnicity, n (%)				0.896	0.042
White	481 (60.0%)	1438 (61.5%)	1919 (61.1%)		
Black	65 (8.1%)	179 (7.6%)	244 (7.8%)		
Hispanic	182 (22.7%)	533 (22.8%)	715 (22.8%)		
Asian	57 (7.1%)	150 (6.4%)	207 (6.6%)		
Other	16 (2.0%)	40 (1.7%)	56 (1.8%)		
IBD ^b , n (%)				0.736	0.030
UC	466 (58.2%)	1367 (58.4%)	1833 (58.4%)		
CD ^c	332 (41.4%)	968 (41.4%)	1300 (41.4%)		
UC+CD	3 (0.4%)	5 (0.2%)	8 (0.3%)		
Medication category, n (%)				0.456	0.087
Category 1	332 (41.4%)	982 (42.0%)	1314 (41.8%)		
Category 2	255 (31.8%)	748 (32.0%)	1003 (31.9%)		
Category 3	126 (15.7%)	369 (15.8%)	495 (15.8%)		
Category 4	87 (10.9%)	227 (9.7%)	314 (10.0%)		
Category 5	1 (0.1%)	14 (0.6%)	15 (0.5%)		

	Vaccinated N=801	Unvaccinated N=2340	Total N=3141	p value	ASD
Number of outpatient visits ^b , n (%)				0.008	0.119
0-4	36 (4.5%)	56 (2.4%)	92 (2.9%)		
5-10	125 (15.6%)	399 (17.1%)	524 (16.7%)		
≥11	640 (79.9%)	1885 (80.6%)	2525 (80.4%)		
Number of ED visits ^b , n (%)				0.957	0.012
0	515 (64.3%)	1491 (63.7%)	2006 (63.9%)		
1	161 (20.1%)	477 (20.4%)	638 (20.3%)		
≥2	125 (15.6%)	372 (15.9%)	497 (15.8%)		
Number of hospitalizations ^b , n (%)				0.845	0.024
0	667 (83.3%)	1930 (82.5%)	2597 (82.7%)		
1	90 (11.2%)	270 (11.5%)	360 (11.5%)		
≥2	44 (5.5%)	140 (6.0%)	184 (5.9%)		
Baseline comorbidities ^b , n (%)					
Kidney disease	121 (15.1%)	368 (15.7%)	489 (15.6%)	0.676	0.017
Heart disease	70 (8.7%)	226 (9.7%)	296 (9.4%)	0.442	0.032
Lung disease	178 (22.2%)	451 (19.3%)	629 (20.0%)	0.072	0.073
Liver disease	84 (10.5%)	222 (9.5%)	306 (9.7%)	0.410	0.033
Diabetes	182 (22.7%)	510 (21.8%)	692 (22.0%)	0.585	0.022
Other autoimmune diseases ^d	49 (6.1%)	158 (6.8%)	207 (6.6%)	0.532	0.026
SARS-CoV-2 infection/ COVID-19 diagnosis	96 (12.0%)	267 (11.4%)	363 (11.6%)	0.661	0.018
Immunocompromised status ^e at index date, n (%)				0.315	0.041
Yes	209 (26.1%)	569 (24.3%)	778 (24.8%)		
No	592 (73.9%)	1771 (75.7%)	2363 (75.2%)		
History of ZVL/varicella vaccination ^f , n (%)				<0.001	0.178
No	540 (67.4%)	1739 (74.3%)	2279 (72.6%)		
Yes, ≤ 5 years	30 (3.7%)	105 (4.5%)	135 (4.3%)		
Yes, > 5 years	231 (28.8%)	496 (21.2%)	727 (23.1%)		
History of HZ ^f , n (%)				0.614	0.021
Yes	103 (12.9%)	285 (12.2%)	388 (12.4%)		
No	698 (87.1%)	2055 (87.8%)	2753 (87.6%)		
Length of continuous KPSC membership ^f , years, n (%)				0.330	0.061
0-5	175 (21.8%)	549 (23.5%)	724 (23.0%)		
6-10	150 (18.7%)	471 (20.1%)	621 (19.8%)		

	Vaccinated N=801	Unvaccinate d N=2340	Total N=3141	p value	ASD
≥11	476 (59.4%)	1320 (56.4%)	1796 (57.2%)		
Concomitant vaccination ^g , n (%)				N/A ^h	N/A
Yes	332 (41.4%)	N/A	N/A		
No	469 (58.6%)	N/A	N/A		

a. Eligible vaccinated individuals in 1-dose RZV cohort either received only 1 dose of RZV by the end of the accrual period or received a 2nd dose more than 6 months after the 1st dose.

b. Defined in the one year prior to index date

c. 8 of the vaccinated individuals in the CD category also had UC but could only be matched to other unvaccinated individuals with CD.

d. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis.

e. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

f. Defined based on all available medical records prior to index date

g. Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (36%), COVID-19 vaccine (5%), PCV13/PCV20/PPSV23 (40%), Tdap (27%), and other (13%)

h. N/A= not applicable

AIDS, acquired immunodeficiency syndrome; ASD, absolute standard difference; ED, emergency department; HIV, human immunodeficiency virus; HZ, herpes zoster; IBD, inflammatory bowel disease; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; sd, standard deviation; Q, quartile; Tdap, tetanus, diphtheria, and acellular pertussis vaccine; ZVL, zoster vaccine live.

Appendix A Table 5 Incidence rate, hazard ratio, and VE of 2 doses of RZV in preventing HZ among individuals with RA

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ⁱ		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Time between first and second doses												
4 weeks to 6 months	1900	57	6348.1	9.0 (6.9, 11.6)	5665	222	11942.1	18.6 (16.3, 21.2)	0.425 (0.306, 0.590)	0.428 (0.301, 0.610)	57.5% (41.0%, 69.4%)	57.2% (39.0%, 69.9%)
>6 months	560	16	1703.0	9.4 (5.8, 15.3)	1661	68	3194.9	21.3 (16.8, 27.0)	0.361 (0.188, 0.694)	0.299 (0.145, 0.617)	63.9% (30.6%, 81.2%)	70.1% (38.3%, 85.5%)
Overall	2460	73	8051.1	9.1 (7.2, 11.4)	7326	290	15137.0	19.2 (17.1, 21.5)	0.410 (0.306, 0.551)	0.413 (0.303, 0.564)	59.0% (44.9%, 69.4%)	58.7% (43.6%, 69.7%)
Age at index date, years												
18-49 ^c	49	4	98.1	40.8 (15.3, 108.6)	143	5	264.8	18.9 (7.9, 45.4)	2.293 (0.614, 8.563)	3.093 (0.620, 15.438)	-56.4% (-88.3%, 38.6%)	-67.7% (-93.5%, 38.0%)
≥50	2411	69	7953.0	8.7 (6.9, 11.0)	7183	285	14872.2	19.2 (17.1, 21.5)	0.384 (0.283, 0.520)	0.382 (0.277, 0.528)	61.6% (48.0%, 71.7%)	61.8% (47.2%, 72.3%)
50-59 ^d	392	6	1238.2	4.8 (2.2, 10.8)	1171	44	2644.2	16.6 (12.4, 22.4)	0.331 (0.139, 0.787)	0.386 (0.151, 0.992)	66.9% (21.3%, 86.1%)	61.4% (0.8%, 84.9%)
60-69	848	20	2812.5	7.1 (4.6, 11.0)	2531	104	5170.0	20.1 (16.6, 24.4)	0.247 (0.138, 0.444)	0.229 (0.120, 0.437)	75.3% (55.6%, 86.2%)	77.1% (56.3%, 88.0%)
≥70	1171	43	3902.2	11.0 (8.2, 14.9)	3481	137	7058.0	19.4 (16.4, 22.9)	0.513 (0.346, 0.761)	0.499 (0.326, 0.763)	48.7% (23.9%, 65.4%)	50.1% (23.7%, 67.4%)
Year after index date												
0-<1	2460	15	2188.2	6.9 (4.1, 11.4)	7326	111	5831.4	19.0 (15.8, 22.9)	0.336 (0.192, 0.588)	0.390 (0.219, 0.694)	66.4% (41.2%, 80.8%)	61.0% (30.6%, 78.1%)
1-<2	2326	27	2246.1	12.0 (8.2, 17.5)	5374	90	4491.9	20.0 (16.3, 24.6)	0.531 (0.333, 0.847)	0.514 (0.309, 0.856)	46.9% (15.3%, 66.7%)	48.6% (14.4%, 69.1%)
2-<3 ^e	2155	13	1802.5	7.2 (4.2, 12.4)	3747	65	2913.2	22.3 (17.5, 28.5)	0.184 (0.079, 0.432)	0.108 (0.037, 0.313)	81.6% (56.8%, 92.1%)	89.2% (68.7%, 96.3%)
3-<4 ^f	1296	7	965.5	7.2 (3.5, 15.2)	1886	13	1214.0	10.7 (6.2, 18.4)	0.611 (0.208, 1.792)	0.567 (0.171, 1.877)	38.9% (-44.2%, 79.2%)	43.3% (-46.7%, 82.9%)
4-<5 ^g	796	9	679.8	13.2 (6.9, 25.4)	788	11	578.0	19.0 (10.5, 34.4)	0.692 (0.232, 2.058)	0.633 (0.198, 2.030)	30.8% (-51.4%, 76.8%)	36.7% (-50.7%, 80.2%)
5-<6	382	2	166.9	12.0 (3.0, 47.9)	270	0	108.3	0.0	N/A	N/A	N/A	N/A
6-<7	20	0	2.0	0.0	6	0	0.3	0.0	N/A	N/A	N/A	N/A

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^d		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
CCI												

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, number of hospitalizations, baseline heart disease, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

c. Adjusted for limited covariates due to convergency issue: IC status and length of continuous KPSC membership.

d. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, number of ED visits, baseline heart disease, and length of continuous KPSC membership.

e. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, number of ED visits, baseline heart disease, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

f. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, and length of continuous KPSC membership.

g. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, and baseline heart disease.

h. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of ED visits, number of hospitalizations, baseline heart disease, and length of continuous KPSC membership.

i. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

Appendix A Table 6 Incidence rate, hazard ratio, and VE of 2 doses of RZV in preventing HZ among individuals with RA (combined categories for years after index date and medication)

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI)		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Time between first and second doses												
4 weeks to 6 months	1900	57	6348.1	9.0 (6.9, 11.6)	5665	222	11942.1	18.6 (16.3, 21.2)	0.425 (0.306, 0.590)	0.428 (0.301, 0.610)	57.5% (41.0%, 69.4%)	57.2% (39.0%, 69.9%)
>6 months	560	16	1703.0	9.4 (5.8, 15.3)	1661	68	3194.9	21.3 (16.8, 27.0)	0.361 (0.188, 0.694)	0.299 (0.145, 0.617)	63.9% (30.6%, 81.2%)	70.1% (38.3%, 85.5%)
Overall	2460	73	8051.1	9.1 (7.2, 11.4)	7326	290	15137.0	19.2 (17.1, 21.5)	0.410 (0.306, 0.551)	0.413 (0.303, 0.564)	59.0% (44.9%, 69.4%)	58.7% (43.6%, 69.7%)
Age at index date, years												
18-49 ^c	49	4	98.1	40.8 (15.3, 108.6)	143	5	264.8	18.9 (7.9, 45.4)	2.293 (0.614, 8.563)	3.093 (0.620, 15.438)	-56.4% (-88.3%, 38.6%)	-67.7% (-93.5%, 38.0%)
≥50	2411	69	7953.0	8.7 (6.9, 11.0)	7183	285	14872.2	19.2 (17.1, 21.5)	0.384 (0.283, 0.520)	0.382 (0.277, 0.528)	61.6% (48.0%, 71.7%)	61.8% (47.2%, 72.3%)
50-59 ^d	392	6	1238.2	4.8 (2.2, 10.8)	1171	44	2644.2	16.6 (12.4, 22.4)	0.331 (0.139, 0.787)	0.386 (0.151, 0.992)	66.9% (21.3%, 86.1%)	61.4% (0.8%, 84.9%)
60-69	848	20	2812.5	7.1 (4.6, 11.0)	2531	104	5170.0	20.1 (16.6, 24.4)	0.247 (0.138, 0.444)	0.229 (0.120, 0.437)	75.3% (55.6%, 86.2%)	77.1% (56.3%, 88.0%)
≥70	1171	43	3902.2	11.0 (8.2, 14.9)	3481	137	7058.0	19.4 (16.4, 22.9)	0.513 (0.346, 0.761)	0.499 (0.326, 0.763)	48.7% (23.9%, 65.4%)	50.1% (23.7%, 67.4%)
Year after index date												
0-<1	2460	15	2188.2	6.9 (4.1, 11.4)	7326	111	5831.4	19.0 (15.8, 22.9)	0.336 (0.192, 0.588)	0.390 (0.219, 0.694)	66.4% (41.2%, 80.8%)	61.0% (30.6%, 78.1%)
1-<3	2326	40	4048.7	9.9 (7.2, 13.5)	5374	155	7405.0	20.9 (17.9, 24.5)	0.385 (0.257, 0.578)	0.368 (0.237, 0.572)	61.5% (42.2%, 74.3%)	63.2% (42.8%, 76.3%)
3-<7 ^e	1296	18	1814.3	9.9 (6.3, 15.7)	1886	24	1900.6	12.6 (8.5, 18.8)	0.768 (0.373, 1.581)	0.649 (0.221, 1.904)	23.2% (-36.8%, 62.7%)	35.1% (-47.5%, 77.9%)

CCI

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, number of hospitalizations, baseline heart disease, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

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- c. Adjusted for limited covariates due to convergency issue: IC status and length of continuous KPSC membership.
- d. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, number of ED visits, baseline heart disease, and length of continuous KPSC membership.
- e. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, number of ED visits, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

Appendix A Table 7 Incidence rate, hazard ratio, and VE of 2 doses of RZV in preventing HZ among individuals with IBD

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^h		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Time between first and second doses												
4 weeks to 6 months	1509	23	4206.3	5.5 (3.6, 8.2)	4049	87	7261.9	12.0 (9.7, 14.8)	0.370 (0.212, 0.645)	0.371 (0.209, 0.657)	63.0% (35.5%, 78.8%)	62.9% (34.3%, 79.1%)
>6 months ^c	302	4	815.9	4.9 (1.8, 13.1)	831	16	1418.0	11.3 (6.9, 18.4)	0.261 (0.058, 1.168)	0.273 (0.052, 1.437)	73.9% (-14.4%, 94.2%)	72.7% (-30.4%, 94.8%)
Overall	1811	27	5022.2	5.4 (3.7, 7.8)	4880	103	8679.9	11.9 (9.8, 14.4)	0.353 (0.209, 0.594)	0.346 (0.201, 0.594)	64.7% (40.6%, 79.1%)	65.4% (40.6%, 79.9%)
Age at index date, years												
18-49	85	1	143.6	7.0 (1.0, 49.5)	251	6	408.0	14.7 (6.6, 32.7)	0.468 (0.056, 3.903)	N/A ⁱ	53.2% (-74.4%, 94.4%)	N/A
≥50	1726	26	4878.6	5.3 (3.6, 7.8)	4629	97	8271.9	11.7 (9.6, 14.3)	0.347 (0.203, 0.594)	0.330 (0.188, 0.578)	65.3% (40.6%, 79.7%)	67.0% (42.2%, 81.2%)
50-59 ^c	330	2	860.4	2.3 (0.6, 9.3)	941	21	1839.9	11.4 (7.4, 17.5)	0.111 (0.015, 0.834)	0.049 (0.004, 0.548)	88.9% (16.6%, 98.5%)	95.1% (45.2%, 99.6%)
60-69	656	10	1872.3	5.3 (2.9, 9.9)	1767	35	3094.8	11.3 (8.1, 15.8)	0.311 (0.120, 0.810)	0.274 (0.093, 0.810)	68.9% (19.0%, 88.0%)	72.6% (19.0%, 90.7%)
≥70	740	14	2145.9	6.5 (3.9, 11.0)	1921	41	3337.2	12.3 (9.0, 16.7)	0.480 (0.237, 0.973)	0.496 (0.228, 1.082)	52.0% (2.7%, 76.3%)	50.4% (-7.5%, 77.2%)
Year after index date												
0-<1	1811	7	1605.0	4.4 (2.1, 9.1)	4880	49	3669.4	13.4 (10.1, 17.7)	0.320 (0.137, 0.752)	0.269 (0.107, 0.675)	68.0% (24.8%, 86.3%)	73.1% (32.5%, 89.3%)
1-<2	1700	2	1585.5	1.3 (0.3, 5.0)	3377	29	2708.9	10.7 (7.4, 15.4)	N/A ⁱ	N/A	N/A	N/A
2-<3 ^d	1148	3	864.8	3.5 (1.1, 10.8)	1798	13	1347.9	9.6 (5.6, 16.6)	0.299 (0.066, 1.353)	0.291 (0.064, 1.324)	70.1% (-26.1%, 93.4%)	70.9% (-24.5%, 93.6%)
3-<4 ^e	647	7	503.3	13.9 (6.6, 29.2)	944	8	610.8	13.1 (6.6, 26.2)	1.500 (0.476, 4.728)	1.629 (0.488, 5.437)	-33.3% (-78.9%, 52.4%)	-38.6% (-81.6%, 51.2%)
4-<5	428	7	371.5	18.8 (9.0, 39.5)	405	3	294.5	10.2 (3.3, 31.6)	1.120 (0.223, 5.619)	N/A ⁱ	-10.7% (-82.2%, 77.7%)	N/A
5-<6	218	1	90.7	11.0 (1.6, 78.3)	124	1	47.8	20.9 (2.9, 148.5)	N/A ⁱ	N/A	N/A	N/A
6-<7	13	0	1.3	0.0	6	0	0.4	0.0	N/A	N/A	N/A	N/A

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HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^h		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
IBD condition UC (including UC+CD) ^f	989	13	2723.9	4.8 (2.8, 8.2)	2750	51	4790.9	10.6 (8.1, 14.0)	0.347 (0.162, 0.740)	0.373 (0.168, 0.828)	65.3% (26.0%, 83.8%)	62.7% (17.2%, 83.2%)
CD (including UC+CD)	827	14	2307.3	6.1 (3.6, 10.2)	2135	52	3899.4	13.3 (10.2, 17.5)	0.358 (0.174, 0.736)	0.298 (0.136, 0.655)	64.2% (26.4%, 82.6%)	70.2% (34.5%, 86.4%)

CCI

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

c. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, and length of continuous KPSC membership.

d. Adjusted for limited covariates due to convergency issue: history of HZ.

e. Adjusted for limited covariates due to convergency issue: IC status and history of HZ.

f. Not including 14 vaccinated individuals with UC+CD who could only be matched to unvaccinated individuals with CD alone.

g. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, and history of ZVL/varicella vaccination.

h. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

i. No covariates could be adjusted in the stratified Cox model. No adjusted models could converge.

j. All unvaccinated individuals matched to vaccinated individuals who developed HZ had already been censored.

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Appendix A Table 8 Incidence rate, hazard ratio, and VE of 2 doses of RZV in preventing HZ among individuals with IBD (combined categories for years after index date and medication)

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI)		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Time between first and second doses												
4 weeks to 6 months	1509	23	4206.3	5.5 (3.6, 8.2)	4049	87	7261.9	12.0 (9.7, 14.8)	0.370 (0.212, 0.645)	0.371 (0.209, 0.657)	63.0% (35.5%, 78.8%)	62.9% (34.3%, 79.1%)
>6 months ^c	302	4	815.9	4.9 (1.8, 13.1)	831	16	1418.0	11.3 (6.9, 18.4)	0.261 (0.058, 1.168)	0.273 (0.052, 1.437)	73.9% (-14.4%, 94.2%)	72.7% (-30.4%, 94.8%)
Overall	1811	27	5022.2	5.4 (3.7, 7.8)	4880	103	8679.9	11.9 (9.8, 14.4)	0.353 (0.209, 0.594)	0.346 (0.201, 0.594)	64.7% (40.6%, 79.1%)	65.4% (40.6%, 79.9%)
Age at index date, years												
18-49	85	1	143.6	7.0 (1.0, 49.5)	251	6	408.0	14.7 (6.6, 32.7)	0.468 (0.056, 3.903)		53.2% (-74.4%, 94.4%)	
≥50	1726	26	4878.6	5.3 (3.6, 7.8)	4629	97	8271.9	11.7 (9.6, 14.3)	0.347 (0.203, 0.594)	0.330 (0.188, 0.578)	65.3% (40.6%, 79.7%)	67.0% (42.2%, 81.2%)
50-59 ^c	330	2	860.4	2.3 (0.6, 9.3)	941	21	1839.9	11.4 (7.4, 17.5)	0.111 (0.015, 0.834)	0.049 (0.004, 0.548)	88.9% (16.6%, 98.5%)	95.1% (45.2%, 99.6%)
60-69	656	10	1872.3	5.3 (2.9, 9.9)	1767	35	3094.8	11.3 (8.1, 15.8)	0.311 (0.120, 0.810)	0.274 (0.093, 0.810)	68.9% (19.0%, 88.0%)	72.6% (19.0%, 90.7%)
≥70	740	14	2145.9	6.5 (3.9, 11.0)	1921	41	3337.2	12.3 (9.0, 16.7)	0.480 (0.237, 0.973)	0.496 (0.228, 1.082)	52.0% (2.7%, 76.3%)	50.4% (-7.5%, 77.2%)
Year after index date												
0-<1	1811	7	1605.0	4.4 (2.1, 9.1)	4880	49	3669.4	13.4 (10.1, 17.7)	0.320 (0.137, 0.752)	0.269 (0.107, 0.675)	68.0% (24.8%, 86.3%)	73.1% (32.5%, 89.3%)
1-<3	1700	5	2450.3	2.0 (0.8, 4.9)	3377	42	4056.8	10.4 (7.7, 14.0)	0.091 (0.022, 0.381)	0.078 (0.016, 0.385)	90.9% (61.9%, 97.8%)	92.2% (61.5%, 98.4%)
3-<7	647	15	966.9	15.5 (9.4, 25.7)	944	12	953.6	12.6 (7.1, 22.2)	1.360 (0.532, 3.473)	1.428 (0.391, 5.212)	-26.5% (-71.2%, 46.8%)	-30.0% (-80.8%, 60.9%)
IBD condition												
UC (including UC+CD) ^d	989	13	2723.9	4.8 (2.8, 8.2)	2750	51	4790.9	10.6 (8.1, 14.0)	0.347 (0.162, 0.740)	0.373 (0.168, 0.828)	65.3% (26.0%, 83.8%)	62.7% (17.2%, 83.2%)
CD (including UC+CD)	827	14	2307.3	6.1 (3.6, 10.2)	2135	52	3899.4	13.3 (10.2, 17.5)	0.358 (0.174, 0.736)	0.298 (0.136, 0.655)	64.2% (26.4%, 82.6%)	70.2% (34.5%, 86.4%)

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI)		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
CCI												

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

c. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, and length of continuous KPSC membership.

d. Not including 14 vaccinated individuals with UC+CD who could only be matched to unvaccinated individuals with CD alone.

e. No covariates could be adjusted in the stratified Cox model. No adjusted models could converge.

Appendix A Table 9 Incidence rate, hazard ratio, and VE of 1 dose of RZV in preventing HZ among individuals with RA

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^d		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Overall	1012	17	1333.7	12.7 (7.9, 20.5)	3023	82	3538.9	23.2 (18.7, 28.8)	0.544 (0.314, 0.941)	0.545 (0.314, 0.945)	45.6% (5.9%, 68.6%)	45.5% (5.5%, 68.6%)
Year after index date												
0-<1	1012	9	766.0	11.7 (6.1, 22.6)	3023	46	2148.1	21.4 (16.0, 28.6)	0.526 (0.256, 1.083)	0.496 (0.236, 1.043)	47.4% (-7.6%, 74.4%)	50.4% (-4.1%, 76.4%)
1-<2	515	5	321.3	15.6 (6.5, 37.4)	1332	22	824.2	26.7 (17.6, 40.5)	0.486 (0.164, 1.437)	0.493 (0.163, 1.496)	51.4% (-30.4%, 83.6%)	50.7% (-33.2%, 83.7%)
2-<3 ^c	208	3	140.1	21.4 (6.9, 66.4)	530	8	352.1	22.7 (11.4, 45.4)	2.046 (0.402, 10.405)	1.842 (0.337, 10.084)	-51.1% (-90.4%, 59.8%)	-45.7% (-90.1%, 66.3%)
3-<4	85	0	61.7	0.0	212	3	144.2	20.8 (6.7, 64.5)	N/A	N/A	N/A	N/A
4-<5	47	0	33.6	0.0	94	3	60.2	49.8 (16.1, 154.4)	N/A	N/A	N/A	N/A
5-<6	20	0	10.6	0.0	27	0	10.0	0.0	N/A	N/A	N/A	N/A
6-<7	2	0	0.4	0.0	0	0	0.0	N/A	N/A	N/A	N/A	N/A

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, and history of ZVL/varicella vaccination.

c. Adjusted for limited covariates due to convergency issue: history of HZ.

d. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

**Appendix A Table 10 Incidence rate, hazard ratio, and VE of 1 dose of RZV in preventing HZ among individuals with RA
(combined categories for years after index date)**

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^c		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Overall	1012	17	1333.7	12.7 (7.9, 20.5)	3023	82	3538.9	23.2 (18.7, 28.8)	0.544 (0.314, 0.941)	0.545 (0.314, 0.945)	45.6% (5.9%, 68.6%)	45.5% (5.5%, 68.6%)
Year after index date												
0-									0.526 (0.256, 1.083)	0.496 (0.236, 1.043)	47.4% (-7.6%, 74.4%)	50.4% (-4.1%, 76.4%)
<1	1012	9	766.0	11.7 (6.1, 22.6)	3023	46	2148.1	21.4 (16.0, 28.6)	0.713 (0.303, 1.681)	0.701 (0.292, 1.680)	28.7% (-40.5%, 69.7%)	29.9% (-40.5%, 70.8%)
1-												
<3	515	8	461.4	17.3 (8.7, 34.7)	1332	30	1176.2	25.5 (17.8, 36.5)				
3-												
<7	85	0	106.3	0.0	212	6	214.5	28.0 (12.6, 62.3)	N/A	N/A	N/A	N/A

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, and history of ZVL/varicella vaccination.

c. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

Appendix A Table 11 Incidence rate, hazard ratio, and VE of 1 dose of RZV in preventing HZ among individuals with IBD

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^d		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Overall	801	8	992.5	8.1 (4.0, 16.1)	2340	37	2525.2	14.7 (10.6, 20.2)	0.637 (0.290, 1.397)	0.711 (0.296, 1.708)	36.3% (-28.4%, 71.0%)	28.9% (-41.5%, 70.4%)
Year after index date												
0-<1	801	5	605.3	8.3 (3.4, 19.8)	2340	21	1586.1	13.2 (8.6, 20.3)	0.684 (0.255, 1.834)	0.664 (0.209, 2.106)	31.6% (-45.5%, 74.5%)	33.6% (-52.5%, 79.1%)
1-<2 ^c	415	3	247.0	12.1 (3.9, 37.7)	1011	12	595.2	20.2 (11.4, 35.5)	0.609 (0.165, 2.252)	0.578 (0.149, 2.245)	39.1% (-55.6%, 83.5%)	42.2% (-55.5%, 85.1%)
2-<3	131	0	78.4	0.0	322	4	202.2	19.8 (7.4, 52.7)	N/A	N/A	N/A	N/A
3-<4	50	0	36.2	0.0	133	0	89.2	0.0	N/A	N/A	N/A	N/A
4-<5	24	0	20.3	0.0	55	0	44.1	0.0	N/A	N/A	N/A	N/A
5-<6	12	0	4.9	0.0	18	0	8.2	0.0	N/A	N/A	N/A	N/A
6-<7	2	0	0.4	0.0	1	0	0.1	0.0	N/A	N/A	N/A	N/A

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, and history of ZVL/varicella vaccination.

c. Adjusted for limited covariates due to convergency issue: history of HZ and history of ZVL/varicella vaccination.

d. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

Appendix A Table 12 Incidence rate, hazard ratio, and VE of 1 dose of RZV in preventing HZ among individuals with IBD (combined categories for years after index date)

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^d		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Overall	801	8	992.5	8.1 (4.0, 16.1)	2340	37	2525.2	14.7 (10.6, 20.2)	0.637 (0.290, 1.397)	0.711 (0.296, 1.708)	36.3% (-28.4%, 71.0%)	28.9% (-41.5%, 70.4%)
Year after index date												
0-<1	801	5	605.3	8.3 (3.4, 19.8)	2340	21	1586.1	13.2 (8.6, 20.3)	0.684 (0.255, 1.834)	0.664 (0.209, 2.106)	31.6% (-45.5%, 74.5%)	33.6% (-52.5%, 79.1%)
1-<3 ^c	415	3	325.4	9.2 (3.0, 28.6)	1011	16	797.4	20.1 (12.3, 32.8)	0.566 (0.155, 2.065)	0.328 (0.063, 1.699)	43.4% (-51.6%, 84.5%)	67.2% (-41.2%, 93.7%)
3-<7	50	0	61.8	0.0	133	0	141.6	0.0	N/A	N/A	N/A	N/A

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, and history of ZVL/varicella vaccination.

c. Adjusted for limited covariates due to convergency issue: IC status, history of HZ and history of ZVL/varicella vaccination.

d. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

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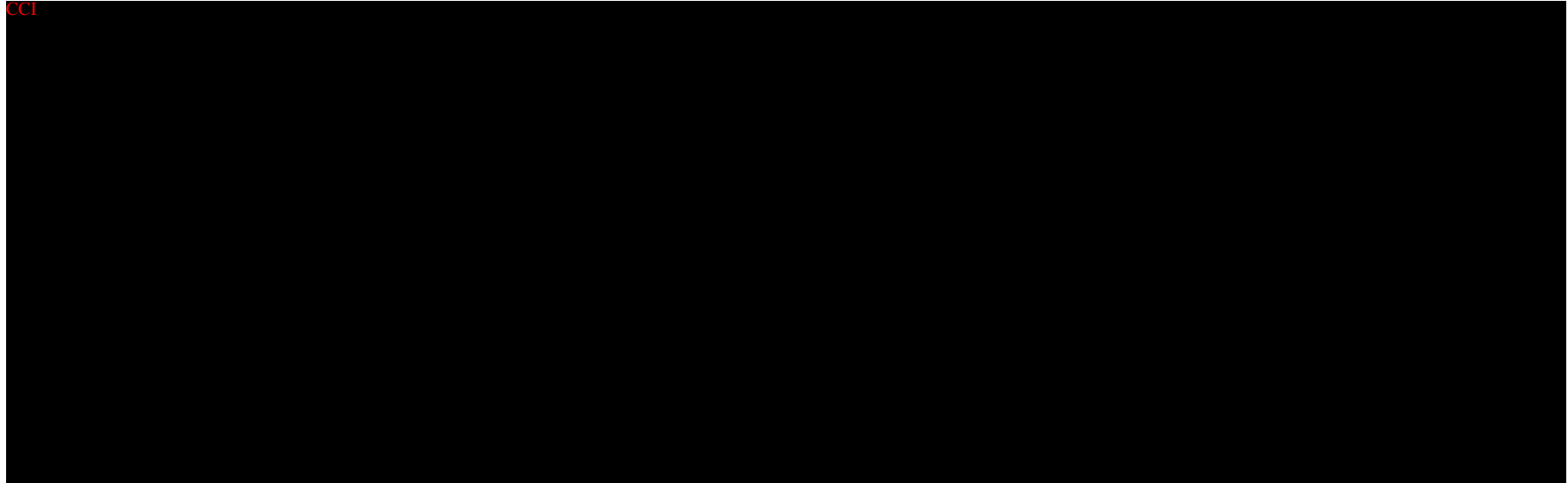
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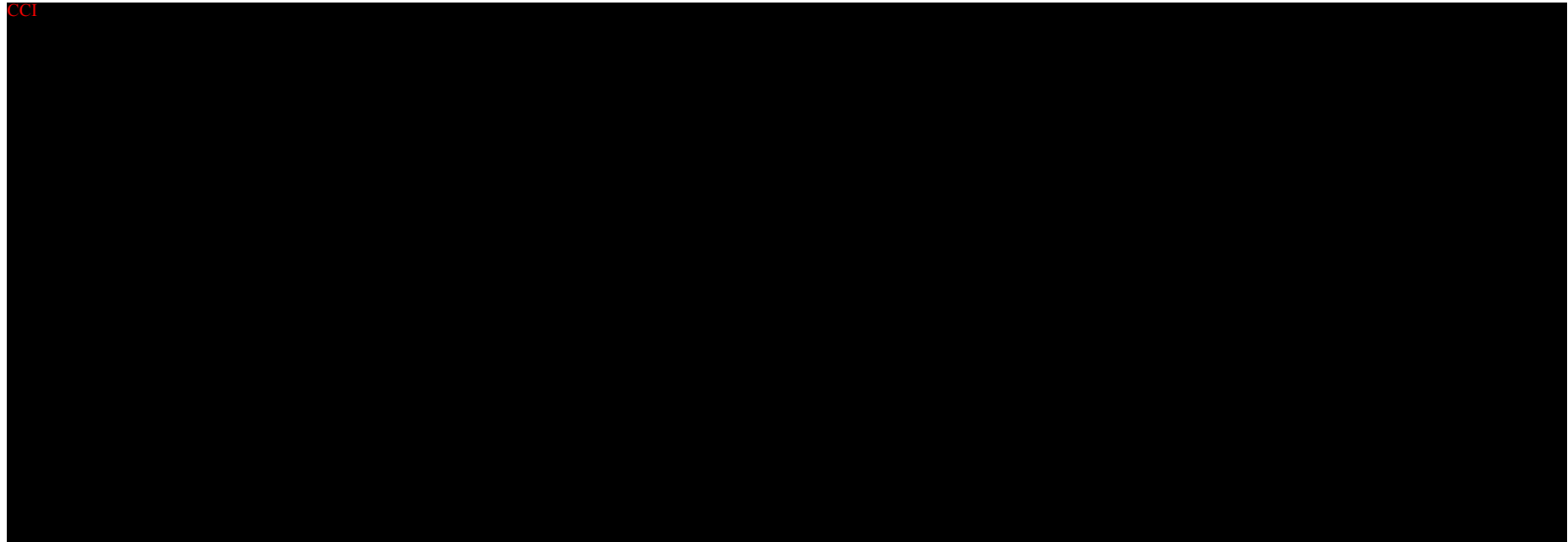
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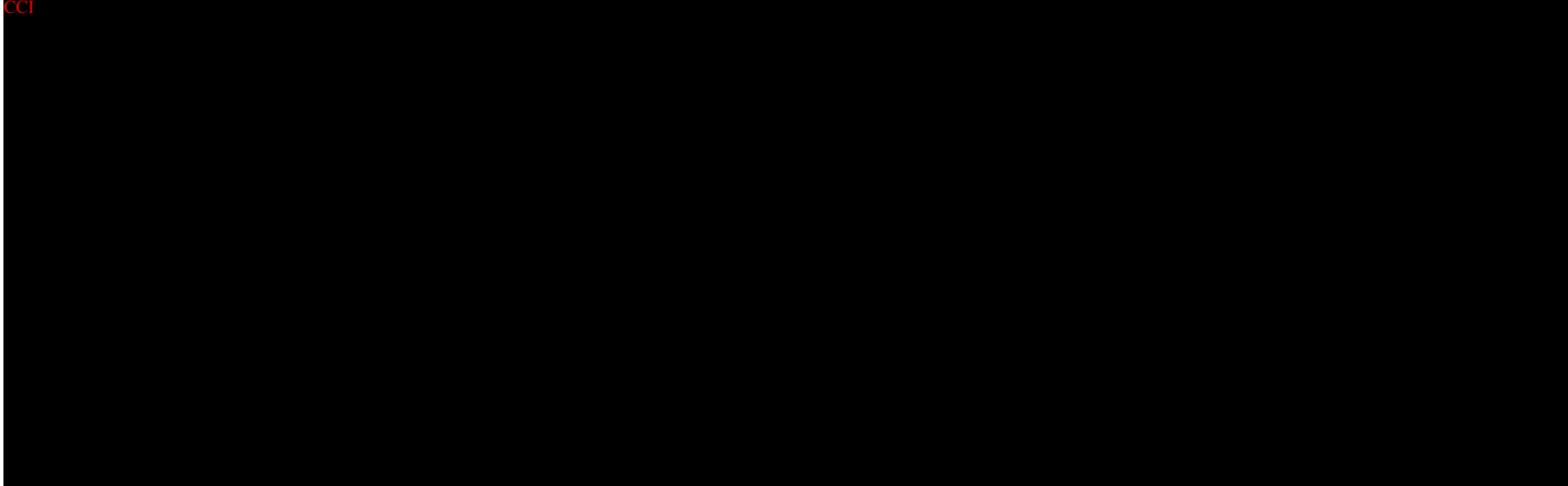


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Appendix A Table 17 Baseline characteristics of 2-dose RZV vaccinated cohort with RA, 2nd dose administered within 4 weeks to 6 months vs. >6 months after the first dose

	2nd dose 4 weeks to 6 months N=1900	2nd dose > 6 months N=560	Total N=2460	p value	ASD
Age at index date, years				<0.001	0.265
mean (sd)	67.98 (9.82)	70.55 (9.58)	68.56 (9.82)		
median	68	71	69		
Q1, Q3	61, 75	64, 77	62, 75		
range	27, 96	31, 94	27, 96		
Age at index date, years, n (%)				<0.001	0.322
18-49	40 (2.1%)	9 (1.6%)	49 (2.0%)		
50-59	340 (17.9%)	52 (9.3%)	392 (15.9%)		
60-69	674 (35.5%)	174 (31.1%)	848 (34.5%)		
70-79	619 (32.6%)	225 (40.2%)	844 (34.3%)		
≥80	227 (11.9%)	100 (17.9%)	327 (13.3%)		
Sex, n (%)				0.072	0.085
Female	1519 (79.9%)	428 (76.4%)	1947 (79.1%)		
Male	381 (20.1%)	132 (23.6%)	513 (20.9%)		
Race/Ethnicity, n (%)				0.020	0.162
White	877 (46.2%)	232 (41.4%)	1109 (45.1%)		
Black	177 (9.3%)	50 (8.9%)	227 (9.2%)		
Hispanic	557 (29.3%)	206 (36.8%)	763 (31.0%)		
Asian	247 (13.0%)	62 (11.1%)	309 (12.6%)		
Other	PPD				
Medication category, n (%)				0.357	0.100
Category 1	435 (22.9%)	134 (23.9%)	569 (23.1%)		
Category 2	1017 (53.5%)	301 (53.8%)	1318 (53.6%)		
Category 3	256 (13.5%)	62 (11.1%)	318 (12.9%)		
Category 4	80 (4.2%)	32 (5.7%)	112 (4.6%)		
Category 5	112 (5.9%)	31 (5.5%)	143 (5.8%)		
Number of outpatient visits ^a , n (%)				0.753 ^f	0.028
0-4	4 (0.2%)	2 (0.4%)	6 (0.2%)		
5-10	165 (8.7%)	49 (8.8%)	214 (8.7%)		
≥11	1731 (91.1%)	509 (90.9%)	2240 (91.1%)		
Number of ED visits ^a , n (%)				<0.001	0.188
0	1408 (74.1%)	370 (66.1%)	1778 (72.3%)		
1	314 (16.5%)	110 (19.6%)	424 (17.2%)		
≥2	178 (9.4%)	80 (14.3%)	258 (10.5%)		

	2nd dose 4 weeks to 6 months N=1900	2nd dose > 6 months N=560	Total N=2460	p value	ASD
Number of hospitalizations ^a , n (%)				<0.001	0.216
0	1736 (91.4%)	483 (86.3%)	2219 (90.2%)		
1	130 (6.8%)	45 (8.0%)	175 (7.1%)		
≥2	34 (1.8%)	32 (5.7%)	66 (2.7%)		
Baseline comorbidities ^a , n (%)					
Kidney disease	278 (14.6%)	104 (18.6%)	382 (15.5%)	0.024	0.106
Heart disease	136 (7.2%)	71 (12.7%)	207 (8.4%)	<0.001	0.185
Lung disease	449 (23.6%)	143 (25.5%)	592 (24.1%)	0.354	0.044
Liver disease	119 (6.3%)	44 (7.9%)	163 (6.6%)	0.183	0.062
Diabetes	426 (22.4%)	165 (29.5%)	591 (24.0%)	0.001	0.161
Other autoimmune diseases ^b	116 (6.1%)	43 (7.7%)	159 (6.5%)	0.183	0.062
SARS-CoV-2 infection/COVID-19 diagnosis	100 (5.3%)	36 (6.4%)	136 (5.5%)	0.289	0.050
Immunocompromised status ^c at index date, n (%)				0.784	0.013
Yes	1230 (64.7%)	359 (64.1%)	1589 (64.6%)		
No	670 (35.3%)	201 (35.9%)	871 (35.4%)		
History of ZVL/varicella vaccination ^d , n (%)				0.420	0.063
No	1250 (65.8%)	355 (63.4%)	1605 (65.2%)		
Yes, ≤ 5 years	66 (3.5%)	17 (3.0%)	83 (3.4%)		
Yes, > 5 years	584 (30.7%)	188 (33.6%)	772 (31.4%)		
History of HZ ^d , n (%)				0.422	0.038
Yes	325 (17.1%)	104 (18.6%)	429 (17.4%)		
No	1575 (82.9%)	456 (81.4%)	2031 (82.6%)		
Length of continuous KPSC membership ^d , years, n (%)				0.537	0.054
0-5	360 (18.9%)	101 (18.0%)	461 (18.7%)		
6-10	339 (17.8%)	91 (16.3%)	430 (17.5%)		
≥11	1201 (63.2%)	368 (65.7%)	1569 (63.8%)		
Concomitant vaccination ^e , n (%)				<0.001	0.232
Yes	654 (34.4%)	256 (45.7%)	910 (37.0%)		
No	1246 (65.6%)	304 (54.3%)	1550 (63.0%)		

a. Defined in the one year prior to index date

b. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease.

c. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenism, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

d. Defined based on all available medical records prior to index date

e. Concomitant vaccines on the same day as RZV:

	2nd dose 4 weeks to 6 months N=1900	2nd dose > 6 months N=560	Total N=2460	p value	ASD
1. Among 654 individuals who received 2nd dose 4 weeks to 6 months after 1st dose: influenza vaccine (46%), COVID-19 vaccine (4%), PCV13/PCV20/PPSV23 (24%), Tdap (31%), and other (10%); 76% concomitant with 1st dose and 35% concomitant with 2nd dose.					
2. Among 256 individuals who received 2nd dose more than 6 months after 1st dose: influenza vaccine (48%), COVID-19 vaccine (5%), PCV13/PCV20/PPSV23 (26%), Tdap (39%), and other (9%); 65% concomitant with 1st dose and 55% concomitant with 2nd dose.					
f. Fisher's Exact p value					

Appendix A Table 18 Baseline characteristics of 2-dose RZV vaccinated cohort with IBD, 2nd dose administered within 4 weeks to 6 months vs. >6 months after the first dose

	2nd dose 4 weeks to 6 months N=1509	2nd dose > 6 months N=302	Total N=1811	p value	ASD
Age at index date, years				0.036	0.122
mean (sd)	66.27 (11.61)	67.68 (11.42)	66.51 (11.59)		
median	67	68	67		
Q1, Q3	60, 74	61, 75	60, 74		
range	18, 98	20, 94	18, 98		
Age at index date, years, n (%)				0.176	0.157
18-49	75 (5.0%)	10 (3.3%)	85 (4.7%)		
50-59	282 (18.7%)	48 (15.9%)	330 (18.2%)		
60-69	547 (36.2%)	109 (36.1%)	656 (36.2%)		
70-79	455 (30.2%)	93 (30.8%)	548 (30.3%)		
≥80	150 (9.9%)	42 (13.9%)	192 (10.6%)		
Sex, n (%)				0.012	0.158
Female	833 (55.2%)	143 (47.4%)	976 (53.9%)		
Male	676 (44.8%)	159 (52.6%)	835 (46.1%)		
Race/Ethnicity, n (%)				0.379	0.126
White	981 (65.0%)	186 (61.6%)	1167 (64.4%)		
Black	95 (6.3%)	27 (8.9%)	122 (6.7%)		
Hispanic	303 (20.1%)	62 (20.5%)	365 (20.2%)		
Asian	99 (6.6%)	23 (7.6%)	122 (6.7%)		
Other	PPD				
IBD ^a , n (%)				0.707 ^g	0.034
UC	816 (54.1%)	168 (55.6%)	984 (54.3%)		
CD ^b	689 (45.7%)	133 (44.0%)	822 (45.4%)		
UC+CD	4 (0.3%)	1 (0.3%)	5 (0.3%)		
Medication category, n (%)				0.244	0.154
Category 1	586 (38.8%)	133 (44.0%)	719 (39.7%)		
Category 2	521 (34.5%)	101 (33.4%)	622 (34.3%)		
Category 3	275 (18.2%)	41 (13.6%)	316 (17.4%)		
Category 4	125 (8.3%)	27 (8.9%)	152 (8.4%)		
Category 5	2 (0.1%)	0 (0.0%)	2 (0.1%)		
Number of outpatient visits ^a , n (%)				0.018	0.153
0-4	7 (0.5%)	5 (1.7%)	12 (0.7%)		
5-10	154 (10.2%)	40 (13.2%)	194 (10.7%)		
≥11	1348 (89.3%)	257 (85.1%)	1605 (88.6%)		
Number of ED visits ^a , n (%)				0.052	0.159
0	1025 (67.9%)	225 (74.5%)	1250 (69.0%)		

	2nd dose 4 weeks to 6 months N=1509	2nd dose > 6 months N=302	Total N=1811	p value	ASD
1	273 (18.1%)	48 (15.9%)	321 (17.7%)		
≥2	211 (14.0%)	29 (9.6%)	240 (13.3%)		
Number of hospitalizations ^a , n (%)				0.068	0.158
0	1271 (84.2%)	269 (89.1%)	1540 (85.0%)		
1	160 (10.6%)	25 (8.3%)	185 (10.2%)		
≥2	78 (5.2%)	8 (2.6%)	86 (4.7%)		
Baseline comorbidities ^a , n (%)					
Kidney disease	277 (18.4%)	52 (17.2%)	329 (18.2%)	0.640	0.030
Heart disease	151 (10.0%)	24 (7.9%)	175 (9.7%)	0.269	0.072
Lung disease	329 (21.8%)	74 (24.5%)	403 (22.3%)	0.303	0.064
Liver disease	146 (9.7%)	20 (6.6%)	166 (9.2%)	0.093	0.112
Diabetes	371 (24.6%)	68 (22.5%)	439 (24.2%)	0.444	0.049
Other autoimmune diseases ^c	111 (7.4%)	22 (7.3%)	133 (7.3%)	0.966	0.003
SARS-CoV-2 infection/ COVID-19 diagnosis	174 (11.5%)	31 (10.3%)	205 (11.3%)	0.526	0.041
Immunocompromised status ^d at index date, n (%)				0.457	0.047
Yes	406 (26.9%)	75 (24.8%)	481 (26.6%)		
No	1103 (73.1%)	227 (75.2%)	1330 (73.4%)		
History of ZVL/varicella vaccination ^e , n (%)				0.278	0.099
No	974 (64.5%)	181 (59.9%)	1155 (63.8%)		
Yes, ≤ 5 years	50 (3.3%)	13 (4.3%)	63 (3.5%)		
Yes, > 5 years	485 (32.1%)	108 (35.8%)	593 (32.7%)		
History of HZ ^e , n (%)				0.065	0.112
Yes	217 (14.4%)	56 (18.5%)	273 (15.1%)		
No	1292 (85.6%)	246 (81.5%)	1538 (84.9%)		
Length of continuous KPSC membership ^e , years, n (%)				0.545	0.070
0-5	283 (18.8%)	52 (17.2%)	335 (18.5%)		
6-10	277 (18.4%)	50 (16.6%)	327 (18.1%)		
≥11	949 (62.9%)	200 (66.2%)	1149 (63.4%)		
Concomitant vaccination ^f , n (%)				<0.001	0.225
Yes	626 (41.5%)	159 (52.6%)	785 (43.3%)		
No	883 (58.5%)	143 (47.4%)	1026 (56.7%)		

a. Defined in the one year prior to index date

b. 14 individuals in the CD category (11 in 2nd dose 4 weeks to 6 months group and 3 in 2nd dose > 6 months group) also had UC but could only be matched to other unvaccinated individuals with CD.

c. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis.

d. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

e. Defined based on all available medical records prior to index date

f. Concomitant vaccines on the same day as RZV:

1. Among 626 individuals who received 2nd dose 4 weeks to 6 months after 1st dose: influenza vaccine (47%), COVID-19 vaccine (11%), PCV13/PCV20/PPSV23 (30%), Tdap (23%), and other (15%); 71% concomitant with 1st dose and 45% concomitant with 2nd dose.
2. Among 159 individuals who received 2nd dose more than 6 months after 1st dose: influenza vaccine (45%), COVID-19 vaccine (7%), PCV13/PCV20/PPSV23 (29%), Tdap (38%), and other (9%); 66% concomitant with 1st dose and 56% concomitant with 2nd dose.

g. Fisher's Exact p value

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Appendix A Table 19 Incidence rate, hazard ratio, and VE of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with RA

Year after index date	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^f		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
0-<1	1900	11	1696.2	6.5 (3.6, 11.7)	5665	86	4520.3	19.0 (15.4, 23.5)	0.312 (0.162, 0.603)	0.360 (0.180, 0.721)	68.8% (39.7%, 83.8%)	64.0% (27.9%, 82.0%)
1-<2	1808	22	1748.9	12.6 (8.3, 19.1)	4176	72	3541.1	20.3 (16.1, 25.6)	0.548 (0.328, 0.916)	0.562 (0.321, 0.987)	45.2% (8.4%, 67.2%)	43.8% (1.3%, 67.9%)
2-<3 ^c	1680	8	1410.0	5.7 (2.8, 11.3)	2989	44	2328.5	18.9 (14.1, 25.4)	0.170 (0.060, 0.479)	0.107 (0.028, 0.413)	83.0% (52.1%, 94.0%)	89.3% (58.7%, 97.2%)
3-<4 ^d	1010	6	778.8	7.7 (3.5, 17.1)	1507	11	988.5	11.1 (6.2, 20.1)	0.732 (0.240, 2.228)	0.929 (0.251, 3.435)	26.8% (-55.1%, 76.0%)	7.1% (-70.9%, 74.9%)
4-<5 ^e	648	8	560.5	14.3 (7.1, 28.5)	633	9	468.5	19.2 (10.0, 36.9)	0.756 (0.223, 2.561)	0.681 (0.183, 2.529)	24.4% (-61.0%, 77.7%)	31.9% (-60.5%, 81.7%)
5-<6	334	2	151.7	13.2 (3.3, 52.7)	229	0	95.0	0.0	N/A	N/A	N/A	N/A
6-<7	20	0	2.0	0.0	6	0	0.3	0.0	N/A	N/A	N/A	N/A

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, number of hospitalizations, baseline heart disease, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

c. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, number of ED visits, baseline heart disease, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

d. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, and length of continuous KPSC membership.

e. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, and baseline heart disease.

f. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

Appendix A Table 20 Incidence rate, hazard ratio, and VE of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by combined years after vaccination among individuals with RA

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI)		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Year after index date												
0-<1	190			6.5	566			19.0	0.312	0.360	68.8%	64.0%
	0	11	1696.2	(3.6, 11.7)	5	86	4520.3	(15.4, 23.5)	(0.162, 0.603)	(0.180, 0.721)	(39.7%, 83.8%)	(27.9%, 82.0%)
1-<3	180			9.5	417			19.8	0.399	0.400	60.1%	60.0%
	8	30	3159.0	(6.6, 13.6)	6	116	5869.6	(16.5, 23.7)	(0.253, 0.628)	(0.245, 0.656)	(37.2%, 74.7%)	(34.4%, 75.5%)
3-<7 ^c	101			10.7	150			12.9	0.891	0.832	10.9%	16.8%
	0	16	1492.9	(6.6, 17.5)	7	20	1552.3	(8.3, 20.0)	(0.411, 1.930)	(0.269, 2.568)	(-48.2%, 58.9%)	(-61.1%, 73.1%)

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, number of hospitalizations, baseline heart disease, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

c. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of ED visits, baseline heart disease, and history of ZVL/varicella vaccination.

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Appendix A Table 21 Incidence rate, hazard ratio, and VE of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with IBD

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI) ^e		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted	Unadjusted	Adjusted
Year after index date												
0-<1 ^b	1509	6	1344.1	4.5 (2.0, 9.9)	404	44	3046.8	14.4 (10.7, 19.4)	0.286 (0.113, 0.726)	0.234 (0.084, 0.654)	71.4% (27.4%, 88.7%)	76.6% (34.6%, 91.6%)
1-<2	1429	1	1325.2	0.8 (0.1, 5.4)	282	25	2265.3	11.0 (7.5, 16.3)	N/A ^f	N/A	N/A	N/A
2-<3 ^c	924	2	700.8	2.9 (0.7, 11.4)	146	10	1118.0	8.9 (4.8, 16.6)	0.183 (0.023, 1.471)	0.177 (0.022, 1.424)	81.7% (-32.0%, 97.7%)	82.3% (-29.8%, 97.8%)
3-<4 ^d	534	7	427.9	16.4 (7.8, 34.3)	801	6	531.4	11.3 (5.1, 25.1)	1.878 (0.564, 6.253)	1.990 (0.570, 6.943)	-46.7% (-84.0%, 43.6%)	-49.7% (-85.6%, 43.0%)
4-<5	366	6	322.9	18.6 (8.3, 41.4)	352	1	257.0	3.9 (0.5, 27.6)	3.000 (0.312, 28.841)	N/A	-66.7% (-96.5%, 68.8%)	N/A
5-<6	196	1	84.1	11.9 (1.7, 84.5)	108	1	43.1	23.2 (3.3, 164.9)	N/A	N/A	N/A	N/A
6-<7	13	0	1.3	0.0	6	0	0.4	0.0	N/A	N/A	N/A	N/A

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

c. Adjusted for limited covariates due to convergency issue: history of HZ.

d. Adjusted for limited covariates due to convergency issue: IC status and history of HZ.

e. If <5 cases were observed in total across the vaccinated and unvaccinated groups, only unadjusted analysis was conducted. If zero cases were observed in either the vaccinated or unvaccinated group, HR and VE were not estimated.

f. All unvaccinated individuals matched to vaccinated individuals who developed HZ had already been censored.

Appendix A Table 22 Incidence rate, hazard ratio, and VE of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by combined years after vaccination among individuals with IBD

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI)		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted	Unadjusted	Adjusted
Year after index date												
0-<1 ^b	1509	6	1344.1	4.5 (2.0, 9.9)	4049	44	3046.8	14.4 (10.7, 19.4)	0.286 (0.113, 0.726)	0.234 (0.084, 0.654)	71.4% (27.4%, 88.7%)	76.6% (34.6%, 91.6%)
1-<3 ^c	1429	3	2026.0	1.5 (0.5, 4.6)	2822	35	3383.3	10.3 (7.4, 14.4)	0.057 (0.008, 0.416)	0.052 (0.007, 0.397)	94.3% (58.4%, 99.2%)	94.8% (60.3%, 99.3%)
3-<7 ^d	534	14	836.2	16.7 (9.9, 28.3)	801	8	831.8	9.6 (4.8, 19.2)	2.097 (0.735, 5.981)	2.001 (0.642, 6.240)	-52.3% (-83.3%, 26.5%)	-50.0% (-84.0%, 35.8%)

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

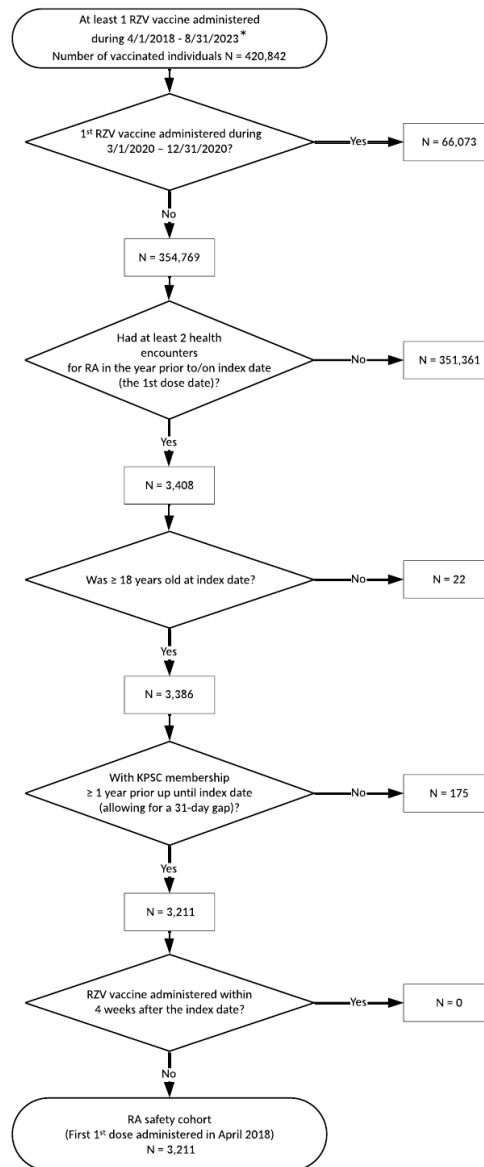
b. Adjusted for covariates: IC status, history of HZ, number of outpatient visits, number of ED visits, history of ZVL/varicella vaccination, and length of continuous KPSC membership.

c. Adjusted for limited covariates due to convergency issue: IC status, history of HZ, number of outpatient visits, number of ED visits, and history of ZVL/varicella vaccination.

d. Adjusted for limited covariates due to convergency issue: IC status and history of HZ, and history of ZVL/varicella vaccination.

14.2. Appendix B - Safety

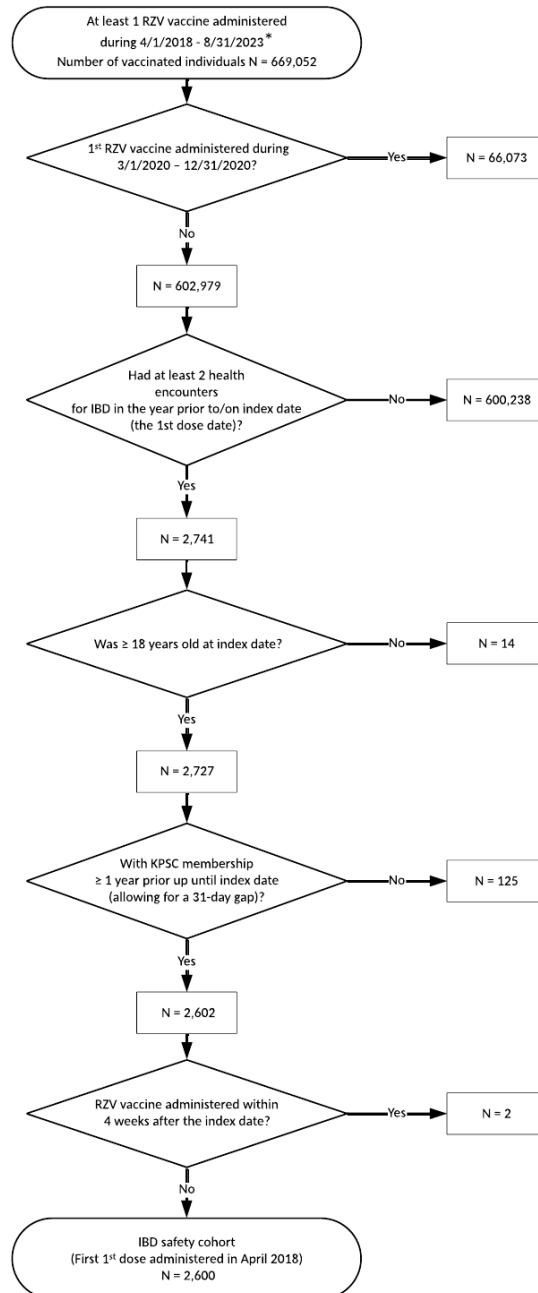
Appendix B Figure 1 Flow chart for RZV recipients with RA



* Accrual period for age 50+ individuals was 4/1/2018 - 5/31/2022

Appendix B Figure 2

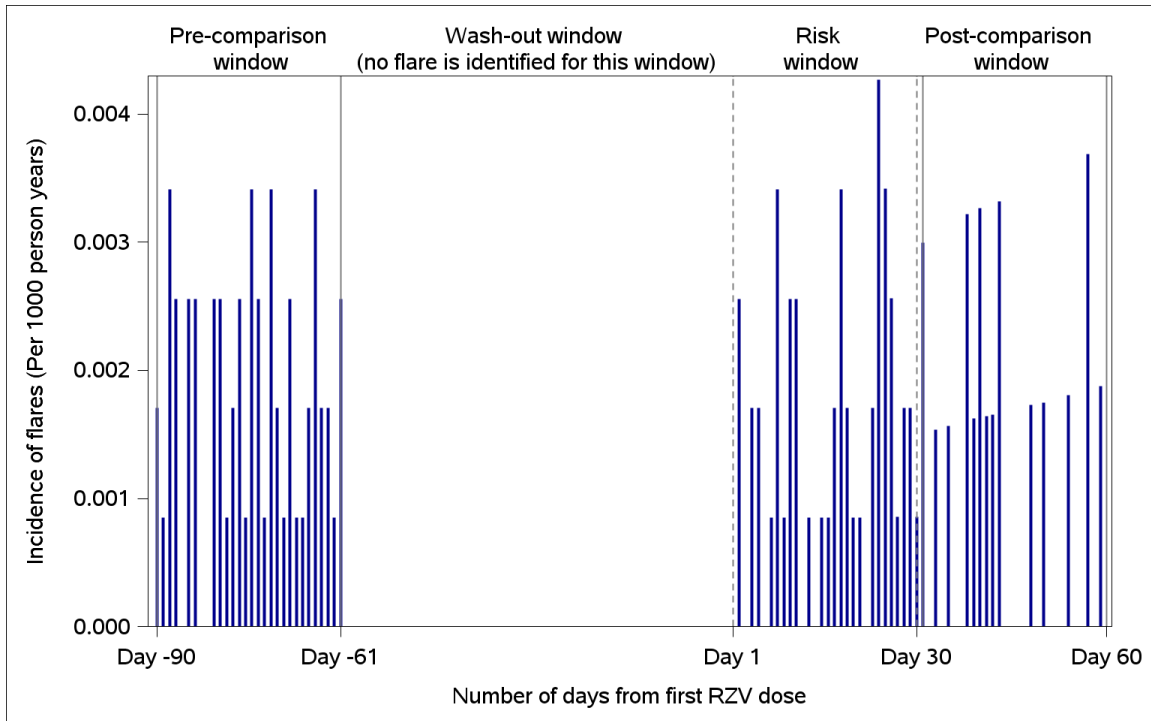
Flow chart for RZV recipients with IBD



* Accrual period for age 50+ individuals was 4/1/2018 - 9/30/202

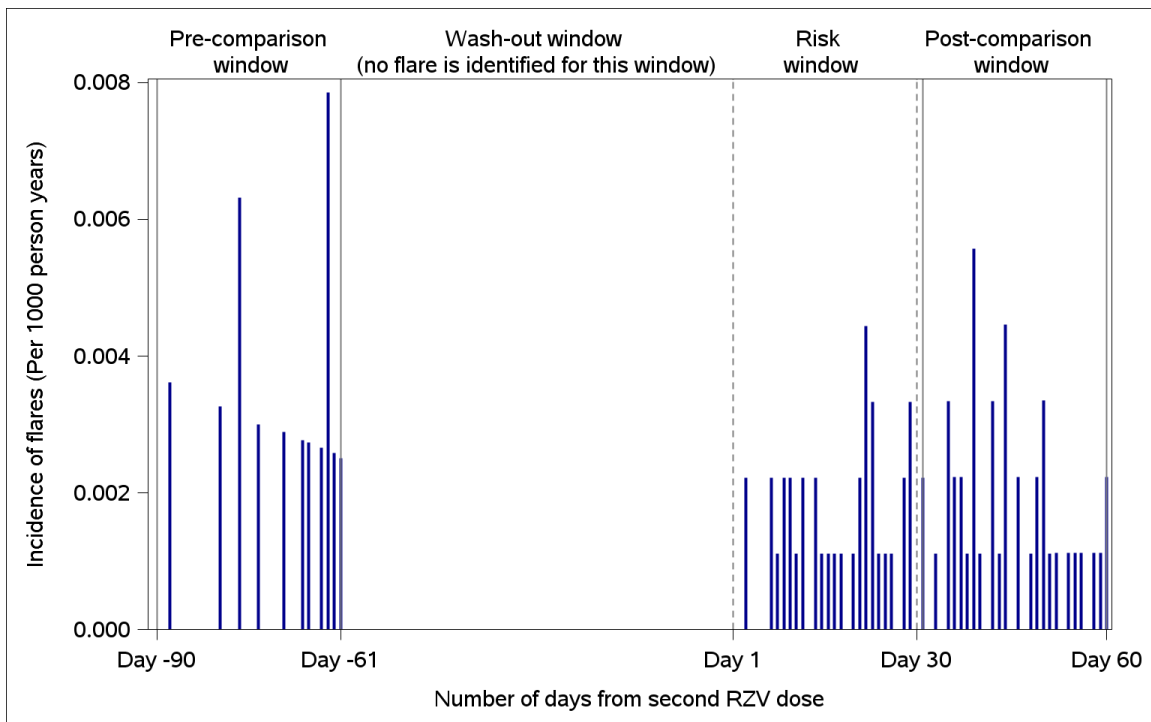
Appendix B Figure 3

Incidence of flare by day during the risk and comparison windows of first dose among RZV recipients with RA



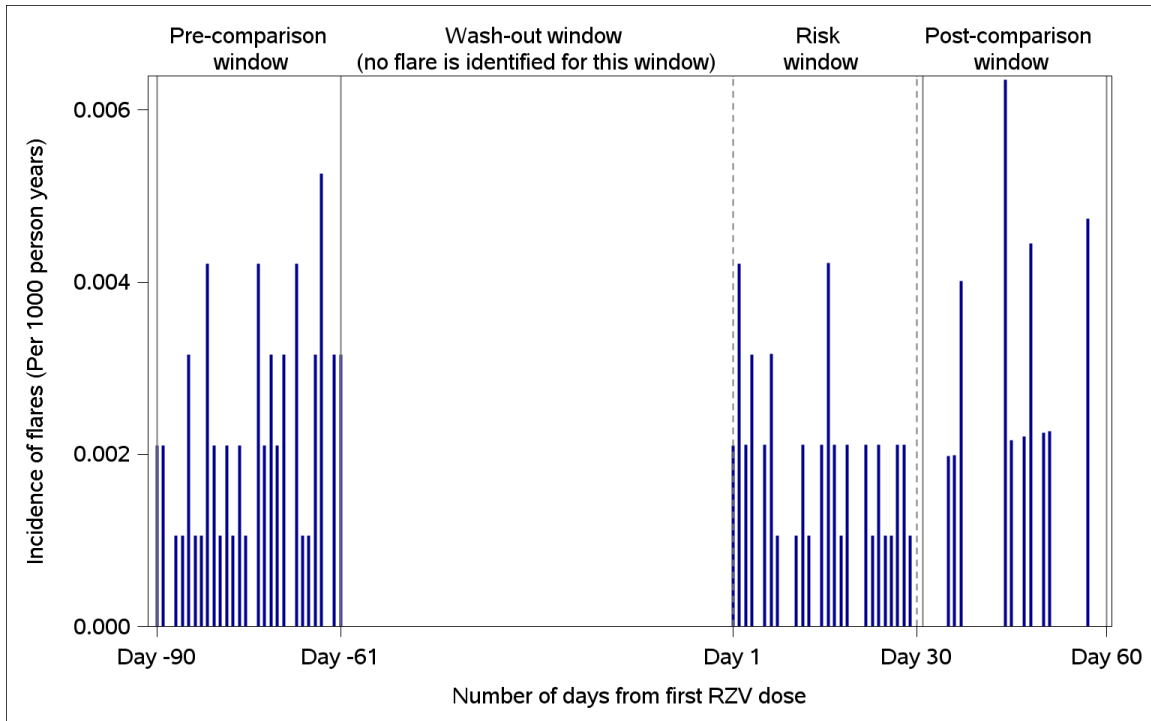
Appendix B Figure 4

Incidence of flare by day during the risk and comparison windows of second dose among RZV recipients with RA



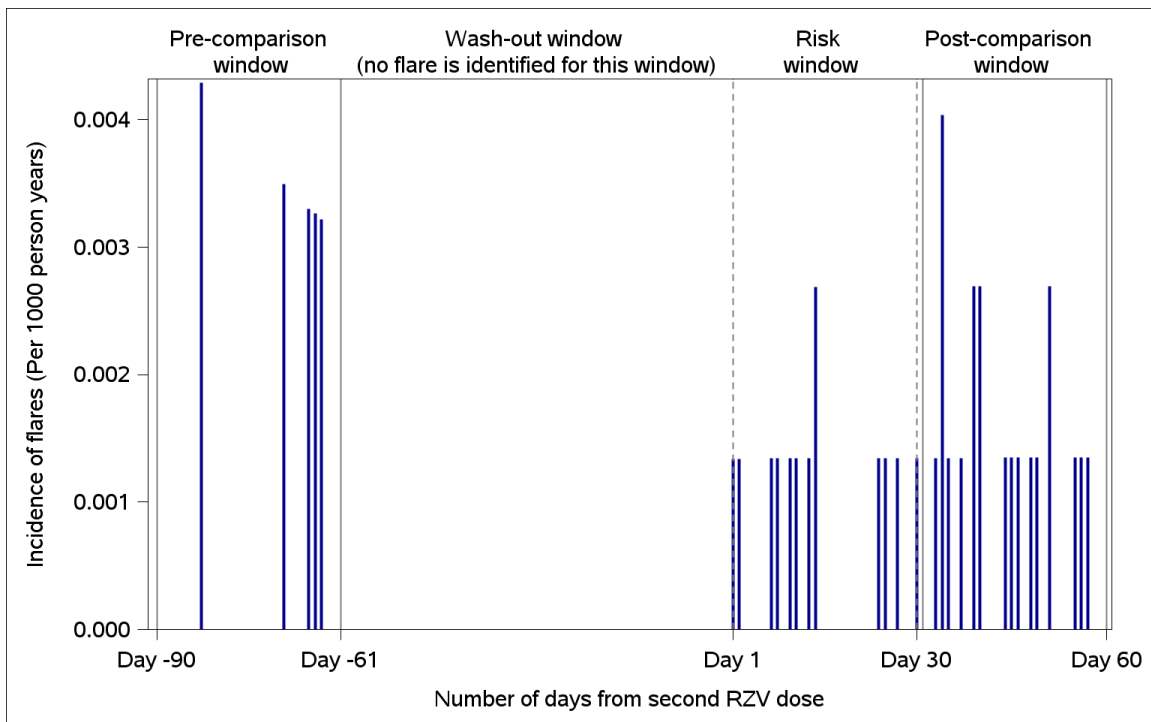
Appendix B Figure 5

Incidence of flare by day during the risk and comparison windows of first dose among RZV recipients with IBD



Appendix B Figure 6

Incidence of flare by day during the risk and comparison windows of second dose among RZV recipients with IBD



Appendix B Table 1 Baseline characteristics of RZV recipients with RA

	Vaccinated N = 3211
Age at index date, years	
mean (sd)	67.74 (10.16)
median	68
Q1, Q3	61, 75
range	22, 98
Age at index date, years, n (%)	
18-49	90 (2.8%)
50-59	591 (18.4%)
60-69	1104 (34.4%)
70-79	1043 (32.5%)
≥80	383 (11.9%)
Sex, n (%)	
Female	2542 (79.2%)
Male	669 (20.8%)
Race/Ethnicity, n (%)	
White	1379 (42.9%)
Black	317 (9.9%)
Hispanic	1042 (32.5%)
Asian	392 (12.2%)
Other	81 (2.5%)
Medication category, n (%)	
Category 1	732 (22.8%)
Category 2	1734 (54.0%)
Category 3	397 (12.4%)
Category 4	155 (4.8%)
Category 5	193 (6.0%)
Number of RZV doses, n (%)	
One dose	739 (23.0%)
Two doses	2472 (77.0%)
Concomitant vaccination ^a , n (%)	
Yes	1070 (33.3%)
No	2141 (66.7%)

a. Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (47%), COVID-19 vaccine (6%), PCV13/PCV20/PPSV23 (25%), Tdap (28%), and other (10%); 76% concomitant with 1st dose and 33% concomitant with 2nd dose

Appendix B Table 2 Baseline characteristics of RZV recipients with IBD

	Vaccinated N = 2600
Age at index date, years	
mean (sd)	65.66 (12.91)
median	67
Q1, Q3	59, 74
range	18, 97
Age at index date, years, n (%)	
18-49	201 (7.7%)
50-59	492 (18.9%)
60-69	855 (32.9%)
70-79	751 (28.9%)
≥80	301 (11.6%)
Sex, n (%)	
Female	1388 (53.4%)
Male	1212 (46.6%)
Race/Ethnicity, n (%)	
White	1587 (61.0%)
Black	216 (8.3%)
Hispanic	543 (20.9%)
Asian	195 (7.5%)
Other	59 (2.3%)
IBD condition, n (%)	
UC	1456 (56.0%)
CD	1122 (43.2%)
UC+CD	22 (0.8%)
Medication category, n (%)	
Category 1	996 (38.3%)
Category 2	860 (33.1%)
Category 3	473 (18.2%)
Category 4	198 (7.6%)
Category 5	73 (2.8%)
Number of RZV doses, n (%)	
One dose	558 (21.5%)
Two doses	2042 (78.5%)
Concomitant vaccination ^a , n (%)	
Yes	1125 (43.3%)
No	1475 (56.7%)

a. Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (47%), COVID-19 vaccine (10%), PCV13/PCV20/PPSV23 (32%), Tdap (23%), and other (14%); 79% concomitant with 1st dose and 34% concomitant with 2nd dose.

Appendix B Table 3 Incidence and relative risk of RA flare after RZV among individuals with RA

	Risk Window			Comparison Window			Relative Risk (95% CI)
	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	
Overall	88	466.25	188.74 (153.15, 232.60)	135	648.10	208.30 (175.97, 246.58)	0.92 (0.70, 1.20)
RZV dose							
First	52	263.56	197.30 (150.35, 258.92)	135	648.10	208.30 (175.97, 246.58)	0.94 (0.68, 1.30)
Second	36	202.69	177.61 (128.12, 246.23)	107	527.75	202.75 (167.75-245.05)	0.88 (0.61, 1.29)

CCI

Appendix B Table 4 Incidence and relative risk of RA flare after RZV among individuals with RA (CCI

CCI

	Risk Window			Comparison Window			Relative Risk (95% CI)
	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	
Overall	88	466.25	188.74 (153.15, 232.60)	135	648.10	208.30 (175.97, 246.58)	0.92 (0.70, 1.20)
RZV dose							
First	52	263.56	197.30 (150.35, 258.92)	135	648.10	208.30 (175.97, 246.58)	0.94 (0.68, 1.30)
Second	36	202.69	177.61 (128.12, 246.23)	107	527.75	202.75 (167.75-245.05)	0.88 (0.61, 1.29)

CCI

Appendix B Table 5 Incidence and relative risk of IBD flare after RZV among individuals with IBD

	Risk Window			Comparison Window			Relative Risk (95% CI)
	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	
Overall	57	380.45	149.82 (115.57, 194.23)	95	524.04	181.29 (148.26, 221.66)	0.80 (0.58, 1.12)
RZV dose							
First	44	213.00	206.58 (153.73, 277.59)	95	524.04	181.29 (148.26, 221.66)	1.03 (0.72, 1.47)
Second	13	167.46	77.63 (45.08, 133.70)	69	433.68	159.10 (125.66-201.44)	0.45 (0.25, 0.81)
IBD condition							
UC (including UC+CD)	35	215.13	162.69 (116.81, 226.59)	55	296.79	185.32 (142.28, 241.37)	0.91 (0.59, 1.40)
CD (including UC+CD)	24	168.20	142.69 (95.64, 212.88)	43	231.99	185.35 (137.46, 249.92)	0.69 (0.41, 1.14)

CCI

Appendix B Table 6 Incidence and relative risk of IBD flare after RZV among individuals with IBD CCI

CCI

	Risk Window			Comparison Window			Relative Risk (95% CI)
	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	
Overall	57	380.45	149.82 (115.57, 194.23)	95	524.04	181.29 (148.26, 221.66)	0.80 (0.58, 1.12)
RZV dose							
First	44	213.00	206.58 (153.73, 277.59)	95	524.04	181.29 (148.26, 221.66)	1.03 (0.72, 1.47)
Second	13	167.46	77.63 (45.08, 133.70)	69	433.68	159.10 (125.66-201.44)	0.45 (0.25, 0.81)
IBD condition							
UC			162.69			185.32	0.91
(including UC+CD)	35	215.13	(116.81, 226.59)	55	296.79	(142.28, 241.37)	(0.59, 1.40)
CD			142.69			185.35	0.69
(including UC+CD)	24	168.20	(95.64, 212.88)	43	231.99	(137.46, 249.92)	(0.41, 1.14)

CCI

Appendix B Table 7 **Baseline characteristics of RZV recipients with RA by age groups**

	Age 18-49 years N=90	Age ≥ 50 years N=3121	p value
Sex, n (%)			0.323
Female	75 (83.3%)	2467 (79.0%)	
Male	15 (16.7%)	654 (21.0%)	
Race/Ethnicity, n (%)			0.039
White	28 (31.1%)	1351 (43.3%)	
Black	PPD		
Hispanic	41 (45.6%)	1001 (32.1%)	
Asian	PPD		
Other			
Medication category, n (%)			<0.001
Category 1	17 (18.9%)	715 (22.9%)	
Category 2	22 (24.4%)	1712 (54.9%)	
Category 3	18 (20.0%)	379 (12.1%)	
Category 4	12 (13.3%)	143 (4.6%)	
Category 5	21 (23.3%)	172 (5.5%)	

Appendix B Table 8 **Baseline characteristics of RZV recipients with IBD by age groups**

	Age 18-49 years N=201	Age ≥ 50 years N=2399	p value
Sex, n (%)			0.222
Female	99 (49.3%)	1289 (53.7%)	
Male	102 (50.7%)	1110 (46.3%)	
Race/Ethnicity, n (%)			<0.001
White	99 (49.3%)	1488 (62.0%)	
Black	PPD		
Hispanic	67 (33.3%)	476 (19.8%)	
Asian	22 (10.9%)	173 (7.2%)	
Other	PPD		
IBD condition, n (%)			<0.001
UC	117 (58.2%)	1339 (55.8%)	
CD	75 (37.3%)	1047 (43.6%)	
UC+CD	9 (4.5%)	13 (0.5%)	
Medication category, n (%)			<0.001
Category 1	42 (20.9%)	954 (39.8%)	
Category 2	36 (17.9%)	824 (34.3%)	
Category 3	51 (25.4%)	422 (17.6%)	
Category 4	22 (10.9%)	176 (7.3%)	
Category 5	50 (24.9%)	23 (1.0%)	

15. ANNEX 1 LIST OF STAND-ALONE DOCUMENTS**15.1. Appendix C: Definition of clinically relevant flare****Definition of “clinically relevant” flare**

For this study, flare was 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 reviewed 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, ED, 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
3. 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 was performed among individuals eligible for the safety analysis. Trained research associates reviewed 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 identified new or worsening signs and/or symptoms suggestive of a flare and captured the date of onset of new or worsening signs and/or symptoms. They determined 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 were reviewed by an RA or IBD specialist.

15.2. Appendix D: Medication categories

- a. Vaccinated and unvaccinated subjects were matched on age, sex, race/ethnicity, 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 date¹
 - Biologics: 3 months before index date²
 - JAK inhibitors, sphingosine-1 phosphate (S1P) receptor modulators, cyclosporine: 3 months before index date to 1 month after index date³
 - Nonsteroidal anti-inflammatory drugs (NSAIDs), 5-aminosalicylate (5-ASA), aminosalicylate, sulfasalazine, thiopurines, steroids, and conventional DMARDs: Medication prescribed/refilled within 6 months prior to index date AND medication duration covers the index date⁴
- c. Medication category was determined by the highest category of medication during the search period.
- d. Medication categories may be consolidated to ensure at least 1:1 matching.

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

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

³The 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.

⁴While 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 D 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), Methotrexate (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-arx (Riabni), tocilizumab (Actemra), tocilizumab-bavi (Tofidence)*, sarilumab (Kevzara), adalimumab (Humira), adalimumab-atto (Amjevita)*, adalimumab-afzb (Abralada)*, 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 (Olmiant), 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 D Table 2 IBD medication category

Category 1	No treatment
Category 2	Aminosalicylate (5-ASA): aminosaliclylate (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 (Abralada)*, 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.	

15.3. Appendix E: Additional Analysis

Additional VE analysis was conducted to collapse categories for secondary and exploratory objectives that were small including time since vaccination and medication categories. These results are presented in the main body of the final report.

Additional analyses were conducted to further investigate the VE results in the 18-49 age group. Additional VE analyses for the 18–49-year-old age group are provided in [Appendix E Table 1](#)–[Appendix E Table 8](#) and [Appendix E Figure 1](#) for RA and IBD patients. The VE of 2 doses stratified by index date for those with RA (18-49 years) is provided in [Appendix E Table 1](#). The distribution of index year for the 18-49 and 50+ year age groups is provided in [Appendix E Table 2](#). Baseline characteristics were compared between vaccinated (2-dose) and unvaccinated 18–49-year-old RA patients ([Appendix E Table 3](#)). Baseline characteristics were compared between vaccinated (2-dose) and unvaccinated HZ cases among 18–49-year-old RA patients ([Appendix E Table 4](#)). Baseline characteristics were compared between vaccinated (2-dose) and unvaccinated 18–49-year-old IBD patients ([Appendix E Table 5](#)). A comparison of baseline characteristics before and after inverse probability of treatment weighting (IPTW) is provided in [Appendix E Table 3](#) (before IPTW) and [Appendix E Table 6](#) (after IPTW) and [Appendix E Figure 1](#) for 18–49-year-old RA patients. IPTW adjusted HR and VE are provided in [Appendix E Table 7](#). The distribution of stabilized weights in the vaccinated and unvaccinated arms is provided in [Appendix E Table 8](#).

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Appendix E Table 1 Incidence rate, hazard ratio, and VE of 2 doses of RZV in preventing HZ among individuals with RA, 18 - 49 years old

HZ	Vaccinated				Unvaccinated				Hazard Ratio (95% CI)		VE (95% CI) ^a	
	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	N	Number of cases	Number of person-years	Incidence per 1000 person-years (95% CI)	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
Age at index date, years	4			40.8				18.9	2.293	3.093	-56.4%	-67.7%
18-49	9	4	98.1	(15.3, 108.6)	143	5	264.8	(7.9, 45.4)	(0.614, 8.563)	(0.620, 15.438)	(-88.3%, 38.6%)	(-93.5%, 38.0%)
18-49 (index date after 07/23/2021)	3			56.0				18.8	3.000	13.303	-66.7%	-92.5%
	6	3	53.6	(18.1, 173.6)	107	3	159.4	(6.1, 58.4)	(0.606, 14.864)	(0.524, 337.537)	(-93.3%, 39.4%)	(-99.7%, 47.6%)

a. $VE (\%) = (1 - HR) \times 100$ if $HR \leq 1$, and $VE (\%) = ([1/HR] - 1) \times 100$ if $HR > 1$

b. Adjusted for limited covariates due to convergence issue: IC status and length of continuous KPSC membership.

Appendix E Table 2 The distribution of index year by age group of 2-dose RZV recipients with RA

Index Year	18-49 years	50+ years
2018	0 (0%)	133 (5.5%)
2019	5 (10.2%)	704 (29.2%)
2020	2 (4.1%)	186 (7.7%)
2021	8 (16.3%)	903 (37.5%)
2022	16 (32.7%)	485 (20.1%)
2023	18 (36.7%)	0 (0%)

Appendix E Table 3 Baseline characteristics of 2-dose RZV vaccinated and unvaccinated cohort with RA, 18 - 49 years old

	Vaccinated N=49	Unvaccinated N=143	Total N=192	p value	ASD
Age at index date, years				0.747	0.043
mean (sd)	42.39 (5.85)	42.14 (5.78)	42.20 (5.79)		
median	43	43	43		
Q1, Q3	39, 47	39, 47	39, 47		
range	27, 49	20, 49	20, 49		
Age at index date, years, n (%)				0.996	0.015
18-29	1 (2.0%)	3 (2.1%)	4 (2.1%)		
30-39	13 (26.5%)	37 (25.9%)	50 (26.0%)		
40-49	35 (71.4%)	103 (72.0%)	138 (71.9%)		
Sex, n (%)				0.841	0.033
Female	43 (87.8%)	127 (88.8%)	170 (88.5%)		
Male	6 (12.2%)	16 (11.2%)	22 (11.5%)		
Race/Ethnicity, n (%)				0.997	0.064
White	12 (24.5%)	35 (24.5%)	47 (24.5%)		
Black	PPD				
Hispanic	24 (49.0%)	72 (50.3%)	96 (50.0%)		
Asian	PPD				
Other					
Medication category, n (%)				0.999	0.053
Category 1	9 (18.4%)	27 (18.9%)	36 (18.8%)		
Category 2	15 (30.6%)	45 (31.5%)	60 (31.3%)		
Category 3	11 (22.4%)	33 (23.1%)	44 (22.9%)		
Category 4	3 (6.1%)	9 (6.3%)	12 (6.3%)		
Category 5	11 (22.4%)	29 (20.3%)	40 (20.8%)		
Number of outpatient visits ^a , n (%)				0.015	0.559
0-4	0 (0.0%)	6 (4.2%)	6 (3.1%)		
5-10	3 (6.1%)	30 (21.0%)	33 (17.2%)		

	Vaccinated	Unvaccinated	Total	p value	ASD
	N=49	N=143	N=192		
≥11	46 (93.9%)	107 (74.8%)	153 (79.7%)		
Number of ED visits ^a , n (%)				0.054	0.384
0	32 (65.3%)	117 (81.8%)	149 (77.6%)		
1	10 (20.4%)	14 (9.8%)	24 (12.5%)		
≥2	7 (14.3%)	12 (8.4%)	19 (9.9%)		
Number of hospitalization ^a , n (%)				0.208	0.265
0	43 (87.8%)	136 (95.1%)	179 (93.2%)		
1	5 (10.2%)	6 (4.2%)	11 (5.7%)		
≥2	1 (2.0%)	1 (0.7%)	2 (1.0%)		
Baseline Comorbidities ^a , n (%)					
Kidney disease	2 (4.1%)	1 (0.7%)	3 (1.6%)	0.099	0.223
Heart disease	1 (2.0%)	1 (0.7%)	2 (1.0%)	0.425	0.116
Lung disease	13 (26.5%)	20 (14.0%)	33 (17.2%)	0.045	0.316
Liver disease	9 (18.4%)	9 (6.3%)	18 (9.4%)	0.012	0.374
Diabetes	7 (14.3%)	14 (9.8%)	21 (10.9%)	0.384	0.138
Other autoimmune diseases ^b	2 (4.1%)	5 (3.5%)	7 (3.6%)	0.85	0.031
SARS-CoV-2 infection/ COVID-19 diagnosis	13 (26.5%)	33 (23.1%)	46 (24.0%)	0.625	0.08
Immunocompromised status ^c at index date, n (%)				0.282	0.182
Yes	35 (71.4%)	90 (62.9%)	125 (65.1%)		
No	14 (28.6%)	53 (37.1%)	67 (34.9%)		
History of ZVL/varicella vaccination ^d , n (%)				0.946	0.053
No	44 (89.8%)	130 (90.9%)	174 (90.6%)		
Yes, ≤ 5 years	1 (2.0%)	2 (1.4%)	3 (1.6%)		
Yes, > 5 years	4 (8.2%)	11 (7.7%)	15 (7.8%)		
History of HZ ^d , n (%)				0.251	0.179
Yes	6 (12.2%)	10 (7.0%)	16 (8.3%)		
No	43 (87.8%)	133 (93.0%)	176 (91.7%)		
Length of continuous membership ^d , years, n (%)				0.958	0.049
0-5	19 (38.8%)	54 (37.8%)	73 (38.0%)		
6-10	15 (30.6%)	42 (29.4%)	57 (29.7%)		
≥11	15 (30.6%)	47 (32.9%)	62 (32.3%)		
Concomitant vaccination, n (%)				N/A ^e	N/A
Yes	26 (53.1%)	N/A	N/A		
No	23 (46.9%)	N/A	N/A		
Time between first and second doses, n (%)				N/A	N/A
4 weeks - 6 months	40 (81.6%)	N/A	N/A		
>6 months	9 (18.4%)	N/A	N/A		

a. Defined in the one year prior to index date

Vaccinated	Unvaccinated	Total	P value	ASD
N=49	N=143	N=192		

- b. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease.
- c. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenism, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.
- d. Defined based on all available medical records prior to index date.
- e. N/A= not applicable.



PPD

- a. Defined in the one year prior to index date.
- b. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease.
- c. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.
- d. Defined based on all available medical records prior to index date.

Appendix E Table 5 Baseline characteristics of 2-dose RZV vaccinated and unvaccinated cohort with IBD, 18 - 49 years old

	Vaccinated N=85	Unvaccinated N=251	Total N=336	p value	ASD
Age at index date, years				0.947	0.006
mean (sd)	34.67 (8.49)	34.72 (8.22)	34.71 (8.28)		
median	35	35	35		
Q1, Q3	28, 41	29, 41	29, 41		
range	18, 49	19, 49	18, 49		
Age at index date, years, n (%)				0.996	0.012
18-29	24 (28.2%)	71 (28.3%)	95 (28.3%)		
30-39	36 (42.4%)	105 (41.8%)	141 (42.0%)		
40-49	25 (29.4%)	75 (29.9%)	100 (29.8%)		
Sex, n (%)				0.909	0.014
Female	38 (44.7%)	114 (45.4%)	152 (45.2%)		
Male	47 (55.3%)	137 (54.6%)	184 (54.8%)		
Race/Ethnicity, n (%)				0.998	0.024

	Vaccinated	Unvaccinated	Total	p value	ASD
	N=85	N=251	N=336		
White	35 (41.2%)	103 (41.0%)	138 (41.1%)		
Hispanic	41 (48.2%)	123 (49.0%)	164 (48.8%)		
Asian	PPD				
Other					
IBD ^a , n (%)				0.723	0.088
UC	47 (55.3%)	140 (55.8%)	187 (55.7%)		
CD ^b	37 (43.5%)	110 (43.8%)	147 (43.8%)		
UC+CD	1 (1.2%)	1 (0.4%)	2 (0.6%)		
Medication category, n (%)				0.394	0.309
Category 1	19 (22.4%)	57 (22.7%)	76 (22.6%)		
Category 2	15 (17.6%)	42 (16.7%)	57 (17.0%)		
Category 3	24 (28.2%)	71 (28.3%)	95 (28.3%)		
Category 4	27 (31.8%)	70 (27.9%)	97 (28.9%)		
Category 5	0 (0.0%)	11 (4.4%)	11 (3.3%)		
Number of outpatient visits ^a , n (%)				<0.001	0.632
0-4	0 (0.0%)	6 (2.4%)	6 (1.8%)		
5-10	3 (3.5%)	55 (21.9%)	58 (17.3%)		
≥11	82 (96.5%)	190 (75.7%)	272 (81.0%)		
Number of ED visits ^a , n (%)				0.095	0.282
0	62 (72.9%)	151 (60.2%)	213 (63.4%)		
1	11 (12.9%)	54 (21.5%)	65 (19.3%)		
≥2	12 (14.1%)	46 (18.3%)	58 (17.3%)		
Number of hospitalizations ^a , n (%)				0.744	0.094
0	70 (82.4%)	214 (85.3%)	284 (84.5%)		
1	11 (12.9%)	25 (10.0%)	36 (10.7%)		
≥2	4 (4.7%)	12 (4.8%)	16 (4.8%)		
Baseline comorbidities ^a , n (%)					
Kidney disease	1 (1.2%)	2 (0.8%)	3 (0.9%)	0.748	0.038
Heart disease	0 (0.0%)	2 (0.8%)	2 (0.6%)	0.409	0.127
Lung disease	11 (12.9%)	23 (9.2%)	34 (10.1%)	0.318	0.121
Liver disease	4 (4.7%)	17 (6.8%)	21 (6.3%)	0.496	0.089
Diabetes	3 (3.5%)	12 (4.8%)	15 (4.5%)	0.629	0.063
Other autoimmune diseases ^c	3 (3.5%)	12 (4.8%)	15 (4.5%)	0.629	0.063
SARS-CoV-2 infection/COVID-19 diagnosis	14 (16.5%)	55 (21.9%)	69 (20.5%)	0.283	0.139
Immunocompromised status ^d at index date, n (%)				0.118	0.194
Yes	35 (41.2%)	80 (31.9%)	115 (34.2%)		

	Vaccinated N=85	Unvaccinated N=251	Total N=336	p value	ASD
No	50 (58.8%)	171 (68.1%)	221 (65.8%)		
History of ZVL/varicella vaccination ^e , n (%)				0.824	0.077
No	67 (78.8%)	194 (77.3%)	261 (77.7%)		
Yes, ≤ 5 years	2 (2.4%)	4 (1.6%)	6 (1.8%)		
Yes, > 5 years	16 (18.8%)	53 (21.1%)	69 (20.5%)		
History of HZ ^e , n (%)				0.275	0.147
Yes	3 (3.5%)	17 (6.8%)	20 (6.0%)		
No	82 (96.5%)	234 (93.2%)	316 (94.0%)		
Length of continuous KPSC membership ^e , years, n (%)				0.157	0.236
0-5	37 (43.5%)	126 (50.2%)	163 (48.5%)		
6-10	29 (34.1%)	59 (23.5%)	88 (26.2%)		
≥11	19 (22.4%)	66 (26.3%)	85 (25.3%)		
Concomitant vaccination ^f , n (%)				N/A	N/A
Yes	51 (60.0%)	N/A	N/A		
No	34 (40.0%)	N/A	N/A		
Time between first and second doses, n (%)				N/A	N/A
4 weeks - 6 months	75 (88.2%)	N/A	N/A		
>6 months ^h	10 (11.8%)	N/A	N/A		

a. Defined in the one year prior to index date

b. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis.

c. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenism, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

d. Defined based on all available medical records prior to index date.

e. N/A= not applicable.

Appendix E Table 6 Baseline characteristics of 18 - 49 years old group in 2-dose RZV cohort with RA (after IPTW)

	Vaccinated N=49	Unvaccinated N=143	Total N=192	Chi-square p value	ASD
Age at index date ^a , years, n (%)				0.7815	0.046
18-39	15 (30.2%)	40 (28.1%)	55 (28.7%)		
40-49	34 (69.8%)	103 (71.9%)	137 (71.3%)		
Sex ^a , n (%)				0.9058	0.020
Female	43 (86.9%)	125 (87.6%)	168 (87.4%)		
Male	6 (13.1%)	18 (12.4%)	24 (12.6%)		
Race/Ethnicity ^a , n (%)				0.9757	0.005

	Vaccinated	Unvaccinated	Total	Chi-square p value	ASD
	N=49	N=143	N=192		
Non-Hispanic	25 (50.7%)	73 (51%)	98 (50.9%)		
Hispanic	24 (49.3%)	70 (49%)	94 (49.1%)		
Medication category ^a , n (%)				0.9798	0.004
Category 1-3	36 (73.8%)	105 (73.6%)	141 (73.7%)		
Category 4-5	13 (26.2%)	38 (26.4%)	51 (26.3%)		
Number of outpatient visits ^b , n (%)				0.0788	0.427
0-4	0 (0%)	6 (3.9%)	6 (2.9%)		
5-10	5 (9.4%)	28 (19.7%)	33 (17.1%)		
≥11	44 (90.6%)	109 (76.4%)	154 (80%)		
Number of ED visits ^{a, b} , n (%)				0.9247	0.016
0	37 (76.1%)	110 (76.7%)	147 (76.6%)		
1+	12 (23.9%)	33 (23.3%)	45 (23.4%)		
Number of hospitalization ^b , n (%)				0.6356	0.148
0	44 (89.7%)	134 (93.6%)	178 (92.6%)		
1	4 (9.2%)	8 (5.3%)	12 (6.3%)		
≥2	1 (1.1%)	1 (1%)	2 (1.1%)		
Baseline comorbidities ^b , n (%)					
Kidney disease	2 (3.4%)	1 (0.7%)	3 (1.4%)	0.1478	0.197
Heart disease	0 (0.7%)	1 (0.7%)	1 (0.7%)	0.9948	0.001
Lung disease ^a	9 (19%)	26 (17.9%)	35 (18.2%)	0.8516	0.031
Liver disease ^a	6 (11.3%)	15 (10.7%)	21 (10.8%)	0.8975	0.021
Diabetes	5 (11%)	14 (10.1%)	20 (10.3%)	0.8454	0.032
Other autoimmune diseases ^c	2 (3.2%)	5 (3.8%)	7 (3.7%)	0.8462	0.033
SARS-CoV-2 infection/ COVID-19 diagnosis	11 (21.7%)	35 (24.6%)	46 (23.9%)	0.6757	0.070
Immunocompromised status ^{a, d} at index date, n (%)				0.6507	0.076
No	15 (31.5%)	50 (35%)	66 (34.1%)		
Yes	34 (68.5%)	93 (65%)	126 (65.9%)		
History of ZVL/varicella vaccination ^e , n (%)				0.9413	0.062
No	45 (91.5%)	130 (91.1%)	175 (91.2%)		
Yes, ≤ 5 years	0 (0.7%)	2 (1.3%)	2 (1.1%)		
Yes, > 5 years	4 (7.8%)	11 (7.6%)	15 (7.7%)		
History of HZ ^{a, e} , n (%)				0.5856	0.088
No	44 (89.1%)	131 (91.7%)	175 (91%)		
Yes	5 (10.9%)	12 (8.3%)	17 (9%)		
Length of continuous membership ^e , years, n (%)				0.9022	0.076

	Vaccinated	Unvaccinated	Total	Chi-square p value	ASD
	N=49	N=143	N=192		
0-5	19 (39%)	53 (36.8%)	72 (37.4%)		
6-10	16 (31.7%)	44 (30.4%)	59 (30.7%)		
≥11	14 (29.3%)	47 (32.8%)	61 (31.9%)		

- a. Variables included in the propensity score model for weight calculation
- b. Defined in the one year prior to index date
- c. Psoriasis/psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, and inflammatory bowel disease.
- d. HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenism, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.
- e. Defined based on all available medical records prior to index date.

Appendix E Table 7 Hazard ratio and VE of 2 doses of RZV in preventing HZ among 18-49-year-old age group with RA, IPTW adjusted

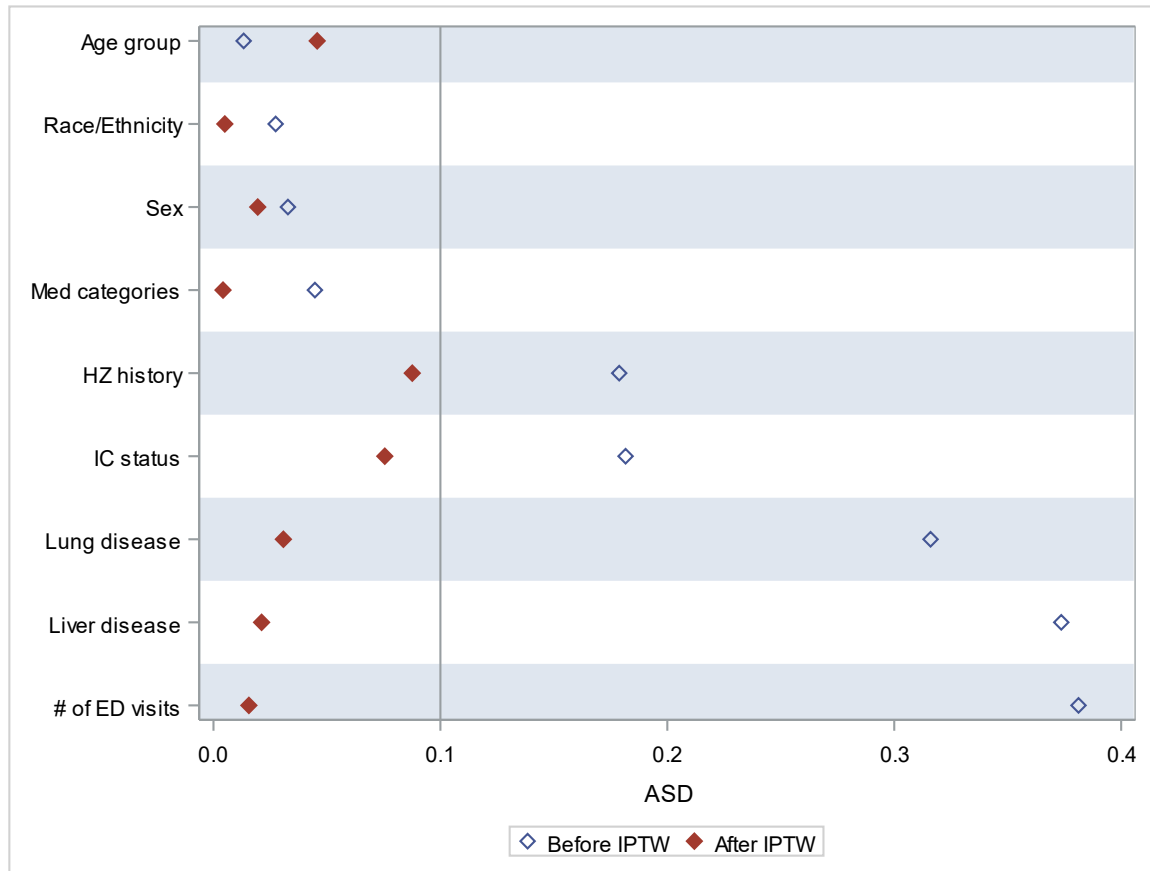
Covariate	Hazard Ratio (95% CI)		VE (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
IPTW	2.293	2.145	-56.4%	-53.4%
	(0.614, 8.563)	(0.562, 8.194)	(-88.3%, 38.6%)	(-87.8%, 43.8%)
IPTW + Number of outpatient visits	2.293	2.267	-56.4%	-55.9%
	(0.614, 8.563)	(0.555, 9.265)	(-88.3%, 38.6%)	(-89.2%, 44.5%)

Appendix E Table 8 Distribution of stabilized weights of 18-49-year-old age group in 2-dose RZV cohort with RA

Arm	N	Min	Q1	Median	Q3	Max
Vaccinated	49	0.3255	0.6708	1.1234	1.2575	2.1528
Unvaccinated	143	0.8397	0.9136	0.9374	0.9883	2.8993

Appendix E Figure 1

ASD before and after IPTW in 18-49-year-old age group
of 2-dose RZV cohort with RA



Signature Page for 213825 TMF-23026450 v1.0

Reason for signing: Approved	Name: PPD Role: Author Date of signature: 10-Dec-2025 17:23:00 GMT+0000
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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 10-Dec-2025 18:50:40 GMT+0000
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Signature Page for TMF-23026450 v1.0

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):	<i>Shingrix</i> (Recombinant Zoster Vaccine, RZV)
Product reference:	<u>For EMA:</u> EU/1/18/1272/001-1 Vial and 1 vial; EU/1/18/1272/002-10 vials and 10 vials <u>For FDA: IND #013879</u>
Procedure number:	EMA/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 [REDACTED], Co-Investigator
PPD [REDACTED], Co-Investigator
PPD [REDACTED], Co-Investigator
PPD [REDACTED], Co-Investigator
PPD [REDACTED], Co-Investigator
PPD [REDACTED], Co-Investigator/Biostatistician

GSK authors

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

MARKETING AUTHORISATION HOLDER

MAH(s):	GlaxoSmithKline Biologicals S.A. Rue de l’Institut, 89, 1330 Rixensart, Belgium
MAH contact person:	PPD [REDACTED]
<i>Based on GlaxoSmithKline Biologicals SA protocol for epidemiology studies WS v 17.2</i>	

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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
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
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.

CONFIDENTIAL

213825 (EPI-ZOSTER-044 VE US)
Protocol Amendment 2 Final

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

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.

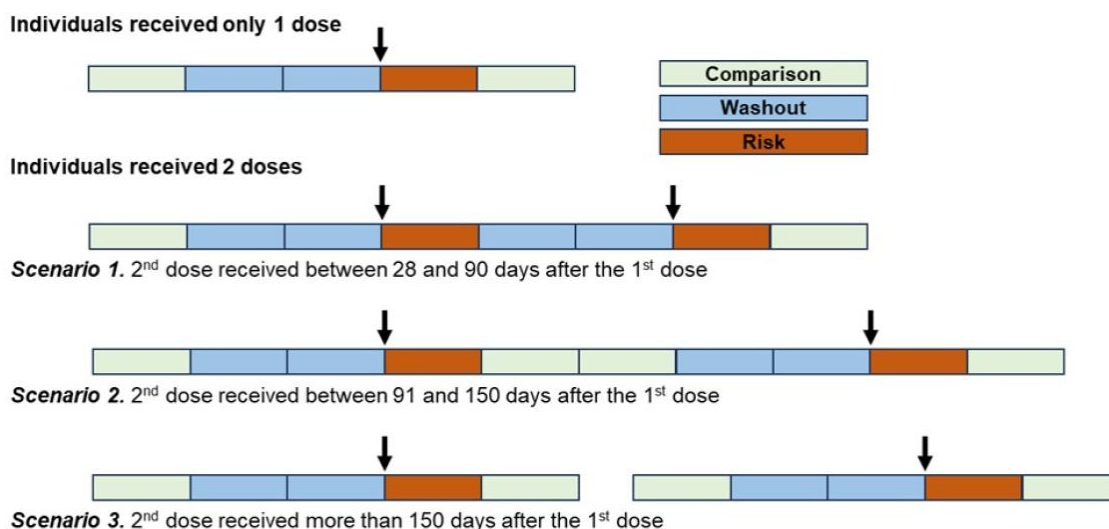
The exposure for secondary VE objectives 6-7 is 1 dose of RZV. The index date will be date of receipt of the first RZV dose. The 1-dose VE will be evaluated in individuals who receive 1 dose of RZV and do not receive a second dose within 6 months after the first dose.

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 index⁴								
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

¹IBD includes UC and CD.

²Index 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.

³Index 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.

⁴Charlson 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/Ethnicity¹		
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

¹All 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	18,309	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

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

²Based 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.

³Based 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.

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

⁵Assuming 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]

²The 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

¹Sample size from [Table 5](#) (total sample size of at least 1-dose recipients).

²[[Bechman](#), 2018 ; [Bykerk](#), 2014 ; [Markusse](#), 2015; [Stevens](#), 2020].

³Compare 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

¹Sample size from Table 5 (total sample size of at least 1-dose recipients).

²[Bolge, 2010 ; Satyam, 2020 ; Rahier, 2011].

³Compare 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 $(1 - \text{HR}) \times 100$ when the HR is less than or equal to 1, and $[(1/\text{HR}) - 1] \times 100$ 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 $(1 - \text{adjusted HR}) \times 100$.

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 $(1 - \text{adjusted HR}) \times 100$. 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 $(1 - \text{adjusted HR}) \times 100$.

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 date¹
 - Biologics: 3 months before index date²
 - JAK inhibitors, sphingosine-1 phosphate (S1P) receptor modulators, cyclosporine: 3 months before index date to 1 month after index date³
 - Nonsteroidal anti-inflammatory drugs (NSAIDs), 5-aminosalicylate (5-ASA), aminosaliclate, sulfasalazine, thiopurines, steroids, and conventional DMARDs: Medication prescribed/refilled within 6 months prior to index date AND medication duration covers the index date⁴
- 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.

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

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

³The 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.

⁴While 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), Methotrexate (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-arx (Riabni), tocilizumab (Actemra), tocilizumab-bavi (Tofidence)*, sarilumab (Kevzara), adalimumab (Humira), adalimumab-atto (Amjevita)*, adalimumab-afzb (Abrigado)*, adalimumab-adbm (Cyltezo)*, adalimumab-bwwd (Hadlima)*, adalimumab-fkjp (Hulio)*, adalimumab-adaz (Hyrimoz)*, adalimumab-aqvh (Yusimry)*, adalimumab-aacf (Idacio)*, adalimumab-aaty (Yuflyma)*, etanercept (Enbrel), etanercept-szss (Erelzi), etanercept-ykro (Eticovo), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflixtra), 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 (Olmiant), 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): aminosaliclate (5-ASA), sulfasalazine (Azulfidine), olsalazine (Dipentum), mesalamine (Canasa, Asacol, Pentasa, Apriso, Lialda, Rowasa, Delzicol), balsalazide (Giazio, 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 (Inflixtra, Zymfentra*), adalimumab (Humira), adalimumab-adaz (Hyrimoz), adalimumab-adbm (Cyltezo), adalimumab-atto (Amjevita), adalimumab-afzb (Abrigado)*, 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 (Olmiant), 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

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

²Based on May 2020 uptake, 0.91% of vaccinees age 50+ are RA patients (2 diagnosis codes in year prior to index).

³Based on May 2020 uptake, 0.55% of vaccinees age 50+ are IBD patients (2 diagnosis codes in year prior to index).

⁴Vaccine 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]²The 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

¹Sample size from [Appendix Table 3](#) (total sample size of at least 1-dose recipients).²[[Bechman](#), 2018; [Bykerk](#), 2014 ; [Markusse](#), 2015; [Stevens](#), 2020].³Compare 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

¹Sample size from [Appendix Table 3](#) (total sample size of at least 1-dose recipients).²[[Bolge](#), 2010 ; [Satyam](#), 2020 ; [Rahier](#), 2011].³Compare 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

<u>Section 1: Milestones</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

<u>Section 2: Research question</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

<u>Section 3: Study design</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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

<u>Section 4: Source and study populations</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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

<u>Section 5: Exposure definition and measurement</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

<u>Section 6: Outcome definition and measurement</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

<u>Section 7: Bias</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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

<u>Section 8: Effect measure modification</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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

<u>Section 9: Data sources</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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:				

<u>Section 9: Data sources</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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

<u>Section 10: Analysis plan</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

<u>Section 11: Data management and quality control</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

<u>Section 12: Limitations</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	5.2.1 and 5.2.2
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

<u>Section 13: Ethical/data protection issues</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

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

Comments:

14.1: Future amendments will be documented as protocol amendments.

<u>Section 15: Plans for communication of study results</u>	<u>Yes</u>	<u>No</u>	<u>N/A</u>	<u>Section Number</u>
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.

Signature Page for 213825 TMF-20120416 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 28-Dec-2024 05:43:27 GMT+0000
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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 09-Jan-2025 15:22:19 GMT+0000
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Signature Page for TMF-20120416 v1.0

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

Version: 2.0

February 13, 2025

Statistical Analysis Plan

Project Name	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
GSK e-Track study number and Abbreviated Title	213825 (EPI-ZOSTER-044 VE US)
Study Delivery Lead (SDL)	PPD
Research Organization	Kaiser Permanente Southern California Department of Research and Evaluation 100 S. Los Robles Ave., Pasadena, CA 91101, US Principal Investigator: Hung-Fu Tseng Co-investigators: PPD PPD
Sponsor Organization	GlaxoSmithKline Biologicals SA (GSK) Clinical R&D 14200 Shady Grove Road, Rockville, MD 20850, US Sponsor representative: Huifeng Yun, Viral Vaccines Epidemiology Head
Prepared by	PPD Research Scientist Biostatistician Kaiser Permanente Southern California

Approvals

Approvers, Organization & Role	Approval Status	Signature	Date
PPD KPSC Research and Evaluation Research Scientist Biostatistician	Approved		02/11/2025
PPD GSK PPD, Real-World Analytics	Approved		02/13/2025

Revision log

Version	Date	Description
Draft 0.1	06/07/2022	Draft- 1 st Draft for GSK Review
Draft 0.2	06/21/2022	GSK Review of 1 st Draft
Draft 0.3	07/06/2022	Draft- 2 nd Draft for GSK Review
Draft 0.4	07/12/2022	GSK Review of 2 nd Draft
Draft 0.5	07/13/2022	Draft for GSK Review and Approval
Draft 0.6	7/14/2022	Additional comments from GSK received
Draft 0.7	7/14/2022	Final Draft for GSK Review and Approval
Draft 1.0	7/15/2022	Approved Final Draft
Draft 1.1	7/21/2025	Draft- 1 st Draft for GSK Review
Draft 1.2	7/28/2025	GSK Review of 1 st Draft
Draft 1.3	2/4/2025	Draft – 2 nd Draft for GSK Review and Approval
Draft 1.5	2/11/2025	GSK Review of 2 nd Draft
Draft 1.6	2/12/2025	Draft – 3 rd Draft for GSK Review and Approval
Draft 2.0		Approved Final Draft

SAP AMENDMENT SUMMARY OF CHANGES TABLE**Amendment 1:**

The SAP has been amended to clarify the study design, document changes made for the early analysis and full analysis, and align with protocol amendments 1 and 2.

List of main changes in the SAP:

Section # and title	Description of change
CCI	
3.1.1 Overview of VE study design	Edited description of censoring events. Added “however, the accrual for individuals ≥ 50 years of age may end earlier than August 2023 once the target sample size is met.”
3.1.2 VE study population	Added explicitly to the exclusion criteria: receipt of a second RZV dose less than 4 weeks after the first RZV dose.
3.1.2.1 VE two-dose RZV cohort	Updated the matching criteria “ $\geq 95\%$ of vaccinated individuals can be matched to at least 1 unvaccinated individual” to allow matching on race/ethnicity. Edited description of censoring events.
3.1.2.2 VE one-dose RZV cohort	Edited description of censoring events.
CCI	
3.1.3.3 VE covariates	Added history of HZ as an important risk factor to be kept in the adjusted model regardless of its association with exposure.
3.1.4 VE Sample size and power estimation	Edited description of censoring events. Updated the sample size calculation using an incidence rate of 12 cases per 1,000 person years, average follow up time 3.5 years, and a censoring rate in the unvaccinated group of 25% for the full analysis.
3.2.1 Overview of safety study design	Added “however, the accrual for individuals ≥ 50 years of age may end earlier than August 2023 once the target sample size is met.”

3.2.3.1 Safety exposures	Updated SCCS design diagram and text description.
4.1.2.1 Analysis primary VE objective 1	Edited description of censoring events.
4.1.3 Analyses of secondary VE objectives	Added “For secondary and exploratory analyses, subgroups may be recategorized in post-hoc analyses if sample size in any subgroup is small.”
4.1.3.1	Revised the wording from “individual” to “matched set.”
4.1.3.2 Analysis of secondary VE objective 2	Added analysis for overall age group 50+ years.
4.1.3.3 Analysis of secondary VE objective 3	Added analysis for overall age group 50+ years.
4.1.4.3 Analysis of exploratory VE objective 3	Edited description of censoring events. CCI Revised the wording regarding when to estimate unadjusted and adjusted HR and VE.
4.1.4.4 Analysis of exploratory VE objective 4	Revised the wording regarding when to estimate unadjusted and adjusted HR and VE.
4.2.1 Description of safety study population	Added comparison of baseline characteristics between the 18-49 and 50+ age groups.
4.2.3 Analyses of secondary safety objectives	Added “For secondary and exploratory analyses, subgroups may be recategorized in post-hoc analyses if sample size in any subgroup is small.”
7.3 Full analysis (individuals ≥18 years) report	Added “however, the accrual for individuals ≥50 years of age may end earlier than August 2023 once the target sample size is met.”
8 List of report tables	Updated Appendix A and B (table shells) and the list of report tables.

ABBREVIATIONS

ASD	Absolute Standardized Difference
CD	Crohn's Disease
CI	Confidence Interval
CIR	Case Identification and Review
COVID-19	Coronavirus Disease 2019
DMP	Data Management Plan
ED	Emergency Department
EHR	Electronic Health Record
FDA	Food and Drug Administration
GSK	GlaxoSmithKline Biologicals SA
HR	Hazard Ratio
HZ	Herpes Zoster
IBD	Inflammatory Bowel Disease
KPSC	Kaiser Permanente Southern California
NDI	National Death Index
CCI	CCI
QC	Quality Control
RA	Rheumatoid Arthritis
RR	Relative Risk
RZV	Recombinant Zoster Vaccine
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SCCS	Self Controlled Case Series
SOP	Standard Operating Procedures
Tdap	Tetanus, Diphtheria and Pertussis Vaccine
UC	Ulcerative Colitis
US	United States
VE	Vaccine Effectiveness
ZVL	Zoster Vaccine Live

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1 INTRODUCTION

Individuals with autoimmune disease are at higher risk of herpes zoster (HZ) compared to immunocompetent individuals. 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 herpes zoster 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) and safety. Through partnership between Kaiser Permanente Southern California (KPSC) and the sponsor, GlaxoSmithKline Biological SA (GSK), we will conduct an observational cohort study to assess the vaccine effectiveness (VE) and safety of RZV among adults with rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), including ulcerative colitis (UC) or Crohn's disease (CD) using real-world electronic health records (EHR) data.

This Statistical Analysis Plan (SAP) provides a detailed description of the data considerations, statistical methods, data analysis and results presentation as previously proposed in the protocol and Data Management Plan (DMP), where applicable. The SAP also describes quality assurance procedures.

2 STUDY OBJECTIVES

2.1 VE

We will assess the VE among individuals with RA or IBD who received RZV compared to individuals who did not receive RZV, addressing the objectives below.

VE objectives refer to 2 doses of RZV given ≥ 4 weeks apart, except where indicated otherwise.

2.1.1 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
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

2.1.2 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)
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)
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)
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
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
6. To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥ 18 years of age with RA
7. To estimate the VE of 1 dose of RZV in preventing HZ in adults ≥ 18 years of age with IBD

2.1.3 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
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
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
4. To estimate the incidence of PHN, disseminated HZ, HZ-related meningoencephalitis, hospitalized HZ in 2-dose RZV vaccinated and unvaccinated adults ≥ 18 years of age with IBD

2.2 Safety

We will assess the risk of flares among individuals with RA or IBD who received at least one dose of RZV, addressing the objectives below.

2.2.1 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
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

2.2.2 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)

2.2.3 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
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

3 STUDY DESIGN

3.1 VE

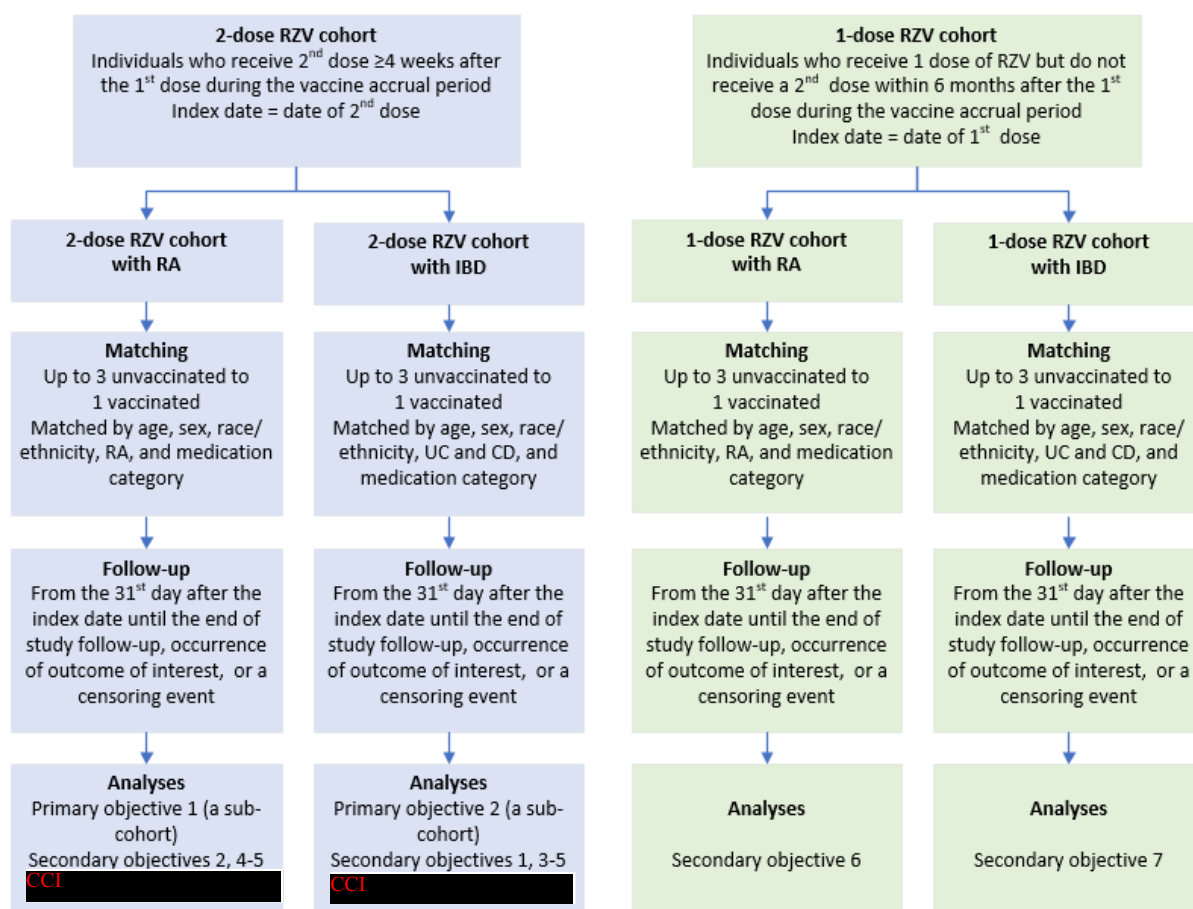
3.1.1 Overview of VE study design

We will use an observational, matched cohort study design to assess RZV effectiveness against HZ. The analysis will be conducted among individuals with RA or with IBD (UC and CD) aged ≥ 18 years who are members of KPSC. RZV unvaccinated individuals will be up to 3:1 matched to RZV vaccinated individuals by age, sex, race/ethnicity (if sample size allows), RA or IBD condition, and medication categories for comparisons of incidence of HZ between the two groups. Individual level data will be collected through the EHR.

The analysis will comprise two RZV cohorts to address different study objectives ([Figure 1](#)). Each cohort will be constructed separately by RA and IBD conditions. The 2-dose RZV cohort will be used to address secondary VE objectives 1-5 and CCI. From the 2-dose cohort, a subset of those with 2 doses given 4 weeks to 6 months apart will be used to address primary VE objectives 1-2. The 1-dose RZV cohort will be used to address secondary VE objectives 6-7.

Approximately 1,900 RZV vaccinated individuals with RA and 1,400 RZV vaccinated individuals with IBD will be included in the full analysis of primary VE objectives. Individuals will be followed from the 31st day after the index date (the date of the second dose for the 2-dose cohort and the date of the first dose for the 1-dose cohort) until the end of study follow-up, occurrence of outcome of interest, or occurrence of a censoring event (death, termination of KPSC membership, or receipt of a dose of zoster vaccine), whichever comes first.

An early analysis in individuals ≥ 50 years of age and a full analysis in individuals ≥ 18 years of age are planned. The vaccine accrual period for the early analysis will occur from April 1, 2018 to December 31, 2021, with follow-up through December 31, 2022. The vaccine accrual period for the full analysis will occur from April 1, 2018 to August 31, 2023, with follow-up through August 31, 2024; however, the accrual for individuals ≥ 50 years of age may end earlier than August 2023 once the target sample size is met. Due to the coronavirus disease 2019 (COVID-19) pandemic, vaccinated individuals with an index date from March 1, 2020 through December 31, 2020 will not be included in the analysis. HZ outcomes will continue to be assessed during this period.

Figure 1 Construction of VE study cohorts

3.1.2 VE study population

Individuals will be eligible for the VE study cohort if the following inclusion and exclusion criteria are met. Two RZV cohorts will be constructed to address different study objectives. Each cohort including index date and follow-up period will be defined in [Section 3.1.2.1](#) and [Section 3.1.2.2](#).

Inclusion criteria:

- Age 18 years or older at the index date (Day 0)
- At least 1 year (365 days) continuous KPSC membership prior to index date and until 31 days after index date, allowing for a 31-day gap in membership
- Has RA or IBD (defined in the DMP) in the year prior to and including index date (Day -365 to Day 0, inclusive)

Exclusion criteria:

- HZ diagnosed in the 6 months prior (-183 days to -1 day, inclusive) to index date
- HZ diagnosed on or within 30 days (0 to 30 days, inclusive) after the index date
- Receipt of RZV vaccine within 30 days after index date (0 to 30 days, inclusive)
- Death during 30 days after index date (0 to 30 days, inclusive)
- Receipt of a second RZV dose less than 4 weeks after the first RZV dose

3.1.2.1 Two-dose RZV cohort

The 2-dose RZV cohort will include eligible individuals who receive 2 doses of RZV separated by at least 4 weeks by the end of the accrual period. The index date is the vaccination date of the second RZV dose.

RZV unvaccinated individuals who meet the inclusion/exclusion criteria and are unvaccinated on the index date will be randomly selected and up to 3:1 matched to the 2-dose RZV vaccinated individuals by age group (18-49 years, 50-59 years, 60-69 years, 70-79 years, and 80+ years), sex, condition (RA, IBD [UC, CD]) and medication category at index date. Further matching will be done on race/ethnicity (White, Black, Hispanic, Asian, and Other) if $\geq 95\%$ of vaccinated individuals can be matched to at least 1 unvaccinated individual. Age 18-49 years may be separated by decade of age (or by 20-year age) if 95% of exposed individuals can be matched to at least one unexposed individual. If matching by 20-year age group is not possible, then we will match by 18-49-year age group, but adjust for decade of age in regression analysis. Individuals with both RA and IBD will be included in both the RA group and the IBD group for matching. Matching for the RA group and the IBD group will be conducted separately. Vaccinated individuals with both UC and CD will be matched to unvaccinated individuals with both conditions if sufficient matches are found. Otherwise they will be matched to unvaccinated individuals with CD (which has a smaller sample size), and will be included only in the CD analysis. The index date for the 2-dose RZV unvaccinated match will be the same as his/her matched 2-dose RZV vaccinated counterpart. Flow charts with inclusion/exclusion criteria applied for the 2-dose RZV cohort with RA and the 2-dose RZV cohort with IBD will be provided. See Appendix A: Figure 1 and Figure 2.

Individuals will be followed from the 31st day after the index date until the end of study follow-up, occurrence of a censoring event (i.e., death, termination of KPSC membership, receipt of a dose of zoster vaccine among the RZV unvaccinated individuals), or occurrence of event of interest (for event-specific analyses), whichever comes first. Due to the nature of this real-world observational study, it is possible for a vaccinated individual to receive a third dose of RZV or receive another zoster vaccine during follow-up. Follow-up will end upon receipt of the third dose of RZV or receipt of another zoster vaccine if this is the case.

3.1.2.2 One-dose RZV cohort

The 1-dose RZV cohort will include eligible individuals who receive 1 dose of RZV but do not receive a 2nd dose within 6 months after the 1st dose during the vaccine accrual period. Such individuals may go on to receive a second RZV dose more than 6 months after the first RZV dose or no subsequent RZV doses by the end of the accrual period. The index date is the vaccination date of the first dose of RZV.

RZV unvaccinated individuals who meet the inclusion/exclusion criteria and are unvaccinated on the index date will be randomly selected and up to 3:1 matched to the 1-dose RZV vaccinated individuals using the same matching algorithm described in [Section 3.1.2.1](#). An unvaccinated individual is allowed to be matched to both a vaccinated individual in the 2-dose RZV cohort and a vaccinated individual in the 1-dose RZV cohort. The index date for the 1-dose RZV unvaccinated match will be the same as his/her matched 1-dose RZV vaccinated counterpart. Flow charts with inclusion/exclusion criteria applied for the 1-dose RZV cohort with RA and the 1-dose RZV cohort with IBD will be provided. See Appendix A: Figure 3 and Figure 4.

Individuals will be followed from the 31st day after the index date until the end of study follow-up, occurrence of a censoring event (i.e., death, termination of KPSC membership, receipt of a dose of zoster vaccine among the RZV unvaccinated individuals, receipt of second dose of RZV dose or receipt of another zoster vaccine among the RZV vaccinated individuals), or occurrence of event of interest (for event-specific analyses), whichever comes first. Unvaccinated individuals will stop contributing person-time upon their matched vaccinated individuals' receipt of the second RZV dose.

3.1.3 Exposures, outcomes, and covariates

3.1.3.1 Exposures

RZV vaccination will be received as part of routine clinical care. We will identify RZV exposure (CVX=187) from the EHR, which is available and accessible in real-time, providing the ability to view vaccine details and collect patient immunization history at the point of care. We are able to determine the dose sequence based on the vaccination dates.

- The exposure for primary VE objectives 1-2 is receipt of 2 doses of RZV, with the second dose received 4 weeks to 6 months (28 to 183 days, inclusive) after the first dose
- The exposure for secondary VE objectives 1-3, 5 and exploratory VE objectives 1-4 is receipt of 2 doses of RZV, with the second dose received ≥ 4 weeks (28 days) after the first dose
- The exposure for secondary VE objective 4 is receipt of 2 doses of RZV, with the second dose received > 6 months (183 days) after the first dose
- The exposure for secondary VE objectives 6-7 is receipt of 1 dose of RZV

3.1.3.2 Outcomes

The outcomes for specific VE objectives are listed below in [Table 1](#). The algorithms for identification of outcomes are described in the DMP and the Case Identification and Review (CIR) Plan. HZ, **CCI** will be identified by automated EHR search algorithms. **CCI**

Table 1 List of outcomes of interest for VE analyses

Outcome	Objectives	Cohorts	Chart Review
HZ	Primary VE objectives 1, 2 Secondary VE objectives 1, 2, 3, 4, 5, 6, 7 Exploratory VE objectives 1, 2	2-dose RZV cohort with RA 2-dose RZV cohort with IBD 1-dose RZV cohort with RA 1-dose RZV cohort with IBD	No chart review

CCI

All outcomes are dichotomous. Analyses of outcomes will be based on automated cases or chart confirmed cases if chart review is required.

3.1.3.3 Covariates

Covariates ([Table 2](#)) to be collected and explored include demographic variables, health care utilization, comorbidities, immunocompromised status, and other relevant baseline characteristics. The algorithms for identification of medication category, comorbidities, and immunocompromised status are described in the DMP. All covariates will be treated as categorical in the multivariable analyses to avoid bias due to outliers and non-linear effects.

Table 2 List of covariates for VE analyses

Demographics (matching variables)
Age at index date, years (18-49/50-59/60-69/70-79/80+)
Sex (Female/Male)
Race/Ethnicity (White/Black/Hispanic/Asian/Other)
Conditions and severity (matching variables)
Condition (RA, IBD [UC, CD, UC+CD])
Medication category (Category 1/2/3/4/5)
Health care utilization

Number of outpatient/virtual visits (0-4/5-10/11+)
Number of Emergency Department (ED) visits (0/1/2+)
Number of hospitalizations (0/1/2+)
Comorbidities
Kidney disease (Yes/No)
Heart disease (Yes/No)
Lung disease (Yes/No)
Liver disease (Yes/No)
Diabetes (Yes/No)
Other autoimmune diseases (Yes/No)
SARS-CoV-2 infection/COVID-19 diagnosis (Yes/No)
Immunocompromised
Immunocompromised status (Yes/No)
Vaccine
History of zoster vaccine live (ZVL) or varicella vaccination (No/Yes; Yes: ≤5 years, >5 years)
Concomitant vaccinations (Yes/No)
Other covariates
History of HZ (Yes/No)
Length of continuous membership prior to index date, years (0-5/6-10/11+)
Time between first and second RZV doses (4 weeks -6 months/>6 months)

The “Other” category of the race/ethnicity variable includes race/ethnicity other than White, Black, Hispanic, and Asian; multiple race; and unknown race/ethnicity. White/Black/Asian means non-Hispanic White, non-Hispanic Black, and non-Hispanic Asian, respectively.

Medication category will be assessed at the index date, as a surrogate of severity of RA or IBD condition.

Health care utilization will be defined as number of outpatient/virtual, ED, and inpatient visits in the one year (-1 to -356 days, inclusive) prior to the index date.

Baseline comorbidities will be defined in the one year prior to the index date.

Immunocompromised status will be assessed at the index date.

ZVL and varicella vaccination history will be ascertained using all available records of vaccination prior to the index date.

Concomitant vaccinations will be defined as receipt of vaccines such as influenza vaccine, pneumococcal vaccine, Tdap vaccine, or COVID-19 vaccine at the time (same date) of either the first or the second dose of RZV. Concomitant vaccinations only apply to vaccinated individuals.

History of HZ will be ascertained using all available diagnosis records prior to the index date. Since individuals with HZ 6 months prior to index date will be excluded, the actual lookback window for a history of HZ events is any time on or prior to -184 days from the index date.

Since history of ZVL/varicella vaccination and HZ will be ascertained using all available records prior to the index date, and since eligible individuals are required to only have one year of KPSC membership prior to the index date, we will also capture length of continuous membership prior to the index date as a covariate.

Time between first and second doses only applies to the 2-dose RZV cohort vaccinated individuals.

The covariates included in adjusted analyses will be determined by scientific relevance, association with exposure, and data availability. Specifically, we will select covariates by following these steps:

1. The distribution of covariates will be reviewed. Some categories of a categorical variable with small sample sizes will likely be redefined or combined into one category.
2. The association of baseline covariates with exposure will be assessed. We will use standardized difference to assess the balance of covariates between exposed and unexposed cohorts. Unlike p-values, for which magnitude is highly related to sample size, standardized difference is a unified approach to quantifying the magnitude of difference between groups regardless of sample size, where an absolute value less than 0.1 is considered a negligible difference [Austin, 2011]. We will use a SAS macro %stddiff developed by Yang and Dalton [Yang, 2012] to calculate the standardized differences for continuous and categorical variables. A categorical variable with multiple categories will be assessed and selected as one variable. Potential confounders will be determined by absolute standardized difference (ASD) >0.1.
3. All potential confounders (identified from step 2) will be included in the analyses. Step 1 and 2 will be repeated for each 2-dose RZV cohort with RA and IBD and for each 1-dose RZV cohort with RA and IBD. Immunocompromised status and history of HZ, which are considered important risk factors, will be kept in the adjusted model regardless of their association with exposure.

3.1.4 Sample size and power estimation

We computed the sample size needed to assess RZV effectiveness against HZ for the primary VE objectives. The calculation 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 hazard ratio (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 3](#) below presents the sample size required to detect various HRs of HZ between the vaccinated and unvaccinated cohorts with an average 3.5 years of follow-up (full analysis, ages ≥ 18 years) or 2.7 years of follow-up (early analysis, ages ≥ 50 years). It shows that in a cohort study with a 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, and 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.

We expect the 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 4/2018 to 8/2023 (full analysis, ages ≥ 18 years) to be 1843 and 1385, respectively, substantially exceeding the required numbers illustrated in [Table 3](#). This demonstrates that the study is sufficiently powered to assess the primary VE objectives.

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

Table 3 VE sample size required to achieve 80% power, given alpha=0.05, and different detectable HR (or VE)

Analysis	Incidence rate in RZV unvaccinated group (cases/1,000 person-years)	HR	VE (%)	Total sample size	Sample size of RZV vaccinated group
Full analysis Ages ≥ 18 years Average length of follow-up: 3.5 years	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

Early analysis Ages ≥ 50 years Average length of follow-up: 2.7 years	12	0.4	60	1696	424
		0.1	90	1388	347
		0.2	80	1832	458
		0.3	70	2492	623
	15	0.4	60	3528	882
		0.1	90	1108	277
		0.2	80	1464	366
		0.3	70	1996	499
	18	0.4	60	2824	706
		0.1	90	924	231
		0.2	80	1220	305
		0.3	70	1664	416
	20	0.4	60	2356	589
		0.1	90	832	208
		0.2	80	1100	275
		0.3	70	1496	374
		0.4	60	2120	530

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

3.2 Safety

3.2.1 Overview of safety study design

We will conduct a self-controlled case series (SCCS) analysis to assess the risk of flares following RZV vaccination. The study will be conducted among individuals aged ≥ 18 years with RA or IBD (UC and CD) who are members of KPSC and receive at least one dose of RZV. The observation time will be partitioned into a 30-day risk window right after each RZV dose, a 30-day pre-vaccination comparison window, and a 30-day post-vaccination comparison window. An individual could have multiple risk windows and comparison windows. Multiple flares per individual are allowed. The incidence of flare in the risk window will be compared with that in the comparison window.

An early analysis in individuals ≥ 50 years of age and a full analysis in individuals ≥ 18 years of age are planned. The vaccine accrual period for the early analysis will occur from April 1, 2018 to December 31, 2021. The vaccine accrual period for the full analysis will occur from April 1, 2018 to August 31, 2023; however, the accrual for individuals ≥ 50 years of age may end earlier than August 2023 once the target sample size is met. Due to the COVID-19 pandemic, vaccinated individuals with an index date from March 1, 2020 through December 31, 2020 will not be included in the study.

3.2.2 Safety study population

Individuals who received at least 1 dose of RZV will be eligible for the safety cohort if the following inclusion and exclusion criteria are met. The index date is the vaccination date of the first RZV dose.

Inclusion criteria:

- Received the first RZV dose during the accrual period
- Age ≥ 18 years at the index date (Day 0)
- Has 1-year continuous KPSC membership prior to and including index date (Day -365 to Day 0, inclusive), allowing for a 31-day gap in membership
- Has RA or IBD (defined in the DMP) in the year prior to and including index date (Day -365 to Day 0, inclusive)

Exclusion criteria:

- Receipt of a second RZV dose less than 4 weeks after the first RZV dose

Flow charts with inclusion/exclusion criteria applied for RZV recipients with RA and RZV recipients with IBD will be provided. See Appendix B: Figure 1 and Figure 2.

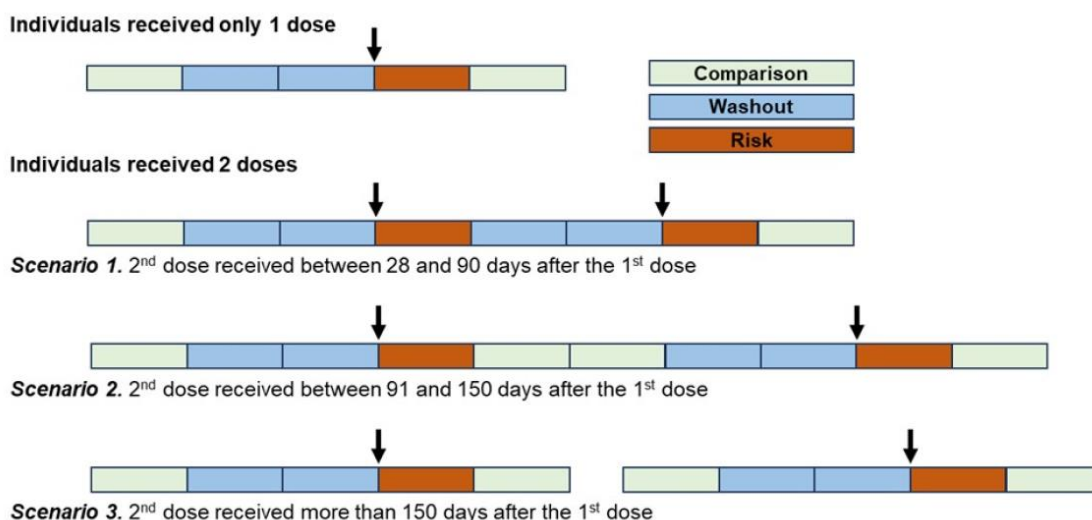
3.2.3 Exposures, outcomes, and other variables

3.2.3.1 Exposures

In the SCCS design, the observation time of a vaccinated individual is partitioned into risk (exposed) windows and comparison (unexposed) windows. The risk window is defined as the 30-day period right after each RZV dose. The comparison window is defined as two 30-day periods, one 90 to 61 days before the vaccination and one right after the risk window. We also build a washout window which is defined as the 60-day period prior to each RZV dose. Outcomes from the washout window will not be counted.

[Figure 2](#) illustrates the risk windows, comparison windows, and washout windows under different scenarios. For example, 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 window will be defined as +1 to +30 days, and comparison windows will be defined as -90 to -61 days and +31 to +60 days. For individuals receiving a second dose of RZV within 300 days of the first RZV dose, additional risk and comparison windows depend on the time interval between the two doses (Scenarios 1-3). The details of the algorithm are described in the DMP. Scenarios 1-3 in [Figure 2](#) represent the maximum time period between the first and second dose.

Figure 2 **SCCS design overview for safety analysis**



The risk and comparison windows will be censored at death, termination of KPSC membership (allowing for a 31-day gap in membership), or a third dose of RZV vaccination, whichever comes first.

3.2.3.2 Outcomes

The outcomes for specific safety objectives are listed below in [Table 4](#). The algorithms for identification RA flare and IBD flare are described in the DMP and the CIR Plan. Flare will be identified by targeted chart review. Flares will be counted in the window (risk or comparison) in which flare onset occurs. Outcomes in each window are counts. Multiple flares per individual is possible.

Table 4 List of outcomes of interest for safety analyses

Outcome	Objectives	Cohort	Chart Review
RA flare	Primary safety objective 1 Exploratory safety objective 1	RZV vaccinated cohort with RA	Chart review
IBD flare	Primary safety objective 2 Secondary safety objective 1 Exploratory safety objective 2	RZV vaccinated cohort with IBD	Chart review

3.2.3.3 Other variables

Other variables ([Table 5](#)) to be collected include demographic variables, conditions, medication category, and concomitant vaccinations for descriptive purposes. The algorithms for identification of medication category are described in the DMP. No covariates are planned for adjusted analysis, as 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.

Table 5 List of variables for safety analyses

Demographics
Age at index date, years (18-49/50-59/60-69/70-79/80+)
Sex (Female/Male)
Race/Ethnicity (White/Black/Hispanic/Asian/Other)
Conditions and severity
Condition (RA, IBD [UC, CD, UC+CD])
Medication category (Category 1/2/3/4/5)
Vaccine
Number of RZV doses (one dose/two doses)
Concomitant vaccinations (Yes/No)

3.2.4 Sample size and power estimation

The sample size calculation for the SCCS design is based on the signed root likelihood ratio method [Musonda, 2006]. Given a 30-day risk window and a total 60-day (pre + post) comparison window, the ratio (k) of the length of comparison window vs. length of risk window is 2. The number of flares that need to be observed in the risk window and comparison window to achieve 80% power is shown in Table 6 for different values of detectable RR. 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%.

The calculations are based on the first RZV dose only which gives the most conservative power estimation. 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 6 Sample size required 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

We expect the number of RA patients who will receive at least one dose of RZV during the accrual period between 4/2018 to 8/2023 (full analysis, ages ≥ 18 years) and between 4/2018 to 12/2021 (early analysis, ages ≥ 50 years) to be 3071 and 1832, respectively. With 3071 RA patients, there will be 154 flares in the 60-day 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 7](#)).

Table 7 Estimated flares and detectable RR for safety among RA patients who receive at least one dose of RZV

Sample size of RA cohort	RA flare rate (per 30 days) ¹	Number of flares in comparison window (60 days)	Detectable RR ²
3071 (Full analysis Ages ≥ 18 years)	1.5%	92	2
	2.5%	154	1.5
	3%	184	1.5
	3.5%	215	1.5
	5%	307	1.5
	7%	430	1.5
1832 (Early analysis Ages ≥ 50 years)	1.5%	55	2.0
	2.5%	92	2.0
	3%	110	2.0
	3.5%	128	1.5
	5%	183	1.5
	7%	256	1.5

RA = Rheumatoid arthritis; RR = Relative risk; RZV = Recombinant zoster vaccine

¹[[Bechman](#), 2018; [Bykerk](#), 2014; [Markusse](#), 2015; [Stevens](#), 2020].

²Compare with [Table 6](#).

We expect the number of IBD patients who will receive at least one dose of RZV during the accrual period between 4/2018 to 8/2023 (full analysis, ages ≥ 18 years) and between 4/2018 to 12/2021 (early analysis, ages ≥ 50 years) to be 2308 and 1267, respectively. With 2308 IBD patients, there will be 138 flares in the 60-day 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 $RR=1.5$ with 80% power and 5% type 1 error rate ([Table 8](#)).

Table 8 Estimated flares and detectable RR for safety among IBD patients who receive at least one dose of RZV

Sample size of IBD cohort	IBD flare rate (per 30 days) ¹	Number of flares in comparison window (60 days)	Detectable RR ²
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2308 (Full analysis Ages ≥18 years)	1%	46	2
	1.5%	69	2
	2%	92	2
	3%	138	1.5
	4%	185	1.5
1267 (Early analysis Ages ≥50 years)	1%	25	3.0
	1.5%	38	2.0
	2%	51	2.0
	3%	76	2.0
	4%	101	2.0

IBD = Inflammatory bowel disease; RR = Relative risk; RZV = Recombinant zoster vaccine

¹[[Bolge](#), 2010; [Satyam](#), 2020; [Rahier](#), 2011].

²Compare with [Table](#)

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

4 ANALYSES OF OBJECTIVES

4.1 VE

All analyses will be performed by statisticians at KPSC using the SAS statistical software package (version 9.4 or later).

4.1.1 Description of VE study population

Baseline characteristics of the 2-dose RZV cohort with RA will be described and compared between the vaccinated and unvaccinated groups. See Appendix A: Table Shell 1 for details. Bivariate analyses will be conducted for all covariates listed in [Section 3.1.3.3](#). Continuous covariates such as age in years will be summarized by mean, standard deviation, median, quartiles, and range, and compared using t-test or Wilcoxon rank-sum test, as appropriate; categorical covariates will be summarized by frequency and percentage and compared using chi-square test or Fisher's exact test, as appropriate. Absolute standardized difference will be calculated to assess the balance of covariates. Potential confounders will be determined based on bivariate analyses and scientific relevance (see [Section 3.1.3.3](#)).

Similar descriptive analyses will be conducted for the 2-dose RZV cohort with IBD. See Appendix A: Table Shell 2 for details.

Similar descriptive analyses will be conducted for the 1-dose RZV cohort with RA and with IBD. See Appendix A: Table Shells 3 and 4 for details.

Similar descriptive analyses will be conducted for individuals in the 2-dose RZV cohort with RA or IBD who receive the 2nd dose within 4 weeks to 6 months vs. >6 months after the first dose. See Appendix A: Table Shells 13 and 14 for details. No potential confounders will be determined from this descriptive analysis.

4.1.2 Analyses of primary VE objectives

Analyses will be conducted to address the primary VE objectives described in [Section 2.1.1](#)

4.1.2.1 Primary VE objective 1

The analysis will be conducted among the 2-dose RZV cohort with RA who receive the 2nd dose within 4 weeks to 6 months after the first dose. The incidence of HZ for the 2-dose (4 weeks to 6 months) RZV vaccinated cohort and matched unvaccinated cohort will be calculated by dividing the number of incident HZ cases by the total number of person-years. The person-years for an individual in the 2-dose (4 weeks to 6 months) RZV cohort will be the time from the 31st day after the index date to the date of event of interest, death, disenrollment, end of follow-up, or receipt of a dose of zoster vaccine, whichever comes first. The date of the incident HZ case is the diagnosis date of the first eligible HZ diagnosis after the index date.

Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) comparing HZ incidence rates in the 2-dose (4 weeks to 6 months) RZV vaccinated cohort and the matched unvaccinated cohort will be estimated by Cox stratified proportional hazards regression models without and with adjustment for potential confounders. The estimates can be obtained from the SAS Proc PHREG with stratification on the matched sets (`STRATA match_id`) [Cummings, 2004]. Death will be considered a competing risk. We will use cause-specific hazards models [Prentice, 1978; So, 2014] in which the competing events are treated as censored observations. Unadjusted VE and adjusted VE (%) will be calculated as $(1 - \text{HR}) \times 100$ when the HR is less than or equal to 1, and $([1/\text{HR}] - 1) \times 100$ when the hazard ratio is greater than 1. The results will be summarized in Appendix A: Table Shell 5.

4.1.2.2 Primary VE objective 2

The analysis will be conducted among the 2-dose (4 weeks to 6 months) RZV cohort with IBD. We will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, and unadjusted and adjusted VEs and 95% CIs for preventing HZ using methods similar to the analysis of primary VE objective 1. See Appendix A: Table Shell 6 for details.

4.1.3 Analyses of secondary VE objectives

Analyses will be conducted to address the secondary VE objectives described in [Section 2.1.2. For secondary and exploratory analyses, subgroups may be recategorized in post-hoc analyses if sample size in a subgroup is small.](#)

4.1.3.1 Secondary VE objective 1

The analysis will be conducted among the 2-dose (≥ 4 weeks) RZV cohort with IBD, separately by UC and CD conditions. We will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, and unadjusted and adjusted VEs and 95% CIs for preventing HZ for the 2-dose RZV cohort with UC and the 2-dose RZV cohort with CD separately using methods similar to the analysis of primary VE objective 1. Matched sets will be maintained in each UC or CD stratum. See Appendix A: Table Shell 6 for details. A matched set with both UC and CD conditions will be included in both the UC and CD analyses.

4.1.3.2 Secondary VE objective 2

The analysis will be conducted among the 2-dose (≥ 4 weeks) RZV cohort with RA, stratified by age at index date (18-49 years, 50+ years, 50-59 years, 60-69 years, and 70+ years). For each age stratum, we will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, and unadjusted and adjusted VEs and 95% CIs for preventing HZ using methods similar to the analysis of primary VE objective 1. Matched sets will be maintained in the analysis of each stratum. See Appendix A: Table Shell 5 for details.

4.1.3.3 Secondary VE objective 3

The analysis will be conducted among the 2-dose (≥ 4 weeks) RZV cohort with IBD, stratified by age at index date (18-49 years, 50+ years, 50-59 years, 60-69 years, and 70+ years). For each age stratum, we will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, and unadjusted and adjusted VEs and 95% CIs for preventing HZ using methods similar to the analysis of primary VE objective 1. Matched sets will be maintained in the analysis of each stratum. See Appendix A: Table Shell 6 for details.

4.1.3.4 Secondary VE objective 4

The analysis will be conducted among the 2-dose RZV cohort with RA or IBD who receive the 2nd dose >6 months after the first dose. For each RA or IBD cohort, we will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, and unadjusted and adjusted VEs and 95% CIs for preventing HZ using methods similar to the analysis of primary VE objective 1. See Appendix A: Table Shells 5 and 6 for details.

4.1.3.5 Secondary VE objective 5

The analysis will be conducted among the 2-dose (≥ 4 weeks) RZV cohort with RA or IBD. For each RA or IBD cohort, we will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, and unadjusted and adjusted VEs and 95% CIs for preventing HZ using methods similar to the analysis of primary VE objective 1. The incidence of HZ by follow-up year after vaccination (index date) will be calculated by dividing the number of incident HZ cases occurring within that year by the number of person-years of follow-up for individuals in that year. VE (%) by follow-up year after vaccination will be estimated as $(1 - \text{HR}) \times 100$, using data from the vaccinated and unvaccinated cohorts at risk for HZ at the start of each year following vaccination. Specifically, time-varying Cox regression models which model the risk of HZ by time interval of year will be used to estimate the unadjusted HRs and adjusted HRs and 95% CIs for each follow-up year. The results will be summarized in Appendix A: Table Shells 5 and 6. The VEs and 95% CIs by follow-up year will also be plotted as Appendix A: Figure 7 and 8.

For each RA or IBD cohort, the cumulative incidence of HZ will be estimated by the Kaplan–Meier method using SAS Proc LIFETEST. Vaccinated and unvaccinated cumulative incidence estimates will be plotted and the difference between two curves will be tested by the log-rank test. See Appendix A: Figure 5 and 6.

4.1.3.6 Secondary VE objective 6

The analysis will be conducted among the 1-dose RZV cohort with RA. We will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, unadjusted and adjusted VEs and 95% CIs for preventing HZ, HZ incidence by follow-up year, and HRs and VEs and 95% CIs by follow-up year using methods similar to the analysis of secondary VE objective 5. See Appendix A: Table Shell 7 for details.

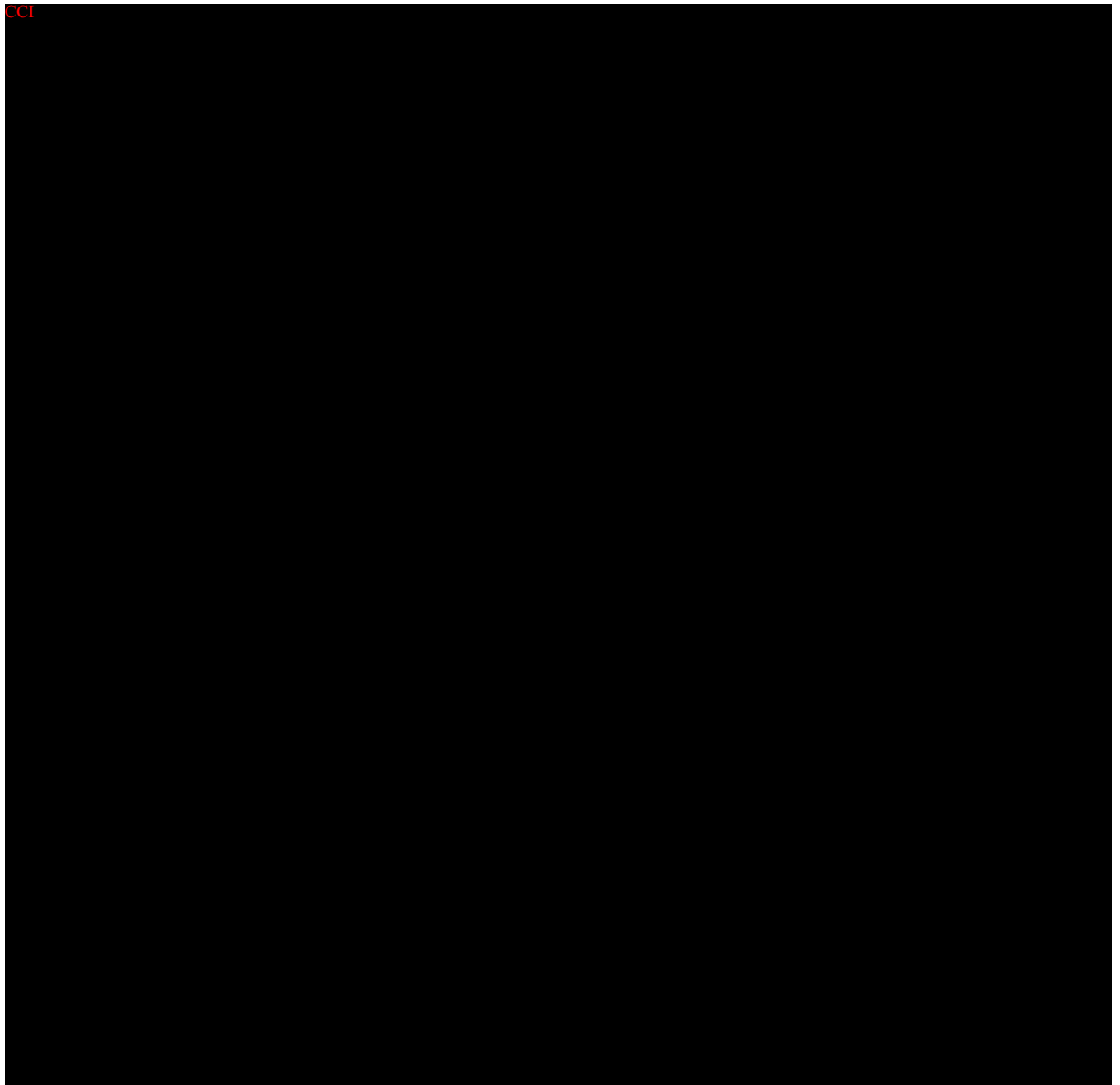
4.1.3.7 Secondary VE objective 7

The analysis will be conducted among the 1-dose RZV cohort with IBD. We will calculate HZ incidence, unadjusted and adjusted HRs and 95% CIs, unadjusted and adjusted VEs and 95% CIs for preventing HZ, HZ incidence by follow-up year, and HRs and VEs and 95% CIs by follow-up year using methods similar to the analysis of secondary VE objective 5. See Appendix A: Table Shell 8 for details.

4.1.4 Analysis of exploratory VE objectives

Analyses will be conducted to address the exploratory VE objectives described in [Section 2.1.3](#).

CCI



CCI

4.1.5 Sensitivity analysis

Sensitivity analysis will be conducted among the 2-dose RZV cohort with RA or IBD who receive the 2nd dose within 4 weeks to 6 months after the first dose. For each RA or IBD cohort, we will estimate the cumulative incidence of HZ by the Kaplan–Meier method similar to the analysis of secondary VE objective 5. See Appendix A: Figure 9 and Figure 10. We will also estimate incidence of HZ by follow-up year after vaccination (index date) using methods similar to the analysis of secondary VE objective 5. See Appendix A: Table Shell 15, Table Shell 16, Figure 11, and Figure 12.

4.2 Safety

All analyses will be performed by statisticians at KPSC using the SAS statistical software package (version 9.4 or later).

4.2.1 Description of safety study population

Baseline characteristics of RZV recipients with RA will be described. See Appendix B: Table Shell 1 for details. Analyses will be conducted for all variables listed in [Section 3.2.3.3](#). Continuous variables will be summarized by mean, standard deviation, median, quartiles, and range; categorical covariates will be summarized by frequency and percentage. We will also compare sex, race/ethnicity, and medication category between the 18-49 and 50+ age groups using chi-square test or Fisher's exact test, as appropriate. See Appendix B: Table Shell 5 for details.

Similar descriptive analyses will be conducted for RZV recipients with IBD. See Appendix B: Table Shell 2 for details. We will also compare sex, race/ethnicity, IBD condition, and medication category between the 18-49 and 50+ age groups using chi-square test or Fisher's exact test, as appropriate. See Appendix B: Table Shell 6 for details.

4.2.2 Analyses of primary safety objectives

Analyses will be conducted to address the primary safety objectives described in [Section 2.2.1](#).

4.2.2.1 Primary safety objective 1

Analysis will be conducted among RZV recipients with RA. We will report number of flares occurring during pre-specified risk and comparison windows. Incidence of flare will be calculated by dividing the number of flares by person-time. To describe the secular pattern, incidence of flare by day from Day -90 to Day 60 of Dose 1 and Dose 2 will be plotted. See Appendix B: Figures 3 and 4 for details. Relative risk (RR) and 95% CI will be estimated by comparing the incidence in the risk windows vs. the incidence in the comparison windows using conditional Poisson regression, accounting for person-time in each window. The first RZV dose and second RZV dose will be treated as repeat exposures with one risk level (assuming same risk for each exposure in the analyses) [Whitaker, 2006]. To estimate the risk of flare by first dose and second dose, we will assign two risk levels to risk windows after first dose and second dose (code risk window after first dose=1, risk window after second dose =2, and all comparison windows=0 as a categorical exposure variable). The conditional Poisson regression will be conducted using SAS macro poisreg.sas, which can be downloaded from SCCS method website (<http://stats-www.open.ac.uk/sccs/sas.htm>)

(%**poisreg**(data=InputData,y=flare,covar=int risk, offset=person_year, elim=studyid)). Only individuals with a flare occurring in a risk window or comparison window will be included. No covariates will be adjusted for in the analysis. The results will be summarized in Appendix B: Table Shell 3.

4.2.2.2 Primary safety objective 2

Analysis will be conducted among RZV recipients with IBD. We will calculate flare incidence, RR and 95% CIs overall and by first and second dose using methods similar to the analysis of primary safety objective 1. The results will be summarized in Appendix B: Table Shell 4, Figure 5 and Figure 6.

4.2.3 Analyses of secondary safety objectives

Analyses will be conducted to address the secondary safety objectives described in [Section 2.2.2](#). [For secondary and exploratory analyses, subgroups may be recategorized in post-hoc analyses if sample size in a subgroup is small.](#)

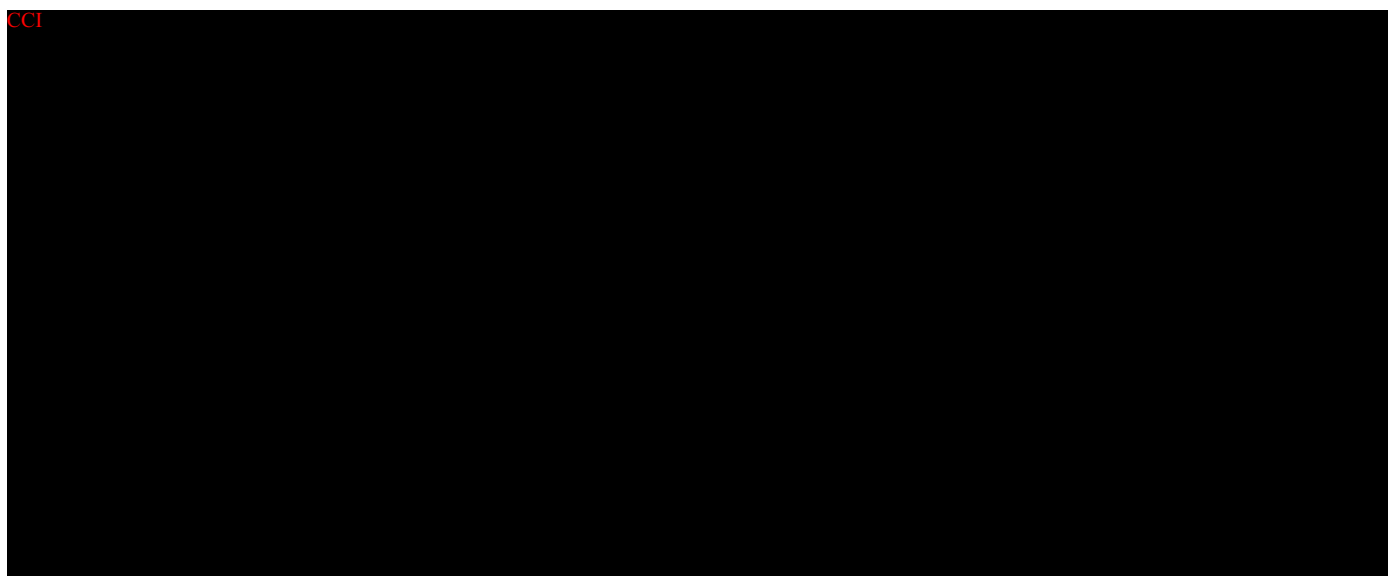
4.2.3.1 Secondary safety objective 1

The analysis will be conducted among RZV recipients with IBD, separately by UC and CD conditions. We will calculate flare incidence, RR and 95% CIs for RZV recipients with UC and RZV recipients with CD separately using methods similar to the analysis of primary safety objective 1. An individual with both UC and CD conditions will be included in both the UC and CD analysis. See Appendix B: Table Shell 4 for details.

4.2.4 Analysis of exploratory safety objectives

Analyses will be conducted to address the exploratory safety objectives described in [Section 2.2.3](#).

CCI



4.2.5 Signal investigation

If a primary analysis detects an elevated risk, i.e., the lower limit of $RR > 1$, further exploration of the data will be completed to investigate alternative potential sources for the RZV-flare association. Risk of flare by age, interval between doses, concomitant vaccination, and other vaccinations within 30 days prior to risk window and during the risk and comparison windows may be explored.

The KPSC team will work together with GSK team to conduct signal investigation, with consideration of timelines and data/resource availability.

5 STATISTICAL CONSIDERATIONS AND LIMITATIONS

5.1 Statistical considerations

5.1.1 SCCS method

The SCCS method was developed to investigate associations between acute outcomes and transient exposures. It has been widely used in vaccine safety studies [[Farrington, 1995](#); [Weldeselassie, 2011](#); [Tseng, 2017](#); [Hechter, 2019](#)]. By design, each individual serves as their own comparator. All time-fixed (or near time-fixed) confounding factors, known and unknown, are controlled for implicitly. 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. The SCCS method requires that the event should not affect the subsequent probability of vaccination. To avoid possible bias, we will exclude the 60-day pre-vaccination time (washout period) from the analysis. The method also requires that the events are recurrent and independent within individuals, and the observation periods are not event-dependent. Our study meets those assumptions.

5.1.2 Multiplicity considerations

Multiplicity refers to the potential inflation of the type I error rate as a result of multiple testing, in this study, specifically due to multiple subgroup comparisons, and multiple analyses of the same outcome at different times. Adjustment for multiple comparisons would reduce the false positives due to multiple comparisons, while possibly increasing the false negatives (e.g., missing the opportunity to detect potential safety findings) due to inadequate power, especially in analyses conducted in early years and in some subgroups with small sample size. Therefore, we will focus the inference of VE and safety of RZV on the full analysis of primary objectives. No formal adjustment for multiple comparisons is planned.

5.1.3 Handling of missing data

No imputation is planned for missing data in covariates. Unknown race/ethnicity is grouped into the “Other” category by convention, which can be matched between exposed and unexposed cohorts. If race/ethnicity is included in the adjusted model, “Other” will be a category for the covariate along with the other categories. History of ZVL/varicella vaccination and HZ will be ascertained using all available EHR records prior to the index date. If a member joined KPSC more recently, we may underestimate his/her ZVL/varicella vaccination and HZ history status. We will include a variable “length of continuous membership prior to index date” as a surrogate for completeness of historical medical information. Length of membership will be included in the adjusted model if it is determined to be a potential confounder. We do not expect missing values in other covariates and outcomes.

5.1.4 Loss to follow-up

For a long-term matched cohort study, loss to follow-up could break the matched sets and possibly cause imbalance on matching variables. We will use stratified proportional hazards models to analyze matched survival data. The HR will be estimated within matched sets where the values of matching variables are the same. Shinozaki et al. showed that the approach unbiasedly estimated a common HR under the proportional hazards within matched sets, which is less sensitive to censoring patterns ([Shinozaki, 2017](#)). For SCCS analysis, we assume that loss to follow-up is not associated with occurrence of the flare. The flare is unlikely to increase short-term mortality.

5.1.5 Impact of COVID-19

On March 4, 2020, the Governor of California declared a State of Emergency following the first official COVID-19 death in the state. On March 13, 2020, the US declared a national emergency, and on March 19, 2020, a stay-at-home order was enacted in California to slow the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As a consequence, vaccination, utilization, and enrollment of KPSC members could be affected by the COVID-19 pandemic. We observed a significant drop in adult vaccinations during the early pandemic period. We will exclude individuals who were vaccinated with index RZV dates during March 2020 to December 2020 to prevent potential selection bias. We observed a significant drop in the number of outpatient visits and an increase in the number of telephone and video encounters after March 2020. Therefore, we included virtual encounters in the HZ case identification algorithm, as described in the DMP. The impact of utilization pattern changes are expected to be similar for the RZV vaccinated and RZV unvaccinated groups. HZ outcomes will continue to be assessed during this period. By the end of 2021, we have not observed a decrease in KPSC member enrollment.

5.2 Limitations

5.2.1 Confounding by indication

Confounding by indication is a potential limitation. We will match vaccinated and unvaccinated individuals on the most important risk factors, i.e., condition (RA, UC, CD), age, sex, race/ethnicity (if sample size allows), and medication category. For the VE analyses, we will adjust for differences in demographic characteristics, health care utilization, and comorbidities, but differences in other unmeasured factors could result in residual confounding. By design, we will follow matched individuals over the same calendar time (index date) to minimize bias due to secular confounding. We will allow RZV unvaccinated individuals to become vaccinated at any time during follow-up to reduce confounding by indication. For the safety analyses, the SCCS design mitigates bias through implicit control for time-fixed confounders. While the short risk window minimizes changes in confounders during follow-up, our design of using pre- and post-vaccination comparison windows can also inherently control for potential time-varying confounders.

5.2.2 Misclassification of outcomes

Despite high validity of diagnostic algorithms, misclassification of HZ status could occur inherently in EHR studies using automated data, but this would only be a concern if misclassification was differential between exposure groups. It is unknown if HZ vaccination leads to modified or atypical HZ presentations that are more likely to be underdiagnosed or misdiagnosed. If these cases are never diagnosed or are diagnosed as other conditions, they will not be identified through ICD-10 codes for HZ. This could lead to a potential over-estimation of VE. It is also possible that there is differential misclassification of HZ due to differential health care seeking behaviors, but to address this, prior health care utilization is included as a covariate.

Given the complexity and potential for misclassification of the safety outcome of disease flare, medical record review using standardized criteria will be performed to ascertain this outcome. In general, there can be a delay between symptom onset and a medical encounter for flare. To avoid missing flare events due to delayed care-seeking, medical records within 30 days after each risk or comparison window will also be reviewed.

5.2.3 Delay of death data

Member death status will be identified by death records from KPSC hospitals and EDs, membership termination information, and outside claims. Deaths outside of KPSC will also be captured from the state death file and National Death Index (NDI). There is usually a 1- to 2-year delay in receiving and processing the state death and NDI files, so these resources will be utilized only if available. Since the study will only include active members during the follow-up period, additional deaths identified from the state death or NDI files beyond those identified through KPSC sources is expected to be small (< 5%).

6 QUALITY CONTROL

KPSC will follow the Department of Research and Evaluation's Analytical Research Project Standard Operating Procedures (SOP), including data extraction, data analysis, communication, and documentation. SAS programs used for the analysis will be reviewed by second statistician. Statistical analysis (results tables) will be discussed in the multisite meetings with GSK prior to study report finalization. KPSC will provide a quality control (QC) checklist of statistical analysis validation signed and dated by statisticians for early (individuals ages ≥ 50 years) and full (individuals ages ≥ 18 years) analyses. A template of the QC checklist is included in Appendix C.

6.1 Quality control steps

During the analysis, when analytic data are created and analyzed, the following quality control steps will be performed by the study statisticians as appropriate:

1. Read study protocol, DMP, CIR Plan, and SAP. Communicate with the principal investigator, senior statistician, and study team with any questions regarding study design and analysis plan. Document any decisions related to statistical analysis.
2. Check data quality (sample size, duplicates, range of values, number of missings, proper data type and format, inconsistency, etc.). Any aberrant data that have been missed by data cleaning and discovered by the statistician will be described in the results table.
3. Develop SAS programs for analysis. Programs will include a program header and section headers. The program header contains information on the purpose of the program, a list of prerequisite programs if applicable, a list of input datasets with full path, a list of output datasets, and a history log if applicable. Revision of the program will be noted in the history log to capture the change made, the change date, identification of the individual making the change, and type of change (e.g., modification, addition, removal). Each program might have several sections executing various analytic steps. Programs will be annotated with comments that describe the intent or purpose.
4. Perform statistical analysis. Use appropriate procedures and tests. SAS logs and outputs will be reviewed for any warnings, error messages, and model convergence issues. Organize the output into results tables. When possible, automate the generation of results tables to minimize the need to copy/paste. Proofread the results tables to prevent any copy/paste and editing errors. SAS logs and outputs will be saved.
5. Use established SAS macros. Use established SAS macros for analyses, including but not limited to the macro for creating baseline covariate tables and the macro for calculating standardized difference.

6.2 Program review

All SAS analysis programs, logs, and outputs will be reviewed by a second statistician. The second statistician will review the program logic against the analysis requirements. Comments from the second statistician will be documented and followed up until resolved.

6.3 Quality control findings

A record of quality problems and resolutions will be kept in the form of an Excel spreadsheet or other method appropriate to the circumstances (e.g., commented code, detailed correspondence).

6.4 Analysis deviation

Any analyses differing from the protocol, DMP, and pre-specified analyses in this SAP will be documented. The rationale for the change in approach will be provided.

7 STUDY REPORTS

7.1 Monthly vaccine uptake report

The monthly vaccine uptake report is described in the DMP. The report will be generated monthly during the accrual period.

7.2 Early analysis (individuals ≥ 50 years) report

The effectiveness and safety of RZV in individuals ages ≥ 50 years with RA or IBD (UC or CD) at KPSC will be examined. The vaccine accrual period for the early analysis will occur from April 1, 2018 to December 31, 2021. The cohorts for VE analysis will be followed through December 31, 2022. All objectives will be included in the early analysis report. The report will be available to GSK during the first half of 2024.

7.3 Full analysis (individuals ≥ 18 years) report

The effectiveness and safety of RZV in individuals ages ≥ 18 years with RA or IBD (UC or CD) at KPSC will be examined. The vaccine accrual period for the full analysis will occur from April 1, 2018 to August 31, 2023; however, the accrual for individuals ≥ 50 years of age may end earlier than August 2023 once the target sample size is met. The cohorts for VE analysis will be followed through August 31, 2024. All objectives will be included in the full analysis report. The report will be available to GSK at the end of the study (late 2025).

8 LIST OF REPORT TABLES

Appendix A	Description	Report
Table 1	Baseline characteristics of 2-dose RZV vaccinated and unvaccinated cohort with RA	Early, Full
Table 2	Baseline characteristics of 2-dose RZV vaccinated and unvaccinated cohort with IBD	Early, Full
Table 3	Baseline characteristics of 1-dose RZV vaccinated and unvaccinated cohort with RA	Early, Full
Table 4	Baseline characteristics of 1-dose RZV vaccinated and unvaccinated cohort with IBD	Early, Full
Table 5	Incidence rate, hazard ratio, and VE of 2 doses of RZV in preventing HZ among individuals with RA	Early, Full
Table 6	Incidence rate, hazard ratio, and VE of 2 doses of RZV in preventing HZ among individuals with IBD	Early, Full
Table 7	Incidence rate, hazard ratio, and VE of 1 dose of RZV in preventing HZ among individuals with RA	Early, Full
Table 8	Incidence rate, hazard ratio, and VE of 1 dose of RZV in preventing HZ among individuals with IBD	Early, Full
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Table 13	Baseline characteristics of 2-dose RZV vaccinated cohort with RA, 2nd dose administered within 4 weeks to 6 months vs. >6 months after the first dose	Early, Full
Table 14	Baseline characteristics of 2-dose RZV vaccinated cohort with IBD, 2nd dose administered within 4 weeks to 6 months vs. >6 months after the first dose	Early, Full
Table 15	Incidence rate, hazard ratio, and VE of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with RA	Early, Full
Table 16	Incidence rate, hazard ratio, and VE of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with IBD	Early, Full
Figure 1	Flow chart for 2-dose RZV cohort with RA	Early, Full
Figure 2	Flow chart for 2-dose RZV cohort with IBD	Early, Full

Figure 3	Flow chart for 1-dose RZV cohort with RA	Early, Full
Figure 4	Flow chart for 1-dose RZV cohort with IBD	Early, Full
Figure 5	Cumulative incidence estimates of HZ by RZV vaccination status in 2-dose RZV cohort with RA	Early, Full
Figure 6	Cumulative incidence estimates of HZ by RZV vaccination status in 2-dose RZV cohort with IBD	Early, Full
Figure 7	Effectiveness of 2 doses of RZV in preventing HZ by year after vaccination among individuals with RA	Early, Full
Figure 8	Effectiveness of 2 doses of RZV in preventing HZ by year after vaccination among individuals with IBD	Early, Full
Figure 9	Cumulative incidence estimates of HZ by RZV vaccination status in 2-dose RZV cohort (4 weeks - 6 months) with RA	Early, Full
Figure 10	Cumulative incidence estimates of HZ by RZV vaccination status in 2-dose RZV cohort (4 weeks - 6 months) with IBD	Early, Full
Figure 11	Effectiveness of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with RA	Early, Full
Figure 12	Effectiveness of 2 doses of RZV (4 weeks - 6 months) in preventing HZ by year after vaccination among individuals with IBD	Early, Full
Appendix B	Description	Report
Table 1	Baseline characteristics of RZV recipients with RA	Early, Full
Table 2	Baseline characteristics of RZV recipients with IBD	Early, Full
Table 3	Incidence and relative risk of RA flare after RZV among individuals with RA	Early, Full
Table 4	Incidence and relative risk of IBD flare after RZV among individuals with IBD	Early, Full
Table 5	Baseline characteristics of RZV recipients with RA by age groups	Full
Table 6	Baseline characteristics of RZV recipients with IBD by age groups	Full
Figure 1	Flow chart for RZV recipients with RA	Early, Full
Figure 2	Flow chart for RZV recipients with IBD	Early, Full
Figure 3	Incidence of flare by day during the risk and comparison windows of first dose among RZV recipients with RA	Early, Full
Figure 4	Incidence of flare by day during the risk and comparison windows of second dose among RZV recipients with RA	Early, Full
Figure 5	Incidence of flare by day during the risk and comparison windows of first dose among RZV recipients with IBD	Early, Full
Figure 6	Incidence of flare by day during the risk and comparison windows of second dose among RZV recipients with IBD	Early, Full

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10 APPENDICES

Appendix A: Table shells for VE analyses

Appendix B: Table shells for safety analyses

Appendix C: Quality control checklist