NON-INTERVENTIONAL STUDY REPORT

TITLE PAGE

Division: Research and Development

Information Type: Non-Interventional Study Report

Title:	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of Shingrix in adults ≥65 years of age in the United States.
Compound Number:	GSK1437173A
Effective Date:	02 Jul 2026
Subject:	*Shingrix* (RZV), PASS, TSS, Safety, New onset GBS, New onset gout, New onset SVT, SCRI design, New onset PMR, Medicare, New onset GCA, New onset ION, cohort study
Authors:	University of Maryland Baltimore Lead/Contributing Authors: • PPD (Principal Investigator/Lead author) • PPD • PPD • PPD GSK Contributing Authors: • PPD • PPD • PPD • PPD • PPD • PPD
Indication Studied:	Prevention of herpes zoster (HZ) (shingles) in adults aged 50 years and older

STUDY INFORMATION

Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of Shingrix in adults ≥65 years of age in the United States
Report version identifier	Version 1.0
Date of last version of report	02 Jul 2026
EU PAS (ENCEPP) register number	EUPAS37133
Active substance	VZV glycoprotein E (gE)
Medicinal product	Shingrix (Recombinant Zoster Vaccine, RZV)
Product reference	**EMA**: EU/1/18/1272/001, EU/1/18/1272/002 **FDA**: IND number 13857
Procedure number	EMEA/H/C/004336/MEA/020.1
Marketing authorization holder(s)	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	The EPI-ZOSTER-032 addresses the question of whether RZV is associated with the risk of new onset GBS, gout, PMR, GCA, SVT, or ION within specified time periods after vaccination in people aged 65 years and older enrolled in Medicare who were vaccinated in 2018 through 2020. The primary objectives of the EPI-ZOSTER-032 study are to estimate the risk of new onset: • GBS within 42 days, • Gout within 30 days, • PMR within 183 days, and • GCA within 183 days following vaccination with RZV.

	The secondary objectives are to estimate the risk of new onset: • SVT within 30 days and • ION within 183 days following vaccination with RZV.
Country of study	United States
Author	PPD PhD Principal Investigator University of Maryland, Baltimore Baltimore, Maryland 21201

MARKETING AUTHORISATION HOLDER(S)

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STUDY DETAILS

UNIQUE IDENTIFIER	CTMS: 209696
TITLE	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of Shingrix in adults ≥65 years of age in the United States
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ASSET ID	Zoster (GSK1437173A)
GSK ASSET	Recombinant Zoster Vaccine (*Shingrix*)
EFFECTIVE DATE	02 Jul 2026
INDICATION	Prevention of herpes zoster (HZ) (shingles) in adults aged 50 years and older

REPORT REVISION HISTORY

Date	Version	Change(s) since last version
02 Jul 2026	Original	N/A

SPONSOR SIGNATORY

Title: A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of Shingrix in adults ≥65 years of age in the United States

Compound Number: Zoster (GSK1437173A)

O'Mareen Spence, PhD Primary Author/NI Scientific Lead	Date (DD Month YYYY)
Huifeng Yun, MD, PhD 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:

Susan dosReis, PhD

_____

Investigator Signature Date (DD Month YYYY)

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LIST OF ABBREVIATIONS

ACIP	Advisory committee on immunization practices
AD	Alzheimer's disease
AE	Adverse event
AIC	Akaike Information Criterion
AR	Attributable Risk
CABG	Coronary artery bypass grafting
CCW	Chronic condition warehouse
CDC	Centers for Disease Control and Prevention
CHF	Congestive heart failure
CI	Confidence interval
CITI	Collaborative Institutional Training Initiative
CKD	Chronic kidney disease
CLD	Chronic lung disease
CMS	Centers for Medicaid and Medicare Services
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease-2019
CPT	Current procedural terminology
CW	Control Window
DM	Diabetes Mellitus
DME	Durable medical equipment
DMP	Data management plan
DUA	Data use agreement

ED	Emergency department
EMA	European Medicines Agency
ESRD	End-stage renal disease
EU	European Union
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GCA	Giant cell arteritis
GSK	GlaxoSmithKline Biologicals S.A.
HCPCS	Healthcare Common Procedure Coding System
HCUP	Healthcare Cost and Utilization Project
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HOI	Health outcome of interest
HR	Hazard ratio
HZ	Herpes zoster
ICD-10	International classification of diseases-10
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IHD	Ischemic heart disease
ION	Ischemic optic neuropathy
IPTW	Inverse probability of treatment weighting
IR	Incidence rate
IRB	Institutional review board
LLR	Log-Likelihood Ratio
MAH	Marketing Authorisation Holder

MBSF	Master beneficiary summary file
MS	Multiple sclerosis
MS-DRG	Medicare Severity Diagnosis Related Group
NDC	National drug code
NIST	National Institute of Standards and Technology
OASIS	Old Age and Survivor's Insurance
PAES	Post-Authorization Efficacy Studies
PASS	Post-authorization safety study
PDE	Prescription drug event
PH	Proportional hazards
PHN	Post-herpetic neuralgia
PI	Principal Investigator
pIMD	Potential immune-mediated disorders
PMR	Polymyalgia rheumatica
PPV	Positive Predictive Value
PRC	Pharmaceutical research computing
PS	Propensity score
P-SHOR	Practice, sciences, and health outcomes research
PY	Person-year
RA	Rheumatoid arthritis
RR	Relative risk
RW	Risk Window
RZV	Recombinant zoster vaccine
SAE	Serious adverse event
SAP	Statistical analysis plan

SAR	Statistical analysis report
SAS	Statistical analysis system
SCRI	Self-Controlled Risk Interval
SD	Standard deviation
SMD	Standardized mean differences
SNF	Skilled nursing facility
SVT	Supraventricular tachycardia
TIA	Transient ischemic attack
Tdap	Tetanus, diphtheria, and pertussis
TSS	Targeted safety study
UMB	University of Maryland Baltimore
US	United States
VZV	Varicella zoster virus
ZVL	Zoster vaccine live

TRADEMARK INFORMATION

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NCSS Statistical Software®

1. RESPONSIBLE PARTIES

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2. SYNOPSIS

Title

A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of Shingrix in adults ≥65 years of age in the United States

Keywords

SHINGRIX (RZV), TSS/PASS older adults, US.

Rationale and background

SHINGRIX, or Recombinant zoster vaccine (RZV), is a subunit, adjuvanted vaccine first approved by the US (United States) FDA (Food and Drug Administration) in October 2017 and by the European Medicines Agency (EMA) in March 2018 for the prevention of Herpes zoster (HZ) in adults ≥50 years of age. Advisory committee on immunization practices (ACIP) recommends RZV vaccination for the prevention of HZ in immunocompetent adults ≥50 years of age. In prelicensure clinical trials, which are not designed to assess rare outcomes, numerical differences between the RZV and placebo groups were noted for certain conditions, including Polymyalgia rheumatica (PMR), Giant cell arteritis (GCA), gout, Ischemic optic neuropathy (ION), and Supraventricular tachycardia (SVT). With respect to reports of Guillain-Barré syndrome (GBS), the Centers for Disease Control and Prevention (CDC) detected a statistical signal for GBS during post licensure safety surveillance of RZV using the Vaccine Safety Datalink. Robust data on the risk of these outcomes following the administration of RZV are currently lacking. Furthermore, data on the use of RZV in complex patient populations are critical in assessing the safety of the vaccine in the real-world setting. The EPI-ZOSTER-032 study was designed to use the Centers for Medicaid and Medicare Services (CMS) Medicare data in the US to evaluate the safety of RZV focusing on the specific outcomes listed above.

Research questions and objectives

The EPI-ZOSTER-032 study addresses the question of whether RZV is associated with the risk of new onset GBS, gout, PMR, GCA, SVT, and ION within specified time periods after RZV vaccination in people ≥65 years of age enrolled in Medicare who were vaccinated in 2018 through 2020.

The primary objectives were to estimate the risk of new onset:

- GBS within 42 days,
- Gout within 30 days,
- PMR within 183 days and,
- GCA within 183 days following vaccination with RZV.

The secondary objectives were to estimate the risk of new onset:

- SVT within 30 days and,

- ION within 183 days following vaccination with RZV.

Study design

Self-Controlled Risk Interval (SCRI)

The SCRI was a case-only design where the analytic cohort experienced the Health outcome of interest (HOI) in the risk or control window, and participants served as their own controls. The risk of new onset of GBS, gout, and SVT was assessed using a SCRI study design. For GBS, Days 1 to 42 following RZV vaccination defined the risk window, and Days 43 to 84 defined the control window, while for gout and SVT, Days 1 to 30 following RZV vaccination defined the risk window and Days 31 to 60 defined the control window. The date of RZV was Day 0 and was not included in the risk window.

Cohort

The cohort design included RZV-exposed and an RZV-unvaccinated comparator who had a preventive care visit but no prior RZV exposure up to this point. A cohort design was implemented to assess the risk of new onset PMR, GCA and ION within 183 days following RZV vaccination compared to an RZV-unvaccinated cohort who had a preventive care visit. The date of RZV or the preventative care visit was Day 0 and was not included in the follow-up period.

Setting

The study population was a nationally representative sample of US Medicare beneficiaries ≥65 years of age, who were enrolled in Medicare fee-for-service Parts A, B, and D and who did not qualify for Medicare due to a disability.

Subjects and study size

Sample size and power were estimated for the primary outcomes as per protocol. An 80% statistical power under a two-sided type I error of 0.05 was used for power and sample size estimations.

SCRI

- Gout: To detect the risk of gout, at least 68 gout cases were needed to reject the null hypothesis of no association for a Relative risk (RR) ≥2.0 with 80% power. A total of 1290 gout cases were included in the analytical cohort, demonstrating that the study achieved the target sample.
- GBS: To detect a RR ≥4.0 with 80% power, at least 20 GBS cases were needed to reject the null hypothesis of no association. A total of 75 GBS cases were included in the analytical cohort, demonstrating that the study achieved that target sample.
- SVT: Sample size and power were not estimated for the secondary outcome of SVT. However, the analytical cohort included 4964 SVT cases.

Cohort

- PMR: It was estimated that a total cohort of 438 239 participants was needed to detect a RR ≥2.0 for PMR. The analytical cohort for PMR included 3 265 790 RZV vaccinated participants and 2 569 783 unvaccinated comparators, demonstrating that the target sample was met.
- GCA: A total of 723 362 participants was needed to detect a RR ≥3.0 for GCA. This sample size target was met, as the analytical cohort for GCA included 3 288 846 RZV-exposed and 2 585 975 RZV-unvaccinated comparators.
- ION: Power and sample size were not estimated for the secondary outcome of ION. However, the RZV-exposed analytic cohort was comprised of 3 289 741 participants, and the RZV-unvaccinated comparator analytic cohort was comprised of 2 587 018 participants.

Variables and data sources

Data source:

The study leveraged the CMS Chronic condition warehouse (CCW) Medicare data. These data include separate files for inpatient, outpatient, physician, and prescription claims and capture all healthcare encounters and prescription medications provided for adults ≥65 years of age enrolled in Medicare fee-for-service Parts A, B, and D.

Exposure

For both the cohort and the SCRI designs, the exposure is the receipt of at least one dose of RZV from January 2018 through December 2020.

For the cohort design, the RZV-unvaccinated comparators had to have at least one preventive care visit from January 2018 through December 2020.

Outcomes

For primary outcomes, the dependent variables were:

- new onset GBS in the risk or control windows, with no evidence of GBS in the 365 days from the GBS case date
- new onset gout in the risk or control windows, with no evidence of gout in the 365 days from the gout case date
- new onset PMR within Days 1 to 183 following RZV vaccination
- new onset GCA within Days 1 to 183 following RZV vaccination.

For the secondary outcomes, the dependent variables were:

- new onset SVT in the risk or control windows, with no evidence of SVT in the 365 days from the SVT case date
- new onset ION within Days 1 to 183 following RZV vaccination.

Baseline characteristics and analysis

In the SCRI design, baseline covariates for descriptive purposes were measured in the 365 days preceding RZV Dose 1. Covariates included age, sex, race, region of the US, calendar year-month of vaccination, number of doses, concomitant vaccination with other preventive immunizations, medical comorbidities, and healthcare service utilization.

Descriptive measures were reported for the overall cohort and stratified by number of doses received; i.e., only Dose 1 or both Dose 1 and 2. Separate conditional Poisson regression models estimated the risk of new onset of each HOI, i.e., GBS, gout, and SVT. Primary and secondary analyses estimated the risk without distinguishing between doses. A dose-compliant sensitivity analysis was conducted in a subgroup who received both doses with a 60 to 183-day spacing between doses. Two sensitivity analyses estimated the dose-specific risk, and a sensitivity analysis adjusted for the potential impact of the COVID-19 pandemic. An additional sensitivity analysis adjusted for seasonality of primary objectives gout and GBS. A temporal scan tested for significant clustering of events.

In the cohort design, baseline covariates measured in the 365 days preceding RZV Dose 1 and Dose 2 were used for descriptive purposes and to adjust for potential confounding. Baseline covariates included age, sex, race, region of the US, calendar year-month of vaccination, number of doses, concomitant vaccination with other preventive immunizations, medical comorbidities, and healthcare service utilization.

Descriptive measures characterized the cohort by RZV-exposed and RZV-unvaccinated comparators. Cumulative incidence was analyzed by exposure status for each HOI. Cox proportional hazards models weighted with stabilized Inverse probability of treatment weighting (IPTW) generated the HR with 95% CI. Primary analyses, separated by dose, estimated the risk of new onset for each HOI for RZV-exposed relative to RZV-unvaccinated comparators. Secondary analyses included a 1) combined dose single risk estimate and 2) separate risk estimate for Dose 1 and Dose 2 using a time-varying Cox proportional hazards regression model. A sensitivity analysis of the primary analysis to address potential bias following the COVID-19 pandemic, follow-up was censored on 01 February 2020. For each HOI, supplemental analyses estimated the risk of new onset, excluding participants from the RZV-unvaccinated comparator who subsequently received RZV, and only included these participants in the RZV-exposed group.

Results

GBS

Of 3 383 799 participants ≥65 years of age who were continuously enrolled in Medicare Parts A, B, and D, did not qualify for Medicare due to a disability, and had received at least one RZV dose in 2018 to 2020, we identified 75 new onset GBS cases. Most cases

(n=57; 76.00%) occurred after Dose 1. Adults diagnosed with GBS were, on average, 75.37 (standard deviation [SD]: ±6.98) years-old, 49.33% were male, and 92.00% were White. Common medical conditions recorded in the year prior to RZV Dose 1 were ischemic heart disease (26.67%), diabetes mellitus (21.33%), chronic kidney disease (20.00%), and chronic lung disease (16.00%). Just over one-quarter (26.67%) had one or more ED visits in the 365 days preceding RZV Dose 1.

Among the 75 cases, the distribution of RZV Dose 1 by calendar year was as follows: 23 in 2018, 33 in 2019, and 19 in 2020. A total of 57 cases were identified in the risk window from Days 1 to 42 and 18 cases were detected in the control window from Days 43 to 84.

In the primary analysis that did not distinguish between doses was statistically significant and the RR of new onset GBS was 3.15 (95% Confidence interval [CI]: 1.82, 5.68) and the AR was 6.59 per 1 000 000 vaccine doses (95% CI: 4.35, 7.96). The secondary analyses with three-week and six-week fixed control window lengths revealed statistically significant increased risks of 3.56 (95% CI: 1.69, 8.65) and 3.17 (95% CI: 1.84, 5.72), respectively. The dose-compliant 60 to 183-day dose spacing sensitivity analysis with 20 cases was not statistically significant (RR = 1.46; 95% CI: 0.55, 4.13). Dose 1 specific sensitivity analysis showed a significantly elevated risk of 5.33 (95% CI: 2.59, 12.36). The Dose 2 specific sensitivity analysis was not statistically significant. The sensitivity analysis adjusting for GBS seasonality was statistically significant, producing results similar to the primary analysis. The COVID-19 sensitivity analysis was also statistically significant with a risk estimate similar to Dose 1 specific analysis.

Gout

Of 3 383 799 participants ≥65 years of age who were continuously enrolled in Medicare Parts A, B, and D, did not qualify for Medicare due to a disability, and received at least one RZV dose in 2018 to 2020, we identified 1290 new onset gout cases. Most of the gout cases were White (86.98%), male (61.16%), and 70 to 79 years of age (55.82%). Chronic kidney disease (41.16%), diabetes mellitus (36.67%), ischemic heart disease (33.57%), congestive heart failure (19.15%), and chronic lung disease (17.13%) were the most common chronic conditions among the 1290 gout cases. Most of the gout cases (n=1061; 82.25%) received two doses of RZV, and 229 (17.75%) received only one dose. Of the 1061 participants who received two RZV doses, 1012 (95.38%) received Dose 2 more than 60 days after receipt of Dose 1. Participants with 28 to 60 days between doses were on average three years older than adults with >60 days between doses. Female participants represented about half of the subgroup with 28 to 60-day dose spacing compared with 38.44% of the subgroup with >60 days between doses. A total of 764 gout cases occurred after Dose 1, and 526 gout cases occurred after Dose 2.

In the primary analysis, the RR of new onset gout was not statistically significant (RR=1.00; 95% CI: 0.90, 1.12). The secondary analysis, which used a fixed 30-day control window, produced the same results as the primary analysis. For the dose-compliant sensitivity analysis, 959 (74.34%) of the 1290 gout cases had 60 to183 days between doses, and a RR=0.99 (95% CI: 0.87, 1.13) of new onset gout. For the dose-specific sensitivity analyses with a fixed 30-day control window, RR=1.02

(95% CI: 0.88, 1.18) for Dose 1 and RR=0.98 (95% CI: 0.82, 1.16) for Dose 2. The seasonality adjusted analysis produced similar results as in the primary analysis (RR = 1.00; 95% CI: 0. 90, 1.12). The findings were robust to the COVID-19 sensitivity analysis (RR = 1.00; 95% CI: 0.89, 1.12). The temporal scan did not detect significant temporal clustering of cases over the 60-day follow-up.

SVT

Of 3 383 799 participants ≥65 years of age who were continuously enrolled in Medicare Parts A, B, and D, did not qualify for Medicare due to a disability, and received at least one RZV dose in 2018 to 2020, we identified 4964 SVT cases. There were 2713 (54.65%) cases after Dose 1 and 2251 (45.35%) cases after Dose 2. Adults diagnosed with SVT were, on average, 76.13 (SD: 6.71) years-old, 41.94% were male and 91.84% were White, 1.91% were Black, and 1.71% were Asian. Common medical conditions recorded in the year prior to RZV Dose 1 were ischemic heart disease (32.09%), chronic kidney disease (25.18%), diabetes mellitus (25.10%), chronic liver disease (19.02%), congestive heart failure (15.15%), and stroke/transient ischemic attack (10.03%). Just over one-quarter (28.14%) had one or more ED visits in the 365-days preceding RZV Dose 1.

The distribution of RZV Dose 1 by calendar year for the 4964 cases was as follows: 1369 in 2018, 2318 in 2019, and 1277 in 2020. The day of the SVT case occurrence was evenly distributed in the risk and control windows after RZV exposure.

The primary analysis that did not distinguish between doses produced a RR=0.94 (95% CI: 0.89, 0.99). The secondary analysis with a 30-day fixed control window generated the same risk estimate. The 60 to 183-day dose-compliant subgroup, COVID19-adjusted, and Dose 2 specific sensitivity analyses were not statistically significant (RR=0.98, 95% CI:0.92, 1.04; RR=0.94, 95% CI: 0.87,1.01; RR=0.99, 95% CI: 0.92,1.08, respectively). The Dose 1 sensitivity analysis had an RR=0.90 (95% CI: 0.83, 0.97).

PMR

The cohort of 3 265 790 RZV-exposed individuals was predominantly White (88.93%), female (58.86%), and had a mean age of 74.33 years. PMR incidence per 10 000 person-years (PY) was 12.73 and 10.72 for RZV Dose 1 exposed and the 2 569 783 RZV-unvaccinated comparators, respectively, and 10.69 and 10.92 among the 2 489 075 RZV Dose 2 recipients and the RZV-unvaccinated comparators, respectively. The primary analysis for Dose 1 used an IPTW-stabilized weighted Cox proportional hazards regression with a time-dependent coefficient in a piecewise model to account for the violation of the proportional hazards assumption. The results did not show a statistically significant risk of PMR from Day 1 to 120 following Dose 1 (HR=1.00; 95% CI: 0.92, 1.09). After Day 120, there was a statistically significant increased risk of PMR following Dose 1: HR=2.05 (95% CI: 1.71, 2.46). Results from the COVID-19 sensitivity analysis for Dose 1, corrected for the non-proportionality of the hazard over time using a piecewise regression model, showed a significantly increased risk of PMR after Day 120 following RZV, but a non-significant risk before Day 120. This was consistent with the primary analysis of Dose 1.

GCA

The cohort of 3 288 846 RZV-exposed individuals was predominantly White (88.97%), female (58.87%), and had a mean age of 74.36 years. GCA incidence per 10 000 PY in the RZV Dose 1 and the 2 585 975 RZV-unvaccinated comparators was 3.27 and 2.86, respectively. The incidence per 10 000 PY in the 2 508 442 RZV Dose 2 and the RZV-unvaccinated comparators was 3.09 and 2.98, respectively. The primary analysis for Dose 1 used an IPTW stabilized weighted Cox proportional hazards regression, with a time-dependent coefficient in a piecewise model to account for violation of the proportional hazards assumption. The results did not reveal a statistically significant increased risk of GCA from Day 1 to 150 following RZV Dose 1 (HR=1.10; 95% CI: 0.94, 1.28) or after Day 150 (HR=1.34; 95% CI: 0.89, 2.01). Results from the Dose 2 primary analysis using an IPTW stabilized weighted Cox proportional hazards regression did not show an increased risk of GCA. The Dose 2 primary analysis did not violate the proportional hazards assumption. The secondary analysis of a combined dose indicated an increased risk of GCA (HR=1.18; 95% CI: 1.03, 1.34). The secondary analysis with a time-varying exposure using an IPTW-weighted Cox proportional hazards regression showed increased risk of GCA after Dose 1 (HR=1.23; 95% CI: 1.05, 1.43) but not Dose 2 (HR=1.07; 95% CI: 0.88, 1.31). The secondary analyses of the combined dose and time-varying dose for the dose-compliant subsample were not statistically significant, suggesting no increased risk of GCA.

ION

The cohort of 3 289 741 RZV-exposed individuals was predominantly White (88.98%), female (58.91%), and had a mean age of 74.36 years. ION incidence per 10 000 PY in the RZV-exposed and the 2 587 018 RZV-unvaccinated comparators was 9.81 and 10.17, respectively. The incidence of ION per 10 000 PY for the 2 509 168 RZV Dose 2 exposed and the RZV--unvaccinated comparators was 8.79 and 10.34, respectively. The primary analysis using an IPTW stabilized weighted Cox proportional hazards regression analysis did not reveal a statistically significant risk of ION following RZV Dose 1 (HR=0.97, 95% CI: 0.90, 1.05) but showed a statistically significant lower risk of ION following RZV Dose 2 (HR=0.85, 95% CI: 0.78, 0.93) relative to the RZV-unvaccinated comparators. Results from the sensitivity analyses were similar to the primary analysis. The primary, secondary, and sensitivity analyses for ION did not violate the proportional hazards assumption.

Discussion

An SCRI case-only design evaluated the risk of new onset of GBS in the 42-day, gout in the 30-day, and SVT in the 30-day risk windows following RZV vaccination. RZV exposure was significantly associated with an increased risk of new onset GBS, with the highest risk observed after Dose 1. For gout and SVT, the findings from the primary analysis, without distinguishing between doses, showed no statistically significant increased risk for each HOI, which was robust to the secondary and all sensitivity analyses.

In the cohort analyses, the results for PMR suggest an increased risk following RZV Dose 1 after Day 120 of the 183-day follow-up period after the index date. For GCA,

primary analysis did not show an increased risk following either dose. However, the secondary analyses suggest a potential increased risk of GCA following RZV Dose 1 given that the lower confidence interval was above one. There was no increased risk of ION following any RZV dose.

Conclusions

The findings of this safety study suggest RZV is associated with a statistically significant increased risk of new onset GBS. In secondary analyses, the elevated risk of new onset GBS was detected after RZV dose 1 but not dose 2. The safety study findings also suggest RZV is associated with a statistically significant increased risk of PMR after Day 120 following RZV dose 1.

This study did not detect a statistically significant risk of gout, SVT, or ION following RZV exposure. The results of most analyses generally indicate no statistically significant increased risk of GCA following RZV, apart from the conflicting findings from the secondary analyses which suggests a higher risk after RZV vaccination.

Marketing authorization holder

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2.1. Abstract

In accordance with Regulation (EU) No 520/2012, an abstract of the final study report is required for Post-Authorization Efficacy Studies (PAES) and Post-Authorization Safety Studies (PASS).

Please refer to ANNEX 3 for non-interventional study report abstract.

3. AMENDMENTS AND UPDATES

None.

4. MILESTONES

Milestone	Actual Date
Start of data collection for EPI-ZOSTER-032 study	11 September 2020[a]
Registration in the EU PAS register for EPI-ZOSTER-032 study	11 September 2020
EPI-ZOSTER-032 study end	10 November 2025
EPI-ZOSTER-032 Final Study report	02 Jul 2026

a. Date represents finalization of original Statistical Analysis Plan.

5. RATIONALE AND BACKGROUND

Herpes zoster, the result of reactivation of latent VZV in dorsal root ganglia, most commonly presents as a painful vesicular dermatomal rash. However, complications such as PHN, as well as disseminated disease in the immunocompromised population, can lead to significant disability and morbidity [John, 2017]. There are an estimated one million cases of HZ in the US annually, resulting in $5 billion in health care expenditures per year [McLaughlin, 2015]. Risk factors for HZ include older age and immunocompromising conditions [Thomas, 2004; Kawai and Yawn, 2017].

SHINGRIX, or RZV, was first approved by FDA in October 2017 for adults ≥50 years of age and in July 2021 for adults ≥18 years of age who currently are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy. The EMA approved *SHINGRIX* in March 2018 for adults ≥50 years of age and in July 2020 for adults ≥18 years of age at increased risk of HZ. *SHINGRIX* is a two-dose vaccine. In Europe, Doses 1 and 2 should be given two months apart, with the possibility of extending the timing of the second dose to six months. In the US, RZV is administered 2 to 6 months apart. For both EMA and FDA, the second dose may be administered 1 to 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. RZV is currently recommended for use in adults ≥50 years of age [Dooling, 2018] and immunocompromised adults ≥19 years of age by the ACIP recommendations [Anderson, 2022].

Vaccine efficacy against HZ in the two pivotal Phase 3 studies was 97.2% in adults ≥50 years of age [Lal, 2015], and 91.5% in adults ≥70 years of age [Cunningham, 2016]. Pooled safety analyses of clinical data from these two Phase 3 studies included a total of 14 645 RZV and 14 660 placebo recipients, with a median follow-up duration of 4.4 years [Lopez-Fauqued, 2019]. The pooled analysis demonstrated a comparable incidence of unsolicited AEs in the Day 7 through Day 29 follow-up period (excluding Day 0 through Day 6 where reactogenicity was observed to be higher in RZV versus placebo recipients). SAEs, and pIMDs between the RZV and placebo groups, and specific SAEs and pIMDs were within the expected incidence for the study age group [Lopez-Fauqued, 2019].

In descriptive analyses, there were numerical differences in AEs for some specific conditions, including 1) PMR; 2) GCA; 3) gout; and 4) ION. During the entire post-vaccination follow-up period, PMR was reported by 32 (0.2% [95% CI: 0.1, 0.3]) and 29 (0.2% [95% CI: 0.1, 0.3]) participants in the RZV and placebo groups, respectively [Lopez-Fauqued, 2019]. GCA was reported by 6 (0.04% [95% CI: 0.0, 0.1]) and 3 (0.02% [95% CI: 0.0, 0.1]) participants in the RZV and placebo groups, respectively [Lopez-Fauqued, 2019].

For gout, there were 27 (0.18% [95% CI: 0.12, 0.27]) and 8 (0.05% [95% CI: 0.02, 0.11]) participants in the RZV and placebo groups, respectively, who reported an event of gout or gouty arthritis.

For ION, 3 cases were reported in the RZV and no cases in the placebo groups (at specific follow-up time points) post-vaccination, 1 versus zero cases at ≤30 days, and 2 versus zero cases at ≤365 days [SHINGRIX, 2026].

Numerical differences were also noted between the RZV group and the placebo group on pooled analyses with respect to other clinical outcomes, SVT: 6 (0.04% [95% CI: 0.02, 0.09]) and 0 (0.00% [95% CI: 0.00, 0.03]) participants in the RZV and placebo groups, respectively, in the 365-day follow-up period post-last vaccination [Lopez-Fauqued, 2019].

With respect to reports of GBS, there were 2 cases reported in the RZV group and 3 in the placebo group during the entire post-vaccination follow-up period (Lopez-Fauqued, 2019). Post licensure safety surveillance by the CDC detected a statistical signal using Vaccine Safety Datalink Rapid Cycle Analysis, which used an algorithm that preferentially maximizes sensitivity over specificity. Additionally, in a post-marketing observational study, an increased risk of GBS was observed during the 42 days following vaccination with RZV among Medicare beneficiaries aged 65 years or older, although the available evidence is insufficient to establish a causal relationship (Goud, 2021).

In prelicensure clinical trials and post licensure safety surveillance by the CDC, which are not designed to assess rare outcomes, numerical differences or a statistical signal between the RZV and placebo groups were noted for certain conditions, including PMR, GCA, gout, ION, SVT and GBS. Robust data among older adults on the risk of these outcomes following the administration of RZV is currently lacking. Furthermore, data on the use of RZV in complex patient populations are critical in assessing the safety of the vaccine in the real-world setting. The EPI-ZOSTER-032 TSS/PASS study utilizing the CMS CCW database, a large and comprehensive database representing US adults ≥65 years of age, allows for evaluation of the real-world safety of RZV related to these outcomes, in heterogeneous, complex populations. The EPI-ZOSTER-032 study was designed to evaluate the risk of GBS, gout, PMR, and GCA following RZV as primary objectives. Assessing the risk of SVT and ION following RZV are secondary objectives of the EPI-ZOSTER-032 study.

6. RESEARCH QUESTION AND OBJECTIVE(S)

The EPI-ZOSTER-032 study addresses the question of whether RZV is associated with the risk of new onset GBS, gout, PMR, GCA, SVT, and ION within specified time periods after RZV vaccination in people ≥65 years of age in the US enrolled in Medicare who were vaccinated with RZV any time from January 2018 through December 2020.

The primary objectives are:

- To assess the risk of new onset GBS within 42 days following RZV vaccination using a SCRI design.

  To assess the risk of new onset gout within 30 days following RZV vaccination using a SCRI design.
- To assess the risk of new onset PMR within 183 days following RZV vaccination using a cohort design.
- To assess the risk of new onset GCA within 183 days following RZV vaccination using a cohort design.

The secondary objectives are:

- To assess the risk of new onset SVT within 30 days following RZV vaccination using a SCRI design.
- To assess the risk of new onset ION within 183 days following RZV vaccination using a cohort design.

7. RESEARCH METHODS

7.1. Study Design

7.1.1. SCRI – GBS, gout, and SVT

In the EPI-ZOSTER-032 study, an observational, retrospective study using secondary data, the risk of three HOIs (GBS, gout, and SVT) is assessed using a SCRI design. This case-only design only includes RZV vaccinees who have evidence of the HOI in the pre-defined risk or the control window following RZV Dose 1 or 2. The SCRI design, where each participant serves as their own control, was used because it is ideal for acute outcomes and transient exposures (Baker, 2015). The advantage of the SCRI design is the implicit control for time-fixed potential confounders such as sex, race/ethnicity, and stable chronic medical conditions.

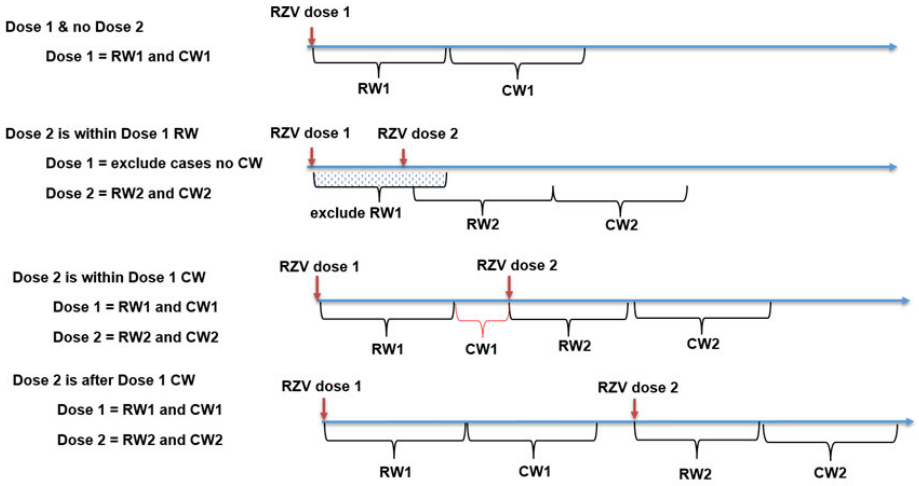
For the SCRI design, the index date (Day 0) is the day of vaccination for RZV Dose 1 and Dose 2 and was not part of the follow-up period. The risk and control windows are defined separately for Dose 1 and Dose 2. Due to the dosing schedule, it is not possible to define a consistent control window for Dose 1. The control window following Dose 1 might overlap with the risk window following Dose 2. Therefore, the Dose 1 control window depended upon the timing between doses. Several scenarios for dose timing were implemented in this study (Figure 1).

The risk and control windows following each dose, for each outcome was defined as:

- GBS: Risk window as Days 1 to 42, and control window as Day 43 to 84 following each dose.
- SVT and gout: Risk window as Days 1 to 30 and control window as Days 31 to 60 following each dose.

If a second RZV dose was received during the Dose 1 control window then the Dose 1 control window was censored at Dose 2 receipt (i.e., the Dose 1 control window only extended through the day before receipt of Dose 2). We excluded post-Dose 1 cases if Dose 2 was received 1 to 43 days after Dose 1 (i.e., within the Dose 1 risk window +1 day) as no Dose 1 control window would exist. This reflects the second and third potential scenarios as illustrated in Figure 1.

Figure 1 Illustration of SCRI design with variable dose spacing



SCRI, self-controlled risk interval; RZV, recombinant zoster vaccine; RW1, Dose 1 risk window; RW2, Dose 2 risk window; CW1, Dose.1 control window; and CW2, Dose 2 control window.

7.1.1.1. GBS

The risk window for GBS started on Day 1 after and ended on Day 42 after each respective RZV dose. The control window started on Day 43 and ended on Day 84 after each respective dose.

7.1.1.2. Gout and SVT

The risk window for either dose was defined as Days 1 to 30 after RZV vaccination; the control window of Dose 1 started on Day 31 and ended on Day 60 after vaccination unless a second dose was received during Days 31 to 60, in which case the control window was censored at Dose 2 receipt (i.e., the control window only extended through the day before receipt of Dose 2). The control window for Dose 2 was defined as Days 31 to 60 after vaccination with Dose 2. The potential scenarios are illustrated in Figure 1.

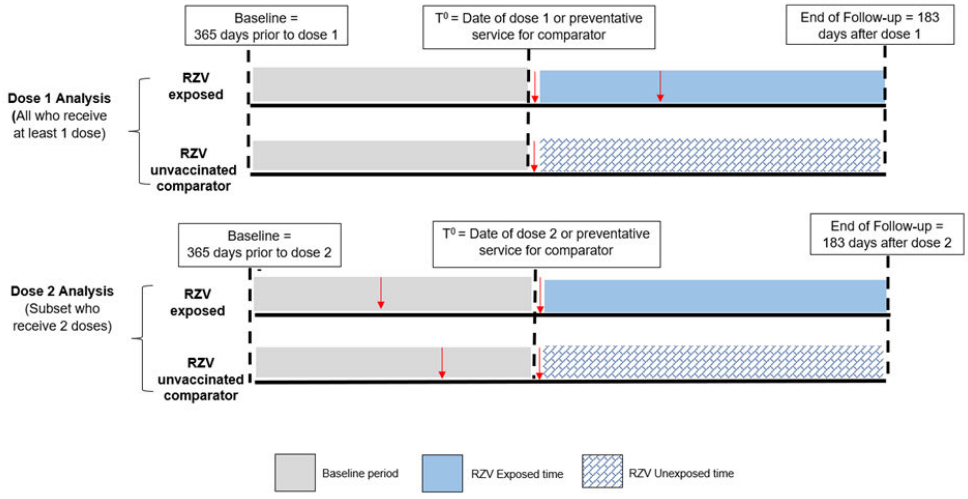
7.1.2. Cohort – PMR, GCA and ION

In the EPI-ZOSTER-032 study, a retrospective study using secondary data, the risks of new onset PMR, GCA, and ION were assessed using a cohort study design with an unvaccinated comparator. The hazards of new onset PMR, GCA, and ION were assessed among RZV-exposed relative to RZV-unvaccinated comparators who had a preventive care visit and no evidence of RZV exposure prior to the preventive care visit.

The RZV-exposed were participants who received at least one dose of RZV from January 2018 through December 2020. The index date for the RZV-exposed group is the date of RZV vaccination, Dose 1 or Dose 2 as shown in Figure 2.

A concurrent RZV-unvaccinated comparator was selected among eligible Medicare beneficiaries who had at least one preventive visit (wellness annual exam OR a preventive screening visit) from January 2018 through December 2020 and had not received RZV prior to or at the time of their index preventive care visit. Since participants could have more than one eligible preventive care visit, the index date for the RZV-unvaccinated comparator was the date of the randomly selected preventive care visit among eligible visits.

Figure 2 Illustration of cohort design



RZV, recombinant zoster vaccine.

7.2. Study Population and Setting

7.2.1. Source population

The source population is US adults who are enrolled in Medicare. Medicare is a federal program fully funded by the US government to subsidize health care services for citizens who are ≥65 years of age or who are entitled due to a qualifying medical condition. CMS is the US federal agency responsible for oversight and management of the Medicare program. As defined by CMS, Medicare is a health insurance program for:

1. People ≥65 years of age
2. People <65 years of age with certain disabilities
3. People of all ages with ESRD

Nearly 80% of US adults in the Medicare program qualify based on >65 years of age, and about 20% are younger than 65 years old and qualify due to a medically disabling condition.

Approximately 55% to 67% of the Medicare population is covered fully or partly through a fee-for-service arrangement as opposed to a supplemental Medicare Advantage plan.

The study population of RZV-exposed is derived from all US Medicare beneficiaries who received ≥1 dose of RZV (i.e., exposed) in calendar years 2018 through 2020 for GBS and SVT, while the study population for gout was derived from those who received at least one dose of RZV in calendar years 2018 and 2019.

Inclusion criteria

US Medicare beneficiaries met the following criteria for study inclusion:

1. Age 65 or older at the date of the RZV vaccination, **AND**
2. Enrolled in Medicare due to age or ESRD as the original and current qualifying reason, **AND**
3. Continuously enrolled in Medicare Parts A, B, and D fee-for-service preceding the date of RZV vaccination. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination and enrollment in at least 11 of the 12 preceding months.

Exclusion criteria

Beneficiaries who met at least one of the following criteria were excluded:

1. Continuously enrolled only in Medicare Part C in the baseline period, **OR**
2. Enrolled in Medicare due to disability as the original qualifying reason for enrollment.

7.2.1.1. SCRI – GBS, Gout and SVT

Only the cases of new-onset gout, GBS, and SVT recorded in the RZV-exposed cohort during either the risk or the control windows were included in the SCRI analyses. Inclusion criteria for the analytic cohort of new-onset cases for each HOI in the SCRI analysis design include:

1. Receipt of RZV vaccine before the new onset case each of the respective HOIs (GBS, gout, SVT)
2. First-in-365-days case of the respective HOI in the risk or control interval (i.e., definition of a new onset case)

3. Continuously enrolled in Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination and enrollment in at least 11 of the 12 preceding months.
4. Continuous enrollment in Parts A and B (and in the case of gout Part D to capture gout-specific medication) from receipt of RZV vaccination through the end of the respective control interval.

7.2.1.2. Cohort – PMR, GCA and ION

RZV-exposed

The RZV-exposed group is any participant who received at least one dose of RZV in 2018 through 2020.

Inclusion criteria for the RZV-exposed group in the cohort design include:

1. RZV vaccine exposed during the study period (2018 through 2020).
2. No HOIs during the 365-day look-back period from the index date.
3. At least 365 days of Parts A, B, and D continuous enrollment prior to the index date. Continuous enrollment is determined by Medicare enrollment in the month of the RZV dose and enrollment in at least 11 of the 12 months preceding the month of the RZV dose.

RZV-unvaccinated comparators

A concurrent RZV-unvaccinated comparator group was selected among individuals who had at least one preventive visit (wellness annual exam OR a preventive screening visit) performed during the study period and had not received RZV prior to or at the time of the selected preventive care visit date.

Inclusion criteria for the RZV-unexposed comparator for the cohort design include:

1. At least one visit for a routine adult annual exam OR at least one preventive screening intervention performed during the study period. The ICD-10, CPT, and HCPCS codes to identify eligible preventive care visits are in Appendix A.
2. No RZV vaccination at any time in the available history prior to the index date.
3. No HOIs on or in the 365-day look-back period from the index date.
4. At least 365 days of Parts A, B, and D continuous enrollment prior to the index date. Continuous enrollment is determined by Medicare enrollment in the month of the preventative care visit and enrollment in at least 11 of the 12 preceding months.

Analytical cohort

The analytic cohort for each of the HOIs (PMR, GCA, and ION) is the subset of the eligible study population who met the above criteria for either the RZV-exposed or RZV-unvaccinated comparator.

7.3. Variables

7.3.1. Exposure

Exposure is defined as receipt of at least one dose of RZV, identified based on the NDC or CPT code. The NDCs from the PDE claim file that were used to identify RZV exposure as a prescription dispensing in an outpatient pharmacy setting are: 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11. The CPT code that was used to identify vaccine administration in a physician's office setting claim is 90750.

To ensure only unique observations were included, the exposure measure considered RZV vaccination records occurring within 27 days after a previous RZV vaccination record (i.e., on Days 1 to 27, where the day of the previous RZV record is Day 0) as a duplicate record. The record identified as a duplicate, not the participant, was deleted. RZV doses beyond two per study participant, even after removing possible duplicates, were excluded from the analysis.

The date of receipt of RZV was the index date of exposure.

Additionally, in the cohort study design, to select RZV-unvaccinated comparators, eligible Medicare beneficiaries who had a preventive care visit (annual wellness exam OR a preventive screening visit) with no prior history of RZV vaccination were selected as the unexposed comparators. The ICD-10, CPT, and HCPCS codes were used to identify eligible preventive care visits as specified in the protocol and statistical analysis plan (Section 14.7).

The index date for the RZV-unvaccinated comparator for the cohort design is the date of the randomly selected preventive care visit.

7.3.2. Health outcomes of interest

A new onset case of GBS, gout, PMR, and GCA were the primary outcomes, while a new onset case of SVT and ION were the secondary outcomes.

7.3.2.1. GBS, gout and SVT

The per-protocol case ascertainment algorithms for GBS, gout and SVT are described in Table 1. Claims-based validated algorithms were used when available.

Table 1 SCRI outcomes case ascertainment criteria

Outcome	ICD-10	Validation Statistics	Other Requirements[a]	Setting	Risk Interval
GBS	G61.0	PPV: 50% (Inpatient visit)[c]		Inpatient primary position OR Diagnosis in any setting followed by an inpatient claim within 7 days	Days 1 to 42 (risk window); Days 43 to 84 (control window) unless dose 2 received in this window.
Gout	M10.x (gout) M1A.x (chronic gout)		At least one gout-specific oral medication (allopurinol, colchicine, probenecid, febuxostat) prescribed within 3 months after the first date of the diagnosis	≥ 2 outpatient claims within the follow-up window[b] OR ≥1 inpatient claim	Days 1 to 30 (risk window); Days 31 to 60 (control window) unless dose 2 received in this window.
SVT	I47.1	Sensitivity-91.7%[d]		≥1 ED or inpatient claim (any position)	Days 1 to 30 (risk window); Days 31 to 60 (control window) unless dose 2 received in this window.

ICD-10, International Classification of Disease version 10; GBS, Guillain-Barré Syndrome; PPV, positive predictive value; SVT, supraventricular tachycardia; ED, emergency department.

a. Based on external expert opinion.

b. Outpatient visits are defined using ≥2 claims for consistency with the methods used by the CMS algorithms applied to the CMS Chronic Condition Warehouse Medicare data. This algorithm defines chronic conditions and avoids misclassification of the outcome due to the potential for 1 visit to reflect a rule-out diagnosis.

c. Funch, 2013

d. Sidney, 2005.

For GBS, gout and SVT, the case date was the date of the first claim in either the risk or the control window following RZV vaccination (i.e., Day 0) with either Dose 1 or Dose 2.

New onset GBS, gout or SVT was defined as the first occurrence in the risk or control window with no evidence of the HOI in 365 days preceding the case. The 365-day look-back, starting the day prior to the case date, was used to identify any evidence of a prevalent HOI.

7.3.2.2. PMR, GCA, and ION

The per-protocol case ascertainment algorithms for PMR, GCA, and ION are described in Table 2. Claims-based validated algorithms were used when available. For PMR and GCA, clinician input was used to bolster the algorithm by requiring 2 oral glucocorticoid prescriptions.

Table 2 Cohort outcomes case ascertainment criteria

Outcome	ICD-10	Validation Statistics	Other Requirements[a]	Setting	Risk Interval	Look-back period	Sensitivity Analysis
PMR	M35.3 – PMR M31.5 – GCA w/ PMR	Sensitivity: 99.5% Specificity: 92.2%[b] (based on the 3 methods used by Bernatsky: diagnosis in inpatient or outpatient, or a visit by a rheumatologist or internist)	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone) prescriptions; The first dispensing within 6 months of PMR diagnosis and the second dispensing date within 6 months after the first dispensing.	≥2 outpatient claims within the follow-up window OR ≥1 inpatient claim	Days 1 to 183	1 year; all settings[c]	N/A
GCA	M31.6 (GCA), M31.5 (GCA with PMR), M31.9 (necrotizing vasculopathy unspecified)	Not available	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone). The first dispensing within 6 months of GCA diagnosis and the second dispensing date within 6 months after the first dispensing.	≥2 outpatient claims within the follow-up window[d] OR ≥1 inpatient claim	Days 1 to 183	1 year; all settings[c]	Use the primary algorithm based on the GCA diagnosis code and steroid prescription but add a requirement for a temporal artery biopsy at the time of diagnosis, as determined by a CPT code=37609
ION	H47.01	Not available	Exclude patients who had CABG surgery[e] or lumbar or lumbosacral spinal fusion and/or laminectomy surgery within 30 days before ION diagnosis date	≥1 claim in all settings	Days 1 to183	1 year; all settings[c] ICD code only	Additional criteria for arteritic: ≥ 40 mg/day of prednisone prescription ± 4 weeks of the diagnosis plus phthalmologist/neuro-ophthalmologist consult (if possible) and GCA diagnosis within 3 months; look-back to rule out prevalent cases will use ICD code only; all settings.

CPT, current procedural terminology; GCA, giant cell arteritis; ION, ischemic optic neuropathy; ICD-10: International Classification of Disease version 10; PMR, polymyalgia rheumatica; N/A, not applicable.

a. Based on external expert opinion.
b. Bernatsky, 2011.
c. Includes inpatient, emergency department, and outpatient settings
d. Outpatient visits are defined using ≥2 claims for consistency with methods used by CMS algorithms using the CMS CCW Medicare data to define chronic conditions, and to avoid misclassification of the outcome due to the potential for 1 visit to reflect rule-out diagnosis.
e. Rubin, 2017.

7.3.3. Covariates

Baseline covariates were measured in the 365 days preceding the index date. Baseline covariates characterize the analytic cohorts with respect to demographics, medical comorbidities, health service utilization, and other preventive vaccinations. Some of the baseline characteristics had to be collapsed/re-categorized to facilitate cell masking due to CMS requirements. A full list of the covariates and associated codes are provided in a standalone Variable List document.

- Demographic characteristics included age at the first RZV vaccination, both as a continuous variable and a categorical age group, in 5-year increments, sex (male, female), race/ethnicity (White, Black, Hispanic, Asian, North American Native, Other, based on the CMS-defined categories in the raw data), and continuous enrollment in Medicare fee-for-service Parts A, B, and D one-year preceding the index date.

- Medical comorbidities were coded as yes/no binary variables. These included DM, AD and related dementia, CKD, CLD, CHF, IHD, chronic liver disease, and stroke/ TIA. Immunocompromised conditions included organ transplant, hematopoietic cell transplant, hematologic or solid malignancy with recent receipt of chemotherapy, HIV, RA, Crohn's disease, colitis, lupus, MS, and psoriasis/psoriatic arthritis.

- Health service utilization measures are categorized as 0, 1, or 2 or more hospitalizations and number of ED visits, separately, and as binary measures of DME, hospice care, home health care, dermatology visit, and ophthalmology visit.

- Preventive vaccinations, measured as binary variables for concomitant receipt on the index date, were separate variables for 1) influenza, 2) pneumococcal, and 3) Tdap.

7.4. Data sources

The data source for this study is the CMS CCW Medicare data. These are secondary administrative databases of all health care services paid on a fee-for-service basis. The CMS CCW data represent all billed and paid claims for the provision of health care services in inpatient and outpatient settings, SNF, hospice, home health services, and for the provision of DME and prescription drugs. The CMS CCW is designed specifically to make Medicare data readily available for research, and data are available in six different datasets (described below). A unique identification number is available in all data files to facilitate accurate data linkage for an individual across all data sets and across multiple years.

- MBSF: This file provides information on the baseline study variables, including original and current enrollment reason, Medicare eligibility, and demographic characteristics. The information in this dataset relevant to this study includes beneficiary enrollment in Medicare Parts A (hospital), B (physician), and D (prescription medication). Medicare Part C, also referred to as Medicare Advantage, is a public or private organization that offers health plan options for Medicare

beneficiaries. Services provided under Part C are not available in the CMS CCW Medicare database, and so all data will be missing for individuals who are only enrolled in Part C. This is why we excluded beneficiaries with Medicare Part C.

- Inpatient File: This dataset contains fee-for-service claims submitted by inpatient hospital providers for reimbursement of facility costs, including hospitalizations and ED visits.

- Outpatient File: This dataset contains fee-for-service claims submitted by *institutional outpatient providers*. Institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, Federally Qualified Health Centers, and community mental health centers.

- Carrier File: This dataset includes fee-for-service claims submitted by *professional providers*, including physicians, physician assistants, clinical social workers, nurses, and practitioners, and by *organizational providers*, including freestanding facilities (i.e., independent clinical laboratories), ambulance providers, freestanding ambulatory surgical centers and freestanding radiology centers.

- SNF File: This dataset includes fee-for-service claims for paid services submitted by SNF *institutional facility providers*.

- PDE File: This dataset includes all prescription medications filled at an *outpatient pharmacy* submitted by the prescription drug plan. The MBSF was used to select the study population and determine eligibility for the HOIs analytic cohorts based on continuous Medicare Parts A, B, and D enrollment 365 days before receipt of the RZV vaccine and through the entire follow-up period. The inpatient, outpatient, carrier, and SNF files were used to ascertain the HOIs and the covariates. The PDE file was used to ascertain RZV exposure and other medications.

7.5. Bias

7.5.1. Mitigation of bias in SCRI design

The following steps were taken to mitigate potential sources of bias in the SCRI design:

1. To mitigate misclassification of gout, we used a published claims-based case ascertainment algorithm with a high PPV in conjunction with clinical expert consultation (Table 1). Requirement of ≥2 outpatient claims in addition to receipt of gout-specific medication within 90 days was intended to minimize bias due to imprecision in coding.
2. To mitigate misclassification of GBS, we used a published claims-based case ascertainment algorithm (Table 1).
3. Misclassification of SVT was minimized by requiring the case to occur in an ED or inpatient setting (Table 1).

4. To mitigate the potential for detection bias due to the COVID-19 pandemic, a sensitivity analysis excluded participants who had RZV exposure for whom the follow-up period would have overlapped with the COVID-19 pandemic. For GBS, any doses administered on or after 08 November 2019 (and their cases) were excluded to allow a full 84 days of follow-up before 01 February 2020. For gout, participants who had RZV exposure on 02 December 2019 through 31 December 2019 were excluded. For SVT, any doses administered on or after 02 December 2019 (and their cases) were excluded to allow a full 60 days of follow-up before 01 February 2020.
5. Participants' Dose 1 control window was censored if receipt of RZV Dose 2 was during the RZV Dose 1 control window. This may have introduced potential bias due to informative censoring. To address this, a secondary analysis was performed that did not censor the RZV Dose 1 control window at receipt of Dose 2, thereby allowing any potential cases to be attributed to the Dose 2 risk window rather than the Dose 1 control window.

7.5.2. Mitigation of bias in the cohort design

7.5.2.1. Propensity score methods

The cohort study employed PS methods to adjust for confounding in observational studies. The PS was estimated using logistic regression, modeled as the probability of receiving RZV as a function of the baseline measured covariates observed in the 365 days preceding (and including) the index date and, as applicable, covariates measured using all available data.

Covariate inclusion in the logistic regression model was driven by investigators' knowledge and empirical evidence, aiming to be as comprehensive as possible. Covariate selection is not based on statistical significance tests as this could result in the omission of variables that can compromise the PS and, ultimately, the ability to control for confounding.

The PS distribution for the RZV-exposed and the RZV-unvaccinated comparator was graphically displayed to assess the extent of overlap. We trimmed non-common range areas prior to the implementation of the IPTW, which is the standard practice for PS methods.

We inspected the IPTW for extreme weights and used stabilized weights to minimize extreme weights. Stabilized weights were estimated as the reciprocal of the probability of receiving treatment multiplied by the marginal probability of treatment. Using stabilized weights, we estimated the hazard ratio in weighted Cox proportional hazards models.

To evaluate the performance of IPTW methods in balancing covariates between RZV-exposed and RZV-unvaccinated comparators, we assessed SMD. An absolute value less than 0.10 was indicative of good confounder balance.

7.5.2.2. Bias analysis

An assumption of propensity score methods is that no unobserved confounders related to RZV exposure and the study outcomes of interest, given the observed covariates. Unobservable factors, such as illness severity or health status, could confound the association between RZV exposure and the outcome of interest. To test the robustness of the risk estimates to potential unobserved confounders, we conducted a quantitative bias analysis. The bounding factor method described by Ding and VanderWeele [Ding, 2016] was applied to correct the relative risk and 95% confidence interval. The bounding factor is calculated using the following formula:

$$(RR_{EU} \times RR_{UD}) \div (RR_{EU} + RR_{UD} - 1)$$

where, RR_{EU} is the relative risk between exposure E and the unobserved confounder U and RR_{UD} is the relative risk between the unobserved confounder U and the outcome D.

The observed HR, the estimate of the relative risk, and 95% CI were divided by the bounding factor to obtain the corrected risk estimate and confidence intervals. We tested a range of RR_{EU} and RR_{UD} to determine the strength of the unobserved confounder that would be needed to nullify the findings.

7.6. Study size

The sample size estimation was conducted only for primary HOIs, i.e., gout, GBS, PMR, and GCA; therefore, we did not estimate the sample size for ION or SVT which are secondary objectives as per the protocol.

7.6.1. SCRI – GBS and Gout

The per protocol sample size was estimated based on a method to estimate the required number of events for self-controlled case study designs [Musonda, 2006].

The per protocol sample size target needed to detect a RR ≥2.0 for gout with 80% power and a two-sided type 1 error of 0.05 was 68 gout events (Table 3). The analytical cohort included 1290 gout cases (Figure 4), demonstrating that the sample size target was achieved.

Similarly, for GBS, 20 GBS events (Table 3) were needed to detect a RR ≥4.0 for GBS with 80% power and a two-sided type 1 error of 0.05. The analytical cohort for GBS included 75 GBS cases (Figure 3), demonstrating that the per-protocol planned sample size target was achieved, and further that the study may be powered to detect a RR <3.

Table 3 Sample size estimates with SCRI design for Gout and GBS with 80% statistical power under two-sided type 1 error of 0.05

Outcome	IR	RR	Total events needed[a]	No. of cases expected in CW	No. of CWs (i.e., vaccinations) needed/100 000[b]	No. vaccinations needed[c]	No. of vaccinated people needed[d]
GBS	2/100 000 PY	3	30	8	41	4 100 000	2 050 000
		4	20	4	20	2 000 000	1 000 000
Gout	200/100 000 PY	2	68	23	140	140 000	70 000

IR, Incidence rate; PY, Person year; RR, Relative risk; CW, Control window; RW, Risk window; GBS, Guillain-Barré Syndrome.

a. Total events needed were calculated using the method described by Musonda, 2006, with 80% statistical power; two-sided type 1 error of 0.05.
b. Vaccinations are synonymous with post-vaccination control windows.
c. Expected vaccinations were obtained assuming the control window was truly not a period of increased risk.
d. Approximate numbers, assuming individuals receive 2 doses.

The sample size estimation was conducted only for primary HOIs; therefore, we did not estimate the sample size for SVT.

7.6.2. Cohort – PMR and GCA

The sample size was estimated using Poisson Regression in the Power Analysis and Sample Size software (NCCS Statistical Software, 2013, version 12.0.2). The analysis performed for the PMR and GCA sample size estimates was based on a 183-day risk period with a cohort ratio of 1:4 exposed to unvaccinated preventive care visit comparator.

Per protocol, the study was planned to have at least 80% power to reject the null hypothesis of no association if the true relative risk is ≥2 for PMR and ≥3 for GCA. As shown in Table 4, the per protocol sample size calculations indicated that a total sample of 438 239 individuals is needed to detect a RR of 2.0 for PMR, and a total sample of 723 362 individuals is needed to detect a relative risk of 3.0 for GCA. Based on these estimates, this study attained sample sizes to detect the specified relative risks with 80% power (PMR total sample of 5 835 573; GCA total sample of 5 874 821).

The sample size estimation was conducted only for primary HOIs; therefore, we did not estimate the sample size for ION which is a secondary objective per the protocol.

Table 4 Sample sizes with cohort design for PMR and GCA with 80% statistical power under a two-sided type I error (alpha) of 0.05, Cohort 1:4 ratio, and 6 months follow-up

Outcome	RR	Baseline Response	Total Cohort Sample Size, N	Vaccinated Population, N	Control Population, N
PMR	2	0.000405	438 239	87 648	350 591
	2.5		242 212	48 442	193 770
	3		164 320	32 864	131 456
	3.5		123 991	24 799	99 192
GCA	2	0.000092	1 929 204	385 841	1 543 363
	2.5		1 066 257	213 252	853 005
	3		723 362	144 673	578 689
	3.5		545 828	109 166	436 682
	4		439 133	87 827	351 306

GCA, giant cell arteritis; PMR, polymyalgia; RR, relative risk; N, number.

7.7. Data Analysis

Descriptive analyses were conducted to characterize participants. Inferential analyses examined the risk of new onset gout, GBS, SVT, PMR, GCA, and ION after RZV exposure, across primary, secondary and sensitivity analyses as described below. All statistical analyses were performed using SAS Studio® 9.4, and statistical significance was determined using a two-sided alpha level of 0.05.

7.7.1. SCRI – GBS, Gout and SVT

7.7.1.1. Descriptive analysis

Baseline characteristics were evaluated prior to receipt of RZV Dose 1. Key baseline covariates are described in Section 7.3.3. The baseline characteristics of participants who received only one dose and participants who received both doses of RZV were evaluated. The distribution of RZV administration by dose and the distribution of cases over the follow-up are graphically displayed.

To determine the applicability of the study results to the European context, a descriptive analysis of all 2-dose recipients was stratified by the proportion who received the second RZV dose on Days 28 to 60 after the first RZV dose relative to the proportion who received the second RZV dose more than 60 days after the first RZV dose.

Descriptive analyses evaluated the distribution of certain gout ICD-10 codes that contributed to the case identification. First, the proportion of gout cases not solely due to chronic gout or to a secondary diagnosis was evaluated by excluding chronic and secondary gout codes from the case ascertainment algorithm. Second, the distribution of ICD-10 codes was inspected to determine if low-frequency codes such as codes for chronic gout (M1A*), lead-induced gout (M10.1*), drug-induced gout (M10.2*), and gout due to renal impairment (M10.3*) were contributing to the new onset gout case ascertainment.

An additional descriptive analysis for GBS identified the number of GBS cases with evidence in the inpatient or outpatient claims of respiratory or gastrointestinal infection (including COVID-19 infection) in the 60 days prior to the GBS diagnosis, noting in which post-RZV windows (risk versus control) these GBS cases occurred.

Descriptive statistics include means, standard deviations, and frequencies, overall and stratified by the number of doses received.

7.7.1.2. Main analytical approach

A conditional Poisson regression model, a multinomial model where time-fixed confounders within each stratum are controlled by conditioning on the sum of events in this stratum [Armstrong, 2014], was implemented. The model accounts for within participant dependence using generalized estimating equations for robust variance estimation. The general form of a conditional Poisson regression model can be written as:

$$\eta_{ik} \sim P\text{oisson}(\lambda_{ik} e_{ik})$$

$$\log(\lambda_{ik}) = \phi_i + \beta_k$$

The response variable is n_{ik}, the number of events for the *i*th individual in the k (risk or control) interval. The log of the time spent in the interval ($ln(e_{ik})$) is the offset term. In the model, λ_{ik} denotes the incidence within each interval, ϕ_i is the effect for individual i (log of baseline incidence of GBS for individual i), and β_k is the effect for risk group k (Whitaker, 2005). The model generates the RR with a 95% CI.

SAS® PROC GENMOD with the Poisson distribution, a log link function, and the EXACT statement was employed to perform a conditional Poisson regression model. The dependent variable (*Y*) was the number of events, a binary independent variable was the interval (risk or control), and the log of person days in the interval was the offset term.

7.7.1.3. Primary analysis

The primary analysis estimated the risk of the respective HOI (GBS, gout or SVT) in the post-RZV risk window relative to the control window without distinguishing between doses (Table 5 and Table 6). Analytical methods as described in Section 7.7.1.2 were implemented.

Table 5 Planned analyses for GBS

Category of analysis	Doses to include	Exclusions[a]	Dose 1 control interval[b]	Risk estimate
Primary Analysis				
Full analytic cohort, Dose 1 CW censored at receipt of Dose 2	1 and 2 without distinguishing	Post-Dose 1 cases excluded if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist	Maximum of Days 43 to 84 after Dose 1, censored at Dose 2	For any dose
Secondary Analysis				
Full analytic cohort, 3-week CW for both doses, no censoring	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 43 to 6343 to 63 after Dose 1 (3 weeks)	For any dose
Full analytic cohort, 6-week CW for both doses, no censoring	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 43 to 84 after Dose 1 (6 weeks)	For any dose
Sensitivity to Primary				
Restrict analytical cohort to 2-dose recipients with 60 to 183-day dose spacing per US dosing recommendations	1 and 2 without distinguishing	People not getting Dose 2 60 183 days inclusive after Dose 1	Maximum of Days 43 to 84 after Dose 1, censored at Dose 2	For any dose
Seasonality adjusted analysis – Full analytic cohort, censor Dose 1 CW at receipt of Dose	1 and 2 without distinguishing	Post-Dose 1 cases excluded if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist	Maximum of Days 43 to 84 after Dose 1, censored at Dose 2	For any dose
COVID-19 Sensitivity Analysis - Full analytic cohort, censor Dose 1 CW at receipt of Dose 2 [c]	Dose 1 and 2 without distinguishing	Post-Dose 1 cases excluded if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist	Maximum of Days 43 to 84 after Dose 1, censored at Dose 2	For any dose
Sensitivity to Secondary				
Dose 1 sensitivity to secondary analysis - Restricted analytic cohort to Dose 1 recipients, 30-d CW, no censoring	Just Dose 1	Dose 1 CW cases if also in Dose 2 RW	Days 43 to 84 after Dose 1 (6 weeks)	For Dose 1
Dose 2 sensitivity to secondary analysis -Restricted analytic cohort to Dose 2 recipients, 30-d CW, no censoring	Just Dose 2	None	N.A.	For Dose 2

CW, control window; N.A., not applicable; RW, risk window; wk, week.

a. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist.

b. GBS: RW for all doses is Days 1 to 42 6-wks after the dose; CW for all doses starts on Day 43 after the dose.

c. Exclude any doses administered on or after 08 November 2019 [and their GBS cases].

Table 6 Planned analyses for Gout and SVT

Category of analysis	Doses to include	Exclusions[a]	Dose 1 control interval[b]	Risk estimate[c]
Primary Analysis				
Full analytic cohort, censor Dose 1 CW at receipt of Dose	1 and 2 without distinguishing	Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist	Maximum of Days 31 to 60 after Dose 1, censored at Dose 2	Dose 1 and 2, without distinguishing
Secondary Analysis				
Full analytic cohort, 30-d CW for both doses, no censoring	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW counted as Dose 2 event	Days 31 to 60 after Dose 1	Dose 1 and 2, without distinguishing
Sensitivity to Primary				
Restrict analytic cohort to 2-dose recipients with 60 to 183-day dose spacing per US dosing recommendations	1 and 2 without distinguishing	Participants not getting Dose 2 60-183 days inclusive after Dose 1	Maximum of Days 31 to 60 after Dose 1, censored at Dose 2	Dose 1 and 2, without distinguishing
Seasonality adjusted analysis - Full analytic cohort, censor Dose 1 CW at receipt of Dose[c]	1 and 2 without distinguishing	Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist	Maximum of Days 31 to 60 after Dose 1, censored at Dose 2	Dose 1 and 2, without distinguishing
COVID-19 Sensitivity Analysis - Full analytic cohort, censor Dose 1 CW at receipt of Dose 2[d]	Dose 1 and 2 without distinguishing	Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist	Maximum of Days 31 to 60 after Dose 1, censored at Dose 2	Dose 1 and 2, without distinguishing
Sensitivity to Secondary				
Dose 1 sensitivity to Secondary - Restricted analytic cohort to Dose 1 recipients, 30-d CW, no censoring	Just Dose 1	Dose 1 CW cases if also in Dose 2 RW	Days 31 to 60 after Dose 1	Dose 1
Dose 2 sensitivity to Secondary -Restricted analytic cohort to Dose 2 recipients, 30-d CW, no censoring	Just Dose 2	None	NA	Dose 2

CW, control window; N.A.=, not applicable; RW, risk window.

a. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist.
b. RW for all doses is Day 1 to 30 after the dose; CW for all doses starts on Day 31 after the dose
c. Only applicable to gout.
d. Exclude any doses administered on or after 02 December, 2019 [and their cases].

7.7.1.4. Secondary analyses

Secondary analyses were conducted to evaluate the impact and potential bias of informative censoring in the primary analysis. Since the primary analysis censored the Dose 1 control window at receipt of Dose 2, this may have distorted the risk estimate away from the null as cases in the Dose 1 control window would have been attributed to

Dose 2. Like the primary analysis, the secondary analysis included Doses 1 and 2, without distinguishing between them.

GBS

Secondary analyses were conducted with a fixed control window length (Table 5). The first secondary analysis used a fixed 3-week control window for both doses, while the second secondary analysis used a fixed 6-week control window for both doses. If a case of GBS occurred during a period of overlap between the Dose 1 control window and the Dose 2 risk window, the case will not be counted as having occurred in the Dose 1 control window but will be counted as having occurred in the Dose 2 risk window.

Gout and SVT

The secondary analysis used a fixed 30-day control window for all doses (Table 6). Cases that occurred during an overlapping period of the Dose 1 control window and the Dose 2 risk window were counted as a Dose 2 risk window event.

7.7.1.5. Sensitivity of the primary analyses

US dosing compliant

A sensitivity analysis was carried out exactly like the primary analysis and restricted to two-dose recipients with 60 to 183 days inclusive between the two doses. This sensitivity analysis follows the US dosing schedule (Table 5 and Table 6). The analysis of dose-compliant participants who receive both doses according to the US schedule is a subset of those who received both RZV doses. The primary analysis assumes the timing between Doses 1 and 2 does not affect the risk, and this sensitivity analysis tests the robustness of the primary analysis to this assumption.

Analytical methods as described in Section 7.7.1.2 were implemented.

Seasonality adjusted

An analysis that adjusts for the seasonal patterns of GBS and gout (Table 5 and Table 6), which conformed to the specifications of the primary analysis, was conducted to assess the robustness of the primary findings. Since these outcomes can follow a seasonal pattern, this could distort the association between RZV exposure and new onset GBS or SVT. The adjustment was by means of an offset term, following the approach used in other SCRI studies of vaccine safety that adjusted for seasonality [Baker, 2019; Yih, 2014; Yih, 2016].

The seasonality adjustment approach uses the HCUP Nationwide Inpatient Sample [HCUP Databases, 2026] to obtain counts of the respective HOI by month. The average daily count of the month in each of the most recent three years available was calculated, and the middle day of the month was tested in a polynomial function, a sine function, and splines to fit a curve to the averaged counts. The best fitting curve was selected based on the model that maximized R-squared and had the lowest AIC metric. Predicted values from the best fitting curve, together with the length of the respective risk or control windows, was used to calculate the area under the HOI-by-calendar-month curve.

The best fitted model for GBS was the quadratic regression model with the following specifications:

$$\hat{y}(t) = 1971.95276 - 3.63861t + 0.00927t^2$$

The integral of the above fitted function is

$$\text{Int}(t) = 1971.95276t - 1.519305t^2 + 0.00309t^3$$

The offset term was calculated as the log of the area under curve

$$\text{Offset}\ (t_0,t_1) = \log\ (\text{Int}(t_1) - \text{Int}(t_0)), \text{if}\ t_1 > t_0$$
$$\text{Offset}(t_0,t_1) = \log\ (\text{Int}(365) - \text{Int}(t_0) + \text{Int}(t_1) - \text{Int}(1)),\ \text{if}\ t_1 < t_0$$

The best fitted model for gout was the quadratic regression model with the following specifications

$$\hat{y}(t) = 2693.1343938 - 1.8476611t + 0.0038515t^2$$

The integral of the above fitted function is

$$\text{Int}(t) = 2693.1343938t - 0.9238305t^2 + 0.0012838t^3$$

The offset term was calculated as the log of the area under curve

$$\text{Offset}\ (t_0,t_1) = \log\ (\text{Int}(t_1) - \text{Int}(t_0)), \text{if}\ t_1 > t_0$$
$$\text{Offset}(t_0,t_1) = \log\ (\text{Int}(365) - \text{Int}(t_0) + \text{Int}(t_1) - \text{Int}(1)), \text{if}\ t_1 < t_0$$

where t_0 and t_1 are the day for the start and end of the window, respectively. For example, if the window was from 01 January to 30 January of the year, then $t_0 = 1$ and $t_1 = 30$. Analytical methods as described in Section 7.7.1.2 were implemented where the offset term thus serves to adjust for both the lengths of the risk and control intervals and the background risk of GBS or gout during the risk and control intervals. Details of the model fitting results for GBS and gout are in Section 14.1.1 and Section 14.2.1, respectively.

COVID-19

The COVID-19 pandemic and subsequent lockdowns resulted in less in-person health care visits, which changed patients' health-seeking behaviors. This could have reduced the ability to identify new onset of HOIs in administrative claims data. A sensitivity analysis was conducted excluding exposures on or after 08 November 2019 for GBS and 02 December 2019 for gout and SVT which allowed a full follow-up before 01 February 2020. The sensitivity analysis was conducted like the primary analysis (Table 5 and Table 6), except limited to the subset of participants who received the RZV vaccination before the cutoff date. Analytical methods as described in Section 7.7.1.2 were implemented.

7.7.1.6. Sensitivity of the secondary analysis

Two sensitivity analyses were conducted to assess the dose-specific risk with fixed control window lengths. The sensitivity analyses generated a separate risk estimate for

Dose 1 and Dose 2. If a HOI case occurred during a period of overlap between the Dose 1 control window and the Dose 2 risk window, the case will not be counted as having occurred in the Dose 1 control window but will be counted as having occurred in the Dose 2 risk window.

Both sensitivity analyses were conducted using a fixed 6-week control window for GBS or fixed 30-day control window for gout and SVT.

Analytical methods as described in Section 7.7.1.2 were implemented.

7.7.1.7. Temporal scan statistics

Temporal scan statistic tested for statistically significant temporal clustering of GBS, gout and SVT cases, the existence of which may suggest, although not confirm, an association. The analysis was performed using TreeScan™ software. The total number of cases, *N*, is distributed in the overall interval length, *W*, which is 60 days in this analysis. The temporal scan statistic is based on the observed to the expected number of events in scanning window length, *w*, within *W* [MCclure, 2012]. The expected number of cases, *E*, is:

$$E = \frac{Nw_i}{W}, with\ W = \Sigma_i w_i$$

The null hypothesis is there is no clustering of *E* in a scan window of width w_i. The LLR of the observed number of cases, *O*, conditioned on *N* is:

$$LLR = Oln(\frac{O}{E}) + (N - O)\ln[\frac{N - O}{N - E}]$$

LLR is maximized over all possible w_i applied to the observed data.

7.7.1.8. Attributable risk

AR was estimated only for outcomes that had a statistically significant increase in risk.

For findings of statistically significant elevated risk, we calculated the AR as the number of excess cases of that HOI per 1 000 000 doses administered, according to the formula 1 000 000 × no. of cases in the risk window × [1 − (1 ÷ RR)] ÷ [no. of vaccine doses] (Funch, 2013).

To compute a 95% confidence interval of the AR, we transformed the Wald-type confidence interval of the log relative risk from the Poisson regression model. Specifically, let **a1** and **a2** be the 95% Wald-type upper and lower bounds of the 95% CI for the log relative risk, then we know that, with large sample sizes, Pr(**a1** ≤ log(RR) ≤ **a2**) = 0.95. The latter is equivalent to Pr(**b1** ≤ AR ≤ **b2**) = 0.95 where

> **b1** = 1 000 000 × no. of cases in the risk window × [1 − (1 ÷ exp(**a1**))] ÷ [no. of vaccine doses], and

b2 = 1 000 000 × no. of cases in the risk window × [1 − (1 ÷ exp(**a2**))] ÷ [no. of vaccine doses]

In this case, **b1** and **b2** are a 95% CI for the AR.

7.7.1.9. Post-hoc analysis

Several post-hoc analyses relevant to GBS were conducted to assess the robustness of the inferences from the primary analysis.

- GBS cases with a respiratory or gastrointestinal infection in the 60-days prior to the GBS case were removed because these infections may be associated with GBS [Bellanti, 2024].
- Preventive vaccines, such as influenza, have been linked to GBS [Perez-Vilar, 2021; Yen, 2022; Kim, 2022; Wang, 2022), which prompted an additional analysis that excluded cases who had received a pneumococcal, influenza, or Tdap vaccine concomitantly on the RZV index date or in the 42 days prior to RZV exposure.
- To address a concern related to age and risk for GBS, we conducted a stratified analysis by age 65 to 74 compared with ages 75 and older.
- Finally, since GBS cases could not be confirmed via a medical chart audit, the HOI algorithm for GBS had a PPV of 50%, and a PPV-adjusted analysis was performed to evaluate the impact on the risk estimate.

7.7.2. Cohort – PMR, GCA and ION

7.7.2.1. Descriptive analysis

Baseline characteristics (Section 7.3.3) of the analytic cohorts were evaluated prior to the index date. For the RZV-exposed group, the baseline period was 365 days prior to receipt of RZV Dose 1 for most analyses and prior to receipt of Dose 2 for the Dose 2 specific analyses. For the RZV-unvaccinated comparator group, the baseline period was 365 days prior to the preventive care visit. We compared the baseline characteristics of participants in the RZV-exposed group with participants in the RZV-unvaccinated comparator group using SMDs. To determine the applicability of the study results to the European context, a descriptive analysis of RZV Dose 2 recipients was stratified by dose spacing of 28 to 60 days and >60 days between doses.

7.7.2.2. Main analytical approach

We conducted the analysis using a Cox proportional hazards regression model (except when otherwise specified) to estimate the HR of each outcome following RZV in the RZV-exposed compared to the RZV-unvaccinated comparator.

Person-time was defined as the period between the start of follow-up, i.e., Dose 1 or Dose 2 vaccination date for RZV-exposed group and the preventive care visit date for the RZV-unvaccinated comparator, and the earliest of the outcome of interest or a censoring event.

The following served as censoring events in the analysis:

- End of the follow-up period (defined as the lesser of 183 days after the index date)
- Date of disenrollment from Medicare Parts A, B, and D
- Date of death
- Date of Shingrix vaccination among unvaccinated comparators
- Date of Zostavax vaccination
- Date of first diagnosis of the outcome of interest

PS with IPTW-adjusted for confounding in this observational study. The PS was estimated using a logistic regression as the probability of RZV exposure conditioned on the baseline covariates. After non-common range trimming, we estimated the IPTW and assessed the values for extreme weights. We implemented the stabilized IPTW by multiplying the IPTW by the prevalence of treatment and assessed the IPTW (stabilized) to ensure there were no extreme weights, i.e., >10. To mitigate against very large weights, we implemented a 1% and 99% asymmetrical trimming and re-estimated the propensity score and calculated the IPTW and IPTW (stabilized).

The IPTW (stabilized) was used to conduct weighted Cox proportional hazards regression models.

The log-log plots were used to assess violation of the proportional hazard assumption. If the lines in the survival plot crossed, the constant hazard assumption was violated. The negative log of survival probability plots determined the day in the follow-up period when the lines crossed. This was used to define a time-dependent coefficient that was added in the Cox proportional hazards regression model to address the non-proportional hazards.

7.7.2.3. Primary analysis

The primary analysis for PMR, GCA and ION included separate analyses, one specific to Dose 1 and one specific to Dose 2 (Table 7). The cohort included in the primary analysis of Dose 1 was derived from participants who met inclusion criteria for RZV Dose 1. The RZV-unvaccinated comparators included participants who met inclusion criterion for the preventive care visit. The cohort included in the primary analysis of Dose 2 was a subset of participants who met inclusion criteria for Dose 1 who received RZV Dose 2.

Analytical methods as described in Section 7.7.2.2 were implemented where the primary analysis incorporates the same risk period after each dose. Each dose is analyzed separately and yields two separate risk estimates, one for Dose 1 and Dose 2 (Figure 2). The follow-up for Dose 1 started on Day 1 after Dose 1 up to Day 183, regardless of receipt of Dose 2. The follow-up for Dose 2 started on Day 1 after Dose 2 up to Day 183.

- Exposed: At least one dose of the RZV vaccine

- Unexposed: At least one eligible preventive care visit and no prior or same day RZV exposure
- Index date for RZV-exposed: Dose 1 and Dose 2 vaccination date
- Index date for the RZV-unvaccinated comparator: Date of the randomly selected preventive care visit
- Risk period: Day 1 to 183 after the Dose 1 and Dose 2 vaccination dates for the RZV-exposed vaccinated group and after the RZV-unvaccinated comparator preventive care visit
- Baseline covariates and capture of new onset cases: Day 1 to 365 preceding the Dose 1 and Dose 2 vaccination dates for the RZV-exposed group and preceding the preventive care visit date for the RZV-unvaccinated comparator group

Table 7 Planned analyses for PMR, GCA, and ION

Category of analysis	Follow-up period	Risk estimate
Primary Analysis		
Separate analytic models for separate estimates of Doses 1 and 2	Days 1 to 183 after the index date	Separate risk estimates for Dose 1 and Dose 2
COVID-19 Sensitivity to the Primary Analysis		
Separate analytic models for separate estimates of Doses 1 and 2, censoring follow-up on 01 February 2020	Days 1 to 183 after the index date	Separate risk estimates for Dose 1 and Dose 2
Secondary Analysis		
Single analytic model for the combined estimate of Dose 1 and Dose 2	Days 1 to 183 after the index date for each dose	Combines Dose 1 and Dose 2 into a single risk estimate
Single analytic model for separate estimate of Dose 1 and Dose 2	Days 1 to 183 after the index date	Separate risk estimate for each dose in a time-varying model
Sensitivity to the Secondary		
Sensitivity analyses for the Dose 1 and 2 compliant subgroup	Days 1 to 183 after the index date	Separate and single risk estimates (mirror the two 2° analyses)

COVID-19, Coronavirus disease-2019; GCA, Giant cell arteritis; ION, Ischemic optic neuropathy; PMR, Polymyalgia rheumatica.

7.7.2.4. Secondary analyses

Combined dose analysis for a single risk estimate

The combined dose analysis did not distinguish between doses and yielded a single risk estimate for the HOI in Days 1 to 183 following vaccination with either Dose 1 or Dose 2. The hazard function modeled accounts for the event time of both Dose 1 and Dose 2 and only conditions on the 365-day baseline covariate history preceding the index date, i.e., Dose 1 or the preventive care visit date. For this analysis, we used a partly conditional survival model, with stabilized IPTW. This model is appropriate as it estimates the effect of longitudinal measures, in this case dose, on survival, allowing for

repeated measures within participants. For this analysis, baseline covariates preceding Dose 2 were not considered given the proximity of the two-dose administration that resulted in overlap in the look-back periods. In this analysis, the follow-up period was Day 1 until the earliest of 183 after Dose 1 and Dose 2 or the preventive care visit date, occurrence of the HOI, or a censoring event.

Time-varying analysis for separate doses risk estimates

Two separate risk estimates for Dose 1 and Dose 2 were obtained using a stabilized IPTW-weighted time-varying Cox proportional hazards regression model. In the time-varying Cox proportional hazards regression models, the time at risk was attributed to the respective dose. The time after Dose 1 until Dose 2 or the end of follow-up if no Dose 2 occurred defined the time at risk for Dose 1, and the time from Dose 2 until the end of follow-up defined the time at risk for Dose 2. In this analysis, the follow-up period was Day 1 until the earliest of 183 after Dose 1 or the preventive care visit date, the occurrence of the HOI, or a censoring event.

7.7.2.5. Sensitivity of the primary analyses

COVID-19

The COVID-19 pandemic and subsequent lockdowns resulted in less in-person health care visits, which changed patients' health-seeking behaviors. This could have reduced the ability to identify new onset cases of PMR, GCA or ION in administrative claims data. Sensitivity analyses of the primary analysis separate for Dose 1 and Dose 2 censored follow-up on 01 February 2020. This date was set as a censoring event in addition to those listed in Section 7.7.2.2. Any doses administered (or preventative care visits for comparators) on or after 01 February 2020, were excluded.

Alternative HOI definition for GCA and ION

Additional planned sensitivity analyses of the primary analysis considered an alternative definition of GCA and ION. For GCA, the alternative definition used the primary algorithm based on the diagnosis code and steroid prescription but added a requirement for a temporal artery biopsy at the time of diagnosis, as determined by a CPT code=37609. For ION, the definition for the sensitivity included additional criteria for arteritic (≥40 mg/day of prednisone prescription ±4 weeks of the diagnosis) plus an ophthalmologist/neuro-ophthalmologist consult (if possible) and GCA diagnosis within 3 months. However, the sensitivity analyses based on the alternative HOI definitions could not be reported because too few events were detected to render meaningful risk estimates.

7.7.2.6. Sensitivity of the secondary analysis

The sensitivity to the two secondary analyses was conducted for PMR, GCA and ION in the subset of participants who had 60 to 183 days dose spacing between Dose 1 and Dose 2, per the US label dosing schedule. The sensitivity analyses for the dose-compliant subgroup generated a combined dose single risk estimate and a separated dose risk estimate in a time-varying model.

7.7.2.7. Supplemental analysis of the primary analysis

Some participants contribute person-time both to the RZV-unvaccinated comparator group and, if they subsequently received RZV, to the RZV-exposed group. To account for this, a supplemental analysis of Dose 1 and Dose 2 was conducted for each of the primary analyses of PMR, GCA and ION whereby participants were excluded from the comparator arm if they subsequently received RZV. In this analysis, each participant contributed person-time to only one comparator arm.

7.7.2.8. Post-hoc analyses

Several post-hoc analyses were undertaken to assess the effect of censoring Dose 1 at receipt of Dose 2 for PMR, GCA, and ION. The primary analysis did not censor Dose 1 at receipt of Dose 2 that occurred in the 183-day period of follow-up after RZV Dose 1. Thus, it is possible that some of the risk in the primary Dose 1 analysis may be due to events occurring after Dose 2. Post-hoc analyses censoring Dose 1 at receipt of Dose 2 for PMR, GCA, and ION included estimates of the crude hazard ratio, the cumulative incidence and time-to-event, and assessment of the assumption of proportional hazards. Additional post-hoc analyses were conducted to evaluate the age- and index year-stratified cumulative incidence for PMR. Given the violation of the proportional hazards assumption, the post-hoc analyses will evaluate whether the non-proportionality of the risk was specific to an age group or time period (i.e., receipt of RZV in 2018 may have been selectively given to individuals more or less susceptible to PMR).

7.8. Amendments to Statistical Plan

Regarding the SCRI cohorts, GBS and gout had an amendment made in SAP Amendment 4 per Section 9.2.4, the planned approach for the seasonality adjusted analysis first obtained counts of the HOI by month from the most recent three years of the HCUP's Nationwide Inpatient Sample. Next, the initial intent was to calculate the average monthly counts for the most recent three years. However, this produced an insufficient number of observations (n=12 points for average by month across three years) to estimate the area under the curve. Therefore, this approach was modified by estimating the average daily count of events for each calendar month from 2017 through 2019 and taking the midpoint from each month. This produced sufficient data points (n=36) from which to estimate the best fitting linear regression model.

There were no amendments for the other HOIs.

7.9. Quality Control and Quality Assurance

The Data Management/Statistical Analysis Quality Checklist is provided as a separate document to accompany the final statistical analysis report for HOIs (see Annex 1 and Annex 2). The checklist details the actions completed along with dates and signatures of the programmers/statisticians who conducted the checks. Documentation is maintained for quality control and validation procedures for the creation of datasets, extraction of analytic cohorts, HOI definitions, and construction of analytic tables and output data. The PI reviews and approves the document.

For the data integrity and quality control steps, all files and program codes were inspected for inconsistencies and errors using the UMB PRC 3-team member approach (i.e., initial programmer, second programmer, project coordinator). The initial programmer is responsible for the first review of his/her programs and output. A second programmer, whose sole responsibility is quality control, is responsible for a secondary review of the task list and all programs. The project coordinator, who oversees the task order for each programming, serves as the third reviewer responsible for reviewing all output to ensure that it adheres to the protocol.

The PI provides final approval of the quality control measures, ensuring the program and associated outputs are in accordance with the protocol and statistical analysis plan specifications. Any identified inconsistencies are reviewed and corrected as applicable. Once the quality check is completed, the data files are transferred in a secure manner, in the required format for a final check, database freeze/archival, and lock of the dataset.

The SAS® logs and lists are kept for each run of the data until the program is finalized. SAS® codes/logs/outputs (e.g., proc genmod, proc logistic, proc phreg, etc.) for the statistical models that generated the final risk estimates are available as standalone documents.

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 are in tabular form and presented as aggregate analyses that omit subject identification, therefore informed consent, ethics committee or IRB approval was not required. Any publications and reports do not include subject identifiers.

Adequate protections include mandatory training in human subjects research for all study team members, including the HIPAA and CITI training. All members of the research team will renew CITI training every three years.

This study was approved by the IRB of the UMB (Protocol number: HP-00083509). Informed consent was exempt in this secondary data design existing administrative claims data. All procedures for this study involve the manipulation of de-identified data to create aggregate summaries.

8.2. Subject Confidentiality

Source files and derived data resources will be maintained in project-specific directories with restricted permissions. Neither source files nor derived products may be placed on personal storage or removable media, as affirmed by the PRC data access agreement for CMS CCW Medicare data. Violations of this policy may result in a criminal penalty or corrective action. Investigators and staff are required to sign the PRC data access agreement and review data security policies for the P-SHOR department. Policy requirements include restricted data access, secure storage, and strict maintenance of privacy as required by HIPAA. To maintain confidentiality and anonymity of the participants, data are de-identified and cannot be linked back to the individual. UMB investigators and GSK do not have access to participant identifiers. As required by the CMS DUA, and this project's DMP, numbers within cells will be suppressed when the size is 1 to 10.

9. RESULTS

9.1. SCRI – Primary objective: GBS and Gout

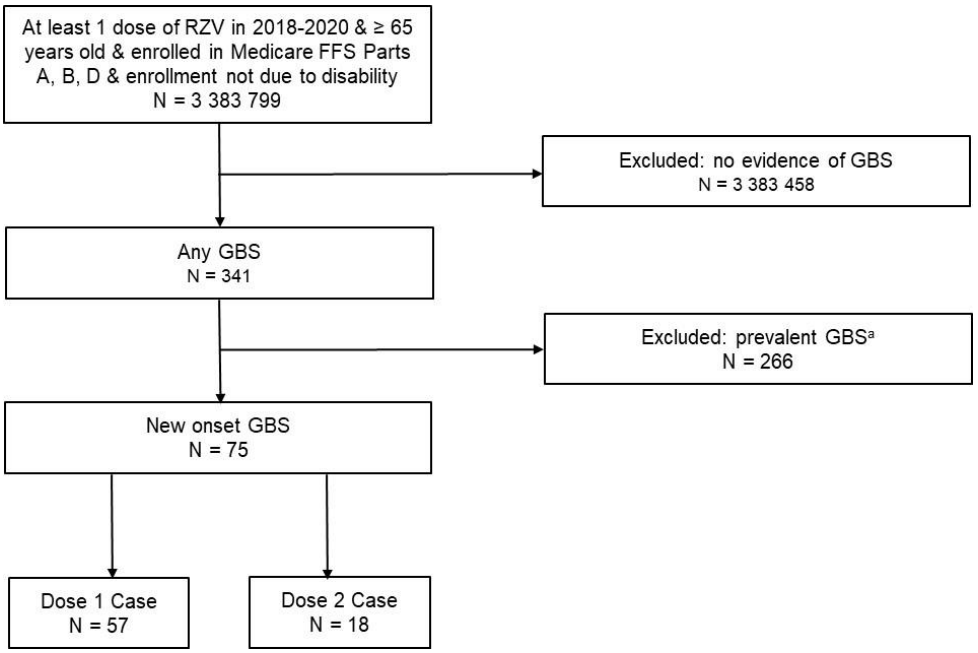
9.1.1. GBS

9.1.1.1. Participants

The study population comprised 3 383 799 US Medicare beneficiaries ≥65 years of age, enrolled in Medicare Parts A, B, and D, whose current, i.e., at the index date, or original qualification for Medicare was not due to disability, who received at least one dose of the RZV vaccine in calendar years 2018, 2019, or 2020 and were continuously enrolled in Medicare for 11 of 12 months preceding the RZV vaccination. There were 341 participants who had any evidence of GBS, of which 75 were new onset GBS in the risk or control window after RZV vaccination. The GBS analytic cohort comprised

57 cases after Dose 1 and 18 cases after Dose 2. Figure 3 illustrates the derivation of the GBS analytic cohort.

Figure 3 Flow diagram of new onset GBS cases among RZV vaccinees



GBS, Guillain-Barré syndrome; RZV, recombinant zoster vaccine; Part A, B, D, enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage).
a. GBS in the year prior to the event observed in the risk or control windows.

9.1.1.2. Descriptive data including baseline characteristics

Descriptive characteristics of the 75 individuals with new onset GBS following RZV exposure are provided for the analytic cohort overall and stratified by the number of doses and dose spacing. No data were missing for the baseline demographic, medical conditions, or health service utilization covariates.

The baseline covariates reflecting the participants' demographic characteristics, medical diagnoses, and healthcare service utilization in the 365 days preceding receipt of RZV Dose 1 are in Section 14.1.2 (Table 35). Among the 75 new onset GBS cases, 28.00% were 80 or more years of age, 50.67% were females, most were White (92.00%), and the largest proportion (44.00%) were vaccinated in 2019. Medical history prior to RZV Dose 1 shows that chronic conditions occurring in 20% or more of cases included: ischemic heart disease (26.67%), diabetes mellitus (21.33%), and chronic kidney disease (20.00%). None of the GBS cases had received concomitant Tdap, and fewer than 11 cases had concomitant influenza or pneumococcal vaccine administered on the same day as the RZV dose.

The graphical distribution of RZV Dose 1 and Dose 2 by calendar month for the 75 GBS cases could not be displayed, even in aggregated months, due to CMS's masking requirements of counts <11. Of the 75 GBS cases, 53 (70.67%) received only Dose 1 and

22 (29.33%) received both doses. Among the 75 cases, the distribution of RZV Dose 1 by calendar year was as follows: 23 in 2018, 33 in 2019, and 19 in 2020.

Those who only received Dose 1 were, on average, two years older than those who received both doses (75.92 [SD: 7.13] versus 74.05 [SD: 6.59], respectively). Over half of Dose 1 only participants were female, and over half of Dose 2 participants were male. Most Dose 1 only and both dose participants were White. Many of the medical conditions and health service utilization covariates could not be displayed due to CMS restrictions on displaying cell sizes less than 11. The small cell sizes also limit meaningful interpretation of group differences. Baseline characteristics by number of doses received are in Section 14.1.2 (Table 36).

All but one participant had >60 days between RZV Dose 1 and Dose 2, therefore it was not possible to conduct the per protocol planned comparison of baseline characteristics between participants who had Dose 2 days 28 to 60 after Dose 1 versus Dose 2 >60 after Dose 1.

Section 14.1.3 (Table 37) includes information on the baseline characteristics for the GBS cases contributing to the secondary and sensitivity analyses, i.e., dose-compliant sensitivity, dose-specific, and the COVID-19 sensitivity analysis. There were no substantial differences in baseline characteristics across the analytic cohorts. Due to small cell sizes, many characteristics had to be masked to comply with the CMS DUA.

There were 14 (18.67%) GBS cases who had evidence of a respiratory or gastrointestinal infection 60 days prior to the GBS diagnosis and 61 (81.33%) GBS cases had no evidence of a respiratory or gastrointestinal infection in the 60 days prior to the GBS diagnosis. Of the 61 GBS cases without a prior respiratory or gastrointestinal infection, 48 (78.69%) were in the risk window and 13 (21.31%) were in the control window. The characteristics of those with and without evidence of a respiratory or gastrointestinal infection could not be displayed due to CMS DUA restrictions on displaying cell sizes less than 11. Additionally, in compliance with the CMS DUA, we cannot report the risk window and control window distribution of the 14 respiratory or gastrointestinal infection cases due to small cell sizes. Instead, we reported on the 61 without these conditions. Baseline descriptive characteristics of the 61 participants who did not have a respiratory or gastrointestinal infection 60 days before the GBS diagnosis are provided in Section 14.1.4 (Table 38).

9.1.1.3. Outcome data

Fifty-seven of the 75 GBS cases were detected in the 1 to 42-day risk window after the RZV exposure index date. Due to the need for masking to align with CMS DUA, the distribution of GBS cases by day post RZV and dose could not be produced graphically. However, of the 57 GBS cases identified during the risk window, 25 cases were detected from Days 1 to 14 and 32 cases from Days 15 to 42 after the RZV index date.

9.1.1.4. Results of primary analyses

The SCRI primary analysis shows a statistically significant increased risk of GBS (RR=3.15; 95% CI: 1.82, 5.68) following RZV vaccination (Table 8). The estimated attributable risk was 6.59 cases per 1 000 000 RZV vaccinations (95% CI: 4.35, 7.96).

9.1.1.5. Results of secondary analyses

The secondary analyses used a fixed 3-week and a fixed 6-week control window for all doses and did not censor the Dose 1 control window at receipt of Dose 2 (Table 8).The relative risk for the fixed 3-week control window was 3.56 (95% CI: 1.69, 8.65), and the attributable risk was 6.95 cases per 1 000 000 RZV vaccinations (95% CI: 3.94, 8.54). The relative risk for the fixed 6-week control window was 3.17 (95% CI: 1.84, 5.72), and the attributable risk was 6.61 cases per 1 000 000 RZV vaccinations (95% CI: 4.41, 7.97).

9.1.1.6. Results of sensitivity to the primary analyses

Table 8 shows the results of the sensitivity analyses.

Dose-compliant sensitivity analysis

The sensitivity analyses for the dose-compliant 60 to 183-day dose spacing subgroup were not statistically significant.

Seasonality adjusted sensitivity analysis

The seasonality-adjusted sensitivity analysis also showed an elevated risk of GBS (RR=3.17; 95% CI: 1.84, 5.72; AR=6.61; 95% CI: 4.41, 7.97), results that mirrored the primary analysis.

COVID-19-adjusted sensitivity analysis

The COVID sensitivity analysis included 49 GBS cases after excluding individuals who received an RZV vaccination on or after 08 November 2019. The results also indicated a statistically significant increased risk of 5.13 (95% CI: 2.37, 12.66) and an attributable risk of 9.37 cases per 1 000 000 RZV vaccinations (95% CI: 6.70, 10.68).

Ad hoc sensitivity analysis

As per the SAP, an ad hoc sensitivity SCRI analysis was deemed appropriate and conducted like the primary SCRI analysis but excluding GBS cases with evidence of respiratory or gastrointestinal infection in the 60 days prior to the GBS diagnosis. Among the 61 GBS cases without evidence of respiratory or gastrointestinal infection 60 days prior to the GBS diagnosis, the results indicated an elevated risk (RR=3.66, 95% CI: 1.95, 7.37) that mirrored the primary analysis.

9.1.1.7. Results of sensitivity to secondary analyses

Dose-specific sensitivity analysis

The Dose 1 specific sensitivity analysis with a fixed 6-week control window included 57 GBS cases. There was an increased risk for GBS (RR=5.33; 95% CI: 2.59, 12.36; and AR=11.83; 95% CI: 8.94, 13.38). The Dose 2 specific analysis with a fixed 6-week control window was not statistically significant.

Table 8 Risk of new onset GBS following RZV exposure

Analysis Type	Mean days (SD) CW length	Total cases	No. cases in RW[a] (%)	No. cases in CW[a] (%)	RR (95% CI)	AR[b] (95% CI)
Primary Analysis						
Dose 1 and 2 without distinguishing[c]	41.8 (2.08)	75	57 (76)	18 (24)	3.15 (1.82 – 5.68)	6.59 (4.35–7.96)
Secondary Analysis						
Fixed 3-wk control window, Dose 1 and 2 without distinguishing	21 (0)	65	>50	<11	3.56 (1.69 – 8.65)	6.95 (3.94–8.54)
Fixed 6-wk control window, Dose 1 and 2 without distinguishing	42 (0)	75	57 (76)	18 (24)	3.17 (1.84 – 5.72)	6.61 (4.41–7.97)
Sensitivity Analysis						
Dose Compliant: 60-183- day dose-spacing, Dose 1 and 2 without distinguishing[c]	41.1 (4.02)	20	>11	<11	1.46 (0.55 – 4.13)	0.84 (-4.55–4.05)
Dose 1 only: Fixed 6-wk control window	42 (0)	57	>40	<11	5.33 (2.59 – 12.36)	11.83 (8.94–13.38)
Dose 2 only: Fixed 6-wk control window	42 (0)	18	<11	<11	1.00 (0.35 – 2.84)	N/A
Seasonality Adjusted Analysis: Dose 1 and Dose 2 without distinguishing[c]	41.8 (2.08)	75	57 (76)	18 (24)	3.17 (1.84 – 5.72)	6.61 (4.41–7.97)
COVID-19 Analysis: Exclude doses on or after November 8, 2019, Dose 1 and 2 without distinguishing[c]	42 (0)	49	>40	<11	5.13 (2.37 – 12.66)	9.34 (6.70–10.68)

SCRI, self-controlled risk interval; RW, risk window; CW, control window; RR, relative risk; AR, attributable risk; wk, week.

a. RW is Days 1 to 42 after vaccination, CW starts on Day 43. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist.

b. 1 000 000 × no. of cases in the risk window × [1-(1/relative risk)] / [no. of vaccine doses]; number of vaccine doses included the entirety of doses administered, included for cases and non-cases.

c. Dose 1 CW censored at receipt of Dose 2.

9.1.1.8. Temporal scan

A total of 45 scan windows were tested. The observed to expected cases in the scan window revealed statistically significant clustering of cases in 42 windows (Section 14.1.5, Table 39). The significant clustering mainly occurred in the risk window following RZV exposure.

9.1.1.9. Results of post-hoc analysis

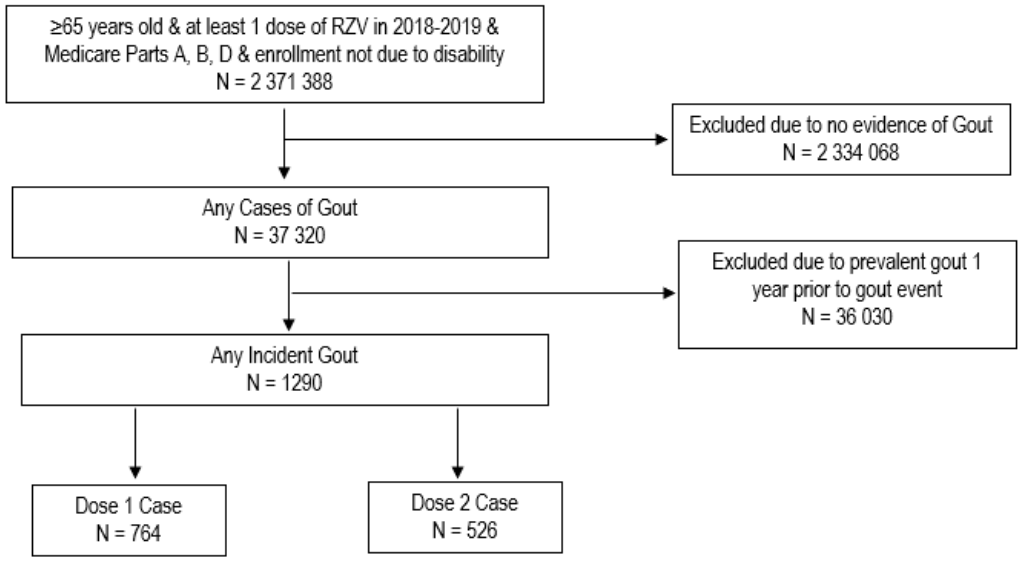
The risk of GBS was attenuated when excluding 24 GBS cases who received a pneumococcal, influenza, or Tdap vaccine concomitantly on the RZV index date or in the 42 days prior to RZV exposure (RR=2.92; 95% CI: 1.52, 5.98). The age-stratified analysis revealed a relative risk of 3.75 (95% CI: 1.68, 9.47) among adults ≥75 years of age compared with a relative risk of 2.66 (95% CI: 1.24, 6.17) among adults 65 to 74 years of age at receipt of RZV. Adjusting for a 50% PPV, the results remained statistically significant but with wider confidence intervals relative to the primary analysis (RR=3.18; 95% CI: 1.47, 7.64).

9.1.2. GOUT

9.1.2.1. Participants

The study population was comprised of 2 371 388 US Medicare beneficiaries ≥65 years of age, enrolled in Medicare Parts A, B, and D did not qualify for Medicare due to disability, who received at least one dose of the RZV vaccine in calendar years 2018 or 2019, and were continuously enrolled in Medicare for 11 of 12 months preceding the RZV vaccination. There were 37 320 participants who had evidence of gout in the risk or control window after RZV vaccination, of which 1290 were new onset gout cases and comprised the gout analytic cohort. See Figure 4 for the derivation of the gout analytic cohort.

Figure 4 Flow diagram of new onset Gout cases among RZV vaccinees



RZV, recombinant zoster vaccine; Part A, B, D, enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage).

9.1.2.2. Descriptive data including baseline characteristics

Descriptive characteristics of the 1290 individuals with new onset gout following RZV exposure are provided for the analytic cohort overall and stratified by the number of doses and dose spacing. The distributions of receipt of Dose 1 and Dose 2 are graphically displayed. There were no data missing for the baseline demographic, medical conditions, or healthcare service utilization covariates.

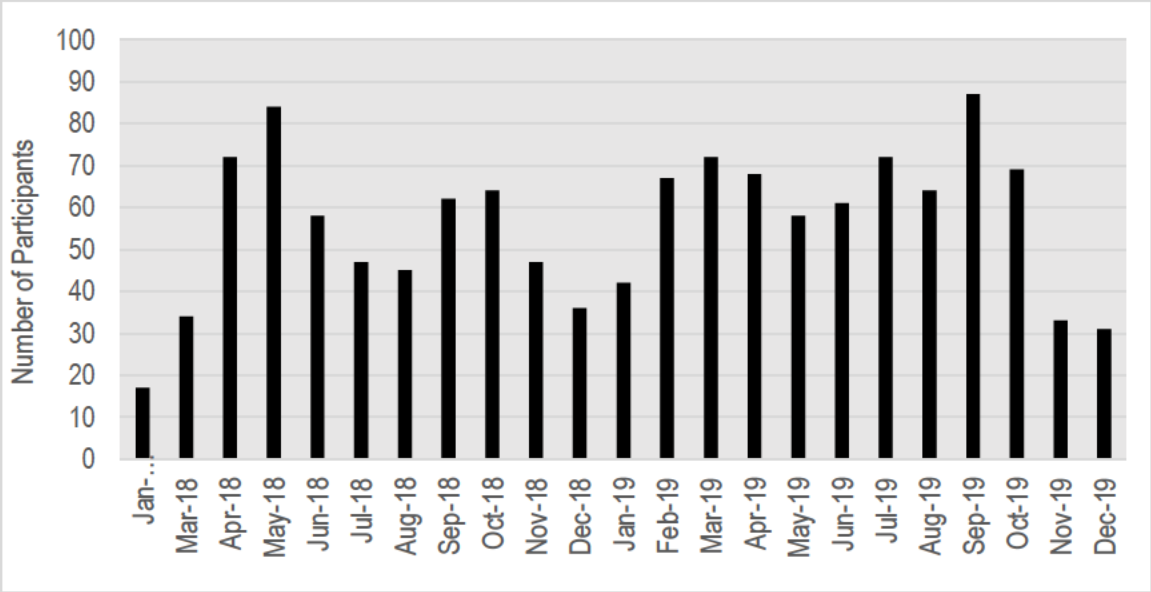
The demographic and health characteristics displayed in Section 14.2.2 (Table 41) are the baseline covariates reflecting the participants' medical history and healthcare service utilization in the 365 days preceding receipt of RZV Dose 1. Among the 1290 new onset gout cases, most are White (n=1122; 86.98%), male (n=789; 61.16%), and 70 to 79 years of age (70 to 74: n=380 [29.46%]; 75 to 79: n=340 [26.36%]). More than half of the cases received the respective RZV vaccination in 2019 (56.12%). The most frequently seen chronic conditions occurring in 20% or more of cases included: chronic kidney disease (41.16%), diabetes mellitus (36.67%), ischemic heart disease (33.57%). Immunocompromised conditions were less prevalent than common chronic conditions.

Distribution of RZV dose 1 and dose 2

The numbers of participants who received RZV Dose 1 and Dose 2 by calendar month in 2018 and 2019 are displayed in Figure 5 and Figure 6, respectively. Data for some of the months were combined when the number was less than 11, which is not reportable in accordance with CMS DUA requirements. Receipt of RZV Dose 1 gradually increased through May 2018 where just over 80 participants received the vaccine. Approximately 40 to 70 participants were vaccinated in any given month, except September 2019, with nearly 90 vaccinations.

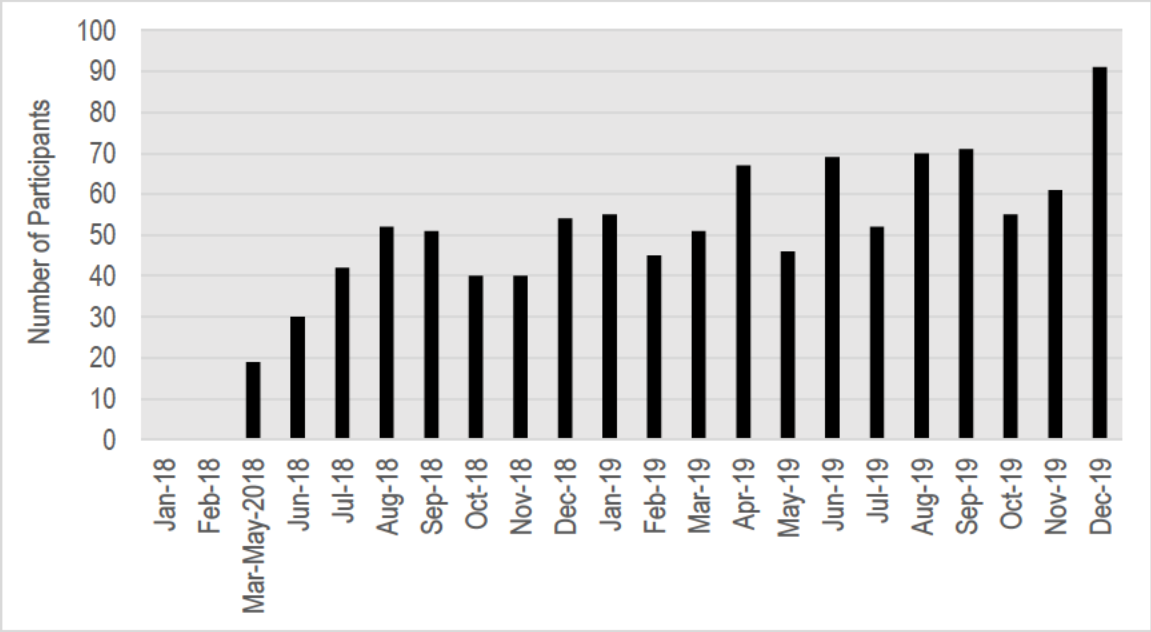
Patterns of Dose 2 show a relatively stable trend. The first two months in 2018 had no Dose 2 administrations because participants had received their first dose during this time. However, Dose 2 vaccinations appear starting in March 2018 through May 2018, which is two to four months after those who received Dose 1 earlier in 2018.

Figure 5 Distribution of RZV Dose 1 by calendar month for gout cases



RZV, recombinant zoster vaccine.
Note: Cases counted from January 2018 to December 2019 out of the total 1290 cases identified. Cases for January and February 2018 (i.e., Jan to Feb2018) were combined because of number <11.

Figure 6 Distribution of RZV Dose 2 by calendar month for gout cases



RZV, recombinant zoster vaccine.
Note: Cases counted from January 2018 to December 2019 out of the total 1290 cases identified. Cases for March to May 2018 (i.e., Mar to May 2018) were combined because of number <11.

Characteristics by number of doses

Of the 1290 participants who developed gout, 1061 (82.25%) participants received two doses of RZV (Section 14.2.2, Table 42). There were no appreciable differences in the distributions by age, sex, or race with the 229 who only received Dose 1. The majority of Dose 1 only participants (n=182; 79.48%) were vaccinated in 2019.

Chronic medical conditions, such as diabetes mellitus, chronic kidney disease, COPD, and ischemic heart disease, were similar between the two groups. However, a slightly higher proportion of participants who only received Dose 1 had congestive heart failure (n=58; 25.33%) relative to the participants who received two doses (n=189; 17.81%). Whereas too few to report on Dose 1 participants with any immunocompromised conditions, these were present, albeit uncommon, in the two-dose participant subgroup.

Characteristics by dose spacing

Of the 1061 participants who received both doses, 1012 (95.38%) received Dose 2 more than 60 days after receipt of Dose 1 (Section 14.2.2, Table 43). Participants with 28 to 60 days between doses were on average three years older than participants with >60 days between doses. Female participants represented about half (n=24; 48.98%) of the subgroup with 28 to 60-day dose spacing compared with 38.44% (n=389) of the subgroup with >60 days between doses. The distribution of medical conditions was similar between subgroups except for diabetes mellitus; 37.45% (n=379) of participants with >60 days between doses had evidence of diabetes mellitus compared with 24.49% (n=12) of participants with 28 to 60 days between doses. DME use was similar between subgroups.

Characteristics by secondary and sensitivity analytic cohorts

Section 14.2.3 (Table 44) includes information on the baseline characteristics for each of the analytic cohorts for secondary and sensitivity analyses, i.e., dose-compliant sensitivity, secondary analysis, separate dose sensitivity analysis, and the COVID-19 sensitivity analysis. There were not substantial differences in baseline characteristics across the analytic cohorts.

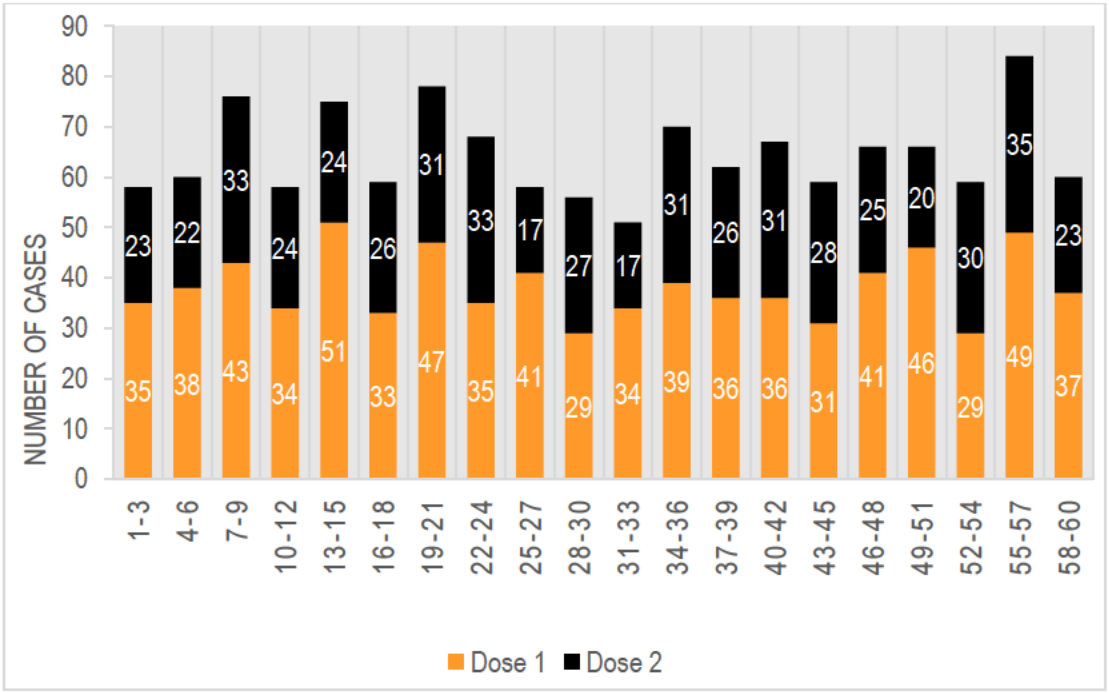
9.1.2.3. Outcome data

The distribution of new onset gout cases by day after the RZV index date is displayed in Figure 7. The case count by day of follow-up displays the dose to which the case is attributed. The total follow-up interval of 60 days is presented in three-day increments because some day case counts were <11 and cannot be displayed in accordance with CMS DUA requirements. Days 1 to 30 represent the risk window and Days 31 to 60 represent the control window. Of the 1290 gout cases, 764 (59.22%) cases occurred after Dose 1 and 526 (40.78%) cases occurred after Dose 2. Most cases (n=84) were observed 55 to 57 days after the respective dose, with 49 occurring after Dose 1 and 35 occurring after Dose 2.

Section 14.2.4 (Table 45) displays the results of the descriptive examination of ICD-10 codes for the gout case ascertainment algorithm. A total of 800 (62.02%) cases met the

gout case ascertainment definition after all chronic and secondary gout codes were excluded. Gout cases associated with the following ICD-10 codes were inspected: chronic gout (M1A*), lead-induced gout (M10.1*), drug-induced gout (M10.2*), and gout due to renal impairment (M10.3*). Overall, only 100 (7.75%) cases were associated with a low-frequency code, and 1190 (low-frequency and other code: n=127 [9.84%]; other code – not a low-frequency code: n=1063 [82.40%]) cases were not associated with a low-frequency gout ICD-10 code.

Figure 7 New onset gout cases by dose and day from the RZV index date



RZV, Recombinant Zoster Vaccine.

9.1.2.4. Results of primary analyses

The results of the primary analysis, which estimated the relative risk of gout without distinguishing between doses are in Table 9. The numbers of cases in the risk and control windows were nearly equal, 646 (50.08%) and 644 (49.92%), respectively. The mean control window length was 29.9 days (±0.91). The relative risk of new onset gout was 1.00 (95% CI: 0.90, 1.12), which indicates that there was no statistically significant increased risk of new onset gout in the risk window following vaccination related to the control window.

9.1.2.5. Results of secondary analyses

The secondary analysis used a fixed 30-day control window for all doses and did not censor the Dose 1 control window at receipt of Dose 2 (Table 9). The mean control window length was 30 days. The relative risk was 1.00 (95% CI: 0.90,1.12). These findings were the same as in the primary analysis

9.1.2.6. Results of sensitivity to the primary analyses

Dose-compliant sensitivity analysis

The dose-compliant sensitivity analysis results in Table 9 show that 959 (74.34%) of the 1290 gout cases had 60 to 183 days between doses. The number of cases in the risk window (n=477; 49.74%) was nearly equal to the number of cases in the control window (n=482; 50.26%). The mean control window length was 30 days. The relative risk of new onset gout was 0.99 (95% CI: 0.87, 1.13), indicating a non-significant association between RZV exposure and onset gout in the dose-compliant spacing subgroup who received both doses.

Seasonality adjusted sensitivity analysis

Adjustment for the seasonal pattern of gout was conducted by using an offset term as the area under the gout-by-calendar-month curve. This sensitivity analysis estimated the relative risk of new onset gout without distinguishing between doses. All 1290 cases in the gout analytic cohort contributed to the analysis, with 646 cases (50.08%) in the risk window and 644 cases (49.92%) in the control window. The mean length of the control window was 29.9 ($\pm$0.91). The relative risk of new onset gout was 1.00 (95% CI: 0.90, 1.12), suggesting no statistically significant association with RZV exposure after accounting for the seasonal pattern of gout (Table 9).

COVID-19-adjusted sensitivity analysis

A total of 1221 (94.65%) of the 1290 new onset gout cases contributed to the COVID-19 adjusted analysis. There were 612 (50.12%) cases in the risk window and 609 (49.88%) cases in the control window. The mean control window length was 29.9 ($\pm$0.94) days. The findings in Table 9 show no statistically significant association between new onset gout and RZV exposure (RR=1.00; 95% CI=0.89, 1.12).

9.1.2.7. Results of sensitivity to the secondary analyses

Dose-specific sensitivity analysis

Sensitivity analyses with a 30-day fixed control window that was not censored at receipt of Dose 2 evaluated the risk of new onset gout separately for Dose 1 and Dose 2 (Table 9). Among the 764 gout cases which occurred following exposure to RZV Dose 386 (50.52%) occurred in the risk window and 378 (49.48%) in the control window. A statistically significant increased risk of new onset gout following RZV Dose 1 was not observed (RR=1.02; 95% CI: 0.88, 1.18). There were 526 new onset gout cases following exposure to RZV Dose 2, of which 260 (49.43%) occurred in the risk window and 266 (50.57%) in the control window. The relative risk of new onset gout was not statistically significant (RR=0.98; 95% CI: 0.82, 1.16).

Table 9 Risk of new onset gout following RZV exposure

Analysis type	Mean days (SD) CW length	Total cases	No. cases in RW[a] (%)	No. cases in CW[a] (%)	RR (95% CI)
Primary Analysis					
Dose 1 and 2 without distinguishing[b]	29.9 (0.91)	1290	646 (50.08)	644 (49.92)	1.00 (0.90, 1.12)
Secondary Analysis					
Fixed 30-day control window, Dose 1 and 2 without distinguishing	30 (0)	1290	646 (50.08)	644 (49.92)	1.00 (0.90, 1.12)
Sensitivity Analysis					
Dose-Compliant: 60-183- day dose spacing, Dose 1 and 2 without distinguishing[b]	30.0 (0)	959	477 (49.74)	482 (50.26)	0.99 (0.87, 1.13)
Fixed 30-day control window, Dose 1 only	30 (0)	764	386 (50.52)	378 (49.48)	1.02 (0.88, 1.18)
Fixed 30-day control window, Dose 2 only	30 (0)	526	260 (49.43)	266 (50.57)	0.98 (0.82, 1.16)
Seasonality Adjusted Analysis: Dose 1 and Dose 2 without distinguishing[b]	29.9 (0.91)	1290	646 (50.08)	644 (49.92)	1.00 (0.90, 1.12)
COVID-19 Analysis: Exclude doses on or after December 2, 2019, Dose 1 and 2 without distinguishing[b]	29.9 (0.94)	1221	612 (50.12)	609 (49.88)	1.00 (0.89, 1.12)

CW, control window; RW, risk window; SCRI, self-controlled risk interval.

a. RW is Days 1 to 30 after vaccination, CW starts on Day 31. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist.

b. Dose 1 CW censored at receipt of Dose 2.

9.1.2.8. Temporal scan

Results from the temporal scan are in Section 14.2.5 (Table 46). A total of 17 scan windows were tested. The observed-to-expected cases in the scan window were not

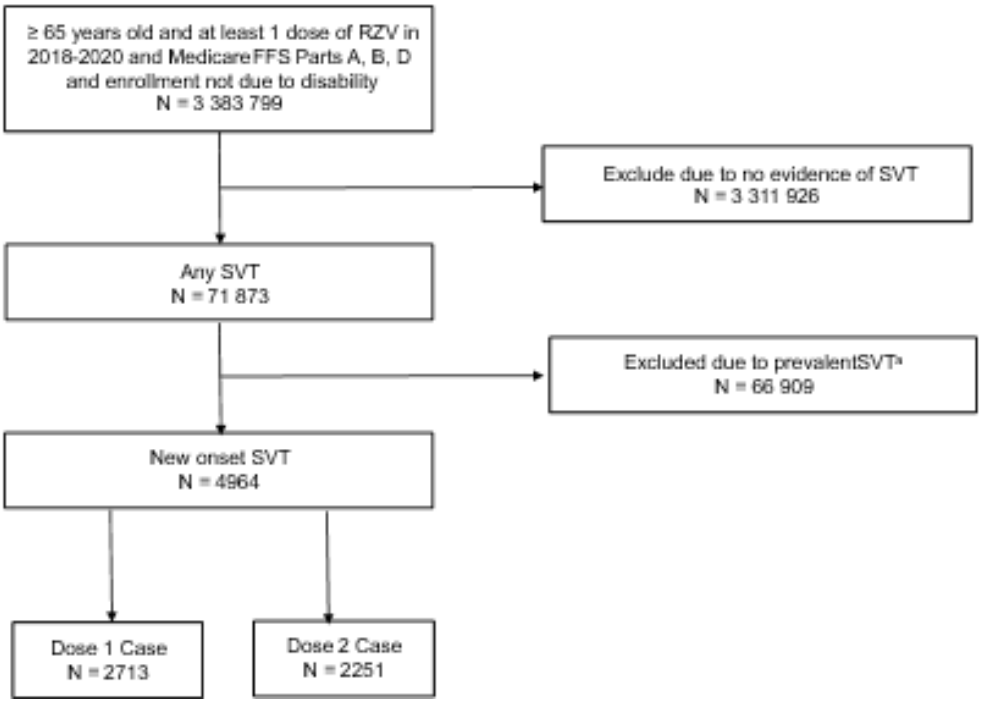
statistically significantly different. The finding suggests that there was not a significant temporal clustering of cases.

9.2. SCRI – Secondary objective: SVT

9.2.1. Participants

The study population comprised 3 383 799 US Medicare beneficiaries ≥65 years of age, continuously enrolled in Medicare Parts A, B, and D for 11 of the 12 months preceding RZV exposure, whose current, i.e., at the index date, or original qualification for Medicare was not due to disability and received at least one dose of the RZV vaccine in calendar years 2018, 2019, or 2020. There were 71 873 participants who had any evidence of SVT, of which 4964 were new onset SVT cases and comprised the SVT analytic cohort. There were 2713 SVT cases after Dose 1 and 2251 cases of SVT after Dose 2. Figure 8 is the consort diagram illustrating the derivation of the SVT analytic cohort.

Figure 8 Flow diagram of new onset SVT among RZV vaccinees



SVT, supraventricular tachycardia; RZV, recombinant zoster vaccine; Part A, B, D – enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage).
a. SVT in the year prior to the event observed in the RW or CW.

9.2.2. Descriptive data including baseline characteristics

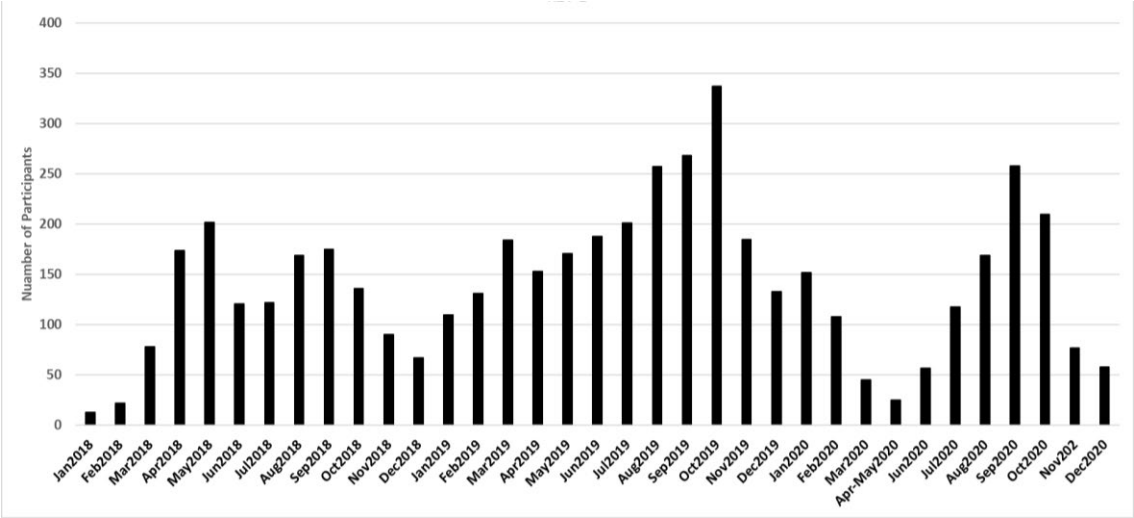
The demographic and health characteristics displayed in Section 14.3.1 (Table 47) are the baseline covariates reflecting the participants' medical diagnoses and health service utilization in the 365 days preceding receipt of RZV Dose 1. Among the 4964 new onset

SVT cases, most are White (n=4559; 91.84%), female (n=2882; 58.06%), and 70 to 79 years of age (70 to 74: n=1405 [28.30%]; 75 to 79: n=1262 [25.42%]). Almost half of the cases received the respective RZV vaccination in 2019 (46.70%). The most frequently seen chronic conditions occurring in 20% or more of cases in the SVT analytic cohort were ischemic heart disease (32.09%), chronic kidney disease (25.18%), diabetes mellitus (25.10%). There was a low prevalence of immunocompromised conditions at baseline, with far less than 5%.

Distribution of RZV Dose 1 and Dose 2

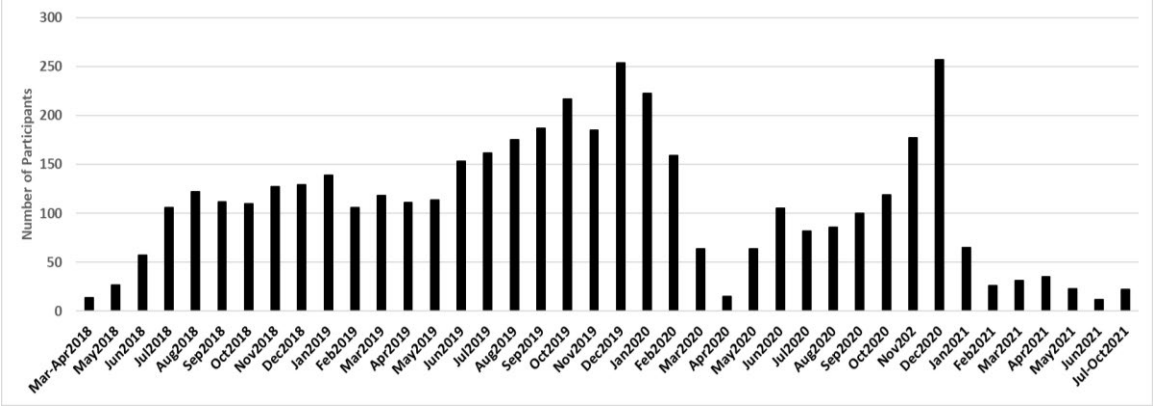
The number of participants who received RZV Dose 1 and Dose 2 by calendar month in 2018, 2019, and 2020 is displayed in Figure 9 and Figure 10, respectively. Data for some of the months were combined when the count was less than 11, which is not reportable in accordance with CMS DUA requirements. The number of participants who received RZV Dose 1 in a given month varied from year to year, with the number of participants peaking in October 2019 at 337. Patterns of RZV Dose 2 show similar monthly fluctuations as seen with Dose 1.

Figure 9 Distribution of RZV Dose 1 by calendar month for SVT cases



RZV, recombinant zoster vaccine; SVT, supraventricular tachycardia.
Note: Cases counted from January 2018 to December 2020 out of the total 4964 cases identified. Cases for April and May 2020 (i.e., Apr to May 2020) were combined because of number <11.

Figure 10 Distribution of RZV Dose 2 by calendar month for SVT cases



RZV, recombinant zoster vaccine; SVT, supraventricular tachycardia.
Note: Cases counted from January 2018 to December 2020 out of the total 4964 cases identified. Cases for March to April 2018 (i.e., Mar-Apr 2018) and for July to October 2021 (i.e., Jul–Oct 2021) were combined because of numbers <11.

Characteristics by number of doses

Of the 4964 participants identified as SVT cases, 4390 (88.44%) received both RZV doses (Section 14.3.1, Table 48). There were no appreciable differences in the distributions by age, sex, or race, with the 574 participants who only received Dose 1. Chronic medical conditions, such as diabetes mellitus, chronic kidney disease, chronic lung disease, and ischemic heart disease, were slightly lower among those who received both doses compared to those who received Dose 1 only. A similar proportion of participants who only received Dose 1 compared with those who received both doses had a stroke/TIA (n=62; 10.80% versus n=436; 9.93%, respectively).

Characteristics by dose spacing

Characteristics of the 4390 participants who received both doses are shown according to dose spacing (Section 14.3.1, Table 49). There were 4209 (95.88%) participants who received Dose 2 more than 60 days after receipt of Dose 1 and 181 (4.12%) participants with 28 to 60 days between doses. Male participants represented about one-third (n=66; 36.46%) of the subgroup with 28 to 60-day dose spacing compared with 42.65% (n=1795) of the subgroup with >60 days between doses. The distribution of medical conditions, hospitalizations, emergency room visits, and use of durable medical equipment were similar between the subgroups. Some cell sizes were suppressed due to the CMS DUA restriction.

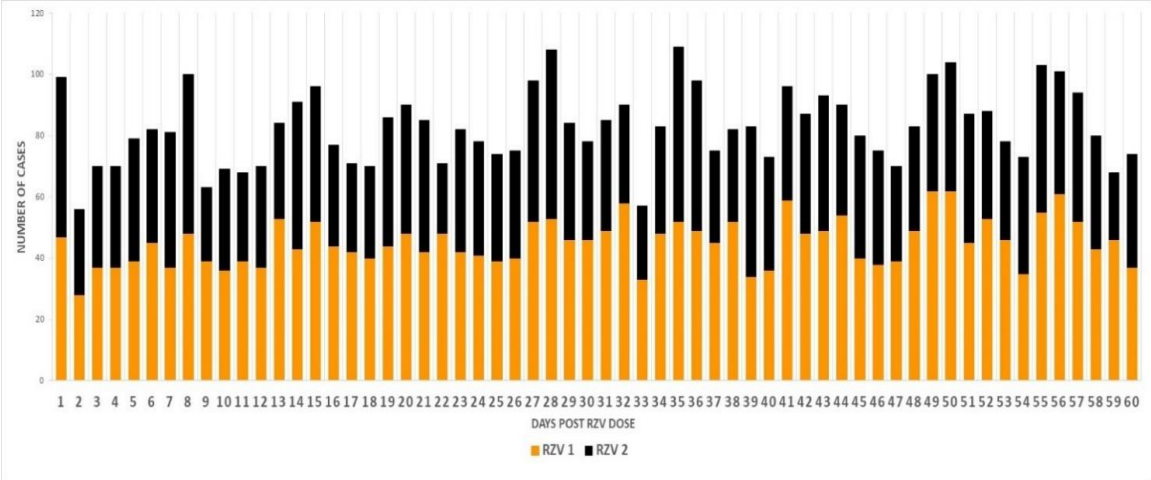
Characteristics by secondary and sensitivity analytic cohorts

The descriptive characteristics of analytics cohorts for sensitivity and secondary analyses is reported in Section 14.3.2 (Table 50).

9.2.3. Outcome data

The distribution of new onset SVT cases by day after the RZV index date is displayed in Figure 11. The case count by day of follow-up displays the dose to which the case is attributed. Days 1 to 30 represent the risk window and Days 31 to 60 represent the control window. The 4964 SVT cases were generally evenly distributed across the Day 1 to 30 risk window and the Day 31 to 60 control window after RZV exposure (Figure 11). A total of 2713 (54.65%) cases occurred after Dose 1, and 2251 (45.35%) cases occurred after Dose 2.

Figure 11 New onset SVT cases by dose and day from the RZV index date



RZV1, recombinant zoster vaccine dose 1; RZV2, recombinant zoster vaccine dose 2; SVT, supraventricular tachycardia.

9.2.4. Results of primary analyses

The results of the primary analysis, which estimated the relative risk of SVT without distinguishing between doses, are in Table 10. The results show a relative risk of 0.94 (95% CI: 0.89, 0.99), which was statistically significant. The mean days of the control window was 29.95 (±0.68) days.

9.2.5. Results of secondary analyses

The secondary analysis generated the same relative risk and 95% CI as the primary analysis (RR=0.94; 95% CI: 0.89, 0.99). Results are shown in Table 10 .

9.2.6. Results of sensitivity to the primary analyses

Dose-compliant sensitivity analysis

The results of the dose-compliant sensitivity analyses are presented in Table 10 and show that 3837 (77.30%) of the 4964 SVT cases had 60 to 183 days between RZV doses. There were 1895 (49.39%) cases in the risk window and 1942 (50.61%) cases in the control window. The mean control window length was 30 days. The relative risk of new onset SVT was 0.98 (95% CI: 0.92, 1.04), indicating a non-significant association between

RZV exposure and new onset SVT in the dose-compliant spacing subgroup who received both doses.

COVID-19-adjusted sensitivity analysis

A total of 3175 (63.96%) of the 4964 new onset SVT cases contributed to the COVID sensitivity analysis. There were 1538 (48.44%) cases in the risk window and 1637 (51.56%) cases in the control window. The mean control window length was 29.96 (±0.76) days. No elevated risk of new onset SVT was observed for the COVID sensitivity analysis that excluded participants who received an RZV vaccination on or after 02 December 2019 (RR=0.94; 95% CI: 0.87, 1.01); Table 10.

9.2.7. Results of sensitivity to the secondary analyses

Dose-specific sensitivity analysis

In the fixed 30-day Dose 1 only sensitivity analysis, 2713 SVT cases occurred following RZV Dose 1, of which 1284 (47.33%) occurred in the risk window and 1429 (52.67%) in the control window. The fixed 30-day control window Dose 1 only sensitivity analysis produced a relative risk of 0.90 (95% CI: 0.83, 0.97), which mirrored the primary and secondary analyses (Table 10). The findings were statistically significant.

A total of 2251 new onset SVT cases occurred after RZV Dose 2, of which 1121 (49.80%) occurred in the risk window and 1130 (50.20%) in the control window. The relative risk of new onset SVT in the fixed 30-day control window Dose 2 only sensitivity analysis was 0.99 (95% CI: 0.92, 1.08), which was not statistically significant.

Table 10 Risk of new onset SVT following RZV exposure

Analysis Type	Mean days (SD) CW length	Total cases	No. cases in RW[a] (%)	No. cases in CW[a] (%)	RR (95% CI)
Primary Analysis					
Dose 1 and 2 without distinguishing[b]	29.95 (0.68)	4964	2405 (48.45)	2559 (51.55)	0.94 (0.89 – 0.99)
Secondary Analysis					
Fixed 30-day control window, Dose 1 and 2 without distinguishing	30 (0)	4964	2405 (48.45)	2559 (51.55)	0.94 (0.89 – 0.99)
Sensitivity Analyses					
Dose Compliant: 60 to 183-day dose-spacing, Dose 1 and 2 without distinguishing[b] subset of Primary Analysis	30 (0)	3837	1895 (49.39)	1942 (50.61)	0.98 (0.92 – 1.04)
Dose 1, subset of Secondary Analysis	30 (0)	2713	1284 (47.33)	1429 (52.67)	0.90 (0.83 – 0.97)
Dose 2, subset of Secondary Analysis	30 (0)	2251	1121 (49.80)	1130 (50.20)	0.99 (0.92 – 1.08)

Analysis Type	Mean days (SD) CW length	Total cases	No. cases in RW[a] (%)	No. cases in CW[a] (%)	RR (95% CI)
COVID-19 Analysis: Exclude doses on or after December 2, 2019, Dose 1 and 2 without distinguishing[b]	29.96 (0.76)	3175	1538 (48.44)	1637 (51.56)	0.94 (0.87 – 1.01)

SVT, supraventricular tachycardia; SCRI, self-controlled risk interval; RW, risk window, CW, control window.

a. RW is Days 1-30 after vaccination, CW starts on Day 31. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist.

b. Dose 1 CW censored at receipt of Dose 2.

9.2.8. Temporal scan

A total of 29 scan windows were tested, and only two were statistically significant. The observed-to-expected cases in the scan window were statistically significantly different in the windows with lengths 27 to 56 (p=0.029) and 28 to 57 (p=0.042). The results suggest that, in these day windows, there is significant temporal clustering of cases but close to 1 (RR=1.11). The temporal scan statistics are in Section 14.3.3 (Table 51).

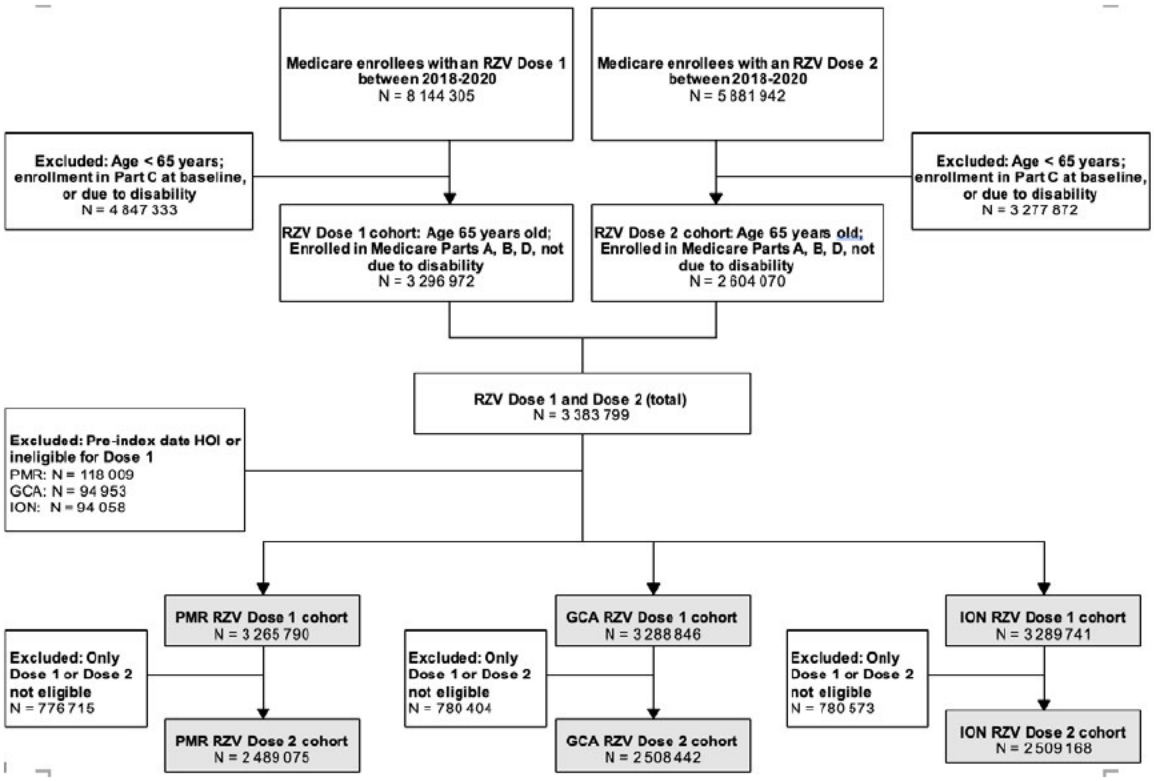
9.3. COHORT – RZV-exposed and RZV-unvaccinated comparators

9.3.1. RZV-Exposed

Figure 12 illustrates the derivation of the RZV-exposed analytic cohorts for PMR, GCA, and ION. We derived the RZV-exposed group from a population comprising Medicare beneficiaries who received RZV vaccine Dose 1 or Dose 2. As per protocol, the RZV Dose 1 sample included 8 144 305 participants who received Dose 1 from 01 January 2018 through 31 December 2020. The RZV Dose 2 sample included 5 881 942 participants who received Dose 2 in calendar years 2018 through 2020. Applying the inclusion criteria of ≥65 years of age at Dose 1, continuously enrolled in Medicare Parts A, B, and D for at least 11 of the 12 months preceding Dose 1, and current, i.e., at the index date, or original qualification for Medicare was not due to disability, this left 3 296 972 Dose 1 eligible participants. For RZV Dose 2, there were 2 604 070 participants who satisfied the above-mentioned inclusion criteria. Overall, the RZV-exposed group was comprised of 3 383 799 participants who had an eligible RZV Dose 1 and/or Dose 2 in calendar years 2018 through 2020.

From the 3 383 799 participants with an eligible RZV Dose 1 and/or Dose 2, we created three analytic cohorts, two for the primary HOIs of PMR and GCA and one for the secondary HOI of ION.

Figure 12 Flow diagram of the derivation of the RZV-exposed analytic cohorts



GCA, giant cell arteritis; HOI, health outcome of interest; ION, ischemic optic neuropathy; PMR, polymyalgia rheumatica; RZV, recombinant zoster vaccine.

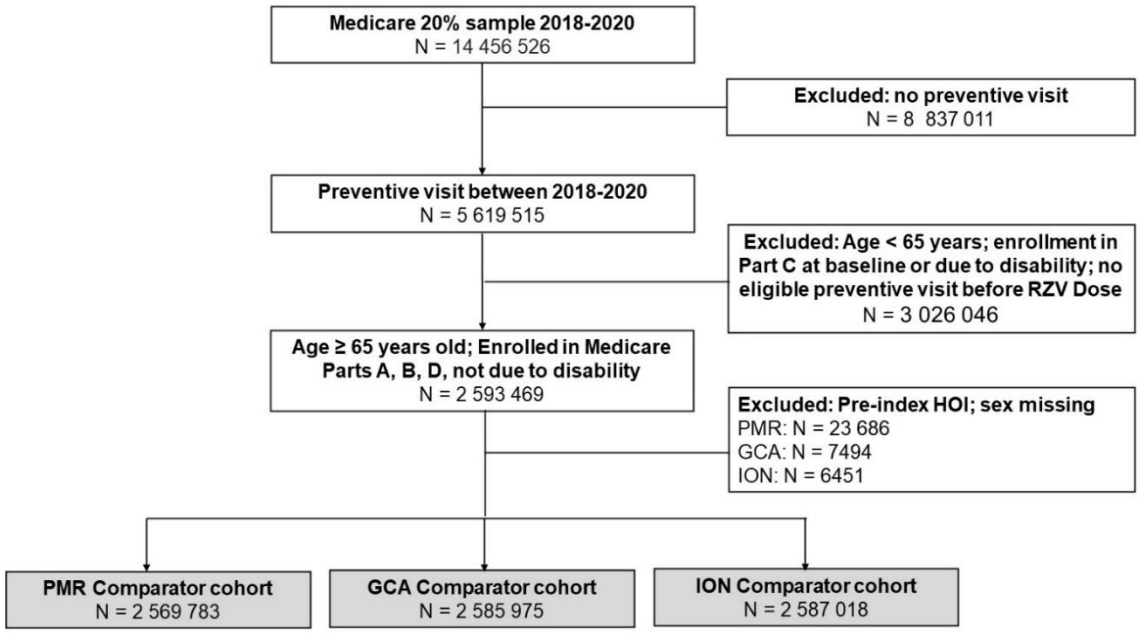
9.3.2. RZV-Unvaccinated Comparators

Figure 13 illustrates the derivation of the RZV-unvaccinated comparator analytic cohorts for PMR, GCA, and ION. We derived the RZV-unvaccinated comparator group from 14 456 526 participants in a 20% random sample of US Medicare beneficiaries from 2018 through 2020. Of these, 5 619 515 had a preventive care visit at any point from 2018 through 2020. Implementing the inclusion criteria, 2 593 469 participants were ≥65 years of age, continuously enrolled in Medicare Parts A, B, and D for 11 of the 12 months preceding the preventive care visit, and had a current, i.e., at the index date, or original qualification for Medicare that was not due to disability.

The 2 593 469 participants who were eligible for the RZV-unvaccinated comparators did not receive RZV at any time in the available history prior to the preventive care visit date.

The comparator cohort had a single index date and was able to serve as a comparator for both RZV doses and was included in analyses for multiple HOIs, provided there was no evidence of the HOI preceding the index date.

Figure 13 Flow diagram of the derivation of the RZV-unvaccinated comparator analytic cohorts



GCA, giant cell arteritis; HOI, health outcome of interest; ION, ischemic optic neuropathy; PMR, polymyalgia rheumatica; RZV, recombinant zoster vaccine.

9.4. COHORT - Primary objective: PMR

9.4.1. Participants

A total of 3 265 790 participants were included in the RZV-exposed analytical cohort and 2 569 783 were included in the RZV-unvaccinated comparator analytical cohort (Section 14.4.1**)**.

9.4.2. Descriptive data including baseline characteristics

Table 52 in Section 14.4.1 reports participants' characteristics, unweighted and IPTW-weighted, on the index date as well as medical diagnoses and health service utilization in the 365 days preceding the index date of RZV Dose 1 for the RZV-exposed and the preventive care visit date for the RZV-unvaccinated comparator. The mean age was 74.33 (±6.33) years and 75.16 (±7.14) years for the RZV-exposed and for the RZV-unvaccinated comparators, respectively. Among the unweighted cohort of 3 265 790 RZV-exposed participants who received RZV Dose 1, most were White (n=2 904 257; 88.93%), female (n=1 922 194; 58.86%), and 70 to 79 years of age (70 to 74: n=1 029 820 [31.53%]; 75 to 79: n=719 804 [22.04%]). Among the unweighted cohort of 2 569 783 RZV-unvaccinated comparator participants, most were White (n=2 217 388; 86.29%), female (n=1 632 006; 63.51%), and 70 to 79 years of age (70 to 74: n=744 195 [28.96%]; 75 to 79: n=521 623 [20.30%]).

The most prevalent chronic conditions in the RZV-exposed and RZV-unvaccinated comparators, respectively, were diabetes mellitus (24.31% and 27.67%), ischemic heart

disease (21.20% and 22.32%), chronic kidney disease (20.56% and 23.20%), and chronic lung disease (12.11% and 14.51%).

Imbalances in baseline demographic covariates preceding RZV Dose 1, as measured by the SMD, included mean age at index date (SMD= −0.12), the proportion aged 85+ at index date (SMD= −0.14), the proportion Black (SMD= −0.16), and both sexes (SMD= 0.10). In the baseline period preceding RZV Dose 1, most medical conditions were balanced except for dementia, which was 3.35% in the RZV-exposed and 6.01% in the RZV-unvaccinated comparator (SMD= −0.13). Several health service utilization covariates measured in the baseline period preceding RZV Dose 1 were imbalanced between groups. The proportions in the RZV-exposed and the RZV-unvaccinated comparators, respectively, which were not balanced include at least one optometry/ophthalmology visits (56.76% and 47.89%; SMD= 0.18), ≥2 ED visits (4.66% and 7.92%; SMD= −0.13), home health care (5.75% and 8.85%; SMD= −0.12), and SNF (1.59% and 3.11%; SMD= −0.10). The receipt of concomitant influenza vaccine (12.44% and 6.01%; SMD= 0.22) or Tdap vaccine (2.06% and 0.13%; SMD= 0.19) with RZV Dose 1 were not balanced between the RZV-exposed and the RZV-unvaccinated comparators, respectively.

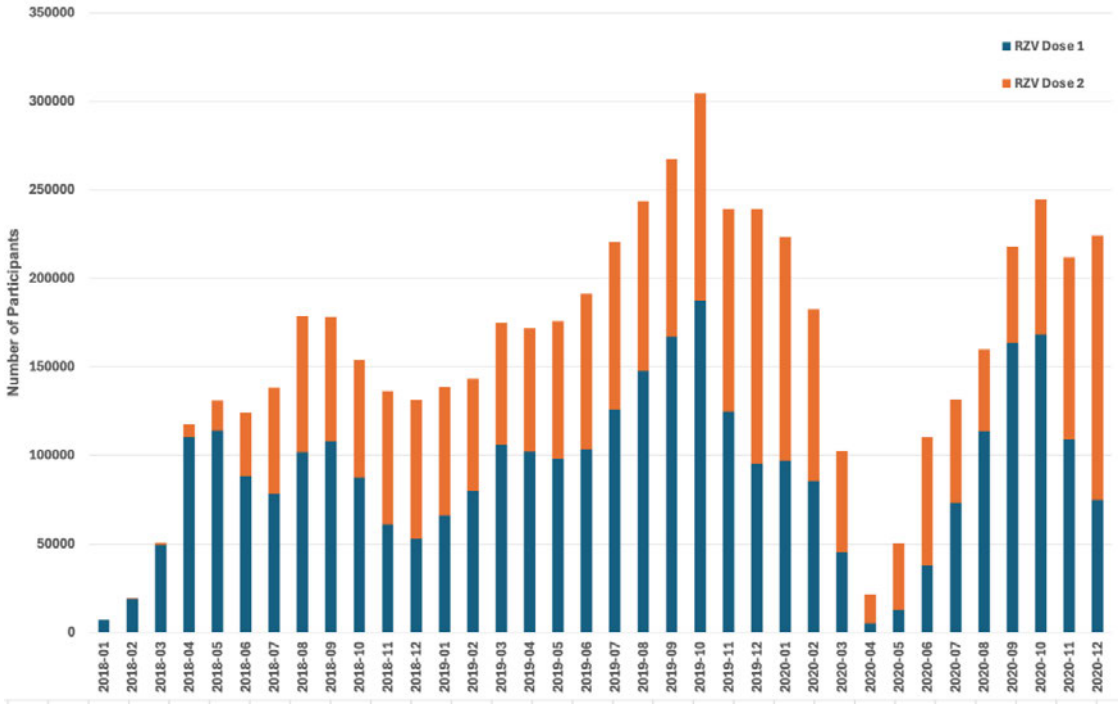
After IPTW (stabilized), all covariates were well balanced, as indicated by SMDs close to zero.

Section 14.4.1 and Section 14.4.2, respectively, provides details on the baseline characteristics by number of doses and dose spacing (Table 53), and for the supplemental cohort (Table 54) that excludes from the RZV-unvaccinated comparator those who were future RZV-exposed.

Distribution of RZV Dose 1 and Dose 2

Figure 14 shows the number of participants who received RZV Dose 1 and Dose 2 by calendar month in 2018, 2019, and 2020. The number of participants who received RZV Dose 1 peaked in October 2019 at 187 342 and was lowest in April 2020 at 4988 after the start of the COVID-19 pandemic. The patterns of RZV Dose 2 show monthly fluctuations like those of RZV Dose 1.

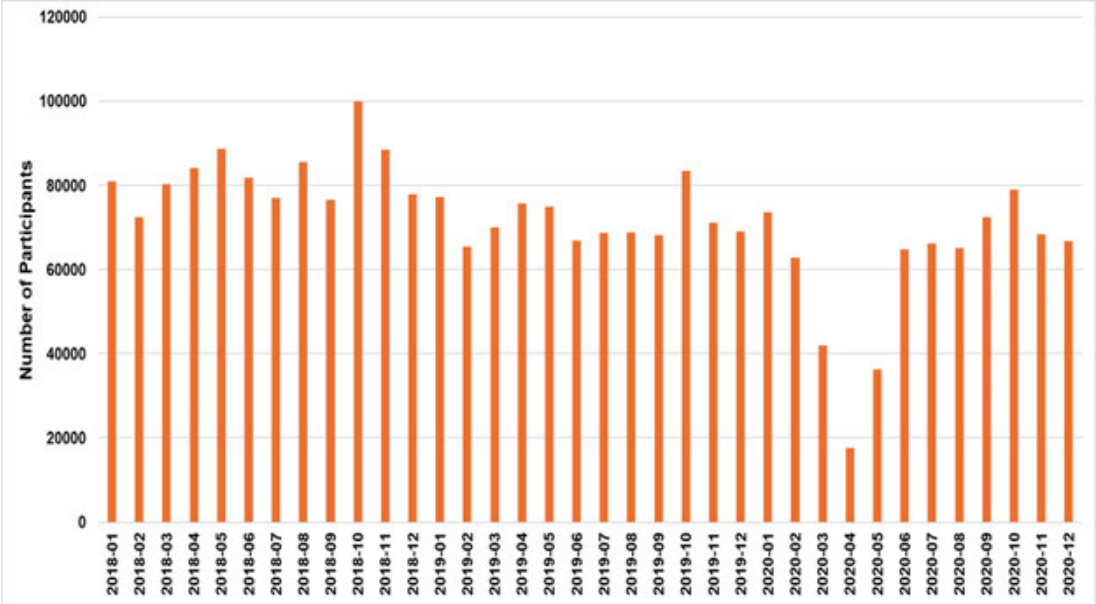
Figure 14 Distribution of RZV Dose 1 and Dose 2 by calendar month of index date (PMR)



PMR, Polymyalgia rheumatica; RZV, Recombinant zoster vaccine.
Note: Index date, date of vaccination for Dose 1 for RZV-exposed, or date of preventive care visit for RZV-unvaccinated comparator; Number of participants counted from January 2018 to December 2020 out of the total 3 265 790 RZV exposed identified.

Figure 15 shows the number of participants in the RZV-unvaccinated comparator group who had a preventive visit by calendar month in 2018, 2019, and 2020. We observe year-to-year variations in the number of comparators with a preventive visit in each month, with the highest in October 2018 at 100 031 and the lowest in April 2020 at 17 608 after the start of the COVID-19 pandemic.

Figure 15 Distribution of comparator preventive visits by calendar month of index date (PMR)



PMR, polymyalgia rheumatica; RZV, Recombinant zoster vaccine.
Note: Index date, date of vaccination for Dose 1 for RZV-exposed, or date of preventive care visit for RZV-unvaccinated comparator; Number of participants counted from January 2018 to December 2020 out of the total 2 569 783 RZV-unvaccinated identified.

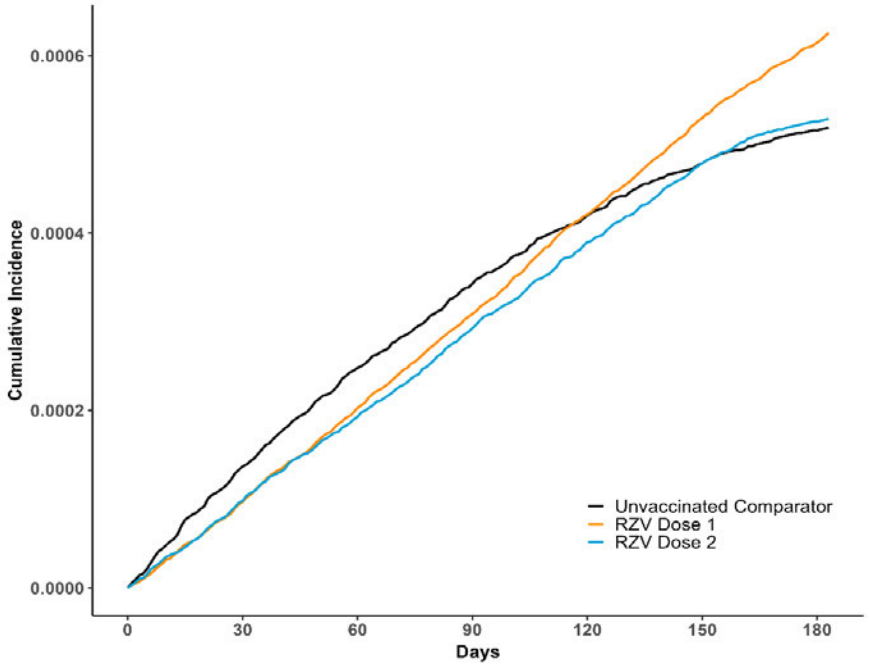
9.4.3. Cumulative incidence of PMR

The average time to event following RZV Dose 1 was 90.42 (SD=51.01) days for the RZV-exposed and 69.05 (SD=47.93) days for the RZV-unvaccinated comparators. The average time to event following RZV Dose 2 was 82.68 (SD=48.62) days.

Figure 16 illustrates the cumulative incidence over time, along with the numerical tabulation of the number at risk over the follow-up period. Of the 3 265 790 (unweighted) Dose 1 RZV-exposed at risk at the start of follow-up, 106 865 were censored and a total of 2012 developed PMR with a cumulative incidence of 0.000615 by Day 180. Of the 2 489 075 (unweighted) Dose 2 RZV-exposed at risk at the start of follow-up, 75 767 were censored and a total of 1297 developed PMR with a cumulative incidence of 0.000526 by Day 180. Of the 2 569 783 (unweighted) unvaccinated comparators, 357 667 were censored and 1249 developed PMR by Day 180, which corresponds with a cumulative incidence of 0.000516.

The cumulative incidence graph shows that the curves begin to separate before 30 days after the index date, with higher cumulative incidence among the RZV-unvaccinated comparators. However, the cumulative incidence curves for Dose 1 and RZV-unvaccinated comparators cross at around 120 days after the index date, with the RZV-unvaccinated comparators showing a lower cumulative incidence after Day 120 of the follow-up. A similar pattern is observed for Dose 2, where the curve crosses around 150 days after the index date. This suggests that the proportional hazards assumption is violated. Results adjusting for the violation of the proportional hazards assumption are provided in Section 9.4.4.

Figure 16 Cumulative incidence of PMR by vaccination status – Primary analysis RZV Dose 1 and Dose 2



	Days After Index Date							
PMR		**0**	**30**	**60**	**90**	**120**	**150**	**180**
RZV Dose 1	At risk	3 265 790	3 253 511	3 237 823	3 216 533	3 193 362	3 173 983	3 156 913
	Cumulative incidence	0	0.000097	0.000203	0.000309	0.000421	0.00053	0.000615
RZV Dose 2	At risk	2 489 075	2 474 158	2 460 217	2 447 485	2 434 983	2 423 417	2 412 011
	Cumulative incidence	0	0.000098	0.000193	0.000293	0.00039	0.000479	0.000526
Unvaccinated comparator	At risk	2 569 783	2 484 570	2 422 409	2 363 881	2 308 270	2 258 649	2 210 867
	Cumulative incidence	0	0.000137	0.000248	0.000343	0.00042	0.000479	0.000516

Index date, date of vaccination for Dose 1 for RZV exposed, or date of preventive care visit for RZV-unvaccinated comparator; RZV, Recombinant zoster vaccine; PMR, polymyalgia rheumatica.

Figures showing the distribution of new onset PMR by dose and week after the index date are in Figure 23, Figure 24, and Figure 25 in Section 14.4.3.

9.4.4. Results of primary analyses

Table 11 shows the IPTW-adjusted results of the primary analysis of Dose 1 and Dose 2 prior to accounting for violation of the proportional hazards assumption. These findings suggest that RZV Dose 1 was associated with a statistically significant increased risk of PMR (IPTW-adjusted HR=1.19 (95% CI: 1.11, 1.28). The primary analysis of Dose 2 was not statistically significant (IPTW-adjusted HR=0.99; 95% CI: 0.91, 1.07).

Table 11 Risk estimates for primary analysis of PMR within a 183-day follow-up period – IPTW-Adjusted

Separate analysis of RZV Dose 1 and Dose 2					
	No. persons	No. events[a]	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
RZV Dose 1					
RZV Dose 1	3 063 091	1922	1 510 028	12.73 (12.17, 13.31)	1.19 (1.11, 1.28)
Comparator	2 433 338	1205	1 123 829	10.72 (10.13, 11.35)	Ref.
RZV Dose 2					
RZV Dose 2	2 386 968	1255	1 174 562	10.69 (10.11, 11.29)	0.99 (0.91, 1.07)
Comparator	2 355 419	1190	1 089 998	10.92 (10.31, 11.55)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; PMR, polymyalgia rheumatica; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.
a. The number of events reflects the IPTW-weighted numbers.

The results of crude and covariate adjusted primary analysis are provided in Table 55 in Section 14.4.4.1. The distribution of the propensity score (Figure 26) and weights (Table 60) are in Section 14.4.5.1.

Assessment of the proportional hazards assumption: Primary analysis

To determine if the hazard between the two groups remained constant over time, we plotted the graph of the log(-log(survival)) by log(event time). The results, shown in Section 14.4.6 (Figure 31), revealed that the PH assumption was violated for the primary analysis of Dose 1. To address this, we conducted weighted Cox regression models with a time-dependent coefficient with a change point at 120 days (i.e., 1 to 120 days versus >120 to 183 days) for Dose 1.

With the time-dependent coefficient included in the model, the HR was generated specific to the change point. The results are in Table 12. For Dose 1 with the time-dependent coefficient, there was no increased risk of PMR from Days 1 to 120 (HR=1.00; 95% CI: 0.92, 1.09) after RZV Dose 1, but a statistically significant higher risk from Day 120 to 183 of the follow-up period (HR=2.05; 95% CI: 1.71, 2.46).

Table 12 IPTW HR estimates for PMR by follow-up time after the index date: Primary analysis

Follow-up Time	HR	95% CI	
RZV Dose 1			
1 to 120 days	1.00	0.92	1.09
> 120 days	2.05	1.71	2.46

CI, confidence interval; HR, hazard ratio; index date, date of vaccination for Dose 1 and Dose 2 for RZV-exposed, date of preventive care visit for RZV-unvaccinated comparator; IPTW, inverse probability of treatment weighting; PMR, polymyalgia rheumatica; RZV, recombinant zoster vaccine.

9.4.5. Results of secondary analyses

Table 13 shows the secondary analyses for PMR using a partly conditional survival model to obtain a single risk estimate and a time-varying model to obtain separate risk estimates. The analysis combining Dose 1 and Dose 2 for a single risk estimate revealed a significantly higher risk of PMR in the RZV-exposed compared to RZV-unvaccinated comparator (IPTW-adjusted HR=1.14, 95% CI: 1.06, 1.23).

The time-varying Cox model, which generated a separate risk estimate for Dose 1 and Dose 2, revealed an IPTW-adjusted HR of 1.26 (95% CI: 1.16, 1.36) for Dose 1. The result for Dose 2 was not statistically significant as the 95% CI included 1.00 (IPTW-adjusted HR=1.10, 95% CI: 1.00, 1.22).

Table 13 Risk estimates for secondary analysis of PMR within a 183-day follow-up period – IPTW-Adjusted

Secondary analyses of combined and time-varying dose					
	No. persons	No. events[a]	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
Combined dose					
RZV Dose 1 and Dose 2	5 400 720	2544	2 124 718	11.97 (11.52, 12.45)	1.14 (1.06, 1.23)
Comparator	2 433 338	1205	1 123 829	10.72 (10.13, 11.35)	Ref.
Time-varying separate dose					
RZV Dose 1	3 063 091	1308	973 002	13.44 (12.73, 14.19)	1.26 (1.16, 1.36)
RZV Dose 2	2 313 408	614	537 026	11.44 (10.57, 12.38)	1.10 (1.00, 1.22)
Comparator	2 433 338	1205	1 123 829	10.72 (10.13, 11.35)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; PMR, polymyalgia rheumatica; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

a. The number of events in the RZV vaccinated for the combined dose analysis exceeds the number of events in the time-varying analysis because the time-varying analysis only includes the 183 days after RZV Dose 1. Only events after Dose 2 within the 183-day follow-up from Dose 1 are counted.

The results of crude and covariate adjusted secondary analyses are provided in Section 14.4.4.2 (Table 56). The distribution of the propensity score (Figure 27 in

Section 14.4.5.2 and Figure 28 in Section 14.4.5.3) and weights (Table 60) are in Section 14.4.5.1.

Assessment of proportional hazards assumption: Secondary analyses

The log(-log(survival)) by log(event time) evaluated the assumption of proportional hazards for the secondary analyses. The results, shown in Section 14.4.6 (Figure 32), revealed that the PH assumption was violated. Since the combined dose and the time-varying dose analyses segmented the follow-up by dose, a time-dependent coefficient was not included in the Cox regression model.

9.4.6. Results of sensitivity to primary analyses

COVID-19 sensitivity results

The results of the COVID-19 sensitivity analysis, before accounting violation of the proportional hazards assumption, are in Table 14. The COVID-19 sensitivity analysis of Dose 1 shows a statistically significant increased risk of PMR; with an IPTW-adjusted HR=1.17 (95% CI: 1.07, 1.28). The COVID-19 sensitivity analysis of Dose 2 did not reveal a statistically significant increased risk with an IPTW-adjusted HR=0.96 (95% CI: 0.86, 1.06).

Table 14 Risk estimates for COVID-19 sensitivity of the primary analysis of PMR within a 183-day follow-up period – IPTW-Adjusted

COVID-19 sensitivity analyses[a]					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
RZV Dose 1					
RZV Dose 1	2 238 692	1335	959 784	13.91 (13.18, 14.67)	1.17 (1.07, 1.28)
Comparator	1 823 034	873	734 081	11.89 (11.13, 12.70)	Ref.
RZV Dose 2					
RZV Dose 2	1 647 310	775	673 995	11.49 (10.71, 12.33)	0.96 (0.86, 1.06)
Comparator	1 760 889	843	699 615	12.05 (11.27, 12.89)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; PMR, polymyalgia rheumatica; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.
a. 01 February 2020 included as a censoring event.

The results of crude and covariate adjusted analysis are provided in Table 57 in Section 14.4.4.3. The propensity score distribution (Figure 29) and weights (Table 61) are provided in Section 14.4.5.4.

Assessment of proportional hazards assumption: COVID-19 sensitivity analysis

The log(-log(survival)) by log(event time) evaluated the assumption of proportional hazards for the COVID-19 sensitivity analyses. The results, shown in Section 14.4.6

(Figure 33), revealed that the PH assumption was violated for the COVID-19 Dose 1 sensitivity analysis, but not for Dose 2. Weighted Cox regression models that included a time-dependent coefficient with a change point at 120 days (i.e., 1 to 120 days versus >120 to 183 days) for Dose 1 (Table 15).

The results for the piecewise weighted Cox regression models revealed no statistically significant increased risk of PMR from Days 1 to 120 (HR=0.99; 95% CI: 0.90, 1.10) and a statistically significant increased risk from Days >120 to 183 (HR=2.15; 95% CI: 1.73, 2.68).

Table 15 IPTW HR estimates for PMR by follow-up time after the index date: COVID-19 sensitivity analysis

Follow-up Time	HR	95% CI
RZV Dose 1		
1 to 120 days	0.99	0.90, 1.10
> 120 days	2.15	1.73, 2.68

CI, confidence interval; HR, hazard ratio; index date, date of vaccination for Dose 1 for RZV-exposed, date of preventive care visit for RZV-unvaccinated comparator; IPTW, inverse probability of treatment weighting; PMR, polymyalgia rheumatica.

9.4.7. Results of sensitivity to secondary analyses

Dose-compliant sensitivity results

Table 16 shows the sensitivity analyses of the secondary partly conditional and time-varying analyses for PMR among a sub-sample of individuals who received both RZV doses spaced within 2 to 6 months per US label (i.e., dose-compliant subgroup). The sensitivity analysis of combined doses in one risk estimate for PMR shows a non-significant IPTW-adjusted HR=1.04 (95% CI: 0.97, 1.13). The sensitivity analysis of the secondary analysis for PMR using a time-varying model also was not significant in the IPTW-adjusted analysis. The HRs for Dose 1 (HR=1.06; 95% CI: 0.96, 1.17) and Dose 2 (HR=1.11; 95% CI: 1.00, 1.24) were not statistically significant.

Table 16 Risk estimates for the dose-compliant sensitivity of the secondary analysis of PMR within a 183-day follow-up period – IPTW-Adjusted

Dose-compliant[a] sensitivity analysis					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
Subset of combined dose					
RZV Dose 1 and Dose 2	4 401 132	1811	1 650 334	10.97 (10.48, 11.49)	1.04 (0.97, 1.13)
Comparator	2 407 809	1198	1 112 193	10.77 (10.18, 11.40)	Ref.
Subset of time-varying separate dose					
RZV Dose 1	2 312 697	717	621 710	11.53 (10.71, 12.40)	1.06 (0.96, 1.17)
RZV Dose 2	2 278 304	599	522 533	11.46 (10.58, 12.41)	1.11 (1.00, 1.24)
Comparator	2 407 809	1198	1 112 193	10.77 (10.18, 11.40)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; PMR, polymyalgia rheumatica; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

a. Dose compliant per US schedule of 2 to 6 months spacing between Dose 1 and Dose 2.

The results of crude and covariate adjusted analysis are provided in Table 58 in Section 14.4.4.4. The distribution of the propensity scores are shown in Figure 27 and Figure 28 in Section 14.4.5.2 and Section 14.4.5.3 and the weights are in Table 62 in Section 14.4.5.5.

Assessment of proportional hazards assumption: Dose-compliant sensitivity analysis

The log(-log(survival)) by log(event time) evaluated the assumption of proportional hazards for the dose-compliant sensitivity of the secondary analyses. The results, shown in Section 14.4.6 (Figure 34), revealed that the PH assumption was violated. The dose-compliant combined dose and the time-varying dose analyses segmented the follow-up by dose. Therefore, a time-dependent coefficient was not included in the Cox regression model.

9.4.8. Results of supplemental analyses of the primary analysis

Exclusion of RZV-exposed from control arm

The primary analysis was repeated using the supplemental cohort that excluded comparators who subsequently received RZV, the results of which are in Table 17. The separate analysis for Dose 1 shows no statistically significant increase in PMR risk between the RZV-exposed and the RZV-unvaccinated comparator, with an IPTW-adjusted HR=0.99 (95% CI: 0.92, 1.07). For Dose 2, we observed a statistically significant lower risk of PMR with IPTW-adjusted HR=0.83 (95% CI: 0.77, 0.90).

Table 17 Risk estimates for the supplemental cohort sensitivity of the primary analysis of PMR within a 183-day follow-up period – IPTW-Adjusted

Supplemental cohort excluding comparators who received RZV					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
RZV Dose 1					
RZV Dose 1	3 064 089	1916	1 510 292	12.69 (12.13, 13.27)	0.99 (0.92, 1.07)
Comparator	1 974 748	1222	954 347	12.80 (12.10, 13.54)	Ref.
RZV Dose 2					
RZV Dose 2	2 381 397	1250	1 171 863	10.67 (10.09, 11.28)	0.83 (0.77, 0.90)
Comparator	1 916 719	1195	927 486	12.88 (12.17, 13.63)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; PMR, polymyalgia rheumatica; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The results of crude and covariate adjusted analysis are provided in Table 59 in Section 14.4.4.5. The propensity score distribution (Figure 30) and weights (Table 63) are provided in Section 14.4.5.6.

Assessment of proportional hazards assumption: Supplemental cohort to the primary

The log(-log(survival)) by log(event time) evaluated the assumption of proportional hazards for the supplemental cohort sensitivity analyses. The results, shown in Section 14.4.6 (Figure 35), revealed that the PH assumption was not violated for Dose 1 or Dose 2 sensitivity analyses.

9.4.9. Quantitative bias

To quantify the potential impact of unmeasured confounding or how much unmeasured confounding would be needed to nullify the findings, we conducted a quantitative bias analysis. The quantitative bias analysis was conducted for the primary analysis of RZV Dose 1. It was not conducted for Dose 2 since the risk estimate was not significant. Table 18 displays risk estimates and 95% CIs adjusted for potential unmeasured confounders. The column headings display the strength of the association of the unmeasured confounder and the outcome. The row headings display the strength of the association of the exposure and unmeasured confounder. The values displayed in the cells reflect the risk estimates and 95% CIs for varying strengths of the unmeasured confounder. The results of the risk ratios needed to explain away the findings are shown in bolded italicized cells. The results indicate that a minimum risk ratio of 1.5 between both an unmeasured confounder and both the exposure and the outcome would nullify the findings.

Table 18 IPTW-corrected HR estimates for PMR for unmeasured confounding

Strength of the risk ratio of the exposure and unmeasured confounder	Strength of the risk ratio of the unmeasured confounder and the outcome			
	1.2	1.3	1.5	1.8
1.2	1.16 (1.08, 1.25)	1.15 (1.07, 1.23)	1.13 (1.05, 1.21)	1.10 (1.03, 1.19)
1.3	1.15 (1.07, 1.23)	1.13 (1.05, 1.22)	1.10 (1.02, 1.19)	1.07 (0.99, 1.15)
1.5	1.13 (1.05, 1.21)	1.10 (1.02, 1.19)	1.06 (0.98, 1.14)	1.02 (0.94, 1.09)
1.8	1.10 (1.03, 1.19)	1.07 (0.99, 1.15)	1.02 (0.94, 1.09)	0.96 (0.89, 1.03)

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting.

Section 14.4.7 (Table 64) includes a broader range of potential risk ratios between the unmeasured confounder and the outcome and exposure.

9.4.10. Post-Hoc analysis

Several post-hoc analyses were undertaken to assess the effect of censoring Dose 1 at receipt of Dose 2 for PMR. The primary analysis did not censor Dose 1 at receipt of Dose 2 that occurred in the 183-day period of follow-up after RZV Dose 1. Thus, it is possible that some of the risk in the primary Dose 1 analysis may be due to events occurring after Dose 2. Post-hoc analyses censoring Dose 1 at receipt of Dose 2 for PMR included estimates of the crude hazard ratio, the cumulative incidence and time-to event, and assessment of the assumption of proportional hazards. Results are provided below based on the crude, unweighted, analyses. Additional post-hoc analyses were conducted to evaluate the age- and index year-stratified cumulative incidence for PMR. Given the violation of the proportional hazards assumption, the post-hoc analyses will evaluate whether the non-proportionality of the risk was specific to an age group or time period (i.e., receipt of RZV in 2018 may have been selectively given to individuals more or less susceptible to PMR).

Post-hoc analysis censoring Dose 1 at Dose 2

Table 19 presents the incident rate per 10 000 person-years and the crude hazards ratio from the Cox proportional hazards regression model for the primary analysis of Dose 1 without and with censoring at Dose 2. The results show a statistically significant increased risk of PMR, without and after censoring at Dose 2. The hazards ratios were similar, and both had a lower bound of the 95% CI above 1.00.

The time to PMR from RZV Dose 1 with censoring was 69.74 (SD=45.46) days and the corresponding time to event for the RZV-unvaccinated comparator was 69.05 (SD=47.93) days. Of the 3 265 790 participants in the unweighted RZV-exposed who were at risk at the start of follow-up for Dose 1, there were 3 264 429 censored and 1361 who developed PMR prior to censoring at RZV Dose 2 with a cumulative incidence of 0.00067 by Day 183. Of the 2 569 783 RZV-unvaccinated comparators who were at risk at the start of follow-up, there were 2 568 534 censored and 1249 who developed PMR for a cumulative incidence of 0.00052 by Day 180.

Table 19 Risk of PMR following RZV Dose 1 with and without censoring at receipt of Dose 2

Post-hoc analysis of the primary analysis of Dose 1 – without and with censoring at Dose 2					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)
RZV Dose 1 – no censoring at Dose 2					
RZV Dose 1	3 265 790	2012	1 609 938	12.50 (11.96, 13.06)	1.19 (1.11, 1.28)
Comparator	2 569 783	1249	1 185 939	10.53 (9.96, 11.13)	Ref.
RZV Dose 1 – with censoring at Dose 2					
RZV Dose 1	3 265 790	1361	1 030 493	13.21 (12.52, 13.93)	1.16 (1.07, 1.25)
Comparator	2 569 783	1249	1 185 939	10.53 (9.96, 11.13)	Ref.

Adj, adjusted; CI, confidence interval; comparator, Unvaccinated comparator; HR, hazard ratio; PMR, polymyalgia rheumatica; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The survival probability function curves crossed around Day 111 of follow-up, indicating a violation of the proportional hazards assumption in the analysis that censored Dose 1 at receipt of Dose 2. The log(-log(survival probability)) function is in Figure 36 in Section 14.8.1.

Age-stratified post-hoc analyses

The post-hoc analyses of PMR by age 65 to 74 years-old relative to those age 75 years and older included crude and IPTW stabilized weighted Cox proportional hazards regression to assess the hazards, a cumulative incidence function, and the log(-log) survival function plots to evaluate the violation of the assumption of proportional hazards. Results are shown in Section 14.4.8.2.

The IPTW-adjusted hazards of PMR from the weighted Cox proportional hazards for participants aged 65 to 74 years old was not statistically significant (HR=1.01; 95% CI: 0.90, 1.13) but there was a statistically significant increased risk among those age 75 years or older (HR=1.36; 95% CI: 1.23, 1.50). The results are in Table 64 in Section 14.4.8.2.

The age-stratified cumulative incidence function and survival probability functions are provided in Section 14.4.8.2, Figure 37 and Figure 38, for ages 65 to 74 and ≥75, respectively.

Of the 1 884 230 participants aged 65 to 74 years-old in the unweighted RZV-exposed who were at risk at the start of follow-up for Dose 1, there were 1 883 412 censored and 818 who developed PMR, with a cumulative incidence of 0.00044 by Day 183 of the follow-up. Of the 1 403 182 participants aged 65 to 74 years-old in the RZV-unvaccinated comparators who were at risk at the start of follow-up, there were 1 402 633 censored and 549 who developed PMR for a cumulative incidence of 0.00042 by Day 183.

Of the 1 381 560 participants aged 75 years or older in the unweighted RZV-exposed who were at risk at the start of follow-up for Dose 1, there were 1 380 366 censored and 1194 who developed PMR, with a cumulative incidence of 0.00088 by Day 183 of the follow-up. Of the 1 166 601 participants aged 75 years or older in the RZV-unvaccinated comparators who were at risk at the start of follow-up, there were 1 165 901 censored and 700 who developed PMR for a cumulative incidence of 0.00064 by Day 183.

The assumption of proportional hazards was violated in both the 65 to 74 years-old and the aged 75 years or older strata. For participants aged 65 to 74 years-old, the survivor function plots show that the lines cross around Day 170 after the index date. For participants aged 75 years or older, the survivor function plots show that the lines cross around Day 90 after the index date.

PMR cumulative incidence function by index year

The post-hoc analyses of PMR by index year estimated the cumulative incidence function to evaluate the potential difference over time. Results are shown in Figure 39 in Section 14.4.8.3.

Of the 876 508 participants in the unweighted RZV-exposed who had an index year in 2018 and were at risk at the start of follow-up for Dose 1, there were 875 903 censored and 605 who developed PMR, with a cumulative incidence of 0.00070 by Day 183 of the follow-up. Of the 994 304 participants in the RZV-unvaccinated comparators who had an index year of 2018 and were at risk at the start of follow-up, there were 993 760 censored and 544 who developed PMR for a cumulative incidence of 0.00059 by Day 183.

Of the 1 403 130 participants in the unweighted RZV-exposed who had an index year in 2019 and were at risk at the start of follow-up for Dose 1, there were 1 402 236 censored and 894 who developed PMR, with a cumulative incidence of 0.00065 by Day 183 of the follow-up. Of the 860 038 participants in the RZV-unvaccinated comparators who had an index year of 2019 and were at risk at the start of follow-up, there were 859 649 censored and 389 who developed PMR for a cumulative incidence of 0.00048 by Day 183.

Of the 986 152 participants in the unweighted RZV-exposed who had an index year in 2020 and were at risk at the start of follow-up for Dose 1, there were 985 639 censored and 513 who developed PMR, with a cumulative incidence of 0.00053 by Day 183 of the follow-up. Of the 715 441 participants in the RZV-unvaccinated comparators who had an index year of 2020 and were at risk at the start of follow-up, there were 715 125 censored and 316 who developed PMR for a cumulative incidence of 0.00047 by Day 183.

The cumulative incidence curves for all index year strata crossed. For 2018 the curves crossed around Day 140, for 2019 the curves crossed around Day 80, and for 2020 the curves around Day 120 after the index date.

9.5. COHORT – Primary objective: GCA

9.5.1. Participants

A total of 3 288 846 participants comprised the RZV-exposed analytic cohort and 2 585 975 comprised the RZV-unvaccinated comparator analytic cohort (Section 14.5.1).

9.5.2. Descriptive data including baseline characteristics

Table 66 in Section 14.5.1 displays participants' characteristics, unweighted and weighted, on the index date along with medical diagnoses and health service utilization in the 365 days preceding receipt of RZV Dose 1 for the RZV-exposed or the preventive care visit date for the RZV-unvaccinated comparators. The mean age was 74.36 (±6.34) years and 75.19 (±7.15) years at receipt of Dose 1 for the RZV-exposed and the preventive care visit date for the RZV-unvaccinated comparators, respectively. Among the 3 288 846 RZV-exposed who received RZV Dose 1, the unweighted sample was mostly White (n=2 926 235; 88.97%), female (n=1 936 120; 58.87%), and 70 to 79 years of age (70 to 74: n=1 035 264 [31.48%]; 75 to 79: n=726 177 [22.08%]). In the unweighted sample of RZV-unvaccinated comparators (n=2 585 975), most were White (n=2 232 768; 86.34%), female (n=1 642 880; 63.53%), and 70 to 79 years of age (70 to 74: n=747 529 [28.91%]; 75 to 79: n=525 566 [20.32%]).

The most prevalent medical conditions in the RZV-exposed and the RZV-unvaccinated comparators, respectively, were diabetes mellitus (24.31% and 27.68%), ischemic heart disease (21.24% and 22.37%), chronic kidney disease (20.60% and 23.24%), and chronic lung disease (12.14% and 14.54%).

Imbalance in demographic covariates on the index date of RZV Dose 1 and the preventive care visit date, as measured by the SMD, included mean age (SMD= −0.12), proportion aged 85+ (SMD= −0.14), the proportion Black (SMD= −0.16), and year of index date for 2018 (SMD= −0.25) and 2019 (SMD= 0.20). In the 365-day baseline period preceding the index date, an imbalance was observed for dementia, which occurred among 3.35% of the RZV-exposed and 6.01% of the RZV-unvaccinated comparator (SMD= −0.13). Health service utilization in the baseline period preceding RZV Dose 1 that were imbalanced between the RZV-exposed and the RZV-unvaccinated comparators, respectively, included optometry/ophthalmology visits (56.80% and 47.93%; SMD= 0.18), two or more ED visits (4.68% and 7.95%; SMD= −0.13), and utilization of home health care (5.78% and 8.89%; SMD= −0.12). Preventive vaccinations received concomitantly with RZV Dose 1 and the preventive care visit were imbalanced between RZV-exposed and RZV-unvaccinated comparators, respectively, including influenza vaccine (12.42% and 6.01%; SMD= 0.22) and Tdap vaccine (2.06% and 0.13%; SMD= 0.19).

After IPTW weighting, all covariates were well balanced, as indicated by SMDs close to zero.

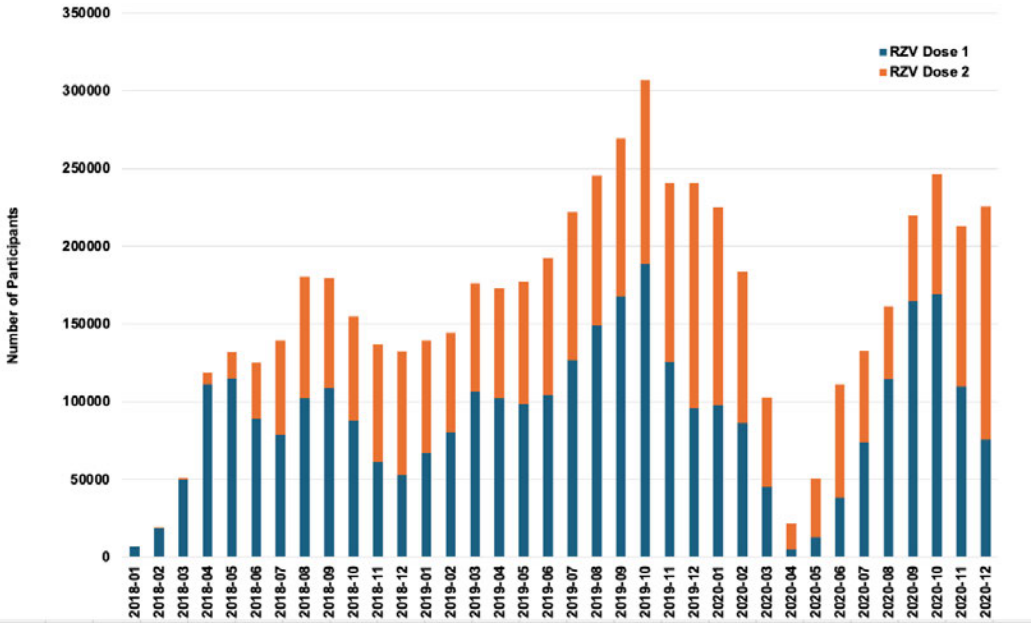
Baseline characteristics by number of doses and dose spacing (Table 67) and for the supplemental cohort that excludes from the RZV-unvaccinated comparator those who

were future RZV-exposed (Table 68) are provided in Section 14.5.1 and Section 14.5.2, respectively.

Distribution of RZV D1 and D2

Figure 17 shows the number of participants who received RZV Dose 1 and Dose 2 by calendar month in 2018, 2019, and 2020. The number of participants who received RZV Dose 1 peaked in October 2019 at 188 609 and was lowest in April 2020 at 5020 after the start of the COVID-19 pandemic. The patterns of RZV Dose 2 show monthly fluctuations like those of RZV Dose 1.

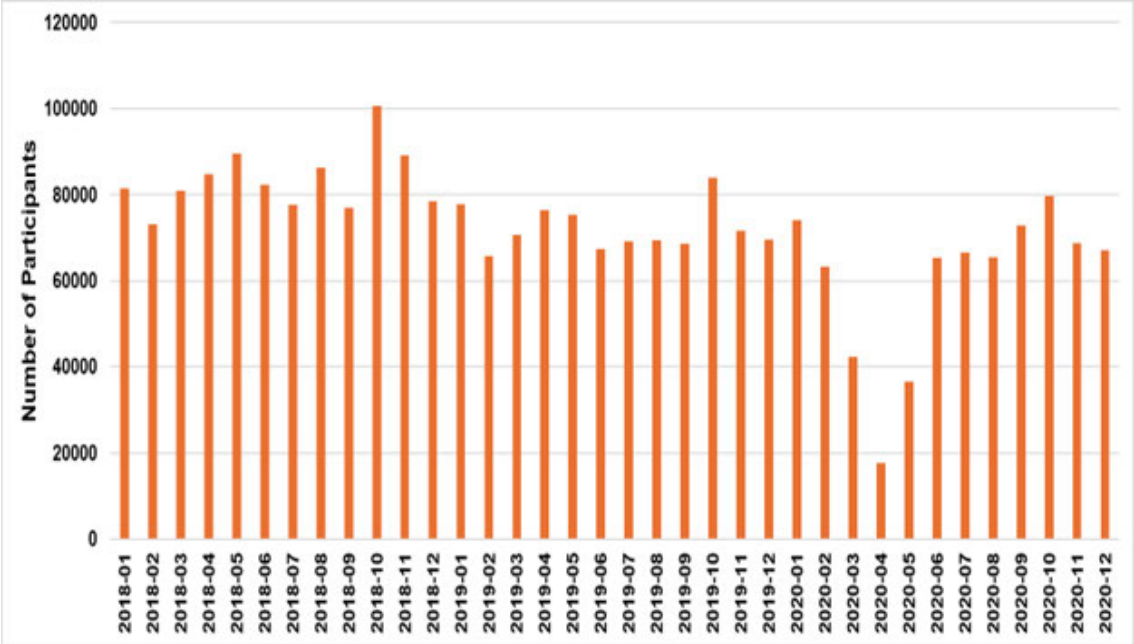
Figure 17 Distribution of RZV Dose 1 and Dose 2 by calendar month of index date (GCA)



GCA, Giant cell arteritis; RZV, Recombinant zoster vaccine.
Note: Index date, date of vaccination with RZV Dose 1 or Dose 2; Number of participants counted from January 2018 to December 2020 out of the total 3 288 846 RZV-exposed identified.

Figure 18 shows the number of participants in the RZV-unvaccinated comparator analytic cohort who had a preventive care visit by calendar month in 2018, 2019, and 2020. We observe year-to-year variations in the number of RZV-unvaccinated comparators with a preventive visit in each month, with the highest in October 2018 at 100 653 and the lowest in April 2020 at 17 715 after the start of the COVID-19 pandemic.

Figure 18 Distribution of comparator preventive visits by calendar month of index date (GCA)



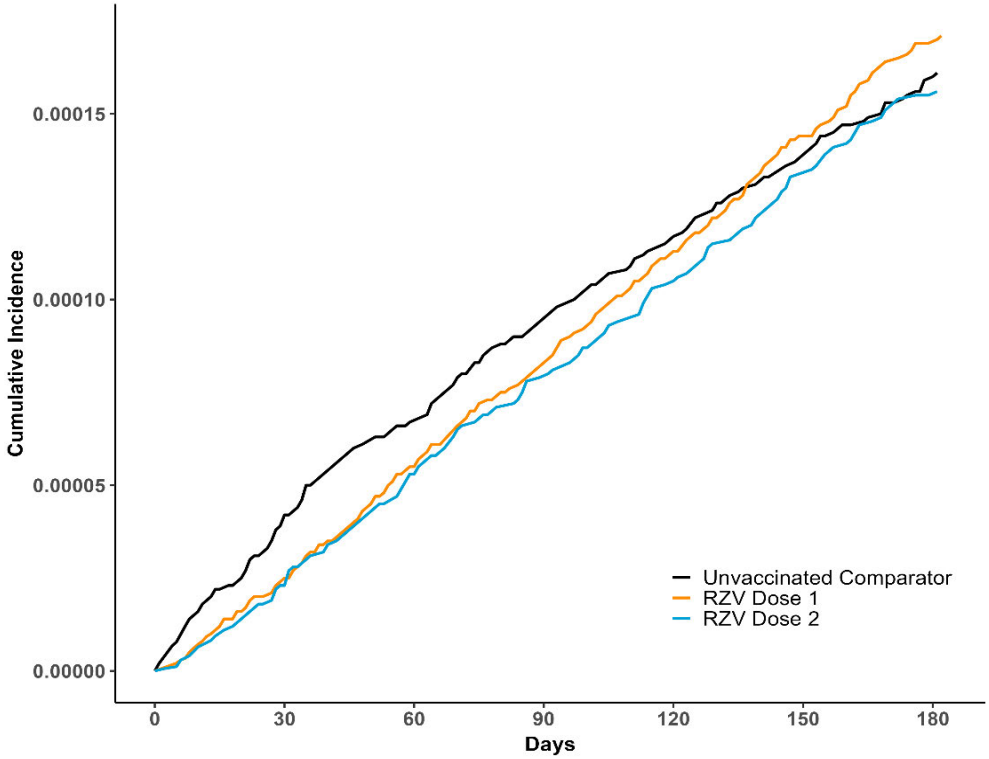
GCA, Giant cell arteritis; RZV, recombinant zoster vaccine.
Note: Index date, date of preventive care visit; Number of participants counted from January 2018 to December 2020 out of the total 2 585 975 RZV-unvaccinated.

9.5.3. Cumulative incidence of GCA

The average time to event following RZV Dose 1 was 92.24 (SD=52.26) days for the Dose 1 RZV-exposed and following the preventive care visit was 77.54 (SD=53.04) days for the RZV-unvaccinated comparators. The average time to event following RZV Dose 2 was 90.45 (SD=50.06) days.

Figure 19 illustrates the cumulative incidence of GCA over time, along with the numerical tabulation of the number at risk over the follow-up period. Of the 3 288 846 Dose 1 RZV-exposed at risk at the start of follow-up, 107 620 were censored and 506 developed GCA with a cumulative incidence of 0.000154 by Day 180. Of the 2 508 442 Dose 2 RZV-exposed at risk at the start of follow-up, 76 284 were censored and 364 developed GCA with a cumulative incidence of 0.000146 by Day 180. Of the 2 585 975 RZV-unvaccinated comparators, 637 351 were censored and 360 developed GCA by Day 180, which corresponds with a cumulative incidence of 0.000149. The cumulative incidence graph shows that the two curves begin to separate during the first week after the index date, with higher cumulative incidence among the RZV-unvaccinated comparators. The two curves cross around 120 days after Dose 1 and 150 days after Dose 2, with the RZV-unvaccinated showing lower cumulative incidence throughout the remainder of the follow-up period. This suggests a violation of the proportional hazards assumption. Results adjusting for the violation of the proportional hazards assumption are provided in Section 9.5.4

Figure 19 Cumulative incidence of GCA by vaccination status – Primary Analysis RZV Dose 1 and Dose 2



	Days After Index Date							
PMR		**0**	**30**	**60**	**90**	**120**	**150**	**180**
RZV Dose 1	At risk	3 288 846	3 276 721	3 261 172	3 240 026	3 216 981	3 197 723	3 180 720
	Cumulative incidence	0	0.000023	0.000052	0.000076	0.000102	0.000129	0.000154
RZV Dose 2	At risk	2 508 442	2 493 636	2 479 763	2 467 125	2 454 700	2 443 201	2 431 794
	Cumulative incidence	0	0.000021	0.000048	0.000074	0.000099	0.000126	0.000146
Unvaccinated comparator	At risk	2 585 975	2 500 562	2 438 249	2 379 535	2 323 679	2 273 771	2 225 735
	Cumulative incidence	0	0.000037	0.000062	0.000087	0.000108	0.000129	0.000149

GCA, giant cell arteritis; RZV, recombinant zoster vaccine.

Figures showing the distribution of new onset GCA by dose by week after the index date are in Figure 40, Figure 41, and Figure 42 in Section 14.5.3.

9.5.4. Results of the primary analyses

The results of the weighted primary analysis, which estimated the HR of GCA separately for Dose 1 and Dose 2 prior to accounting for violation of the proportional hazards assumption, are in (Table 20). The primary analysis for Dose 1 shows that the risk of GCA was not statistically significantly different (IPTW-adjusted HR=1.15, 95% CI: 1.00, 1.32) among the RZV-exposed relative to the RZV-unvaccinated comparators. Similarly,

the primary analysis for Dose 2 did not show a statistically significant difference GCA risk between the RZV-exposed and the RZV-unvaccinated comparators (IPTW-adjusted HR=1.04, 95% CI: 0.89, 1.22).

Table 20 Risk estimates for primary analysis of GCA within a 183-day follow-up period – IPTW-Adjusted

Separate analysis for RZV Dose 1 and Dose 2					
	No. persons	**No. events**	**PY of follow-up**	**IR per 10 000 PY (95% CI)**	**PS IPTW Adj. HR (95% CI)**
RZV Dose 1					
RZV Dose 1	3 084 667	498	1 521 036	3.27 (3.00 –3.57)	1.15 (1.00 – 1.32)
Comparator	2 448 678	324	1 131 245	2.86 (2.57 – 3.19)	Ref.
RZV Dose 2					
RZV Dose 2	2 405 574	366	1 183 999	3.09 (2.79 – 3.42)	1.04 (0.89 – 1.22)
Comparator	2 370 225	327	1 097 185	2.98 (2.68 – 3.32)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; GCA, giant cell arteritis; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The results of crude and covariate adjusted analysis are provided in Table 69 in Section 14.5.4.1. The distribution of the propensity score (Figure 43 in Section 14.5.5.1) and weights (Table 74 in Section 14.5.5.1) are provided**.**

Assessment of the proportional hazards assumption: Primary analyses

To determine if the HR between two groups remained constant over time, we plotted the graph of the log(-log(survival)) by log(event time). The results, shown in Section 14.5.6 (Figure 48), revealed that the PH assumption was violated for Dose 1 only. Dose 2 did not violate the proportional hazards assumption as the curves did not cross. To address the non-proportional hazards for the Dose 1 analysis, we conducted a weighted Cox model including a time-dependent coefficient and tested a change point at 150 days (i.e., 1 to 150 days versus >150 to 183 days).

The results of the piecewise weighted Cox model with a change point coefficient shows no statistically significant difference in risk of GCA between the RZV-exposed and the RZV-unvaccinated comparators (Table 21). For the Dose 1 analysis, in the 1 to 150 days of follow-up, the IPTW-adjusted HR=1.10 (95% CI: 0.94, 1.28) and after 150 to 183 days of follow-up, the IPTW-adjusted HR=1.34 (95% CI: 0.89, 2.01).

Table 21 IPTW HR estimates for GCA by follow-up time after the index date: Primary analysis

Follow-up Time Strata	Hazard Ratio	95% Confidence Interval	
RZV Dose 1			
1 to 150 days	1.10	0.94	1.28
>150 days	1.34	0.89	2.01

CI, confidence interval; GCA, giant cell arteritis; HR, hazard ratio; index date, date of vaccination for Dose 1 and Dose 2 for RZV exposed; date of preventive care visit for unvaccinated comparator; RZV, recombinant zoster vaccine.

9.5.5. Results of the secondary analyses

Table 22 shows the secondary analyses for GCA using a partly conditional survival model to obtain a single risk estimate and a time-varying model to obtain separate risk estimates. The analysis combining Dose 1 and Dose 2 for a single risk estimate showed a significantly higher risk of GCA in the RZV-exposed relative to the RZV-unvaccinated comparator (IPTW-adjusted HR=1.18, 95% CI: 1.03, 1.34).

The time-varying analysis, which generated a separate risk estimate for Dose 1 and Dose 2, revealed a statistically significant higher risk of GCA for Dose 1 (IPTW-adjusted HR=1.23, 95% CI: 1.05, 1.43). The risk estimate for Dose 2 was not significant (IPTW-adjusted HR=1.07, 95% CI: 0.88, 1.31).

Table 22 Risk estimates for secondary analysis of GCA within a 183-day follow-up period – IPTW-Adjusted

Secondary analyses of combined and time-varying dose					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
Combined dose					
RZV Dose 1 and Dose 2	5 440 528	699	2 141 094	3.26 (3.03, 3.51)	1.18 (1.03, 1.34)
Comparator	2 448 678	324	1 131 245	2.86 (2.57, 3.19)	Ref.
Time-varying separate dose					
RZV Dose 1	3 084 667	342	980 124	3.49 (3.14, 3.88)	1.23 (1.05, 1.43)
RZV Dose 2	2 330 151	156	540 911	2.89 (2.47, 3.38)	1.07 (0.88, 1.31)
Comparator	2 448 678	324	1 131 245	2.86 (2.57, 3.19)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; GCA, giant cell arteritis; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The results of crude and covariate adjusted analysis are provided Table 70 in Section 14.5.4.2. The distribution of the propensity scores (Figure 44 and Figure 45) are provided in Section 14.5.5.2 and Section 14.5.5.3, respectively. The propensity score weights are provided in Table 74 in Section 14.5.5.1.

Assessment of the proportional hazards assumption: Secondary analyses

The log(-log(survival)) by log(event time) evaluated the assumption of proportional hazards for the secondary analyses. The results, shown in Section 14.5.6 (Figure 49), revealed that the PH assumption was violated. Since the combined dose and the time-varying dose analyses segmented the follow-up by dose, a time-dependent coefficient was not included in the Cox regression model.

9.5.6. Results of sensitivity to primary analyses

COVID-19 sensitivity results

Table 23 shows the results of the COVID-19 sensitivity analysis for the primary analysis. The sensitivity analysis for Dose 1 does not show a statistically significant increased risk of GCA (IPTW-adjusted HR=1.14, 95% CI: 0.96, 1.35) in the RZV-exposed relative to RZV-unvaccinated comparator. The separate Dose 2 analysis also revealed no statistically significant difference in the risk of GCA for RZV-exposed relative to the RZV-unvaccinated comparator (IPTW-adjusted HR=0.99, 95% CI: 0.82, 1.21).

Table 23 Risk estimates for COVID-19 sensitivity of the primary analysis of GCA within a 183-day follow-up period – IPTW-Adjusted

COVID-19 sensitivity analysis[a]					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
RZV Dose 1					
RZV Dose 1	2 255 118	351	967 072	3.63 (3.27, 4.03)	1.14 (0.96,1.35)
Comparator	1 834 933	236	739 105	3.19 (2.81, 3.63)	Ref.
RZV Dose 2					
RZV Dose 2	1 658 181	220	678 647	3.25 (2.85, 3.71)	0.99 (0.82, 1.21)
Comparator	1 771 647	230	704 132	3.27 (2.88, 3.72)	Ref.

Adj, adjusted; CI, confidence interval; comparator, Unvaccinated comparator; COVID-19, coronavirus disease; GCA, giant cell arteritis; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, Incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.
a. 01 February 2020 included as a censoring event.

The results of crude and covariate adjusted analysis are provided in Table 71 in Section 14.5.4.3. The distribution of the propensity score (Figure 46) and weights (Table 75) are provided in Section 14.5.5.4.

Assessment of the proportional hazards assumption: COVID-19 sensitivity analysis

To determine if the hazards remained constant over time, we plotted the graph of the log(-log(survival)) by log(event time). The results, shown in Section 14.5.6 (Figure 50), revealed that the PH assumption was violated for the COVID-19 sensitivity analysis of Dose 1 but not Dose 2. To address the non-proportional hazards for Dose 1, we conducted a weighted Cox model including a time-dependent coefficient and tested a change point at 120 days (i.e., 1 to 120 days versus >120 to 183 days) as this was the point in time after the index date where the curves crossed.

The results of the change point model (Table 24) show no statistically significant difference in risk of GCA between the RZV-exposed and the RZV-unvaccinated comparators. The IPTW-adjusted HR=1.07 (95% CI: 0.88, 1.31) for follow-up from Days 1 to 120 and from Days >120 to 183, the IPTW-adjusted HR=1.26 (95% CI: 0.85, 1.85).

Table 24 IPTW HR estimates for GCA by follow-up time after the index date: COVID-19 sensitivity analysis

Follow-up Time Strata	Hazard Ratio	95% Confidence Interval
RZV Dose 1		
1 to 120 days	1.07	0.88, 1.31
>120 days	1.26	0.85, 1.85

CI, confidence interval; GCA, giant cell arteritis; HR, hazard ratio; RZV, recombinant zoster vaccine.

Alternative GCA outcome definition sensitivity results

The sensitivity analysis incorporating the alternative GCA definition could not be presented due to a large reduction in the number of events, which rendered estimates that were not meaningful for inference.

9.5.7. Results of sensitivity to secondary analyses

Dose-compliant sensitivity results

Table 25 shows the sensitivity analyses of the secondary partly conditional and time-varying analyses for GCA among a sub-sample of participants who received both RZV doses spaced within 2 to 6 months per US label (i.e., dose-compliant subgroup). The sensitivity analysis of combined doses in one risk estimate for GCA shows a non-significant IPTW-adjusted HR=1.01 (95% CI: 0.87, 1.17).

The sensitivity analysis using a time-varying model that generated a separate risk estimate for Dose 1 and Dose 2 revealed non-significant risk estimates, with the IPTW-adjusted HR=0.93 (95% CI: 0.76, 1.13) for Dose 1 and IPTW-adjusted HR=1.08 (95% CI: 0.88, 1.32) for Dose 2.

Table 25 Risk estimates for the dose-compliant sensitivity of the secondary analysis of GCA within a 183-day follow-up period – IPTW-Adjusted

Dose-compliant[a] sensitivity analysis					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
Subset of combined doses					
RZV Dose 1 and Dose 2	4 433 359	472	1 662 967	2.84 (2.59, 3.10)	1.01 (0.87, 1.17)
Comparator	2 422 867	325	1 119 479	2.90 (2.60, 3.23)	Ref.
Subset of time-varying separate dose					
RZV Dose 1	2 328 880	169	626 192	2.70 (2.32, 3.14)	0.93 (0.76, 1.13)
RZV Dose 2	2 294 819	153	526 321	2.91 (2.49, 3.41)	1.08 (0.88, 1.32)
Comparator	2 422 867	325	1 119 479	2.90 (2.60, 3.23)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; GCA, giant cell arteritis; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

a. Dose compliant per US schedule of 2 to 6 months spacing between Dose 1 and Dose 2.

The results of crude and covariate adjusted analysis are provided Table 72 in Section 14.5.4.4. The distribution of the propensity scores is found in Figure 44 in Section 14.5.5.2. and Figure 45 in Section 14.5.5.3. The propensity score weights provided in Table 76 in Section 14.5.5.5.

Assessment of the proportional hazards assumption: Dose-compliant sensitivity analysis

The log(-log(survival)) by log(event time) evaluated the assumption of proportional hazards for the dose-compliant sensitivity of the secondary analyses. The results, shown in Section 14.5.6 (Figure 51), revealed that the PH assumption was not violated.

9.5.8. Results of supplemental analyses of the primary analysis

Exclusion of RZV-exposed from control arm

The results of the supplemental analysis for the primary analysis, excluding comparators who subsequently received RZV, are in Table 26. The separate analysis for Dose 1 shows no statistically significant increase in the risk of GCA between the RZV-exposed and the RZV-unvaccinated comparator (IPTW-adjusted HR=0.95, 95% CI: 0.82, 1.10). For Dose 2, the results were not statistically significant, with an IPTW-adjusted HR=0.86 (95% CI: 0.73, 1.01).

Table 26 Risk estimates for the supplemental cohort sensitivity analysis of the primary analysis of GCA within a 183-day follow-up period – IPTW-Adjusted

Supplemental cohort excluding comparators who received RZV					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
RZV Dose 1					
RZV Dose 1	3 085 663	494	1 521 298	3.25 (2.97, 3.55)	0.95 (0.82, 1.10)
Comparator	1 986 106	328	960 195	3.42 (3.07, 3.81)	Ref.
RZV Dose 2					
RZV Dose 2	2 399 946	355	1 181 272	3.01 (2.71, 3.34)	0.86 (0.73, 1.01)
Comparator	1 927 812	327	933 204	3.51 (3.15, 3.91)	Ref.

Adj, adjusted; CI, confidence interval; comparator, Unvaccinated comparator; GCA, giant cell arteritis; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The results of crude and covariate adjusted analysis are provided in Table 73 in Section 14.5.4.5. The distribution of the propensity score (Figure 47) and weights (Table 77) are provided in Section 14.5.5.5.

Assessment of the proportional hazards assumption: Supplemental cohort to the primary

Tests for the proportional hazards assumption revealed that neither Dose 1 nor Dose 2 analyses violated this assumption. The negative log of estimated survivor function plots revealed that the lines did not cross (Section 14.5.6; Figure 52).

9.5.9. Quantitative bias

Primary analysis revealed no statistically significant difference in the risk of GCA, and therefore, the quantitative bias analysis was not conducted.

9.5.10. Post-Hoc Analysis

The primary analysis did not censor Dose 1 at receipt of Dose 2 that occurred in the 183-day period of follow-up after RZV Dose 1. Thus, it is possible that some of the risk in the primary Dose 1 analysis may be due to events occurring after Dose 2. Post-hoc analyses censoring Dose 1 at receipt of Dose 2 for GCA, included estimates of the crude hazard ratio, the cumulative incidence and time-to event, and assessment of the assumption of proportional hazards. Results are provided below based on the crude, unweighted, analyses.

Table 27 presents the incident rate per 10 000 person-years and the crude hazards ratio from the Cox proportional hazards regression model for the primary analysis of Dose 1 without and with censoring at Dose 2. The results show a statistically non-significant

increased risk of GCA, without and after censoring at Dose 2. The hazards ratios were similar, and both had a lower bound of the 95% CI below 1.00.

The time to GCA from RZV Dose 1 with censoring was 71.12 (SD=47.57) days and the corresponding time to event for the RZV-unvaccinated comparator was 77.54 (SD=53.04) days. Of the 3 288 846 participants in the unweighted RZV-exposed who were at risk at the start of follow-up for Dose 1, there were 3 288 507 censored and 339 who developed GCA prior to censoring at RZV Dose 2 with a cumulative incidence of 0.00017 by Day 183. Of the 2 585 975 RZV-unvaccinated comparators who were at risk at the start of follow-up, there were 2 585 615 censored and 360 who developed GCA for a cumulative incidence of 0.00015 by Day 183.

Table 27 Risk of GCA following RZV Dose 1 with and without censoring at receipt of Dose 2

Post-hoc analysis of the primary analysis of Dose 1 – without and with censoring at Dose 2					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)
RZV Dose 1 – no censoring at Dose 2					
RZV Dose 1	3 288 846	506	1 621 702	3.12 (2.86, 3.40)	1.04 (0.91, 1.19)
Comparator	2 585 975	360	1 193 742	3.02 (2.72, 3.34)	Ref.
RZV Dose 1 – with censoring at Dose 2					
RZV Dose 1	3 288 846	339	1 038 052	3.27 (2.94, 3.63)	1.04 (0.89, 1.22)
Comparator	2 585 975	360	1 193 742	3.02 (2.72, 3.34)	Ref.

Adj, adjusted; CI, confidence interval; comparator, Unvaccinated comparator; HR, hazard ratio; GCA, giant cell arteritis; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The survival probability function curves crossed around Day 130 of follow-up, indicating a violation of the proportional hazards assumption in the analysis that censored Dose 1 at receipt of Dose 2. The log(-log(survival probability)) function is in Figure 53 in Section 14.5.7.

9.6. COHORT – Secondary objective: ION

9.6.1. Participants

The RZV-exposed analytic cohort was comprised of 3 289 741 participants, and the RZV-unvaccinated comparator analytic cohort was comprised of 2 587 018 participants (Section 14.6.1**)**.

9.6.2. Descriptive data including baseline characteristics

Table 78 in Section 14.6.1 displays participants' characteristics, unweighted and weighted, on the index date as well as medical diagnoses and health service utilization in the 365 days preceding the index date of RZV Dose 1 for the RZV-exposed or the

preventive care visit date for the RZV-unvaccinated comparators. The mean age was 74.36 (±6.34) years and 75.19 (±7.15) years for the RZV-exposed at receipt of Dose 1 and for the RZV-unvaccinated comparators at the preventive care visit date, respectively. Among the unweighted cohort of 3 289 741 participants who received RZV Dose 1, most were White (n=2 927 058; 88.98%), female (n=1 938 121; 58.91%), and 70 to 79 years of age (70 to 74: n=1 035 268; [31.47%]; 75 to 79: n=726 474 [22.08%]). Most of the 2 587 018 RZV-unvaccinated comparators were White (n=2 233 750; 86.34%), female (n=1684; 63.57%), and 70 to 79 years of age (70 to 74: n=747 664 [28.90%]; 75 to 79: n=525 955 [20.33%]).

The most prevalent medical conditions in the RZV-exposed and RZV-unvaccinated comparators, respectively, were diabetes mellitus (24.30% and 27.67%), ischemic heart disease (21.24% and 22.37%), chronic kidney disease (20.60% and 23.25%), and chronic lung disease (12.15% and 14.55%).

Imbalance in demographic covariates on the index date of RZV Dose 1 and the preventive care visit, as measured by the SMD, included mean age (SMD= −0.12), the proportion aged 85+ (SMD= −0.14), the proportion Black (SMD= −0.16), and index year of 2018 (SMD= 0.25) and 2019 (SMD= 0.20). In the 365-day baseline period preceding the index date, imbalances between RZV-exposed and RZV-unvaccinated comparators, respectively, was observed for dementia, (3.35% and 6.02%; SMD= −0.13), optometry/ophthalmology visit (56.78% and 47.91%; SMD= 0.18), two or more ED visits (4.69% and 7.97%; SMD= −0.13), and utilization of home health care (5.79% and 8.90%; SMD= −0.12). We observed imbalances between RZV-exposed and RZV-unvaccinated comparators, respectively, in receipt of concomitant influenza (12.42% and 6.01%; SMD= 0.22) and Tdap (2.06% and 0.13%; SMD= −0.19).

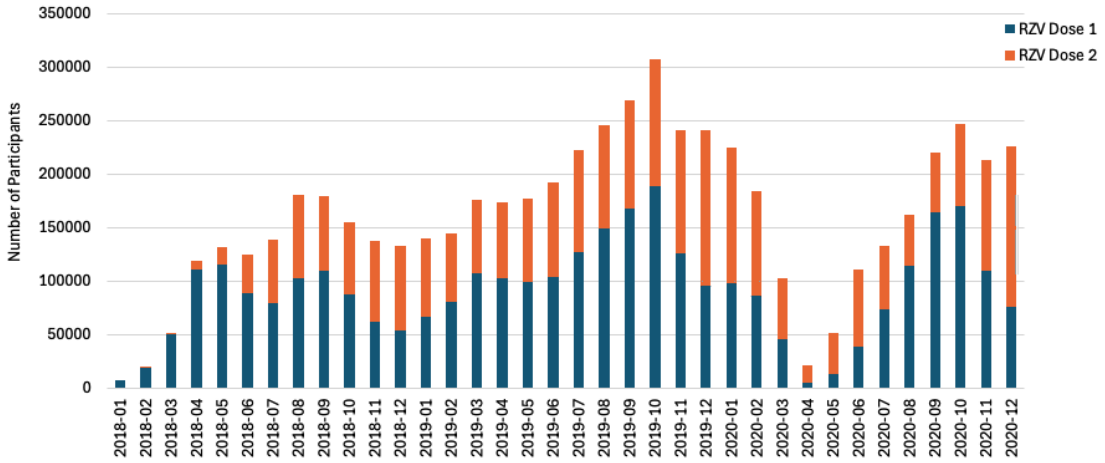
After applying an IPTW stabilized weight, all covariates were well balanced, as indicated by SMDs close to zero (Table 78 in Section 14.6.1).

Baseline characteristics by number of doses and dose spacing are shown in Table 79 in Section 14.6.1. The baseline characteristics for the supplemental cohort are provided in Table 80 in Section 14.6.2.

Distribution of RZV D1 and D2

Figure 20 shows the number of RZV-exposed participants who received RZV Dose 1 and Dose 2 by calendar month in 2018, 2019, and 2020 for the ION analytic cohort. The number of participants who received RZV Dose 1 peaked in October 2019 at 188 644 and was lowest in April 2020 at 5026 after the start of the COVID-19 pandemic. The patterns of RZV Dose 2 show monthly fluctuations.

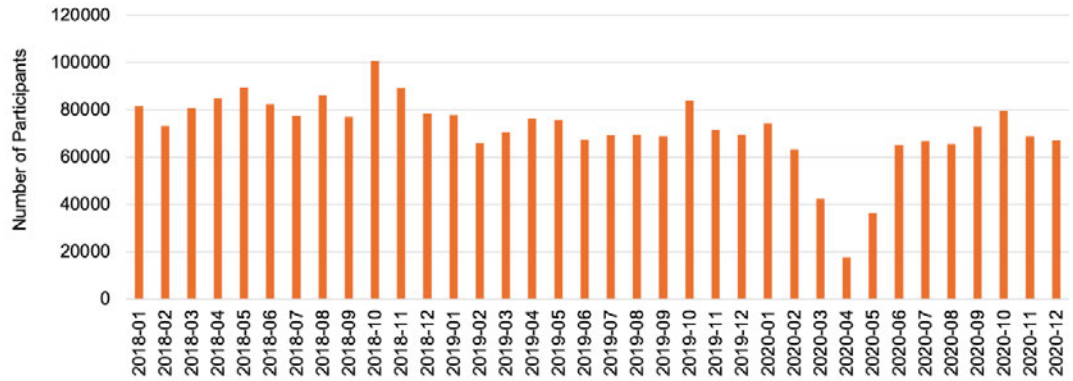
Figure 20 Distribution of RZV Dose 1 and Dose 2 by calendar month of index date (ION)



ION, Ischemic optic neuropathy; RZV, recombinant zoster vaccine.
Note: Index date, date of vaccination for Dose 1 for RZV-exposed; Number of participants counted from January 2018 to December 2020 out of the total 3 289 741 RZV-exposed.

Figure 21 shows the number of participants in the RZV-unvaccinated comparator analytic cohort who had a preventive visit by calendar month in 2018, 2019, and 2020. We observe year-to-year fluctuations in the number of RZV-unvaccinated comparators by calendar month, with the highest in October 2018 at 100 683 and the lowest in April 2020 at 17 711 after the start of the COVID-19 pandemic.

Figure 21 Distribution of comparator preventive care visits by calendar month following the index date (ION)



ION, Ischemic optic neuropathy; RZV, recombinant zoster vaccine.
Note: Index date, date of preventive care visit for the RZV-unvaccinated comparator; Number of participants counted from January 2018 to December 2020 out of the total 2 587 018 RZV-unvaccinated comparators.

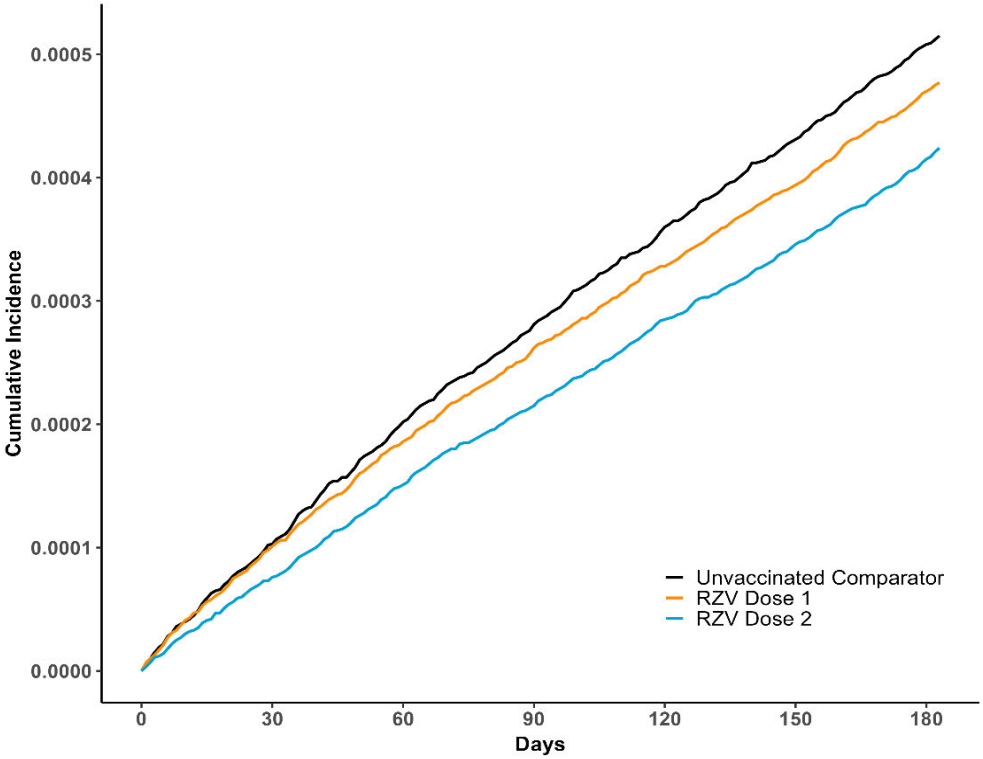
9.6.3. Cumulative incidence of ION

The average time to event following RZV Dose 1 was 84.89 (SD=54.65) days for the RZV-exposed and 82.85 (SD=53.75) days for the RZV-unvaccinated comparators. The average time to event following RZV Dose 2 was 89.44 (SD=54.47) days for the RZV-exposed.

Figure 22 illustrates the cumulative incidence of ION over time, along with the numerical tabulation of the number at risk over the follow-up period. Of the 3 289 741 participants in the unweighted RZV-exposed who were at risk at the start of follow-up for RZV Dose 1, there were 107 618 censored and 1547 developed ION following RZV Dose 1 with a cumulative incidence of 0.00047 by Day 180. Of the 2 509 168 participants in the unweighted RZV-exposed who were at risk at the start of follow-up for RZV Dose 2, 282 258 were censored and 1047 developed ION following RZV Dose 2 with a cumulative incidence of 0.000415 by Day 180. Of the 2 587 018 participants in the unweighted RZV-unvaccinated comparators who were at risk at the start of follow-up, 637 568 were censored and 1234 developed ION by Day 180, which corresponds to a cumulative incidence of 0.000508. The cumulative incidence graph shows that the Dose 1 and RZV-unvaccinated comparator curves begin to separate before 40 days of follow-up, and the distance between them continues to widen over time. At no point do the lines for RZV Dose 1 or Dose 2 and the RZV-unvaccinated comparator cross, with the RZV-exposed maintaining a lower cumulative incidence throughout the follow-up period.

Section 14.6.3 includes the figures with the distribution of new onset ION by dose and week after the index date (Figure 54, Figure 55, and Figure 56).

Figure 22 Cumulative incidence of ION by vaccination status – Primary Analysis RZV Dose 1 and Dose 2



	Days After Index Date							
PMR		**0**	**30**	**60**	**90**	**120**	**150**	**180**
RZV Dose 1	At risk	3 289 741	3 277 369	3 261 635	3 240 307	3 217 106	3 197 723	3 180 576
	Cumulative incidence	0	0.000101	0.000186	0.000262	0.000328	0.000394	0.00047
RZV Dose 2	At risk	2 509 168	2 501 421	2 438 914	2 380 048	2 324 047	2 274 014	2 225 863
	Cumulative incidence	0	0.000081	0.000151	0.000215	0.000285	0.000346	0.000415
Unvaccinated comparator	At risk	2 587 018	2 494 212	2 480 199	2 467 468	2 454 925	2 443 356	2 431 825
	Cumulative incidence	0	0.000103	0.000202	0.000281	0.00036	0.000431	0.000508

ION, Ischemic optic neuropathy; RZV, recombinant zoster vaccine.

9.6.4. Results of the primary analyses

The primary analysis using a weighted Cox proportional hazards model (Table 28) showed no statistical difference in the risk of ION after Dose 1 (IPTW-adjusted HR=0.97; 95% CI: 0.90, 1.05). For Dose 2, the primary analysis showed a statistically significant lower risk of ION among the RZV-exposed relative to the RZV-unvaccinated comparator (IPTW-adjusted HR=0.85; 95% CI: 0.78, 0.93).

Table 28 Risk estimates for primary analysis of ION within a risk 183-day follow-up period – IPTW-Adjusted

Separate analysis of RZV Dose 1 and Dose 2					
	No. persons	**No. events**	**PY of follow-up**	**IR per 10 000 PY (95% CI)**	**PS IPTW Adj. HR (95% CI)**
RZV Dose 1					
RZV Dose 1	3 085 493	1492	1 521 168	9.81 (9.32, 10.32)	0.97 (0.90, 1.05)
Comparator	2 449 702	1151	1 131 517	10.17 (9.60, 10.77)	Ref.
RZV Dose 2					
RZV Dose 2	2 406 236	1041	1 184 142	8.79 (8.27, 9.34)	0.85 (0.78, 0.93)
Comparator	2 371 281	1135	1 097 472	10.34 (9.76, 10.96)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; ION, ischemic optic neuropathy; IR, incidence rate; PS, propensity score; IPTW, inverse probability of treatment weighting; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The results of crude and covariate adjusted analysis are provided in Table 81 in Section 14.6.4.1. The distribution of the propensity score (Figure 57) and weights (Table 86) are provided in Section 14.6.5.1.

Assessment of the proportional hazards assumption: Primary analysis

Tests for the proportional hazards assumption revealed that neither Dose 1 nor Dose 2 analyses violated this assumption. The negative log of estimated survivor function plots revealed that the lines did not cross (Section 14.6.6; Figure 62).

9.6.5. Results of the secondary analyses

Table 29 shows the secondary analyses for ION. The analysis combining Dose 1 and Dose 2 to obtain a single risk estimate shows there was not a statistically significant difference in the risk of ION between the RZV-exposed and the RZV-unvaccinated comparator (IPTW-adjusted HR=0.94, 95% CI: 0.87, 1.01). The analysis using a time-varying dose exposure model to generate a separate risk for RZV Dose 1 and Dose 2 also revealed a statistically non-significant difference in the risk of ION for RZV Dose 1 and Dose 2 between RZV-exposed and the RZV--unvaccinated comparator, with an IPTW-adjusted HR=1.01 (95% CI: 0.93, 1.10) for Dose 1 and an IPTW-adjusted HR=0.90 (95% CI: 0.81, 1.01) for Dose 2.

Table 29 Risk estimates for secondary analysis of ION within a 183-day follow-up period – IPTW-Adjusted

Secondary analysis combined and time-varying dose					
	No. persons	**No. events**	**PY of follow-up**	**IR per 10 000 PY (95% CI)**	**PS IPTW Adj. HR (95% CI)**
Combined dose					
RZV Dose 1 and Dose 2	5 442 040	2018	2 141 425	9.42 (9.02, 9.84)	0.94 (0.87, 1.01)
Comparator	2 449 702	1151	1 131 517	10.17 (9.60, 10.77)	Ref.
Time-varying separate dose					
RZV Dose 1	3 085 493	1005	980 292	10.25 (9.64, 10.91)	1.01 (0.93, 1.10)
RZV Dose 2	2 330 178	487	540 875	9.00 (8.24, 9.84)	0.90 (0.81, 1.01)
Comparator	2 449 702	1151	1 131 517	10.17 (9.60, 10.77)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; ION, ischemic optic neuropathy; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The results of crude and covariate adjusted analysis are provided in Table 82 in Section 14.6.4.2. The distribution of the propensity scores is in Figure 58 in Section 14.6.5.2 and Figure 59 in Section 14.6.5.3. The propensity score weights are provided in Table 86 in Section 14.6.5.1.

Assessment of the proportional hazards assumption: Secondary analyses

Tests for the proportional hazards assumption for the secondary analyses revealed that neither Dose 1 nor Dose 2 analyses violated this assumption. The negative log of estimated survivor function plots revealed that the lines did not cross (Section 14.6.6; Figure 63).

9.6.6. Results of the sensitivity to primary analyses

COVID-19 sensitivity results

The results of the COVID-19 sensitivity analysis for the primary analysis of ION are in Table 30. The COVID-19 sensitivity analysis for RZV Dose 1 shows there was a statistically non-significant difference in the risk of ION among the RZV-exposed relative to the RZV-unvaccinated comparator (IPTW-adjusted HR=0.97, 95% CI: 0.88, 1.07). The COVID-19 sensitivity analysis for RZV Dose 2 revealed a statistically significant lower risk of ION among the RZV-exposed relative to the RZV-unvaccinated comparator (IPTW-adjusted HR=0.86, 95% CI: 0.77, 0.96).

Table 30 Risk estimates for COVID-19 sensitivity of the primary analysis of ION within a 183-day follow-up period – IPTW-Adjusted

COVID-19 sensitivity analysis[a]					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
RZV Dose 1					
RZV Dose 1	2 255 680	979	967 154	10.12 (9.50 – 10.77)	0.97 (0.88 – 1.07)
Comparator	1 835 718	775	739 326	10.49 (9.77 – 11.25)	Ref.
RZV Dose 2					
RZV Dose 2	1 661 130	629	679 757	9.25 (8.56 – 10.01)	0.86 (0.77 – 0.96)
Comparator	1 773 362	763	704 695	10.83 (10.09 – 11.62)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; ION, ischemic optic neuropathy; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.
a. 01 February 2020 included as a censoring event.

The results of crude and covariate adjusted analysis are provided in Table 83 in Section 14.6.4.3. The distribution of the propensity score (Figure 60) and weights (Table 87) are provided in Section 14.6.5.4.

Assessment of the proportional hazards assumption: COVID-19 sensitivity analysis

Tests for the proportional hazards assumption revealed that neither Dose 1 nor Dose 2 analyses violated this assumption. The negative log of estimated survivor function plots revealed that the lines did not cross (Section 14.6.6; Figure 64).

Alternative ION outcome definition sensitivity results

The sensitivity analysis incorporating the alternative ION definition could not be presented due to a large reduction in the number of events, which rendered estimates that were not meaningful for inference.

9.6.7. Results of sensitivity to secondary analyses

Dose-compliant sensitivity results

Table 31 shows the sensitivity of the secondary analyses for ION among the subgroup of participants who received both RZV doses spaced within 2 to 6 months per US label (i.e., dose-compliant subgroup). The sensitivity analysis of combined doses in one risk estimate shows a statistically significant lower risk of ION (IPTW-adjusted HR=0.92, 95% CI: 0.84, 0.99). The sensitivity analysis using a time-varying model that generated a separate risk estimate for Dose 1 and Dose 2 shows statistically non-significant difference in the risk of ION, with an IPTW-adjusted HR=0.99 (95% CI: 0.89, 1.09) for Dose 1 and an IPTW-adjusted HR=0.93 (95% CI: 0.83, 1.04) for Dose 2.

Table 31 Risk estimates sensitivity for dose-compliant sensitivity of the secondary analysis of ION within a 183-day follow-up period – IPTW-Adjusted

Dose compliant[a] sensitivity analyses of combined and time-varying doses					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
Subset of combined doses					
RZV Dose 1 and Dose 2	4 434 313	1534	1 663 116	9.22 (8.77, 9.70)	0.92 (0.84, 0.99)
Comparator	2 423 802	1133	1 119 715	10.12 (9.55, 10.73)	Ref.
Subset of time-varying separate dose					
RZV Dose 1	2 329 325	631	626 252	10.08 (9.32, 10.90)	0.99 (0.89, 1.09)
RZV Dose 2	2 294 796	488	526 265	9.27 (8.48, 10.13)	0.93 (0.83, 1.04)
Comparator	2 423 802	1133	1 119 715	10.12 (9.55, 10.73)	Ref.

Adj, adjusted; CI, confidence interval; comparator, RZV-unvaccinated comparator; HR, hazard ratio; ION, ischemic optic neuropathy; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

a. Dose compliant per US schedule of 2 to 6 months spacing between Dose 1 and Dose 2.

The results of crude and covariate adjusted analysis are provided in Table 84 in Section 14.6.4.4. The distribution of the propensity scores is in Figure 58 in Section 14.6.5.2 and Figure 59 in Section 14.6.5.3. The propensity score weights provided in Table 88 in Section 14.6.5.5.

Assessment of the proportional hazards assumption: Dose-compliant sensitivity analysis

Tests for the proportional hazards assumption for the dose-compliant sensitivity of the secondary analyses revealed that the assumption was not violated. The log(-log) of estimated survivor function plots revealed that the lines did not cross (Section 14.6.6; Figure 65).

9.6.8. Results of supplemental analyses of the primary

Exclusion of RZV-exposed from control arm

Table 32 shows the results of the sensitivity analysis for the primary analysis of ION with the supplemental cohort, which excludes participants from the RZV-unvaccinated comparator analytic cohort who subsequently received RZV. The separate analysis for Dose 1 shows a statistically significant lower risk of ION among the RZV-exposed relative to the RZV-unvaccinated comparator (IPTW-adjusted HR=0.82, 95% CI: 0.76, 0.89). For Dose 2, we observed statistically significant lower risk of ION, with an IPTW-adjusted HR=0.72 (95% CI: 0.66, 0.79).

Table 32 Risk of ION in the supplemental analysis of the primary analysis within a 183-day follow-up period – IPTW-Adjusted

Supplemental cohort excluding comparators who received RZV					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	PS IPTW Adj. HR (95% CI)
RZV Dose 1					
RZV Dose 1	3 086 370	1495	1 521 372	9.83 (9.34, 10.34)	0.82 (0.76, 0.89)
Comparator	1 986 809	1155	960 327	12.03 (11.35, 12.74)	Ref.
RZV Dose 2					
RZV Dose 2	2 400 711	1033	1 181 464	8.74 (8.23, 9.29)	0.72 (0.66, 0.79)
Comparator	1 928 592	1128	933 384	12.08 (11.40, 12.81)	Ref.

Adj, adjusted; CI, confidence interval; comparator, Unvaccinated comparator; HR, hazard ratio; ION, ischemic optic neuropathy; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The results of crude and covariate adjusted analysis are provided Table 85 in Section 14.6.4.5. The distribution of the propensity score (Figure 61) and weights (Table 89) are provided in Section 14.6.5.6.

Assessment of the proportional hazards assumption: Supplemental cohort to the primary

Tests for the proportional hazards assumption revealed that neither Dose 1 nor Dose 2 analyses violated this assumption. The negative log of estimated survivor function plots revealed that the lines did not cross (Section 14.6.6; Figure 66).

9.6.9. Quantitative bias

Primary analysis revealed no differences in the risk of ION, and therefore, the bias analysis was not conducted.

9.6.10. Post-hoc Analyses

Several post-hoc analyses were undertaken to assess the effect of censoring Dose 1 at receipt of Dose 2 for ION. The primary analysis did not censor Dose 1 at receipt of Dose 2 that occurred in the 183-day period of follow-up after RZV Dose 1. Thus, it is possible that some of the risk in the primary Dose 1 analysis may be due to events occurring after Dose 2. Post-hoc analyses censoring Dose 1 at receipt of Dose 2 for ION included estimates of the crude hazard ratio, the cumulative incidence and time-to-event, and assessment of the assumption of proportional hazards. Results are provided below based on the crude, unweighted, analyses.

Table 33 presents the incident rate per 10 000 person-years and the crude hazards ratio from the Cox proportional hazards regression model for the primary analysis of Dose 1 without and with censoring at Dose 2. The results show a statistically non-significant increased risk of ION, without and after censoring at Dose 2. The hazards ratios were similar, and both had a lower bound of the 95% CI below 1.00 and an upper bound at 1.00.

The time to ION from RZV Dose 1 with censoring was 61.77 (SD=47.81) days and the corresponding time to event for the RZV-unvaccinated comparator was 82.85 (SD=53.75) days. Of the 3 289 741 participants in the unweighted RZV-exposed who were at risk at the start of follow-up for Dose 1, there were 3 288 704 censored and 1037 who developed ION prior to censoring at RZV Dose 2 with a cumulative incidence of 0.00048 by Day 183. Of the 2 587 018 RZV-unvaccinated comparators who were at risk at the start of follow-up, there were 2 585 784 censored and 1234 who developed ION for a cumulative incidence of 0.00052 by Day 183.

Table 33 Risk of ION following RZV Dose 1 with and without censoring at receipt of Dose 2

Post-hoc analysis of the primary analysis of Dose 1 – without and with censoring at Dose 2					
	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)
RZV Dose 1 – no censoring at Dose 2					
RZV Dose 1	3 289 741	1547	1 621 853	9.54 (9.07, 10.03)	0.93 (0.86, 1.00)
Comparator	2 587 018	1234	1 194 007	10.34 (9.77, 10.93)	Ref.
RZV Dose 1 – with censoring at Dose 2					
RZV Dose 1	3 289 741	1037	1 038 238	9.99 (9.40, 10.61)	0.92 (0.85, 1.00)
Comparator	2 587 018	1234	1 194 007	10.33 (9.77, 10.93)	Ref.

Adj, adjusted; CI, confidence interval; comparator, Unvaccinated comparator; HR, hazard ratio; ION, ischemic optic neuropathy; IPTW, inverse probability of treatment weighting; IR, incidence rate; PS, propensity score; PY, persons-years; Ref, reference group; RZV, recombinant zoster vaccine.

The survival probability function curves did not cross, indicating no violation of the proportional hazards assumption in the analysis that censored Dose 1 at receipt of Dose 2. The log(-log(survival probability)) function is in Figure 67 in Section 14.6.7.

9.7. Adverse events/adverse reactions

The study was not designed to identify solicited safety events. There was no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents were not present in the data source. Specifically, patient identifiers were not available in the data source, and the data were insufficient to establish attribution between a potential safety event and an individual patient using a GSK product as the data are de-identified. This study used secondary data, involving de-identified healthcare claims, where it is not feasible to make a causality assessment at the individual case level.

10. DISCUSSION

This report implemented two study designs, an SCRI and a cohort design, to evaluate the safety of RZV among US Medicare beneficiaries ≥65 years of age using CMS CCW data, a large secondary real-world dataset.

The SCRI study design was used to evaluate new onset GBS and gout (primary outcomes), and new onset SVT (secondary outcome). The cohort design was used for new onset PMR and GCA (primary outcomes) and new onset ION (secondary outcome).

10.1. Key Results

10.1.1. SCRI

10.1.1.1. Main findings for GBS

The risk of new onset of GBS was examined in the 42-day risk window following RZV exposure. Of the 75 new onset GBS cases detected, 57 occurred in the 42-day risk window. In the primary analysis, which did not distinguish between doses, this corresponded with a statistically significant increased risk of GBS (RR=3.15; 95% CI: 1.82, 5.68) and an attributable risk of 6.59 cases per 1 000 000 RZV vaccinations. A sensitivity analysis of a dose-compliant subgroup of 20 cases who had 60 to 183 days between doses was not statistically significant (RR=1.46; 95% CI: 0.55, 4.13). A seasonality-adjusted analysis that accounted for the background rate of GBS provided nearly similar results as the primary analysis.

Two secondary analyses for GBS evaluated the potential impact of informative censoring. The first secondary analysis used a fixed 3-week control window, and the second used a fixed 6-week control window. Both secondary analyses revealed a statistically significant increased risk of GBS (fixed 3-week: RR=3.56; 95%CI, 1.69, 8.65); fixed 6-week: RR=3.17; 95% CI: 1.84, 5.72). Dose-specific sensitivity analyses using a fixed 6-week control window only revealed a statistically significant increased risk following RZV Dose 1 (RR=5.33; 95% CI: 2.59, 12.36). The dose-specific analysis aligned with the observed larger number of cases following Dose 1.

The COVID-19 pandemic-imposed isolation and quarantine to mitigate viral spread meant that many individuals were not seeking care. This introduced the potential for

detection bias because individuals were not seeking care during isolation, and thus, GBS cases would not be detected in the secondary claims data. A sensitivity analysis restricted the GBS analytic cohort to participants who received the RZV vaccine before 08 November 2019, so that the full 84-day follow-up period would not have been affected by the COVID-19 quarantine measures, thereby mitigating detection bias. The COVID sensitivity analysis revealed a relative risk of 5.13 (95% CI: 2.37, 12.66).

Post-hoc analyses conducted to contextualize the findings and account for lack of chart review, also demonstrated a statistically significant increased risk of GBS in the risk window relative to the control window. These analyses further highlighted the potential for added risk due to recent use of other vaccines as well as a potential effect modification due to age.

These findings are consistent with previously published study [Goud, 2021], also in Medicare beneficiaries using a self-controlled case series analysis, which found an increased risk of GBS following RZV following any dose, with significant dose-specific risk after Dose 1.

10.1.1.2. Main findings for Gout

This analysis evaluated the risk of incident gout in the 30-day risk window following exposure to RZV using an SCRI design. The findings from the primary analysis show that the incident gout cases were nearly equally distributed across risk and control windows. The relative risk of gout in the risk window relative to the control window following any dose was 1.00 and was not statistically significant with a 95% CI of 0.90 to 1.12. This finding was robust to a dose-compliant sensitivity analysis (i.e., 60 to 183 days between Dose 1 and Dose 2) that conformed to the approved dosing regimen in the US. A seasonality adjusted analysis that accounted for the background rate of gout also produced results equivalent to the primary analysis.

The secondary analysis evaluated whether informative censoring affected the estimated relative risk. The secondary analysis used a fixed 30-day control window for both doses and did not censor the Dose 1 control window at receipt of Dose 2. Any cases that were in the Dose 1 control window were attributed to the Dose 2 risk window. The relative risk estimate in the secondary analysis was no different than in the primary analysis, suggesting that informative censoring in the primary analysis was not appreciable to affect the risk estimate. Two dose-specific sensitivity analyses were conducted to further investigate the impact of informative censoring on risk estimate for Dose 1 and Dose 2 separately. The results also show no significant increased risk of incident gout following RZV Dose 1 or Dose 2.

The COVID-19 pandemic-imposed isolation and quarantine to mitigate viral spread meant that many individuals were not seeking care. The ability to detect gout cases in the secondary data could have been diminished because a claim would not be generated if individuals did not seek care. A sensitivity analysis restricted the gout analytic cohort to participants who received the RZV vaccine before 02 December 2019, so that the full 60-day follow-up period would not have been affected by the COVID-19 quarantine measures, thereby mitigating detection bias. Similar to the primary analysis, the results of

this sensitivity analysis did not suggest a significantly increased risk of gout in the risk window relative to the control window (RR=1.00; 95% CI: 0.89, 1.12).

Though pre-approval clinical trial data showed a numerical difference in gout between the RZV and placebo groups, the results of this analysis using population-level data did not show evidence of a statistically significant increased risk of gout following RZV. Differences in the study population, study design and data source could explain the difference in risk estimates. However, the analysis employed a rigorous SCRI design commonly used in vaccine safety studies. Additionally, secondary and sensitivity analyses that tested key assumptions of the primary analysis produced risk estimates that were no different than the primary analysis. The rigor of the design and the robust findings in additional analyses suggest no statistically significant increased risk of gout in the 30-days following RZV exposure in US adults age ≥65 years of age.

10.1.1.3. Main findings for SVT

The risk of new onset of SVT, a secondary objective, was examined in the 30-day risk window following RZV exposure. Of the 4964 new onset SVT cases detected, 48.45% (n=2405) occurred in the 30-day risk window. Graphical display of cases by days since RZV vaccination did not reveal any specific pattern of distribution of the SVT cases across the total 60 days of follow-up. In the primary analysis, which did not distinguish between doses, this corresponded with a relative risk of 0.94 (95% CI: 0.89, 0.99), which is a statistically significant lower risk of SVT in the risk window relative to the control window. The sensitivity analysis of a dose-compliant subgroup of 3837 cases who had 60 to 183 days between doses was not statistically significant (RR=0.98; 95% CI: 0.92, 1.04).

A secondary analysis using a fixed 30-day control window evaluated the potential impact of informative censoring. The secondary analyses revealed the same results as the primary analysis. The dose-specific sensitivity analyses differed in statistical interpretation. The RZV Dose 1 analysis was statistically significant, showing a lower risk of SVT following dose 1 (RR=0.90; 95% CI: 0.83, 0.97), but the RZV Dose 2 analysis was not statistically significant (RR=0.99, 95% CI: 0.92, 1.08).

The COVID sensitivity analysis restricted the SVT analytic cohort to participants who received the RZV vaccine before 02 December 2019, so that the full 60-day follow-up period would not have been affected by the COVID-19 quarantine measures. The COVID sensitivity analysis revealed a relative risk of 0.94 (95% CI: 0.87, 1.01), suggesting no difference in the risk of SVT in the risk window relative to the control window.

The numerical differences in SVT events found in the pre-approval clinical trial data were not replicated in this analysis using population-level real-world claims data. This could, in part, be due to differences in the study population, study design and data source. However, the rigor of the design and the robust findings in additional analyses suggest no statistically significant increased risk of SVT in the 30-days following RZV exposure in US adults age ≥65 years of age.

10.1.2. Cohort

10.1.2.1. Main findings for PMR

The risk of new onset PMR was examined in the 183-day risk window following the index date of RZV for the RZV-exposed and the preventive care visit date for the RZV-unvaccinated comparators. The primary analysis evaluated RZV exposure separately for Dose 1 and Dose 2. Overall, 2012 new onset PMR events occurred among the Dose 1 RZV-exposed, 1297 new onset PMR occurred among Dose 2 RZV-exposed, and 1249 new onset PMR events occurred among the RZV-unvaccinated comparators (unweighted analysis). In the Dose 1 weighted analysis, the overall incidence rate over a 183-day follow-up for PMR per 10 000 person-years was 12.73 (95% CI: 12.17, 13.31) for the RZV-exposed and 10.72 (95% CI: 10.13, 11.35) for the RZV-unvaccinated comparator group. In the Dose 2 weighted analysis, the PMR incidence rate per 10 000 person-years was 10.69 (95% CI: 10.11, 11.29) for the RZV-exposed and 10.92 (95% CI: 10.31, 11.55) for the RZV-unvaccinated comparator, over the 183-day follow-up period.

Adjusting the primary analysis of separate doses to account for violation of the proportional hazards assumption using a time-dependent coefficient [Bardo, 2024], there was no statistically significant difference in the risk of PMR from Days 1 to 120 after Dose 1 (IPTW-adjusted HR=1.00, 95% CI: 0.92, 1.09). However, an increased risk of PMR was observed after 120 days of follow-up after Dose 1 (IPTW-adjusted HR=2.05, 95% CI: 1.71, 2.46). The primary analysis of Dose 2, which did not violate the assumption of proportional hazards, did not reveal a statistically non-significant elevated risk of PMR (HR=0.99; 95% CI: 0.91, 1.07).

The COVID-19 pandemic-imposed isolation and quarantine to mitigate viral spread meant that many individuals were not seeking care. This introduced the potential for detection bias, as PMR cases may not have been captured in the claims data if individuals were not seeking care. A sensitivity analysis of the primary analysis censored participants as of 01 February 2020, the point prior to the onset of the pandemic and the implementation of quarantine measures. The results of the COVID-19 sensitivity analysis for Dose 1, adjusted for violation of the proportional hazards assumption, indicated a statistically significant increased risk of PMR after Day 120 of the follow-up period (HR=2.15; 95% CI: 1.73, 2.68) but a non-significant risk up to and including Day 120 (HR=0.99; 95% CI: 0.90, 1.10). The findings were similar to those from the primary analysis, even after accounting for violation of the proportional hazard assumption. The primary analysis of Dose 2 did not violate the assumption of proportional hazards, and the results show no statistically significant increased risk of new onset PMR following RZV Dose 2. The results suggest that pandemic–imposed isolation and quarantine did not bias the primary findings.

At the FDA’s request, a supplemental cohort was used for the primary analysis for each dose. The supplemental cohort removed participants from the RZV-unvaccinated comparator if they had a future RZV exposure. In contrast to the primary analysis, the results of the supplemental analyses revealed no statistically significant increased risk of PMR for RZV Dose 1 (IPTW-adjusted HR=0.99, 95% CI: 0.92, 1.07) and a statistically significant lower risk of PMR for Dose 2 (IPTW-adjusted HR=0.83, 95% CI: 0.77, 0.90) compared to the RZV-unvaccinated comparator. Compared to the primary analysis, the

supplemental analysis showed that removing 473 234 participants from the RZV-unvaccinated comparator who later received RZV shifted the risk estimates either to the null, as in the Dose 1 analysis, or to the left of the null as in Dose 2. Exclusion of participants from the RZV-unvaccinated arm did not alter the number of events in the RZV-exposed or the RZV-unvaccinated groups. Rather, this decreased the person-time in the denominator of the RZV-unvaccinated, which resulted in an incidence that was similar to the RZV-exposed. The results of the supplemental analyses provide a different risk inference and should be interpreted with caution because this analysis is subject to survivor bias. If an RZV-unvaccinated comparator experienced PMR prior to the receipt of RZV, they were ineligible for the RZV-exposed group because the PMR would be a prevalent case. This survivor bias is a form of selection bias and likely contributed to the observed shift in effect estimates.

Secondary analyses of the combined dose single risk estimate and the time-varying dose exposure censored Dose 1 at receipt of Dose 2, and both analyses demonstrated a statistically significant increased risk of PMR. The combined dose showed a statistically significant 14% higher risk of PMR (IPTW-adjusted HR=1.14, 95% CI: 1.06, 1.23). A sensitivity analysis of the combined dose secondary analysis, limited to a subgroup of those who received Dose 2 within 2 to 6 months after Dose 1, did not show a statistically significant increased risk of PMR (IPTW-adjusted HR=1.04, 95% CI: 0.97, 1.13).

The secondary analysis, using a time-varying model, showed a statistically significant increased risk for PMR after Dose 1 (HR=1.26; 95% CI: 1.16, 1.36) but not Dose 2 (HR=1.10; 95% CI: 1.00, 1.22). A sensitivity analysis for the time-varying dose in the 2 to 6-month dose-compliant subgroup revealed no statistically significant difference in the risk of PMR for either Dose 1 or Dose 2.

Several additional analyses were conducted to better understand the PMR risk following RZV. The risk estimates for the primary analysis of Dose 1, adjusted for non-proportional hazards, revealed no statistically significant elevated risk of PMR in the first 120 days after the index date, yet a statistically significant elevated risk was detected after Day 120 up to Day 183 of the follow-up. Inspecting the time to censoring of the RZV-unvaccinated at receipt of RZV revealed that overall, 203 790 were censored due to receipt of RZV. Of the 263 122 RZV-unvaccinated with 120 days or less of follow-up, 153 209 (58%) were censored on or before Day 120. Most of the RZV-unvaccinated who were censored due to receipt of RZV occurred from Day 1 to 120 of the follow-up. Thus, censoring of the unvaccinated does not explain the higher risk of PMR in the latter period of the follow-up due.

The post-hoc analysis to determine if cases attributed to the Dose 1 follow-up period may have occurred after the receipt of Dose 2 revealed that this constituted 651 (32%) of all 2012 PMR cases. Crude post-hoc analyses that censored RZV Dose 1 at receipt of Dose 2 demonstrated an elevated risk of PMR (HR=1.16; 95% CI: 1.07, 1.25), which was attenuated relative to the primary analysis without censoring. Thus, the higher risk of PMR later in the follow-up is not likely due to a post-Dose 2 effect.

10.1.2.2. Main findings for GCA

The risk of new onset GCA was examined in the 183-day risk window following RZV exposure, separately for Dose 1 and Dose 2 compared to the RZV-unvaccinated comparators. Overall, 506 GCA events occurred among the Dose 1 RZV-exposed, 364 GCA events occurred among the Dose 2 RZV-exposed, and 360 GCA events occurred among the RZV-unvaccinated comparators (unweighted results) over the 183-day follow-up period. In the weighted results, the incidence rate for GCA following Dose 1 in the RZV-exposed was 3.27 per 10 000 person-years (95% CI: 3.00, 3.57) and 2.86 per 10 000 person-years (95% CI: 2.57, 3.19) in the RZV-unvaccinated comparators. In the weighted analysis, the incidence for GCA following Dose 2 in the RZV-exposed was 3.09 (95% CI: 2.79, 3.42) and 2.98 (95% CI: 2.68, 3.32) per 10 000 person-years in the RZV-unvaccinated comparators. The primary analysis of Dose 1 revealed a violation of the proportional hazards assumption. To adjust for this, a piecewise regression with a time-dependent coefficient examined the risk of GCA up to Day 150 (HR=1.10; 95% CI: 0.94, 1.28) and after Day 150 (HR=1.34; 95% CI: 0.89, 2.01). The analysis adjusted for non-proportional hazards also demonstrated a statistically non-significant elevated risk of GCA following RZV Dose 1. The Dose 2 primary analysis did not violate the proportional hazards assumption, with a HR=1.04 (95% CI: 0.89, 1.22).

The COVID-19 sensitivity analyses for Dose 1 and Dose 2 did not show a statistically significant elevated risk of GCA after Dose 1 (HR=1.14; 95% CI: 0.96, 1.35) or after Dose 2 (HR=0.99; 95% CI: 0.82, 1.21). The proportional hazards assumption was violated for the COVID-19 Dose 1 sensitivity analysis but not the COVID-19 Dose 2 sensitivity analysis. Adjustment of the Dose 1 risk estimate using the piecewise regression analysis revealed a similar result as the primary Dose 1 analysis. The COVID-19 Dose 1 adjusted analysis did not detect a statistically significant elevated risk of GCA up to Day 120 (HR=1.07; 95% CI; 0.88, 1.31) or after Day 120 (HR=1.26; 95% CI: 0.85, 1.85).

Supplemental cohorts for Dose 1 and Dose 2 were created whereby participants in the RZV-unvaccinated who subsequently received RZV were removed from the comparator arm. As a result, participants could only contribute person-time in one of the groups. The results of the IPTW-weighted Cox proportional hazards regression revealed no statistically significant elevated risk of GCA (Dose 1: HR=0.95; 95% CI: 0.82, 1.10 and Dose 2: HR=0.86; 95% CI: 0.73, 1.01). The supplemental analyses did not violate the proportional hazards assumption.

The secondary analyses of the combined dose risk estimate and the time-varying dose estimate revealed a significant increased risk of GCA. The combined dose hazard ratio in the IPTW-weighted analysis was 1.18 (95% CI: 1.03, 1.34). The time-varying analysis revealed a significant increased risk of GCA after Dose 1 (HR=1.23; 95% CI: 1.05, 1.43) and a non-significant increased risk after Dose 2 (HR=1.07; 95% CI: 0.88, 1.31). Sensitivity analyses for the combined dose risk estimate and the time-varying dose in the dose-compliant subgroup showed no significant increase in the risk of GCA.

10.1.2.3. Main findings for ION

There was no statistically significant elevated risk of new onset ION in the 183-day risk window following RZV exposure, separately for Dose 1 and Dose 2, compared to the RZV-unvaccinated comparator. Overall, 1547 ION events occurred following Dose 1 among the RZV-exposed, 1047 ION events following Dose 2 among the RZV-exposed, and 1234 ION events among the RZV-unvaccinated comparators (unweighted results). In the weighted analysis for Dose 1, the incidence rate for ION was 9.81 per 10 000 person-years (95% CI: 9.32, 10.32) in the RZV-exposed and 10.17 per 10 000 person-years (95% CI: 9.60, 10.77) in the RZV-unvaccinated comparator. In the weighted analysis for Dose 2, the incidence rate for ION was 8.79 per 10 000 person-years (95% CI: 8.27, 9.34) in the RZV-exposed and 10.34 per 10 000 person-years (95% CI: 9.76, 10.96) in the RZV-unvaccinated comparator.

The results of the IPTW-adjusted Cox proportional hazards regression models revealed consistent estimates across all primary, secondary, and sensitivity analyses with exception of the primary Dose 2, COVID-19 Dose 2 sensitivity, and the supplemental cohort analyses. None of the analyses violated the assumption of proportional hazards. The primary analysis for each dose showed no statistically significant higher risk of ION after RZV Dose 1 (IPTW-adjusted HR=0.97, 95% CI: 0.90, 1.05) and a statistically significant lower risk of ION after RZV Dose 2 (IPTW-adjusted HR=0.85, 95% CI: 0.78, 0.93) in the RZV-exposed compared to the RZV-unvaccinated comparator. The analyses using the supplemental cohort revealed a statistically significant lower risk with hazard ratios of 0.82 (95% CI: 0.76, 0.89) for Dose 1 and 0.72 (95% CI: 0.66, 0.79) for Dose 2. The COVID-19 Dose 2 sensitivity analyses also revealed a statistically significant lower risk with a hazard ratio of 0.86 (95% CI: 0.77, 0.96). The secondary analyses, sensitivity of the secondary analyses, and the COVID-19 Dose 1 sensitivity analysis produced risk estimates similar to the primary Dose 1 analysis.

10.2. Limitations

10.2.1. SCRI

While the SCRI design mitigates bias through implicit control for time-fixed confounders, it does not control for time-varying confounders. However, with the short risk windows for this study, there may be minimal change in confounders, and thus, minimal bias from time-varying confounders would be introduced.

Data on clinical metrics, such as laboratory values and illness severity, and medical record notes that could have been used to confirm cases were not available. It was not possible to conduct a chart review to validate the HOI diagnoses because CMS does not share the person’s identity, and attainment of charts from 4 years ago is not feasible. Although case-finding algorithms using administrative data are rarely sensitive and specific, we used claims-based algorithms with established PPV [Funch, 2013 and Harrold, 2007].

For gout, in addition to the ICD-10 codes, clinical experts suggested additional criteria to enhance the rigor of the case ascertainment algorithm. Loss of Medicare fee-for-service eligibility may have affected the ability to identify gout cases. Any person who lost

Medicare eligibility after the 60-day follow-up period and before the 90-day observation period for gout-related medication use would not have contributed to a case. It is unlikely that many individuals would lose coverage in the 30-day window to appreciably affect the results.

The process for handling possible duplicate RZV doses could potentially have excluded a 'true' second dose. However, the specified periods for dose spacing were aligned with the US RZV regimen, and thus, the findings are still likely applicable in the US, and justifiable in this context.

The Dose 2 analysis was conditioned on the subset of individuals who self-select to receive 2 doses within the study period. This may introduce selection bias if there are characteristic differences in measured and unmeasured factors that influence why some individuals receive two doses whereas some only receive one dose. It is unlikely that this issue produced any substantial bias since most of the analytic cohorts received both doses. For gout, it is possible that those who only received RZV Dose 1 may have had Dose 2 in 2020 and thus were not observable in the study's timeline.

While efforts to mitigate bias due to random error were conducted, it is possible that random sources of error will occur since this is an observational study using secondary claims data. All attempts have been made to ensure the findings were robust through several planned analyses. The findings remained consistent across the different analyses, and thus, the potential for distortion due to random error is likely negligible.

The primary analyses included cases of GBS, SVT or gout where other vaccines were co-administered on the same day as the RZV dose or received within the immediate baseline period. Therefore, we cannot distinguish the effects of RZV from potential effects of other vaccines. Post-hoc analyses for GBS provides some insight as the exclusion of cases with prior influenza, pneumococcal or Tdap vaccine on the same day as the RZV dose, or in the previous 42-days demonstrated attenuated effects.

Despite the above-mentioned limitations, the study has several notable strengths. Notably, an appropriate and rigorous study design was used, one that is commonly used in vaccine safety studies. The investigative team employed a well thought out case identification algorithm that has been validated by CMS. Expert consultation was used to ensure clinical validity of the algorithm. Finally, several planned sensitivity analyses addressed key assumptions and the potential for bias that would distort the risk estimate.

10.2.2. Cohort

The cohort studies have several limitations that warrant consideration. Data on clinical metrics and medical record notes that could have been used to confirm the outcomes were not available. It was not possible to conduct a chart review to validate the PMR, GCA, and ION diagnoses because CMS does not share the person's identity, and attainment of charts from 4 years ago is not feasible.

The process for handling possible duplicate RZV doses could potentially have excluded a 'true' second dose. However, the specified periods for dose spacing were aligned with the

US RZV label, and thus, the findings are still likely applicable in the US, and justifiable in this context.

The Dose 2 analysis was conditioned on the subset of individuals who self-select to receive 2 doses within the study period. This may introduce selection bias if there are characteristic differences in measured and unmeasured factors that influence why some individuals receive two doses whereas some only receive one dose. It is unlikely that this issue produced any substantial bias since most participants across all analytic cohorts received both doses.

While efforts to mitigate bias due to random error were conducted, it is possible that random sources of error will occur since this is an observational study using secondary claims data. All attempts have been made to ensure the findings were robust through several planned analyses and sensitivity analyses. For HOIs GCA and ION the findings remained consistent across the different analyses, and thus, the potential for distortion due to random error is likely negligible. However, for PMR, the sensitivity analysis estimates were inconsistent.

While propensity score methods and IPTW controlled imbalances in measured confounders, this does not rule out the possibility that unmeasured confounders may have biased the effect estimate. A quantitative bias analysis for PMR to assess the robustness of the effect estimate to unmeasured confounding suggested that a moderately strong unmeasured confounder (RR $\geq$1.5) above what has already been controlled for would be needed to explain away the effect. Given the extensive list of confounders accounted for in this study, while it is possible that such an unmeasured confounder exists in this context, many of the key covariates adjusted for did not exceed a hazard of 1.5, thus it is unlikely the case.

The primary analyses included cases of HOIs where other vaccines were co-administered on the same day as the RZV dose or received within the immediate baseline period. Therefore, we cannot distinguish the effects of RZV from potential effects of other vaccines.

10.3. Interpretation of the Results

The findings are to be interpreted in relation to the overall study objective and what is known about the association between primary and secondary HOIs and RZV exposure using SCRI and cohort study designs.

10.3.1. SCRI

10.3.1.1. GBS

This study was conducted using population-level secondary data to enrich the understanding of RZV safety in older adults. A study by Goud et al. using Medicare claims data from 01 October 2017 through 29 February 2020 identified 44 GBS cases following RZV. They reported a statistically significant increased risk of GBS (RR=2.84; 95% CI: 1.53, 5.27) [Goud, 2021] following RZV. The investigators also reported a higher risk of GBS after RZV Dose 1 and a non-significant risk after RZV Dose 2. These

findings resemble the present study using Medicare data for beneficiaries who received RZV from 01 January 2018 through 31 December 2020. The PPV-adjusted post-hoc analysis in this study revealed a statistically significant increased risk of GBS, a finding that Goud and colleagues also reported in their analysis of medical record confirmed cases [Goud, 2021].

Several studies have reported fewer cases of GBS following RZV exposure than reported here or in the previous study in Medicare population [Goud, 2021]. Yih and colleagues investigated GBS cases following RZV exposure using a claims database for individuals ≥50 years of age who had commercial insurance [Yih, 2022]. The investigators found nine cases of GBS, of which a clinician who reviewed the claims data confirmed five were likely new onset [Yih, 2022]. Another study in adults ≥50 years of age detected six GBS cases using the Vaccine Safety Datalink, of which three were confirmed through medical chart review [Nelson, 2023]. These studies involve individuals who were younger than the present study, which raises a question about the potential age-related risk of new-onset of GBS with RZV exposure. The present study included Medicare beneficiaries, whereas these prior studies were primarily of adults with commercial insurance [Yih, 2022, Nelson, 2023], and the populations may differ on health status.

10.3.1.2. Gout

The hypothetical increased risk of gout with RZV exposure is believed to be through a biological mechanism of NLRP3 inflammation [Yokose, 2019]. However, the risk of gout associated with other vaccines that share this biological mechanism is small [Yokose, 2019]. Taken together, the evidence does not suggest a significant increased risk, which is what the present analysis has found. The findings from the present analysis to assess the risk of gout following RZV vaccinations indicates that RZV is not associated with a statistically significant increased risk of gout 30-days following vaccination.

10.3.1.3. SVT

The evidence from this study does not suggest a statistically significant increased risk of SVT following RZV exposure. A cohort study comparing the risk of SVT among RZV-exposed relative to well-visit comparators also did not find a statistically significant higher risk of SVT among the RZV participants [Nelson, 2023].

10.3.2. Cohort

10.3.2.1. PMR

The emerging evidence suggests an association between other vaccines and PMR (e.g., COVID-19 vaccine [Jarrot, 2024]; however, none have evaluated the risk of this condition after RZV vaccination. The findings of this post-authorization safety study for the risk of PMR were consistent across several analyses but require additional context to interpret the risk. Overall, there appears to be no significant risk of PMR following Dose 2, as seen in the primary and sensitivity analyses. However, the risk of PMR after Dose 1 appears to change over time, such that there is no immediate elevated risk detected in the first 120 days after vaccination, but there appears to be an elevated risk that is detected

after Day 120 through the 183-day follow-up period. Both secondary analyses embedded time-dependent censoring in the combined risk estimate and the time-varying dose, and both demonstrated an elevated risk of PMR. The secondary analysis of the time-varying dose produced a hazard ratio that was higher than the combined dose estimate but trended towards the higher risk consistent with the risk after Day 120 in the primary analysis of Dose 1. The delayed onset of PMR has been reported following exposure to an influenza vaccine, whereby PMR was detected within three months of vaccination [Soriano, 2012].

To determine if the elevated risk after Dose 1 in the primary analysis, which did not censor at Dose 2, could be attributed to the second RZV dose, post-hoc analyses were conducted. The post-hoc analyses with censoring of Dose 1 at Dose 2 in the primary analysis also showed an elevated risk after Dose 1. Participants in the RZV-unvaccinated group who later received RZV were largely censored prior to Day 120 and thus also do not explain a higher risk due to censoring later in the follow-up.

Considering the supplemental analyses did not show an elevated risk of PMR, one must interpret these results with caution as it may be subject to selection bias. The supplemental analysis may have been biased towards RZV-exposed who did not experience the outcome.

Analyses that restricted the cohort to the dose-compliant subgroup who received both RZV doses 60 to 180 days apart according to the US dosing schedule, also did not show an increased risk of PMR. It is possible that these results may not be generalizable as they could reflect a select population of vaccinees who did not experience an adverse effect after Dose 1 and thus received the second dose per the U.S. label.

The quantitative bias analysis indicated that an unmeasured confounder with a 1.5 risk association with the outcome could explain away the findings. This means, after adjusting for all other covariates, it would not take a very strong unmeasured confounder to bring the lower 95% confidence interval below 1.00; i.e., nullifying the estimate of a significant elevated risk.

Taking all analyses into consideration, we place this in context of what is known about the prevalence of PMR in the general US population, risk factors for PMR, and co-occurrence of PMR and GCA. The incidence of PMR varies considerably by geographic region, with some of the highest rates in northern Europe [Lundberg, 2022]. A study based in the United Kingdom reported an incidence of 9.6 per 10 000 person-years [Partington, 2018]. A study using a 5% Medicare sample reported the incidence of PMR in adults aged 65 years or older, with and without gout [Singh, 2018]. Those without gout, which is comparable to our RZV-unvaccinated, had an incidence of PMR of 10.9 per 10 000 person-years [Singh, 2018]. The incidence of PMR in this study was 12.73 per 10 000 person-years in the RZV-exposed and 10.72 per 10 000 person-years in the RZV-unvaccinated. The higher incidence in the vaccinated follows prior studies showing evidence of PMR following influenza [Soriano, 2012] and, more recently, RZV [Lenfant, 2021].

In the protocol development for the EPI-ZOSTER-032 study, key risk factors specific to PMR were included as baseline covariates. These included age, sex, race/ethnicity, hematologic malignancies, checkpoint inhibitors, and immunocompromising conditions.

RZV-exposed and the RZV-unvaccinated comparators were balanced on these covariates to mitigate confounding. However, the study could not account for genetic predisposition to PMR [Lundberg, 2022].

The co-occurrence of PMR and GCA was lower than what has been reported in the literature [Nielsen, 2022]. Several factors may explain this discrepancy. For one, among individuals with PMR, the time to GCA can be as long as 4 to 24 months [Nielsen, 2022]. This study was not designed to evaluate the time to GCA following PMR, as these were distinct outcomes. Further, the 183-day follow-up period may not have been sufficient to detect the development of GCA. Finally, the PMR and GCA cohorts in the EPI-ZOSTER-032 study represent participants without pre-existing conditions who met specific inclusion criteria. The analytic cohorts are not representative of the general population from which the background rate of PMR is estimated. The key inclusion and exclusion criteria also limit extrapolation of the co-occurrence with GCA from clinical populations.

In summary, there is a consistent trend towards a statistically significant elevated risk of PMR after Dose 1 that was detected after 120 days following RZV exposure. The incidence of PMR is 12.73 per 10 000 (or 0.001273), which is very rare. The findings may reflect a possible delay in the detection of PMR.

10.3.2.2. GCA

For the primary outcome of GCA, the limited and inconclusive research available focused on the varicella zoster virus vaccination. Lotan and Steiner [Lotan, 2017], for instance, in a study using electronic medical records data from Israel, reported no differences in the incidence of newly diagnosed GCA between those vaccinated against varicella zoster virus and the unvaccinated. However, a more recent study by Agger et al. [Agger, 2020] using retrospective data from one health system in the US, found and increased risk of GCA among those who received ZVL compared to the unvaccinated. The present study, using nationally representative data from US Medicare beneficiaries age ≥65 years, did not detect a statistically significant increased risk of GCA among the RZV-exposed relative to the RZV-unvaccinated comparators, a finding that was robust to different analytical specifications. The secondary analyses with a combined dose risk estimate and a time-varying risk estimate were the only two analyses with a statistically significant increased risk of GCA.

10.3.2.3. ION

Regarding secondary outcome of ION, no prior studies estimating the risk of this condition are available. Despite the numerical imbalances observed in the pivotal trials of Shingrix, 3 subjects (0.02%) who received *Shingrix* (all within 50 days after vaccination) and 0 subjects who received placebo [SHINGRIX, 2026], the present real-world study shows that the risk of new onset ION did not increase after receiving RZV.

10.4. Generalizability

Medicare is the most comprehensive data on older adults, and so the findings will generalize to US adults age ≥65 years. Appreciable differences between those in the

study and those age 65 years and older who are not enrolled in Medicare Parts A, B, and D that would affect the HOI risk estimate following RZV are not expected.

11. OTHER INFORMATION

There is no additional information that was not previously addressed in this statistical analysis report.

12. CONCLUSIONS

In conclusion, this full study report provides results of the EPI-ZOSTER-032 PASS/TSS study to assess the risk of incident gout, GBS, and SVT using an SCRI design, and assess the risk of incident PMR, GCA, and ION using cohort design, following RZV exposure.

This study revealed a significantly higher risk of GBS following RZV exposure. These findings were robust and consistent across many of the planned secondary and sensitivity analyses. Additionally, the secondary analyses for GBS were consistent with an elevated risk following RZV Dose 1 but not Dose 2. The findings suggest that RZV is not significantly associated with an increased risk of incident gout, which were also robust and consistent across all planned secondary and sensitivity analyses. RZV exposure was associated with significantly lower risk of SVT.

The cohort studies compared the risk of HOI within 183 days of RZV exposure among those vaccinated with RZV to RZV-unvaccinated comparators who had a preventive care visit. The findings for PMR suggest a statistically significant elevated risk of PMR that occurred in the 121 to 183-days following RZV Dose 1. The incidence of PMR was rare in this large population of Medicare beneficiaries. Most of the analyses for GCA revealed a non-significant elevated risk. Although the secondary analyses of GCA were contrary to all other analyses, showing an elevated risk, this may be due to the smaller number of events and the different analytic models. The study did not find evidence of an elevated risk of ION following RZV Dose 1 or Dose 2.

13. REFERENCES

Agger WA, Deviley JA, Borgert AJ, et al. Increased Incidence of Giant Cell Arteritis After Introduction of a Live Varicella Zoster Virus Vaccine. *Open Forum Infect Dis*. 2020;8(2):ofaa647. doi: 10.1093/ofid/ofaa647.

Anderson TC, Masters NB, Guo A, et al. Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(3):80-4.

Armstrong BG, Gasparrini A, and Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. BMC Med Res Methodol. 2014;14:122.

Baker MA, Lieu TA, Li L, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. Am J Epidemiol. 2015;181(8):608-18.

Baker MA, Baer B, Kulldorff M, et al. Kawasaki disease and 13-valent pneumococcal conjugate vaccination among young children: A self-controlled risk interval and cohort study with null results. *PLoS Med*. 2019;16:e1002844.

Bardo M, Huber C, Benda N, et al. Methods for Non-proportional Hazards in Clinical Trials: A Systematic Review. *Stat Methods Med Res*. 2024; 33(6):1069-92.

Bellanti R, Rinaldi S. Guillain-Barré syndrome: a comprehensive review. Eur J Neurol 2024;31:e16365. https://doi.org/10.1111/ene.16365.

Bernatsky S, Linehan T, Hanly JG. The accuracy of administrative data diagnoses of systemic autoimmune rheumatic diseases. *J Rheumatology*. 2011;38(8):1612-16.

Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. *N Engl J Med*. 2016;375(11):1019-32.

Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology*. 2016;27(3):368-77.

Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103-08.

Funch D, Holick C, Velentgas P, et al. Algorithms for identification of Guillain-Barre Syndrom among adolescents in claims databases. Vaccine. 2013;31(16):2075-9.

Goud R, Lufkin B, Duffy J, et al. Risk of Guillain-Barre Syndrome Following Recombinant Zoster Vaccine in Medicare Beneficiaries. *JAMA Intern Med*. 2021;181:1623-30.

Harrold, L. R., K. G. Saag, R. A. Yood, T. R. Mikuls, S. E. Andrade, H. Fouayzi, J. Davis, K. A. Chan, M. A. Raebel, A. Von Worley, and R. Platt. Validity of gout diagnoses in administrative data. *Arthritis Rheum*. 2007;57:103-08.

HCUP Databases. Healthcare Cost and Utilization Project (HCUP). May 2026. Agency for Healthcare Research and Quality, Rockville, MD. hcup-us.ahrq.gov/nisoverview.jsp.

Jarrot PA, Mirouse A, Ottaviani S, et al. Polymyalgia rheumatica and giant cell arteritis following COVID-19 vaccination: Results from a nationwide survey. *Hum Vaccin Immunother*. 2024;20(1):2334084. doi: 10.1080/21645515.2024.2334084.

John AR, Canaday DH. Herpes Zoster in the Older Adult. *Infect Dis Clin North Am*. 2017;31(4):811-26.

Kawai K, Yawn BP. Risk Factors for Herpes Zoster: A Systematic Review and Meta-analysis. *Mayo Clin Proc*. 2017;92(12):1806-21.

Kim JE, Park J, Min YG, et al. Associations of Guillain-Barré syndrome with coronavirus disease 2019 vaccination: Disproportionality analysis using the World Health Organization pharmacovigilance database. *J Peripher Nerv Syst*. 20226:10.1111/jns.12507. doi: 10.1111/jns.12507.

Lal H, Cunningham AL, Godeauz O, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. *N Engl J Med*. 2015;372(22): 2087-96.

Lenfant T, Jin Y, Kirchner E, et al. Safety of recombinant zoster vaccine: a retrospective study of 622 rheumatology patients. *Rheumatology*. 2021;60:5149-5157. doi:10.1093/rheumatology/keab139

Lopez-Fauqued M, Campora L, Delannois F, et al. Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials. *Vaccine*. 2019;37(18):2482-93.

Lotan I, Steiner I. Giant cell arteritis following varicella zoster vaccination. *J Neurol Sci*. 2017;375:158-9. doi: 10.1016/j.jns.2017.01.053.

Lundberg IE, Sharma A, Turesson C, et al. An update on polymyalgia rheumatica. *J Intern Med*. 2022; 292:717-732. doi: 10.1111/joim.13525

McClure DL, Xu S, E. Weintraub E, et al. An efficient statistical algorithm for a temporal scan statistic applied to vaccine safety analyses. *Vaccine*. 2012;30(27):3986-91.

McLaughlin JM, McGinnis JJ, Tan L, et al. Estimated Human and Economic Burden of Four Major Adult Vaccine-Preventable Diseases in the United States. *J Prim Prev*. 2015;36(4):259-73.

Musonda, P., C. P. Farrington, and H. J. Whitaker. Sample sizes for self-controlled case series studies. *Statistics in Medicine.* 2006;25:2618-31.

Nelson JC, Ulloa-Pérez E, Yu O, et al. Active postlicensure safety surveillance for recombinant zoster vaccine using electronic health record data. *Am J Epidemiol*. 2023;192(2):205–16.

Nielsen AW, Frolund LL, Vaben C, et al. Concurrent baseline diagnosis of giant cell arteritis and polymyalgia rheumatica – A systematic review and meta-analysis. *Semin Arthritis Rheum*. 2022;56:152069. doi.org/10.1016/j.semarthrit.2022.152069

Partington RJ, Muller S, Helliwell T, et al. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. *Ann Rheum Dis*. 2018;77:1750-1756. doi:10.1136/annrheumdis-2018-213883

Perez-Vilar S, Hu M, Weintraub E, et al. Guillain-Barré Syndrome After High-Dose Influenza Vaccine Administration in the United States, 2018–2019 Season. *J Infect Dis*. 2021;223(3):416–25.

Rubin DS, Matsumoto MM, Moss HE, et al. Ischemic Optic Neuropathy in Cardiac Surgery: Incidence and Risk Factors in the United States from the National Inpatient Sample 1998 to 2013. *Anesthesiology*. 2017;126(5):810-21.

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted) Product Information. February, 2026.

Sidney S, Sorel M, Quesenberry CP, Jr., et al. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest*. 2005;128(4):2068-75.

Singh JA, Cleveland JD. The risk of polymyalgia rheumatica in older adults with gout: a Medicare claims study. *Rheumatol Adv Pract*. 2018;0:1-7. doi:10.1093/rap/rky024

Soriano A, Verrecchia E, Marinaro A, et al. Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: report of 10 cases and review of the literature. *Lupus*. 2012; 21:153-157.

Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infect Dis*. 2004;4(1):26-33.

Wang F, Wang D, Wang Y, et al. Population-Based Incidence of Guillain-Barré Syndrome During Mass Immunization With Viral Vaccines: A Pooled Analysis. *Front Immunol*. 2022;13:782198. Published online 2022 Feb 3. doi: 10.3389/fimmu.2022.782198.

Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in Biostatistics: The self-controlled case series method. *Stat Med*. 2005;25(10):1768-97.

Yen CC, Wei KC, Wang WH, et al. Risk of Guillain-Barré Syndrome Among Older Adults Receiving Influenza Vaccine in Taiwan. *JAMA Netw Open*. 2022 Sep;5(9): e2232571.

Yih WK, Lieu TA, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in U.S. infants. *N Engl J Med*. 2014;370(6):503-12.

Yih WK, Greene SK, Zichittella L, et al. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. *Vaccine*. 2016;34(1):172-8.

Yih WK, Kulldorff M, Dashevsky I, Maro JC. A Broad Safety Assessment of the Recombinant Herpes Zoster Vaccine. *Am J Epidemiol*. 2022 Mar 24;191(5):957-964.

Yokose C, McCormick N, Chen C, et al. Risk of gout flares after vaccination: a prospective case cross-over study. *Ann Rheum Dis*. 2019;78(11):1601-04.

14. TABLES AND FIGURES

This section contains the supplemental tables and figures for the outcomes: Gout, GBS, SVT, PMR, GCA, and ION. The data in this section is intended to support the key findings in main body of the report. In some cases, the data in the supplemental material can assist with the interpretation of the tables and figures in the main report.

14.1. GBS

14.1.1. Model selection for seasonality adjustment for GBS

Based on the results in Table 34, we selected Linear Regression 2 parameters for the seasonality adjustment as this model had the lowest AIC value (349.18).

Table 34 Results of the model selection for GBS seasonality adjustment

Model	Coefficient	SE	AIC
Linear regression 1			
Intercept	1766.34069	50.74029	363.87
day	-0.25855	0.24143	
Linear regression 2			
Intercept	1971.95276	61.96152	**349.18**
day	-3.63861	0.79023	
day^2	0.00927	0.0021	
Linear regression 3			
Intercept	2047.80796	84.86272	349.34
day	-6.06822	2.03476	
day^2	0.02579	0.01295	
day^3	-0.00003014	0.0000233	
Sine function			
Intercept	1712.3253	26.22233	365.37
sin(day)	-47.92904	38.17072	
cos(day)	-4.95437	35.24249	
B-spline			
intercept/bs(day 0)	1957.19637	15570000	349.3438207
bs(day 1)	1370.92173	1370771	
bs(day 2)	1690.03848	2075305	
bs(day 3)	1791.60794	12610000	

AIC, Akaike Information Criterion; SE, standard error.
day=middle day of a month, defined it as the last day of each month minus 15.
day^2 =x21, used in linear regression with degree=2; day^3 =x31, used in linear regression with degree=3.
sin(day)=sin(x1), used in sine model; cos(day)=cos(x1), used in sine model.

14.1.2. Characteristics of the primary GBS cohort

Table 35 Baseline demographic and health characteristics of GBS analytic cohort

Descriptive Characteristics	GBS Cases[a]	
	N	%
Number of unique participants	75	100
Demographics	**Mean**	**SD**
Mean Age at Index Date	75.37	6.98
Age Category	N	%
65-69	19	25.33
70-74	18	24.00
75-79	17	22.67
80+	21	28.00
Sex		
Male	37	49.33
Female	38	50.67
Race		
American Indian or Alaskan Native	0	---
Hispanic	<11	---
Asian	<11	---
Black or African American	<11	---
White	69	92.00
Unknown	0	---
Other	<11	---
Parts A, B, D Continuous enrollment in year prior to Dose 1[b]	75	100.00
Year of Vaccination[c]		
2018	23	30.67
2019	33	44.00
2020	19	25.33
Recorded Medical History in Year Prior to Dose 1		
Diabetes mellitus	16	21.33
Chronic kidney disease	15	20.00
Chronic lung disease (COPD, bronchiectasis)	12	16.00
Congestive heart failure	<11	---
Ischemic heart disease	20	26.67
Alzheimer's/Dementia	<11	---
Chronic liver disease	<11	---
Stroke/TIA	<11	---
At least 1 dermatology visit	<11	---
At least 1 optometry/ ophthalmology visit	43	57.33
Immunocompromised Conditions		
Any IC conditions[d]	<11	---
Any AID conditions[e]	<11	---
Recorded Service Use History in Year Prior to Dose 1		
Hospitalizations		
0	>64	>80.00
1 or more	<11	---
Emergency department visits		
0	55	73.33
1 or more	20	26.67
Durable medical equipment	18	24.00
Hospice care	0	---
Home health care	<11	---

Descriptive Characteristics	GBS Cases[a]	
	N	%
Skilled nursing facility care	0	---
Concomitant Vaccine Use at Index Date		
Influenza	<11	---
Pneumococcal	<11	---
Tetanus- Diphtheria- Pertussis	0	---

SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.
Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

a. Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.
b. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment.
c. Based on the year Dose 1 was received.
d. IC – immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.
e. AID – autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease- Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

Table 36 Baseline demographic and health characteristics of the GBS cohort by number of doses received

Descriptive Characteristic	RZV Dose 1 Only		RZV Dose 2	
	N	%	N	%
Number of unique participants	53	100	22	100
Demographics	**Mean**	**SD**	**Mean**	**SD**
Mean Age at Index Date	75.92	7.13	74.05	6.59
Age Categories	N	%	N	%
65-69	>11	>20.00	<11	---
70-74	>11	>20.00	<11	---
75-79	>11	>20.00	<11	---
80+	>15	>30.00	<11	---
Sex				
Male	>20	>46.00	>11	>50.00
Female	>25	>50.00	<11	---
Race				
American Indian or Alaskan Native	0	---	0	---
Hispanic	0	---	<11	---
Asian	<11	---	0	---
Black or African American	<11	---	<11	---
White	50	94.34	19	86.36
Unknown	0	---	0	---
Other	0	---	<11	---
Parts A, B, D Continuous enrollment in year prior to Dose 1[a]	53	100.00	22	100.00
Year of Vaccination[b]				
2018	20	37.74	<11	---
2019	22	41.51	11	50.00
2020	11	20.75	<11	---
Recorded Medical History in Year Prior to Dose 1				
Diabetes mellitus	<11	---	<11	---
Chronic kidney disease	>11	>20.00	<11	---
Chronic lung disease (COPD, bronchiectasis)	<11	---	<11	---
Congestive heart failure	<11	---	<11	---
Ischemic heart disease	>11	>20.00	<11	---

Descriptive Characteristic	RZV Dose 1 Only		RZV Dose 2	
	N	%	N	%
Alzheimer's/Dementia	<11	---	0	---
Chronic liver disease	<11	---	<11	---
Stroke/TIA	<11	---	<11	---
At least 1 dermatology visit	<11	---	0	---
At least 1 optometry/ ophthalmology visit	32	60.38	11	50.00
Immunocompromised Conditions				
Any IC condition[c]	0	---	<11	---
Any AID condition[d]	<11	---	<11	---
Recorded Service Use History in Year Prior to Dose 1				
Hospitalizations				
0	>44	>80.00	>18	>85.00
1 or more	<11	---	<11	---
Emergency department visits				
0	40	75.47	15	68.18
1 or more	>11	>24.00	<11	---
Durable medical equipment	>11	>25.00	<11	---
Hospice care	0	---	0	---
Home health care	<11	---	<11	---
Skilled nursing facility care	0	---	0	---
Concomitant Vaccine Use at Index Date				
Influenza	<11	---	<11	---
Pneumococcal	0	---	<11	---
Tetanus- Diphtheria- Pertussis	0	---	0	---

SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; RZV, recombinant zoster vaccine; RZV Dose 1 includes those who did not get Dose 2; RZV Dose 2 includes those who received Doses 1 and 2; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.
Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.

a. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and (Prescription Drug Coverage); allows one calendar month gap in enrolment.
b. Based on the year Dose 1 was received.
c. IC, immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.
d. AID, autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease-Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

14.1.3. Characteristics of secondary and sensitivity GBS analytic cohorts

There were not substantial differences in baseline demographic and health characteristics for participants in each of the analytic cohorts for the sensitivity and secondary analyses (Table 37).

Table 37 Descriptive characteristics of the secondary and sensitivity GBS analytic cohorts

Descriptive Characteristic	Sensitivity (restricted to 2-dose recipients with 60-183-day dose spacing per US dosing recommendation, subset of #1)		Secondary (3-wk CW for both doses)		Secondary (6-wk CW for both doses)		Sensitivity (Dose 1, subset of Secondary 6-wk CW for both doses)		Sensitivity (Dose 2, subset of Secondary (6-wk CW for both doses)		COVID-19 Sensitivity Analysis	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Number of unique participants	20	100	65	100	75	100	57	100	18	100	49	100
Demographics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Mean Age at Index Date	73.8	6.43	75.2	7.04	75.4	6.98	75.5	7.06	74.9	6.92	76.1	6.73
Age Categories	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
65-69	<11	---	16	24.62	19	25.33	13	22.81	<11	---	<11	---
70-74	<11	---	17	26.15	18	24.00	15	26.32	<11	---	13	26.53
75-79	<11	---	16	24.62	17	22.67	12	21.05	<11	---	12	24.49
80+	<11	---	16	24.62	21	28.00	17	29.82	<11	---	>11	>25.00
Sex												
Male	>10	>50.00	32	49.23	37	49.33	27	47.37	<11	---	21	42.86
Female	<10	---	33	50.77	38	50.67	30	52.63	<11	---	28	57.14
Race												
American Indian or Alaskan Native	0	---	0	---	0	---	0	---	0	---	0	---
Hispanic	<11	---	0	---	<11	---	0	---	<11	---	0	---
Asian	0	---	<11	---	<11	---	<11	---	0	---	<11	---
Black or African American	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
White	17	85.00	60	92.31	69	92.00	54	94.74	15	83.30	46	93.88
Unknown	0	---	0	---	0	---	0	---	0	---	0	---
Other	<11	---	<11	---	<11	---	0	---	<11	---	0	---
Parts A, B, D Continuous enrollment in year prior to Dose 1[a]	20	100.00	65	100.00	75	100.00	57	100.00	18	100.00	49	100.00
Year of Vaccination[b]												
2018	<11	---	23	35.38	23	30.67	20	35.09	<11	---	23	46.94

Descriptive Characteristic	Sensitivity (restricted to 2-dose recipients with 60-183-day dose spacing per US dosing recommendation, subset of #1)		Secondary (3-wk CW for both doses)		Secondary (6-wk CW for both doses)		Sensitivity (Dose 1, subset of Secondary 6-wk CW for both doses)		Sensitivity (Dose 2, subset of Secondary (6-wk CW for both doses)		COVID-19 Sensitivity Analysis	
	N	%	N	%	N	%	N	%	N	%	N	%
2019	<11	---	28	43.08	33	44.00	22	38.60	11	61.10	26	53.06
2020	<11	---	14	21.54	19	25.33	15	26.32	<11	---	0	---
Recorded Medical History in Year Prior to Dose 1												
Diabetes mellitus	<11	---	13	20.00	16	21.33	11	19.30	<11	---	12	24.49
Chronic kidney disease	<11	---	13	20.00	15	20.00	12	21.05	<11	---	<11	---
Chronic lung disease (COPD, bronchiectasis)	<11	---	11	16.92	12	16.00	<11	---	<11	---	<11	---
Congestive heart failure	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
Ischemic heart disease	<11	---	18	27.69	20	26.67	13	22.81	<11	---	12	24.49
Alzheimer's/Dementia	0	---	<11	---	<11	---	<11	---	0	---	<11	---
Chronic liver disease	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
Stroke/TIA	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
At least 1 dermatology visit	0	---	<11	---	<11	---	<11	---	0	---	<11	---
At least 1 optometry/ ophthalmology visit	<11	---	39	60.0	43	57.33	33	57.89	<11	---	31	63.27
Immunocompromised Conditions												
Any IC conditions[c]	<11	---	<11	---	<11	---	0	---	<11	---	<11	---
Any AID conditions[d]	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
Recorded Service Use History in Year Prior to Dose 1												
Hospitalizations												
0	>11	>85.00	>50	>85.00	>60	>80.00	>40	>85.00	>11	>90.00	>40	>80.0
1 or more	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
Emergency department visits												
0	>11	>60.00	48	73.85	55	73.33	41	71.93	>11	>70.00	36	73.47

Descriptive Characteristic	Sensitivity (restricted to 2-dose recipients with 60-183-day dose spacing per US dosing recommendation, subset of #1)		Secondary (3-wk CW for both doses)		Secondary (6-wk CW for both doses)		Sensitivity (Dose 1, subset of Secondary 6-wk CW for both doses)		Sensitivity (Dose 2, subset of Secondary (6-wk CW for both doses)		COVID-19 Sensitivity Analysis	
	N	%	N	%	N	%	N	%	N	%	N	%
1 or more	<11	---	17	26.16	20	26.67	16	28.07	<11	---	13	26.53
Durable medical equipment	<11	---	16	24.62	18	24.00	14	24.56	<11	---	15	30.61
Hospice care	0	---	0	---	0	---	0	---	0	---	0	---
Home health care	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
Skilled nursing facility care	0	---	0	---	0	---	0	---	0	---	0	---
Concomitant Vaccine Use at Index Date												
Influenza	<11	---	<11	---	<11	---	<11	---	<11	---	<11	---
Pneumococcal	<11	---	<11	---	<11	---	<11	---	<11	---	0	---
Tetanus- Diphtheria-Pertussis	0	---	0	---	0	---	0	---	0	---	0	---

RZV, recombinant zoster vaccine; RZV Dose 1 includes those who did not get Dose 2; RZV Dose 2 includes those who received Doses 1 and 2; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.

a. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and (Prescription Drug Coverage); allows one calendar month gap in enrolment.

b. Based on the year Dose 1 was received.

c. IC, immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.

d. AID, autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease-Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

14.1.4. Characteristics of GBS cases without prior infection 60 days prior to GBS diagnosis

Table 38 Descriptive characteristics of the GBS cases without prior respiratory or gastrointestinal infection 60 days prior to GBS diagnosis

Descriptive Characteristic	Excluding GBS Cases with Prior Respiratory or Gastrointestinal Infection	
	N	%
Number of unique participants	61	100
Demographics	Mean	SD
Mean Age at Index Date	75.74	7.24
Age Categories	N	%
65-69	15	24.59
70-74	13	21.31
75-79	15	24.59
80+	18	29.51
Sex		
Male	31	50.82
Female	30	49.18
Race		
American Indian or Alaskan Native	0	---
Hispanic	<11	---
Asian	0	---
Black or African American	<11	---
White	56	91.80
Unknown	0	---
Other	<11	---
Parts A, B, D Continuous enrollment in year prior Dose 1[a]	61	100
Year of Vaccination[b]		
2018	21	34.43
2019	26	42.62
2020	14	22.95
Recorded Medical History in Year Prior to Dose 1		
Diabetes mellitus	14	22.95
Chronic kidney disease	13	21.31
Chronic lung disease (COPD, bronchiectasis)	<11	---
Congestive heart failure	<11	---
Ischemic heart disease	18	29.51
Alzheimer's/Dementia	<11	---
Chronic liver disease	<11	---
Stroke/TIA	<11	---
At least 1 dermatology visit	<11	---
At least 1 optometry/ ophthalmology visit	33	54.10
Immunocompromised Conditions		
Any IC condition[c]	0	---
Any AID condition[d]	<11	---
Recorded Service Use History in Year Prior to Dose 1		
Hospitalizations		
0	---	---
1 or more	<11	---
Emergency department visits		

Descriptive Characteristic	Excluding GBS Cases with Prior Respiratory or Gastrointestinal Infection	
	N	%
0	43	70.49
1 or more	18	29.51
Durable medical equipment	16	26.23
Hospice care	0	---
Home health care	<11	---
Skilled nursing facility care	0	---
Concomitant Vaccine Use at Index Date		
Influenza	<11	---
Pneumococcal	<11	---
Tetanus- Diphtheria- Pertussis	0	---

RZV, recombinant zoster vaccine; RZV Dose 1 includes those who did not get Dose 2; RZV Dose 2 includes those who received Doses 1 and 2; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.
Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.

a. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and (Prescription Drug Coverage); allows one calendar month gap in enrolment.
b. Based on the year Dose 1 was received.
c. IC, immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy.
d. AID, autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease-Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

14.1.5. Results of GBS temporal scan analysis

A total of 45 scan windows were tested. The observed to expected cases in the scan window revealed statistically significant clustering of cases in 42 windows (Table 39).

Table 39 Temporal scan statistic for GBS cases

Scan Number	Window Length	Cases in Window	Expected Cases	Relative Risk	Excess Cases	LLR	p-value
PPD	9 to 26	45	16.07	5.5	36.82	26.07901	0.001
	9 to 25	43	15.18	5.3	34.88	24.75647	0.001
	9 to 27	45	16.96	5.13	36.23	24.10401	0.001
	9 to 28	46	17.86	5.08	36.94	23.85744	0.001
	9 to 24	41	14.29	5.12	33.00	23.51296	0.001
	9 to 19	34	9.82	5.5	27.82	23.21509	0.001
	9 to 20	35	10.71	5.25	28.33	22.45363	0.001
	9 to 29	46	18.75	4.76	36.33	22.0698	0.001
	9 to 21	36	11.61	5.04	28.86	21.80255	0.001
	9 to 22	37	12.5	4.87	29.4	21.24395	0.001
	9 to 18	31	8.93	5.21	25.05	20.6986	0.001
	9 to 30	46	19.64	4.47	35.71	20.39389	0.001
	9 to 32	48	21.43	4.44	37.2	20.21101	0.001
	9 to 17	29	8.04	5.25	23.48	19.94477	0.001
	9 to 23	37	13.39	4.48	28.74	19.23798	0.001

Scan Number	Window Length	Cases in Window	Expected Cases	Relative Risk	Excess Cases	LLR	p-value
PPD	9 to 31	46	20.54	4.21	35.07	18.82066	0.001
	8 to 35	51	25.00	4.25	39.00	18.74518	0.001
	9 to 33	48	22.32	4.2	36.56	18.70535	0.001
	8 to 34	50	24.11	4.22	38.16	18.70457	0.001
	8 to 39	54	28.57	4.18	41.08	17.7139	0.001
	8 to 37	52	26.79	4.07	39.22	17.4718	0.001
	8 to 36	51	25.89	4.03	38.35	17.38797	0.001
	9 to 14	22	5.36	5.4	17.92	16.60378	0.001
	8 to 40	54	29.46	3.97	40.41	16.46001	0.001
	8 to 38	52	27.68	3.87	38.55	16.19664	0.001
	9 to 16	25	7.14	4.75	19.74	16.04999	0.001
	8 to 42	55	31.25	3.85	40.71	15.43707	0.001
	8 to 41	54	30.36	3.78	39.72	15.26381	0.001
	8 to 44	56	33.04	3.74	41.04	14.49948	0.001
	8 to 43	55	32.14	3.67	40.00	14.30006	0.001
	9 to 15	22	6.25	4.57	17.18	13.89635	0.001
	8 to 45	56	33.93	3.57	40.3	13.41468	0.001
	9 to 12	16	3.57	5.42	13.05	12.7155	0.001
	8 to 46	56	34.82	3.4	39.53	12.37765	0.001
	9 to 10	11	1.79	7.05	9.44	11.39037	0.001
	8 to 47	56	35.71	3.24	38.73	11.38683	0.001
	9 to 13	17	4.46	4.63	13.33	11.38155	0.001
	9 to 11	13	2.68	5.66	10.7	10.98852	0.001
	8 to 48	56	36.61	3.09	37.88	10.44085	0.001
	8 to 49	56	37.5	2.95	37.00	9.538465	0.004
	9 to 50	56	37.5	2.95	37.00	9.538465	0.004
	8 to 9	9	1.79	5.59	7.39	7.710091	0.008
	10 to 51	48	37.5	1.78	21.00	2.979674	0.423
	11 to 52	46	37.5	1.59	17.00	1.943513	0.781
	12 to 53	44	37.5	1.42	13.00	1.132377	0.978

LLR=Log-Likelihood Ratio

a. Analysis was performed using TreeScan™ software.

b. Columns definitions:

Scan number=scan windows were tested.

Window Length=The temporal window of the cluster.

Cases in window=The number of observed cases in the cluster.

Expected cases=The number of expected cases in the cluster, under the assumption that the null hypothesis is true, and conditioned on whatever the analysis is conditioned on.

Relative Risk=The risk in the cluster divided by the risk outside the cluster. For purely temporal scan statistics, outside means outside the cluster time window but inside the same node. The formula is different for different probability models.

Excess Cases=The excess number of cases.

LLR=The natural logarithm of the likelihood ration for the cut. This is the test statistic, and a larger value is evidence for a cluster and against the null hypothesis.

P-value=The p-values are adjusted for the multiple testing stemming from the multitude of cuts evaluated. This means that under the null hypothesis of complete randomness there is a 5% chance that the p-value for the most likely cut will be smaller than 0.05 and a 95% chance that it will be bigger. Under the null hypothesis there will always be some area with a rate higher than expected just by chance alone. Hence, even though the most likely cut always has an excess rate, the p-value may be very close or identical to one.

14.2. Gout

14.2.1. Model selection for seasonality adjustment for gout

Linear regression model 2 has the lowest AIC and was selected as the best fitted model (Table 40).

Table 40 Results of the model selection for gout seasonality adjustment

Model	Coefficient	SE	AIC
Linear regression 1			
Intercept	2607.6690	21.87701	
day	-0.44270	0.10409	341.3025
Linear regression 2			
Intercept	2693.13388	27.26583	
day	-1.84766	0.34774	328.0752
day^2	0.00385	0.00092401	
Linear regression 3			
Intercept	2673.36753	37.97199	
day	-1.21455	0.91046	329.4424
day^2	-0.00045550	0.00579	
day^3	0.00000785	0.00001043	
Sine function			
Intercept	2520.93621	13.14536	
sin(day)	-42.38144	19.13513	334.4775
cos(day)	-2.50111	17.66720	
B-spline			
intercept/bs(day 0)	2653.85033		329.4424
bs(day 1)	2517.67939		
bs(day 2)	2378.58820		
bs(day 3)	2529.19212		

AIC, Akaike Information Criterion; SE, standard error.
day=middle day of a month, defined it as the last day of each month minus 15.
day^2 =x21, used in linear regression with degree=2.
day^3 =x31, used in linear regression with degree=3.
sin(day)=sin(x1), used in sine model.
cos(day)=cos(x1), used in sine model.

14.2.2. Characteristics of the primary gout cohort

Table 41 Baseline demographic and health characteristics of the gout analytic cohort

Descriptive Characteristics	All Eligible Gout Cases[a]	
	N	%
Number of unique participants	1290	100
Demographics	**Mean**	**SD**
Mean Age at Index Date	75.77	6.61
Age Category	**N**	**%**

Descriptive Characteristics	All Eligible Gout Cases[a]	
	N	%
65-69	233	18.06
70-74	380	29.46
75-79	340	26.36
80-84	192	14.88
85+	145	11.24
Sex		
Male	789	61.16
Female	501	38.84
Race		
American Indian or Alaskan Native	<11	---
Hispanic	<11	---
Asian	43	3.33
Black or African American	46	3.57
White	1122	86.98
Unknown	36	2.79
Other	33	2.56
Parts A, B, D Continuous enrollment in year prior to dose 1[b]	1280	99.22
Year of Vaccination[c]		
2018	566	43.88
2019	724	56.12
Recorded Medical History in Year Prior to Dose 1		
Diabetes mellitus	473	36.67
Chronic kidney disease	531	41.16
Chronic lung disease (COPD, bronchiectasis)	221	17.13
Congestive heart failure	247	19.15
Ischemic heart disease	433	33.57
Alzheimer's/Dementia	41	3.18
Chronic liver disease	90	6.98
Stroke/TIA	102	7.91
At least 1 dermatology visit	42	3.26
At least 1 optometry/ ophthalmology visit	771	59.77
Immunocompromised Conditions		
Any IC conditions[d]	15	1.16
Any AID conditions[e]	112	8.68
Recorded Service Use History in Year Prior to Dose 1		
Hospitalizations		
0	1116	86.51
1	124	9.61
2 or more	50	3.88
Emergency department visits		
0	994	77.05
1	202	15.66
2 or more	94	7.29
DME	509	39.46
Hospice care	0	---
Home health care	84	6.51
Skilled nursing facility care	23	1.78
Concomitant Vaccine Use at Index Date		
Influenza	121	9.38
Pneumococcal	44	3.41
Tetanus- Diphtheria- Pertussis	28	2.17

AID, autoimmune condition; COPD, chronic obstructive pulmonary disease; DME, durable medical equipment; IC, immunocompromised conditions; SD, standard deviation; TIA, transient ischemic attack.
Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

a. Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.
b. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment. Defined prior to dose 1 therefore participants who met enrolment criteria prior to dose 2 but not dose 1 are not captured.
c. Based on the year the dose preceding the gout cases was received. This can be dose 1 or dose 2.
d. IC – immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.
e. AID – autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease- Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

Table 42 Baseline demographic and health characteristics of the gout cohort by number of doses received

Descriptive Characteristic	RZV Dose 1 Only[a]		RZV Dose 2[b]	
	N[c]	%	N[c]	%
Number of unique participants	229	17.75	1061	82.25
Demographics	**Mean**	**SD**	**Mean**	**SD**
Mean Age at Index Date	75.81	6.49	75.76	6.63
Age Categories	**N**	**%**	**N**	**%**
65-69	40	17.47	193	18.19
70-74	70	30.57	310	29.22
75-79	63	27.51	277	26.11
80-84	33	14.41	159	14.99
85+	23	10.04	122	11.50
Sex				
Female	88	38.43	413	38.93
Male	141	61.57	648	61.07
Race				
American Indian or Alaskan Native	<11	---	<11	---
Asian	<11	---	>30	>3.00
Black or African American	12	5.24	34	3.20
White	189	82.53	933	87.94
Hispanic	<11	---	<11	---
Unknown[d]	<11	---	>25	>2.00
Other[d]	<11	---	>22	>2.00
Parts A, B, D Continuous enrollment in Year Prior to respective Dose[e]	229	100	1051	99.06
Year of Vaccination				
2018	47	20.52	519	48.92
2019	182	79.48	542	51.08
Recorded Medical History in Year Prior to Dose 1				
Diabetes mellitus	82	35.81	391	36.85
Chronic kidney disease	95	41.48	436	41.09
Chronic lung disease (COPD, bronchiectasis)	40	17.47	181	17.06
Congestive heart failure	58	25.33	189	17.81
Ischemic heart disease	84	36.68	349	32.89
Alzheimer's/Dementia	<11	---	>30	>2.00
Chronic liver disease	17	7.42	73	6.88
Stroke/TIA	20	8.73	82	7.73
At least 1 dermatology visit	<11	---	>30	>3.00

Descriptive Characteristic	RZV Dose 1 Only[a]		RZV Dose 2[b]	
	N[c]	%	N[c]	%
At least 1 optometry/ ophthalmology visit	127	55.46	644	60.70
Immunocompromised Conditions				
Any IC conditions[f]	<11	---	>10	>1.00
Any AID conditions[g]	20	8.73	92	8.67
Recorded Service Use History in Year Prior to Dose 1				
Hospitalizations				
0	184	80.35	932	87.84
1	29	12.66	95	8.95
2 or more	16	6.99	34	3.21
Emergency department visits				
0	187	81.66	807	76.06
1	26	11.35	176	16.59
2 or more	16	6.99	78	7.35
DME	84	36.68	425	40.06
Hospice care	0	---	0	---
Home health care	24	10.48	60	5.66
Skilled nursing facility care	11	4.80	12	1.13
Concomitant Vaccine Use at Index Date				
Influenza	37	16.16	84	7.92
Pneumococcal	11	4.80	33	3.11
Tetanus- Diphtheria- Pertussis	<11	---	>20	>2.00

AID, autoimmune disease; COPD, chronic obstructive pulmonary disease; DME, durable medical equipment; IC, immunocompromised conditions; RZV, recombinant zoster vaccine; SD, standard deviation; TIA, transient ischemic attack.

a. RZV Dose 1 includes those who did not get Dose 2
b. RZV Dose 2 includes those who received Doses 1 and 2
c. Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed
d. Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.
e. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment.
f. IC – immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.
g. AID – autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease- Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

Table 43 Baseline demographic and health characteristics of the gout cohort by dose spacing

Descriptive Characteristic	RZV Dose 2 received 28 to 60 days after Dose 1[a]		RZV Dose 2 received >60 days after Dose 1[a]	
	N	%	N	%
Number of unique participants	49	4.62	1012	95.38
Demographics	**Mean**	**SD**	**Mean**	**SD**
Mean Age at Index Date	78.33	8.54	75.64	6.51
Age Categories	N	%	N	%
65-69	<11	---	>190	>18.00
70-74	11	22.45	299	29.55
75-79	<11	---	>268	>26.00
80-84	12	24.49	147	14.53
85+	<11	---	>110	>10.00
Sex				
Female	24	48.98	389	38.44
Male	25	51.02	623	61.66
Race				
American Indian or Alaskan Native	0	0	< 11	---
Asian	<11	---	>30	>3.00
Black or African American	<11	---	>30	>3.00
White	45	91.84	888	87.75
Hispanic	0	---	< 11	---
Unknown	0	---	29	2.87
Other	<11	---	>20	>2.00
Parts A, B, D Continuous enrollment in Year Prior to respective Dose[b]	49	100	1002	99.01
Year of Vaccination				
2018	22	44.90	497	49.11
2019	27	55.10	515	50.89
Recorded Medical History in Year Prior to Dose 1				
Diabetes mellitus	12	24.49	379	37.45
Chronic kidney disease	23	46.94	413	40.81
Chronic lung disease (COPD, bronchiectasis)	<11	---	>168	>16.00
Congestive heart failure	11	22.45	178	17.59
Ischemic heart disease	15	30.61	334	33.00
Alzheimer's/Dementia	<11	---	>25	>2.00
Chronic liver disease	<11	---	>65	>6.00
Stroke/TIA	<11	---	>75	>7.00
At least 1 dermatology visit	<11	---	>35	>3.00
At least 1 optometry/ ophthalmology visit	29	59.18	615	60.77
Immunocompromised Conditions				
Any IC conditions[c]	<11	---	>10	>1.00
Any AID conditions[d]	<11	---	>85	>8.00
Recorded Service Use History in Year Prior to Dose 1				
Hospitalizations				
0	45	91.84	887	87.65
1	<11	---	>90	>9.00
2 or more	<11	---	>30	>3.00
Emergency department visits				
0	35	71.43	772	87.80
1	<11	---	>165	>16.00
2 or more	<11	---	>70	>6.00
DME	20	40.82	405	40.02

Descriptive Characteristic	RZV Dose 2 received 28 to 60 days after Dose 1[a]		RZV Dose 2 received >60 days after Dose 1[a]	
	N	%	N	%
Hospice care	0	---	0	---
Home health care	<11	---	>55	>5.00
Skilled nursing facility care	<11	---	>10	>1.00
Concomitant Vaccine Use at Index Date				
Influenza	<11	---	>75	>7.00
Pneumococcal	<11	---	>25	>2.00
Tetanus- Diphtheria- Pertussis	<11	---	>15	>1.00

AI AID, autoimmune disease; COPD, chronic obstructive pulmonary disease; DME, durable medical equipment; IC, immunocompromised conditions; RZV, recombinant zoster vaccine; SD, standard deviation; TIA, transient ischemic attack.
Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

a. Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.
b. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment.
c. IC – immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.
d. AID – autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease- Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

14.2.3. Characteristics of Secondary and Sensitivity gout analytic cohorts

There were not substantial differences in baseline characteristics across the analytic cohorts for the sensitivity and secondary analysis (Table 44).

Table 44 Descriptive characteristics of the secondary and sensitivity gout analytic cohorts

Descriptive Characteristic	Dose-Compliant Sensitivity[a]		Secondary 30-d Control Window[a]		Sensitivity Analysis: Fixed 30-day control window, Dose 1 only[a]		Sensitivity Analysis: Fixed 30-day control window, Dose 2 only[a]		COVID-19 Sensitivity Analysis[a]	
	N	%	N	%	N	%	N	%	N	%
Number of unique participants	959	100	1290	100	764	100	526	100	1221	100
Demographics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Mean Age at Index Date	75.66	6.64	75.77	6.61	75.77	6.41	75.77	6.88	75.71	6.52
Age Categories	N	%	N	%	N	%	N	%	N	%
65-69	180	18.77	233	18.06	136	17.80	97	18.44	222	18.18
70-74	281	29.30	380	29.46	223	29.19	157	29.85	360	29.48
75-79	249	25.96	340	26.36	211	27.62	129	24.52	323	26.45
80-84	140	14.60	192	14.88	109	14.27	83	15.78	181	14.82
85+	109	11.37	145	11.24	85	11.13	60	11.41	135	11.06
Sex										
Male	584	60.90	789	61.16	483	63.22	306	58.17	747	61.18
Female	375	39.10	501	38.84	281	36.78	220	41.83	474	38.82
Race										

Descriptive Characteristic	Dose-Compliant Sensitivity[a]		Secondary 30-d Control Window[a]		Sensitivity Analysis: Fixed 30-day control window, Dose 1 only[a]		Sensitivity Analysis: Fixed 30-day control window, Dose 2 only[a]		COVID-19 Sensitivity Analysis[a]	
	N	%	N	%	N	%	N	%	N	%
American Indian or Alaskan Native	<11	---	< 11	---	<11	---	<11	---	<11	---
Asian	30	3.13	43	3.33	24	3.14	19	3.61	40	3.28
Black or African American	30	3.13	46	3.57	27	3.53	19	3.61	44	3.60
White	844	88.01	1122	86.98	660	86.39	462	87.83	1060	86.81
Hispanic	<11	---	<11	---	<11	---	<11	---	<11	---
Unknown	29	3.02	36	2.79	26	3.40	<11	---	36	2.95
Other	21	2.19	33	2.56	18	2.36	15	2.85	31	2.54
Parts A, B, D Continuous enrollment in Year Prior to Dose 1[b]	950	99.06	1280	99.22	764	100	516	98.1	1211	99.18
Year of Vaccination										
2018	446	46.51	566	43.88	309	40.45	257	48.86	566	46.36
2019	513	53.49	724	56.12	455	59.55	269	51.14	655	53.64
Recorded Medical History in Year Prior to Dose 1										
Diabetes mellitus	350	36.50	473	36.67	279	36.52	194	36.88	454	37.18
Chronic kidney disease	386	40.25	531	41.16	308	40.31	223	42.4	499	40.87
Chronic lung disease (COPD, bronchiectasis)	161	16.79	221	17.13	134	17.54	87	16.54	205	16.79
Congestive heart failure	168	17.52	247	19.15	144	18.85	103	19.58	228	18.67
Ischemic heart disease	310	32.33	433	33.57	255	33.38	178	33.84	406	33.25
Alzheimer's/Dementia	26	2.71	41	3.18	25	3.27	16	3.04	38	3.11
Chronic liver disease	64	6.67	90	6.98	59	7.72	31	5.89	90	7.37
Stroke/TIA	75	7.82	102	7.91	54	7.07	48	9.13	100	8.19
At least 1 dermatology visit	35	3.65	42	3.26	25	3.27	17	3.23	40	3.28
At least 1 optometry/ ophthalmology visit	570	59.44	771	59.77	452	59.16	319	60.65	733	60.03
Immunocompromised Conditions										
Any IC conditions[c]	12	1.25	15	1.16	<11	---	<11	---	14	1.15
Any AID conditions[d]	83	8.65	112	8.68	73	9.55	39	7.41	105	8.60
Recorded Service Use History in Year Prior to Dose 1										
Hospitalizations										
0	845	88.11	1116	86.51	660	86.39	456	86.69	1055	86.40
1	82	8.55	124	9.61	70	9.16	54	10.27	118	9.66
2 or more	32	3.34	50	3.88	34	4.45	16	3.04	48	3.93
Emergency department visits										
0	727	76.81	994	77.05	599	78.40	395	75.1	939	76.90
1	163	17.00	202	15.66	104	13.61	98	18.63	193	15.81
2 or more	69	7.19	94	7.29	61	7.99	33	6.27	89	7.29
DME	386	40.25	509	39.46	297	38.87	212	40.3	482	39.48
Hospice care	0	0	0	0	0	0	0	0	0	0

Descriptive Characteristic	Dose-Compliant Sensitivity[a]		Secondary 30-d Control Window[a]		Sensitivity Analysis: Fixed 30-day control window, Dose 1 only[a]		Sensitivity Analysis: Fixed 30-day control window, Dose 2 only[a]		COVID-19 Sensitivity Analysis[a]	
	N	%	N	%	N	%	N	%	N	%
Home health care	52	5.42	84	6.51	56	7.33	28	5.32	73	5.98
Skilled nursing facility care	<11	---	23	1.78	16	2.09	<11	---	19	1.56
Concomitant Vaccine Use at Index Date										
Influenza	79	8.24	121	9.38	85	11.13	36	6.84	107	8.76
Pneumococcal	30	3.13	44	3.41	27	3.53	17	3.23	38	3.11
Tetanus-Diphtheria-Pertussis	18	1.88	28	2.17	18	2.36	<11	---	27	2.21

AID, autoimmune disease; COPD, chronic obstructive pulmonary disease; DME, durable medical equipment; IC, immunocompromised conditions; RZV, recombinant zoster vaccine; SD, standard deviation; TIA, transient ischemic attack.

Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

a. Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.
b. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment.
c. IC=immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.
d. AID=autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease- Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis.

14.2.4. Descriptive examination of gout ICD-10 codes

A total of 800 cases met the gout case ascertainment definition after all chronic and secondary gout codes were excluded. Gout cases associated with the following ICD-10 codes were inspected: chronic gout (M1A*), lead-induced gout (M10.1*), drug-induced gout (M10.2*), and gout due to renal impairment (M10.3*). Overall, only 100 (7.75%) of cases were associated with a low-frequency code and 1190 (low-frequency and other code: n=127 [9.84%]; other code – not a low-frequency code: n=1063 [82.40%]) of cases were not associated with a low-frequency gout ICD-10 code (Table 45).

Table 45 Distribution of low-frequency ICD-10 codes contributing to the 1290 gout cases

Gout Code Examination	N	%
Claims in the 60-day Window from Index Date		
Unique number of claims	3532	
Claims by Gout Code		
M1A[a]	381	10.79
M101[b]	<11	---
M102[c]	23	0.65
M103[d]	81	2.29
Cases by Low-Frequency Codes		
Unique number of individuals	1290	
Individuals after all chronic and secondary gout codes were excluded from the case ascertainment algorithm	800	62.02
Low-frequency only	100	7.75
Low-frequency and other code	127	9.84
Other code (not a low-frequency code)	1063	82.40

ICD-10, International Code of Disease version 10.
a. M1A=ICD-10 code for chronic gout.
b. M101=ICD-10 code for lead-induced gout.
c. M102=ICD-10 code for drug-induced gout.
d. M103=ICD-10 code for gout due to renal impairment.

14.2.5. Results of gout temporal scan analysis

A total of 17 scan windows were tested. The observed to expected cases in the scan window were not statistically significantly different. The finding suggests that there was not a significant temporal clustering of cases (Table 46).

Table 46 Temporal scan statistic for 1290 gout cases in a 60-day interval[a,b]

Scan Number	Window Length	Cases in Window	Expected Cases	Relative Risk	Excess Cases	LLR	p-value
PPD	7 to 8	58	43	1.37	15.52	2.446668	0.546
	6 to 7	55	43	1.29	12.41	1.595244	0.867
	19 to 23	125	107.5	1.18	19.09	1.482997	0.895
	7 to 24	414	387	1.1	38.57	1.328429	0.938
	45 to 57	303	279.5	1.11	30	1.236744	0.949
	7 to 22	369	344	1.1	34.09	1.220477	0.952
	7 to 21	346	322.5	1.1	31.33	1.123871	0.978
	7 to 9	76	64.5	1.19	12.11	1.023304	0.988
	13 to 17	121	107.5	1.14	14.73	0.89162	0.996
	21 to 25	121	107.5	1.14	14.73	0.89162	0.996
	7 to 10	98	86	1.15	12.86	0.860778	0.997
	13 to 15	75	64.5	1.17	11.05	0.856827	0.997
	45 to 58	321	301	1.09	26.09	0.853807	0.997

Scan Number	Window Length	Cases in Window	Expected Cases	Relative Risk	Excess Cases	LLR	p-value
PPD	7 to 14	188	172	1.11	18.46	0.837168	0.998
	45 to 59	342	322.5	1.08	26	0.775845	0.998
	21 to 27	165	150.5	1.11	16.42	0.769743	0.998
	45 to 60	363	344	1.08	25.91	0.707401	0.999

LLR, log-likelihood ratio

a. Analysis was performed using TreeScan™ software.

b. Columns definitions:

Scan number=scan windows were tested.

Window Length=The temporal window of the cluster.

Cases in window=The number of observed cases in the cluster.

Expected cases=The number of expected cases in the cluster, under the assumption that the null hypothesis is true, and conditioned on whatever the analysis is conditioned on.

Relative Risk=The risk in the cluster divided by the risk outside the cluster. For purely temporal scan statistics, outside means outside the cluster time window but inside the same node. The formula is different for different probability models.

Excess Cases=The excess number of cases.

LLR=The natural logarithm of the likelihood ration for the cut. This is the test statistic, and a larger value is evidence for a cluster and against the null hypothesis.

P-value=The p-values are adjusted for the multiple testing stemming from the multitude of cuts evaluated. This means that under the null hypothesis of complete randomness there is a 5% chance that the p-value for the most likely cut will be smaller than 0.05 and a 95% chance that it will be bigger. Under the null hypothesis there will always be some area with a rate higher than expected just by chance alone. Hence, even though the most likely cut always has an excess rate, the p-value may be very close or identical to one.

14.3. SVT

14.3.1. Characteristics of the primary SVT analytic cohort

Table 47 Baseline demographic and health characteristics of the SVT analytic cohort

Descriptive Characteristics	SVT Cases	
	N	%
Number of unique participants	4964	100
Demographics	**Mean**	**SD**
Mean Age at Index Date	76.13	6.71
Age Category	**N**	**%**
65-69	855	17.22
70-74	1405	28.30
75-79	1262	25.42
80-84	815	16.42
85+	627	12.63
Sex		
Male	2082	41.94
Female	2882	58.06
Race		
American Indian or Alaskan Native	<11	---
Asian	85	1.71
Black or African American	95	1.91
White	4559	91.84
Hispanic	>20	<1.00
Unknown	126	2.54
Other	68	1.37
Parts A, B, D Continuous enrollment in year prior to Dose 1[a]	4928	99.27
Year of Vaccination[b]		
2018	1369	27.58
2019	2318	46.70
2020	1277	25.73
Recorded Medical History in Year Prior to Dose 1		
Diabetes mellitus	1246	25.10
Chronic kidney disease	1250	25.18
Chronic lung disease (COPD, bronchiectasis)	944	19.02
Congestive heart failure	752	15.15
Ischemic heart disease	1593	32.09
Alzheimer's/Dementia	219	4.41
Chronic liver disease	326	6.57
Stroke/TIA	498	10.03
At least 1 dermatology visit	172	3.46
At least 1 optometry/ ophthalmology visit	2955	59.53
Immunocompromised Conditions		
Organ transplant during the pre-period	24	0.48
Hematopoietic stem cell transplant	13	0.26
Hematologic or solid malignancy & chemotherapy	78	1.57
Human Immunodeficiency Virus	<11	---
Rheumatoid Arthritis	196	3.95
Inflammatory bowel disease (Chron's disease)	33	0.66
Inflammatory bowel disease (Ulcerative Colitis)	47	0.95
Lupus	25	0.50

Descriptive Characteristics	SVT Cases	
	N	%
Multiple Sclerosis	18	0.36
Psoriasis/Psoriatic Arthritis	102	2.05
Recorded Service Use History in Year Prior to Dose 1		
Hospitalizations		
0	4072	82.03
1	626	12.61
2 or more	266	5.36
Emergency department visits		
0	3567	71.86
1	944	19.02
2 or more	453	9.12
Durable medical equipment	1745	35.15
Hospice care	<11	---
Home health care	433	8.72
Skilled nursing facility care	122	2.46
Concomitant Vaccine Use at Index Date		
Influenza	630	12.69
Pneumococcal	182	3.67
Tetanus- Diphtheria- Pertussis	96	1.93

SVT, supraventricular tachycardia; SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.

a. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment. Defined prior to Dose 1 therefore participants who met enrolment criteria prior to Dose 2 but not Dose 1 are not captured.

b. Based on the year Dose 1 was received.

Table 48 Baseline demographic and health characteristics of the SVT analytic cohort by number of doses received

Descriptive Characteristic	RZV Dose 1 Only		RZV Dose 2	
	N	%	N	%
Number of unique participants	574	100	4390	100
Demographics	Mean	SD	Mean	SD
Mean Age at Index Date	77.48	7.54	75.96	6.58
Age Categories	N	%	N	%
65-69	89	15.51	766	17.45
70-74	140	24.39	1265	28.82
75-79	134	23.34	1128	25.69
80-84	104	18.12	711	16.20
85+	107	18.64	520	11.85
Sex				
Male	221	38.50	1861	42.39
Female	353	61.50	2529	57.61
Race				
American Indian or Alaskan Native	<11	---	<11	---
Asian	13	2.26	72	1.64
Black or African American	24	4.18	71	1.62
White	505	87.98	4054	92.35
Hispanic	<11	---	>12	<1.00
Unknown	11	1.92	115	2.62
Other	12	2.09	56	1.28
Parts A, B, D Continuous enrollment in year prior to Dose 1[a]	574	100.00	4354	99.18
Year of Vaccination[b]				
2018	115	20.03	1254	28.56
2019	263	45.82	2055	46.81
2020	196	34.15	1081	24.62
Recorded Medical History in Year Prior to Dose 1				
Diabetes mellitus	177	30.84	1069	24.35
Chronic kidney disease	190	33.10	1060	24.15
Chronic lung disease (COPD, bronchiectasis)	146	25.44	798	18.18
Congestive heart failure	121	21.08	631	14.37
Ischemic heart disease	202	35.19	1391	31.69
Alzheimer's/Dementia	53	9.23	166	3.78
Chronic liver disease	53	9.23	273	6.22
Stroke/TIA	62	10.80	436	9.93
At least 1 dermatology visit	<11	---	>150	>3.00
At least 1 optometry/ ophthalmology visit	306	53.31	2649	60.34
Immunocompromised Conditions				
Any IC condition[c]	22	3.83	88	2.00
Any AID condition[d]	46	8.01	347	7.90
Recorded Service Use History in Year Prior to Dose 1				
Hospitalizations				
0	438	76.31	3634	82.78
1	91	15.85	535	12.19
2 or more	45	7.84	221	5.03
Emergency department visits				
0	383	66.72	3184	72.53
1	108	18.82	836	19.04
2 or more	83	14.46	370	8.43
Durable medical equipment	257	44.77	1488	33.90
Hospice care	<11	---	<11	---

Descriptive Characteristic	RZV Dose 1 Only		RZV Dose 2	
	N	%	N	%
Home health care	82	14.29	351	8.00
Skilled nursing facility care	24	4.18	98	2.23
Concomitant Vaccine Use at Index Date				
Influenza	100	17.42	530	12.07
Pneumococcal	41	7.14	141	3.21
Tetanus- Diphtheria- Pertussis	11	1.92	85	1.94

SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; RZV, recombinant zoster vaccine; RZV Dose 1 includes those who did not get Dose 2; RZV Dose 2 includes those who received Doses 1 and 2 irrespective of which dose the HOI is attributed; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.
Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed.

a. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment. Defined prior to Dose 1 therefore participants who met enrolment criteria prior to Dose 2 but not Dose 1 are not captured.
b. Based on the year Dose 1 was received.
c. IC – immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. Ics were grouped to facilitate interpretation, as most conditions in the “RZV Dose 1 Only” group had n <11 and were masked according to the CMS DUA. ICs were grouped as all conditions in the group had n <11 and were masked according to the CMS DUA.
d. AID – autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease- Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis. AICs were grouped to facilitate interpretation, as most conditions in the "RZV Dose 1 Only" group had n <11 and were masked according to the CMS DUA.

Table 49 Baseline demographic and health characteristics of the SVT analytic cohort by dose spacing

Descriptive Characteristic	RZV Dose 2 received 28 to 60 days after Dose 1		RZV Dose 2 received >60 days after Dose 1	
	N	%	N	%
Number of unique participants	181	100	4209	100
Demographics	Mean	SD	Mean	SD
Mean Age at Index Date	76.35	7.13	75.94	6.55
Age Categories	N	%	N	%
65-69	32	17.68	734	17.44
70-74	47	25.97	1218	28.94
75-79	43	23.76	1085	25.78
80-84	34	18.78	677	16.08
85+	25	13.81	495	11.76
Sex				
Male	66	36.46	1795	42.65
Female	115	63.54	2414	57.35
Race				
American Indian or Alaskan Native	<11	---	<11	---
Asian	<11	---	>65	>1.00
Black or African American	<11	---	>60	>1.00
White	170	93.92	3884	92.28
Hispanic	0	---	15	0.36
Unknown	<11	---	>100	>2.00
Other	<11	---	>50	>1.00
Parts A, B, D Continuous enrollment in year prior to Dose 1[a]	179	98.9	4175	99.19
Year of Vaccination[b]				
2018	35	19.34	1219	28.96
2019	88	48.62	1967	46.73
2020	58	32.04	1023	24.31
Recorded Medical History in Year Prior to Dose 1				
Diabetes mellitus	40	22.10	1029	24.45
Chronic kidney disease	43	23.76	1017	24.16
Chronic lung disease (COPD, bronchiectasis)	39	21.55	759	18.03
Congestive heart failure	27	14.92	604	14.35
Ischemic heart disease	62	34.25	1329	31.58
Alzheimer's/Dementia	<11	---	>150	>3.00
Chronic liver disease	<11	---	>200	>6.00
Stroke/TIA	18	9.94	418	9.93
At least 1 dermatology visit	<11	---	>150	>3.00
At least 1 optometry/ ophthalmology visit	96	53.04	2553	60.66
Immunocompromised Conditions				
Any IC condition[c]	<11	---	>80	>2.00
Any AID condition[d]	13	7.18	334	7.94
Recorded Service Use History in Year Prior to Dose 1				
Hospitalizations				
0	150	82.87	3484	82.78
1	20	11.05	515	12.24
2 or more	11	6.08	210	4.99
Emergency department visits				
0	131	72.38	3053	72.54
1	26	14.36	810	19.24
2 or more	24	13.26	346	8.22

Descriptive Characteristic	RZV Dose 2 received 28 to 60 days after Dose 1		RZV Dose 2 received >60 days after Dose 1	
	N	%	N	%
Durable medical equipment	61	33.70	1427	33.90
Hospice care	<11	---	<11	---
Home health care	20	11.05	331	7.86
Skilled nursing facility care	<11	---	>85	>2.00
Concomitant Vaccine Use at Index Date				
Influenza	31	17.13	499	11.86
Pneumococcal	<11	---	>130	>3.00
Tetanus- Diphtheria- Pertussis	<11	---	>80	>1.00

SVT, supraventricular tachycardia; SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; RZV, recombinant zoster vaccine; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.
Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed; N=809 cases met the SVT sensitivity health outcome of interest (HOI) definition.

a. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment. Defined prior to Dose 1 therefore participants who met enrolment criteria prior to Dose 2 but not Dose 1 are not captured.
b. Based on the year Dose 1 was received.
c. IC – immunocompromised conditions; organ transplant, hematopoietic cell transplant, and hematologic or solid malignancy w/recent receipt of chemotherapy. ICs were grouped to facilitate interpretation, as all conditions in the "RZV Dose 2 received 28 to 60 days after Dose 1" group had n <11 and were masked according to the CMS DUA.
d. AID – autoimmune disease; HIV infection, rheumatoid arthritis, inflammatory bowel disease- Crohn's disease, inflammatory bowel disease- colitis, lupus, multiple sclerosis, and psoriasis/psoriatic arthritis. AICs were grouped to facilitate interpretation, as all conditions in the "RZV Dose 2 received 28 to 60 days after Dose 1" group had n <11 and were masked according to the CMS DUA.

14.3.2. Characteristics of Secondary and Sensitivity SVT analytic cohorts

There were not substantial differences in baseline demographic and health characteristics for participants in each of the analytic cohorts for the sensitivity and secondary analyses (Table 50).

Table 50 Descriptive characteristics of the secondary and sensitivity SVT analytic cohorts

Descriptive Characteristic	Sensitivity (60 to 183-day dose spacing)		Secondary (30-d CW for both doses)		Sensitivity (Dose 1, subset of Secondary 30-d CW for both doses)		Sensitivity (Dose 2, subset of Secondary 30-d CW for both doses)		Sensitivity (COVID)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Number of unique participants	3837	100	4964	100	2713	100	2251	100	3175	100
Demographics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Mean Age at Index Date	75.9	6.54	76.1	6.71	76.3	6.80	75.9	6.60	76.5	6.74
Age Categories	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
65-69	674	17.57	855	17.22	451	16.62	404	17.95	494	15.56
70-74	1114	29.03	1405	28.3	763	28.12	642	28.52	879	27.69
75-79	981	25.57	1262	25.42	693	25.54	569	25.28	829	26.11
80-84	629	16.39	815	16.42	440	16.22	375	16.66	553	17.42
85+	439	11.44	627	12.63	366	13.49	261	11.59	420	13.23
Sex										
Male	1631	42.51	2082	41.94	1103	40.66	979	43.49	1309	41.23
Female	2206	57.49	2882	58.06	1610	59.34	1272	56.51	1866	58.77
Race										
American Indian or Alaskan Native	<11	---	<11	---	<11	---	<11	---	<11	---
Asian	66	1.72	85	1.71	52	1.92	33	1.47	60	1.89
Black or African American	61	1.59	95	1.91	53	1.95	42	1.87	50	1.57
White	3540	92.26	4559	91.84	2478	91.34	2081	92.45	2930	92.28
Hispanic	>11	<1.00	>11	<1.00	>11	<1.00	<11	---	>11	<1.00
Unknown	100	2.61	126	2.54	70	2.58	56	2.49	70	2.20
Other	50	1.30	68	1.37	39	1.44	29	1.29	48	1.51
Parts A, B, D Continuous enrollment in Year prior to Dose 1[a]	3806	99.19	4928	99.27	2713	100.00	2215	98.4	3158	99.46
Year of Vaccination[b]										
2018	1076	28.04	1369	27.58	649	23.92	720	31.99	1368	43.09
2019	1813	47.25	2318	46.70	1245	45.89	1073	47.67	1807	56.91
2020	948	24.71	1277	25.73	819	30.19	458	20.35	0	---

Descriptive Characteristic	Sensitivity (60 to 183-day dose spacing)		Secondary (30-d CW for both doses)		Sensitivity (Dose 1, subset of Secondary 30-d CW for both doses)		Sensitivity (Dose 2, subset of Secondary 30-d CW for both doses)		Sensitivity (COVID)	
	N	%	N	%	N	%	N	%	N	%
Recorded Medical History in Year Prior to Dose 1										
Diabetes mellitus	938	24.45	1246	25.10	676	24.92	570	25.32	790	24.88
Chronic kidney disease	924	24.08	1250	25.18	733	27.02	517	22.97	775	24.41
Chronic lung disease (COPD, bronchiectasis)	687	17.90	944	19.02	517	19.06	427	18.97	629	19.81
Congestive heart failure	545	14.20	752	15.15	440	16.22	312	13.86	470	14.80
Ischemic heart disease	1190	31.01	1593	32.09	912	33.62	681	30.25	1021	32.16
Alzheimer's/Dementia	143	3.73	219	4.41	140	5.16	79	3.51	151	4.76
Chronic liver disease	240	6.25	326	6.57	186	6.86	140	6.22	207	6.52
Stroke/TIA	376	9.80	498	10.03	275	10.14	223	9.91	327	10.3
At least 1 dermatology visit	140	3.65	172	3.46	98	3.61	74	3.29	109	3.43
At least 1 optometry/ ophthalmology visit	2321	60.49	2955	59.53	1621	59.75	1334	59.26	1977	62.27
Immunocompromised Conditions										
Another/other transplant during the pre-period	18	0.47	24	0.48	20	0.74	<11	---	14	0.44
Hematopoietic stem cell transplant	12	0.31	13	0.26	<11	---	<11	---	<11	---
Hematologic or solid malignancy & chemotherapy	49	1.28	78	1.57	49	1.81	29	1.29	48	1.51
Human Immunodeficiency Virus	<11	---	<11	---	<11	---	<11	---	<11	---
Rheumatoid Arthritis	144	3.75	196	3.95	95	3.50	101	4.49	117	3.69
Inflammatory bowel disease (Chron's disease)	27	0.70	33	0.66	19	0.70	14	0.62	22	0.69
Inflammatory bowel disease (ulcerative colitis)	35	0.91	47	0.95	32	1.18	15	0.67	31	0.98
Lupus	20	0.52	25	0.50	18	0.66	<11	---	14	0.44
Multiple Sclerosis	15	0.39	18	0.36	<11	---	<11	---	12	0.38
Psoriasis/Psoriatic Arthritis	85	2.22	102	2.05	50	1.84	52	2.31	64	2.02
Recorded Service Use History in Year Prior to Dose 1	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hospitalizations										
0	3181	82.90	4072	82.03	2215	81.64	1857	82.50	2604	82.02
1	463	12.07	626	12.61	338	12.46	288	12.79	403	12.69
2 or more	193	5.03	266	5.36	160	5.90	106	4.71	168	5.29
Emergency department visits										
0	2806	73.13	3567	71.86	1907	70.29	1660	73.75	2277	71.72
1	721	18.79	944	19.02	525	19.35	419	18.61	605	19.06
2 or more	310	8.08	453	9.12	281	10.36	172	7.64	293	9.22
Durable medical equipment	1297	33.80	1745	35.15	992	36.56	753	33.45	1117	35.18
Hospice care	<11	---	<11	---	<11	---	0	---	<11	---
Home health care	298	7.77	433	8.72	258	9.51	175	7.77	267	8.41
Skilled nursing facility care	84	2.19	122	2.46	75	2.76	47	2.09	90	2.83

Descriptive Characteristic	Sensitivity (60 to 183-day dose spacing)		Secondary (30-d CW for both doses)		Sensitivity (Dose 1, subset of Secondary 30-d CW for both doses)		Sensitivity (Dose 2, subset of Secondary 30-d CW for both doses)		Sensitivity (COVID)	
	N	%	N	%	N	%	N	%	N	%
Concomitant Vaccine Use at Index Date										
Influenza	472	12.30	630	12.69	363	13.38	267	11.86	284	8.94
Pneumococcal	125	3.26	182	3.67	115	4.24	67	2.98	105	3.31
Tetanus- Diphtheria-Pertussis	71	1.85	96	1.93	55	2.03	41	1.82	43	1.35

SVT, supraventricular tachycardia; SD, standard deviation; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; RZV, recombinant zoster vaccine; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.
Cell sizes will be suppressed if the total number is <11; 0 values are not suppressed

a. Parts A, B, D continuous enrollment in Medicare Parts A (Hospital Insurance) B (Medical Insurance) and D (Prescription Drug Coverage); allows one calendar month gap in enrolment. Defined prior to Dose 1 therefore participants who met enrolment criteria prior to Dose 2 but not Dose 1 are not captured.
b. Based on the year Dose 1 was received.

14.3.3. Results of SVT temporal scan analysis

A total of 29 scan windows were tested. The observed to expected cases in the scan window were statistically significantly in the windows with lengths 27 to 56 and 28 to 57. The finding suggests that there is significant temporal clustering of cases but close to 1 (Table 51).

Table 51 Temporal scan statistic for SVT cases

Scan Number	Window Length	Cases in Window	Expected Cases	Relative Risk	Excess Cases	LLR	p-value
PPD	27 to 56	2611	2482	1.11	258	6.707695	0.029
	28 to 57	2607	2482	1.11	250	6.29799	0.042
	35 to 58	2102	1985.6	1.1	194	5.651784	0.063
	27 to 55	2510	2399.27	1.09	214.32	4.94255	0.103
	27 to 52	2256	2151.07	1.09	185.18	4.500809	0.149
	35 to 59	2170	2068.33	1.09	174.29	4.264712	0.167
	27 to 51	2168	2068.33	1.09	170.86	4.098899	0.194
	27 to 53	2334	2233.8	1.08	182.18	4.076049	0.197
	27 to 50	2081	1985.6	1.08	159	3.800384	0.244
	35 to 60	2244	2151.07	1.08	164	3.531566	0.282
	27 to 54	2407	2316.53	1.08	169.62	3.307506	0.336
	27 to 44	1569	1489.2	1.08	114	3.024289	0.408
	27 to 36	890	827.33	1.09	75.2	2.792689	0.482
	27 to 45	1649	1571.93	1.07	112.78	2.741195	0.501
	27 to 43	1479	1406.47	1.07	101.21	2.583478	0.543
	27 to 49	1977	1902.87	1.06	120.22	2.330677	0.621

Scan Number	Window Length	Cases in Window	Expected Cases	Relative Risk	Excess Cases	LLR	p-value
PPD	27 to 46	1724	1654.67	1.06	104	2.16414	0.687
	27 to 37	965	910.07	1.07	67.27	1.999436	0.74
	27 to 42	1386	1323.73	1.07	84.91	1.977631	0.751
	27 to 38	1047	992.8	1.07	67.75	1.824823	0.803
	27 to 41	1299	1241	1.06	77.33	1.788874	0.822
	27 to 35	792	744.6	1.08	55.76	1.744915	0.83
	27 to 39	1130	1075.53	1.07	69.53	1.739687	0.831
	26 to 32	618	579.13	1.08	44	1.448736	0.912
	27 to 47	1794	1737.4	1.05	87.08	1.411447	0.923
	27 to 48	1877	1820.13	1.05	89.79	1.396672	0.925
	27 to 40	1203	1158.27	1.05	58.35	1.116849	0.969
	13 to 15	271	248.2	1.1	24	1.071756	0.977
	7 to 8	181	165.47	1.1	16.07	0.732471	0.996

LLR, Log-Likelihood Ratio.

a. Analysis was performed using TreeScan™ software.

b. Columns definitions:

Scan number=scan windows were tested.

Window Length=The temporal window of the cluster.

Cases in window=The number of observed cases in the cluster.

Expected cases=The number of expected cases in the cluster, under the assumption that the null hypothesis is true, and conditioned on whatever the analysis is conditioned on.

Relative Risk=The risk in the cluster divided by the risk outside the cluster. For purely temporal scan statistics, outside means outside the cluster time window but inside the same node. The formula is different for different probability models.

Excess Cases=The excess number of cases.

LLR=The natural logarithm of the likelihood ration for the cut. This is the test statistic, and a larger value is evidence for a cluster and against the null hypothesis.

P-value=The p-values are adjusted for the multiple testing stemming from the multitude of cuts evaluated. This means that under the null hypothesis of complete randomness there is a 5% chance that the p-value for the most likely cut will be smaller than 0.05 and a 95% chance that it will be bigger. Under the null hypothesis there will always be some area with a rate higher than expected just by chance alone. Hence, even though the most likely cut always has an excess rate, the p-value may be very close or identical to one.

14.4. PMR

14.4.1. Baseline characteristics of the primary analytic cohort

Table 52 below displays the baseline characteristics of the cohort for the primary analysis, and Table 53 displays the baseline characteristics stratified by the number of doses and the dose spacing. The stratification by number of doses received reflects how many RZV doses a participant received. Of the 3 265 790 participants in the primary cohort, 481 358 only received Dose 1 and 2 784 432 received both RZV Dose 1 and Dose 2, some of which Dose 2 was not eligible for the analytic cohort due to prevalent PMR or insufficient enrollment preceding Dose 2. There were no appreciable differences in the characteristics by number of RZV doses received.

The subset of the cohort for the primary analysis that included participants who received two RZV doses was stratified by dose spacing of 28 to 60 days versus >60 days (Table 53). This dose spacing aligns with the European label, whereas in the US it is 2 to 6 months spacing between RZV Dose 1 and Dose 2. There were no differences in the baseline covariates between those who received the doses 28 to 60 days apart versus those who had >60 days between doses.

Table 52 Baseline demographic and health characteristics of the PMR analytic cohort: before and after IPTW weighting

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Number of unique participants	3 265 790	2 569 783		3 063 091	2 433 338	
Demographics						
Age at Index Date, Mean (SD)	74.33 (6.33)	75.16 (7.14)	-0.1233	74.53 (6.54)	74.65 (6.68)	-0.0180
Age categories						
65-69	854 410 (26.16)	658 987 (25.64)	0.0118	802 782 (26.21)	636 481 (26.16)	0.0012
70-74	1 029 820 (31.53)	744 195 (28.96)	0.0561	938 124 (30.63)	744 664 (30.60)	0.0005
75-79	719 804 (22.04)	521 623 (20.30)	0.0427	653 227 (21.33)	519 249 (21.34)	-0.0003
80-84	400 680 (12.27)	332 324 (12.93)	-0.0200	385 355 (12.58)	306 787 (12.61)	-0.0008
85+	261 076 (7.99)	312 654 (12.17)	-0.1389	283 604 (9.26)	226 156 (9.29)	-0.0012
Sex						
Male	1 343 596 (41.14)	937 777 (36.49)	0.0955	1 198 644 (39.13)	955 357 (39.26)	-0.0027
Female	1 922 194 (58.86)	1 632 006 (63.51)	-0.0955	1 864 447 (60.87)	1 477 981 (60.74)	0.0027
Race						
American Indian/Alaskan Native	7 799 (0.24)	6183 (0.24)	-0.0004	7 445 (0.24)	5 896 (0.24)	0.0002
Asian	81 148 (2.48)	58 690 (2.28)	0.0132	74 852 (2.44)	59 950 (2.46)	-0.0013
Black or African American	78 866 (2.41)	145 059 (5.64)	-0.1648	85 942 (2.81)	68 294 (2.81)	-0.0001
White	2 904 257 (88.93)	2 217 388 (86.29)	0.0803	2 725 264 (88.97)	2 164 161 (88.94)	0.0011
Hispanic	23 005 (0.70)	37 507 (1.46)	-0.0730	24 310 (0.79)	19 228 (0.79)	0.0004
Unknown	108 232 (3.31)	64 488 (2.51)	0.0479	90 487 (2.95)	72 009 (2.96)	0.0003
Other	62 483 (1.91)	40 468 (1.57)	0.0259	54 791 (1.79)	43 799 (1.80)	-0.0009
Parts A, B, D Continuous enrollment[c]	3 265 790 (100.00)	2 569 783 (100.00)	0.0000	3 063 091 (100.00)	2 433 338 (100.00)	0.0000
Year of Index Date						
2018	876 508 (26.84)	994 304 (38.69)	-0.2546	977 717 (31.92)	779 849 (32.05)	-0.0028
2019	1 403 130 (42.96)	860 038 (33.47)	0.1964	1 186 261 (38.73)	941 341 (38.69)	0.0009
2020	986 152 (30.20)	715 441 (27.84)	0.0519	899 113 (29.35)	712 148 (29.27)	0.0019
Medical History[d]						
Diabetes mellitus	793 810 (24.31)	711 153 (27.67)	-0.0768	773 239 (25.24)	614 201 (25.24)	0.0001
Chronic kidney disease	671 299 (20.56)	596 143 (23.20)	-0.0640	644 747 (21.05)	512 061 (21.04)	0.0001

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Chronic lung disease[e]	395 650 (12.11)	372 966 (14.51)	-0.0707	392 435 (12.81)	311 416 (12.80)	0.0004
Congestive heart failure	226 237 (6.93)	242 298 (9.43)	-0.0914	227 816 (7.44)	180 849 (7.43)	0.0002
Ischemic heart disease	692 304 (21.20)	573 562 (22.32)	-0.0272	649 807 (21.21)	516 264 (21.22)	-0.0001
Dementia	109 259 (3.35)	154 387 (6.01)	-0.1263	113 883 (3.72)	90 598 (3.72)	-0.0003
Chronic liver disease	181 005 (5.54)	145 824 (5.67)	-0.0057	169 349 (5.53)	134 361 (5.52)	0.0003
Stroke/TIA	200 476 (6.14)	186 518 (7.26)	-0.0448	193 472 (6.32)	153 738 (6.32)	-0.0001
Immunocompromised Conditions						
Organ transplant	7698 (0.24)	7032 (0.27)	-0.0075	7477 (0.24)	5938 (0.24)	0.0000
Hematopoietic cell transplant	4666 (0.14)	430 (0.09)	0.0140	3524 (0.12)	2845 (0.12)	-0.0006
Hematologic or solid malignancy w/recent receipt of chemotherapy	26 386 (0.81)	28 526 (1.11)	-0.0310	27 544 (0.90)	21 893 (0.90)	-0.0001
HIV infection	4803 (0.15)	2968 (0.12)	0.0087	3862 (0.13)	3080 (0.13)	-0.0001
Rheumatoid arthritis	95 669 (2.93)	79 728 (3.10)	-0.0101	90 718 (2.96)	71 987 (2.96)	0.0002
IBD - Crohn's disease	17 245 (0.53)	11 507 (0.45)	0.0115	14 954 (0.49)	11 874 (0.49)	0.0000
IBD - Colitis	30 773 (0.94)	20 048 (0.78)	0.0176	26 319 (0.86)	20 902 (0.86)	0.0000
Lupus	11 962 (0.37)	10 330 (0.4)	-0.0058	11 552 (0.38)	9149 (0.38)	0.0002
Multiple sclerosis	7941 (0.24)	6200 (0.24)	0.0004	7381 (0.24)	5858 (0.24)	0.0001
Psoriasis/Psoriatic arthritis	71 586 (2.19)	47 093 (1.83)	0.0256	62 378 (2.04)	49 627 (2.04)	-0.0002
Service Use History[d]						
≥1 dermatology visit	116 390 (3.56)	55 646 (2.17)	0.0839	87 533 (2.86)	69 889 (2.87)	-0.0009
≥1 optometry/ ophthalmology visit	1 853 617 (56.76)	1 230 677 (47.89)	0.1783	1 619 839 (52.88)	1 288 385 (52.95)	-0.0013
Number of hospitalizations						
0	2 915 904 (89.29)	2 219 432 (86.37)	0.0894	2 718 130 (88.74)	2 159 578 (88.75)	-0.0004
1	264 976 (8.11)	243 149 (9.46)	-0.0476	259 282 (8.46)	205 722 (8.45)	0.0004
2 or more	84 910 (2.60)	107 202 (4.17)	-0.0870	85 679 (2.80)	68 038 (2.80)	0.0001
Number of ED visits						
0	2 672 440 (81.83)	2 002 994 (77.94)	0.0971	2 477 168 (80.87)	1 968 220 (80.89)	-0.0004
1	441 272 (13.51)	363 327 (14.14)	-0.0182	423 251 (13.82)	335 932 (13.81)	0.0004
2 or more	152 078 (4.66)	203 462 (7.92)	-0.1346	162 673 (5.31)	129 186 (5.31)	0.0001
Durable medical equipment	925 237 (28.33)	741 289 (28.85)	-0.0114	858 879 (28.04)	682 152 (28.03)	0.0001

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Hospice care	1859 (0.06)	5904 (0.23)	-0.0457	1116 (0.04)	888 (0.04)	0.0000
Home health care	187 699 (5.75)	227 421 (8.85)	-0.1195	193 299 (6.31)	153 507 (6.31)	0.0001
Skilled nursing facility care	51 782 (1.59)	79 863 (3.11)	-0.1007	54 415 (1.78)	43 316 (1.78)	-0.0003
Concomitant Vaccine Use[f]						
Influenza	406 144 (12.44)	154 569 (6.01)	0.2233	237 328 (7.75)	187 411 (7.70)	0.0017
Pneumococcal	144 138 (4.41)	127 714 (4.97)	-0.0263	141 713 (4.63)	113 048 (4.65)	-0.0009
Tetanus- Diphtheria- Pertussis	67 389 (2.06)	3387 (0.13)	0.1862	105 (0.00)	83 (0.00)	0.0000

COPD, chronic obstructive pulmonary disease; ED, emergency department; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; RZV, recombinant zoster vaccine; PMR, polymyalgia rheumatica; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data. Index date is the RZV Dose 1 date in the exposed group and preventive visit date in the comparator group.

a. The N for the RZV-exposed cohort is shown for individuals who received at least one RZV dose, representing the Dose 1 analytical cohort.
b. RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening.
c. Allows one calendar month gap in enrolment; measured in the year preceding the index date.
d. Measured in the year prior to the index date.
e. Chronic lung disease includes COPD and bronchiectasis.
f. Measured on the index date.

Table 53 Baseline demographic and health characteristics of the PMR analytic cohort by number of doses and dose spacing

Descriptive Characteristic	RZV Dose 1 only	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
Number of unique participants	481 358	2 784 432	121 886	2 662 546
Demographics				
Age at Index Date, Mean (SD)	74.99 (6.93)	74.22 (6.21)	74.89 (6.39)	74.19 (6.2)
Age categories				
65-69	123 012 (25.56)	731 398 (26.27)	28 304 (23.22)	703 094 (26.41)
70-74	139 388 (28.96)	890 432 (31.98)	36 888 (30.26)	853 544 (32.06)
75-79	101 362 (21.06)	618 442 (22.21)	28 552 (23.43)	589 890 (22.16)
80-84	63 863 (13.27)	336 817 (12.10)	17 310 (14.20)	319 507 (12.00)
85+	53 733 (11.16)	207 343 (7.45)	10 832 (8.89)	196 511 (7.38)
Sex				
Male	198 508 (41.24)	1 145 088 (41.12)	50 613 (41.52)	1 094 475 (41.11)
Female	282 850 (58.76)	1 639 344 (58.88)	71 273 (58.48)	1 568 071 (58.89)
Race				
American Indian/Alaskan Native	3 280 (0.68)	4 519 (0.16)	255 (0.21)	4 264 (0.16)
Asian	16 765 (3.48)	64 383 (2.31)	3 611 (2.96)	60 772 (2.28)
Black or African American	20 732 (4.31)	58 134 (2.09)	4 263 (3.50)	53 871 (2.02)
White	406 947 (84.54)	2 497 310 (89.69)	107 107 (87.87)	2 390 203 (89.77)
Hispanic	9 284 (1.93)	13 721 (0.49)	921 (0.76)	12 800 (0.48)
Unknown	14 137 (2.94)	94 095 (3.38)	3 472 (2.85)	90 623 (3.40)
Other	10 213 (2.12)	52 270 (1.88)	2 257 (1.85)	50 013 (1.88)
Parts A, B, D Continuous enrollment[a]	481 358 (100.00)	2 784 432 (100.00)	121 886 (100.00)	2 662 546 (100.00)
Year of Index Date				
2018	121 535 (25.25)	754 973 (27.11)	23 383 (19.18)	731 590 (27.48)
2019	191 825 (39.85)	1 211 305 (43.50)	55 355 (45.42)	1 155 950 (43.42)
2020	167 998 (34.9)	818 154 (29.38)	43 148 (35.40)	775 006 (29.11)

Descriptive Characteristic	RZV Dose 1 only	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
Medical History[b]				
Diabetes mellitus	135 591(28.17)	658 219(23.64)	31 747(26.05)	626 472(23.53)
Chronic kidney disease	117 000(24.31)	554 299(19.91)	27 354(22.44)	526 945(19.79)
Chronic lung disease[c]	71 036(14.76)	324 614(11.66)	15 634(12.83)	308 980(11.6)
Congestive heart failure	46 615(9.68)	179 622(6.45)	9 052(7.43)	170 570(6.41)
Ischemic heart disease	114 750(23.84)	577 554(20.74)	27 285(22.39)	550 269(20.67)
Dementia	28 575(5.94)	80 684(2.90)	4 401(3.61)	76 283(2.87)
Chronic liver disease	29 682(6.17)	151 323(5.43)	6 932(5.69)	144 391(5.42)
Stroke/TIA	36 035(7.49)	164 441(5.91)	7 554(6.20)	156 887(5.89)
Immunocompromised Conditions				
Organ transplant	1 557(0.32)	6 141(0.22)	320(0.26)	5 821(0.22)
Hematopoietic stem cell transplant	914(0.19)	3 752(0.13)	284(0.23)	3 468(0.13)
Hematologic or solid malignancy w/recent receipt of chemotherapy	5 114(1.06)	21 272(0.76)	1 104(0.91)	20 168(0.76)
HIV infection	1 067(0.22)	3 736(0.13)	227(0.19)	3 509(0.13)
Rheumatoid Arthritis	15 704(3.26)	79 965(2.87)	3 848(3.16)	76 117(2.86)
IBD - Crohn's disease	2 372(0.49)	14 873(0.53)	639(0.52)	14 234(0.53)
IBD - Colitis	4 266(0.89)	26 507(0.95)	1 157(0.95)	25 350(0.95)
Lupus	2 092(0.43)	9 870(0.35)	502(0.41)	9 368(0.35)
Multiple Sclerosis	1 208(0.25)	6 733(0.24)	316(0.26)	6 417(0.24)
Psoriasis/Psoriatic Arthritis	9 960(2.07)	61 626(2.21)	2 608(2.14)	59 018(2.22)
Service Use History[b]				
≥1 dermatology visit	13 194(2.74)	103 196(3.71)	4 015(3.29)	99 181(3.73)
≥1 optometry/ ophthalmology visit	246 880(51.29)	1 606 737(57.70)	69 333(56.88)	1 537 404(57.74)
Number of hospitalizations				
0	417 681(86.77)	2 498 223(89.72)	108 352(88.9)	2 389 871(89.76)
1	45 109(9.37)	219 867(7.90)	10 338(8.48)	209 529(7.87)
2 or more	18 568(3.86)	66 342(2.38)	3196(2.62)	63 146(2.37)
Number of ED visits				

Descriptive Characteristic	RZV Dose 1 only	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
0	376 185(78.15)	2 296 255(82.47)	99 233(81.41)	2 197 022(82.52)
1	73 362(15.24)	367 910(13.21)	16 734(13.73)	351 176(13.19)
2 or more	31 811(6.61)	120 267(4.32)	5 919(4.86)	114 348(4.29)
Durable medical equipment	145 724(30.27)	779 513(28)	35 618(29.22)	743 895(27.94)
Hospice care	894(0.19)	965(0.03)	73(0.06)	892(0.03)
Home health care	41 182(8.56)	146 517(5.26)	7 191(5.90)	139 326(5.23)
Skilled nursing facility care	12 514(2.60)	39 268(1.41)	2014(1.65)	37 254(1.40)
Concomitant Vaccine Use[d]				
Influenza	76 944(15.98)	329 200(11.82)	16 955(13.91)	312 245(11.73)
Pneumococcal	36 887(7.66)	107 251(3.85)	5 227(4.29)	102 024(3.83)
Tetanus-Diphtheria-Pertussis	15 112(3.14)	52 277(1.88)	2 639(2.17)	49 638(1.86)

COPD, chronic obstructive pulmonary disease; ED, emergency department; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; PMR, polymyalgia rheumatica; RZV, recombinant zoster vaccine; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

a. Allows one calendar month gap in enrollment; measured in the year preceding the index date. Index date is the RZV Dose 1 date.
b. Measured in the year prior to the index date.
c. Chronic lung disease includes COPD and bronchiectasis.
d. Measured on the index date.

14.4.2. Baseline characteristics of the Supplemental cohort

A supplemental cohort that excluded from the comparator arm any participant that received at least one dose of RZV was used to conduct a sensitivity analysis to the primary separate dose analysis. The RZV-exposed included 3 265 790 participants and the RZV-unvaccinated included 2 096 549 participants.

Table 54 displays the baseline characteristics in each group along with the corresponding SMDs for the unweighted and the weighted sample. The unweighted sample demonstrated some imbalance in age, race, diabetes, congestive heart failure, dementia, dermatology visits, optometry/ophthalmology visit, hospitalizations or ED visits, home health care, skilled nursing facility, and concomitant vaccines before implementing IPTW weighting. The baseline characteristics with an SMD >0.10 before weighting were balanced after weighting. All covariates were balanced with SMDs around zero, suggesting that weighting worked well to ensure covariate balance.

Table 54 Baseline demographic and health characteristics of the supplemental cohort: Before and after IPTW weighting

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N(%)	N(%)		N(%)	N(%)	
Number of unique participants	3 265 790	2 096 549		3 064 089	1 974 748	
Demographics						
Age at Index Date, Mean (SD)	74.33 (6.33)	75.43 (7.35)	-0.1602	74.59 (6.57)	74.73 (6.75)	-0.0214
Age categories						
65-69	854 410 (26.16)	531 482 (25.35)	0.0186	799 834 (26.10)	513 967 (26.03)	0.0017
70-74	1 029 820 (31.53)	588 149 (28.05)	0.0762	931 092 (30.39)	599 276 (30.35)	0.0009
75-79	719 804 (22.04)	417 249 (19.9)	0.0526	653 255 (21.32)	421 173 (21.33)	-0.0002
80-84	400 680 (12.27)	277 824 (13.25)	-0.0295	389 468 (12.71)	251 902 (12.76)	-0.0014
85+	261 076 (7.99)	281 845 (13.44)	-0.1768	290 440 (9.48)	188 431 (9.54)	-0.0022
Sex						
Male	1 343 596 (41.14)	769 850 (36.72)	0.0908	1 206 810 (39.39)	781 237 (39.56)	-0.0036
Female	1 922 194 (58.86)	1 326 699 (63.28)	-0.0908	1 857 279 (60.61)	1 193 511 (60.44)	0.0036
Race						
American Indian/Alaskan Native	7 799 (0.24)	5 354 (0.26)	-0.0033	7 741 (0.25)	4 997 (0.25)	-0.0001
Asian	81 148 (2.48)	47 822 (2.28)	0.0134	75 187 (2.45)	49 204 (2.49)	-0.0024
Black or African American	78 866 (2.41)	133 571 (6.37)	-0.1939	87 493 (2.86)	56 294 (2.85)	0.0003
White	2 904 257 (88.93)	1 794 419 (85.59)	0.1003	2 724 718 (88.92)	1 755 208 (88.88)	0.0013
Hispanic	23 005 (0.7)	34 605 (1.65)	-0.0878	25 868 (0.84)	16 605 (0.84)	0.0004
Unknown	108 232 (3.31)	48 923 (2.33)	0.0592	88 630 (2.89)	57 088 (2.89)	0.0001
Other	62 483 (1.91)	31 855 (1.52)	0.0303	54 452 (1.78)	35 352 (1.79)	-0.0010
Parts A, B, D Continuous enrollment[c]	3 265 790 (100)	2 096 549 (100)	0.0000	3 064 089 (100.00)	1 974 748 (100.00)	0.0000
Year of Index Date						
2018	876 508 (26.84)	714 264 (34.07)	-0.1576	909 856 (29.69)	589 549 (29.85)	-0.0035
2019	1 403 130 (42.96)	709 898 (33.86)	0.1880	1 197 809 (39.09)	769 389 (38.96)	0.0027
2020	986 152 (30.2)	672 387 (32.07)	-0.0405	956 424 (31.21)	615 810 (31.18)	0.0006
Medical History in Year[d]						
Diabetes mellitus	793 810 (24.31)	605 751 (28.89)	-0.1039	782 498 (25.54)	504 807 (25.56)	-0.0006
Chronic kidney disease	671 299 (20.56)	512 209 (24.43)	-0.0929	654 767 (21.37)	421 951 (21.37)	0.0000

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N(%)	N(%)		N(%)	N(%)	
Chronic lung disease[e]	395 650 (12.11)	319 632 (15.25)	-0.0912	397 293 (12.97)	255 903 (12.96)	0.0002
Congestive heart failure	226 237 (6.93)	216 063 (10.31)	-0.1206	232 806 (7.60)	149 888 (7.59)	0.0003
Ischemic heart disease	692 304 (21.2)	486 444 (23.2)	-0.0482	658 060 (21.48)	423 899 (21.47)	0.0003
Dementia	109 259 (3.35)	143 125 (6.83)	-0.1589	116 665 (3.81)	75 152 (3.81)	0.0001
Chronic liver disease	181 005 (5.54)	121 077 (5.78)	-0.0101	170 376 (5.56)	109 583 (5.55)	0.0005
Stroke/TIA	200 476 (6.14)	159 559 (7.61)	-0.0582	195 353 (6.38)	125 874 (6.37)	0.0001
Immunocompromised Conditions						
Another/other transplant	7 698 (0.24)	6 071 (0.29)	-0.0105	7 573 (0.25)	4 896 (0.25)	-0.0002
Hematopoietic stem cell transplant	4 666 (0.14)	1 918 (0.09)	0.0150	3 447 (0.11)	2 291 (0.12)	-0.0011
Hematologic or solid malignancy w/recent receipt of chemotherapy	26 386 (0.81)	24 918 (1.19)	-0.0383	28 106 (0.92)	18 097 (0.92)	0.0001
HIV infection	4 803 (0.15)	2 424 (0.12)	0.0087	3 746 (0.12)	2 410 (0.12)	0.0001
Rheumatoid Arthritis	95 669 (2.93)	66 131 (3.15)	-0.0131	91 199 (2.98)	58 704 (2.97)	0.0002
IBD - Crohn's disease	17 245 (0.53)	9 091 (0.43)	0.0137	14 808 (0.48)	9 515 (0.48)	0.0002
IBD - Colitis	30 773 (0.94)	15 813 (0.75)	0.0205	26 038 (0.85)	16 769 (0.85)	0.0001
Lupus	11 962 (0.37)	8 571 (0.41)	-0.0069	11 573 (0.38)	7 434 (0.38)	0.0002
Multiple Sclerosis	7 941 (0.24)	5 014 (0.24)	0.0008	7 361 (0.24)	4 733 (0.24)	0.0001
Psoriasis/Psoriatic Arthritis	71 586 (2.19)	37 050 (1.77)	0.0305	61 773 (2.02)	39 867 (2.02)	-0.0002
Service Use History[d]						
≥1 dermatology visit	116 390 (3.56)	39 172 (1.87)	0.1045	79 552 (2.60)	51 692 (2.62)	-0.0013
≥1 optometry/ophthalmology visit	1 853 617 (56.76)	957 653 (45.68)	0.2231	1 606 744 (52.44)	1 036 689 (52.50)	-0.0012
Number of hospitalizations						
0	2 915 904 (89.29)	1 795 718 (85.65)	0.1100	2 716 326 (88.65)	1 751 180 (88.68)	-0.0009
1	264 976 (8.11)	204 971 (9.78)	-0.0583	260 691 (8.51)	167 738 (8.49)	0.0005
2 or more	84 910 (2.6)	95 860 (4.57)	-0.1062	87 072 (2.84)	55 830 (2.83)	0.0009
Number of ED visits						
0	2 672 440 (81.83)	1 616 655 (77.11)	0.1171	2 474 262 (80.75)	1 594 913 (80.77)	-0.0004
1	441 272 (13.51)	301 519 (14.38)	-0.0251	425 510 (13.89)	274 166 (13.88)	0.0001
2 or more	152 078 (4.66)	178 375 (8.51)	-0.1558	164 317 (5.36)	105 669 (5.35)	0.0005
Durable medical equipment	925 237 (28.33)	612 257 (29.2)	-0.0193	862 299 (28.14)	555 513 (28.13)	0.0003

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N(%)	N(%)		N(%)	N(%)	
Hospice care	1 859 (0.06)	5 812 (0.28)	-0.0540	1 065 (0.03)	684 (0.03)	0.0001
Home health care	187 699 (5.75)	202 961 (9.68)	-0.1478	196 246 (6.40)	126 199 (6.39)	0.0006
Skilled nursing facility care	51 782 (1.59)	72 841 (3.47)	-0.1205	55 039 (1.80)	35 478 (1.80)	0.0000
Concomitant Vaccine Use[f]						
Influenza	406 144 (12.44)	130 526 (6.23)	0.2148	254 846 (8.32)	165 457 (8.38)	-0.0022
Pneumococcal	144 138 (4.41)	101 800 (4.86)	-0.0210	139 700 (4.56)	92 066 (4.66)	-0.0049
Tetanus- Diphtheria- Pertussis	67 389 (2.06)	2 188 (0.1)	0.1901	80 (0.00)	52 (0.00)	0.0000

COPD, chronic obstructive pulmonary disease; ED, emergency department; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; PMR, polymyalgia rheumatica; RZV, recombinant zoster vaccine; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

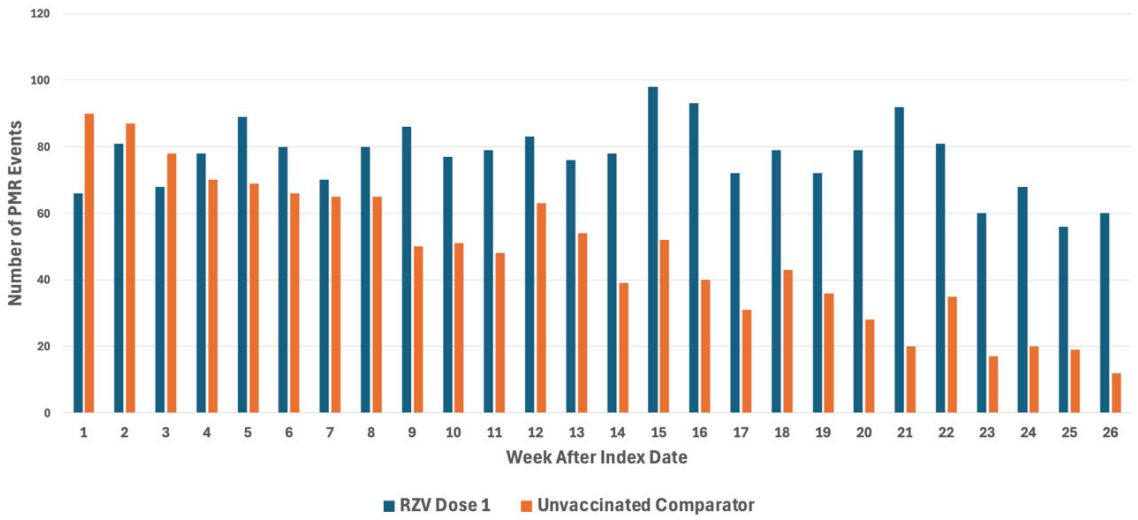
a. Allows one calendar month gap in enrollment; measured in the year preceding the index date. Index date is the RZV Dose 1 date.
b. Measured in the year prior to the index date.
c. Chronic lung disease includes COPD and bronchiectasis.
d. Measured on the index date.
e. Chronic lung disease includes COPD and bronchiectasis.
f. Measured on the index date.

14.4.3. PMR events in the 183-day follow-up period

The distribution of incident PMR events is illustrated with respect to the week of follow-up after the index date (i.e., the date of vaccination with RZV Dose 1 or Dose 2 for the RZV-exposed and the date of the preventive care visit for the RZV-unvaccinated comparator). The distribution of incident PMR events is compared by each RZV dose among the RZV-exposed with the RZV-unvaccinated comparator. The numbers are based on the analytic cohort used in the primary analysis.

Figure 23 shows the distribution of PMR cases from the index date for Dose 1 RZV-exposed relative to the RZV-unvaccinated comparator. The 2012 new-onset PMR events following RZV Dose 1 were generally evenly distributed over the follow-up after the index date. There were 1249 new-onset PMR events following the RZV-unvaccinated comparator preventive care visit index date, which were higher early in the follow-up and decreased over time. The data were aggregated by week of follow-up to avoid counts <11, which cannot be displayed per the CMS data use agreement.

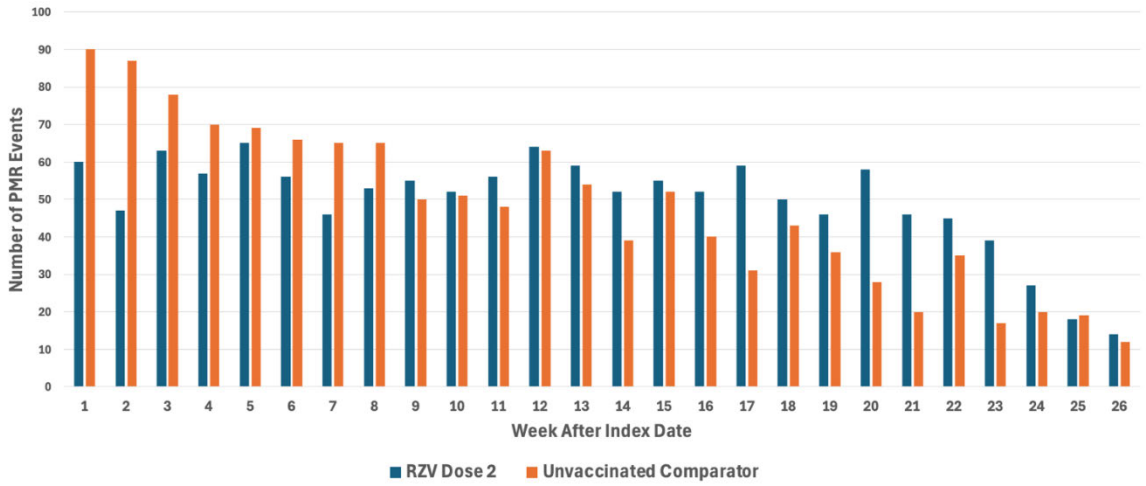
Figure 23 Distribution of incident PMR events by week from the index date: RZV Dose 1 and unvaccinated comparators



RZV, recombinant zoster vaccine; PMR, polymyalgia rheumatica
Note: Index date is the date of vaccination for Dose 1 for RZV-exposed, or date of preventive care visit for RZV-unvaccinated comparator.

In the Dose 2 analytical cohort, there were 1297 and 1249 PMR events in the RZV-exposed group and RZV-unvaccinated comparator group, respectively (Figure 24). The PMR events declined over time in both the RZV-exposed Dose 2 and the RZV-unvaccinated comparator groups. For the RZV-unvaccinated comparators, PMR cases decreased during the follow-up period from 90 cases (Week 1) to 13 cases (Week 26).

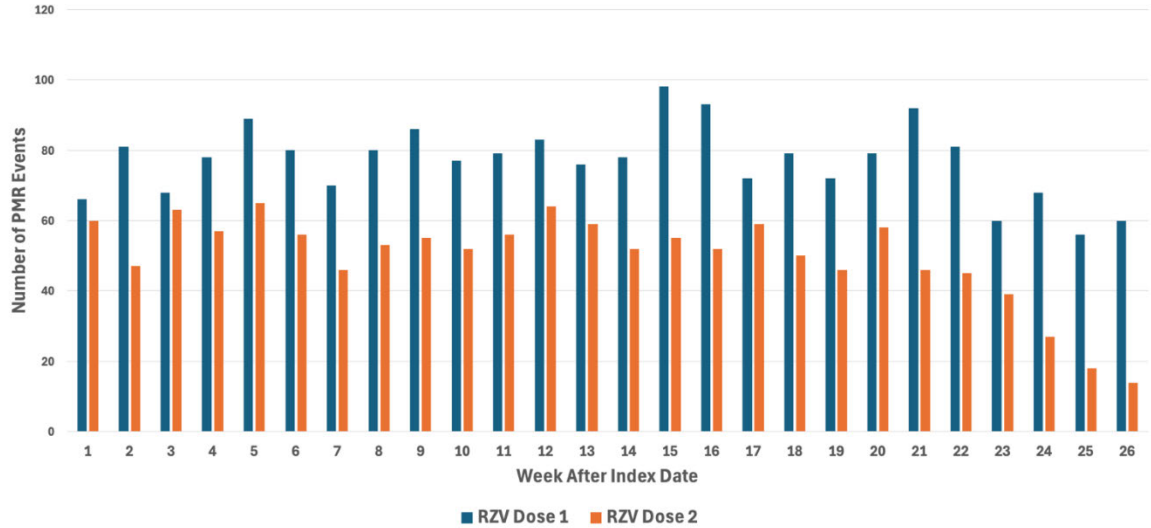
Figure 24 Distribution of incident PMR events by week from the index date: RZV Dose 2 and RZV-unvaccinated comparators



RZV, recombinant zoster vaccine; PMR, polymyalgia rheumatica.
Note: Index date is the date of vaccination for Dose 2 for RZV-exposed, or date of preventive care visit for RZV-unvaccinated comparator.

Figure 25 below shows the distribution of new-onset PMR events relative to RZV Dose 1 and Dose 2 by the week of follow-up. The graph depicts the number of events per week and visually shows that the number of cases after RZV Dose 1 was greater than the number of cases after RZV Dose 2. The number of cases per week of follow-up, combined for Dose 1 and Dose 2, is approximately 120 to 140 through Week 22. The last few weeks of follow-up show a drop in incident PMR events, particularly after Dose 2.

Figure 25 Distribution of incident PMR by week after index date: RZV Dose 1 and Dose 2



RZV, recombinant zoster vaccine; PMR, polymyalgia rheumatica.
Note: Index date is the date of vaccination for RZV Dose 1 and Dose 2, respectively.

14.4.4. Crude and covariate adjusted risk estimates for PMR

This section includes the hazard ratios for the crude and covariate adjusted models for all the PMR analyses. The tables in this section are provided as a reference to the IPTW-adjusted analyses provided in the main text.

14.4.4.1. Primary analysis

Table 55 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the PMR primary analysis of RZV Dose 1 and RZV Dose 2, not accounting for violation of the proportional hazards assumption. The estimates are the same as the IPTW-adjusted estimates. The sample was very large and many of the baseline covariates were balanced between comparators, which led to tight confidence intervals.

Table 55 Risk estimates for primary analysis of PMR within a 183-day follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Separate analysis						
RZV Dose 1	3 265 790	2012	1 609 938	12.50 (11.96 – 13.06)	1.19 (1.11 – 1.28)	1.19 (1.11 – 1.29)
Comparator	2 569 783	1249	1 185 939	10.53 (9.96 –11.13)	Ref.	Ref.
RZV Dose 2	2 489 075	1297	1 226 359	10.58 (10.02 – 11.17)	1.01 (0.94 – 1.10)	0.99 (0.92 – 1.08)
Comparator	2 569 783	1249	1 185 939	10.53 (9.96 –11.13)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; PMR, polymyalgia rheumatica; PY, persons-years; RZV, recombinant zoster vaccine; Ref., reference.

14.4.4.2. Secondary analysis

Table 56 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the PMR secondary analysis of a combined dose single risk estimate and a time-varying analysis separate estimate for RZV Dose 1 and RZV Dose 2. The HR for the combined dose analysis was like the primary analysis. The time-varying HRs showed an elevated risk for RZV Dose 1, which mirrored the IPTW-adjusted estimate. The time-varying RZV Dose 2 HR was lower than for RZV Dose 1, and it mirrored the IPTW-adjusted analysis reported in the main text.

Table 56 Risk estimates for secondary analysis of PMR within a 183 day - follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Combined dose						
RZV Dose 1 and Dose 2	3 265 790	2658	2 250 071	11.81 (11.37 – 12.27)	1.18 (1.10 – 1.26)	1.18 (1.10 – 1.27)
Comparator	2 569 783	1249	1 185 939	10.53 (9.96 – 11.13)	Ref.	Ref.
Time-varying separate dose						
RZV Dose 1	3 265 790	1361	1 023 712	13.29 (12.61 – 14.02)	1.29 (1.20 – 1.40)	1.27 (1.17 – 1.37)
RZV Dose 2	2 476 525	651	579 445	11.23 (10.40 – 12.13)	1.13 (1.02 – 1.24)	1.12 (1.01 – 1.24)
Comparator	2 569 783	1249	1 185 939	10.53 (9.96 – 11.13)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; PMR, polymyalgia rheumatica; PY, persons-years; RZV, recombinant zoster vaccine.

14.4.4.3. COVID-19 sensitivity analysis

Table 57 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the PMR COVID-19 sensitivity analysis. Risk estimates were generated for RZV Dose 1 and RZV Dose 2. The estimates are the same as the IPTW-adjusted estimates.

Table 57 Risk estimates for COVID-19 sensitivity of the primary analysis of PMR with a 183-day- follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
COVID-19 analysis[a]						
RZV Dose 1	2 376 592	1355	999 723	13.55 (12.85 – 14.30)	1.17 (1.08 – 1.28)	1.18 (1.08 – 1.29)
Comparator	1 927 910	909	789 154	11.52 (10.79 – 12.29)	Ref.	Ref.
RZV Dose 2	1 721 309	756	669 724	11.29 (10.51 – 12.12)	0.97 (0.88 – 1.07)	0.95 (0.86 – 1.06)
Comparator	1 927 910	909	789 154	11.52 (10.79 – 12.29)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; COVID-19: coronavirus disease; HR, hazard ratio; IR, incidence rate; No., number; PMR, polymyalgia rheumatica; PY, persons-years; RZV, recombinant zoster vaccine.

a. 01 February 2020 included as a censoring event.

14.4.4.4. Dose-compliant sensitivity analysis

Table 58 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the PMR dose-compliant sensitivity analysis. This is a sensitivity analysis to the secondary analysis that incorporates a combined dose and a time-varying exposure. This sensitivity analysis includes the subset of the primary

analysis cohort with RZV Dose 1 and Dose 2 spacing 2 to 6 months apart, i.e., compliant with the US label. The IPTW-adjusted estimates were non-significant with the lower confidence intervals below or at 1.0, which differs from the crude and covariate adjusted models.

Table 58 Risk estimates for the dose-compliant sensitivity of the secondary analysis of PMR

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Subset of combined dose						
RZV Dose 1 and Dose 2	2 462 083	1884	1 745 141	10.80 (10.32 – 11.29)	1.08 (1.00 – 1.16)	1.09 (1.01 – 1.17)
Comparator	2 569 783	1249	1 185 939	10.53 (9.96 – 11.13)	Ref.	Ref.
Subset of time-varying separate dose						
RZV Dose 1	2 462 083	742	6 49 684	11.42 (10.63 – 12.27)	1.10 (1.01 – 1.21)	1.06 (0.96 – 1.17)
RZV Dose 2	2 426 320	631	561 862	11.23 (10.39 – 12.14)	1.15 (1.04 – 1.27)	1.15 (1.04 – 1.28)
Comparator	2 569 783	249	1 185 939	10.53 (9.96 – 11.13)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; PMR, polymyalgia rheumatica; PY, persons-years; RZV, recombinant zoster vaccine.

14.4.4.5. Supplemental cohort sensitivity analysis

Table 59 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the PMR in the supplemental cohort. This is a sensitivity analysis to the primary analysis where individuals are removed from the comparator arm if they receive RZV after their preventive care visit. The crude and covariate adjusted models produced results similar to the IPTW-adjusted estimates.

Table 59 Risk estimates for the primary analysis of PMR in the supplemental cohort

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Exclude comparators who received RZV						
RZV Dose 1	3 265 790	2012	1 609 938	12.50 (11.96 – 13.06)	1.01 (0.94 – 1.09)	1.00 (0.92 – 1.07)
Comparator	2 096 549	1249	1 008 662	12.38 (11.71 – 13.09)	Ref.	Ref.
RZV Dose 2	2 489 075	1297	1 226 359	10.58 (10.02 – 11.17)	0.86 (0.79 – 0.93)	0.83 (0.77 – 0.91)
Comparator	2 096 549	1249	1 008 662	12.38 (11.71 – 13.09)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; PMR, polymyalgia rheumatica; PY, persons-years; RZV, recombinant zoster vaccine.

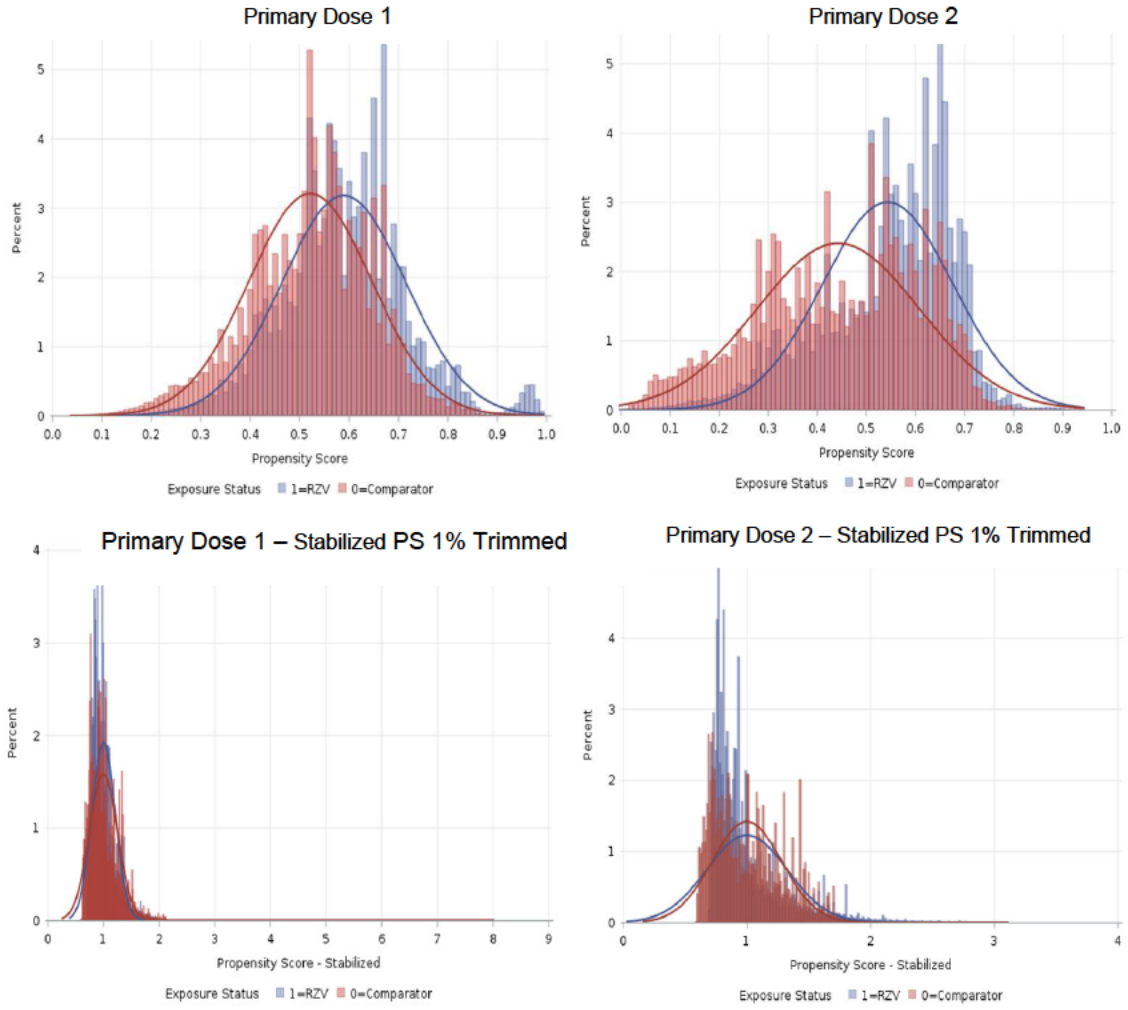
14.4.5. Propensity score distribution and weights for PMR

This section provides the PS distribution and associated weights for the analytic cohorts. This information is intended to complement the IPTW-adjusted analyses provided in the main text.

14.4.5.1. Primary analysis

The PS distributions for the primary analysis of RZV Dose 1 and Dose 2 are shown in Figure 26 below for both the common range distribution and the IPTW stabilized with 1% asymmetrical trimmed distribution. There was moderate overlap before applying the stabilized IPTW, which improved after applying the stabilized weight and 1% asymmetrical trim. The IPTW stabilized weight tempered the extreme weights and ensured covariate balance between RZV-exposed and the RZV-unvaccinated comparators.

Figure 26 PMR primary analysis propensity score distribution: Dose 1 and Dose 2



Primary Dose 1, primary analysis for RZV Dose 1; Primary Dose 2, primary analysis for RZV Dose 2.

Table 60 Propensity score weights for primary and secondary analyses

Primary Analysis Dose 1 and Secondary Analyses Combined and Time-Varying Dose				
Common Range		**Mean**	**Minimum**	**Maximum**
RZV-unvaccinated comparator	Original PS	0.5216226	0.0452829	0.9933187
	IPTW	2.275122	1.0474307	149.6707695
	IPTW Stabilized	1.00188	0.4612499	65.9094982
RZV-exposed	Original PS	0.5895467	0.0448311	0.9932222
	IPTW	1.787177	1.0068241	22.3059508
	IPTW Stabilized	1.00017	0.5634558	12.4832311
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5313731	0.2676127	0.9446972
	IPTW	2.2563545	1.3653978	18.0822608
	IPTW Stabilized	0.9994241	0.604786	8.0093123
RZV-exposed	Original PS	0.5774887	0.2659078	0.9461267
	IPTW	1.7957341	1.0569409	3.7607013
	IPTW Stabilized	1.0003361	0.5887821	2.0949455
Primary Analysis Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.4423838	0.0073416	0.9419535
	IPTW	1.9694812	1.0073959	17.2275776
	IPTW Stabilized	1.0004464	0.5117315	8.7511715
RZV-exposed	Original PS	0.5432864	0.0103947	0.9411963
	IPTW	2.0333826	1.0624776	96.2032938
	IPTW Stabilized	1.0004759	0.522766	47.334466
1%Trimmed				
RZV-unvaccinated comparator	Original PS	0.4652334	0.1621324	0.7435632
	IPTW	2.0139416	1.1935059	3.8995958
	IPTW Stabilized	1.0001605	0.592717	1.9366111
RZV-exposed	Original PS	0.5410173	0.1620692	0.7395988
	IPTW	1.9864442	1.3520844	6.1702054
	IPTW Stabilized	0.9999394	0.6806144	3.1059678

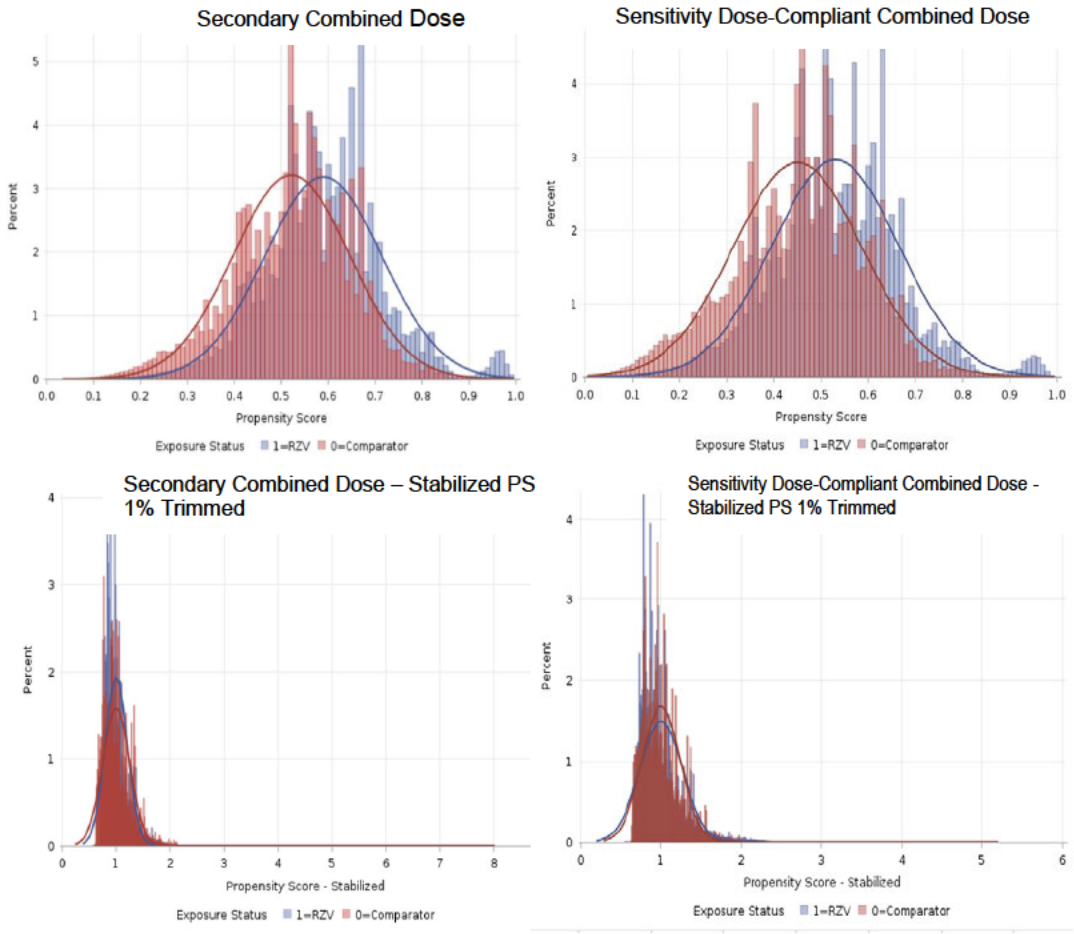
PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.4.5.2. Secondary analysis: combined dose estimate

The PS distributions for the secondary analysis with a single risk estimate for RZV Dose 1 and Dose 2, using a partly conditional survival model, are shown in Figure 27. The distributions are shown for both the common range distribution and the IPTW stabilized with 1% asymmetrical trimmed cohort for the secondary analysis. The PS distribution for the sensitivity analysis of the dose-compliant subsample (also based on the partly conditional model to obtain a single risk estimate) who received both doses 60 to 183 days apart is also shown.

There was moderate overlap before applying the stabilized IPTW, which improved after applying the stabilized weight and 1% asymmetrical trim. As in the primary analysis, the IPTW stabilized weight tempered the extreme weights and ensured covariate balance between RZV-exposed and the RZV-unvaccinated comparators.

Figure 27 PMR secondary and sensitivity analyses propensity score distribution: Combined Dose 1 and Dose 2

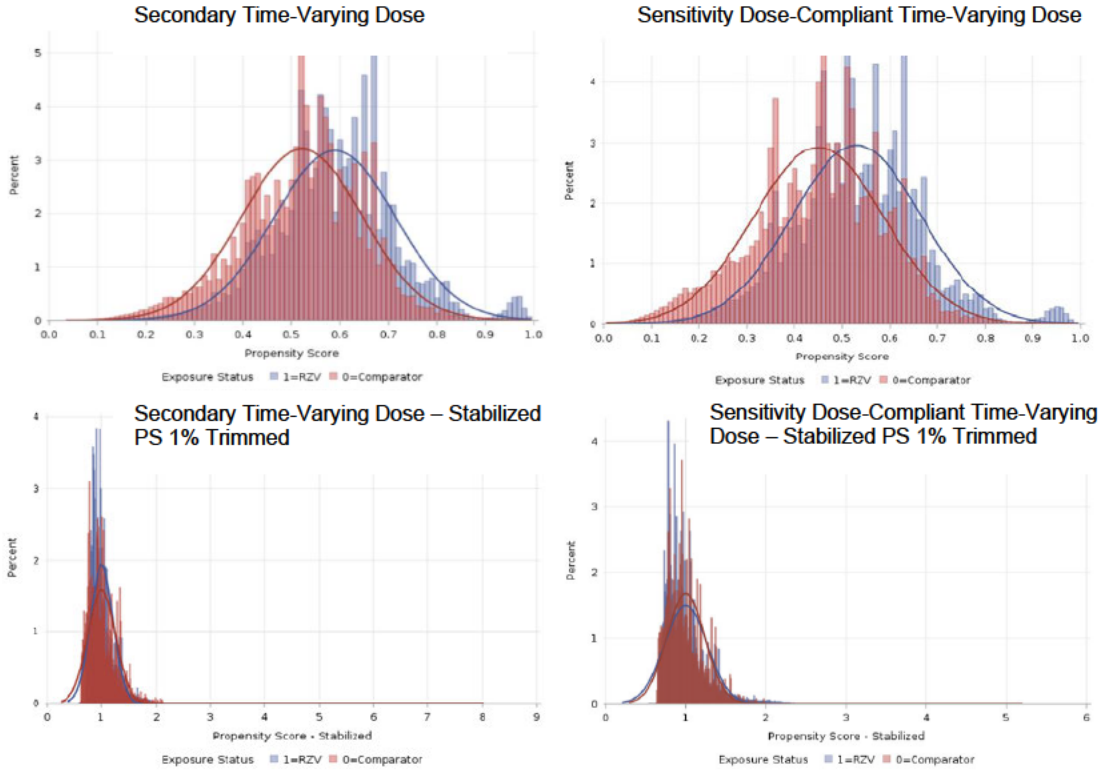


Note: Secondary analysis using a partly conditional survival model for a single risk estimate for both RZV doses; Sensitivity to the secondary analysis using a partly conditional survival model for a single risk estimate for both RZV doses in the dose-compliant subsample with 60 to 183 dose spacing.

14.4.5.3. Secondary analysis: Time-varying separate dose estimate

The PS distributions for the secondary analysis with a time-varying dose exposure for RZV Dose 1 and Dose 2 are shown in Figure 28. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for the secondary analysis and for the sensitivity analysis of the dose-compliant subsample who received both doses 60 to 183-days apart (based on the time-varying model) show good overlap with the 1% trimmed stabilized IPTW.

Figure 28 PMR secondary and sensitivity analyses propensity score distribution: Time-varying Dose 1 and Dose 2



Note: Secondary analysis using a time-varying Cox proportional hazards model with RZV doses as a time-varying covariate for a separate risk estimate for RZV Dose 1 and Dose 2; Sensitivity to the secondary analysis using time-varying Cox proportional hazards model for a separate risk estimate for RZV Dose 1 and Dose 2 in the dose-compliant subsample with 60 to 183 dose spacing.

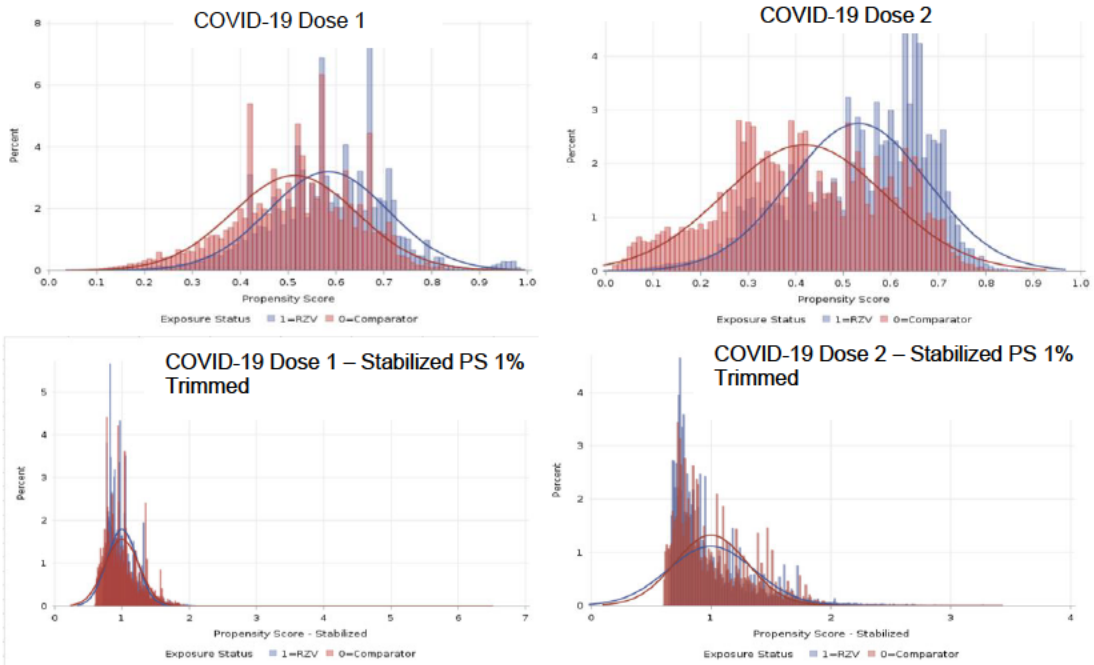
The PS weights for the primary analysis of RZV Dose 1 and Dose 2 and secondary analyses of the combined dose and time-varying dose are shown in Table 60 above for the RZV-exposed and the RZV-unvaccinated comparator. The weights for these analytic cohorts are the same as those for the primary Dose 1 cohort was used for the secondary analyses since the only difference was in the statistical analysis procedures.

The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. For Dose 1, the RZV-unvaccinated comparator had a large IPTW stabilized weight >65, which was reduced to 8 after 1% asymmetrical trimming and applying the IPTW stabilized weight. For Dose 2, the RZV-exposed had a large IPTW stabilized weight >47, which was reduced to 3 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The 1% trimming with stabilized weight avoided extreme weights influencing the analysis.

14.4.5.4. COVID-19 sensitivity analysis

The COVID-19 sensitivity analysis includes 01 February 2020, as a censoring event, which excluded events that occurred after this date. The PS distributions for the COVID-19 sensitivity analysis for Dose 1 and Dose 2 are shown in Figure 29 . The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for RZV Dose 1 and for RZV Dose 2 are provided to illustrate the overlap between the RZV-exposed and the RZV-unvaccinated comparators.

Figure 29 PMR COVID-19 sensitivity analysis propensity score distribution: Dose 1 and Dose 2



COVID-19 Dose 1, COVID-19 sensitivity analysis for RZV Dose 1; COVID-19 Dose 2, COVID-19 sensitivity analysis for Dose 2.

The PS weights for the COVID-19 sensitivity analysis to the primary analysis of separate RZV Dose 1 and RZV Dose 2 are shown in Table 61 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original P. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. The common range in the COVID-19 sensitivity analysis of Dose 1 for the RZV-unvaccinated comparator had an IPTW stabilized weight >46, which was reduced to 6.5 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The common range in the COVID-19 sensitivity analysis of Dose 2, the RZV-exposed had an IPTW stabilized weight >54, which was reduced to 3.43 after 1% trimming was applied.

Table 61 Propensity score weights for PMR COVID-19 sensitivity analysis to the primary analysis of separate Dose 1 and Dose 2 risk estimates

COVID-19 Sensitivity Analysis: Dose 1				
Common Range		**Mean**	**Minimum**	**Maximum**
RZV-unvaccinated comparator	Original PS	0.5131418	0.0436402	0.9902886
	IPTW	2.2353343	1.0456316	102.9716456
	IPTW Stabilized	1.0011567	0.4683152	46.1187173
RZV-exposed	Original PS	0.5837422	0.0434575	0.9901634
	IPTW	1.8124359	1.0099343	23.0110078
	IPTW Stabilized	1.0006861	0.5576071	12.7048875
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5233335	0.2441599	0.9309843
	IPTW	2.2258985	1.3230312	14.4894513
	IPTW Stabilized	0.9995307	0.5941018	6.5064297
RZV-exposed	Original PS	0.5734656	0.2389417	0.9334742
	IPTW	1.8157491	1.0712669	4.1851221
	IPTW Stabilized	1.0003943	0.5902188	2.3058099
COVID-19 Sensitivity Analysis: Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.417818	0.0062764	0.9244699
	IPTW	1.8933602	1.0063161	13.239761
	IPTW Stabilized	1.0002732	0.5316426	6.9946429
RZV-exposed	Original PS	0.5320365	0.0087298	0.9244517
	IPTW	2.1231396	1.0817223	114.5505057
	IPTW Stabilized	1.0014726	0.5102421	54.0328061
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4407214	0.1437045	0.7468073
	IPTW	1.9353921	1.1678211	3.9495615
	IPTW Stabilized	1.0000036	0.603405	2.0407107
RZV-exposed	Original PS	0.5288345	0.1407154	0.7463928
	IPTW	2.0693373	1.3397772	7.1065404
	IPTW Stabilized	1.0001252	0.6475237	3.4346408

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.4.5.5. Dose-compliant sensitivity analysis

The PS weights for the dose-compliant sensitivity analyses of the combined and time-varying RZV Dose 1 and Dose 2 are shown in Table 62 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. For the dose-compliant subsample, the RZV-unvaccinated comparator had a large IPTW stabilized weight >54, which was reduced to 5.19, and the RZV-exposed had a large IPTW stabilized weight >23, which was reduced to <3.

Table 62 Propensity score weights for PMR dose-compliant sensitivity analyses: Combined dose and time-varying dose

Sensitivity Analysis: Combined and Time-varying Dose with 60 to 183-dose spacing				
Common Range		**Mean**	**Minimum**	**Maximum**
RZV-unvaccinated comparator	Original PS	0.450176	0.0114683	0.9905591
	IPTW	1.9607906	1.0116014	105.921581
	IPTW Stabilized	1.0013782	0.5166261	54.0942807

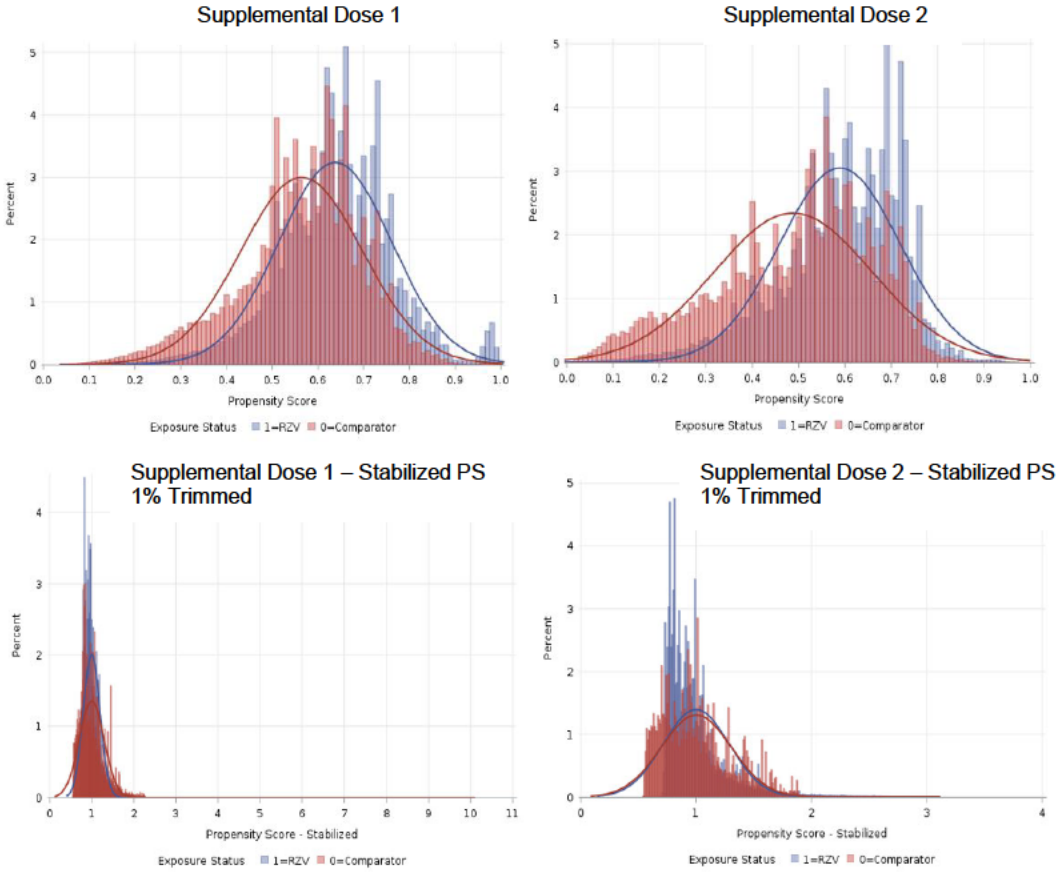
RZV-exposed	Original PS	0.5301324	0.0211552	0.9909596
	IPTW	2.044442	1.0091228	47.2697842
	IPTW Stabilized	1.000343	0.4937626	23.1290477
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4630058	0.1888116	0.901638
	IPTW	1.9584272	1.2327592	10.1665281
	IPTW Stabilized	0.9994733	0.6291324	5.1884358
RZV-exposed	Original PS	0.5174305	0.1888116	0.9048584
	IPTW	2.0433887	1.1051453	5.2962852
	IPTW Stabilized	1.0005557	0.54114	2.593353

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.4.5.6. Supplemental cohort: Dose 1 and Dose 2

The supplemental cohort that excludes from the comparator arm individuals who receive RZV in the future was performed as a sensitivity to the primary analysis, which was a separate analysis for RZV Dose 1 and Dose 2. The PS distributions for the two supplemental analyses are shown in Figure 30. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for RZV Dose 1 (i.e., Supp 1) and for RZV Dose 2 (i.e., Supp 2) are provided to illustrate the overlap between the RZV-exposed and the RZV-unvaccinated comparators.

Figure 30 PMR supplemental cohort propensity score distribution: Dose 1 and Dose 2



Supplemental Dose 1, supplemental cohort for RZV Dose 1; Supplemental Dose 2, supplemental cohort for Dose 2.

The PS weights for the supplemental cohort of RZV Dose 1 and RZV Dose 2 are shown in Table 63 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. The common range in the supplementary analysis of Dose 1 for the RZV-unvaccinated comparator had an IPTW stabilized weight >100, which was reduced to 10 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The common range in the supplementary analysis of Dose 2, the RZV-exposed had an IPTW stabilized weight >55, which was reduced to approximately 3 after 1% trimming was applied.

Table 63 Propensity score weights for PMR supplemental cohort: Dose 1 and Dose 2

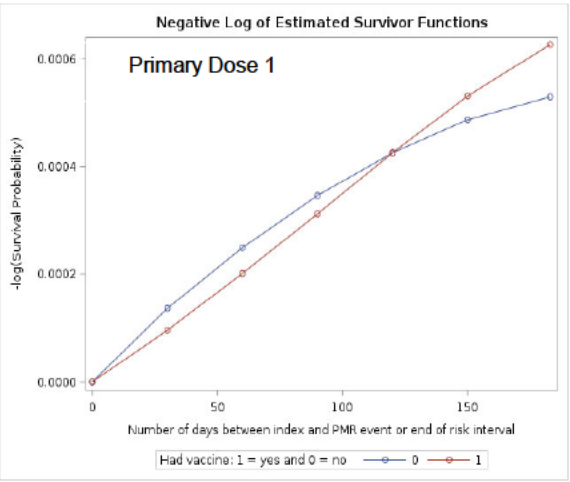
Supplemental Cohort: Dose 1				
Common Range		**Mean**	**Minimum**	**Maximum**
RZV-unvaccinated comparator	Original PS	0.5642225	0.0404643	0.9964202
	IPTW	2.5682968	1.0421707	279.3449218
	IPTW Stabilized	1.0041394	0.4074625	109.2168298
RZV-exposed	Original PS	0.6377871	0.0510805	0.9963897
	IPTW	1.6419554	1.0036234	19.5769264
	IPTW Stabilized	0.9999922	0.6112319	11.9228411
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.577425	0.2802169	0.9611824
	IPTW	2.5513396	1.3893074	25.7615347
	IPTW Stabilized	0.9999585	0.5445178	10.0968393
RZV-exposed	Original PS	0.6278147	0.2761201	0.9644974
	IPTW	1.6446934	1.0368094	3.6216122
	IPTW Stabilized	1.000081	0.6304478	2.2021767
Supplemental Cohort: Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.4879045	0.0076897	0.9708891
	IPTW	2.1901782	1.0077493	34.3513597
	IPTW Stabilized	1.0013434	0.4607402	15.7053462
RZV-exposed	Original PS	0.5890455	0.009723	0.9697409
	IPTW	1.8422397	1.0312033	102.8487395
	IPTW Stabilized	0.9999728	0.55974	55.8265817
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5141836	0.1780887	0.8190881
	IPTW	2.2458793	1.2166763	5.5275517
	IPTW Stabilized	1.0007386	0.5421373	2.4630149
RZV-exposed	Original PS	0.5867428	0.178161	0.819896
	IPTW	1.8024544	1.2196669	5.6129002
	IPTW Stabilized	0.999301	0.676197	3.111855

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.4.6. Assessment of the proportional hazards assumption

The assumption of constant hazards was assessed for the primary, secondary, and sensitivity analyses of PMR. To assess whether the assumption was violated, we plotted the log(-log(survival)) by the log(event time). The figures that follow illustrate the survival function for each analytical cohort. The assumption of proportional hazards was violated when the lines crossed. To correct for the non-proportionality, we conducted a piecewise Cox regression where a time-dependent coefficient was included in the model. The results for all proportional hazards adjusted analyses are provided in the main text of this study report.

Figure 31 Survivor function plot to assess the proportional hazards assumption for the PMR primary analyses



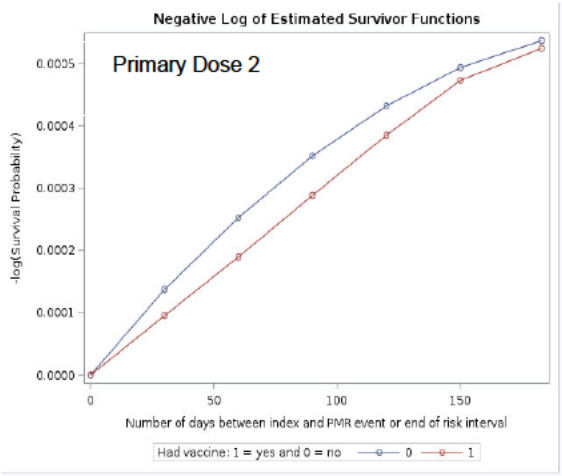
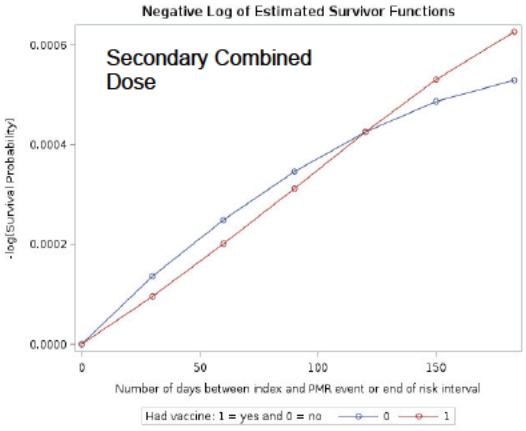


Figure 32 Survivor function plot to assess the proportional hazards assumption for the PMR secondary analyses – combined dose and time-varying dose



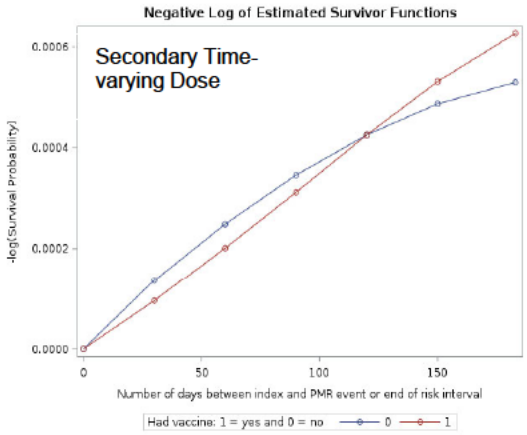
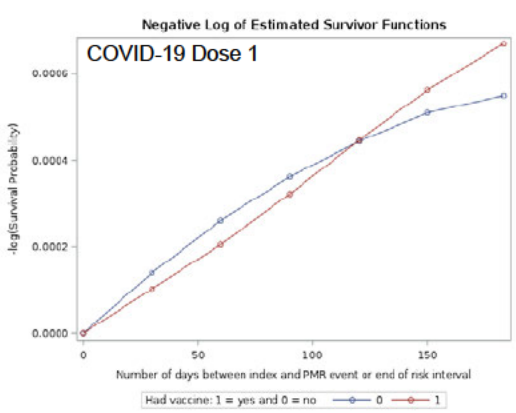


Figure 33 Survivor function plot to assess the proportional hazards assumption for the PMR sensitivity analyses – COVID-19



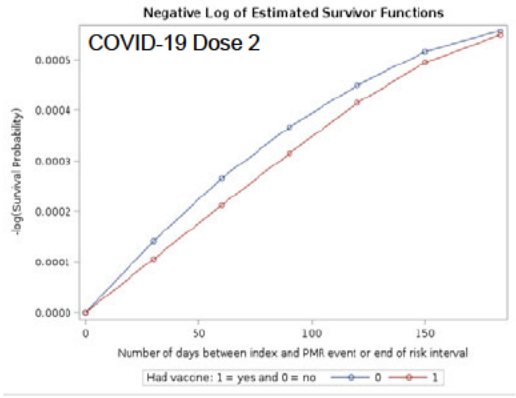
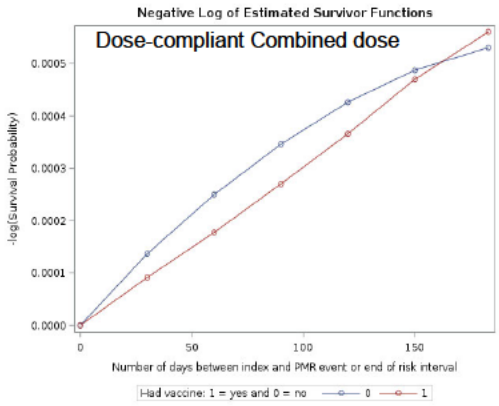


Figure 34 Survivor function plot to assess the proportional hazards assumption for the PMR sensitivity analyses – dose-compliant



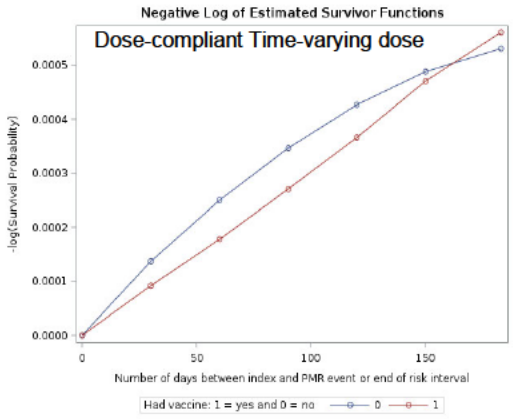
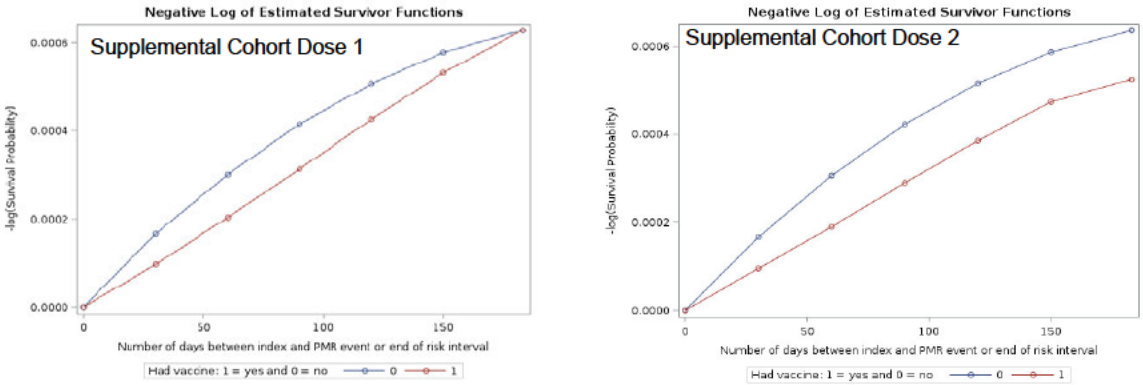


Figure 35 Survivor function plot to assess the proportional hazards assumption for the PMR supplemental cohort



14.4.7. Quantitative Bias Analysis

The quantitative bias analysis for the primary analysis of Dose 1 suggests that an unmeasured confounder with an association on the risk ratio scale of 1.5 with the outcome and 1.5 with the exposure would explain away the effect (Table 64).

Table 64 Bounds on IPTW corrected HR estimates and 95% CI for unmeasured confounding

		Strength of the unmeasured confounder with the outcome					
Strength of the unmeasured confounder with the exposure		**1.2**	**1.3**	**1.5**	**1.8**	**2**	**2.5**
	1.2	1.16 (1.08, 1.25)	1.15 (1.07, 1.23)	1.13 (1.05, 1.21)	1.10 (1.03, 1.19)	1.09 (1.02, 1.18)	1.07 (1.00, 1.16)
	1.3	1.15 (1.07, 1.23)	1.13 (1.05, 1.22)	1.10 (1.02, 1.19)	1.07 (0.99, 1.15)	1.06 (0.98, 1.14)	1.03 (0.95, 1.11)
	1.5	1.13 (1.05, 1.21)	1.10 (1.02, 1.19)	1.06 (0.98, 1.14)	1.02 (0.94, 1.09)	0.99 (0.92, 1.07)	0.95 (0.89, 1.03)
	1.8	1.10 (1.03, 1.19)	1.07 (0.99, 1.15)	1.02 (0.94, 1.09)	0.96 (0.89, 1.03)	0.93 (0.86, 1.00)	0.87 (0.81, 0.94)
	2	1.09 (1.02, 1.18)	1.06 (0.98, 1.14)	0.99 (0.92, 1.07)	0.93 (0.86, 1.00)	0.89 (0.83, 0.96)	0.84 (0.78, 0.90)
	2.5	1.07 (1.00, 1.16)	1.03 (0.95, 1.11)	0.95 (0.89, 1.03)	0.87 (0.81, 0.94)	0.84 (0.78, 0.90)	0.76 (0.71, 0.82)
	3	1.06 (0.98, 1.14)	1.01 (0.94, 1.09)	0.93 (0.86, 1.00)	0.84 (0.78, 0.90)	0.80 (0.74, 0.86)	0.72 (0.66, 0.77)
	4	1.04 (0.97, 1.12)	0.99 (0.92, 1.06)	0.89 (0.83, 0.96)	0.80 (0.74, 0.86)	0.75 (0.69, 0.80)	0.66 (0.61, 0.71)
	5	1.03 (0.96, 1.11)	0.97 (0.90, 1.05)	0.87 (0.81, 0.94)	0.77 (0.71, 0.83)	0.72 (0.66, 0.77)	0.62 (0.58, 0.67)
	6	1.03 (0.95, 1.11)	0.96 (0.89, 1.04)	0.86 (0.80, 0.93)	0.75 (0.70, 0.81)	0.70 (0.65, 0.75)	0.60 (0.55, 0.64)
	8	1.02 (0.95, 1.10)	0.95 (0.88, 1.02)	0.85 (0.78, 0.91)	0.73 (0.68, 0.78)	0.67 (0.62, 0.72)	0.57 (0.53, 0.61)
	10	1.01 (0.94, 1.09)	0.95 (0.88, 1.02)	0.84 (0.78, 0.90)	0.72 (0.66, 0.77)	0.66 (0.61, 0.71)	0.55 (0.51, 0.59)
		3	**4**	**5**	**6**	**8**	**10**
	1.2	1.06 (0.98, 1.14)	1.04 (0.97, 1.12)	1.03 (0.96, 1.11)	1.03 (0.95, 1.11)	1.02 (0.95, 1.10)	1.01 (0.94, 1.09)
	1.3	1.01 (0.94, 1.09)	0.99 (0.92, 1.06)	0.97 (0.90, 1.05)	0.96 (0.89, 1.04)	0.95 (0.88, 1.02)	0.95 (0.88, 1.02)
	1.5	0.93 (0.86, 1.00)	0.89 (0.83, 0.96)	0.87 (0.81, 0.94)	0.86 (0.80, 0.93)	0.85 (0.78, 0.91)	0.84 (0.78, 0.90)
	1.8	0.84 (0.78, 0.90)	0.80 (0.74, 0.86)	0.77 (0.71, 0.83)	0.75 (0.70, 0.81)	0.73 (0.68, 0.78)	0.72 (0.66, 0.77)
	2	0.80 (0.74, 0.86)	0.75 (0.69, 0.80)	0.72 (0.66, 0.77)	0.70 (0.65, 0.75)	0.67 (0.62, 0.72)	0.66 (0.61, 0.71)
	2.5	0.72 (0.66, 0.77)	0.66 (0.61, 0.71)	0.62 (0.58, 0.67)	0.60 (0.55, 0.64)	0.57 (0.53, 0.61)	0.55 (0.51, 0.59)
	3	0.66 (0.62, 0.71)	0.60 (0.55, 0.64)	0.56 (0.52, 0.60)	0.53 (0.49, 0.57)	0.50 (0.46, 0.54)	0.48 (0.44, 0.51)
	4	0.60 (0.55, 0.64)	0.52 (0.48, 0.56)	0.48 (0.44, 0.51)	0.45 (0.42, 0.48)	0.41 (0.38, 0.44)	0.39 (0.36, 0.42)
	5	0.56 (0.52, 0.60)	0.48 (0.44, 0.51)	0.43 (0.40, 0.46)	0.40 (0.37, 0.43)	0.36 (0.33, 0.39)	0.33 (0.31, 0.36)
	6	0.53 (0.49, 0.57)	0.45 (0.42, 0.48)	0.40 (0.37, 0.43)	0.36 (0.34, 0.39)	0.32 (0.30, 0.35)	0.30 (0.28, 0.32)
	8	0.50 (0.46, 0.54)	0.41 (0.38, 0.44)	0.36 (0.33, 0.39)	0.32 (0.30, 0.35)	0.28 (0.26, 0.30)	0.25 (0.24, 0.27)
	10	0.48 (0.44, 0.51)	0.39 (0.36, 0.42)	0.33 (0.31, 0.36)	0.30 (0.28, 0.32)	0.25 (0.24, 0.27)	0.23 (0.21, 0.24)

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability weighting.

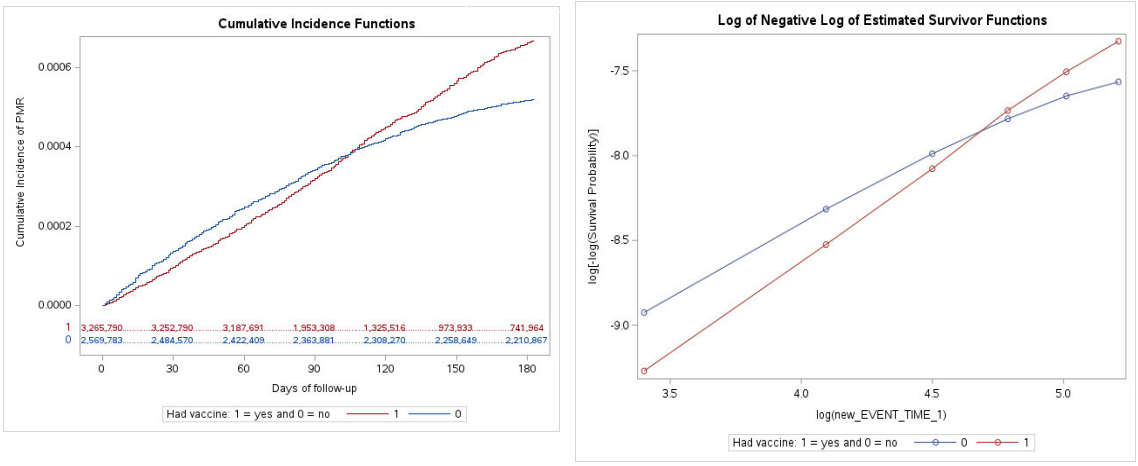
14.4.8. PMR post-hoc analyses

Several post-hoc analyses were conducted for the primary analyses for PMR. The survival probability function was examined to assess the impact of censoring RZV Dose 1 at receipt of Dose 2, the age-stratified and the RZV index year-stratified analyses. The following figures show the cumulative incidence function along with the survivor probability function.

14.4.8.1. Censoring Dose 1 at receipt of Dose 2

Figure 36 PMR: Cumulative incidence function and survival probability function with censoring of Dose 1 at Dose 2 in the primary analysis

PMR



14.4.8.2. Age-stratified risk estimates for the primary analysis of Dose 1

The crude and IPTW-weighted risk were assessed by the age-strata, as seen in Table 65.

Table 65 Age-stratified PMR risk estimates for the primary analysis of Dose 1

Comparator cohort	Crude HR (95% CI)	PS IPTW Adj. HR (95% CI)
Primary Analysis		
RZV Dose 1	1.19 (1.11, 1.28)	1.19 (1.11, 1.28)
Comparator	Ref.	Ref.
Age 65 – 74 years-old		
RZV Dose 1	1.04 (0.93, 1.16)	1.01 (0.90, 1.13)
Comparator	Ref.	Ref.
Age ≥75 years-old		
RZV Dose 1	1.36 (1.24, 1.49)	1.36 (1.23, 1.50)

Comparator cohort	Crude HR (95% CI)	PS IPTW Adj. HR (95% CI)
Comparator	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; PMR, polymyalgia rheumatica; RZV, recombinant zoster vaccine.

Figure 37 Cumulative incidence function and survival probability function for the primary Dose 1 analysis of PMR: Age 65 – 74 years-old

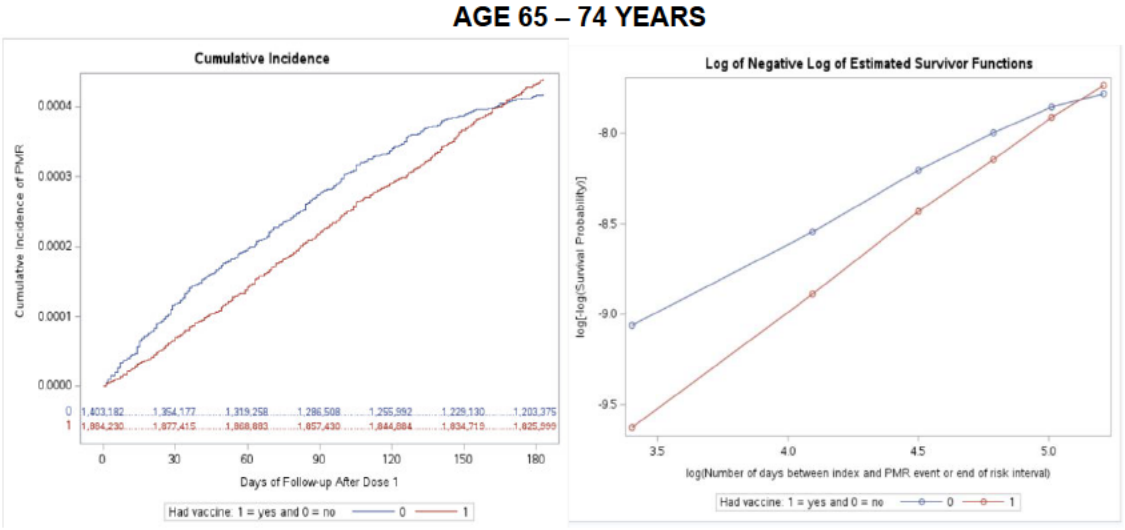
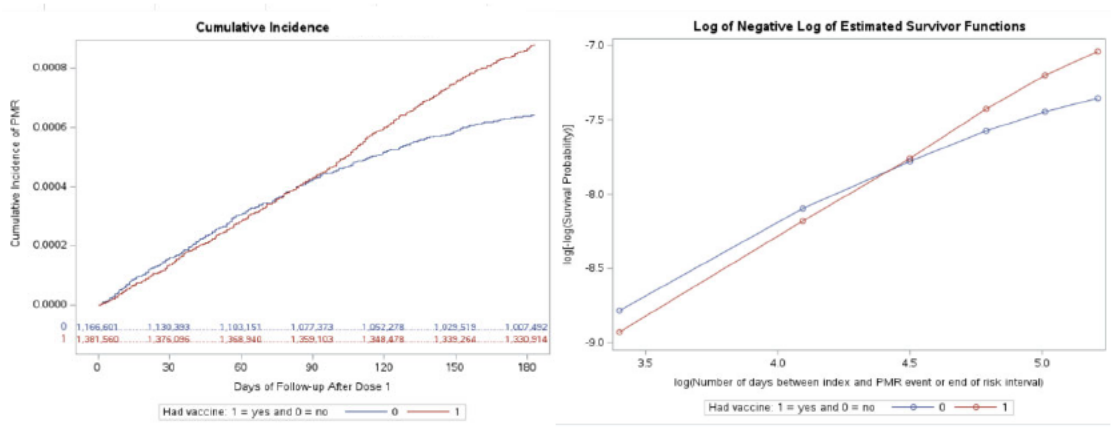
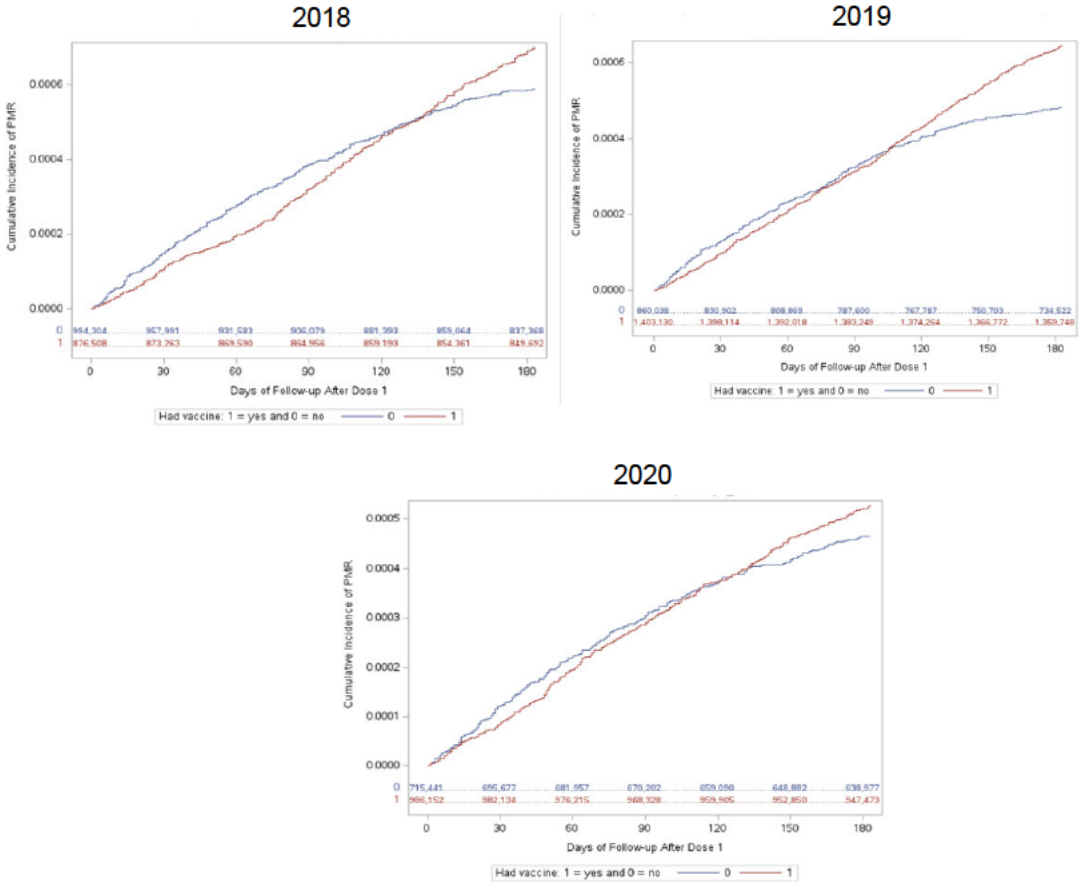


Figure 38 Cumulative incidence function and survival probability function for the primary Dose 1 analysis of PMR: Age ≥75 years-old



14.4.8.3. Index year-stratified cumulative incidence function of Dose 1

Figure 39 Cumulative incidence of PMR following Dose 1 stratified by index year



14.5. GCA

14.5.1. Baseline characteristics of the primary analytic cohort

Table 66 below displays the baseline characteristics of the cohort for the primary analysis. Table 67 shows the baseline characteristics stratified by the number of doses and the dose spacing. The stratification by number of doses received reflects how many RZV doses a participant received. Of the 3 288 846 participants in the primary cohort who received Dose 1, 484 736 received only Dose 1 and 2 804 110 received both RZV Dose 1 and Dose 2. A higher proportion of those who only received RZV Dose 1 were diagnosed with comorbidities, had 2 or more hospitalization or ED visits and received concomitant vaccines. The subset of the 2 804 110 who received two RZV doses 28 to 60 days apart included 122 702 adults and those who received the two doses >60 days apart included 2 681 408 adults (Table 67). The 28 to 60-day dose spacing aligns with the European label, whereas in the US it is 2 to 6 months dose spacing. There were no meaningful differences in the baseline covariates between those who had the doses 28 to 60 days apart versus those who had >60 days between doses.

Table 66 Baseline demographic and health characteristics of the GCA analytic cohorts by RZV exposure

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Number of unique participants	3 288 846	2 585 975		3 084 667	2 448 677	
Demographics						
Age at Index Date, Mean (SD)	74.36 (6.34)	75.19 (7.15)	-0.1232	74.55 (6.54)	74.67 (6.69)	-0.0180
Age categories						
65-69	857 091 (26.06)	660 714 (25.55)	0.0117	805 349 (26.11)	638 033 (26.06)	0.0012
70-74	1 035 264 (31.48)	747 529 (28.91)	0.0560	943 107 (30.57)	748 080 (30.55)	0.0005
75-79	726 177 (22.08)	525 566 (20.32)	0.0430	658 817 (21.36)	523 295 (21.37)	-0.0003
80-84	405 477 (12.33)	335 764 (12.98)	-0.0197	389 823 (12.64)	310 116 (12.66)	-0.0008
85+	264 837 (8.05)	316 402 (12.24)	-0.1389	287 571 (9.32)	229 152 (9.36)	-0.0012
Sex						
Male	1 352 726 (41.13)	943 095 (36.47)	0.0958	1 206 671 (39.12)	961 050 (39.25)	-0.0027
Female	1 936 120 (58.87)	1 642 880 (63.53)	-0.0958	1 877 997 (60.88)	1 487 628 (60.75)	0.0027
Race						
American Indian/Alaskan Native	7 820 (0.24)	6 193 (0.24)	-0.0004	7 461 (0.24)	5 904 (0.24)	0.0002
Asian	81 270 (2.47)	58 759 (2.27)	0.0131	74 978 (2.43)	60 006 (2.45)	-0.0013
Black or African American	79 095 (2.40)	145 382 (5.62)	-0.1645	86 137 (2.79)	68 402 (2.79)	-0.0001
White	2 926 235 (88.97)	2 232 768 (86.34)	0.0801	2 745 861 (89.02)	2 178 915 (88.98)	0.0011
Hispanic	23 049 (0.70)	37 556 (1.45)	-0.0729	24 356 (0.79)	19 249 (0.79)	0.0004
Unknown	108 730 (3.31)	64 749 (2.50)	0.0478	90 927 (2.95)	72 309 (2.95)	0.0003
Other	62 647 (1.90)	40 568 (1.57)	0.0257	54 948 (1.78)	43 893 (1.79)	-0.0008
Parts A, B, D Continuous enrollment[c]	3 288 846 (100.00)	2 585 975 (100.00)	0.0000	3 084 667 (100.00)	2 448 677 (100.00)	0.0000
Year of Index Date						
2018	883 174 (26.85)	1 001 056 (38.71)	-0.2546	985 029 (31.93)	785 103 (32.06)	-0.0028
2019	1 412 910 (42.96)	865 366 (33.46)	0.1964	1 194 645 (38.73)	947 286 (38.69)	0.0009
2020	992 762 (30.19)	719 553 (27.83)	0.0520	904 994 (29.34)	716 288 (29.25)	0.0019
Medical History[d]						
Diabetes mellitus	799 428 (24.31)	715 722 (27.68)	-0.0769	778 696 (25.24)	618 092 (25.24)	0.0001
Chronic kidney disease	677 543 (20.60)	601 089 (23.24)	-0.0639	650 687 (21.09)	516 414 (21.09)	0.0001
Chronic lung disease[e]	399 317 (12.14)	375 946 (14.54)	-0.0705	395 948 (12.84)	313 977 (12.82)	0.0004

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Congestive heart failure	228 646 (6.95)	244 699 (9.46)	-0.0916	230 279 (7.47)	182 679 (7.46)	0.0002
Ischemic heart disease	698 649 (21.24)	578 389 (22.37)	-0.0272	655 777 (21.26)	520 629 (21.26)	-0.0001
Dementia	110 204 (3.35)	155 520 (6.01)	-0.1263	114 879 (3.72)	91 315 (3.73)	-0.0003
Chronic liver disease	182 515 (5.55)	146 884 (5.68)	-0.0057	170 742 (5.54)	135 371 (5.53)	0.0003
Stroke/TIA	202 178 (6.15)	187 937 (7.27)	-0.0448	195 085 (6.32)	154 912 (6.33)	-0.0001
Immunocompromised Conditions						
Organ transplant	7 725 (0.23)	7 046 (0.27)	-0.0075	7 502 (0.24)	5 954 (0.24)	0.0000
Hematopoietic cell transplant	4 690 (0.14)	2 444 (0.09)	0.0140	3 545 (0.11)	2 860 (0.12)	-0.0006
Hematologic or solid malignancy w/recent receipt of chemotherapy	26 569 (0.81)	28 703 (1.11)	-0.0310	27 729 (0.90)	22 024 (0.90)	-0.0001
HIV infection	4 810 (0.15)	2 977 (0.12)	0.0086	3 873 (0.13)	3 086 (0.13)	-0.0001
Rheumatoid arthritis	100 467 (3.05)	83 299 (3.22)	-0.0095	95 153 (3.08)	75 456 (3.08)	0.0002
IBD - Crohn's disease	17 400 (0.53)	11 637 (0.45)	0.0113	15 111 (0.49)	11 993 (0.49)	0.0000
IBD - Colitis	31 097 (0.95)	20 273 (0.78)	0.0175	26 615 (0.86)	21 122 (0.86)	0.0000
Lupus	12 246 (0.37)	10 585 (0.41)	-0.0059	11 834 (0.38)	9 368 (0.38)	0.0002
Multiple sclerosis	7 994 (0.24)	6 231 (0.24)	0.0004	7 432 (0.24)	5 895 (0.24)	0.0000
Psoriasis/Psoriatic arthritis	72 388 (2.20)	47 594 (1.84)	0.0256	63 082 (2.05)	50 152 (2.05)	-0.0002
Service Use History[d]						
≥1 dermatology visit	117 291 (3.57)	56 099 (2.17)	0.0838	88 265 (2.86)	70 419 (2.88)	-0.0009
≥1 optometry/ ophthalmology visit	1 868 167 (56.80)	1 239 500 (47.93)	0.1783	1 632 680 (52.93)	1 297 661 (52.99)	-0.0013
Number of hospitalizations						
0	2 934 874 (89.24)	2 232 071 (86.31)	0.0893	2 735 751 (88.69)	2 171 980 (88.70)	-0.0004
1	267 966 (8.15)	245 456 (9.49)	-0.0474	262 138 (8.50)	207 837 (8.49)	0.0004
2 or more	86 006 (2.62)	108 448 (4.19)	-0.0871	86 778 (2.81)	68 860 (2.81)	0.0001
Number of ED visits						
0	2 689 692 (81.78)	2 014 213 (77.89)	0.0971	2 493 108 (80.82)	1 979 424 (80.84)	-0.0004
1	445 321 (13.54)	366 194 (14.16)	-0.0180	427 040 (13.84)	338 704 (13.83)	0.0003
2 or more	153 833 (4.68)	205 568 (7.95)	-0.1348	164 519 (5.33)	130 550 (5.33)	0.0001
Durable medical equipment	932 931 (28.37)	746 966 (28.89)	-0.0115	866 011 (28.07)	687 328 (28.07)	0.0001
Hospice care	1 885 (0.06)	5 940 (0.23)	-0.0456	1 143 (0.04)	910 (0.04)	-0.0001
Home health care	190 092 (5.78)	229 951 (8.89)	-0.1196	195 759 (6.35)	155 349 (6.34)	0.0001
Skilled nursing facility care	52 607 (1.60)	80 906 (3.13)	-0.1008	55 287 (1.79)	43 973 (1.80)	-0.0003

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Concomitant Vaccine Use[f]						
Influenza	408 534 (12.42)	155 402 (6.01)	0.2231	238 622 (7.74)	188 294 (7.69)	0.0017
Pneumococcal	144 830 (4.40)	128 255 (4.96)	-0.0263	142 379 (4.62)	113 494 (4.63)	-0.0009
Tetanus- Diphtheria- Pertussis (Tdap)	67 788 (2.06)	3 404 (0.13)	0.1861	104 (0.00)	83 (0.00)	0.0000

COPD, chronic obstructive pulmonary disease; ED, emergency department; GCA, giant cell arteritis; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IPTW, inverse probability of treatment weighting; RZV, recombinant zoster vaccine; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack.
Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data. Index date is the RZV Dose 1 date in the exposed group and preventive visit date in the comparator group.

a. The N for the RZV-exposed cohort is shown for individuals who received at least one RZV dose, representing the Dose 1 analytical cohort.
b. RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening.
c. Allows one calendar month gap in enrolment; measured in the year preceding the index date.
d. Measured in the year prior to the index date.
e. Chronic lung disease includes COPD and bronchiectasis.
f. Measured on the index date.

Table 67 Baseline demographic and health characteristics of GCA analytic cohort by number of doses and dose spacing

Descriptive Characteristic	RZV Dose 1 only	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
Number of unique participants	484 736	2 804 110	122 702	2 681 408
Demographics				
Age at Index Date, Mean (SD)	75.01 (6.94)	74.24 (6.22)	74.91 (6.40)	74.21 (6.21)
Age categories				
65-69	123 373 (25.45)	733 718 (26.17)	28 379 (23.13)	705 339 (26.30)
70-74	140 145 (28.91)	895 119 (31.92)	37 066 (30.21)	858 053 (32.00)
75-79	102 210 (21.09)	623 967 (22.25)	28 777 (23.45)	595 190 (22.20)
80-84	64 583 (13.32)	340 894 (12.16)	17 499 (14.26)	323 395 (12.06)
85+	54 425 (11.23)	210 412 (7.50)	10 981 (8.95)	199 431 (7.44)
Sex				
Male	199 810 (41.22)	1 152 916 (41.12)	50 939 (41.51)	1 101 977 (41.10)
Female	284 926 (58.78)	1 651 194 (58.88)	71 763 (58.49)	1 579 431 (58.90)
Race				
American Indian/Alaskan Native	3 281 (0.68)	4 539 (0.16)	255 (0.21)	4 284 (0.16)
Asian	16 793 (3.46)	64 477 (2.30)	3 617 (2.95)	60 860 (2.27)
Black or African American	20 791 (4.29)	58 304 (2.08)	4 272 (3.48)	54 032 (2.02)
White	410 132 (84.61)	2 516 103 (89.73)	107 889 (87.93)	2 408 214 (89.81)
Hispanic	9 294 (1.92)	13 755 (0.49)	922 (0.75)	12 833 (0.48)
Unknown	14 197 (2.93)	94 533 (3.37)	3 489 (2.84)	91 044 (3.40)
Other	10 248 (2.11)	52 399 (1.87)	2 258 (1.84)	50 141 (1.87)
Parts A, B, D Continuous enrollment [a]	484 736 (100.00)	2 804 110 (100.00)	122 702 (100.00)	2 681 408 (100.00)
Year of Index Date				
2018	122 444 (25.26)	760 730 (27.13)	23 550 (19.19)	737 180 (27.49)
2019	193 140 (39.84)	1 219 770 (43.50)	55 739 (45.43)	1 164 031 (43.41)
2020	169 152 (34.90)	823 610 (29.37)	43 413 (35.38)	780 197 (29.10)

Descriptive Characteristic	RZV Dose 1 only	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
Medical History[b]				
Diabetes mellitus	136 491 (28.16)	662 937 (23.64)	31 950 (26.04)	630 987 (23.53)
Chronic kidney disease	118 134 (24.37)	559 409 (19.95)	27 572 (22.47)	531 837 (19.83)
Chronic lung disease[c]	71 720 (14.80)	327 597 (11.68)	15 763 (12.85)	311 834 (11.63)
Congestive heart failure	47 084 (9.71)	181 562 (6.47)	9 132 (7.44)	172 430 (6.43)
Ischemic heart disease	115 800 (23.89)	582 849 (20.79)	27 499 (22.41)	555 350 (20.71)
Dementia	28 811 (5.94)	81 393 (2.90)	4 437 (3.62)	76 956 (2.87)
Chronic liver disease	29 929 (6.17)	152 586 (5.44)	6 968 (5.68)	145 618 (5.43)
Stroke/TIA	36 297 (7.49)	165 881 (5.92)	7 629 (6.22)	158 252 (5.90)
Immunocompromised Conditions				
Organ transplant	1 571 (0.32)	6 154 (0.22)	321 (0.26)	5 833 (0.22)
Hematopoietic stem cell transplant	918 (0.19)	3 772 (0.13)	286 (0.23)	3 486 (0.13)
Hematologic or solid malignancy w/recent receipt of chemotherapy	5 153 (1.06)	21 416 (0.76)	1 112 (0.91)	20 304 (0.76)
HIV infection	1 069 (0.22)	3 741 (0.13)	227 (0.19)	3 514 (0.13)
Rheumatoid Arthritis	16 490 (3.40)	83 977 (2.99)	4 032 (3.29)	79 945 (2.98)
IBD - Crohn's disease	2 395 (0.49)	15 005 (0.54)	648 (0.53)	14 357 (0.54)
IBD - Colitis	4 312 (0.89)	26 785 (0.96)	1 166 (0.95)	25 619 (0.96)
Lupus	2 131 (0.44)	10 115 (0.36)	518 (0.42)	9 597 (0.36)
Multiple Sclerosis	1 214 (0.25)	6 780 (0.24)	318 (0.26)	6 462 (0.24)
Psoriasis/Psoriatic Arthritis	10 095 (2.08)	62 293 (2.22)	2 641 (2.15)	59 652 (2.22)
Service Use History[b]				
≥1 dermatology visit	13 302 (2.74)	103 989 (3.71)	4 039 (3.29)	99 950 (3.73)
≥1 optometry/ ophthalmology visit	248 897 (51.35)	1 619 270 (57.75)	69 844 (56.92)	1 549 426 (57.78)
Number of hospitalizations				
0	420 354 (86.72)	2 514 520 (89.67)	109 029 (88.86)	2 405 491 (89.71)
1	45 609 (9.41)	222 357 (7.93)	10 432 (8.50)	211 925 (7.90)
2 or more	18 773 (3.87)	67 233 (2.40)	3 241 (2.64)	63 992 (2.39)
Number of ED visits				

Descriptive Characteristic	RZV Dose 1 only	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
0	378 569 (78.10)	2 311 123 (82.42)	99 819 (81.35)	2 211 304 (82.47)
1	74 028 (15.27)	371 293 (13.24)	16 889 (13.76)	354 404 (13.22)
2 or more	32 139 (6.63)	121 694 (4.34)	5 994 (4.89)	115 700 (4.31)
Durable medical equipment	146 918 (30.31)	786 013 (28.03)	35 884 (29.24)	750 129 (27.98)
Hospice care	902 (0.19)	983 (0.04)	74 (0.06)	909 (0.03)
Home health care	41 664 (8.60)	148 428 (5.29)	7 282 (5.93)	141 146 (5.26)
Skilled nursing facility care	12 695 (2.62)	39 912 (1.42)	2 043 (1.67)	37 869 (1.41)
Concomitant Vaccine Use[d]				
Influenza	77 370 (15.96)	331 164 (11.81)	17 047 (13.89)	314 117 (11.71)
Pneumococcal	37 047 (7.64)	107 783 (3.84)	5 262 (4.29)	102 521 (3.82)
Tetanus-Diphtheria-Pertussis	15 192 (3.13)	52 596 (1.88)	2 657 (2.17)	49 939 (1.86)

COPD, chronic obstructive pulmonary disease; ED, emergency department; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; GCA, giant cell arteritis; RZV, recombinant zoster vaccine; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data.

a. Allows one calendar month gap in enrolment; measured in the year preceding the index date.
b. Measured in the year prior to the index date. Index date is the RZV Dose 1 date in the exposed group.
c. Chronic lung disease includes COPD and bronchiectasis.
d. Measured on the index date.

14.5.2. Baseline characteristics of the Supplemental cohort

A supplemental cohort for GCA, which excluded from the comparator arm any participant that received at least one dose of RZV, was used to conduct a sensitivity analysis to the primary separate dose analysis. The RZV-exposed included 3 288 846 and the RZV-unvaccinated comparator included 2 108 742 participants.

Table 68 displays the baseline characteristics in each group along with the corresponding SMDs for the unweighted and the weighted sample in the supplemental cohort. The baseline characteristics with an SMD >0.10 before weighting were balanced after weighting. All covariates were balanced with SMDs around zero, suggesting that weighting worked well to ensure covariate balance.

Table 68 Baseline demographic and health characteristics of the GCA supplemental cohort: before and after IPTW weighting

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Number of unique participants	3 288 846	2 108 742		3 085 663	1 986 106	
Demographics						
Age at Index Date, Mean (SD)	74.36 (6.34)	75.45 (7.35)	0.1601	74.61 (6.58)	74.75 (6.75)	0.0215
Age categories						
65-69	857 091 (26.06)	532 739 (25.26)	0.0183	802 486 (26.01)	514 992 (25.93)	0.0018
70-74	1 035 264 (31.48)	590 435 (28.00)	0.0762	935 876 (30.33)	601 599 (30.29)	0.0009
75-79	726 177 (22.08)	420 091 (19.92)	0.0530	658 857 (21.35)	424 225 (21.36)	0.0002
80-84	405 477 (12.33)	280 454 (13.30)	0.0291	393 958 (12.77)	254 473 (12.81)	0.0014
85+	264 837 (8.05)	285 023 (13.52)	0.1768	294 485 (9.54)	190 818 (9.61)	0.0022
Sex						
Male	1 352 726 (41.13)	773 817 (36.70)	0.0911	1 214 944 (39.37)	785 486 (39.55)	0.0036
Female	1 936 120 (58.87)	1 334 925 (63.30)	0.0911	1 870 719 (60.63)	1 200 620 (60.45)	0.0036
Race						
American Indian/Alaskan Native	7 820 (0.24)	5 357 (0.25)	0.0033	7 757 (0.25)	5 001 (0.25)	0.0001
Asian	81 270 (2.47)	47 871 (2.27)	0.0132	75 313 (2.44)	49 219 (2.48)	0.0024
Black or African American	79 095 (2.40)	133 861 (6.35)	0.1937	87 585 (2.84)	56 283 (2.83)	0.0003
White	2 926 235 (88.97)	1 805 975 (85.64)	0.1002	2 745 457 (88.97)	1 766 307 (88.93)	0.0013
Hispanic	23 049 (0.70)	34 651 (1.64)	0.0877	25 872 (0.84)	16 587 (0.84)	0.0004
Unknown	108 730 (3.31)	49 095 (2.33)	0.0591	89 059 (2.89)	57 293 (2.88)	0.0001
Other	62 647 (1.90)	31 932 (1.51)	0.0301	54 620 (1.77)	35 415 (1.78)	0.0010
Parts A, B, D Continuous enrollment[c]	3 288 846 (100.00)	2 108 742 (100.00)	0.0000	3 085 663 (100.00)	1 986 106 (100.00)	0.0000
Year of Index Date						
2018	883 174 (26.85)	718 487 (34.07)	0.1573	916 535 (29.70)	593 091 (29.86)	0.0035
2019	1 412 910 (42.96)	714 066 (33.86)	0.1879	1 206 370 (39.10)	773 916 (38.97)	0.0027

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
2020	992 762 (30.19)	676 189 (32.07)	0.0406	962 757 (31.20)	619 099 (31.17)	0.0006
Medical History[d]						
Diabetes mellitus	799 428 (24.31)	609 382 (28.90)	0.1040	787 913 (25.53)	507 666 (25.56)	0.0006
Chronic kidney disease	677 543 (20.60)	516 189 (24.48)	0.0929	660 672 (21.41)	425 235 (21.41)	0.0000
Chronic lung disease[e]	399 317 (12.14)	322 014 (15.27)	0.0911	400 903 (12.99)	257 891 (12.98)	0.0002
Congestive heart failure	228 646 (6.95)	218 114 (10.34)	0.1209	235 321 (7.63)	151 309 (7.62)	0.0003
Ischemic heart disease	698 649 (21.24)	490 323 (23.25)	0.0483	664 161 (21.52)	427 274 (21.51)	0.0003
Alzheimer's/Dementia	110 204 (3.35)	144 118 (6.83)	0.1590	117 660 (3.81)	75 693 (3.81)	0.0001
Chronic liver disease	182 515 (5.55)	121 880 (5.78)	0.0100	171 776 (5.57)	110 341 (5.56)	0.0005
Stroke/TIA	202 178 (6.15)	160 697 (7.62)	0.0582	197 000 (6.38)	126 782 (6.38)	0.0000
Immunocompromised Conditions						
Organ transplant	7 725 (0.23)	6 083 (0.29)	0.0105	7 598 (0.25)	4 907 (0.25)	0.0002
Hematopoietic stem cell transplant	4 690 (0.14)	1 928 (0.09)	0.0150	3 464 (0.11)	2 300 (0.12)	0.0011
Hematologic or solid malignancy w/recent receipt of chemotherapy	26 569 (0.81)	25 062 (1.19)	0.0383	28 299 (0.92)	18 199 (0.92)	0.0001
HIV infection	4 810 (0.15)	2 433 (0.12)	0.0085	3 764 (0.12)	2 418 (0.12)	0.0001
Rheumatoid Arthritis	100 467 (3.05)	68 912 (3.27)	0.0122	95 594 (3.10)	61 468 (3.09)	0.0002
IBD - Crohn's disease	17 400 (0.53)	9 186 (0.44)	0.0135	14 952 (0.48)	9 595 (0.48)	0.0002
IBD - Colitis	31 097 (0.95)	15 978 (0.76)	0.0204	26 321 (0.85)	16 925 (0.85)	0.0001
Lupus	12 246 (0.37)	8 780 (0.42)	0.0070	11 861 (0.38)	7 610 (0.38)	0.0002
Multiple Sclerosis	7 994 (0.24)	5 037 (0.24)	0.0009	7 410 (0.24)	4 758 (0.24)	0.0001
Psoriasis/Psoriatic Arthritis	72 388 (2.20)	37 418 (1.77)	0.0306	62 455 (2.02)	40 256 (2.03)	0.0002
Service Use History[d]						
≥1 dermatology visit	117 291 (3.57)	39 484 (1.87)	0.1043	80 236 (2.60)	52 074 (2.62)	0.0014
≥1 optometry/ ophthalmology visit	1 868 167 (56.80)	963 986 (45.71)	0.2232	1 619 567 (52.49)	1 043 650 (52.55)	0.0012
Number of hospitalizations						
0	2 934 874 (89.24)	1 804 992 (85.60)	0.1100	2 733 908 (88.60)	1 760 260 (88.63)	0.0009

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
1	267 966 (8.15)	206 806 (9.81)	0.0581	263 557 (8.54)	169 366 (8.53)	0.0005
2 or more	86 006 (2.62)	96 944 (4.60)	0.1065	88 197 (2.86)	56 480 (2.84)	0.0009
Number of ED visits						
0	2 689 692 (81.78)	1 624 890 (77.05)	0.1171	2 490 200 (80.70)	1 603 126 (80.72)	0.0004
1	445 321 (13.54)	303 736 (14.40)	0.0249	429 301 (13.91)	276 272 (13.91)	0.0001
2 or more	153 833 (4.68)	180 116 (8.54)	0.1560	166 161 (5.38)	106 708 (5.37)	0.0005
Durable medical equipment	932 931 (28.37)	616 624 (29.24)	0.0193	869 302 (28.17)	559 311 (28.16)	0.0003
Hospice care	1 885 (0.06)	5 846 (0.28)	0.0538	1 087 (0.04)	697 (0.04)	0.0001
Home health care	190 092 (5.78)	205 120 (9.73)	0.1480	198 728 (6.44)	127 636 (6.43)	0.0006
Skilled nursing facility care	52 607 (1.60)	73 767 (3.50)	0.1207	55 926 (1.81)	36 002 (1.81)	0.0000
Concomitant Vaccine Use[f]						
Influenza	408 534 (12.42)	131 191 (6.22)	0.2145	256 339 (8.31)	166 217 (8.37)	0.0022
Pneumococcal	144 830 (4.40)	102 212 (4.85)	0.0211	140 371 (4.55)	92 387 (4.65)	0.0049
Tetanus- Diphtheria- Pertussis	67 788 (2.06)	2 191 (0.10)	0.1900	79 (0.00)	51 (0.00)	0.0001

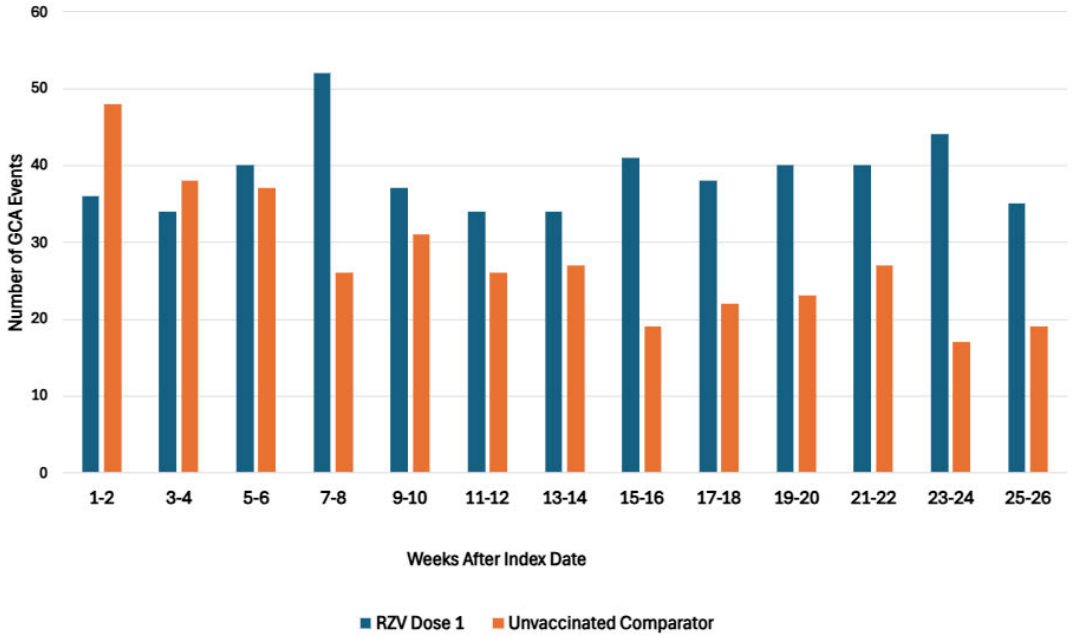
COPD, chronic obstructive pulmonary disease; ED, emergency department; RZV, recombinant zoster vaccine; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; GCA, giant cell arteritis; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data. Index date is the RZV Dose 1 date in the exposed group and preventive visit date in the comparator group.

a. The Ns for the RZV exposed cohorts are shown for those who at least received RZV Dose1.
b. RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening.
c. Allows one calendar month gap in enrolment; measured in the year preceding the index date.
d. Measured in the year prior to the index date.
e. Chronic lung disease includes COPD and bronchiectasis.
f. Measured on the index date.

14.5.3. GCA events in the 183-day follow-up period

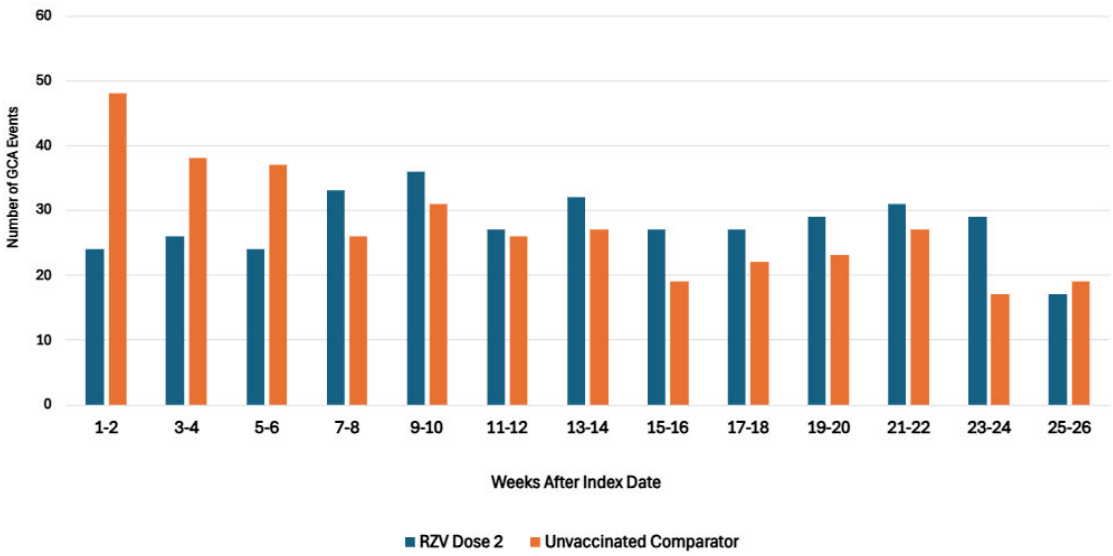
Figure 40 and Figure 41 show the distribution of incident GCA events from RZV Dose 1 and Dose 2, respectively, relative to the RZV-unvaccinated comparator. The 506 GCA cases after RZV Dose 1 were generally evenly distributed across the weeks after the index date. For RZV Dose 2, there were 364 cases that seemed evenly distributed across the weeks of follow-up after the index date. For the RZV-unvaccinated comparators, GCA there were 360 cases. In this group, the number of cases decreased during the follow-up period from 48 cases (Weeks 1-2) to 17 cases (Weeks 23-24). Data were aggregated by week to avoid counts <11.

Figure 40 Distribution of incident GCA events by week from the index date: RZV Dose 1 and unvaccinated comparators



Note: Index date is the date of vaccination for Dose 1 for RZV exposed, or date of preventive care visit for unvaccinated comparator; RZV, recombinant zoster vaccine; GCA, giant cell arteritis.
Week after index date is grouped into 2 weeks interval to mask weeks where cases were <11.

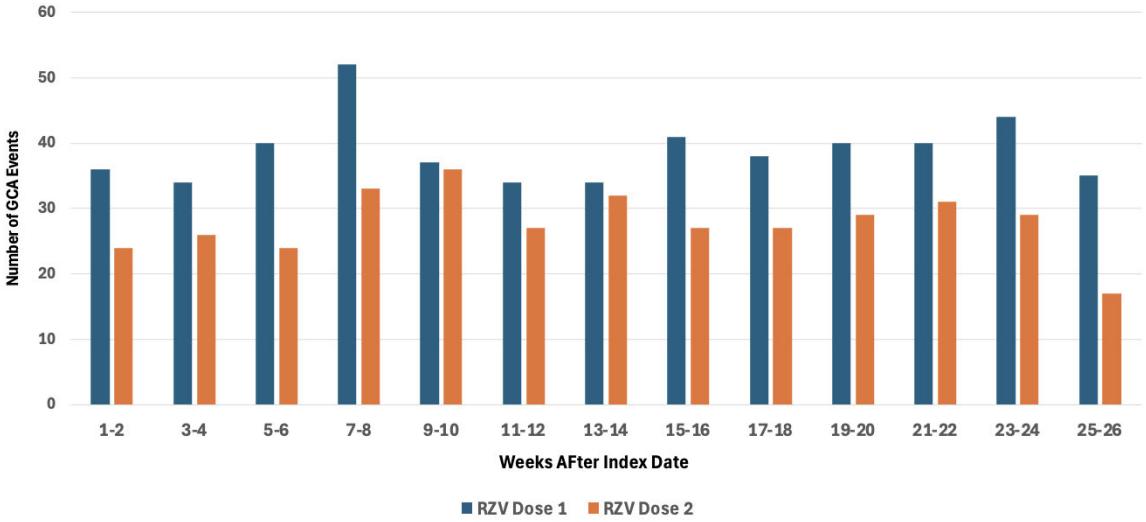
Figure 41 Distribution of incident GCA events by week from the index date: RZV Dose 2 and unvaccinated comparators



Note: Index date is the date of vaccination for Dose 2 for RZV exposed, or date of preventive care visit for unvaccinated comparator; RZV, recombinant zoster vaccine; GCA, giant cell arteritis.
Week after index date is grouped into 2 weeks interval to mask weeks where cases were <11.

Figure 42 below shows the distribution of incident GCA events by the week of follow-up relative to RZV Dose 1 and Dose 2. The graph depicts the number of events per week and visually shows that the number of cases after RZV Dose 1 was greater than the number of cases after RZV Dose 2. The number of cases per week of follow-up is relatively stable.

Figure 42 Distribution of incident GCA events by week from the index date: RZV Dose 1 and Dose 2



Note: Index date is the date of vaccination for RZV Dose 1 and Dose 2, respectively; RZV, recombinant zoster vaccine; GCA, giant cell arteritis.
Week after index date is grouped into 2 weeks interval to mask weeks where cases were <11.

14.5.4. Crude and covariate adjusted risk estimates for GCA

This section includes the hazard ratios for the crude and covariate adjusted models for all the GCA analyses. The tables in this section are provided for reference to the IPTW-adjusted analyses provided in the main text.

14.5.4.1. Primary analysis

Table 69 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the GCA primary analysis of RZV Dose 1 and RZV Dose 2. The estimates are nearly the same as the IPTW-adjusted estimates and the interpretation is the same. The sample was very large and many of the baseline covariates were balanced between comparators, which led to tight confidence intervals around the effect estimate.

Table 69 Risk estimates for primary analysis of GCA within a 183-day follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Separate analysis						
RZV Dose 1	3 288 846	506	1 621 702	3.12 (2.86 – 3.40)	1.04 (0.91 – 1.19)	1.15 (1.00 – 1.32)
Comparator	2 585 975	360	1 193 742	3.02 (2.72 – 3.34)	Ref.	Ref.
RZV Dose 2	2 508 442	364	1 236 192	2.94 (2.66 – 3.26)	0.98 (0.85 – 1.13)	1.05 (0.90 – 1.23)
Comparator	2 585 975	360	1 193 742	3.02 (2.72 – 3.34)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; GCA, giant cell arteritis; PY, persons-years; RZV, recombinant zoster vaccine.

14.5.4.2. Secondary analysis

Table 70 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the GCA secondary analysis of a combined dose single risk estimate and a time-varying analysis separate estimate for RZV Dose 1 and RZV Dose 2. The time-varying HRs showed an elevated risk for RZV Dose 1, which mirrored the IPTW-adjusted estimate. The time-varying RZV Dose 2 HR was not statistically significant and was lower than for RZV Dose 1, and it mirrored the IPTW-adjusted analysis.

Table 70 Risk estimates for secondary analysis of GCA within a of 183-day follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Combined dose						
RZV Dose 1 and Dose 2	3 288 846	703	2 267 415	3.10 (2.88 – 3.34)	1.11 (0.97 – 1.26)	1.18 (1.03 – 1.35)
Comparator	2 585 975	360	1 193 742	3.02 (2.72 – 3.34)	Ref.	Ref.
Time-varying separate dose						
RZV Dose 1	3 288 846	339	1 031 223	3.29 (2.96 – 3.66)	1.15 (0.99 – 1.33)	1.22 (1.04 – 1.42)
RZV Dose 2	2 494 461	167	583 650	2.86 (2.46 – 3.33)	1.06 (0.88 – 1.27)	1.11 (0.92 – 1.34)
Comparator	2 585 975	360	1 193 742	3.02 (2.72 – 3.34)	Ref.	Ref.

Adj., adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; GCA, giant cell arteritis; PY, persons-years; RZV, recombinant zoster vaccine.

14.5.4.3. COVID-19 sensitivity analysis

Table 71 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the GCA COVID-19 sensitivity analysis. Risk estimates

were generated for RZV Dose 1 and RZV Dose 2. The estimates resemble the IPTW-adjusted estimates.

Table 71 Risk estimates for COVID-19 sensitivity of the primary analysis of GCA with a 183-day-follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
COVID-19 analysis[a]						
RZV Dose 1	2 393 728	345	1 007 210	3.43 (3.08 – 3.81)	1.03 (0.88 – 1.21)	1.16 (0.98 – 1.36)
Comparator	1 940 446	263	794 550	3.31 (2.93 – 3.74)	Ref.	Ref.
RZV Dose 2	1 734 948	212	675 236	3.14 (2.74 – 3.59)	0.94 (0.79 – 1.13)	1.03 (0.85 – 1.25)
Comparator	1 940 446	263	794 550	3.31 (2.93 – 3.74)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; GCA, giant cell arteritis; PY, persons-years; RZV, recombinant zoster vaccine.
a. 01 February 2020 included as a censoring event.

14.5.4.4. Dose-compliant sensitivity analysis

Table 72 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the GCA dose-compliant sensitivity analysis. This is a sensitivity analysis to the secondary analysis that incorporates a combined dose and a time-varying exposure. This sensitivity analysis includes the subset of the primary analysis cohort with RZV Dose 1 and Dose 2 spacing two to six months apart, i.e., compliant with the US label. The HRs are like the IPTW-adjusted estimates.

Table 72 Risk estimates for the dose-compliant sensitivity of the secondary analysis of GCA

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Subset of combined dose						
RZV Dose 1 and Dose 2	2 479 348	479	1 758 444	2.72 (2.49 – 2.98)	0.97 (0.84 – 1.11)	1.04 (0.90 – 1.21)
Comparator	2 585 975	360	1 193 742	3.02 (2.72 – 3.34)	Ref.	Ref.
Subset of time-varying separate dose						
RZV Dose 1	2 479 348	163	654 365	2.49 (2.14 – 2.90)	0.86 (0.72 – 1.04)	0.92 (0.76 – 1.12)
RZV Dose 2	2 443 934	163	565 951	2.88 (2.47 – 3.36)	1.07 (0.88 – 1.30)	1.14 (0.94 – 1.39)
Comparator	2 585 975	360	1 193 742	3.02 (2.72 – 3.34)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; GCA, giant cell arteritis; PY, persons-years; RZV, recombinant zoster vaccine.

14.5.4.5. Supplemental cohort sensitivity analysis

Table 73 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the GCA supplemental sensitivity analysis. This is a sensitivity analysis to the primary analysis where individuals are removed from the comparator arm if they receive RZV after their preventive care visit. The crude and covariate adjusted models produced results akin to the IPTW-adjusted estimates.

Table 73 Risk estimates for the primary analysis of GCA in the supplemental cohort

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Exclude comparators who received RZV						
RZV Dose 1	3 288 846	506	1 621 702	3.12 (2.86 – 3.40)	0.88 (0.77 – 1.01)	0.96 (0.83 – 1.10)
Comparator	2 108 742	360	1 014 879	3.55 (3.20 – 3.93)	Ref.	Ref.
RZV Dose 2	2 508 442	364	1 236 192	2.94 (2.66 – 3.26)	0.83 (0.72 – 0.96)	0.89 (0.76 – 1.04)
Comparator	2 108 742	360	1 014 879	3.55 (3.20 – 3.93)	Ref.	Ref.

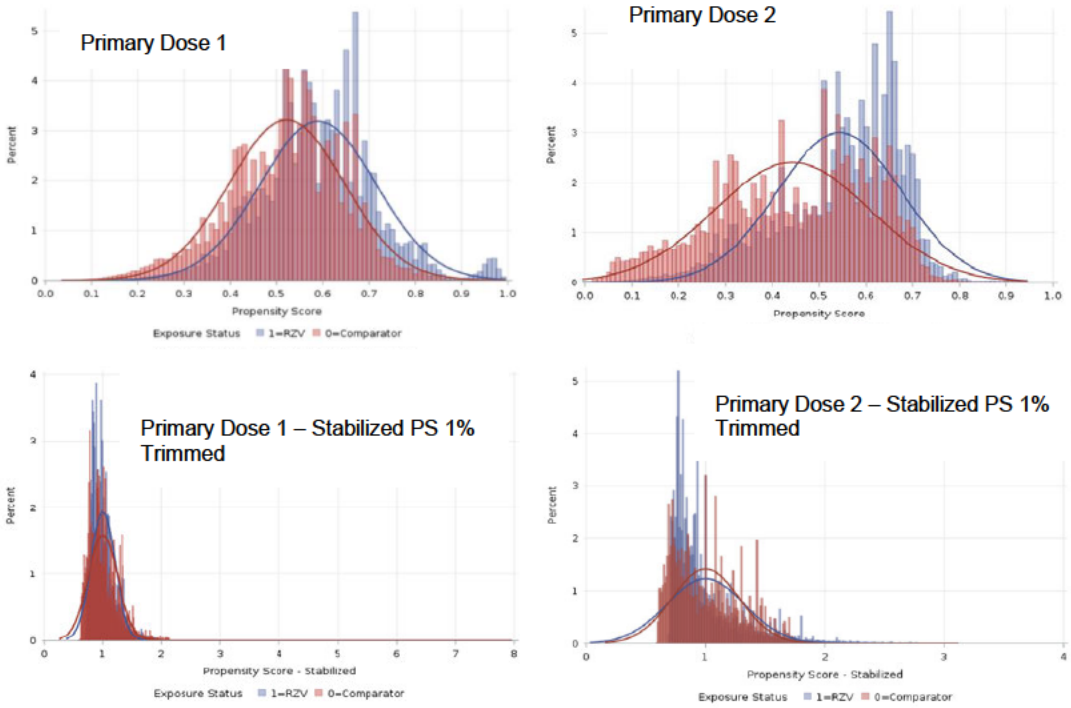
Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; GCA, giant cell arteritis; PY, persons-years; RZV, recombinant zoster vaccine.

14.5.5. Propensity score distribution and weights for GCA

14.5.5.1. Primary Analysis

The PS distributions for the primary analysis of RZV Dose 1 and Dose 2 are shown in Figure 43 below for both the common range distribution and the IPTW stabilized with 1% asymmetrical trimmed distribution. There was moderate overlap before applying the stabilized IPTW, which improved after applying the stabilized weight and 1% asymmetrical trim. The IPTW stabilized weight tempered the extreme weights and ensured covariate balance between RZV-exposed and the RZV-unvaccinated comparators (Table 74).

Figure 43 GCA primary analysis propensity score distribution: Dose 1 and Dose 2



Primary Dose 1, primary analysis for RZV Dose 1; Primary Dose 2, primary analysis for RZV Dose 2.

Table 74 Propensity score weights for GCA primary and secondary analyses

Primary Analysis Dose 1 and Secondary Analyses Combined and Time-Varying Dose				
Common Range		**Mean**	**Minimum**	**Maximum**
RZV-unvaccinated comparator	Original PS	0.521823	0.0457285	0.9931649
	IPTW	2.276034	1.0479198	146.303054
	IPTW Stabilized	1.0018586	0.4612705	64.3992874
RZV-exposed	Original PS	0.5896986	0.0452777	0.993218
	IPTW	1.7865692	1.0068283	22.0859156
	IPTW Stabilized	1.0001619	0.5636453	12.3641963
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5315788	0.2678449	0.9443923
	IPTW	2.2573085	1.3658308	17.9831289
	IPTW Stabilized	0.9994308	0.6047261	7.96209
RZV-exposed	Original PS	0.5776407	0.2659573	0.9457385
	IPTW	1.7951317	1.0573747	3.7600023
	IPTW Stabilized	1.0003312	0.5892185	2.0952488
Primary Analysis Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.4427332	0.0073696	0.9410298
	IPTW	1.9709194	1.0074244	16.9577064
	IPTW Stabilized	1.0004527	0.5113758	8.6078523

RZV-exposed	Original PS	0.543597	0.0104549	0.9412588
	IPTW	2.0317911	1.0624071	95.6486419
	IPTW Stabilized	1.0004395	0.5231217	47.0967115
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4656039	0.1630294	0.743769
	IPTW	2.015464	1.1947851	3.9027278
	IPTW Stabilized	1.0001621	0.592905	1.9367056
RZV-exposed	Original PS	0.5413391	0.162037	0.7395236
	IPTW	1.984973	1.3522219	6.1714291
	IPTW Stabilized	0.9999418	0.6811897	3.1088938

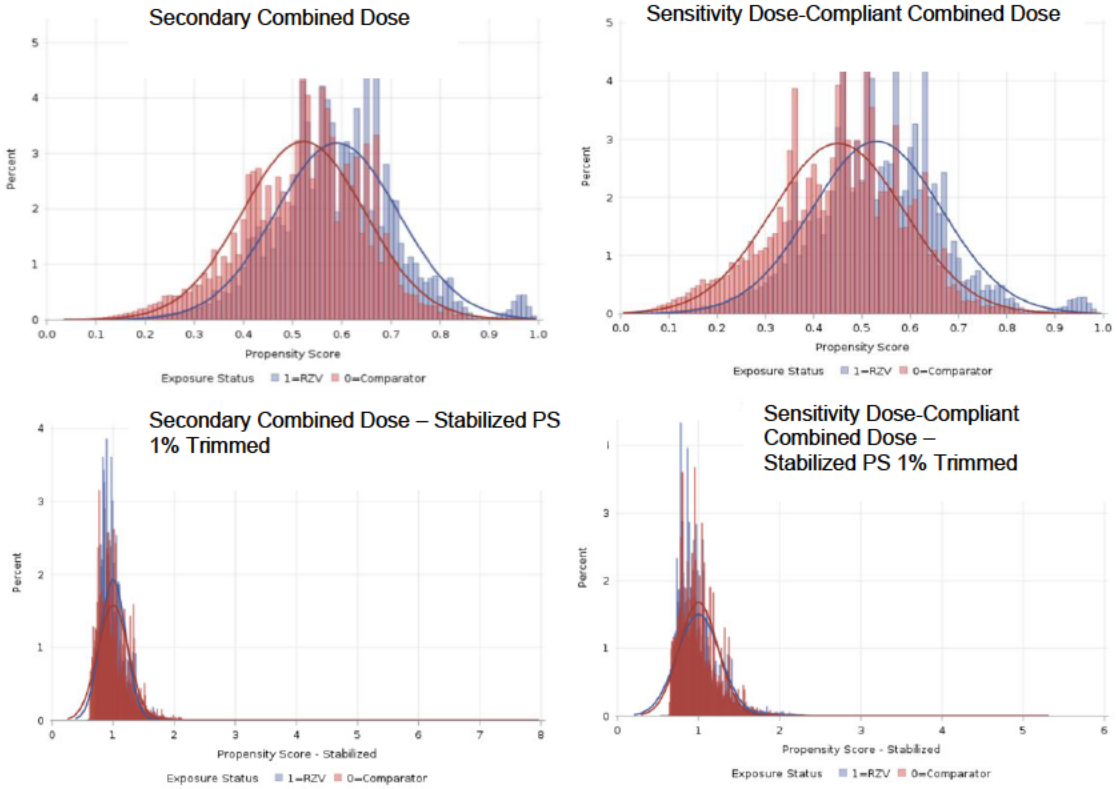
PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.5.5.2. Secondary and sensitivity analysis: Combined dose estimate

The PS distributions for the secondary analysis with a single risk estimate for RZV Dose 1 and Dose 2, using a partly conditional survival model, are shown in Figure 44. The distributions are shown for both the common range distribution and the IPTW stabilized with 1% asymmetrical trimmed cohort for the secondary analysis. The PS distribution for the sensitivity analysis (also based on the partly conditional survival analysis) of the dose-compliant subsample who received both doses 60 to 183-days apart is also shown.

There was moderate overlap before applying the stabilized IPTW, which improved after applying the stabilized weight and 1% asymmetrical trim. As in the primary analysis, the IPTW stabilized weight tempered the extreme weights and ensured covariate balance between RZV-exposed and the RZV-unvaccinated comparators.

Figure 44 GCA secondary and sensitivity analyses propensity score distribution: Combined Dose 1 and Dose 2

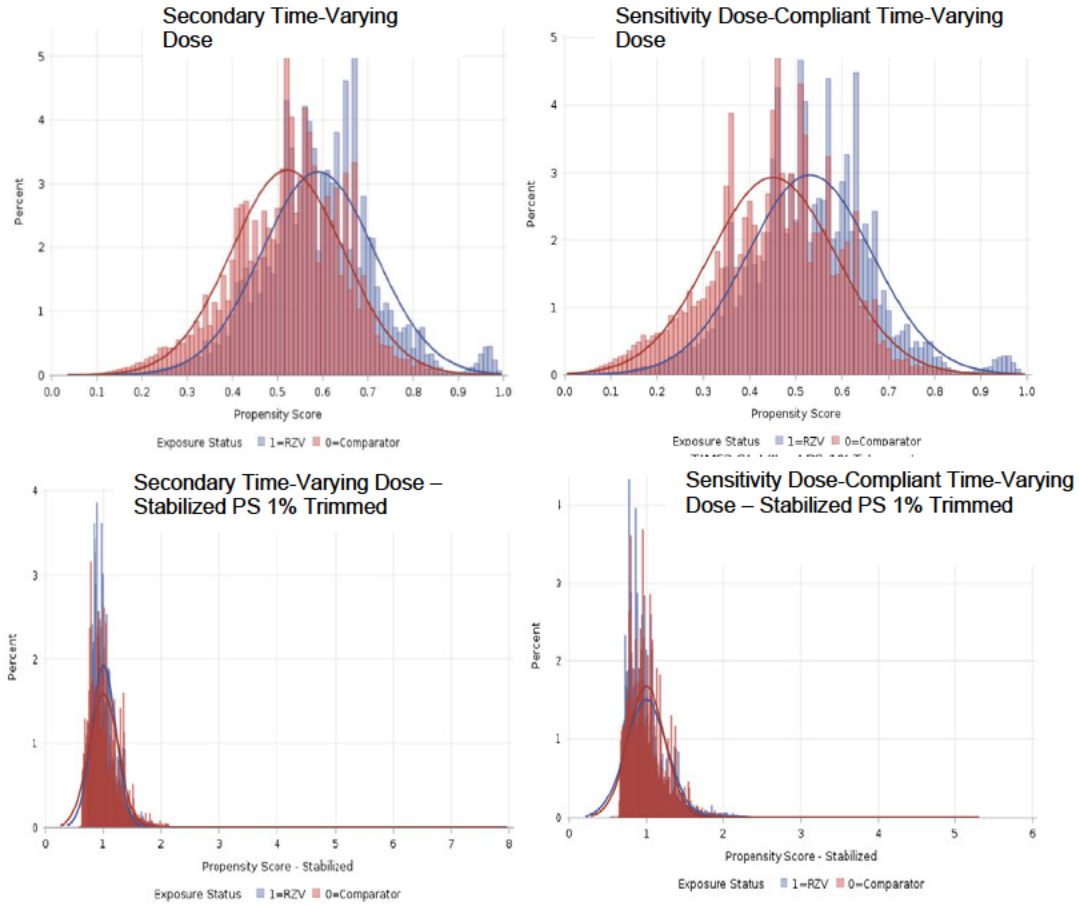


Note: Secondary analysis using a partly conditional survival model for a single risk estimate for both RZV doses; Sensitivity to the secondary analysis using a partly conditional survival model for a single risk estimate for both RZV doses in the dose-compliant subsample with 60 to 183 dose spacing.

14.5.5.3. Secondary and sensitivity analysis: Time-varying dose estimate

The PS distributions for the secondary analysis with a time-varying dose exposure for RZV Dose 1 and Dose 2 are shown in Figure 45. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for the secondary analysis and for the sensitivity analysis of the dose-compliant subsample who received both doses 60 to 183-days apart show good overlap with the 1% trimmed stabilized IPTW.

Figure 45 GCA secondary and sensitivity analyses propensity score distribution: Time-varying Dose 1 and Dose 2



Note: Secondary analysis using a time-varying Cox proportional hazards model with RZV doses as a time-varying covariate for a separate risk estimate for RZV Dose 1 and Dose 2; Sensitivity to the secondary analysis using time-varying Cox proportional hazards model for a separate risk estimate for RZV Dose 1 and Dose 2 in the dose-compliant subsample with 60-183 dose spacing.

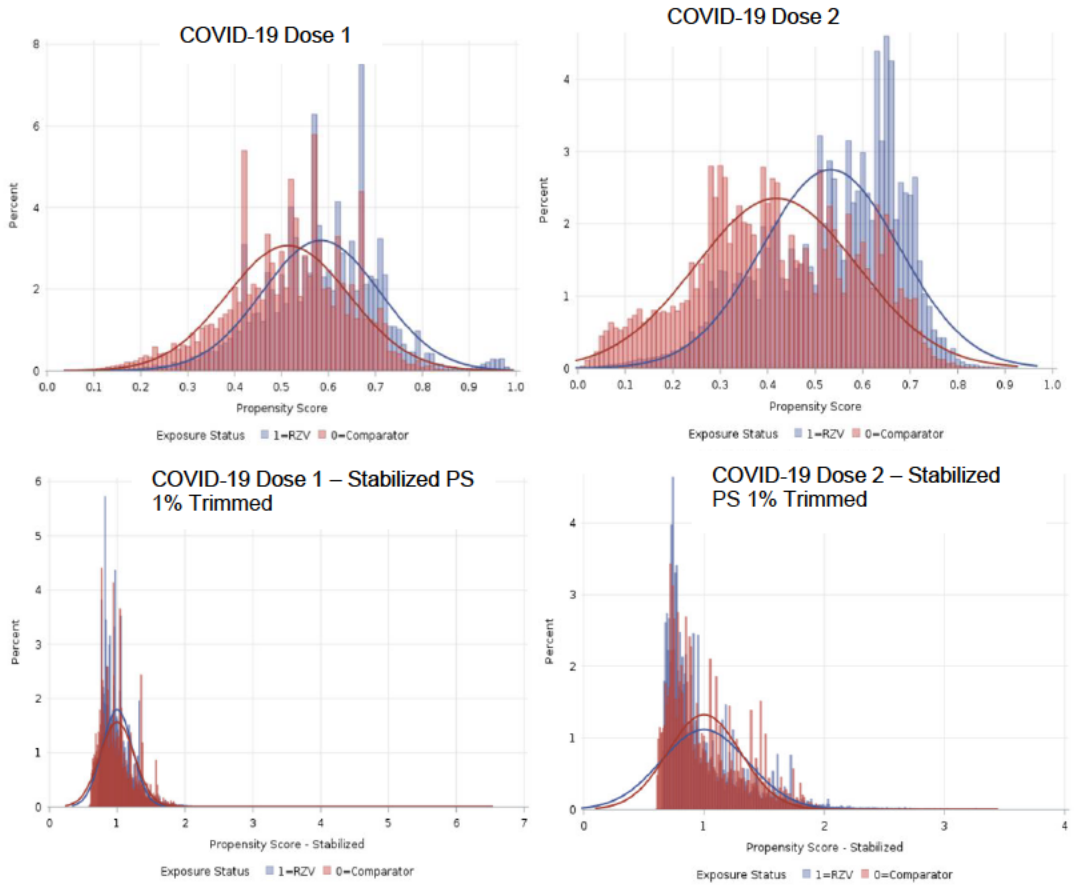
The PS weights for the primary analysis of RZV Dose 1 and Dose 2 and the secondary analyses of the combined dose and time-varying dose are shown in Table 74 above for the RZV-exposed and the RZV-unvaccinated comparator. The weights for these analytic cohorts are the same as those for the primary Dose 1 cohort was used for the secondary analyses since the only difference was in the statistical analysis procedures.

The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. For the common range of the combined dose analysis, the RZV-unvaccinated comparator had a large IPTW stabilized weight >64 but reduced to 7.9 after 1% asymmetrical trimming and applying the IPTW stabilized weight. For Dose 2, the RZV-exposed had a large IPTW stabilized weight >47, which was reduced to 3.10 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The 1% trimming with stabilized weight avoided extreme weights influencing the analysis.

14.5.5.4. COVID-19 sensitivity analysis

COVID-19 sensitivity analysis includes 01 February 2020 as a censoring event, which will exclude events that may have occurred after this date. The PS distributions for the COVID-19 sensitivity analysis for Dose 1 and Dose 2 are shown in Figure 46. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for RZV Dose 1 and for RZV Dose 2 are provided to illustrate the overlap between the RZV-exposed and the RZV-unvaccinated comparators.

Figure 46 GCA COVID-19 sensitivity analysis propensity score distribution: Dose 1 and Dose 2



COVID-19 Dose 1, sensitivity analysis for RZV Dose 1; COVID-19 Dose 2, sensitivity analysis for Dose 2.

The PS weights for the COVID-19 sensitivity analysis to the primary analysis of separate RZV Dose 1 and RZV Dose 2 are shown in Table 75 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. The common range in the COVID-19 sensitivity analysis of Dose 1 for the RZV-unvaccinated comparator had an IPTW stabilized weight >46, which was reduced to 6.5 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The common range in the COVID-19 sensitivity analysis of Dose 2, the RZV-exposed had an IPTW stabilized weight >53, which was reduced to 3.43 after 1% trimming was applied.

Table 75 Propensity score weights for GCA COVID-19 sensitivity analysis to the primary analysis of separate Dose 1 and Dose 2 risk estimates

COVID-19 Sensitivity Analysis: Dose 1				
Common Range		**Mean**	**Minimum**	**Maximum**
RZV-unvaccinated comparator	Original PS	0.5133339	0.0441708	0.9903125
	IPTW	2.2362672	1.046212	103.225377
	IPTW Stabilized	1.0011858	0.4683933	46.2144136
RZV-exposed	Original PS	0.5838789	0.0439162	0.990144
	IPTW	1.811837	1.0099541	22.7706504
	IPTW Stabilized	1.0006703	0.5577936	12.5761393
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5235574	0.2440422	0.9313124
	IPTW	2.2269187	1.3228252	14.558663
	IPTW Stabilized	0.9995383	0.5937417	6.5345636
RZV-exposed	Original PS	0.5736319	0.2424753	0.9344613
	IPTW	1.8150728	1.0701353	4.1241318
	IPTW Stabilized	1.0003889	0.5898118	2.2730414
COVID-19 Sensitivity Analysis: Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.4181631	0.0063731	0.9243067
	IPTW	1.8946489	1.006414	13.2112034
	IPTW Stabilized	1.0002878	0.5313405	6.9749103
RZV-exposed	Original PS	0.5323103	0.0087849	0.9212331
	IPTW	2.1213981	1.0855015	113.831184
	IPTW Stabilized	1.0013971	0.5124064	53.7335321
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4409456	0.1434696	0.7473243
	IPTW	1.9358875	1.1675008	3.957642
	IPTW Stabilized	1.000013	0.6030909	2.044382
RZV-exposed	Original PS	0.5288351	0.1406969	0.7465114
	IPTW	2.0687637	1.3395643	7.1074796
	IPTW Stabilized	1.0001113	0.6475914	3.4359996

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.5.5.5. Dose compliant sensitivity analysis

The PS weights for the dose-compliant sensitivity analyses of the combined and time-varying RZV Dose 1 and Dose 2 are shown in Table 76 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. For the dose-compliant subsample, the RZV-unvaccinated comparator had a large IPTW stabilized weight >54, which was reduced to 5.31, and the RZV-exposed had a large IPTW stabilized weight >43, which was reduced to 2.59.

Table 76 Propensity score weights for GCA dose-compliant sensitivity analyses: Combined dose and time-varying dose

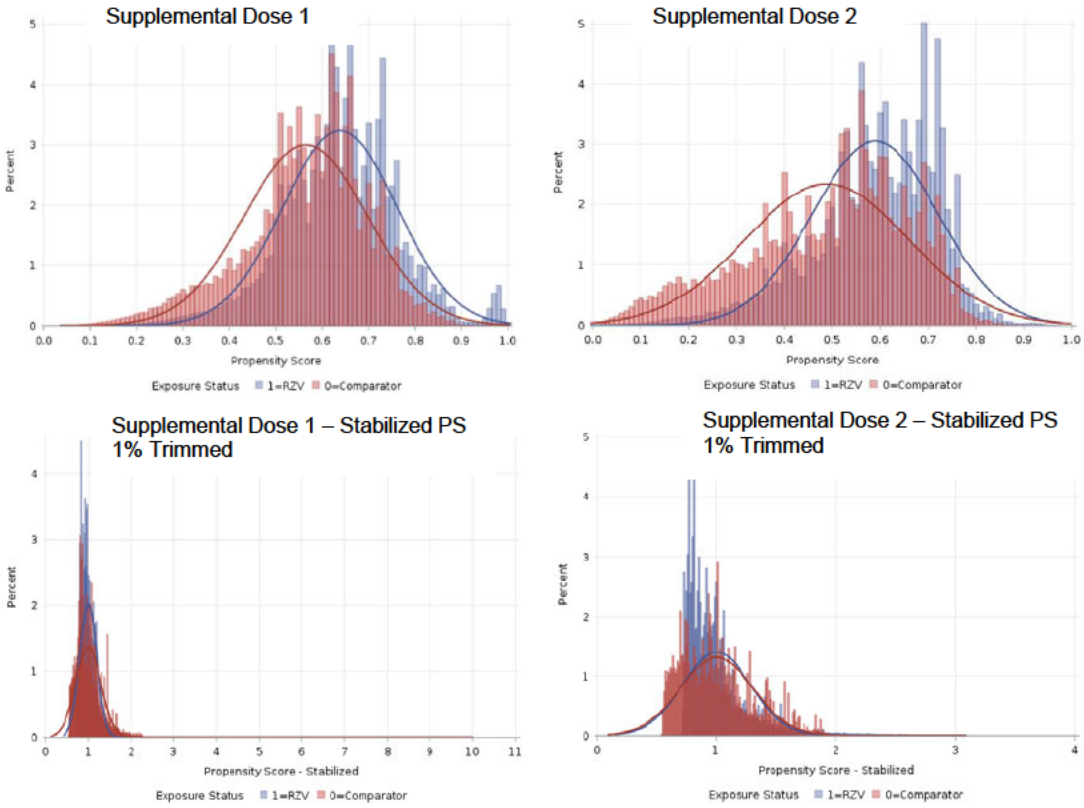
Sensitivity Analysis: Combined and Time-Varying Dose with 60-183-dose spacing				
Common Range				
RZV-unvaccinated comparator	Original PS	0.4503699	0.0116801	0.9905499
	IPTW	1.961469	1.0118181	105.8192574
	IPTW Stabilized	1.001378	0.516558	54.0233256
RZV-exposed	Original PS	0.5302623	0.0113511	0.9909468
	IPTW	2.0437187	1.0091359	88.0971456
	IPTW Stabilized	1.0003502	0.4939473	43.1213926
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4632072	0.1890608	0.9038424
	IPTW	1.9591618	1.233138	10.3995962
	IPTW Stabilized	0.9994783	0.6290928	5.305417
RZV-exposed	Original PS	0.5175852	0.188648	0.9072075
	IPTW	2.0425771	1.1022837	5.3008778
	IPTW Stabilized	1.000544	0.539947	2.5966029

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.5.5.6. Supplemental cohort: Dose 1 and Dose 2

The supplemental cohort that excludes from the comparator arm participants who received RZV in the future was performed as a supplemental to the primary analysis, with a separate analysis for RZV Dose 1 and Dose 2. The PS distributions for the two supplemental analyses are shown in Figure 47. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for RZV Dose 1 and for RZV Dose 2 are provided to illustrate the overlap between the RZV-exposed and the RZV-unvaccinated comparators.

Figure 47 GCA supplemental cohort propensity score distribution: Dose 1 and Dose 2



Supplemental Dose 1, supplemental cohort for RZV Dose 1; Supplemental Dose 2, supplemental cohort for Dose 2.

The PS weights for the supplemental cohort of RZV Dose 1 and RZV Dose 2 are shown in Table 77 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. The common range in Dose 1 for the RZV-unvaccinated comparator had an IPTW stabilized weight >100, which was reduced to 10 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The common range in Dose 2, the RZV-exposed had an IPTW stabilized weight >54, which was reduced to 3.09 after 1% trimming was applied.

Table 77 Propensity score weights for GCA supplemental cohort: Dose 1 and Dose 2

Supplemental Cohort: Dose 1				
Common Range		Mean	Minimum	Maximum
RZV-unvaccinated comparator	Original PS	0.5645269	0.0408159	0.9961163
	IPTW	2.5701062	1.0425527	257.4865691
	IPTW Stabilized	1.00409	0.4073048	100.5949397
RZV-exposed	Original PS	0.6380396	0.0403385	0.9963972
	IPTW	1.6411604	1.0036158	24.7902184
	IPTW Stabilized	0.9999913	0.6115228	15.1051675
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5777597	0.2825953	0.9608668
	IPTW	2.5533854	1.3939134	25.5537418
	IPTW Stabilized	0.9999704	0.5458918	10.0074922
RZV-exposed	Original PS	0.6280822	0.2761792	0.9641967
	IPTW	1.6438478	1.0371328	3.6208379
	IPTW Stabilized	1.0000754	0.6309653	2.2028261
Supplemental Cohort: Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.4883793	0.0077963	0.9677302
	IPTW	2.1925366	1.0078576	30.9886788
	IPTW Stabilized	1.001359	0.4603012	14.1529187
RZV-exposed	Original PS	0.5894482	0.0098942	0.9698649
	IPTW	1.8405316	1.0310715	101.0690403
	IPTW Stabilized	0.9999377	0.5601682	54.9095407
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5146902	0.1790784	0.8193088
	IPTW	2.2483795	1.2181431	5.5343028
	IPTW Stabilized	1.0007455	0.542191	2.4632978
RZV-exposed	Original PS	0.5871595	0.1794058	0.8194149
	IPTW	1.8008571	1.2203829	5.5739553
	IPTW Stabilized	0.9993022	0.677195	3.0930083

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.5.6. Assessment of the proportional hazards assumption

The assumption of constant hazards was assessed for the primary analysis of GCA. To assess whether the assumption of proportional hazards was violated, we plotted the log(- log(survival)) by the log(event time). The following figures show that the assumption of proportional hazards was violated given that the lines cross. To correct for the non-proportionality, we conducted a piecewise Cox regression where a time-dependent coefficient was included in the model. The results for all proportional hazards adjusted analyses are provided in the main text of this study report.

Figure 48 Survivor function plot to assess the proportional hazards assumption for the GCA primary analyses

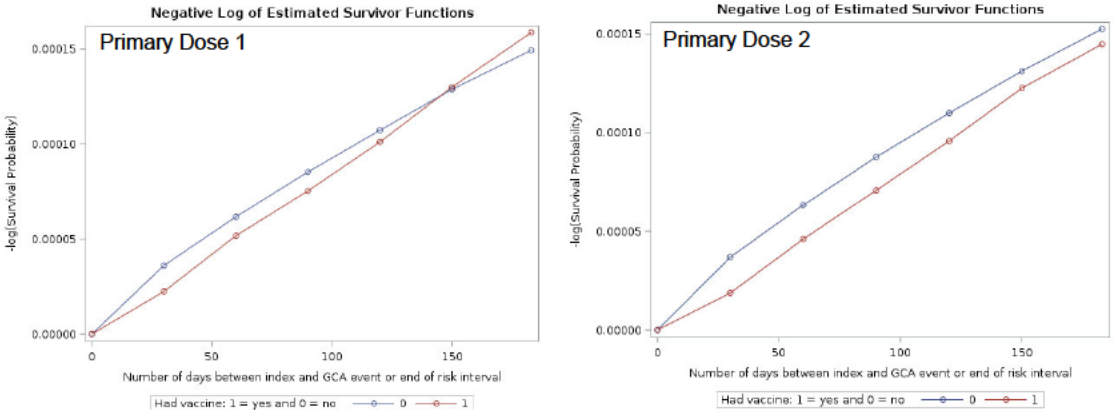


Figure 49 Survivor function plot to assess the proportional hazards assumption for the GCA secondary analyses – combined dose and time-varying dose

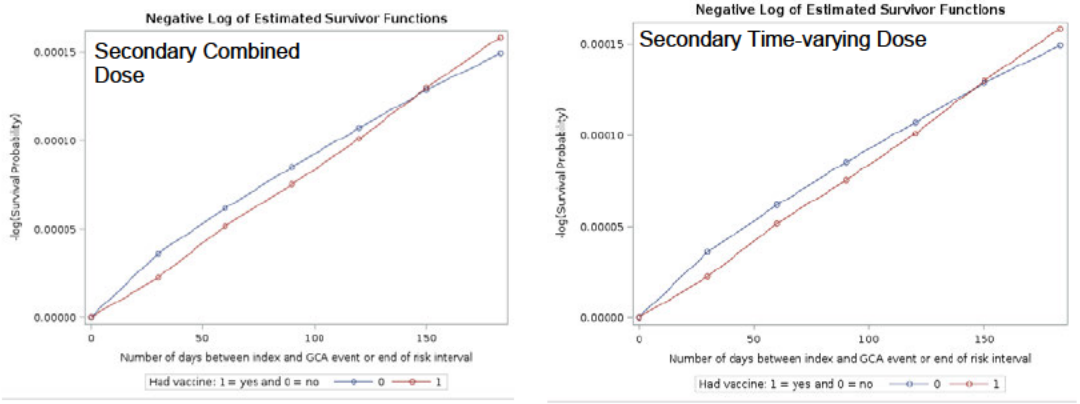


Figure 50 Survivor function plot to assess the proportional hazards assumption for the GCA sensitivity analyses – COVID-19

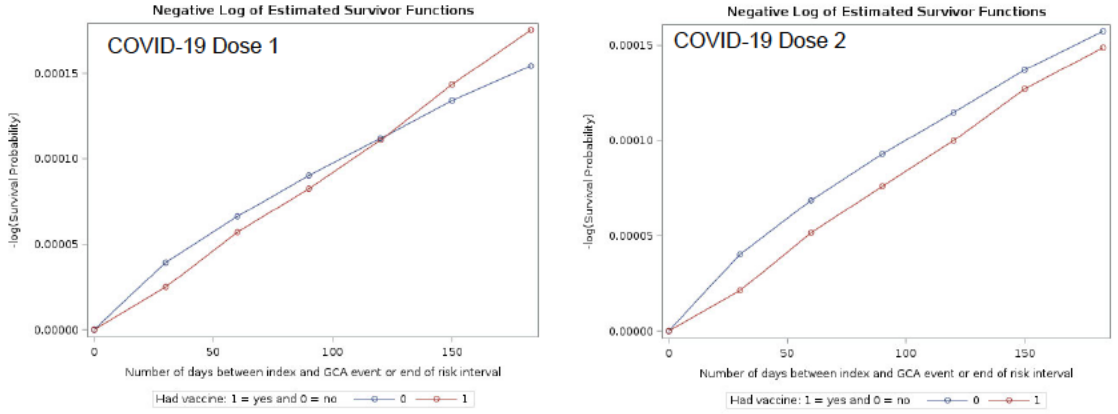


Figure 51 Survivor function plot to assess the proportional hazards assumption for the GCA sensitivity analyses – dose-compliant

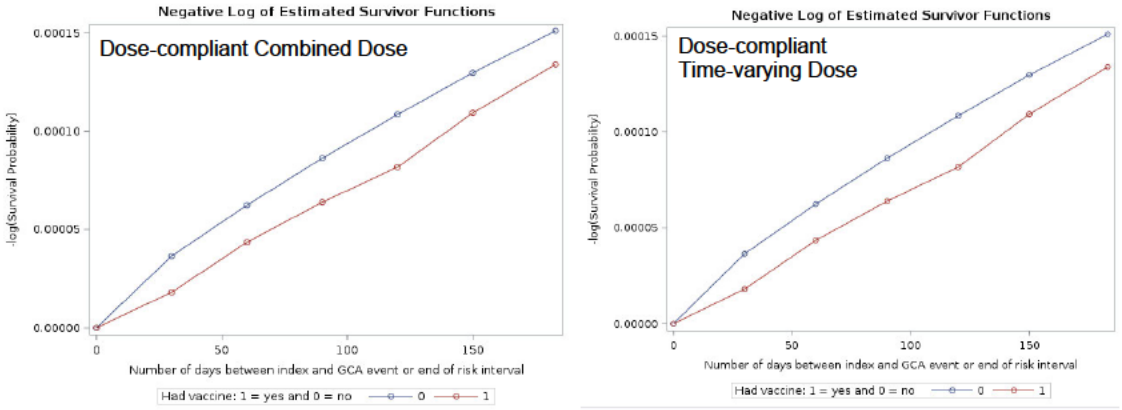
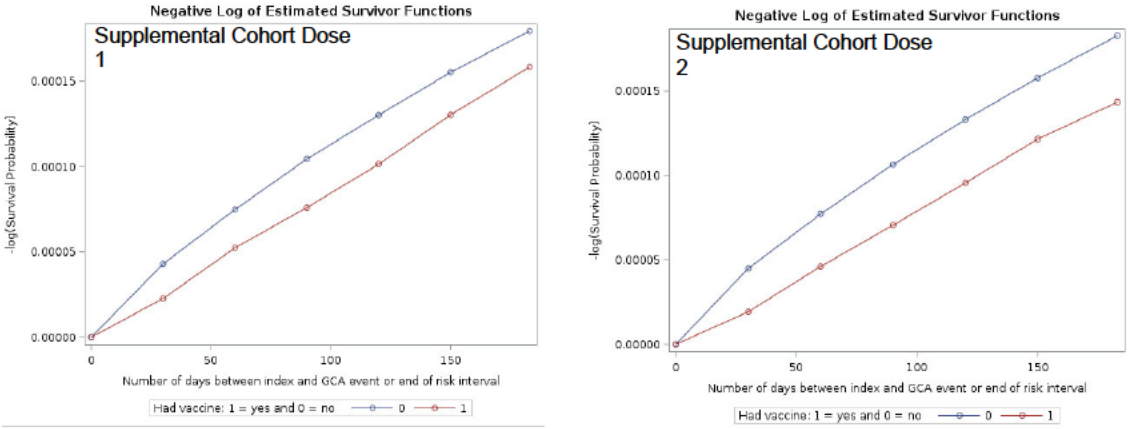


Figure 52 Survivor function plot to assess the proportional hazards assumption for the GCA sensitivity analyses – Supplemental cohort

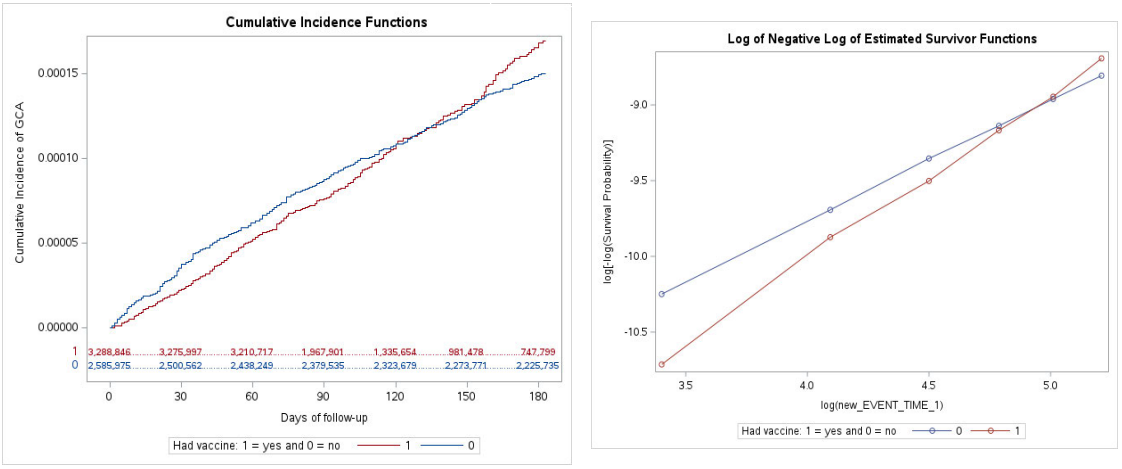


14.5.7. Post-hoc analyses

Post-hoc analyses were conducted for the primary analyses for GCA. The survival probability function was examined to assess the impact of censoring RZV Dose 1 at receipt of Dose 2, Figure 53 shows the cumulative incidence function along with the survivor probability function.

Figure 53 GCA: Cumulative incidence function and survival probability function with censoring of Dose 1 at Dose 2 in the primary analysis

GCA



14.6. ION

14.6.1. Baseline characteristics of the primary analytic cohort

Table 78 below displays the baseline characteristics of the cohort for the primary analysis, unweighted and IPTW-weighted. Table 79 shows the baseline characteristics stratified by the number of doses and the dose spacing. The stratification by number of doses received reflects how many RZV doses a participant received. Of the 3 289 741 participants in the primary cohort, 485 024 only received Dose 1 and 2 804 717 received both RZV Dose 1 and Dose 2. There were no appreciable differences in the characteristics by number of RZV doses received.

The subset of the 2 804 717 who received two RZV doses was stratified by dose spacing of 28 to 60 days versus >60 days (Table 79). This dose spacing aligns with the European label, whereas in the US it is 2 to 6 months spacing between RZV Dose 1 and Dose 2. The distribution of the baseline covariates was similar between those who received the doses 28 to 60 days apart versus those who had >60 days between doses.

Table 78 Baseline demographic and health characteristics of the ION analytic cohort: Before and after IPTW weighting

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Number of unique participants	3 289 741	2 587 018		3 085 493	2 449 701	
Demographics						
Age at Index Date, Mean (SD)	74.36 (6.34)	75.19 (7.15)	-0.12318	74.56 (6.54)	74.68 (6.69)	-0.0180
Age categories						
65-69	857 044 (26.05)	660 694 (25.54)	0.01173	805 286 (26.10)	638 079 (26.05)	0.0012
70-74	1 035 268 (31.47)	747 664 (28.90)	0.05598	943 127 (30.57)	748 207 (30.54)	0.0005
75-79	726 474 (22.08)	525 955 (20.33)	0.04288	659 120 (21.36)	523 616 (21.37)	-0.0003
80-84	405 878 (12.34)	336 052 (12.99)	-0.01961	390 154 (12.64)	310 429 (12.67)	-0.0008
85+	265 077 (8.06)	316 653 (12.24)	-0.13883	287 806 (9.33)	229 371 (9.36)	-0.0012
Sex						
Male	1 351 620 (41.09)	942 334 (36.43)	0.09577	1 205 601 (39.07)	960 346 (39.20)	-0.0027
Female	1 938 121 (58.91)	1 644 684 (63.57)	-0.09577	1 879 892 (60.93)	1 489 356 (60.80)	0.0027
Race						
American Indian/Alaskan Native	7822 (0.24)	6196 (0.24)	-0.00036	7461 (0.24)	5906 (0.24)	0.0002
Asian	81 310 (2.47)	58 782 (2.27)	0.01311	75 015 (2.43)	60 045 (2.45)	-0.0013
Black or African American	79 103 (2.40)	145 399 (5.62)	-0.16441	86 146 (2.79)	68 419 (2.79)	-0.0001
White	2 927 058 (88.98)	2 233 750 (86.34)	0.08005	2 746 633 (89.02)	2 179 858 (88.98)	0.0011
Hispanic	23 069 (0.70)	37 573 (1.45)	-0.07283	24 372 (0.79)	19 264 (0.79)	0.0004
Unknown	108 694 (3.30)	64 734 (2.50)	0.04777	90 889 (2.95)	72 287 (2.95)	-0.0003
Other	62 685 (1.91)	40 584 (1.57)	0.02577	54 976 (1.78)	43 922 (1.79)	-0.0008
Parts A, B, D Continuous enrollment[c]	3 289 741 (100.00)	2 587 018 (100.00)	0.00000	3 085 493 (100.00)	2 449 701 (100.00)	0.0000
Year of Index Date						
2018	883 530 (26.86)	1 001 531 (38.71)	0.25461	985 385 (31.94)	785 499 (32.07)	-0.0028
2019	1 413 174 (42.96)	865 767 (33.47)	0.19627	1 194 914 (38.73)	947 643 (38.68)	0.0009
2020	993 037 (30.19)	719 720 (27.82)	0.05215	905 194 (29.34)	716 559 (29.25)	0.0019
Medical History[d]						
Diabetes mellitus	799 473 (24.30)	715 854 (27.67)	-0.07688	778 769 (25.24)	618 245 (25.24)	0.0001
Chronic kidney disease	677 815 (20.60)	601 369 (23.25)	-0.06388	650 948 (21.10)	516 699 (21.09)	0.0001

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
Chronic lung disease[e]	399 752 (12.15)	376 444 (14.55)	-0.07060	396 384 (12.85)	314 365 (12.83)	0.0004
Congestive heart failure	228 884 (6.96)	244 925 (9.47)	-0.09151	230 487 (7.47)	182 873 (7.47)	0.0002
Ischemic heart disease	698 777 (21.24)	578 729 (22.37)	-0.02735	655 938 (21.26)	520 836 (21.26)	-0.0001
Dementia	110 360 (3.35)	155 629 (6.02)	-0.12618	115 019 (3.73)	91 439 (3.73)	-0.0003
Chronic liver disease	182 766 (5.56)	147 106 (5.69)	-0.00567	170 968 (5.54)	135 572 (5.53)	0.0003
Stroke/TIA	202 424 (6.15)	188 195 (7.27)	-0.04482	195 350 (6.33)	155 145 (6.33)	-0.0001
Immunocompromised Conditions						
Organ transplant	7708 (0.23)	7031 (0.27)	-0.00746	7486 (0.24)	5943 (0.24)	0.0000
Hematopoietic stem cell transplant	4688 (0.14)	2439 (0.09)	0.01402	3542 (0.11)	2858 (0.12)	-0.0006
Hematologic or solid malignancy w/recent receipt of chemotherapy	26 557 (0.81)	28 695 (1.11)	-0.03100	27 719 (0.90)	22 020 (0.90)	-0.0001
HIV infection	4805 (0.15)	2973 (0.11)	0.00863	3869 (0.13)	3083 (0.13)	-0.0001
Rheumatoid Arthritis	101 163 (3.08)	83 918 (3.24)	-0.00965	95 827 (3.11)	76 004 (3.10)	0.0002
IBD - Chron's disease	17 415 (0.53)	11 652 (0.45)	0.01131	15 129 (0.49)	12 008 (0.49)	0.0000
IBD - Colitis	31 110 (0.95)	20 302 (0.78)	0.01737	26 631 (0.86)	21 137 (0.86)	0.0000
Lupus	12 324 (0.37)	10 657 (0.41)	-0.00596	11 917 (0.39)	9435 (0.39)	0.0002
Multiple sclerosis	7963 (0.24)	6223 (0.24)	0.00031	7408 (0.24)	5877 (0.24)	0.0000
Psoriasis/Psoriatic arthritis	72 481 (2.20)	47 631 (1.84)	0.02573	63 142 (2.05)	50 209 (2.05)	-0.0002
Service Use History[d]						
≥1 dermatology visit	117 317 (3.57)	56 111 (2.17)	0.08379	88 273 (2.86)	70 433 (2.88)	-0.0009
≥1 optometry/ ophthalmology visit	1 868 057 (56.78)	1 239 480 (47.91)	0.17836	1 632 488 (52.91)	1 297 704 (52.97)	-0.0013
Number of hospitalizations						
0	2 935 250 (89.22)	2 232 535 (86.30)	0.08939	2 736 045 (88.67)	2 172 548 (88.69)	-0.0004
1	268 267 (8.15)	245 780 (9.50)	-0.04745	262 436 (8.51)	208 102 (8.49)	0.0004
2 or more	86 224 (2.62)	108 703 (4.20)	-0.08717	87 011 (2.82)	69 052 (2.82)	0.0001
Number of ED visits						
0	2 689 630 (81.76)	2 014 318 (77.86)	0.09716	2 492 980 (80.80)	1 979 624 (80.81)	-0.0004
1	445 833 (13.55)	366 569 (14.17)	-0.01787	427 471 (13.85)	339 093 (13.84)	0.0004
2 or more	154 278 (4.69)	206 131 (7.97)	-0.13495	165 042 (5.35)	130 985 (5.35)	0.0001
Durable medical equipment	933 046 (28.36)	747 282 (28.89)	-0.01158	866 178 (28.07)	687 552 (28.07)	0.0001

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
Hospice care	1887 (0.06)	5952 (0.23)	-0.04560	1144 (0.04)	911 (0.04)	-0.0001
Home health care	190 429 (5.79)	230 321 (8.90)	-0.11959	196 100 (6.36)	155 635 (6.35)	0.0001
Skilled nursing facility care	52 736 (1.60)	81 070 (3.13)	-0.10079	55 432 (1.80)	44 097 (1.80)	-0.0003
Concomitant Vaccine Use[f]						
Influenza	408 522 (12.42)	155 354 (6.01)	0.22313	238 538 (7.73)	188 259 (7.68)	0.0017
Pneumococcal	144 791 (4.40)	128 232 (4.96)	-0.02630	142 321 (4.61)	113 468 (4.63)	-0.0009
Tetanus- Diphtheria- Pertussis	67 769 (2.06)	3410 (0.13)	-0.18601	105 (0.00)	84 (0.00)	0.0000

COPD, chronic obstructive pulmonary disease; ED, emergency department; RZV, recombinant zoster vaccine; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; ION, ischemic optic neuropathy; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack; Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data. Index date is the RZV Dose 1 date in the RZV-exposed group and preventive visit date in the RZV-unvaccinated comparator group.

a. The N for the RZV-exposed cohort is shown for individuals who received RZV Dose 1.
b. RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening.
c. Allows one calendar month gap in enrolment; measured in the year preceding the index date.
d. Measured in the year prior to the index date.
e. Chronic lung disease includes COPD and bronchiectasis.
f. Measured on the index date.

Table 79 Baseline demographic and health characteristics of the ION analytic cohort by number of doses and dose spacing

Descriptive Characteristic	RZV Dose 1	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
Number of unique participants	485 024	2 804 717	122 768	2 681 949
Demographics				
Age at Index Date, Mean (SD)	75.01 (6.94)	74.24 (6.22)	74.91 (6.40)	74.21 (6.21)
Age categories				
65-69	123 375 (25.44)	733 669 (26.16)	28 389 (23.12)	705 280 (26.30)
70-74	140 168 (28.90)	895 100 (31.91)	37 075 (30.20)	858 025 (31.99)

Descriptive Characteristic	RZV Dose 1	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
75-79	102 289 (21.09)	624 185 (22.25)	28 801 (23.46)	595 384 (22.20)
80-84	64 702 (13.34)	341 176 (12.16)	17 512 (14.26)	323 664 (12.07)
85+	54 490 (11.23)	210 587 (7.51)	10 991 (8.95)	199 596 (7.44)
Sex				
Male	199 712 (41.18)	1 151 908 (41.07)	50 904 (41.46)	1 101 004 (41.05)
Female	285 312 (58.82)	1 652 809 (58.93)	71 864 (58.54)	1 580 945 (58.95)
Race				
American Indian/Alaskan Native	3 283 (0.68)	4 539 (0.16)	255 (0.21)	4 284 (0.16)
Asian	16 802 (3.46)	64 508 (2.30)	3 620 (2.95)	60 888 (2.27)
Black or African American	20 789 (4.29)	58 314 (2.08)	4 273 (3.48)	54 041 (2.01)
White	410 390 (84.61)	2 516 668 (89.73)	107 945 (87.93)	2 408 723 (89.81)
Hispanic	9 310 (1.92)	13 759 (0.49)	924 (0.75)	12 835 (0.48)
Unknown	14 196 (2.93)	94 498 (3.37)	3 490 (2.84)	91 008 (3.39)
Other	10 254 (2.11)	52 431 (1.87)	2 261 (1.84)	50 170 (1.87)
Parts A, B, D Continuous enrollment[a]	485 024 (100.00)	2 804 717 (100.00)	122 768 (100.00)	2 681 949 (100.00)
Year of Index Date				
2018	122 545 (25.27)	760 985 (27.13)	23 550 (19.18)	737 435 (27.50)
2019	193 240 (39.84)	1 219 934 (43.50)	55 776 (45.43)	1 164 158 (43.41)
2020	169 239 (34.89)	823 798 (29.37)	43 442 (35.39)	780 356 (29.10)

Descriptive Characteristic	RZV Dose 1	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
Medical History[b]				
Diabetes mellitus	136 592 (28.16)	662 881 (23.63)	31 962 (26.03)	630 919 (23.52)
Chronic kidney disease	118 250 (24.38)	559 565 (19.95)	27 579 (22.46)	531 986 (19.84)
Chronic lung disease[c]	71 804 (14.80)	327 948 (11.69)	15 776 (12.85)	312 172 (11.64)
Congestive heart failure	47 196 (9.73)	181 688 (6.48)	9 148 (7.45)	172 540 (6.43)
Ischemic heart disease	115 855 (23.89)	582 922 (20.78)	27 507 (22.41)	555 415 (20.71)
Alzheimer's/Dementia	28 862 (5.95)	81 498 (2.91)	4 449 (3.62)	77 049 (2.87)
Chronic liver disease	30 000 (6.19)	152 766 (5.45)	6 989 (5.69)	145 777 (5.44)
Stroke/TIA	36 403 (7.51)	166 021 (5.92)	7 630 (6.21)	158 391 (5.91)
Immunocompromised Conditions				
Organ transplant	1 572 (0.32)	6 136 (0.22)	319 (0.26)	5 817 (0.22)
Hematopoietic stem cell transplant	916 (0.19)	3 772 (0.13)	286 (0.23)	3 486 (0.13)
Hematologic or solid malignancy w/recent receipt of chemotherapy	5 161 (1.06)	21 396 (0.76)	1 114 (0.91)	20 282 (0.76)
HIV infection	1 068 (0.22)	3 737 (0.13)	227 (0.18)	3 510 (0.13)
Rheumatoid Arthritis	16 606 (3.42)	84 557 (3.01)	4 065 (3.31)	80 492 (3.00)
IBD - Crohn's disease	2 400 (0.49)	15 015 (0.54)	647 (0.53)	14 368 (0.54)
IBD - Colitis	4 326 (0.89)	26 784 (0.95)	1 166 (0.95)	25 618 (0.96)
Lupus	2 146 (0.44)	10 178 (0.36)	518 (0.42)	9 660 (0.36)
Multiple Sclerosis	1 213 (0.25)	6 750 (0.24)	313 (0.25)	6 437 (0.24)
Psoriasis/Psoriatic Arthritis	10 103 (2.08)	62 378 (2.22)	2 645 (2.15)	59 733 (2.23)
Service Use History[b]				
≥1 dermatology visit	13 316 (2.75)	104 001 (3.71)	4 047 (3.30)	99 954 (3.73)
≥1 optometry/ ophthalmology visit	248 958 (51.33)	1 619 099 (57.73)	69 876 (56.92)	1 549 223 (57.76)
Number of hospitalizations				
0	420 501 (86.70)	2 514 749 (89.66)	109 062 (88.84)	2 405 687 (89.70)
1	45 674 (9.42)	222 593 (7.94)	10 462 (8.52)	212 131 (7.91)
2 or more	18 849 (3.89)	67 375 (2.40)	3 244 (2.64)	64 131 (2.39)

Descriptive Characteristic	RZV Dose 1	RZV Dose 2	RZV Dose 2 28 to 60-day dose spacing	RZV Dose 2 >60 days dose spacing
	N (%)	N (%)	N (%)	N (%)
Number of ED visits				
0	378 674 (78.07)	2 310 956 (82.40)	99 853 (81.33)	2 211 103 (82.44)
1	74 119 (15.28)	371 714 (13.25)	16 904 (13.77)	354 810 (13.23)
2 or more	32 231 (6.65)	122 047 (4.35)	6 011 (4.90)	116 036 (4.33)
Durable medical equipment	147 027 (30.31)	786 019 (28.02)	35 891 (29.23)	750 128 (27.97)
Hospice care	900 (0.19)	987 (0.04)	75 (0.06)	912 (0.03)
Home health care	41 758 (8.61)	148 671 (5.30)	7 295 (5.94)	141 376 (5.27)
Skilled nursing facility care	12 742 (2.63)	39 994 (1.43)	2 049 (1.67)	37 945 (1.41)
Concomitant Vaccine Use[d]				
Influenza	77 390 (15.96)	331 132 (11.81)	17 046 (13.88)	314 086 (11.71)
Pneumococcal	37 063 (7.64)	107 728 (3.84)	5 259 (4.28)	102 469 (3.82)
Tetanus- Diphtheria- Pertussis	15 179 (3.13)	52 590 (1.88)	2 652 (2.16)	49 938 (1.86)

COPD, chronic obstructive pulmonary disease; ED, emergency department; ION, ischemic optic neuropathy; RZV, recombinant zoster vaccine; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack;

Note: Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data; Index date is the RZV Dose 1 date in the exposed group and preventive visit date in the comparator group.

a. Allows one calendar month gap in enrolment; measured in the year preceding the index date.
b. Measured in the year prior to the index date.
c. Chronic lung disease includes COPD and bronchiectasis.
d. Measured on the index date.

14.6.2. Baseline characteristics of supplemental cohort

A supplemental cohort that excluded from the comparator arm any participant that received at least one dose of RZV was used to conduct a sensitivity analysis to the primary analysis of separate Dose 1 and Dose 2. The RZV-exposed included 3 289 741 and the RZV-unvaccinated included 2 109 522 participants.

Table 80 displays the baseline characteristics in each group along with the corresponding SMDs for the unweighted and the weighted sample in the supplemental cohort. All covariates had SMDs around zero, suggesting that weighting worked well to ensure covariate balance.

Table 80 Baseline demographic and health characteristics of the supplemental cohort: Before and after IPTW weighting

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Number of unique participants	3 289 741	2 109 522		3 086 370	1 986 809	
Demographics						
Age at Index Date, Mean (SD)	74.36 (6.34)	75.46 (7.35)	-0.1600	74.61 (6.58)	74.75 (6.76)	-0.0214
Age categories						
65-69	857 044 (26.05)	532 691 (25.25)	0.0183	802 393 (26.00)	514 999 (25.92)	0.0018
70-74	1 035 268 (31.47)	590 548 (27.99)	0.0761	935 948 (30.33)	601 721 (30.29)	0.0009
75-79	726 474 (22.08)	420 375 (19.93)	0.0529	659 161 (21.36)	424 478 (21.36)	-0.0002
80-84	405 878 (12.34)	280 698 (13.31)	-0.0290	394 099 (12.77)	254 594 (12.81)	-0.0014
85+	265 077 (8.06)	285 210 (13.52)	-0.1768	294 768 (9.55)	191 017 (9.61)	-0.0022
Sex						
Male	1 351 620 (41.09)	773 235 (36.65)	0.0910	1 213 730 (39.33)	784 799 (39.50)	-0.0036
Female	1 938 121 (58.91)	1 336 287 (63.35)	-0.0910	1 872 640 (60.67)	1 202 010 (60.50)	0.0036
Race						
American Indian/Alaskan Native	7 822 (0.24)	5 361 (0.25)	-0.0033	7 760 (0.25)	5 004 (0.25)	-0.0001
Asian	81 310 (2.47)	47 899 (2.27)	0.0132	75 358 (2.44)	49 258 (2.48)	-0.0024
Black or African American	79 103 (2.40)	133 863 (6.35)	-0.1936	87 545 (2.84)	56 265 (2.83)	0.0003
White	2 927 058 (88.98)	1 806 707 (85.65)	0.1002	2 746 142 (88.98)	1 766 965 (88.93)	0.0013
Hispanic	23 069 (0.70)	34 665 (1.64)	-0.0876	25 890 (0.84)	16 601 (0.84)	0.0004
Unknown	108 694 (3.30)	49 080 (2.33)	0.0591	89 022 (2.88)	57 273 (2.88)	0.0001
Other	62 685 (1.91)	31 947 (1.51)	0.0302	54 652 (1.77)	35 443 (1.78)	-0.0010
Parts A, B, D Continuous enrollment[c]	3 289 741 (100.00)	2 109 522 (100.00)	0.0000	3 086 370 (100.00)	1 986 809 (100.00)	0.0000
Year of Index Date						
2018	883 530 (26.86)	718 776 (34.07)	-0.1573	916 860 (29.71)	593 374 (29.87)	-0.0035
2019	1 413 174 (42.96)	714 401 (33.87)	0.1877	1 206 501 (39.09)	774 093 (38.96)	0.0027
2020	993 037 (30.19)	676 345 (32.06)	-0.0405	963 009 (31.20)	619 343 (31.17)	0.0006
Medical History[d]						
Diabetes mellitus	799 473 (24.30)	609 507 (28.89)	-0.1041	788 003 (25.53)	507 794 (25.56)	-0.0006
Chronic kidney disease	677 815 (20.60)	516 420 (24.48)	-0.0929	660 991 (21.42)	425 488 (21.42)	0.0000
Chronic lung disease[e]	399 752 (12.15)	322 403 (15.28)	-0.0911	401 360 (13.00)	258 208 (13.00)	0.0002

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Congestive heart failure	228 884 (6.96)	218 291 (10.35)	-0.1208	235 596 (7.63)	151 506 (7.63)	0.0003
Ischemic heart disease	698 777 (21.24)	490 611 (23.26)	-0.0485	664 386 (21.53)	427 465 (21.52)	0.0003
Alzheimer's/Dementia	110 360 (3.35)	144 218 (6.84)	-0.1588	117 849 (3.82)	75 822 (3.82)	0.0001
Chronic liver disease	182 766 (5.56)	122 060 (5.79)	-0.0100	172 022 (5.57)	110 515 (5.56)	0.0005
Stroke/TIA	202 424 (6.15)	160 932 (7.63)	-0.0583	197 300 (6.39)	126 990 (6.39)	0.0000
Immunocompromised Conditions						
Organ transplant	7 708 (0.23)	6 071 (0.29)	-0.0105	7 584 (0.25)	4 899 (0.25)	-0.0002
Hematopoietic stem cell transplant	4 688 (0.14)	1 924 (0.09)	0.0150	3 461 (0.11)	2 300 (0.12)	-0.0011
Hematologic or solid malignancy w/recent receipt of chemotherapy	26 557 (0.81)	25 057 (1.19)	-0.0383	28 287 (0.92)	18 193 (0.92)	0.0001
HIV infection	4 805 (0.15)	2 431 (0.12)	0.0085	3 758 (0.12)	2 414 (0.12)	0.0001
Rheumatoid Arthritis	101 163 (3.08)	69 405 (3.29)	-0.0123	96 287 (3.12)	61 919 (3.12)	0.0002
IBD - Crohn's disease	17 415 (0.53)	9 200 (0.44)	0.0135	14 974 (0.49)	9 608 (0.48)	0.0002
IBD - Colitis	31 110 (0.95)	16 006 (0.76)	0.0203	26 346 (0.85)	16 941 (0.85)	0.0001
Lupus	12 324 (0.37)	8 844 (0.42)	-0.0071	11 946 (0.39)	7 665 (0.39)	0.0002
Multiple Sclerosis	7 963 (0.24)	5 035 (0.24)	0.0007	7 391 (0.24)	4 747 (0.24)	0.0001
Psoriasis/Psoriatic Arthritis	72 481 (2.20)	37 445 (1.78)	0.0307	62 531 (2.03)	40 315 (2.03)	-0.0002
Service Use History[d]						
≥1 dermatology visit	117 317 (3.57)	39 476 (1.87)	0.1044	80 009 (2.59)	51 925 (2.61)	-0.0013
≥1 optometry/ ophthalmology visit	1 868 057 (56.78)	963 830 (45.69)	0.2233	1 619 195 (52.46)	1 043 531 (52.52)	-0.0012
Number of hospitalizations						
0	2 935 250 (89.22)	1 805 280 (85.58)	0.1101	2 734 021 (88.58)	1 760 562 (88.61)	-0.0009
1	268 267 (8.15)	207 082 (9.82)	-0.0581	263 897 (8.55)	169 600 (8.54)	0.0005
2 or more	86 224 (2.62)	97 160 (4.61)	-0.1065	88 452 (2.87)	56 647 (2.85)	0.0009
Number of ED visits						
0	2 689 630 (81.76)	1 624 907 (77.03)	0.1172	2 489 895 (80.67)	1 603 132 (80.69)	-0.0004
1	445 833 (13.55)	304 018 (14.41)	-0.0248	429 792 (13.93)	276 621 (13.92)	0.0001
2 or more	154 278 (4.69)	180 597 (8.56)	-0.1561	166 683 (5.40)	107 057 (5.39)	0.0005
Durable medical equipment	933 046 (28.36)	616 913 (29.24)	-0.0195	869 541 (28.17)	559 530 (28.16)	0.0003
Hospice care	1 887 (0.06)	5 857 (0.28)	-0.0539	1 088 (0.04)	698 (0.04)	0.0001
Home health care	190 429 (5.79)	205 420 (9.74)	-0.1480	199 088 (6.45)	127 872 (6.44)	0.0006

Descriptive Characteristic	Unweighted			IPTW Weighted		
	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD	RZV-exposed[a]	RZV-unvaccinated comparator[b]	SMD
	N (%)	N (%)		N (%)	N (%)	
Skilled nursing facility care	52 736 (1.60)	73 911 (3.50)	-0.1207	56 087 (1.82)	36 110 (1.82)	0.0000
Concomitant Vaccine Use[f]						
Influenza	408 522 (12.42)	131 137 (6.22)	0.2146	256 370 (8.31)	166 255 (8.37)	-0.0022
Pneumococcal	144 791 (4.40)	102 196 (4.84)	-0.0211	140 352 (4.55)	92 385 (4.65)	-0.0049
Tetanus- Diphtheria- Pertussis	67 769 (2.06)	2 195 (0.10)	0.1899	79 (0.00)	51 (0.00)	0.0000

COPD, chronic obstructive pulmonary disease; ED, emergency department; RZV, recombinant zoster vaccine; ION, ischemic optic neuropathy; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack;

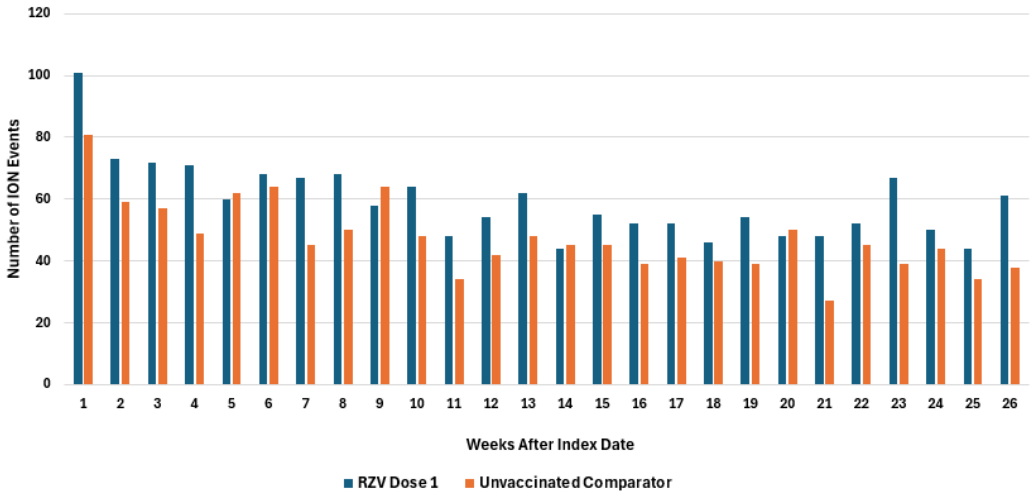
Note: Race Unknown (was not specified by the individual) and Other (all other races) are CMS-defined categories in the raw data. Index date is the RZV Dose 1 date in the exposed group and preventive visit date in the comparator group.

a. The Ns for the RZV exposed cohorts are shown for those who at least received RZV Dose1
b. RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening.
c. Allows one calendar month gap in enrolment; measured in the year preceding the index date.
d. Measured in the year prior to the index date.
e. Chronic lung disease includes COPD and bronchiectasis.
f. Measured on the index date.

14.6.3. ION events in the 183-day follow-up period

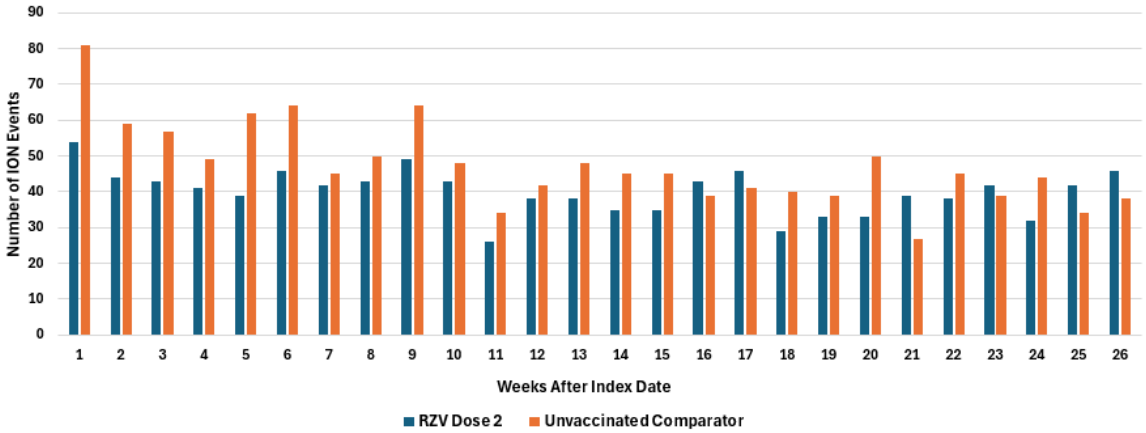
Figure 54 and Figure 55 show the distribution of ION cases from the index date by RZV Dose. The 1547 ION cases after RZV Dose 1 were generally evenly distributed across the weeks from the index date. The highest number of cases were observed in Week 1 (101 cases) and the lowest in Weeks 14 and 25 (44 cases each). The 1047 cases after Dose 2 were evenly distributed during follow-up with the highest number of cases (n=54) in Week 1 after the index date. For the RZV-unvaccinated comparators, ION cases after the index date totaled 1234, with 81 cases in Week 1 after the index date. The cases were nearly evenly distributed across the weeks for both RZV Dose 1 and Dose 2 as well as the preventive care comparators.

Figure 54 Distribution of incident ION events by week from the index date: RZV Dose 1 and unvaccinated comparators



Note: Index date, date of vaccination for Dose 1 for RZV-exposed, or date of preventive care visit for RZV-unvaccinated comparator; RZV, recombinant zoster vaccine; ION, ischemic optic neuropathy.

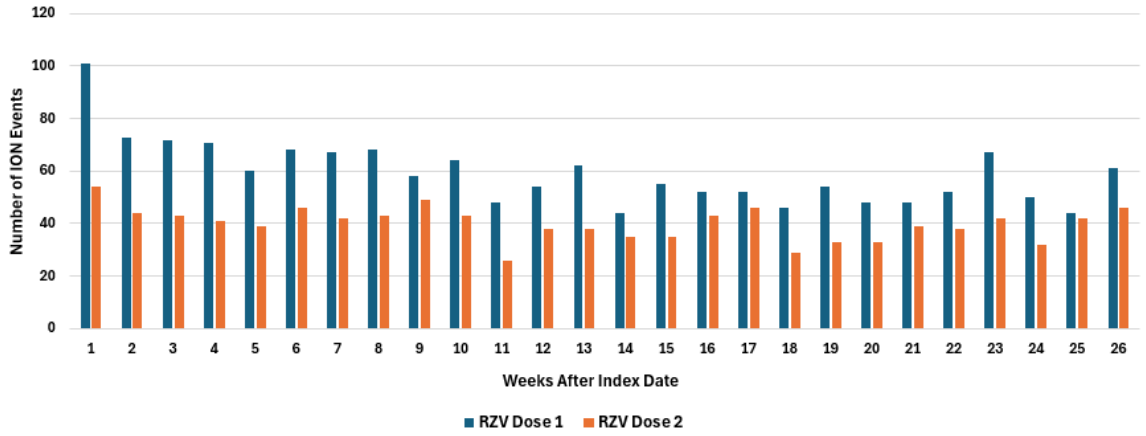
Figure 55 Distribution of incident ION events by week from the index date: RZV Dose 2 and unvaccinated comparators



Note: Index date, date of vaccination for Dose 2 for RZV-exposed, or date of preventive care visit for RZV-unvaccinated comparator; RZV, recombinant zoster vaccine; ION, ischemic optic neuropathy.

Figure 56 below shows the distribution of incident ION events by the week of follow-up relative to RZV Dose 1 and Dose 2. The graph depicts the number of events per week and visually shows that the number of cases after RZV Dose 1 was greater than the number of cases after RZV Dose 2. The number of cases per week of follow-up is relatively stable.

Figure 56 Distribution of incident ION events by week from the index date: RZV Dose 1 and Dose 2



Note: Index date, date of vaccination for Dose 1 or Dose 2; RZV, recombinant zoster vaccine; ION, ischemic optic neuropathy.

14.6.4. Crude and covariate adjusted risk estimated for ION

This section includes the hazard ratios for the crude and covariate adjusted models for all the ION analyses. The tables in this section are provided for reference to the IPTW-adjusted analyses provided in the main text.

14.6.4.1. Primary analysis

Table 81 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the ION primary analysis of RZV Dose 1 and RZV Dose 2. The estimates are the same as the IPTW-adjusted estimates. In this large sample that had good balance in the extensive baseline covariates, the risk estimates had narrow confidence intervals.

Table 81 Risk estimates for primary analysis of ION within a 183-days follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Separate analysis						
RZV Dose 1	3 289 741	1547	1 621 853	9.54 (9.07 – 10.03)	0.93 (0.86 – 1.00)	0.97 (0.90 – 1.05)
Comparator	2 587 018	1234	1 194 007	10.34 (9.77 – 10.93)	Ref.	Ref.
RZV Dose 2	2 509 168	1047	1 236 365	8.47 (7.97 – 9.00)	0.82 (0.76 – 0.89)	0.84 (0.77 – 0.92)
Comparator	2 587 018	1234	1 194 007	10.33 (9.77 – 10.93)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; ION, Ischemic Optic Neuropathy; PY, persons-years; RZV, recombinant zoster vaccine.

14.6.4.2. Secondary analysis

Table 82 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the ION secondary analysis of a combined dose single risk estimate and a time-varying analysis separate estimate for RZV Dose 1 and RZV Dose 2. The HR for the combined dose analysis was not statistically significant after covariate adjustment. The time-varying HR did not demonstrate a risk of ION after RZV Dose 1, which mirrored the IPTW-adjusted estimate. The time-varying RZV Dose 2 HR was lower than for RZV Dose 1, and it mirrored the IPTW-adjusted analysis reported in the main text.

Table 82 Risk estimates for secondary analysis of ION within a 183-day-follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Combined dose						
RZV Dose 1 and Dose 2	3 289 741	2084	2 267 774	9.19 (8.80 – 9.59)	0.91 (0.85 – 0.98)	0.97 (0.90 – 1.05)
Comparator	2 587 018	1234	1 194 007	10.33 (9.77 – 10.93)	Ref.	Ref.
Time-varying separate dose						
RZV Dose 1	3 289 741	1037	1 031 409	10.05 (9.46 – 10.69)	0.98 (0.90 –1.07)	1.01 (0.93 – 1.10)

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
RZV Dose 2	2 494 504	510	583 615	8.74 (8.01 – 9.53)	0.87 (0.78 – 0.97)	0.93 (0.83 – 1.03)
Comparator	2 587 018	1234	1 194 007	10.33 (9.77 – 10.93)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; ION, Ischemic Optic Neuropathy; PY, persons-years; RZV, recombinant zoster vaccine.

14.6.4.3. COVID-19 sensitivity analysis

Table 83 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the ION COVID-19 sensitivity analysis. Risk estimates were generated for RZV Dose 1 and RZV Dose 2. The estimates align with the inference from the IPTW-adjusted estimates.

Table 83 Risk estimates for COVID-19 sensitivity of the primary analysis of ION with a 183-day-follow-up period

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
COVID-19 analysis [a]						
RZV Dose 1	2 394 418	985	1 007 328	9.78 (9.19 – 10.41)	0.91 (0.83 – 1.00)	0.96 (0.87 – 1.05)
Comparator	1 941 341	850	794 804	10.69 (10.00 – 11.44)	Ref.	Ref.
RZV Dose 2	1 735 472	618	675 375	9.15 (8.46 – 9.90)	0.85 (0.77 – 0.95)	0.87 (0.78 – 0.97)
Comparator	1 941 341	850	794 804	10.69 (10.00 – 11.44)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; ION, Ischemic Optic Neuropathy; PY, persons-years; RZV, recombinant zoster vaccine.
a. 01 February 2020 included as a censoring event.

14.6.4.4. Dose-compliant sensitivity analysis

Table 84 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the ION dose-compliant sensitivity analysis. This is a sensitivity analysis to the secondary analysis that incorporates a combined dose and a time-varying exposure. This sensitivity analysis includes the subset of the primary analysis cohort with RZV Dose 1 and Dose 2 spacing two to six months apart, i.e., compliant with the US label. The IPTW-adjusted estimates were not significant with the lower confidence intervals below or at 1.0, which aligns with the covariate adjusted models.

Table 84 Risk estimates for the dose-compliant sensitivity of the secondary analysis of ION

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Subset of combined dose						
RZV Dose 1 and Dose 2	2 479 828	1562	1 758 609	8.88 (8.45 – 9.33)	0.87 (0.81 – 0.94)	0.95 (0.87 – 1.02)
Comparator	2 587 018	1234	1 194 007	10.33 (9.77 – 10.93)	Ref.	Ref.
Subset of time-varying separate dose						
RZV Dose 1	2 479 828	645	654 428	9.86 (9.12 – 10.65)	0.95 (0.86 – 1.05)	0.99 (0.90 – 1.10)
RZV Dose 2	2 443 933	496	565 903	8.76 (8.03 – 9.57)	0.87 (0.78 – 0.97)	0.93 (0.83 – 1.04)
Comparator	2 587 018	1234	1 194 007	10.33 (9.77 – 10.93)	Ref.	Ref.

Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; ION, Ischemic Optic Neuropathy; PY, persons-years; RZV, recombinant zoster vaccine.

14.6.4.5. Supplemental sensitivity analysis

Table 85 includes the unweighted numbers, IR along with the crude and covariate adjusted HR and 95% CIs for the ION supplemental sensitivity analysis. This is a sensitivity analysis to the primary analysis where individuals are removed from the comparator arm if they receive RZV after their preventive care visit. The crude and covariate adjusted models produced results that align with the IPTW-adjusted estimates.

Table 85 Risk estimates for the primary analysis of ION in the supplemental cohort

Comparator cohort	No. persons	No. events	PY of follow-up	IR per 10 000 PY (95% CI)	Crude HR (95% CI)	Covariate Adj. HR (95% CI)
Exclude comparators who received RZV						
RZV Dose 1	3 289 741	1547	1 621 853	9.54 (9.07 – 10.03)	0.79 (0.73 – 0.85)	0.83 (0.77 – 0.90)
Comparator	2 109 522	1234	1 015 035	12.16 (11.50 – 12.85)	Ref.	Ref.
RZV Dose 2	2 509 168	1047	1 236 365	8.47 (7.97 – 9.00)	0.70 (0.64 – 0.76)	0.72 (0.66 – 0.79)
Comparator	2 109 522	1234	1 015 035	12.16 (11.50 – 12.85)	Ref.	Ref.

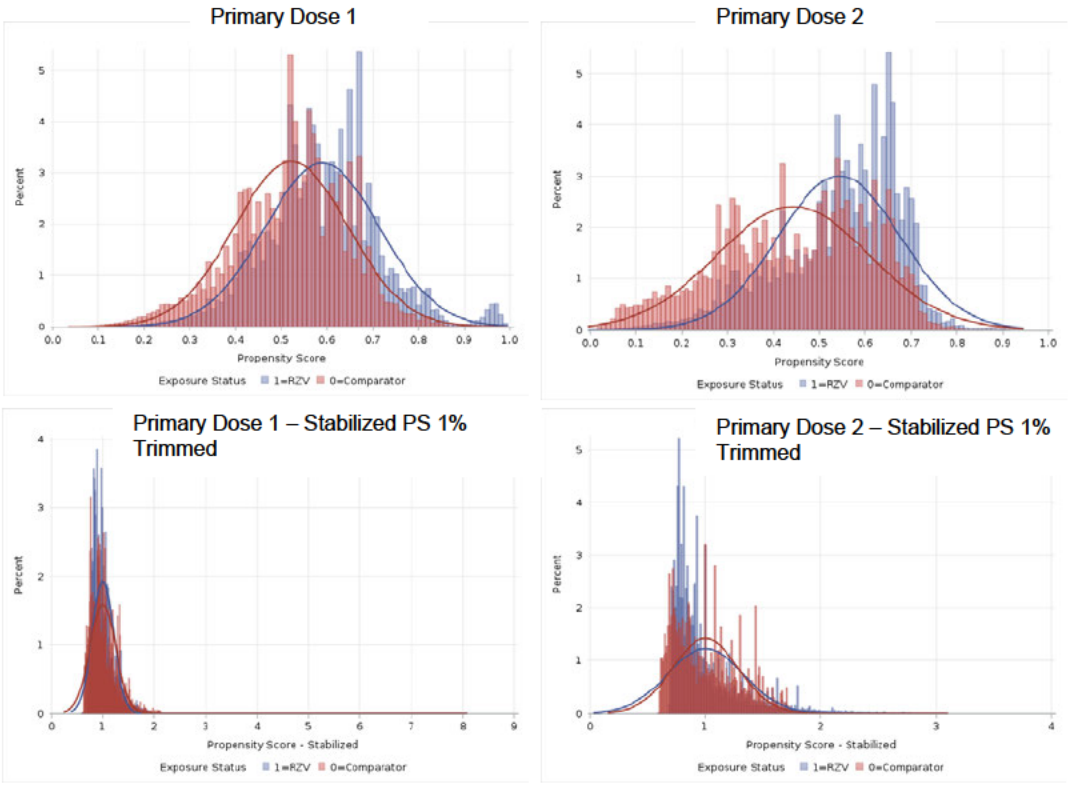
Adj, adjusted; CI, confidence interval; comparator is the RZV-unvaccinated comparator; HR, hazard ratio; IR, incidence rate; No., number; ION, Ischemic Optic Neuropathy; PY, persons-years; RZV, recombinant zoster vaccine.

14.6.5. Propensity score distribution and weights for ION

14.6.5.1. Primary analysis

The PS distributions for the primary analysis of RZV Dose 1 and Dose 2 are shown in Figure 57 below for both the common range distribution and the IPTW stabilized with 1% asymmetrical trimmed distribution. There was moderate overlap before applying the stabilized IPTW, which improved after applying the stabilized weight and 1% asymmetrical trim. The IPTW stabilized weight tempered the extreme weights and ensured covariate balance between RZV-exposed and the RZV-unvaccinated comparators.

Figure 57 ION primary analysis propensity score distribution: Dose 1 and Dose 2



Primary Dose 1, primary analysis for RZV Dose 1; Primary Dose 2, primary analysis for RZV Dose 2.

The PS weights for the primary and secondary combined dose and time-varying dose analyses of RZV Dose 1 and Dose 2 are shown in Table 86 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS predicted. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. For Dose 1 and the combined and time-varying dose, the RZV-unvaccinated comparator had a large IPTW stabilized weight >65, which was reduced to approximately 8 after 1% asymmetrical trimming and applying the IPTW stabilized weight.

For Dose 2, the RZV-exposed had a large IPTW stabilized weight >67, which was reduced to approximately 3 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The 1% trimming with stabilized weight avoided extreme weights influencing the analysis.

Table 86 Propensity score weights for ION primary and secondary analyses

Primary Analysis Dose 1 and Secondary Analyses of Combined and Time-Varying Dose				
Common Range		Mean	Minimum	Maximum
RZV-unvaccinated comparator	Original PS	0.52176	0.045742	0.9932983
	IPTW	2.2756073	1.0479346	149.2169555
	IPTW Stabilized	1.0018866	0.4613765	65.6960764
RZV-exposed	Original PS	0.5895902	0.045321	0.9931963
	IPTW	1.7868656	1.0068503	22.0648492

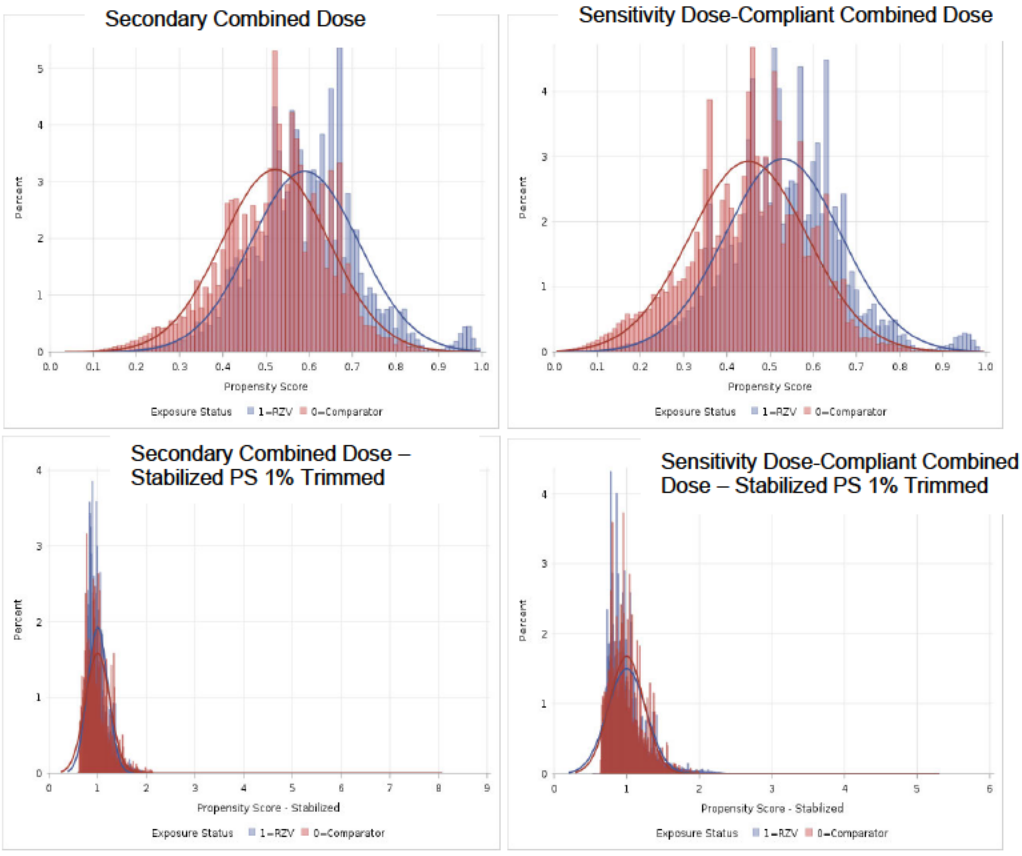
Primary Analysis Dose 1 and Secondary Analyses of Combined and Time-Varying Dose				
Common Range		Mean	Minimum	Maximum
	IPTW Stabilized	1.0001584	0.5635621	12.3503097
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5315483	0.2680497	0.945116
	IPTW	2.2571232	1.366213	18.2202322
	IPTW Stabilized	0.9994319	0.6049456	8.067739
RZV-exposed	Original PS	0.5776019	0.2662474	0.9465108
	IPTW	1.7952498	1.056512	3.7559046
	IPTW Stabilized	1.0003309	0.5886989	2.0928271
Primary Analysis Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.442699	0.0074016	0.9409041
	IPTW	1.9705655	1.0074568	16.9216556
	IPTW Stabilized	1.0004541	0.5114848	8.5911074
RZV-exposed	Original PS	0.5434644	0.0073354	0.9410741
	IPTW	2.0322193	1.0626156	136.325526
	IPTW Stabilized	1.0004636	0.5231267	67.1131942
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4655669	0.1610151	0.743055
	IPTW	2.0152886	1.1919166	3.891883
	IPTW Stabilized	1.000162	0.591533	1.9314918
RZV-exposed	Original PS	0.5412964	0.1625926	0.7392214
	IPTW	1.9851462	1.3527747	6.1503419
	IPTW Stabilized	0.9999435	0.6814099	3.0980059

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.6.5.2. Secondary and sensitivity analysis: Combined dose estimate

The PS distributions for the secondary analysis with a single risk estimate for RZV Dose 1 and Dose 2, using a partly conditional survival model, are shown in Figure 58. The distributions are shown for both the common range distribution and the IPTW stabilized with 1% asymmetrical trimmed cohort for the secondary analysis. The PS distribution for the sensitivity analysis of the dose-compliant subsample who received both doses 60 to 183-days apart is also shown. There was moderate overlap before applying the stabilized IPTW, which improved after applying the stabilized weight and 1% asymmetrical trim. As in the primary analysis, the IPTW stabilized weight tempered the extreme weights and ensured covariate balance between RZV-exposed and the RZV-unvaccinated comparators.

Figure 58 ION secondary and sensitivity analyses propensity score distribution: Combined Dose 1 and Dose 2

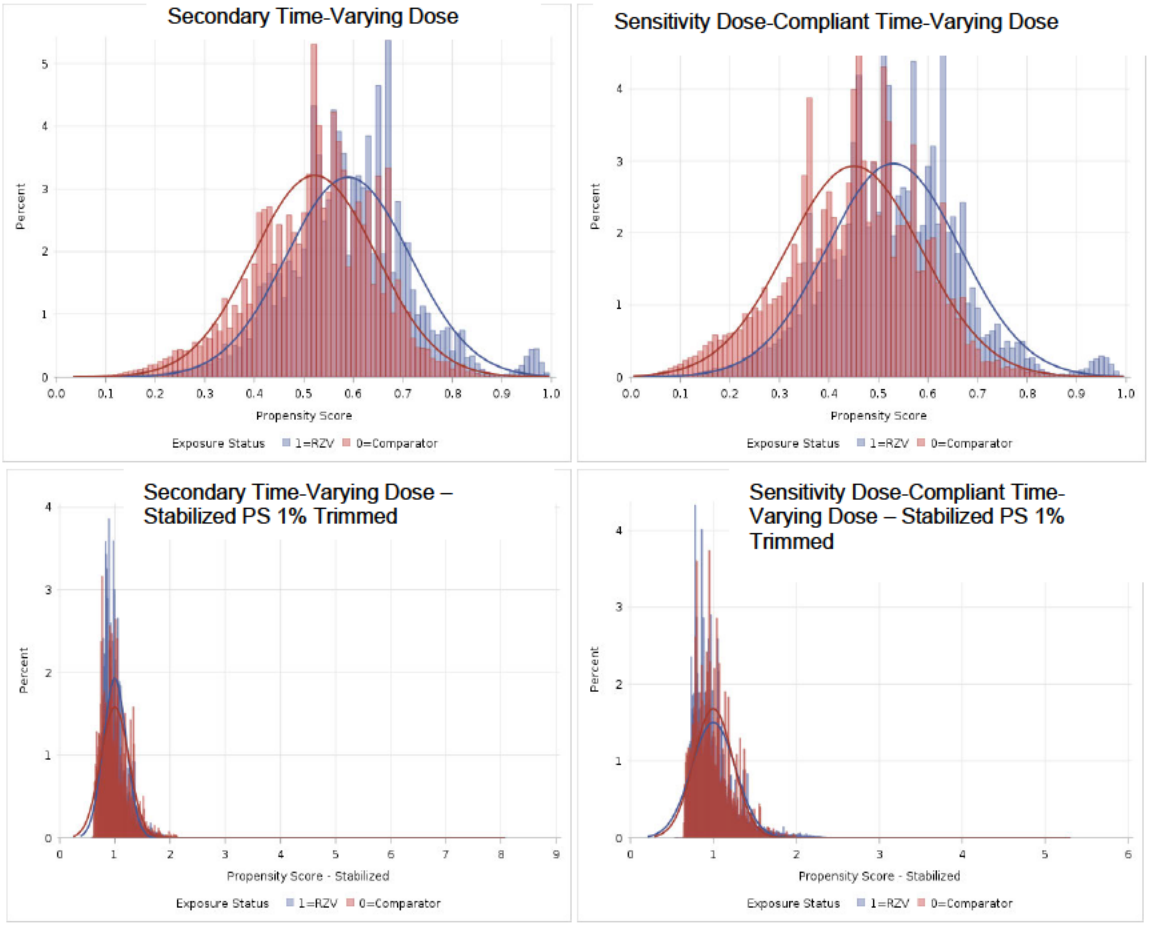


Secondary analysis using a partly conditional survival model for a single risk estimate for both RZV doses; Sensitivity to the secondary analysis using a partly conditional survival model for a single risk estimate for both RZV doses in the dose-compliant subsample with 60 to 183 dose spacing.

14.6.5.3. Secondary and sensitivity analysis: Time-varying dose estimate

The PS distributions for the secondary analysis with a time-varying dose exposure for RZV Dose 1 and Dose 2 are shown in Figure 59. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for the secondary analysis and for the sensitivity analysis of the dose-compliant subsample who received both doses 60 to 183-days apart show good overlap with the 1% trimmed stabilized IPTW.

Figure 59 ION secondary and sensitivity analyses propensity score distribution: Time-varying Dose 1 and Dose 2

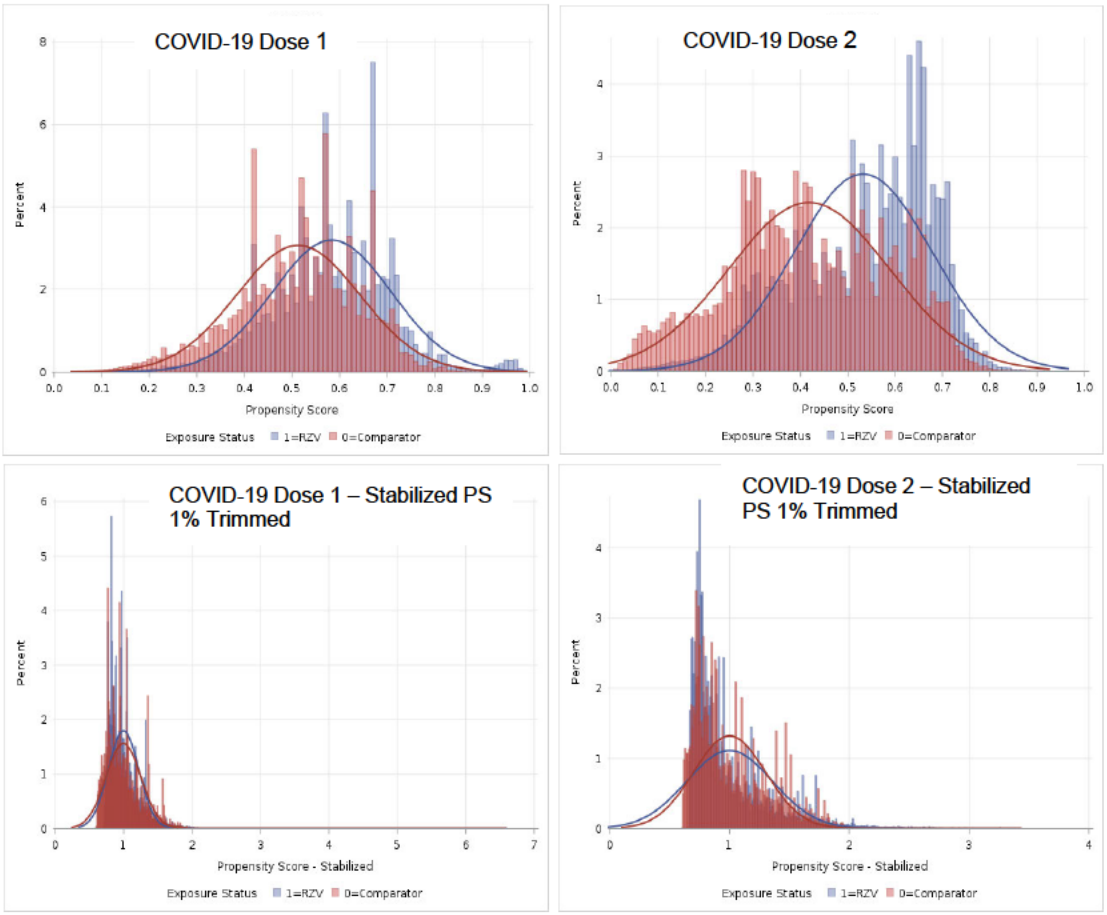


Secondary analysis using a time-varying Cox proportional hazards model with RZV doses as a time-varying covariate for a separate risk estimate for RZV Dose 1 and Dose 2; Sensitivity to the secondary analysis using time-varying Cox proportional hazards model for a separate risk estimate for RZV Dose 1 and Dose 2 in the dose-compliant subsample with 60 to 183 dose spacing.

14.6.5.4. COVID-19 sensitivity analysis

The COVID-19 sensitivity analysis includes 01 February 2020 as a censoring event, which will exclude events that may have occurred after this date. The PS distributions for the COVID-19 sensitivity analysis for Dose 1 and Dose 2 are shown in Figure 60. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for RZV Dose 1 and for RZV Dose 2 are provided to illustrate the overlap between the RZV-exposed and the RZV-V-unvaccinated comparators.

Figure 60 ION COVID-19 sensitivity analysis propensity score distribution: Dose 1 and Dose 2



COVID-19 Dose 1, COVID-19 sensitivity analysis for RZV Dose 1; COVID-19 Dose 2, COVID-19 sensitivity analysis for Dose 2.

The PS weights for the COVID-19 sensitivity analysis to the primary analysis of separate RZV Dose 1 and RZV Dose 2 are shown in Table 87 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well.

The common range in the COVID-19 sensitivity analysis of Dose 1 for the RZV-unvaccinated comparator had an IPTW stabilized weight >46, which was reduced to approximately 6.5 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The common range in the COVID-19 sensitivity analysis of Dose 2, the RZV-exposed had an IPTW stabilized weight >74 which was reduced to approximately 3.43 after 1% trimming was applied.

Table 87 Propensity score weights for ION COVID-19 sensitivity analysis to the primary analysis of separate Dose 1 and Dose 2 risk estimates

COVID-19 Sensitivity Analysis: Dose 1				
Common Range		Mean	Minimum	Maximum
RZV-unvaccinated comparator	Original PS	0.5132956	0.0441463	0.9902844
	IPTW	2.2360065	1.0461852	102.9275208
	IPTW Stabilized	1.0011886	0.4684372	46.086563
RZV-exposed	Original PS	0.58382	0.0439534	0.9901158
	IPTW	1.812008	1.0099829	22.7513547
	IPTW Stabilized	1.0006679	0.5577555	12.5642664
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5235206	0.2446162	0.931841
	IPTW	2.2266919	1.3238303	14.6715667
	IPTW Stabilized	0.9995364	0.5942522	6.5858978
RZV-exposed	Original PS	0.5735846	0.2392569	0.9351673
	IPTW	1.8152223	1.0693274	4.1796082
	IPTW Stabilized	1.0003899	0.5893186	2.3034301
COVID-19 Sensitivity Analysis: Dose 2				
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4181416	0.0063948	0.921552
	IPTW	1.894457	1.006436	12.7472943
	IPTW Stabilized	1.0002811	0.5314024	6.730624
RZV-exposed	Original PS	0.5322407	0.0063221	0.9210686
	IPTW	2.1217502	1.0856954	158.1756931
	IPTW Stabilized	1.0014573	0.5124438	74.6582746
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4410456	0.1436551	0.7474636
	IPTW	1.9366066	1.1677538	3.9598257
	IPTW Stabilized	1.0000038	0.602992	2.0447316
RZV-exposed	Original PS	0.5290991	0.1409656	0.7464635
	IPTW	2.0679501	1.3396502	7.0939277
	IPTW Stabilized	1.0001246	0.6478962	3.4308427

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.6.5.5. Dose compliant sensitivity analysis

The PS weights for the secondary and sensitivity (dose-compliant) analyses of time-varying RZV Dose 1 and Dose 2 are shown in Table 88 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well.

For the dose-compliant subsample, the RZV-unvaccinated comparator had an IPTW stabilized weight >53, which was reduced to 5.3, and the RZV-exposed had an IPTW stabilized weight >36, which was reduced to 2.59.

Table 88 Propensity score weights for ION dose-compliant sensitivity analyses: Combined dose and time-varying dose

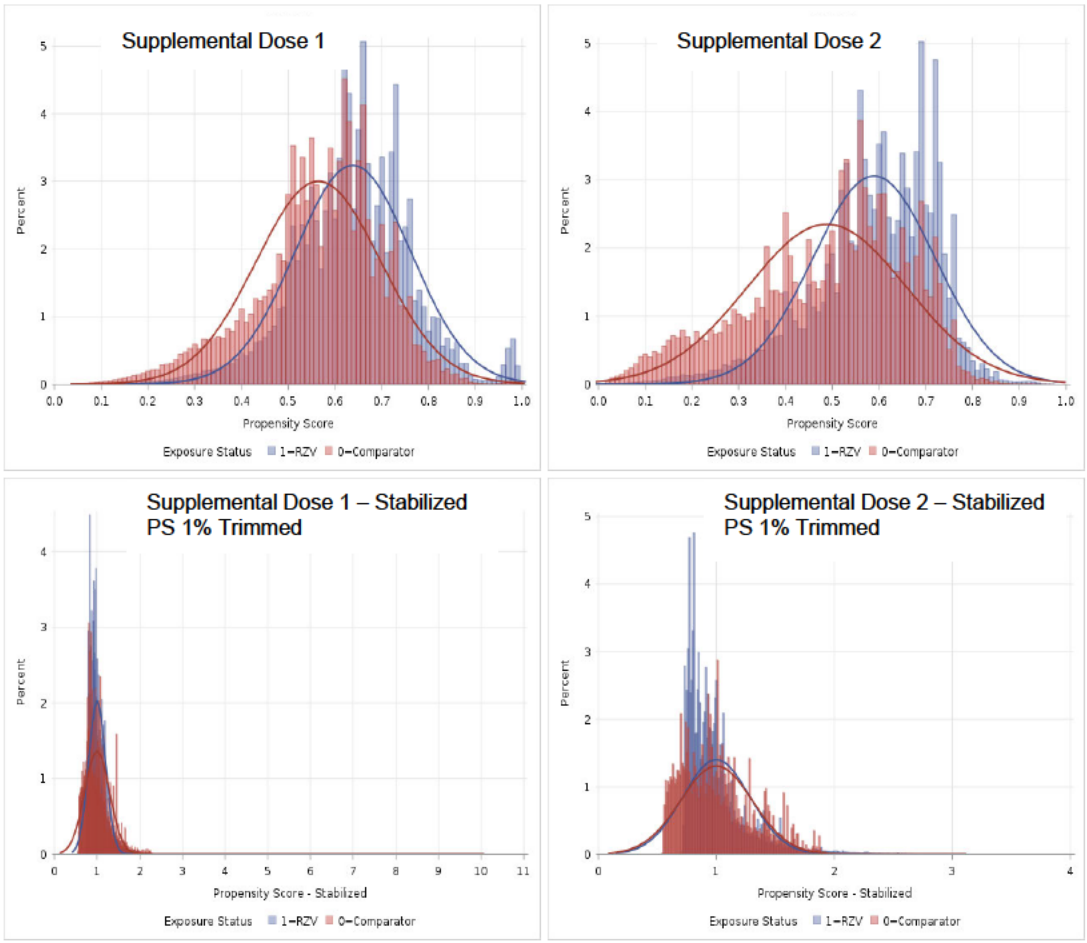
Sensitivity Analysis: Combined and Time-Varying Dose with 60 to 183-dose spacing				
Common Range				
RZV-unvaccinated comparator	Original PS	0.4502862	0.0116969	0.990529
	IPTW	1.9610338	1.0118353	105.585619
	IPTW Stabilized	1.0013823	0.5166836	53.9162403
RZV-exposed	Original PS	0.5301325	0.0134314	0.9909202
	IPTW	2.0441581	1.009163	74.4524282
	IPTW Stabilized	1.0003292	0.493844	36.4340404
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.4631651	0.18915	0.9038152
	IPTW	1.9589753	1.2332737	10.3966528
	IPTW Stabilized	0.9994783	0.629222	5.3044206
RZV-exposed	Original PS	0.5175352	0.1886452	0.9086157
	IPTW	2.0427796	1.1005753	5.3009557
	IPTW Stabilized	1.000544	0.5390567	2.5963834

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.

14.6.5.6. Supplemental Cohort: Dose 1 and Dose 2

The supplemental cohort that excludes from the comparator arm individuals who receive RZV in the future was performed as a sensitivity to the primary analysis, which was a separate analysis for RZV Dose 1 and Dose 2. The PS distributions for the two supplemental analyses are shown in Figure 61. The common range distribution and the IPTW stabilized with 1% asymmetrical trimming for RZV Dose 1 and for RZV Dose 2 are provided to illustrate the overlap between the RZV-exposed and the RZV-unvaccinated comparators.

Figure 61 ION supplemental cohort propensity score distribution: Dose 1 and Dose 2



Supplemental dose 1, supplemental cohort for RZV Dose 1; Supplemental dose 2, supplemental cohort for Dose 2.

The PS weights for the supplemental cohort of RZV Dose 1 and RZV Dose 2 are shown in Table 89 below for the RZV-exposed and RZV-unvaccinated comparator. The PS estimated from the logistic regression is shown as the original PS. The IPTW – before stabilizing – and the IPTW stabilized are shown as well. The common range in Dose 1 for the RZV-unvaccinated comparator had an IPTW stabilized weight >100, which was reduced to approximately 10 after 1% asymmetrical trimming and applying the IPTW stabilized weight. The common range in the Dose 2, the RZV-exposed had an IPTW stabilized weight >54, which was reduced to approximately 3.1 after 1% trimming was applied.

Table 89 Propensity score weights for ION supplemental cohort: Dose 1 and Dose 2

Supplemental Cohort: Dose 1				
Common Range		Mean	Minimum	Maximum
RZV-unvaccinated comparator	Original PS	0.5645173	0.0407853	0.9961151
	IPTW	2.5699635	1.0425195	257.4052544
	IPTW Stabilized	1.0040924	0.4073155	100.5690013
RZV-exposed	Original PS	0.6380113	0.0474012	0.9963923
	IPTW	1.6412118	1.0036208	21.0965227
	IPTW Stabilized	0.9999854	0.6115032	12.8540483
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5777396	0.2792188	0.9610685
	IPTW	2.55318	1.3873836	25.6861642
	IPTW Stabilized	0.9999679	0.5433769	10.0601372
RZV-exposed	Original PS	0.6280473	0.276614	0.9643892
	IPTW	1.6439321	1.0369257	3.6151461
	IPTW Stabilized	1.0000764	0.6308077	2.1992529
Supplemental Cohort: Dose 2				
Common Range				
RZV-unvaccinated comparator	Original PS	0.488385	0.0078002	0.9709124
	IPTW	2.1924592	1.0078615	34.3788928
	IPTW Stabilized	1.0013667	0.4603228	15.7019476
RZV-exposed	Original PS	0.5894108	0.0098832	0.9697708
	IPTW	1.8405969	1.0311715	101.1815165
	IPTW Stabilized	0.999937	0.5602023	54.9686591
1% Trimmed				
RZV-unvaccinated comparator	Original PS	0.5146845	0.1787873	0.8195423
	IPTW	2.2482747	1.2177114	5.5414637
	IPTW Stabilized	1.0007468	0.5420249	2.4666034
RZV-exposed	Original PS	0.5871284	0.1786346	0.8195365
	IPTW	1.8009293	1.2202019	5.5980183
	IPTW Stabilized	0.9993038	0.6770685	3.1062414

PS, propensity score; IPTW, inverse probability of treatment weight; RZV, recombinant zoster vaccine.
Supp 1, supplemental cohort Dose 1; Supp 2, supplemental cohort Dose 2.

14.6.6. Assessment of the Proportional Hazards Assumption

The assumption of constant hazards was assessed for the primary analysis of ION. To assess whether the assumption was violated, we plotted the log(-log(survival)) by the log(event time). The following figures show that the assumption of proportional hazards was not violated given that the lines do not cross.

Figure 62 Survivor function plot to assess the proportional hazards assumption for the primary analysis

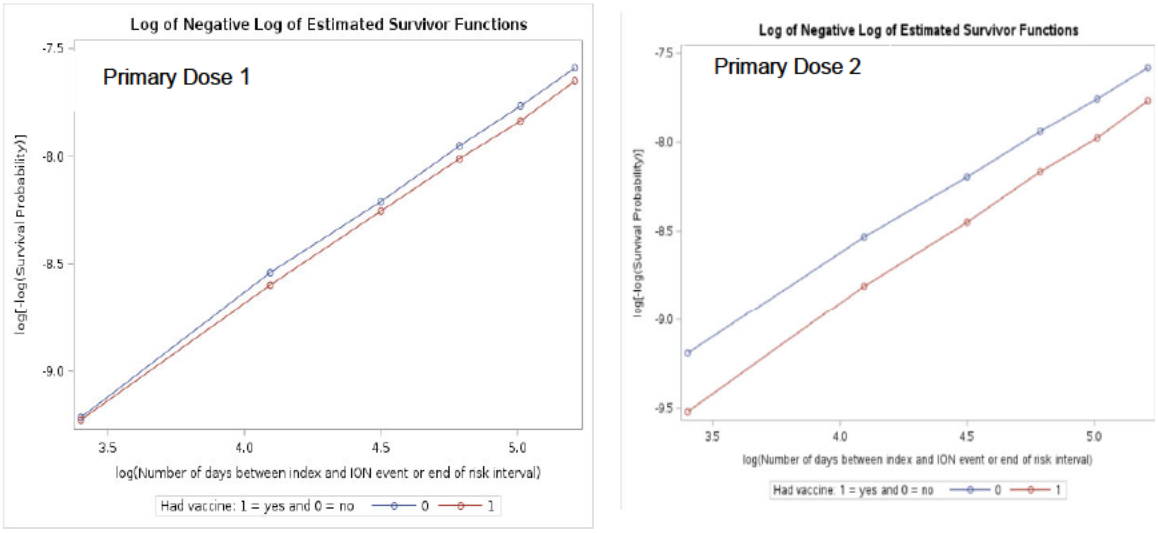


Figure 63 Survivor function plot to assess the proportional hazards assumption for the secondary analyses

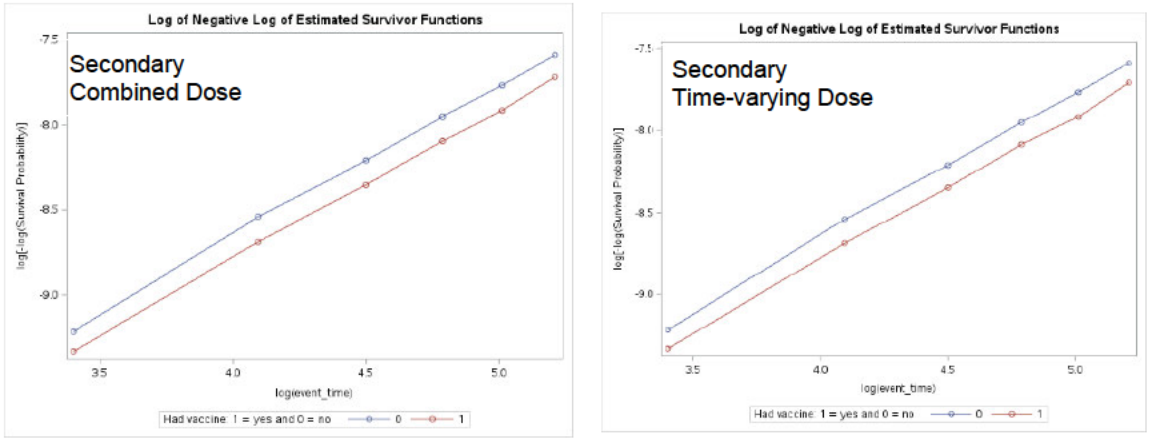


Figure 64 **Survivor function plot to assess the proportional hazards assumption for the COVID sensitivity analyses**

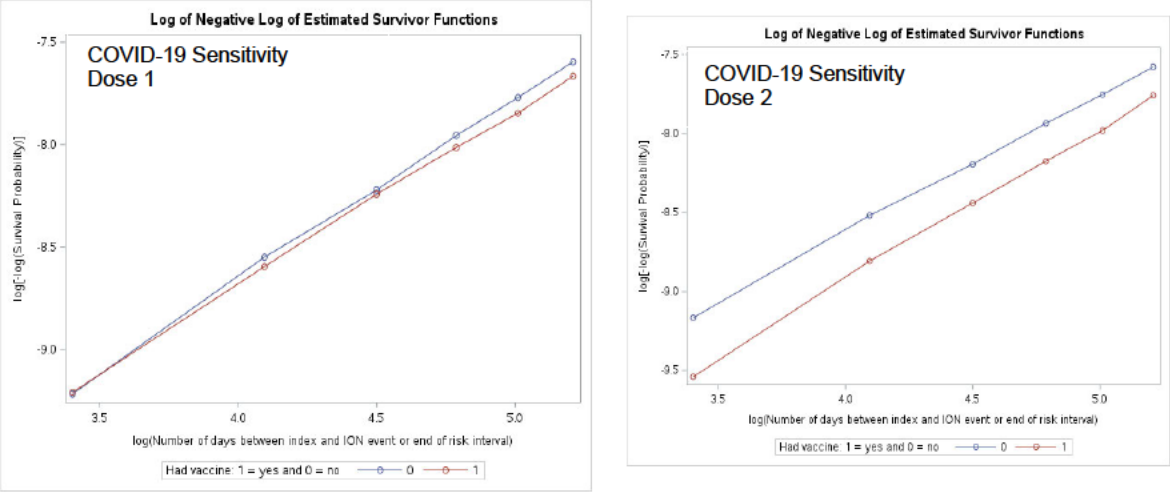


Figure 65 **Survivor function plot to assess the proportional hazards assumption for the dose-compliant sensitivity analyses**

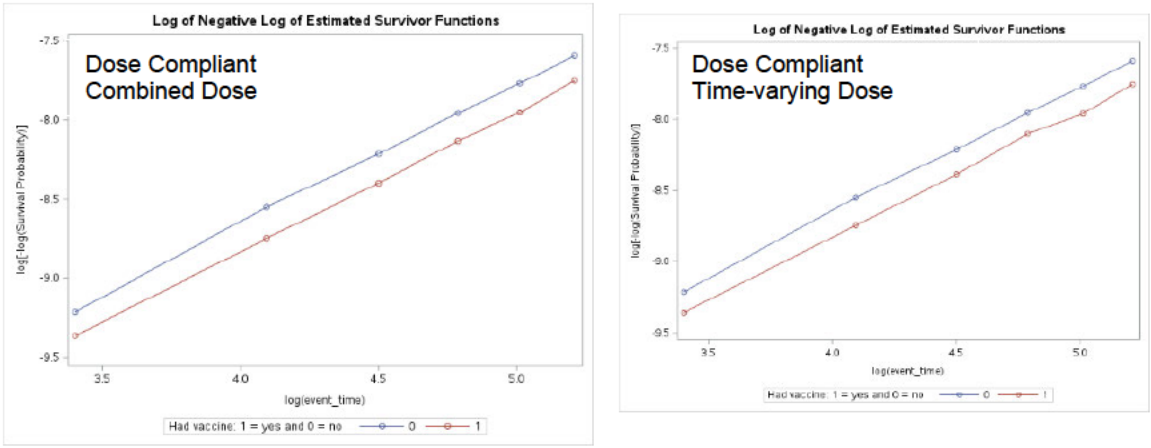
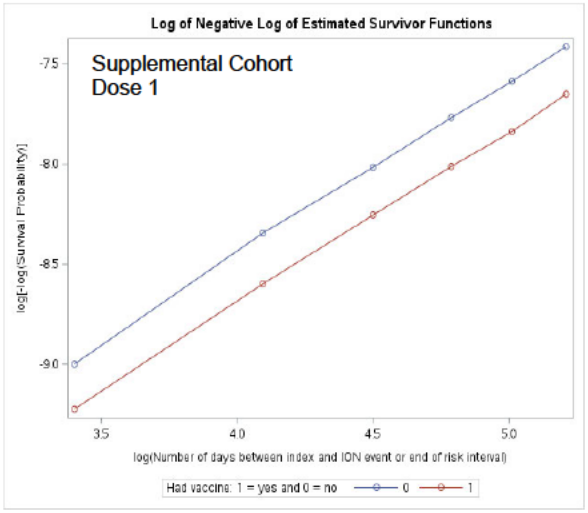
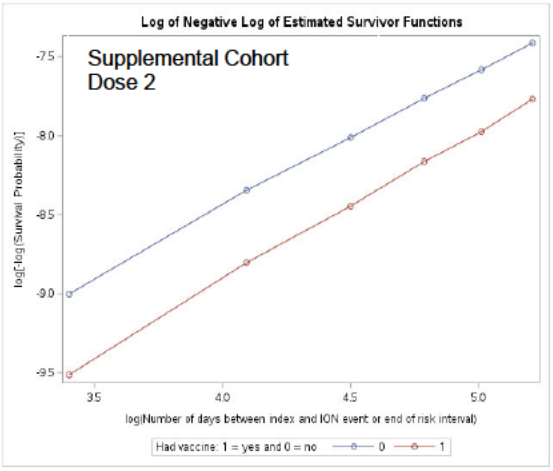


Figure 66 Survivor function plot to assess the proportional hazards assumption for the supplemental analyses



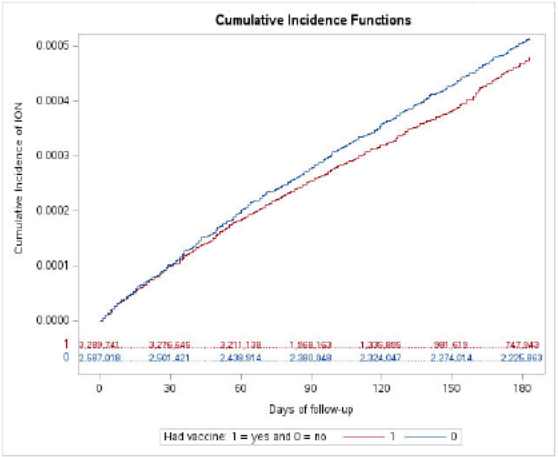


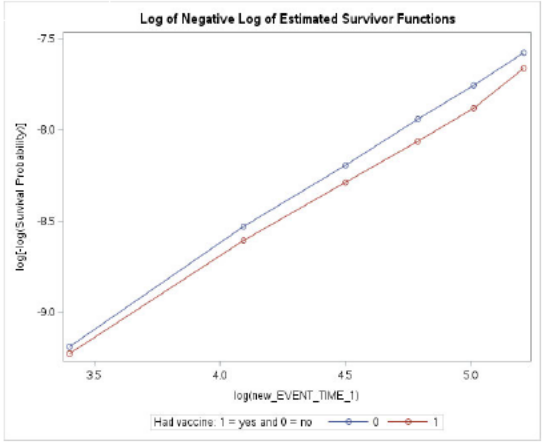
14.6.7. Post-hoc analyses

Post-hoc analyses were conducted to assess the impact of censoring RZV Dose 1 at receipt of Dose 2 in the primary analyses for ION. The following figures show the cumulative incidence function along with the survivor probability function.

Figure 67 ION: Cumulative incidence function and survival probability function with censoring of Dose 1 at Dose 2 in the primary analysis

ION





14.7. Preventive care visit codes for the comparator cohort

Table 90 below provides a list of the codes used to identify preventive care visit dates. The codes were used to select participants for the RZV-unvaccinated comparator group.

Table 90 Procedure codes to identify preventive care visits

Preventive Care Visit Description	Code	Source	Type
Routine Adult Annual Exam			
Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 40-64 years	99386	CPT-4	Procedure
Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 65 years and older	99387	CPT-4	Procedure
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	99396	CPT-4	Procedure
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 65 years and older	99397	CPT-4	Procedure
Annual wellness visit; includes a personalized prevention plan of service (pps), initial visit	G0438	HCPCS	Procedure
Annual wellness visit, includes a personalized prevention plan of service (pps), subsequent visit	G0439	HCPCS	Procedure
Federally qualified health center (fqhc) visit, ippe or awv; a fqhc visit that includes an initial preventive physical examination (ippe) or annual wellness visit (awv) and includes a typical bundle of medicare-covered services that would be furnished per diem to a patient receiving an ippe or awv	G0468	HCPCS	Procedure
Wellness assessment, performed by non-physician	S5190	HCPCS	Procedure
Initial preventive physical examination; face-to-face visit, services limited to new beneficiary during the first 12 months of medicare enrollment	G0402	HCPCS	Procedure
Encounter for general adult medical exam without abnormal findings	Z00.00	ICD-10-CM	Diagnosis
Encounter for general adult medical examination with abnormal findings	Z00.01	ICD-10-CM	Diagnosis
Colonoscopy Preventive Screening Intervention			
Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)	45378	CPT-4	Procedure
Colorectal cancer screening; colonoscopy on individual at high risk	G0105	HCPCS	Procedure
Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk	G0121	HCPCS	Procedure
Patients greater than 85 years of age who received a routine colonoscopy for a reason other than the following: an assessment of signs/symptoms of gi tract illness, and/or the patient is considered high risk, and/or to follow-up on previously diagnosed advance lesions	G9661	HCPCS	Procedure
Patients greater than 85 years of age who did not have a history of colorectal cancer or valid medical reason for the colonoscopy, including: iron deficiency anemia, lower gastrointestinal bleeding, crohn's disease (i.e., regional enteritis), familial adenomatous polyposis, lynch syndrome (i.e., hereditary non-polyposis colorectal cancer), inflammatory bowel disease, ulcerative colitis, abnormal finding of gastrointestinal tract, or changes in bowel habits	G9659	HCPCS	Procedure
Ca screen;flexi sigmoidscope	G0104	HCPCS	Procedure
colorecteral screeningn ca screen;barium enema	G0106	HCPCS	Procedure

Preventive Care Visit Description	Code	Source	Type
colorecteral screeningRECTAL CANCER SCREENING; FECAL-OCCULT BLOOD TEST	G0107	HCPCS	Procedure
colorecteral screeningn ca scrn; barium enema	G0120	HCPCS	Procedure
colorecteral screeningn ca scrn; barium enema	G0122	HCPCS	Procedure
colorecteral screeningrectal cancer screening, fecal occult blood test,	G0328	HCPCS	Procedure
Encounter for screening for malignant neoplasm of colon	Z12.11	ICD-10-CM	Diagnosis
Mammography Preventive Screening Intervention			
Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed	77067	CPT-4	Procedure
Screening mammography, bilateral (2-view film study of each breast) Office/Freestanding (Global)	77057	CPT-4	Procedure
Screening mammography, bilateral (two view film study of each breast).	76092	CPT-4	Procedure
Screening mammography, bilateral (2-view study of each breast), including computer- aided detection (CAD) when performed.	G0202	HCPCS	Procedure
Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.	G0203	HCPCS	Procedure
Screening mammogram for high-risk patient	V7611	HCPCS	Procedure
Encounter for screening mammogram for malignant neoplasm of breast	V7612	HCPCS	Procedure
Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.	G0204	HCPCS	Procedure
Diagnostic mammography, including computer-aided detection (CAD) when performed; unilateral.	G0206	HCPCS	Procedure
Encounter for screening for malignant neoplasm of breast	Z12.3	ICD-10-CM	Diagnosis
Encounter for screening mammogram for malignant neoplasm of breast	Z12.31	ICD-10-CM	Diagnosis
Encounter for other screening for malignant neoplasm of breast	Z12.39	ICD-10-CM	Diagnosis
Osteoporosis Preventive Screening Interventions			
Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine)	77080	CPT-4	Procedure
Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; appendicular skeleton (peripheral) (eg, radius, wrist, heel)	77081	CPT-4	Procedure
PERIPHERAL SKELETAL BONE MINERAL DENSITYN20030626	G0062	HCPCS	Procedure
CENTRAL SKELETAL BONE MINERAL DENSITY STN20030626	G0063	HCPCS	Procedure
SINGLE ENERGY X-RAY ABSORPTIOMETRY (SEXAN20110101: Single energy x-ray absorptiometry (sexa) bone density study, one or more sites; appendicular skeleton (peripheral) (e.g., radius, wrist, heel) (Single energy x-ray study)	G0130	HCPCS	Procedure
COMPUTERIZED TOMOGRAPHY BONE MINERAL DENN20060101	G0131	HCPCS	Procedure
ULTRA-SOUND BONE MINERAL STUDY, ONE OR MORE SITES, APPENDICULAR SKELETON	G0132	HCPCS	Procedure
Bone mineral density	G0133	HCPCS	Procedure
Encounter screening for osteoporosis	Z13.820	ICD-10-CM	Diagnosis

15. ANNEX 1 LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1	TMF-2051647	31 Jul 2020	EPI-ZOSTER-032 Protocol
2	TMF-12916191	17 May 2021	EPI-ZOSTER-032 Protocol Amendment 1
3	TMF-14603945	18 Apr 2022	EPI-ZOSTER-032 Protocol Amendment 2
4	TMF-14833531	15 Jul 2022	EPI-ZOSTER-032 Protocol Amendment 3
5	TMF-2107275	11 Sept 2020	EPI-ZOSTER-032 SAP
6	TMF-2107275	13 Oct 2020	EPI-ZOSTER-032 SAP Amendment 1
7	TMF-13778224	20 May 2021	EPI-ZOSTER-032 SAP Amendment 2
8	TMF-13778244	27 April 2022	EPI-ZOSTER-032 SAP Amendment 3
9	TMF-13778224	21 Jul 2022	EPI-ZOSTER-032 SAP Amendment 4
10	TMF-14064009; TMF-13908969	7 Oct 2021	EPI-ZOSTER-032 SAP Supplement and Code list
11	TMF-23333813	10 December 2025	Data quality checklist for SAR 3
12	TMF-20486806	11 Dec 2024	Data quality checklist for SAR 2A and 2B
13	TMF-19601551	8 July 2024	Data quality checklist for SAR 1

16. ANNEX 2 QUALITY CHECKLIST

The Data Management/Statistical Analysis Quality Checklist was provided as a separate document to accompany each of the three previous statistical analysis reports.

17. ANNEX 3 NON-INTERVENTIONAL STUDY REPORT (ABSTRACT)

Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of Shingrix in adults ≥65 years of age in the United States.
Date of the Abstract	02 Jul 2026
Name and affiliation of main author	PPD , PhD Principal Investigator University of Maryland, Baltimore Baltimore, Maryland 21201
Keywords	*SHINGRIX* (RZV), TSS/PASS, , older adults, US
Marketing authorisation holder(s)	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Names and affiliations of principal investigators	Susan dosReis, PhD Principal Investigator University of Maryland, Baltimore Baltimore, Maryland, USA

Rationale and background

In prelicensure clinical trials and post licensure safety surveillance by the Centers for Disease Control and Prevention , which are not designed to assess rare outcomes, numerical differences or a statistical signal between the Recombinant zoster vaccine (RZV) and placebo groups were noted for certain conditions, including: 1) Polymyalgia rheumatica (PMR); 2) Giant cell arteritis (GCA); 3) gout; 4) Ischemic optic neuropathy (ION); 5) Supraventricular tachycardia (SVT) and 6) Guillain-Barré syndrome (GBS). The EPI-ZOSTER-032 TSS/PASS study utilizing the Centers for Medicaid and Medicare Services (CMS) Chronic condition warehouse (CCW) database, a large and comprehensive database representing US adults ≥65 years of age, allows for evaluation of the real-world safety of RZV related to these outcomes, in heterogeneous, complex populations.

Research questions and objectives

The EPI-ZOSTER-032 study was designed to evaluate the risk of GBS, gout, PMR, and GCA following RZV as primary objectives. Assessing the risk of SVT and ION following RZV are secondary objectives of the EPI-ZOSTER-032 study.

Study design

The risk of new onset of GBS, gout, and SVT was assessed using a Self-Controlled Risk Interval (SCRI) study design. A cohort design was implemented to assess the risk of new

onset PMR, GCA and ION within 183 days following RZV vaccination compared to an RZV-unvaccinated cohort who had a preventive care visit.

Setting

The study population is a nationally representative sample of US Medicare beneficiaries ≥65 years of age, who were enrolled in Medicare fee-for-service Parts A, B, and D and who did not qualify for Medicare due to a disability.

Subjects and study size, including dropouts

The analytical cohort for each outcome included 1290 gout cases, 75 GBS cases, 4964 SVT cases, 3 265 790 RZV vaccinated participants and 2 569 783 unvaccinated comparators for PMR, 3 288 846 RZV-exposed and 2 585 975 RZV-unvaccinated comparators for GCA and 3 289 741 RZV-exposed and 2 587 018 RZV-unvaccinated comparators for ION.

Variables and data sources

The study leveraged the CMS CCW Medicare data. The exposure is the receipt of at least one dose of RZV from January 2018 through December 2020. Primary outcomes were GBS, gout, PMR and GCA. Secondary outcomes were SVT and ION. Baseline characteristics captured demographic characteristics, comorbidities and healthcare service use.

Results

In the primary analysis of outcomes evaluated using the SCRI design, that did not distinguish between doses, the RR of new onset GBS was 3.15 (95% CI: 1.82, 5.68) and the AR was 6.59 per 1 000 000 vaccine doses (95% CI: 4.35, 7.96), the RR of new onset gout was 1.00 (95% CI: 0.90, 1.12, and the RR of new onset SVT was 0.94 (95% CI: 0.89, 0.99).

The primary analysis of outcomes evaluated using a cohort design, that evaluated the risk after Dose 1 and Dose 2 separately, did not show a statistically significant risk of PMR from Day 1 to 120 following Dose 1 (HR=1.00; 95% CI: 0.92, 1.09). After Day 120, there was a statistically significant increased risk of PMR following Dose 1: HR=2.05 (95% CI: 1.71, 2.46). The results did not reveal a statistically significant increased risk of GCA from Day 1 to 150 following RZV Dose 1 (HR=1.10; 95% CI: 0.94, 1.28) or after Day 150 (HR=1.34; 95% CI: 0.89, 2.01). Results from the Dose 2 primary analysis did not show an increased risk of GCA. The primary analysis using an IPTW stabilized weighted Cox proportional hazards regression analysis did not reveal a statistically significant risk of ION following RZV Dose 1 (HR=0.97, 95% CI: 0.90, 1.05) but showed a statistically significant lower risk of ION following RZV Dose 2 (HR=0.85, 95% CI: 0.78, 0.93) relative to the RZV-unvaccinated comparators.

Discussion

This study leveraged a nationally representative sample of US Medicare beneficiaries ≥65 years of age. The results of the primary analysis were robust to secondary and sensitivity analyses conducted for each outcome, and demonstrated consistency with previously published studies, particularly for GBS.

Conclusion

This safety study findings suggest RZV is associated with statistically significant increased risk of new onset GBS and PMR. The elevated risk of new onset GBS was detected after RZV Dose 1 but not Dose 2. The risk of PMR is elevated after Day 120 following RZV Dose 1.

This study did not detect a statistically significant risk of gout, SVT, or ION following RZV exposure. While the results of most analyses generally indicate no statistically significant increased risk of GCA following RZV, findings from the secondary analyses suggest a higher risk after RZV vaccination.

Signature Page for 209696 TMF-24064856 v1.0

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PASS INFORMATION

Title:	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Protocol version identifier:	209696 (EPI-ZOSTER-032 VS US DB)
Date of last version of the protocol:	Final, 31 July 2020 Amendment 1 Final, 17 May 2021 Amendment 2 Final, 18 April 2022 Amendment 3 Final, 15 July 2022
EU PAS Register No:	EUPAS37133
Active substance:	VZV glycoprotein E (gE)
Medicinal product:	*Shingrix* (Recombinant Zoster Vaccine, RZV)
Product reference:	For EMA: EU/1/18/1272/001, EU/1/18/1272/002 For FDA: IND number 13857
Procedure number:	EMEA/H/C/004336/MEA/020.1
Marketing Authorization Holder (MAH):	GlaxoSmithKline Biologicals S.A. Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	To assess whether *Shingrix*, or RZV, is associated with an increased risk of new-onset Guillain-Barré syndrome, gout, polymyalgia rheumatica, giant cell arteritis, ischemic optic neuropathy (ION) or supraventricular tachycardia (SVT) within specified time periods after vaccination in people ≥ 65 years of age beginning January 2018 in CMS Medicare. SVT and ION will be investigated as secondary objectives.
Country of study:	United States
Authors:	PPD , University of Maryland, Baltimore

	PPD , GSK
Contributing authors *(Amended 15 July 2022):*	PPD , University of Maryland, Baltimore PPD , GSK PPD , GSK PPD , GSK PPD , GSK PPD , GSK PPD , GSK PPD GSK

MARKETING AUTHORIZATION HOLDER

MAH:	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
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Based on GSK Biologicals' protocol template for post-authorization safety studies v17.0

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
CBER	Center for Biologics Evaluation and Research
CCW	Chronic Condition Warehouse
CDC	Centers for Disease Control and Prevention
CITI	Collaborative Institutional Training Initiative
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DME	Durable Medical Equipment
DMP	Data Management Plan
DUA	Data Use Agreement
ED	Emergency Department
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration, United States
GBS	Guillain-Barre Syndrome
GCA	Giant Cell Arteritis
GSK	GlaxoSmithKline SA
HIPAA	Health Insurance Portability and Accountability Act
HOI	Health Outcome of Interest
HZ	Herpes Zoster
ICD	International Classification of Diseases
ID	Identification
ION	Ischemic Optic Neuropathy
MAH	Marketing Authorization Holder

MBSF	Medicare Beneficiary Summary File
NDC	National Drug Code
PASS	Post-Authorization Safety Study
PDE	Prescription Drug Event
PHN	Post-Herpetic Neuralgia
PHSR	Pharmaceutical Health Services Research
pIMD	potential Immune-Mediated Disorders
PMR	Polymyalgia Rheumatica
PPV	Positive Predictive Value
PRC	Pharmaceutical Research Computing
PVP	Pharmacovigilance Plan
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SCRI	Self-Controlled Risk Interval
SNF	Skilled Nursing Facility
SVT	Supraventricular Tachycardia
TSS	Targeted Safety Study
UMB	University of Maryland, Baltimore
US	United States
VZV	Varicella Zoster Virus
ZVL	Zoster Vaccine Live (*Zostavax*)

3. RESPONSIBLE PARTIES

Principal investigator:	Susan dosReis, University of Maryland, Baltimore
Sponsor contacts:	Agnes Mwakingwe-Omari, Clinical and Epidemiology Project Lead GSK 14200 Shady Grove Rd Rockville, MD 20850 PPD
Other contacts:	Not applicable
Collaborator:	***University of Maryland, Baltimore***
Study Teams *(Amended 15 July 2022)*:	Core UMB study team members: • PPD • PPD Core GSK study team members: • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD • PPD

4. ABSTRACT

Title:	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Version and date of the protocol	Final: 31 July 2020 Amendment 1 Final, 17 May 2021 Amendment 2 Final, 18 April 2022 ***Amendment 3 Final: 15 July 2022***
Main author:	PPD, PhD, Principal Investigator, University of Maryland, Baltimore
Rationale and background:	*Shingrix*, or recombinant zoster vaccine (RZV), is a subunit, adjuvanted vaccine that was approved by the Food and Drug Administration in October 2017 and by the EMA in March 2018 for the prevention of herpes zoster (HZ) in adults ≥ 50 years of age. The Advisory Committee on Immunization Practices recommends RZV vaccination for the prevention of HZ in immunocompetent adults ≥ 50 years of age. In pre-licensure clinical trials, which are not designed to assess rare outcomes, numerical differences between the RZV and placebo groups were noted for certain conditions, including: 1) polymyalgia rheumatica (PMR); 2) giant cell arteritis (GCA); 3) gout; 4) ischemic optic neuropathy (ION); and 5) supraventricular tachycardia (SVT). The Centers for Disease Control and Prevention (CDC) detected a statistical signal for Guillain-Barré syndrome (GBS) during post-licensure safety surveillance of RZV using the Vaccine Safety Datalink. CDC applied an iterative algorithm that preferentially maximizes sensitivity over specificity that was designed for hypothesis (signal) generation. This targeted safety study will use the Centers for Medicare and Medicaid Services (CMS) Medicare data in the United States (US) to evaluate the real-world safety of RZV, focusing on the specific outcomes listed above.
Research question and objectives:	The study will address the question of whether RZV is associated with the risk of new-onset GBS, gout, PMR, GCA, SVT, or ION within specified time periods after vaccination in people aged 65 years and older enrolled in Medicare who were vaccinated in 2018 through 2020.

The primary objectives are to estimate the risk of new onset:

- GBS within 42 days,
- Gout within 30 days,
- PMR within 183 days and,
- GCA within 183 days following vaccination with RZV.

The secondary objective is to estimate the risk of new-onset:

- SVT within 30 days and,
- ION within 183 days following vaccination with RZV.

Study design:

- This is a Targeted Safety Study and a Post-Authorization Safety Study.
- A self-controlled risk interval design will be used to assess the risks of GBS, gout, and SVT (a secondary outcome).
- A cohort design with concurrent controls will be used to assess the risks of PMR, GCA and ION (a secondary outcome).

Population: The study population is a nationally representative sample of US Medicare beneficiaries aged 65 years and older, who are enrolled in Medicare Parts A, B, and D.

Variables: The exposure is receipt of at least one dose of RZV. The dependent variable is the occurrence of the health outcome of interest. Several covariates include age, sex, region of residence within US, calendar year-month, concomitant vaccination with other preventive immunizations, certain comorbidities, healthcare visits.

Data sources: The study will use the CMS Chronic Conditions Warehouse Medicare database that includes inpatient, outpatient, physician, and prescription claims for all health services and medications provided for Medicare enrollees with Parts A, B, and D. Data from January 2017 through December 2021 will be used in this study.

Study size: Sample size calculations suggest that the study will ultimately have at least 80% power to reject the null hypothesis of no association if the true relative risk is ≥ 4 for GBS, ≥ 2 for gout, ≥ 2 for PMR, and ≥ 3 for GCA.

The estimated number of individuals for each primary outcome (assuming all individuals receive 2 doses) is:

- GBS: 1 000 000 to detect a relative risk of 4.0 or more;

- Gout: 70 000 to detect a relative risk of 2.0 or more;
- PMR: 438 239 to detect a relative risk of 2.0 or more;
- GCA: 723 362 to detect a relative risk of 3.0 or more.

Data analysis: The analysis plan will include descriptive measures to characterize exposed and unexposed individuals, conditional Poisson regression models for the SCRI, and Cox proportional hazards regression models for the cohort design outcomes.

Milestones: The milestones are 11 September 2020 (Actual date) for start of data collection, Q4, 2024 (Tentative) for end of data collection and final report submitted to the Center for Biologics Evaluation and Research (CBER) and the European Medicines Agency (EMA) 30 June 2027.

Note: the above timelines are tentative and subject to change.

5. AMENDMENTS AND UPDATES

Protocol Amendment 2 dated 18 April 2022 was amended to address feedback received from regulatory authorities.

Amendment number	Date	Amendment or update	Section of study protocol	Reason
3	15 July 2022	Updated continuous enrollment requirement to clarify the allowable gap that defines continuous enrollment	9.2.2; 9.4.1; 9.7.3; 9.7.5; 9.7.6;	As requested by CBER to update sections of the protocol for consistency

6. MILESTONES

Milestone	Planned date
Start of data collection[1]	11 September 2020 (Actual date)
End of data collection	2024 (Tentative)
Final report submitted to the FDA's Center for Biologics Evaluation and Research (CBER) and to European Medicines Agency (EMA)	30 June 2027

Note: the above timelines are tentative and subject to change.
[1] Start of study activities

7. RATIONALE AND BACKGROUND

Herpes zoster (HZ), the result of reactivation of latent varicella zoster virus (VZV) in dorsal root ganglia, most commonly presents as a painful vesicular dermatomal rash. However, complications such as post-herpetic neuralgia (PHN), as well as disseminated disease in the immunocompromised population, can lead to significant disability and morbidity[1]. There are an estimated one million cases of HZ in the United States (US) annually, resulting in $5 billion in healthcare expenditures per year[2]. Risk factors for HZ include older age and immunocompromising conditions[3,4].

Shingrix, recombinant zoster vaccine (RZV), is a subunit, adjuvanted VZV vaccine. It is approved for the prevention of HZ in adults ≥ 50 years of age in several countries within Europe and the US. *Shingrix* is a two-dose vaccine, in Europe, Doses 1 and 2 should be given 2 months apart, with the possibility of extending the timing of Dose 2 to 6 months. In the US, RZV is given 2 to 6 months apart. Since this study is being conducted in the US, the recommended dosing schedule in the US will be considered. The Advisory Committee on Immunization Practices recommendations for RZV include the following: 1) RZV (as two doses 2 to 6 months apart) is recommended for immunocompetent adults aged 50 years and older; 2) RZV is recommended for immunocompetent adults previously vaccinated with the zoster vaccine live (ZVL, *Zostavax*); and 3) RZV is preferred over ZVL[5]. Vaccine efficacy against HZ in the two pivotal Phase III studies was 97.2% in adults ≥ 50 years of age (ZOE-50)[6] and 91.5% in adults ≥ 70 years of age[7]. Pooled safety analyses of clinical data from these two Phase III studies included a total of 14 645 RZV and 14 660 placebo recipients, with a median follow-up duration of 4.4 years[8]. The pooled analysis demonstrated a comparable incidence of unsolicited adverse

events (AE) in the Day 7 through Day 29 follow-up period (excluding Day 0 through Day 6 where reactogenicity was observed to be higher in RZV versus placebo recipients). Serious adverse events (SAE), and potential immune-mediated disorders (pIMDs) between the RZV and placebo groups, and specific SAEs and pIMDs were within the expected incidence for the study age group[8].

In descriptive analyses, there were numerical differences in AEs for some specific conditions, including 1) polymyalgia rheumatica (PMR); 2) giant cell arteritis (GCA); 3) gout; and 4) ischemic optic neuropathy (ION). During the entire post-vaccination follow-up period, PMR was reported by 32 (0.2% [95% confidence interval (CI): 0.1-0.3]) and 29 (0.2% [95% CI: 0.1-0.3]) ***participants*** in the RZV and placebo groups, respectively. GCA was reported by 6 (0.04% [95% CI: 0.0-0.1]) and 3 (0.02% [95% CI: 0.0-0.1]) ***participants*** in the RZV and placebo groups, respectively. For gout, there were 27 (0.18% [95% CI: 0.12-0.27]) and 8 (0.05% [95% CI: 0.02-0.11]) ***participants*** in the RZV and placebo groups, respectively, who reported an event of gout or gouty arthritis (relative risk = 3.38 [95% CI: 1.49- 8.60]. Among ***participants*** without a known history of gout at study entry, 19 ***participants*** in the RZV group versus 3 ***participants*** in the placebo group reported new-onset gout in the 30-day period following the last vaccination. For ION, at specific follow-up timepoints post-vaccination, 1 versus 0 cases at ≤ 30 days, and 2 versus 0 cases at ≤ 365 days, were reported in the RZV and placebo groups, respectively.

With respect to clinical trials, numerical differences were also noted between the RZV group and the placebo group on pooled analyses with respect to other clinical outcomes, including supraventricular tachycardia (SVT): 6 (0.04% [95% CI: 0.02-0.09]) and 0 (0.00% [95% CI: 0.00-0.03]) ***participants*** in the RZV and placebo groups, respectively, in the 365-day follow-up period post-last vaccination.

With respect to reports of GBS, there were 2 cases reported in the RZV group and 3 in the placebo group during the entire post-vaccination follow-up period. Recent RZV post-licensure safety surveillance by the Centers for Disease Control and Prevention detected a statistical signal using Vaccine Safety Datalink Rapid Cycle Analysis, using an algorithm that preferentially maximizes sensitivity over specificity. Specifically, at the time of the preliminary signal, there were 3 presumptive events compared to 0.57 expected events when comparing RZV to a historical cohort of ZVL users, with a relative risk of 5.25[9]. As of the most recent publicly available analysis, five presumptive events have been observed compared to 1.6 expected with a relative risk of 3.18. Of these 5, one case was confirmed as Brighton Criteria level 2, one case was confirmed as Brighton Criteria level 3 (with probable respiratory infection prior to GBS symptom onset), and three cases were ruled out as not being representative of true incident cases post-vaccination.

Robust data on the risk of these outcomes following administration of RZV are currently lacking. Furthermore, data on the use of RZV in complex patient populations are critical in assessing the safety of the vaccine in the real-world setting. An observational study utilizing the Centers for Medicare and Medicaid Services (CMS) Chronic Condition Warehouse (CCW) database, a large and comprehensive database representing US adults aged 65 and older, allows us to evaluate the real-world safety of RZV, including in

heterogeneous, complex populations, with a focus on the specific safety outcomes outlined above. A detailed description of this database is in Section 9.4.1 of the protocol.

8. RESEARCH QUESTION AND OBJECTIVES

This study will assess whether there is a risk of new onset GBS, gout, PMR, GCA, SVT and ION within specified time periods after RZV vaccination in people age 65 years and older enrolled in Medicare who were vaccinated in 2018 through 2020. A self-controlled risk interval (SCRI) design will be used to assess the risk of new onset GBS, gout, and SVT. A cohort design using a concurrent preventive care visit comparison group will be used to assess the risk of new onset PMR, GCA and ION.

8.1. Primary objectives

1. To assess the risk of new onset GBS within 42 days following RZV vaccination using a SCRI design.
2. To assess the risk of new onset gout within 30 days following RZV vaccination using a SCRI design.
3. To assess the risk of new onset PMR within 183 days following RZV vaccination using a cohort design.
4. To assess the risk of new onset GCA within 183 days following RZV vaccination using a cohort design.

8.2. Secondary objectives

1. To assess the risk of new onset SVT within 30 days following RZV vaccination using a SCRI design.
2. To assess the risk of new onset ION within 183 days following RZV vaccination using a cohort design.

9. RESEARCH METHODS

The University of Maryland, Baltimore (UMB) School of Pharmacy, Pharmaceutical Health Services Research (PHSR) department conducted a feasibility assessment to inform the methodological approaches to be implemented in this safety study. The feasibility assessment, conducted January through May of 2019, had two key objectives: (1) to provide a distribution of the primary and secondary outcomes of interest and (2) to provide a distribution of select covariates within the CMS Medicare population. The results informed the study methods and estimated timelines. The data source for the feasibility assessment was the CMS CCW Medicare claims data from 2007 through 2015 for a 5% random sample of US Medicare beneficiaries age 65 years and older, which was approximately three million individuals. Some of the study outcomes occurred in less than 1% of the individuals in the feasibility assessment. RZV exposure was not assessed in the feasibility because the vaccine was licensed in 2017. The distribution of primary and secondary outcomes of interest were identified using International Classification of

Diseases (ICD)-9 and 10 codes only, case definition algorithm had not been developed yet. The overall conclusion from the feasibility assessment was that it was feasible to conduct the safety study using CMS CCW Medicare claims data.

9.1. Study design

This study is a Targeted Safety Study (TSS) and a Post-Authorization Safety Study (PASS) that will assess the risk of new-onset GBS, gout, and SVT following RZV exposure using a SCRI design; and the risk of new-onset PMR, GCA, and ION following RZV exposure using a cohort design with a concurrent comparator.

The study population will comprise approximately 4 to 5 million CMS Medicare beneficiaries age 65 years and older who received at least one dose of RZV.

RZV exposure will be defined as receipt of at least one dose of vaccine; sensitivity analyses will be conducted to assess the risk of outcomes when Dose 2 is received per US dosing schedule, i.e. 2-6 months after Dose 1.

This study will be conducted using CMS CCW Medicare claims data (described in Section 9.4.1).

Table 1 provides an overview of the study designs for the primary health outcomes of interest (HOI).

Primary objectives 1 & 2: SCRI

To assess the risk of new-onset GBS and gout, a SCRI design will be used[10]. This design is a special (and simpler) case of both the case-crossover[11,12] and the self-controlled case series[12,13] designs, in which the cumulative number of cases in pre-specified risk and control intervals (or "window") are compared. Individuals serve as their own control. The analysis is conditioned on the interval (or "window"), and only RZV vaccinees who experience the HOI in the risk or the control interval contribute to the analysis. The SCRI design is ideal for acute outcomes and transient exposures[13]. The advantage of the SCRI design is the implicit control for time-fixed potential confounders such as sex, race/ethnicity and stable chronic medical conditions. However, potential time-varying confounders, such as age, seasonality, and possibly medication use, may introduce bias unless they are explicitly controlled for with in the analysis.

Primary objectives 3 & 4: Cohort design

A cohort design will be used to assess the risk of new onset PMR and GCA by comparing the hazard of these HOIs among individuals exposed to RZV relative to individuals with a preventive care visit who did not receive RZV. Given that the HOIs assessed using the cohort design are rare, the analyses will be unmatched so as not to arbitrarily reduce the size of the comparison group, which would reduce statistical power. Potential confounders between RZV recipients and comparators (e.g., age, sex, certain chronic conditions, calendar time, etc.) will be adjusted for in multivariable Cox proportional hazards regression models (details described in Sections 9.7.6 and 9.7.8 below).

The 183-day (6-month) follow-up period post-RZV exposure for new-onset PMR, GCA and ION makes the use of the SCRI design impractical, due to time-varying confounding and overlapping observation windows for Doses 1 and 2. The self-controlled designs, including the self-controlled case series are not ideal for outcomes that have an insidious onset or non-acute outcomes due to the difficulty of specifying an appropriate control and risk windows and the introduction of bias from time-varying confounding with long follow-up period post-exposure. The cohort design also maximizes statistical power because this approach leverages the large sample size of the exposed and comparator groups.

Details of the RZV unvaccinated comparator selection for the cohort design are described in Section 9.7.5 below.

Secondary objectives

The risk of new onset SVT following RZV exposure will be estimated using a SCRI design with a 30-day risk interval.

The risk of new onset ION following RZV exposure will be estimated using a cohort design with a 183-day risk period.

Index date

The vaccination date for RZV exposed individuals is the index date for both the SCRI and cohort design outcomes. The start of follow-up for the cohort design outcomes will commence at the index date, which is the vaccination date for the RZV exposed and the preventive care visit date for the RZV unvaccinated comparator.

Baseline period for the cohort design

The baseline period is specific to the HOIs assessed using a cohort design. This is defined as the 365 days prior to the index date during which prevalent cases of the HOI will be identified for exclusion from the analytical cohort and covariates will be assessed to control for confounding in statistical analyses. Individuals who experienced an HOI during the baseline period will be excluded from the cohort design analyses for that HOI. In addition, potential confounders such as demographics, receipt of age-recommended vaccinations, and health status/medical comorbidities will be identified in the baseline period for inclusion as covariates in statistical analyses.

Unlike EPI-ZOSTER-030 VS US DB, which uses a 730-day baseline period to exclude prevalent cases of gout, a 365 day baseline period will be used for all HOIs (including gout) in EPI-ZOSTER-032 VS US DB to retain as much sample size as possible, because the entry age into Medicare for this study, is age 65 years so those who received RZV close to their Medicare enrolment will not have enough medical history to be included in the study. (e.g., if a 730-day baseline period was required for gout, then this study would only be able to assess the risk of gout in patients 67 years and older).

Table 1 Features of the study design to be used for primary HOIs

Outcome	Study Design	Primary and Secondary Analyses	Post-RZV Risk Interval	Control Interval or Comparator Group	Comments	Sensitivity Analysis
GBS	SCRI	1°: At least 1 dose -Combined Doses 1 and 2 2°: At least 1 dose – Combined Dose 1 and Dose 2 – 3-week control window for both doses 2°: At least 1 dose- Combined Dose 1 and Dose 2 – 6-week control window for both doses	Days 1-42	Days 43-84	1^{o} : Dose 1 control window maximum of days 43-84 after Dose 1; if dose 2 occurs in the Dose 1 control window then censor at Dose 2 (i.e. use a shortened control window for Dose 1) and days 43-84 after Dose 2 as control window for Dose 2. 2^{o}: Dose 1 control window is days 43-63 (3-weeks) and days 43-84 (6-weeks) after Dose 1 Exclusions: 1^{o}: Dose 1 cases excluded if Dose 2 received in Dose 1 risk window – no Dose 1 control window exists; 2^{o}: Dose 1 control window cases if also in Dose 2 risk window	Dose 1 and 2 compliant – dose spacing 2-6 months apart (subset of 1^{o} analysis) Separate analysis for Dose 1 with control window days 43-84 after Dose 1 (subset of second 2^{o} analysis) Separate analysis for Dose 2 with control window days 43-84 after Dose 2 (subset of second 2^{o} analysis)
Gout	SCRI	1°: At least 1 dose -Combined Doses 1 and 2 2°: At least 1 dose – Combined Dose 1 and Dose 2 – 30-day control window for both doses	Days 1-30	Days 31-60	1^{o} : Dose 1 control window maximum of days 31-60 after Dose 1; if dose 2 occurs in the Dose 1 control window then censored at Dose 2, (i.e. use a shortened control window for Dose 1) and days 31-60 after Dose 2 as control window for Dose 2. Exclusions: 1^{o}: Dose 1 cases excluded if Dose 2 received in Dose 1 risk window – no Dose 1 control window exists; 2^{o}: Dose 1 control window cases if also in Dose 2 risk window	Dose 1 and 2 compliant – dose spacing 2-6 months apart (subset of 1^{o} analysis) Separate analysis for Dose 1 with control window days 31-60 after Dose 1 (subset of 2^{o} analysis) Separate analysis for Dose 2 with control interval days 31-60 after Dose 2 (subset of 2^{o} analysis)

Outcome	Study Design	Primary and Secondary Analyses	Post-RZV Risk Interval	Control Interval or Comparator Group	Comments	Sensitivity Analysis
PMR	Cohort	1°: Dose 1 and Dose 2 - separate analyses for Doses 1 and 2 separate risk estimates 2°: Combined Dose 1 and Dose 2 in one analysis for a single risk estimate 2°: Combined Dose 1 and Dose 2 in one analysis with 2 separate risk estimates	Days 1-183	Days 1-183 (from index date)		Analysis with a sub-sample that received Dose 1 and Dose 2 per US dosing schedule, i.e., 2-6 months apart for both combined secondary analyses – yielding a single and separate risk estimates.
GCA	As for PMR	As for PMR	As for PMR	As for PMR	As for PMR	As for PMR

9.2. Setting

9.2.1. Source population

The source population includes US adults age 65 and older who are enrolled in Medicare any time from 2017 through 2021. Medicare is fully funded by the US government to subsidize healthcare services for individuals aged 65 and older or who are entitled because of a qualifying condition other than age. CMS is the US federal agency responsible for oversight and management of the Medicare program. As defined by CMS, Medicare is a health insurance program for:

1. People age 65 and older
2. People under age 65 years old with certain disabilities
3. People of all ages with End-Stage Renal Disease (ESRD)

Most US adults in the Medicare program (80%) qualify based on age 65 years and older and about 20% are younger than 65 years old and qualify due to a disabling condition. Approximately 55%-67% of the Medicare population is covered fully or partly through a fee-for-service arrangement as opposed to a supplemental Medicare Advantage plan (see below).

Individuals enrolled in Medicare receive benefits from different 'parts' of Medicare insurance that pay for all or a portion of specific healthcare services. These parts are referred to as Parts A, B, C and D. Each is described below.

- Medicare Part A: Also referred to as Hospital Insurance, Part A pays for healthcare services provided in inpatient settings including hospitals, critical access hospitals, skilled nursing facilities (SNFs) (not custodial or long-term care), hospice care and some home health care.
- Medicare Part B: Also referred to as Medical Insurance, Part B pays for doctors' services and outpatient care as well as services not covered by Part A, such as physical and occupational therapists and some home health care. Certain vaccines are covered under Part B: influenza, pneumococcal, and Hepatitis B.
- Medicare Part C: Also referred to as supplemental coverage, Part C was first established in 1997 under the name Medicare + Choice but was renamed in 2003 to the Medicare Advantage program. Under Part C, CMS contracts with public or private organizations to offer a variety of health plan options for Medicare beneficiaries, such as health maintenance organizations, provider sponsored associations, and preferred provider organizations. These health plans must provide all Medicare Parts A and B benefits, and most offer additional benefits beyond those covered under the original Medicare program. Individuals pay a monthly premium for Part C. Services provided under Part C are not available in the CMS CCW Medicare database, and so all data will be missing for individuals who are only enrolled in Part C during the study period.
- Medicare Part D: Also referred to as Prescription Drug Coverage, Part D first became available in January 2006. It is available to everyone with Medicare, but

individuals must enroll in a Medicare-approved plan that offers Medicare drug coverage. Individuals must pay a monthly premium to receive Part D benefits.

9.2.2. Study population *(Amended 15 July 2022)*

The study population will be comprised of all US Medicare beneficiaries who received the RZV vaccine (i.e., exposed) in 2018 through 2020 as well as a random sample of Medicare beneficiaries who did not receive the RZV vaccine but who had at least one preventive care visit ***(i.e., comparator group)***, as defined in Section 9.7.5. The study population is a longitudinal cohort that is followed over time until they are no longer in Medicare. This means there will be continuity of their data over time, i.e., there is not a new random sample selected each study year.

Study inclusion / exclusion criteria

US Medicare beneficiaries who meet the following criteria will be included in the study:

1. Age 65 and older at the date of the RZV vaccination or preventive care visit for the RZV unvaccinated comparator, **AND**
2. Enrolled in Medicare due to age or ESRD as the original and current qualifying reason, **AND**
3. Continuously enrolled in Medicare Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination or preventive care visit for the RZV unvaccinated comparator. Continuous ***enrollment*** is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and ***enrollment*** in at least 11 of the 12 preceding months.

Beneficiaries enrolled due to ESRD or receiving dialysis are included in the study population as this condition is prevalent among US Medicare beneficiaries aged 65 and older, and this is a subgroup in which RZV use may be common. The requirement for continuous enrollment in Medicare Parts A, B, and D in the 365 days***, allowing one calendar month gap,*** before the RZV vaccination or preventive care visit will ensure complete data on all services covered by Medicare on a fee-for-service basis in the baseline study period for the cohort design. Parts A and B provide information on the HOI and Part D provides information on RZV exposure.

Beneficiaries who satisfy the following criteria will be excluded:

1. Continuously enrolled only in Medicare Part C in the baseline period, OR
2. Enrolled in Medicare due to disability as the original qualifying reason for enrollment.

Individuals who qualify for Medicare due to a disability are likely not comparable to the population of adults age 65 and older within the Medicare health insurance program in many important aspects, such as medical comorbidities, illness severity, and health seeking behavior.

It will be possible to obtain sufficient sample sizes for all HOIs with a study population accrual from 2018 through 2020. Conservative estimates are that 1.5 million Medicare beneficiaries with Parts A, B, and D will receive RZV in each year from 2018 through 2020, for a total RZV exposed of 4.5 million across all three years. If 50% are enrolled in Parts A, B, and D for at least 365 days, there will be a little more than 2 million individuals exposed to RZV who meet the study criteria. It will be possible to accrue 8 million unvaccinated individuals with a preventive care visit in 2018 through 2020 to achieve a 1:4 ratio of exposed to comparators for the cohort design.

All CMS CCW Medicare claims data from January 2017 through December 2021 will be obtained for the RZV exposed and the unvaccinated comparators accrued from 2018 through 2020. Data spanning five years are needed to cover a) the 365 days prior to the HOI for the SCRI design; b) the 365 days prior to the index date for the cohort design; c) the 60- and 84-day risk and control intervals for the SCRI design; and d) the 183-day risk window for the cohort design.

9.3. Variables

9.3.1. Exposure measure

RZV exposure will be defined as receipt of at least one dose of RZV for the primary analyses; per-dose analyses will be performed in secondary analyses. RZV vaccination will be identified by means of the national drug code (NDC) and by the Current Procedural Terminology (CPT) code. Part D generally pays for commercially available vaccines. The NDCs from the prescription drug events (PDE) file that will be used to identify RZV exposure as a prescription dispensing in an outpatient pharmacy setting are: 58 160-0828-01; 58 160-0829-01; 58 160 082 311; 58 160-0828-03; 58 160-0829-03; 58 160 082 311; and 58 160-0823-11. The CPT code 90750 for RZV will identify vaccine administration in a Part B (physician office setting) claim. It is anticipated that most will be identified from the PDE file and should only occur in one of the claims files since Medicare will not pay for the same vaccine administration twice, i.e., exposure will not be counted twice.

RZV vaccination records occurring within 27 days after a previous RZV vaccination record (i.e., on days 1-27, where the day of the previous RZV record is day 0) will be considered a duplicate record and will be deleted. The ***participant*** will be retained for the analytic cohort. For ***participants*** who receive more than two doses of RZV, even after removal of possible duplicates, we will exclude from analysis RZV doses beyond two per study ***participant***.

Preventive care visits for comparison with RZV vaccinations will be identified by means of CPT, ICD-10, and Healthcare Common Procedure Coding System (HCPCS) codes, as shown in Table 2. The presence of any of the below codes qualifies as an eligible "preventive care visit."

Table 2 Preventive care visit description for the comparators in the cohort analyses

ICD10	HCPS	CPT	Code Description
			Routine Adult Annual Exam
		99386	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 40-64 years
		99387	Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 65 years and older
		99396	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years
		99397	Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 65 years and older
	G0438		Annual wellness visit; includes a personalized prevention plan of service (pps), initial visit
	G0439		Annual wellness visit, includes a personalized prevention plan of service (pps), subsequent visit
	G0468		Federally qualified health center (fqhc) visit, ippe or awv; a fqhc visit that includes an initial preventive physical examination (ippe) or annual wellness visit (awv) and includes a typical bundle of medicare-covered services that would be furnished per diem to a patient receiving an ippe or awv
	S5190		Wellness assessment, performed by non-physician
	G0402		Initial preventive physical examination; face-to-face visit, services limited to new beneficiary during the first 12 months of medicare enrollment
Z00.00			Encounter for general adult medical exam without abnormal findings
Z00.01			Encounter for general adult medical examination with abnormal findings
			Colonoscopy Screening
		45378	Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
	G0105		Colorectal cancer screening; colonoscopy on individual at high risk
	G0121		Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk
	G9661		Patients greater than 85 years of age who received a routine colonoscopy for a reason other than the following: an assessment of signs/symptoms of gi tract illness, and/or the patient is considered high risk, and/or to follow-up on previously diagnosed advance lesions
	G9659		Patients greater than 85 years of age who did not have a history of colorectal cancer or valid medical reason for the colonoscopy, including: iron deficiency anemia, lower gastrointestinal bleeding, crohn's disease (i.e., regional enteritis), familial adenomatous polyposis, lynch syndrome (i.e., hereditary non-polyposis colorectal cancer), inflammatory bowel disease, ulcerative colitis, abnormal finding of gastrointestinal tract, or changes in bowel habits
	G0104		Ca screen;flexi sigmoidscope

ICD10	HCPS	CPT	Code Description
	G0106		colorecteral screeningn ca screen;barium enema
	G0107		colorecteral screening / rectal cancer screening; fecal-occult blood test
	G0120		colorecteral screeningn ca scrn; barium enema
	G0122		colorecteral screeningn ca scrn; barium enema
	G0328		colorecteral screeningrectal cancer screening, fecal occult blood test
Z12.11			Encounter for screening for malignant neoplasm of colon
			Mammography Screening
		77067	Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed
		77057	Screening mammography, bilateral (2-view film study of each breast) Office/Freestanding (Global)
		76092	Screening mammography, bilateral (two view film study of each breast).
	G0202		Screening mammography, bilateral (2-view study of each breast), including computer- aided detection (CAD) when performed.
	G0203		Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.
	V7611		Screening mammogram for high-risk patient
	V7612		Encounter for screening mammogram for malignant neoplasm of breast
	G0204		Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.
	G0206		Diagnostic mammography, including computer-aided detection (CAD) when performed; unilateral.
Z12.3			Encounter for screening for malignant neoplasm of breast
Z12.31			Encounter for screening mammogram for malignant neoplasm of breast
Z12.39			Encounter for other screening for malignant neoplasm of breast
			Osteoporosis Screening
		77080	Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine)
		77081	Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; appendicular skeleton (peripheral) (eg, radius, wrist, heel)
	G0062		PERIPHERAL SKELETAL BONE MINERAL DENSITYN20030626
	G0063		CENTRAL SKELETAL BONE MINERAL DENSITY STN20030626
	G0130		SINGLE ENERGY X-RAY ABSORPTIOMETRY (SEXAN20110101: Single energy x-ray absorptiometry (sexa) bone density study, one or more sites; appendicular skeleton (peripheral) (e.g., radius, wrist, heel) (Single energy x-ray study)
	G0131		COMPUTERIZED TOMOGRAPHY BONE MINERAL DENN20060101
	G0132		ULTRA-SOUND BONE MINERAL STUDY, ONE OR MORE SITES, APPENDICULAR SKELETON
	G0133		Bone mineral density
Z13.820			Encounter screening for osteoporosis

9.3.2. Outcome identification algorithms

The primary HOIs are GBS, gout, PMR, and GCA. Secondary HOIs are SVT and ION. Table 3 describes the case definition algorithm for the primary and secondary HOIs, which also details the sensitivity analyses where validated outcome identification algorithms are not available in the literature for reference.

- All algorithms use medical claims from the inpatient, outpatient or carrier claim files and are based on the ICD-10 codes.
- An inpatient claim is defined as a claim generated from an admission to a hospital.
- An ED (Emergency Department) visit is defined as a claim generated from a visit to an urgent care unit within a hospital, but it is not a hospital admission.
- An outpatient claim is defined as a claim generated by a visit to a provider in an ambulatory practice setting, e.g., physician office, health clinic.
- For algorithms that require ≥ 2 claims, the date of the first claim will define the first occurrence of the HOI. The two claims must occur within the designated follow-up interval.
- For the SCRI design, new onset of the HOI, i.e., incident case, is determined based on the first occurrence and no record of the HOI in the preceding 365 days.
- For the cohort design, new onset of the HOI, i.e., incident case, is determined based on the first occurrence after the index date (i.e., RZV vaccination or the preventive care visit date for RZV unvaccinated comparators) and no record of the HOI in the 365 days preceding the index date (i.e., baseline period).
- For GBS, the earliest onset date is the hospitalization date for claims in the inpatient setting or the earlier GBS claim when the diagnosis occurs in any setting followed by an inpatient claim within 7 days.

Table 3 HOI case identification algorithms

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
GBS (SCRI)	G61.0	PPV: 50% (Inpatient visit)[14]	None	Inpatient primary position OR Diagnosis in any setting followed by an inpatient claim within 7 days	Days 1-42	1 year; inpatient; primary position only	Same as in Col.2	HOI	N/A
Gout (SCRI)	M10.x, M1A.x (chronic gout)	PPV: 61% (≥ 2 visits associated with the diagnosis)[15]	At least one gout-specific oral medication (allopurinol, colchicine, probenecid, febuxostat) prescribed within 3 months after the first date of the diagnosis.	≥2 outpatient claims within the follow-up window[a] OR ≥1 inpatient claim	Days 1-30	1 year; diagnosis code –all settings[b] OR At least one gout-specific oral medication (allopurinol, colchicine, probenecid, febuxostat);	Same as in Col. 2 OR Col. 4	HOI	-Exclude chronic and secondary gout codes. -Examine frequency distribution of ICD-10 codes and consider low-frequency codes such as codes for chronic gout (M1A*), lead-induced gout (M10.1*, drug-induced gout (M10.2*), and gout due to renal impairment (M10.3*) (note: this exclusion of gout codes does not apply in assessing prevalent gout)[d]

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
PMR (Cohort)	M35.3 – PMR M31.5 – GCA w/ PMR	Sensitivity: 99.5% Specificity: 92.2%[16] (based on the 3 methods used by Bernatsky: diagnosis in inpatient or outpatient, or a visit by a rheumatologist/ internist)	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone) prescriptions; The first dispensing within 6 months of PMR diagnosis and the second dispensing date within 6 months after the first dispensing.	≥2 outpatient claims within the follow up window a OR ≥1 inpatient claim	Days 1-183	1 year; all settings[b]	Same as in Col. 2	Exposure	N/A
GCA (Cohort)	M31.6 (GCA), M31.5 (GCA with PMR), M31.9 (necrotizing vasculopathy unspecified)	Not available	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone). The first dispensing within 6 months of GCA diagnosis and the second dispensing date within 6 months after the first dispensing.	≥2 outpatient claims within the follow up window[a] OR ≥1 inpatient claim	Days 1-183	1 year; all settings[b]	Same as in Col. 2	Exposure	-Use the primary algorithm based on the GCA diagnosis code and steroid prescription but ADD a requirement for a temporal artery biopsy at the time of diagnosis, as determined by a CPT code=37609

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
ION (Cohort)	H47.01	Not available	Exclude patients who had coronary artery bypass graft (CABG) surgery[17] or lumbar or lumbosacral spinal fusion and/or laminectomy surgery within 30 days before ION diagnosis date	≥1 claim in all settings	Days 1-183	1 year; all settings[b] ICD code only	Same as in Col. 2	Exposure	Additional criteria for arteritic: ≥ 40 mg/day of prednisone prescription ± 4 weeks of the diagnosis plus an ophthalmologist/neuro-ophthalmologist consult (if possible) and GCA diagnosis within 3 months; lookback to rule out prevalent cases will use ICD code only; all settings
SVT (SCRI)	I47.1	Sensitivity-91.7% [18]	None	≥1 ED or inpatient claim any position	Days 1-30	1 year; all settings[b] any position	Same as in Col. 2	HOI	N/A

Definitions: ALS - Amyotrophic Lateral Sclerosis; CVA - Cerebrovascular Accident; GCA - Giant Cell Arteritis; GSB - Guillain-Barré Syndrome; ION - Ischemic Optic Neuropathy; PMR - Polymyalgia Rheumatica; SCRI - Self-controlled Risk Interval; SVT - Supraventricular Tachycardia;

[a] Outpatient visits are defined using ≥2 claims for consistency with methods used by CMS algorithms using the CMS CCW Medicare data to define chronic conditions, and to avoid misclassification of the outcome due to the potential for 1 visit to reflect rule-out diagnosis.

[b] Includes inpatient, emergency department, and outpatient settings.

[c] Based on external expert opinion.

[d] Consistent with the study EPI-ZOSTER-030 VS US DB, no analysis will be conducted for the gout sensitivity HOI definitions. These definitions are for administrative purposes only .

9.3.3. Covariates

Covariates to be evaluated include the following, some of which will be used to adjust or stratify the cohort during the analytic modeling:

- Region of residence within US [as defined by either Department of Health and Human Services (11 regions) or Census Bureau (4 regions)]
- Calendar year-month of vaccination or preventive care visit
- Age in years at vaccination or preventive care visit (aggregated into age groups: 65-69, 70-74, 75-79, 80-84, 85+)
- Sex (binary as male/female)
- Race and ethnicity (e.g., white, black, Asian, Hispanic, North American Native, other)
- Concomitant vaccination (e.g., influenza, pneumococcal, etc.)
- Certain immunocompromising conditions (e.g., transplant, cancer, autoimmune/inflammatory condition, etc.)
- Certain other co-morbidities (e.g., diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, etc.)

9.3.4. Potential confounding variables and effect modifiers

A confounder is defined as any variable that is associated with both the exposure and the study HOI. Since a confounder cannot be on the causal pathway from exposure to the outcome, all confounders will be captured in the 365 days preceding the index date, i.e., RZV Dose 1 and Dose 2 vaccination date and the RZV unvaccinated comparator preventive care visit for the cohort design. All confounders identified using Medicare enrollment and medical or prescription claims data will be used for covariate adjustment in multivariable models. Propensity score methods will be considered for confounding adjustment, depending on identified imbalances in the observed covariates between the exposed and comparator groups. Confounding variables defined by health care services and comorbidities will be identified using a combination of ICD-10, CPT and HCPCS codes.

- **Demographic variables** will include age, sex, and race and ethnicity (i.e., white, black, Asian, Hispanic, North American Native, and other/unknown based on the US government categories)
- **Healthcare service variables** will include admissions to skilled nursing facilities (SNFs), number of hospitalizations, number of ED visits and Durable Medical Equipment (DME) use. These will be considered to control for potential imbalances between RZV vaccinees and RZV unvaccinated comparators in health impairment requiring more intensive services. The place of service and revenue code on the claim are used to designate the type of service setting.
- **Preventive care services** will include receipt of age-recommended vaccine (e.g., influenza, pneumococcal, and tetanus, diphtheria, pertussis). These will be

considered to control for potential healthy adherer bias that could result in imbalances in healthcare services and prior health seeking behavior patterns between RZV vaccinees and RZV unvaccinated comparators. Table 2 lists the preventive care services. Since mammography, bone mineral density, and colorectal screening are criteria for the unvaccinated comparator selection, these are not included as confounders in the analysis.

- **Medical comorbidities specific to PMR/GCA**. Potential risk factors specific to these conditions may include:
  - Age, which is found to be the strongest risk factor;[19]
  - Female sex is found to be a risk factor;[19]
  - Race/ethnicity as a significantly lower incidence is reported in African, Asian, Latinos;[19]
  - Gout has been associated in a few studies (from same group using CMS data);[20,21]
  - Prior hematologic malignancy has conflicting results on the association, but has been shown in some studies;[22]
  - Case reports/series with use of checkpoint inhibitors show development of PMR or PMR-like syndrome;[23]
  - Immunocompromising conditions, given that PMR is an immune-mediated disorder, potentially imbalance in T-regulatory lymphocytes and proinflammatory T-helper 17 cells.
- **Medical comorbidities specific to ION**. Risk factors specific to ION include:[24-28]
  - Arteritic ION is significantly less common than non-arteritic and is strongly associated with GCA, thus we will consider similar risk factors/potential confounders.
  - Non-arteritic ION Anterior Ischemic Optic Neuropathy has reported associations with obstructive sleep apnea, vasculopathic/ prothrombotic conditions (e.g., diabetes, hypertension, spinal and cardiac surgery, some medications (amiodarone, phosphodiesterase type 5 inhibitors).
- **General medical comorbidities**. Other comorbidities or chronic conditions may be important to address confounding by indication, e.g., relatively common conditions that are indicative of functional status or illness severity.
  - Diabetes mellitus
  - Chronic kidney disease
  - Chronic lung disease - chronic obstructive pulmonary disease and chronic bronchiectasis
  - Congestive heart failure
  - Ischemic heart disease
  - Dementia - Alzheimer’s Disease and Related Disorders or Senile Dementia

  - Chronic liver disease - cirrhosis and other liver conditions except hepatitis
  - Stroke/Transient Ischemic Attack

- **Immunocompromised conditions**. This includes solid organ transplant, hematopoietic cell transplant, hematologic or solid malignancy with recent receipt of chemotherapy, autoimmune/inflammatory condition ***or*** on an immunosuppressive regimen, and human immunodeficiency virus infection.

9.4. Data sources

9.4.1. Description of the databases (*Amended 15 July 2022*)

CMS CCW Medicare data is a secondary administrative database of all paid claims for fee-for-service billable healthcare services in inpatient and outpatient settings, SNF, hospice, home health services, and for the provision of DME and prescription drugs for older and disabled US citizens. The claims data are available in six different datasets and a unique identification (ID) is used to link an individual across all data sets. Annex 1 provides a detailed description of the data sets and the variables within each dataset.

Master Beneficiary Summary File (MBSF): The information in this dataset relevant to this study includes beneficiary enrollment ***each calendar month*** in Medicare Parts A, B, and D. This file will be used to obtain information on the baseline study variables, including original and current enrollment reason, eligibility, and demographic characteristics.

Inpatient Claim File: This dataset contains fee-for-service claims submitted by inpatient hospital providers for reimbursement of facility costs, including hospitalizations and ED visits. Up to 25 diagnosis fields, including the admission diagnosis as well as a principal diagnosis, are available on each claim. CPT codes for services rendered are available on each claim.

Outpatient Claim File: This dataset contains fee-for-service claims submitted by *institutional outpatient providers*. Institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, Federally Qualified Health Centers and community mental health centers. The outpatient files contain up to 25 diagnosis fields as well as CPT codes.

Carrier File: This dataset includes fee-for-service claims submitted by *professional providers*, including physicians, physician assistants, clinical social workers, nurse practitioners and by *organizational providers*, including freestanding facilities (i.e., independent clinical laboratories), ambulance providers, freestanding ambulatory surgical centers and freestanding radiology centers. The Carrier files contain up to 12 diagnosis fields as well as CPT codes.

SNF Claim File: This dataset includes fee-for-service claims for paid services that are submitted by SNF *institutional facility providers*.

PDE File: This dataset includes all medications filled at an *outpatient pharmacy* that have been submitted by the prescription drug plan. The NDC variable will be used in this study to identify all medications dispensed during the baseline and follow-up period.

The MBSF will be used primarily to select the study population and determine eligibility for this study. The inpatient, outpatient, carrier and SNF files will be used to ascertain the HOIs and the confounding variables. The PDE file will be used to ascertain RZV exposure.

9.4.2. Quality of the data

Quality of the ICD Codes for Identifying HOIs: The chronic medical condition variables were developed using algorithms based on ICD-9-CM diagnoses codes, Medicare Severity Diagnosis Related Group codes, or procedure codes. CMS has confirmed the consistency of the prevalence of the chronic conditions between the ICD-9 and ICD-10 codes. The link to the document is found here: https://www2.ccwdata.org/web/guest/ccw-medicare-datra-white-papers. All of the algorithms used to identify CCW chronic conditions from the claims data were updated for the conversion from ICD-9 to ICD-10. However, the validation statistics for these algorithms are not reported in the CCW white paper. Specifications for the algorithms are located under the 'Conditions Categories' tab at www.ccwdata.org. With regards to the HOIs in this study, gout (see Sentinel report) has demonstrated consistent prevalence during the period of transition from ICD-9 to ICD-10.

Completeness of the CMS CCW Medicare Claims for Assessment of Study Outcomes: The claims from each of the databases are over 99% complete by 12 months post-service date. This will reduce the likelihood of missing information as all data measured for this study will have a minimum of a one-year lag period.

This study uses de-identified Medicare data curated for research; investigators cannot access medical charts for case adjudication. Case identification will be limited to use of an algorithm that combines medical billing diagnosis code, procedure and/or drug codes.

9.4.3. Number of years and duration of data availability

For this study, five years of CCW Medicare data will be purchased: 2017 through 2021. This is necessary to ensure an adequate sample size for the primary HOIs (see Section 9.5 for a detailed description of the sample size). The span of five years (2017 through 2021) will ensure claims data are available for 365 days preceding the HOI (in the SCRI design) and the index date (in the cohort design) and throughout the duration of the study follow up for all of the Dose 1 and Dose 2 analyses. All individuals will be followed longitudinally throughout the study.

CCW Medicare data are available for request in December for the prior year's claims (e.g., the 2018 data should be available for request in December 2019).

9.4.4. Rationale for selecting the database and advantages

Rationale for Selecting the Database: Several factors support the rationale for using the CMS CCW Medicare data.

- It is the largest comprehensive dataset of healthcare service utilization of US adults age 65 and older.
- Data linkage across different data sets permits evaluation across the continuum of healthcare settings and services.

Advantages of the CMS CCW Medicare Data: The CMS CCW Medicare data offers many strengths for a vaccine safety study using observational data. The relevant strengths of CCW Medicare for this study include:

1. There is continuity of medical and prescription claims data. Once enrolled, most beneficiaries remain enrolled in Medicare for the rest of their lives because Medicare is the only entitlement health insurance coverage for older adults in the US. The exception is adults who enroll in Part C, and all of their data are missing because it is not captured in the CMS CCW fee-for-service data. The feasibility assessment revealed that, 54% of the Medicare beneficiaries had continuous enrollment in Parts A, B, and D for at least one-year preceding the first occurrence of a claim with a diagnosis corresponding the one of the HOIs in this study. Most Medicare beneficiaries (56%) were continuously enrolled in Parts A, B, and D for at least one-year after the first occurrence of a claim with a diagnosis corresponding to one of the HOIs in this study. Approximately 20% were continuously enrolled in Parts A, B, and D for five or more years. This will ensure sufficient data for the baseline and follow up assessments in this study with minimal loss to follow-up.
2. Comprehensive data that are linkable across service settings. The data will include medical and prescription encounter data from inpatient, institutional, outpatient physician, outpatient hospital, and outpatient pharmacies that are linked via a beneficiary identification number. This permits assessment of the study outcomes in relation to the timing of a medication exposure, including vaccines. Key variables include those related to diagnoses, procedures, and place of service.
3. Large population. The Medicare population is large and will permit detection of rare outcomes, as some HOI in this study like GBS, GCA and ION are rare.
4. Representation of geographic diversity of the US, since the data represent all Medicare enrollees across all states. The data provide geographic diversity within the context of the US.

9.5. Study size

9.5.1. Projected study size

CMS CCW Medicare claims data will be obtained for up to 20 million Medicare beneficiaries. This will include all RZV vaccinees in 2018 through 2020 in addition to a random sample of Medicare beneficiaries who did not receive RZV and had a preventive care visit. The estimated sample size for the SCRI design with vaccinees (Table 4) and the cohort design with vaccinees and the unvaccinated comparators (Table 4) needed to detect the specified relative risk with 80% power is attainable.

9.5.2. Sample size considerations

SCRI design sample size estimates

For the SCRI design, the required number of events was calculated based on the method for self-controlled case series studies[29]. The sample size estimates shown in Table 4 indicate that 1 000 000 individuals are needed to detect a relative risk of at least 4.0 for GBS and 70 000 individuals are needed to detect a relative risk of 2.0 for gout. The sample size calculation only takes into consideration the control window because the risk of GBS or gout in the control window would reflect the background risk. Due to the dose spacing and the possibility of Dose 1 control window overlapping the risk window for Dose 2, the full 42-day control window for Dose 1 may not be observed, we expect this to occur in about 50% of 2 dose vaccine recipients (based on internal GSK data from 2018-2019 regarding timing of Dose 2 receipt in the US). Hence the average length of the control window observed would be about 36 days.

Table 4 SCRI design sample size estimates for GBS and gout with 80% statistical power under a two-sided type 1 error (alpha) of 0.05

Outcome	IR	CW (days)	Scalar of Risk Window	No. of cases expected per 100 000 CWs [a]	RR	Total events needed	*No. of cases expected in CW	No. of CWs (aka vaccinations) needed/100 000 [b]	**No. vaccinations needed	***No. of vaccinated people needed
GBS	2/100 000 PY	36	0.098563	0.197125	3	30	8	41	4,100,000	2,050,000
					4	20	4	20	2,000,000	1,000,000
Gout	200/100 000 PY	30	0.082136	8.706365503	2	68	23	140	140,000	70,000
					2.5	40	11	67	67,000	33,500

IR: Incidence rate; RR: Relative risk; CW: Control window
[a] Assuming no risk from vaccination exists in CW
[b] vaccinations are synonymous with post-vaccination control windows
*Total events needed were calculated using the method described by Musonda et al [29].
** Expected vaccinations were obtained assuming the control window was truly not a period od=f increased risk
*** Approximate numbers, assuming that individuals receive 2 doses

In order to use the control window (assumed to be free of risk due to vaccination) to project the number of vaccinations needed, we scaled the background risk to the length of the control window, i.e., multiplied the respective background rate by 36/365.25 for GBS and by 30/365.25 for gout.

We then calculated the number of cases we would need in the control window for each relative risk scenario, given the minimum total number of events needed in risk and control windows combined.

For example, for a true relative risk of 2, a total of 71 cases are needed to achieve 80% power to see an association. We would expect about 47 of the 71 cases to be in the risk window and 24 to be in the control window.

To generalize to other relative risk scenarios, the number of cases in the control window out of the total events needed is [total events needed/(RR+1)]. The expected numbers in the control window (vaccinations) needed is simply the ratio of the number of cases in the control window (i.e., the number expected on the basis of the true relative risk and the total number of events needed in risk and control windows combined) and the background rate scaled to the control window length.

Cohort design sample size estimates:

For the cohort design, the sample size was estimated using Poisson Regression in the Power Analysis and Sample Size software (NCCS Statistical Software, 2013, version 12.0.2). The analysis performed for the PMR and GCA sample size estimates was based on a 183-day risk period with a cohort ratio of 1:4 exposed to unvaccinated preventive care visit comparator.

The sample size estimates shown in Table 5 indicate that a total sample of 438 239 individuals is needed to detect a relative risk of 2.0 for PMR and a total sample of 723 362 individuals are needed to detect a relative risk of 3.0 for GCA. The study is powered for the primary outcomes of PMR and GCA.

Table 5 Sample sizes with cohort design for PMR and GCA with 80% statistical power under a two-sided type I error (alpha) of 0.05, Cohort 1:4 ratio, and 6 months follow up

Outcome	RR	Baseline Response	Total Cohort Sample Size, N	Vaccinated Population, N	Control Population, N
PMR	2	0.000405	438,239	87,648	350,591
	2.5		242,212	48,442	193,770
	3		164,320	32,864	131,456
	3.5		123,991	24,799	99,192
GCA	2	0.000092	1,929,204	385,841	1,543,363
	2.5		1,066,257	213,252	853,005
	3		723,362	144,673	578,689
	3.5		545,828	109,166	436,682
	4		439,133	87,827	351,306

The estimated sample sizes for the SCRI design with vaccinees (Table 4) and the cohort design with vaccinees and the unvaccinated comparators (Table 5) needed to detect the specified relative risks (≥ 4 for GBS, ≥ 2 for gout, ≥ 2 for PMR, and ≥ 3 for GCA) with 80% power is attainable.

9.6. Data management

Full details of the data management will be described in the Data Management Plan (DMP). The DMP is bound by the provisions of CMS. Included in the DMP are (1) description of data acquisition procedures (2) physical possession and storage of data files and (3) data sharing, electronic transmission and distribution.

9.6.1. Data collection

Data collection. Through a Data Use Agreement (DUA) with CMS, University of Maryland, Baltimore (UMB) acquires adjudicated administrative claims data for the US Medicare population. There is no data collection occurring at the UMB site. The data acquired through CMS are deemed research identifiable files, which means dates of service visits, dates of birth, and zip code information are available in the data.

Physical possession and storage of data files. All original media containing sensitive data files are kept onsite by the Pharmaceutical Research Computing (PRC) Center at UMB in an access-controlled room in a fireproof locked safe. The PRC System Administrator is responsible for the upload of data onto the secure servers, which are accessible only to study personnel. Database management at PRC is built with multiple layers of security and follows best practices for securing sensitive data.

Projects requiring special handling of backups especially at the termination of the project are stored in a specific directory on the PRC system. Files are backed-up and encrypted as a whole and saved on their own non-removable backup drive.

Data access. Only study personnel approved by the Project Officer/Principal Investigator are allowed access to the assigned secure private workspace. PRC employs the principle of least privilege, allowing only authorized access for users which are necessary to accomplish assigned tasks. Study personnel must have current Health Insurance Portability and Accountability Act (HIPAA), Collaborative Institutional Training Initiative (CITI) and security training records on file with PRC before an account or access is finalized. To increase security, external access to PRC's secure environment is blocked by a UMB campus firewall, as well as a local software-based server firewall. All study personnel access is monitored on an ongoing basis using a digital footprint.

Data inventory. The staff at PRC maintain custodianship over the data files contained on the PRC server and PRC staff maintain compliance with DUA expirations.

Data Breach. In order to comply with the Privacy Act of 1974, HIPAA, federal security requirements outlined by National Institute of Standards and Technology, and DUA-required standards, PRC has adopted measures to prevent or minimize potential system security breaches.

Data sharing, electronic transmission, and distribution. Data analysis is conducted with SAS 9.4. Users are unable to upload or download data from the PRC. Files may only be outputted to directories with write access permissions. All users must abide by the project specific DUAs when sharing or distributing data.

9.7. Data analysis

- All the statistical analyses will be done in SAS 9.4.
- All the statistical tests will be two-sided at alpha level of 0.05.
- All 95% CIs will be estimated as the point estimate ± 1.96*standard error.

9.7.1. Hypothesis testing

9.7.1.1. Hypothesis for the SCRI analysis

Hypothesis (HA1): The incidences of new onset GBS and gout in the RZV exposed person will differ in the risk window compared to the control window, as determined by an incident rate ratio not equal to 1.

These hypotheses will be tested separately for each of the two primary HOIs using the specific risk periods provided that at least 68 cases be recorded for gout (with a total cohort size of 70 000 we will have 80% power to detect relative risk of ≥ 2); and at least 20 cases recorded for GBS (with a total cohort size of 1 000 000 we will have 80% power to detect relative risk of ≥ 4).

9.7.1.2. Hypothesis for cohort analysis

Hypothesis (HA2): The incidence of new onset PMR and GCA in the RZV exposed cohort will differ from the incidence in the RZV unvaccinated comparator, as determined by a hazard ratio not equal to 1.

These hypotheses will be tested separately for each of the two primary HOIs during a 183-day risk period. With a cohort ratio of 1:4 RZV vaccinated to RZV unvaccinated comparator, a total sample size of 438 239 for PMR has 80% power to detect a relative risk of ≥ 2.0 and a total sample size of 723 362 for GCA has 80% power to detect a relative risk of ≥ 3.0.

9.7.1.3. Statistical analysis sequence

Since the sample sizes needed are HOI dependent, the statistical analysis will be staggered in phases. The proposed sequence is: gout; PMR and GBS; GCA, SVT, and ION as noted in Table 6. A comprehensive final report will be prepared upon completion of all primary and secondary analyses. This final comprehensive report will be submitted to the FDA Center for Biologics Evaluation and Research (CBER) and the EMA.

Table 6 Sequence of analyses to be conducted

Outcome	Target risk to detect	Analysis Sequence
Gout	RR of ≥2	Phase 1
GBS	RR of ≥4	Phase 2
PMR	RR of ≥2	
GCA	RR of ≥3	Phase 3
SVT	N.a.	
ION	N.a.	

N.a.:Not Applicable

9.7.2. Handling of missing data

Based on the feasibility assessment study, we do not anticipate any missing data on age and sex. Approximately 0.01% of the population has missing information on the state of residence and 1.42% report "unknown" race. Individuals may be lost to follow-up if they lose eligibility or switch to Part C and all their data will be missing, at which point they will be censored in the analysis. Under the assumption that data are missing at random, multiple imputation will be used to impute missing values.

9.7.3. *Participant* disposition (*Amended 15 July 2022*)

Participant disposition will be summarized for the overall study population and for the RZV vaccinated and RZV unvaccinated comparators with a preventive health visit by computing:

- Number of individuals screened overall to determine eligibility for the study.
- Number and percent of individuals who do not satisfy criteria for inclusion in the study, overall and by cohort, for each of the following reasons:
  - Age < 65 at the index date
  - Not continuously enrolled in Medicare Parts A, B, and D for 365 days***, allowing one calendar month gap,*** preceding the index date
  - Only enrolled in Medicare Part C
  - Qualify for Medicare due to a disabling condition
- Number of eligible ***participants*** in each cohort.

9.7.4. Descriptive analyses

Baseline characteristics of the RZV vaccinees and the RZV unvaccinated comparators will be compared using chi-square tests for categorical data and t-tests and simple linear regression for continuous data. According to the central limit theorem, with large sample sizes, as will be the case with the CMS CCW Medicare data, a two-sample t-test is robust to data that are not normally distributed. The Wilcoxon two-sample test is an alternative to the t-test because it makes no assumption about the underlying distribution of the data. It is best when the distribution of the two groups is similar, but it performs less optimally when the groups' distribution differs due to extreme outliers[30]. Data will be inspected

using graphical plots to first test that statistical assumptions are met before implementing an approach.

- Comparisons on key baseline characteristics (i.e., before the index date) will include (see Section 9.3.4 for list of confounders):
  - Demographic characteristics: age at the index date, gender, race, ethnicity, region of residence, and the duration of Medicare Parts A, B, and D enrollment preceding cohort entry.
  - Medical comorbidities: common chronic conditions being considered that may confound the exposure-outcome association.
  - Health service use: number of all cause inpatient and ED visits, use of DME, hospice, home health, and SNF.
  - Preventive health services: Receipt of vaccine (age-recommended vaccine: influenza, pneumococcal, and tetanus, diphtheria, pertussis).
- Evaluation of the characteristics by patterns of RZV dosing will include:
  - Comparison of the baseline characteristics of individuals who receive only one dose with individuals who receive both doses of RZV.
  - Characterize RZV dosing patterns such as the mean and median time between Dose 1 and Dose 2.
  - The EMA wishes to see whether a meaningful number of study ***participants*** receive Dose 2 within 2 months after Dose 1 in order to determine the applicability of the study results to the European context. In accordance with this request, we will report the proportion of all 2-dose recipients receiving the second dose on days 28-60 after the first dose.
  - Report on the number of GBS cases with evidence in the inpatient or outpatient claims of respiratory or gastrointestinal infection (including COVID-19) in the 60 days prior to the GBS diagnosis, noting in which post-RZV windows (risk versus control) these GBS cases occurred.

9.7.5. Analysis population (*Amended 15 July 2022*)

Population for the SCRI design analyses

Only the cases of new-onset gout, GBS and SVT recorded in the RZV exposed cohort during either the risk or the control windows will be included in the respective HOI SCRI analysis.

Population for the cohort design analyses

The study population for the cohort design will comprise all RZV exposed and RZV unvaccinated comparators with a preventive care visit who satisfy the inclusion criteria. With the cohort design, to exclude prevalent cases of the HOI prior to the index date, all ***participants*** who had the HOI at any point in the 365-day pre-vaccination baseline period will be excluded.

Generating an index date for unexposed comparators. In an attempt to control healthy user bias among individuals who receive the RZV vaccine, the unvaccinated comparators will be selected from individuals who have at least one preventive care visit. The steps described below will be performed separately for Dose 1 and Dose 2.

1. Create a pool of eligible comparators with at least one preventive care visit.
   - The pool of eligible comparators are unvaccinated individuals who had at least one preventive care visit, which is defined as having at least one visit for a routine adult annual exam OR at least one preventive screening intervention performed (Table 2).
   - To ensure complete data for the baseline period preceding cohort follow-up, individuals must be continuously enrolled in Medicare Parts A, B, and D for a minimum of 365 days preceding the preventive care visit***. Continuous enrollment is determined by Medicare enrollment in the month of the preventative care visit and enrollment in at least 11 of the 12 preceding months.*** Visits that do not satisfy this criterion will be excluded. For individuals with multiple preventive care visits, only visits that do not meet the eligibility criterion will be excluded. For individuals with only one preventive care visit, the entire person will be excluded if the visit does not meet eligibility criterion.
2. Randomly select one preventive care visit from eligible comparators. For an individual to be eligible as a comparator, the individual must not have had RZV at any time in available history prior to or on the day of the preventive care visit.
3. The preventive care visit is the index date for the unexposed comparator.

9.7.6. Inferential analyses for the primary outcomes (*Amended 15 July 2022*)

An overview of the planned primary, secondary, and sensitivity analyses were presented earlier in Table 1. Details of the analysis are described here.

- GBS and gout will be analyzed using a SCRI design
- PMR and GCA will be analyzed using a cohort design

Analysis of the SCRI Design

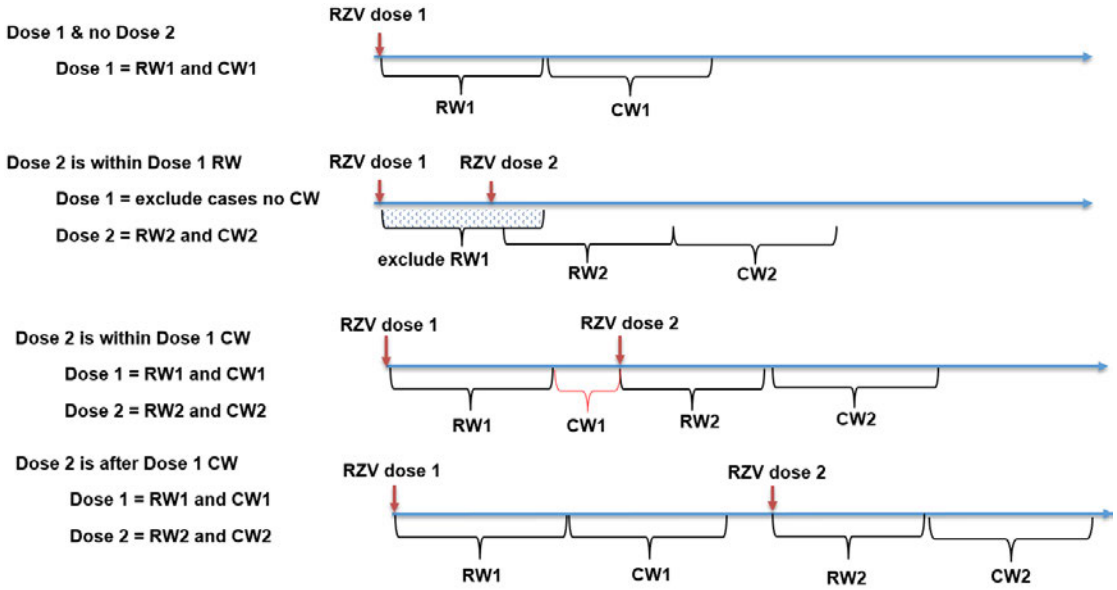
Additional inclusion requirements for the SCRI design analyses for new onset (i.e., incidence) primary HOIs GBS and gout include:

1. Receipt of RZV vaccination;
2. First occurrence in a 365-day look-back from the HOI in the risk or control interval;
3. ***Continuously enrolled in Medicare Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination and enrollment in at least 11 of the 12 preceding months.***
4. ***Continuous*** enrollment in Parts A and B (and in the case of gout Part D to capture gout-specific medication) through the end of the respective control interval.

The use of a first-in-365-days definition of HOI incidence is important and customary with the SCRI design to establish an equal opportunity for a case to be ascertained regardless of where in the follow-up (risk and control) period it might appear. The enrollment requirement for the defined amount of follow-up time, i.e., through the end of the control interval, will exclude people who die or lose eligibility before that time. However, because the HOIs addressed in this study are usually not fatal, we do not expect this requirement to produce any appreciable bias in our analyses. Moreover, the follow-up time (risk and control) is relatively short (84 and 60 days for GBS and gout, respectively), and we do not expect exclusion due to death would impact many individuals. In the relatively short follow-up time, we also do not anticipate loss of eligibility will produce appreciable bias in the analyses.

Per US schedule, RZV is indicated as a two-dose schedule, 2 to 6 months apart, thus it is not possible to define a consistent control interval for Dose 1. The control interval following Dose 1 may overlap with the risk interval following Dose 2. Therefore, the control interval following Dose 1 will depend upon the time between doses. The potential scenarios are illustrated in Figure 1.

Figure 1 SCRI design with variable spacing between Dose 1 and Dose 2



RW1: Risk window for dose 1; RW2: Risk window for dose 2; CW1: Control window for dose 1; CW2: Control window for dose 2;
Risk window: GBS days 1-42 following vaccination; Gout days 1-30 following vaccination
Control window (may be shorted in some scenarios): GBS days 43-84 following vaccination; Gout days 31-60 following vaccination.

Primary SCRI design analysis of combined doses.

The primary analysis for the SCRI design will combine both doses (i.e. the number of events in risk windows and number of events in the control windows, regardless of dose), yielding one risk estimate. Although RZV dose spacing is 2 to 6 months according to the US product label, there might be variations in schedule in real-world settings resulting in overlapping risk and control window. This presents some challenges with the two-dose analysis. GBS is used as an example to illustrate this (also depicted in Figure 1).

- Risk interval: Days 1-42 following vaccination with Dose 1 and days 1-42 following vaccination with Dose 2.
- Control interval: This will depend upon the spacing between doses (see Figure 1).
  - If Dose 2 is 1-43 days after Dose 1 (i.e. within Dose 1 risk window): Dose 1 cases excluded since no control window exists; Day 43-84 following vaccination with Dose 2 is the control window for Dose 2 (second scenario of Figure 1; anticipate that this scenario will rarely happen).
  - Dose 2 is 43-60 days after Dose 1 (i.e., within Dose 1 risk window and before the 2-month US product label indication): Day 43 up to Dose 2 following vaccination with Dose 1 is the control window for Dose 1 (i.e., shortened control window in third scenario of Figure 1.)
  - Dose 2 is 43-84 days after Dose 1 (i.e. within Dose 1 control window): Day 43 up to the receipt of Dose 2 following vaccination with Dose 1 is the control window for Dose 1 (i.e., shortened control window in third scenario of Figure 1). Days 43-84 following vaccination with Dose 2 is the control window for Dose 2.
  - Dose 2 is > 84 days after Dose 1 (i.e. after Dose 1 control window): Days 43-83 following vaccination with Dose 1 is the control window for Dose 1 and days 43-84 following vaccination with Dose 2 is the control window for Dose 2 (i.e., fourth scenario of Figure 1).

Secondary SCRI design analyses. The secondary analyses will vary the length of the control windows for Dose 1 and 2.

- Shortened control window for both doses: This will yield a single risk estimate but will use a 3-week (days 43-63) control window for both doses. Dose 1 control window cases will be excluded if also in the Dose 2 risk window.
- Allow a 6-week control window for both doses: This will yield a single risk estimate and will use days 43-84 after Dose 1. The Dose 1 control window cases will be excluded if also in the Dose 2 risk window.

Sensitivity analyses for SCRI design

- Separate dose analysis for Dose 1 and Dose 2: This will yield separate risk estimates for Dose 1 and Dose 2. This risk and control windows for each dose will be defined according to the primary analysis.
- Subgroup analysis of dose compliant individuals who receive both doses according to the US schedule, i.e. within 2 to 6 months: The analysis will be similar to the primary combined dose analysis yielding one risk estimate, but in a subset of the vaccines who receive the vaccine as indicated.

Potential seasonality adjusted SCRI analyses for GBS and gout We will assess any seasonal pattern of RZV vaccination graphically, and will adjust for seasonality in secondary SCRI analyses for GBS and gout, as both of these outcomes are known to have a seasonal pattern.

Analysis of the Cohort Design

Additional inclusion requirements for the cohort design analyses for new onset (i.e., incidence) primary HOIs PMR and GCA include:

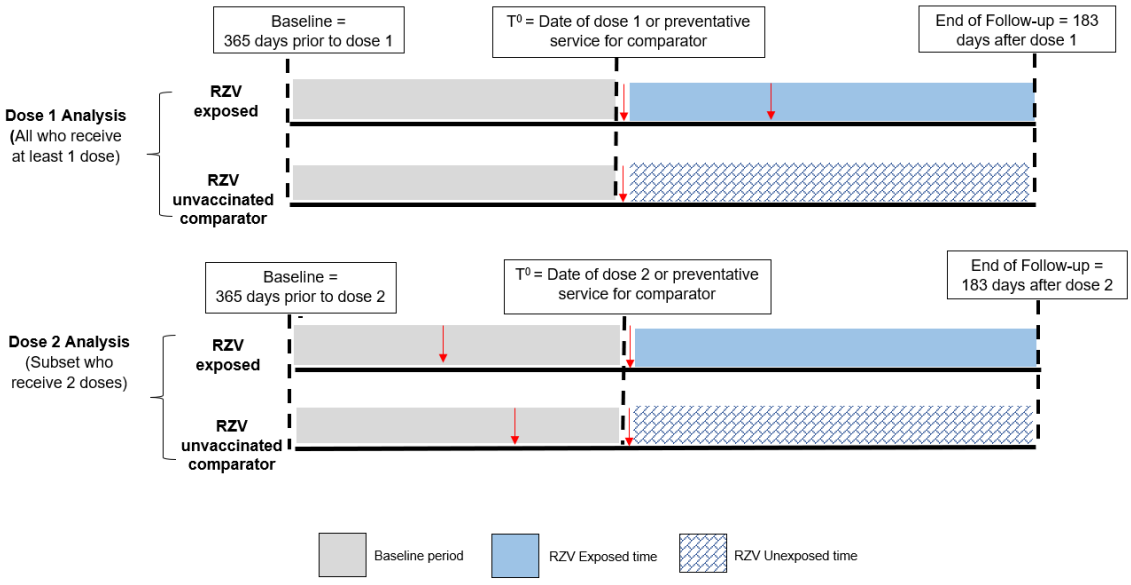
1. RZV vaccine exposed and a preventive care visit comparator;
2. A 365-day look-back from the index date (i.e., vaccination or preventive care visit date) to rule out prevalent cases;
3. At least 365 days (1 year) of Parts A, B, and D ***continuous*** enrollment prior to the index date. ***Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and enrollment in at least 11 of the 12 preceding months.***

Primary analysis of separate doses.

The analysis accounts for the variation in the interval between Dose 1 and Dose 2. The risk period after Dose 1 may overlap in part with the risk period after Dose 2 and/or the baseline period before Dose 2. To mitigate time-window bias, there is similar risk period after each dose.

The primary analysis will assess each dose separately and will yield two separate risk estimates for Dose 1 and Dose 2. Exposure is defined as at least one dose of the RZV vaccine. The risk period for the cohort analysis is 183 days from index date. The index dates are Doses 1 and 2 is the vaccination date for the RZV cohort and preventive care visit date for the RZV unvaccinated cohort. The scenarios for the primary analysis are illustrated in Figure 2.

Figure 2 Cohort Design: Primary analysis with separate Dose 1 and Dose 2 analysis



Secondary analyses of the cohort design.

The secondary analyses will combine Dose 1 and Dose 2.

- One risk estimate: This secondary analysis of combined doses does not distinguish between doses to yield one risk estimate.
- Two separate risk estimates: An additional secondary analysis combines Dose 1 and Dose 2 in the same analytic model but yields two separate risk estimates.

All individuals will be followed up for 183 days from the Dose 1. The maximum allowable spacing between doses will be 365 days. This means that Dose 2 is not included in the analysis if it is received more than 365 days after Dose 1. We anticipate the majority of individuals will receive Dose 2 within 365 days. RZV vaccinated individuals may have up to two measures (i.e., one for Dose 1 and one for Dose 2). The RZV unvaccinated comparators similarly will have up to two measures for the index dates for preventive care visits. Robust variance estimators will be used to account for repeated measures on the same individual.

Sensitivity analysis of the cohort design.

- Dose compliant analysis: The sensitivity analysis is restricted to the sub-sample that received Dose 1 and Dose 2 per US dosing schedule, i.e., 2-6 months apart. Analysis will be conducted similar to the secondary analysis (i.e combined doses yielding a single risk estimate and separate doses yielding two risk estimates).

Sensitivity analysis of alternative definition of GCA

- The number of cases and the incidence rate (or cumulative incidence) among vaccinated and preventative care comparators who are identifed using the sensitivity analysis HOI definition of GCA (Table 3 Column 10) will be reported. Futher analysis consistent with the primary (1^{o}) analysis for the cohort design (i.e. analysis of separate doses) will be conducted, if an appropriate number of cases are identified to allow meaningful inference.

Censoring events. Exposed person-time will be defined as the period between the index date and the earliest of the following events:

- End of study period (defined as the lesser of 183 days after the index date or Dec 31. 2021)
- Date of disenrollment from Medicare Parts A, B, and D
- Date of death
- Date of *Shingrix* vaccination among comparators
- Date of *Zostavax* vaccination
- Date of first diagnosis of the outcome of interest.

9.7.7. Inferential analyses of the secondary outcomes

The analysis of SVT will be similar to the SCRI design analyses for gout. The analysis of ION will be similar to the cohort design analysis for PMR and GCA.

Sensitivity analysis of alternative definition of ION

- The number of cases and the incidence rate (or cumulative incidence) among vaccinated and preventative care comparators who are identified using the sensitivity analysis HOI definition of ION (Table 3 Column 10) will be reported.Further analyses consistent with the primary (1^{o}) analysis for the cohort design (i.e.analysis of separate doses) will be conducted if an appropriate number of cases are identified to allow meaningful inference.

9.7.8. Sensitivity analysis to evaluate the impact of the COVID-19 pandemic

Sensitivity analyses will exclude exposures from the analytical cohort for which follow-up ended after February 1, 2020. These sensitivity analyses will be conducted for each HOI and will be aligned with the primary (1°) SCRI and cohort analysis as described in Table 1 and sections 9.7.6 and 9.7.7. These sensitivity analyses will allow for an evaluation of the robustness of the primary findings after excluding cases and vaccinations during the COVID-19 pandemic. The sensitivity analyses will be descriptive if the exclusion of ***participants*** after February 1, 2020 compromises the sample size such that there is insufficient power to generate meaningful estimates. Such descriptive analysis will report the number of cases in the risk and control windows (for the SCRI design) or the incidence rate (or cumulative incidence) for the cohort design.

9.7.9. Statistical models

Statistical models for the SCRI design

The primary, secondary and sensitivity analyses of the SCRI design will use a conditional Poisson regression model. This will estimate the incidence rates generated in risk and control windows of the same individual accounting for the within ***participant*** dependence using generalized estimating equations for robust variance estimation. The conditional Poisson regression model is a multinomial model, where time-fixed confounders within each stratum are controlled by conditioning on the sum of events in this stratum[31]. The general form of a conditional Poisson regression model can be written as:

$$n_{ik} \sim \text{Poisson}(\lambda_{ik} e_{ik})$$

$$\log(\lambda_{ijk}) = \phi_i + \theta_k$$

The response variable is n_{ik}, the number of events for the *i*th individual in the k (risk or control) interval. The log of the time spent in the interval ($ln e_{ik}$) is the offset term.

In the model, λ_{ik} denotes the incidence within each interval, ϕ_i is the effect for individual i (log of baseline incidence of HOI for individual i), and β_k is the effect for risk group k[32]. The model generates incidence rate ratio with a 95% CI.

PROC GENMOD with the Poisson distribution, a log link function, and the EXACT statement will be employed using SAS 9.4 to perform a conditional Poisson regression model. The main model will include the dependent variable (*Y*) as the number of events, a binary independent variable as the interval (risk or control), and the log of person days in the interval as the offset term.

The Deviance goodness of fit test will be used to evaluate the Poisson model fit. When using PROC GENMOD to fit a Poisson regression model, the "Criteria For Assessing Goodness Of Fit" output provides the Value/DF ratio. The ratio should be close to 1 to denote a good fit of the model to the data. If the Value/DF ratio is ≥ 2, there is over-dispersion, which can result in underestimation of standard error and thus overestimate statistical significance. The "DSCALE" or "PSCALE" options in the GENMOD procedure use "deviance chi-square" and "Pearson chi-square" to make the adjustment for over-dispersion. A negative binomial link function will be used should there be over-dispersion.

Temporal scan statistics

Temporal scan statistics will be used as a supplemental method for assessing the possibility of an association between RZV vaccination and an HOI during the respective follow-up period. This method evaluates whether there is any statistically significant temporal clustering of cases, the existence of which may suggest, although not confirm, an association.

Statistical models for the cohort design

Separate analysis for Dose 1 and Dose 2. The primary analysis for the cohort design will be conducted using a Cox proportional hazards regression model. This is a semi-parametric model in that it assumes a parametric form for the effects of the explanatory variables and an unspecified form for the underlying survival function. The general form of a Cox proportional hazards regression model can be written as:

$$h_i(t,x) = \lambda_0(t)\ \exp[\beta_1 x_{i1} + \ldots. \beta_k x_{ik}]$$

where, $h(t)$ is the expected hazard at time t; $\lambda_0(t)$ is the baseline hazard function and represents the hazard when all predictors are equal to 0.

PROC PHREG will be employed using SAS 9.4 to estimate the Cox proportional hazards regression model. The effect estimate generated from Cox proportional hazards model is hazard ratio, expressed as:

$$HR(t,1,0,\beta) = \frac{h(t \mid x=1,\beta)}{h(t \mid x=0,\beta)} = \exp(\beta)$$

where x (1,0) denotes to exposure status, and β is the estimated parameter from the regression model. Violations of the proportional hazard assumption will be evaluated

using a graphical approach by plotting the log[-logS(t)] versus log(t) and the Schoenfeld residuals by time, by testing the interaction between the covariates and log(t), and by using the assess statement available in the PROC PHREG procedure. Non-parallel lines or none-zero slope in the graphical approach, a significant interaction term, and a significant supremum test would indicate a violation of the proportional hazards assumption. If the proportional hazard assumption is violated, an interaction term of time and the variable of interest will be included in the model.

Combined analysis of Dose 1 and Dose 2 yielding one risk estimate. A partly conditional survival model will be used in the secondary analysis of combined doses. Since an individual may contribute more than one observation in the analysis (i.e., Dose 1 and Dose 2), this model is appropriate as it estimates the effect of longitudinal measures, in this case dose, on survival allowing for repeated measures for each individual[33,34].

Whereas typically survival is modeled as the time from study entry to the event, i.e., event time, D_i, in partly conditional survival analysis, regression parameters depend upon the time of measurement, S_i, for the predictor (i.e., dose receipt) and the time of measurement for the event to measure the follow up time since the measurement, $D_i - S_i$. This is considered partly conditional since the hazard function that is being modeled conditions on the covariate history through S_i. As a result, there are multiple event times for each individual which corresponds with the repeated measures for each dose.

A general form of the regression model for the hazard is shown below,

$$\lambda_{ik}(t* \,/\mathbf{Z}_{ik},\, 0 \le s_{ik} \le T_i) = g[\lambda_0(t*, s), \boldsymbol{\beta}(t*, s)^{\top} \mathbf{Z}_{ik}]$$

where T_i is the time to event (or censor) for ***participant*** i, s_{ik} denotes measurement times for each dose, $t^* = t - s_{ik}$ measures the follow-up time since dose, $g(\lambda, \eta)$ is a link function, $\lambda_0(t^*, s)$, is the baseline hazard, $\beta(t^*, s)$ is the regression coefficient, and Z_{ik} is a vector of covariates associated with ***participant*** i, at time s_{ik}.

The analysis will be conducted using SAS 9.4, and standard errors will be calculated using a robust sandwich estimator for repeated measures survival data.

Combined analysis of Dose 1 and Dose 2 yielding separate risk estimates. To generate a separate risk estimate for each dose in a combined analysis, where a binary indicator defines the Dose 1 and Dose 2 risk windows, a time-varying Cox proportional hazards regression models will be used. In the time-dependent model, we allow the risk window to vary for each dose. The time after dose 1 until dose 2 or end of follow-up if no dose 2 occurs defines the dose 1 risk window, and the time from dose 2 until end of follow-up defines the dose 2 risk window. Thus, a ***participant*** who receives two doses will contribute time to the dose 1 risk window and the dose 2 risk window. In the unvaccinated comparators the time from index date to end of follow-up is considered unexposed time. A general form of time-dependent Cox models can be written as:

$$h_i(t,x) = \lambda_0(t)\, \exp[\beta_1 x_{i1} + \ldots. \beta_2 x_{i2}(t)]$$

where x_{i1} represents a time-independent variable, and x_{i2} represents the time-dependent variable. This analysis will use the full cohort and obtain estimates for both doses

whereas the primary separate dose analysis either ignores dose 2 or includes only the subset of the sample who received 2 doses.

This analysis allows us to use the full cohort to compare the findings to the primary separate dose analysis. The primary Dose 1 analysis ignores Dose 2, and as such the events after Dose 2 may be attributed to Dose 1, thereby increasing the HR for Dose 1 (and its unknown which dose carries the highest risk). The primary Dose 2 analysis only includes individuals who did not experience the event after Dose 1, which could reflect potentially the more robust individuals. This could bias the estimate towards the null, and it is difficult to determine whether the estimate is a function of the vaccine or the characteristics of the Dose 2 subgroup. The time-varying model for this analysis uses the entire cohort, and attributes events to the respective dose risk window yielding a HR for each dose. Therefore, the full cohort sensitivity analysis allows us to estimate the hazard for each individual dose risk and to compare the results with the primary analysis estimates.

The effect estimates generated from the time-dependent Cox proportional hazards model will be a hazard ratio for Dose 1 relative to unexposed and a hazard ratio for Dose 2 relative to unexposed. Both hazards are generated in the same model with the full cohort, using time since the Dose 1 index date or the preventive care visit.

Sensitivity analysis for receipt of the Dose 1 and Dose 2 on schedule. The sensitivity analysis will be restricted to the sub-sample of individuals who receive both RZV doses on schedule per US label. This will test the sensitivity of the primary and secondary analyses, which examine the HOI incidence regardless of the dose spacing. This will follow the primary separate dose analysis and the secondary combined dose analysis.

Supplemental analysis

Some individuals in the analysis may contribute person-time both to the comparison group and (subsequently) to the RZV-vaccinated group. At CBER's request, a supplemental analysis will be conducted for the primary analysis, excluding from the control arm those ***participants*** who received RZV at any point, so that each ***participant*** contributes person-time to only one arm.

9.7.10. Methods to control for confounding

Covariate-adjusted analysis. A multivariable model adjusted for baseline covariates will be the primary method to control for confounding. These include the demographic (age, sex, race, US region), vaccination or preventive care visit (calendar year/month, care setting), comorbidities and immunocompromising conditions. The list of covariates to be evaluated are detailed in Section 9.3.4. Variables between the RZV exposed and the RZV unvaccinated comparators that differ by a standardized mean difference greater than 0.10 will be adjusted for in the statistical models. The standardized mean difference is preferred over a p-value metric that can be influenced by large sample sizes when in fact there is little meaningful difference between groups.

Propensity score methods for the cohort design analysis. We may consider using propensity score methods to correct for imbalance in confounders between RZV exposed and RZV unvaccinated comparators. A logistic regression model will be used to estimate the conditional probability of receiving the RZV vaccine predicted by the baseline covariates observed in the 365 days preceding the start of follow-up (i.e., index date) and that were listed in Section 9.3.4. Variables are selected empirically based on a statistically significant association, as determined from bivariate analyses, between the confounder and the exposure and the confounder and the outcome of interest.

We will select the propensity score implementation method, such as inverse probability of treatment weighting, that yields the best covariate balance between the groups[35]. To determine whether the propensity score method adequately addressed imbalances in covariates, we will evaluate the standardized mean differences between RZV vaccinated and RZV unvaccinated comparators less than 0.10, i.e., indicative of good confounder balance.

Bias analysis to test for unmeasured confounders for the cohort design analysis. One assumption underlying the cohort analyses is that there are no unobserved confounders related to RZV exposure and the study outcomes of interest, given the observed covariates. Unobservable factors, related to illness severity and health status, could influence RZV receipt and the outcomes of interest. The goal of the bias analysis is to estimate the magnitude of effect an unobserved confounder needed to change the statistical inference[36-38].

9.8. Quality control

Outline of data extraction procedures. The study team will request CMS CCW claims data for all beneficiaries who received the RZV vaccine and a random sample of beneficiaries who did not receive the RZV vaccine that will enable a 1:4 ratio of exposed to unexposed. CMS provides research identifiable data that contain dates of service, date of birth, and zip code. However, to preserve anonymity and confidentiality, the data do not contain personal identifying information, such as name, address, Medicare identification number, or social security numbers. A de-identifiable beneficiary ID is used to link data files; however, CMS does not provide the key that links the de-identified beneficiary ID to personal identifying information.

The data extraction procedures to ensure the quality and integrity of the data are:

- **CMS data acquisition-retrospective data collection/analysis**. All claims data acquired will include year's 2017 (baseline pre-period for 2018), 2018, 2019, 2020, and 2021 (follow-up period for 2019) for beneficiaries identified for the study.
- **Extraction of individual data**. All data extracted for individual level analyses will undergo reviewed by a second programmer to ensure accuracy of the programming code. Programming code includes those used to identify exposed and unexposed individuals eligible for the study, to apply the inclusion and exclusion criteria to identify the study cohort and to identify individuals eligible for the planned analyses.

- **Dataset check**. All programs and outputted datasets will undergo a 3-person review-initial programmer, second programmer and project coordinator. The initial programmer is responsible for the first review of his/her programs and output. A second programmer, whose sole responsibility is quality control, will be responsible for secondary review of the task list and all programs. The project coordinator who oversees the task order for each programming serves as the third reviewer who will be responsible for review of all output to ensure that it adheres to the protocol.
- **Perform consistency checks**. Files will be inspected for correct application of inclusion criteria as outlined in this document and stored in a manner consistent with DUA specifications. Once the list of inconsistencies is reviewed, discrepancies can either be confirmed or corrected, as applicable. Once completed, the data files will again be re-transferred in a secure manner, in the required format for a final check, database freeze/archival, and lock of the dataset.

9.9. Limitations of the research methods

The section describes the potential limitations that impact the inferences that can be drawn from this study along with the likely success of efforts taken to reduce bias.

Study design. Despite the careful selection of appropriate study designs to address the study objectives, there are some limitations. The SCRI design mitigates bias through implicit control for time-fixed confounders. A limitation is that it does not control for time-varying confounders. With the short risk windows for this study, there may be minimal change in confounders, and thus minimal bias would be introduced.

A limitation of the cohort analysis is dis-enrollment from Medicare Parts A, B, and D, which could impact the 365-day baseline period. The feasibility assessment showed that requiring more than 365 days would reduce the sample size because individuals lose Parts A, B, or D coverages. Further, individuals who receive RZV close to age 65, the age at which individuals qualify for Medicare, may not have a full year of enrollment prior to the vaccination date. Consultation with clinical experts confirmed that the 365-day baseline would be adequate to exclude prevalent cases of the HOIs. According to the sample size estimates, the large sample size in the CMS Medicare population should be sufficient, even if the sample is reduced due to less than 365 days of enrollment in Parts A, B, and D prior to the vaccination or preventive care visit date.

Data sources: limitations of the CCW Medicare data.

Services covered by Medicare Advantage (Part C) plans are not included in the CCW Medicare data. Older adults who opt to purchase supplemental insurance are covered under the Medicare Advantage plans, or Part C. All medical encounters and services are paid for by the supplemental insurance, and thus data on these individuals are missing.

Data on clinical metrics, such as laboratory values and illness severity, that could have been used for case identification are not available in the claims data.

Analytic methods. The analytic models selected for the analyses have minimal assumptions, and most of which can be verified through analytic tests and graphical display of the data. However, they could still have some unverifiable assumptions.

Methods to Control for Confounding and Bias. A primary source of confounding in this study are healthy user bias, which refers to the fact that individuals who seek preventive care service may also participate in other healthy behaviors, thus are less likely to experience an outcome. In the cohort analyses, our proposed use of a concurrent preventive care visit as the comparison group will mitigate the effects of healthy user bias on the risk estimate as both RZV vaccinated and unvaccinated will be users of preventive care services.

While other measurable confounding variables that differ between the two groups will be adjusted for in multivariable regression models and possible by using propensity score methods, the risk estimates could still be biased by confounders that were not measured (unmeasured confounders) or not properly measured (residual confounding). A bias analysis is planned to identify how strong an unmeasured confounder must be to explain away the observed effect estimate.

The Dose 2 analysis is conditioned on the subset of individuals who self-select to receive 2 doses within the study period. This may introduce selection bias if there are characteristic differences in measured and unmeasured factors that influence why some individuals receive two doses whereas some only receive one dose. This can underestimate the risk relative to the unvaccinated.

Generalizability. Medicare is the most comprehensive data on older adults, and so the findings will generalize to US adults aged 65 and older. We do not expect appreciable differences between those in the study and those age 65 and older who are not enrolled in Medicare Parts A, B, and D that would affect the HOI risk estimate post-vaccination with RZV.

Sources of random error. The goal is to mitigate bias due to random error. However, it is possible that random sources of error will occur since this is an observational study using secondary claims data. All attempts have been made to ensure appropriate study designs, well-thought out case identification algorithms, appropriate confounder adjustment methods, and planned sensitivity analyses are implemented in the conduct of the study.

Temporal variation. There may be temporal variation due to availability of the vaccine. To address variability in the timing of the vaccine and the preventive care visit, the calendar month-year will be a covariate in the analytic models.

Case ascertainment. It will not be possible to conduct a chart review to validate HOIs. Case-finding algorithms using administrative data are rarely sensitive and specific. The algorithms used in this study are found to have high positive predictive value in published case validation studies and we consulted with experts.

9.10. Other aspects

To comply with regulatory requirements and GSK standards, administrative obligations relating to protocol amendments, protocol administrative changes and termination of the study must be fulfilled.

Record retention

Data files and programs will be retained on PRC secure servers for the duration of the study as stipulated in the DUA. However, a DUA may be renewed for an indefinite duration of time, depending upon the study needs.

During project closeout, project specific programs, output, data sets and documentation are archived unless stipulated otherwise. A custodial server assessment determines what, if any, resources remain after this process.

Upon completion of research activities or expiration of the DUA, data resources covered by the DUA must be destroyed to prevent breach of confidentiality. This data destruction is then certified and reported to CMS within 30 days. Additional project files may be preserved on the PRC server archive for up to 3 years following the closure of the DUA; however, the DUA may remain active for as long as needed for the study purpose and requirement to maintain the data for a specified period of time. In this study, the project files will be preserved for 15 years, per contractual agreement.

Quality assurance

The PHSR department and PRC are guided the management concept of Total Quality Management. PHSR and PRC highly value quality assurance measures utilizing standardized project management procedures managing projects and project files. Best practices have been established to assist in assuring outputs are as accurate as possible.

Posting of information on publicly available clinical trial registers and publication policy.

<u>Observational studies evaluating a product:</u>

- The key design elements of this protocol and results summaries will be posted on the GSK Clinical Study register in compliance with GSK policy according to the timelines described below.
  - Protocol summaries will be registered prior to study start.
  - Results summaries along with redacted protocol and SAP will be posted within 12 months of analysis completion date.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results.

- GSK also aims to publish the results of these studies in the searchable, peer-reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. Any publications will follow guidelines, including those for authorship (e.g., guidelines established by the International Committee of Medical Journal Editors 2018) and for reporting of observational studies in epidemiology (e.g. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE,) 2007)[39].

PASS studies:

- Protocol summaries for non-interventional post-authorization safety studies will be registered along with redacted protocol in the EU PAS register prior to study start.
- Redacted Clinical Study Report (CSR) will be submitted in the EU PAS register within 12 months of end of data collection.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK Biologicals will also provide the investigator with the full summary of the study results.

Provision of study reports to regulatory authorities

The final study report will provide an overview of the study background, objectives, methods, and findings and will be submitted to regulatory agency authorities by the vaccine manufacturer. Final study results, as well as the main methodological components developed as part of this study, will be disseminated as oral or poster presentations at scientific meetings and as peer-reviewed publications

10. PROTECTION OF HUMAN SUBJECTS

Adequate protections include mandatory training in human subjects research for all study team members, including HIPAA and CITI training. The study will be reviewed and approved by the UMB Institutional Review Board. Annual study reports are required for continuing review and approval for ongoing study conduct. Any concerns during the study conduct will be reported to the Institutional Review Board as soon as it is identified.

Source files and derived data resources will be maintained in project specific directories with restricted permissions. Neither source files nor derived products may be placed on personal storage or removable media, as affirmed by the PRC data access agreement for CMS CCW Medicare data. Violations of this policy may result in criminal penalty or corrective action. Investigators and staff are required to sign the PRC data access agreement and review data security policies for the PHSR department. Policy requirements include restricted data access, secure storage and strict maintenance of privacy as required by HIPAA. To maintain confidentiality and anonymity of the ***participants***, data are de-identified and cannot be linked back to the individual. As required by the CMS DUA, and this project's DMP, cells of tables will be suppressed when size less than 11.

Ethical conduct of the study

The study will be conducted in accordance with all legal and regulatory requirements. Additionally, we will adhere to commonly accepted research practices, including those described in the following guidance documents:

- The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. Available at: [http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideonMethStandardsinPE_Rev7.pdf]
- International Society of Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices. Pharmacoepidemiology and drug safety. 2008;17(2):200-208. doi: 10.1002/pds.1471 [published Online First: 2007/09/18] [https://www.pharmacoepi.org/resources/policies/guidelines-08027/]
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment [https://www.fda.gov/media/71546/download]
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data. Rockville, MD. May 2013. [https://www.fda.gov/media/79922/download]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is an observational, retrospective, post-authorization safety study, based on data extracted from the US CMS CCW Medicare databases. Individual medical records will not be directly examined, and ***participant*** reports linked between databases will be de-identified prior to analysis. Therefore, individual case adverse event/adverse reaction reports will not be generated from this study.

12. REFERENCES

1. John AR, Canaday DH. Herpes Zoster in the Older Adult. Infectious Disease Clinics of North American. 2017;31(4):811-826.

2. McLaughlin JM, McGinnis JJ, Tan L, et al. Estimated Human and Economic Burden of Four Major Adult Vaccine-Preventable Diseases in the United States, 2013. Journal of Primary Prevention. 2015;36(4):259-273.

3. Kawai K, Yawn BP. Risk Factors for Herpes Zoster: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2017;92(12):1806-1821.

4. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infectious Disease. 2004;4(1):26-33.

5. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morb Mortal Wkly Rep. 2018;67(3):103-108.

6. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. New England Journal of Medicine. 2015;372(22):2087-2096.

7. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med. 2016;375(11):1019-1032.

8. Lopez-Fauqued M, Campora L, Delannois F, et al. Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials. Vaccine. 2019;37(18):2482-2493.

9. Shimabukuro T. Update on post-licensure safety monitoring of recombinant zoster vaccine (RZV, Shingrix). Atlanta, GA: Advisory Committee on Immunization Practice (ACIP) meeting; February 27, 2019 2019.

10. Baker MA, Lieu TA, Li L, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. American Journal of Epidemiology. 2015;181(8):608-618.

11. Schneeweiss S, Sturmer T, Maclure M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. Pharmacoepidemiology and Drug Safety. 1997;6 Suppl 3:S51-59.

12. Hallas J, Pottegard A. Use of self-controlled designs in pharmacoepidemiology. Journal of Internal Medicine. 2014;275(6):581-589.

13. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515.

14. Funch D, Holick C, Velentgas P, et al. Algorithms for identification of Guillain-Barre Syndrome among adolescents in claims databases. Vaccine. 2013;31:2075-2079.

15. Harrold LR, Saag KG, Yood RA, et al. Validity of gout diagnoses in administrative data. Arthritis Rheum. 2007;57(1):103-108.

16. Bernatsky S, Linehan T, Hanly JG. The accuracy of administrative data diagnoses of systemic autoimmune rheumatic diseases. Journal of Rheumatology. 2011;38(8):1612-1616.

17. Rubin DS, Matsumoto MM, Moss HE, et al. Ischemic Optic Neuropathy in Cardiac Surgery: Incidence and Risk Factors in the United States from the National Inpatient Sample 1998 to 2013. Anesthesiology. 2017;126(5):810-821.

18. Sidney S, Sorel M, Quesenberry CP, Jr., et al. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. Chest. 2005;128(4):2068-2075.

19. Buttgereit F, Dejaco C, Matteson EL, et al. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. JAMA. 2016;315(22):2442-2458.

20. Singh JA, Cleveland JD. The risk of polymyalgia rheumatica in older adults with gout: a Medicare claims study. Rheumatology Advances in Practice. 2018;2(2):rky024.

21. Singh JA, Cleveland JD. The association of gout with incident giant cell arteritis in older adults. Joint Bone Spine. 2019;86(2):219-224.

22. Partington R, Helliwell T, Muller S, et al. Comorbidities in polymyalgia rheumatica: a systematic review. Arthritis Res Ther. 2018;20(258):1-10.

23. Calabrese C, Cappelli LC, Kostine M, et al. Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: case series and systematic review of the literature. RMD Open. 2019;5(1):e000906.

24. Laties AM. Vision disorders and phosphodiesterase type 5 inhibitors: a review of the evidence to date. Drug Safety. 2009;32(1):1-18.

25. Purvin V, Kawasaki A, Borruat FX. Optic neuropathy in patients using amiodarone. Archives of Ophthalmology. 2006;124(5):696-701.

26. Shen Y, Drum M, Roth S. The prevalence of perioperative visual loss in the United States: a 10-year study from 1996 to 2005 of spinal, orthopedic, cardiac, and general surgery. Anesth Analg. 2009;109(5):1534-1545.

27. Chen T, Song D, Shan G, et al. The association between diabetes mellitus and nonarteritic anterior ischemic optic neuropathy: a systematic review and meta-analysis. pLoS One. 2013;8(9):e76653.

28. Yang HK, Park SJ, Byun SJ, et al. Obstructive sleep apnoea and increased risk of non-arteritic anterior ischaemic optic neuropathy. British Journal of Ophthalmology. 2019;103(8):1123-1128.

29. Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Statistics in Medicine. 2006;25(15):2618-2631.

30. Lumley T, Diehr P, Emerson S, et al. The importance of the normality assumption in large public health data sets. Annual Review of Public Health. 2002;23:151-169.

31. Armstrong BG, Gasparrini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. BMC Med Res Methodol. 2014;14:122.

32. Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in Biostatistics: The self-controlled case series method. Statistics in Medicine. 2005:1-31.

33. Gong Q, Schaubel DE. Partly conditional estimation of the effect of a time-dependent factor in the presence of dependent censoring. Biometrics. 2013;69(2):338-347.

34. Zheng Y, Heagerty PJ. Partly conditional survival models for longitudinal data. Biometrics. 2005;61(2):379-391.

35. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychological Methods. 2010;15(3):234-249.

36. Ding P, VanderWeele TJ. Sensitivity Analysis Without Assumptions. Epidemiology. 2016;27(3):368-377.

37. Vanderweele TJ, Arah OA. Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. Epidemiology. 2011;22(1):42-52.

38. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiology & Drug Safety. 2006;15(5):291-303.

39. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-1457.

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	209696	31-Jul-2020	List of stand-alone documents
2	209696	31-Jul-2020	Glossary of terms
3	*209696*	*17 May 2021*	*List of principal and coordinating investigators*
4	209696	31-Jul-2020	Sponsor Information
5	*209696*	***15 July 2022***	*Amendments to the protocol*
6	*209696*	***15 July 2022***	*Protocol Amendment **3** Sponsor Signatory Approval*
7	*209696*	***15 July 2022***	*Protocol Amendment **3** Investigator Agreement*
8	209696	31-Jul-2020	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Adverse event:	Any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Anonymized data:	Information about an individual that GSK or a third party cannot reasonably attribute to the individual or could only attribute to the individual by expending a disproportionate amount of time, effort or expense (e.g. de-identified or aggregated information). For the purpose of this policy, Key-Coded personally identifiable information shall not be considered Anonymized Information
Cohort study:	A form of epidemiological study where participants in a study population are classified according to their exposure status/disease and followed over time (prospective/ retrospective) to ascertain the outcome(s).
Commitment:	Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorization, either made at the time of product approval or during the lifecycle of the approved product.
Database:	A database is a set of pre-existing tables and views containing data. The term “pre-existing” implies that the analysis will be done on retrospective data and the term “views” implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc.).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-)encoding via CRF/eCRF and retesting of human biological samples.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
eTrack:	GSK's tracking tool for clinical/ epidemiological trials.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post-Authorization Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorization and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorization' means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).
Prospective study:	A study in which the participants/cases are identified and then followed forward in time in order to address one or more study objectives. A prospective study usually involves primary data collection.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. Note: Any change that falls under the definition of a protocol amendment (e.g., a change that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Protocol amendment:	The International Council on Harmonization defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.

Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Self-controlled risk interval (SCRI):	Statistical method for assessing the association between a transient exposure and an adverse event. The method was developed to study adverse reactions to vaccines. The method uses only cases; no controls are required as the cases act as their own controls. Each cas''s given observation time is divided into control and risk periods. Risk periods are defined during or after the exposure. The method estimates a relative incidence rate, that is, the incidence in the risk period relative to the incidence in the control period. An advantage of the method is that confounding factors that do not vary with time, such as genetics, location, socio-economic status, are controlled for implicitly.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 List of principal and coordinating investigators

The list of all investigators and their contact details are available upon request.

Annex 4 Sponsor Information

Sponsor:

GlaxoSmithKline Biologicals (GSK)
Rue de l'Institut, 89
1330 Rixensart, Belgium

Annex 5 Amendments to the protocol

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

GlaxoSmithKline Biologicals SA **Vaccines R & D** **Protocol Amendment *3***	
eTrack study number and Abbreviated Title:	209696 (EPI-ZOSTER-032 VS US DB)
Amendment number:	Amendment 3 Final
Amendment date:	15 July 2022
	Amendment 2 Final: 18 April 2022
	Amendment 1 Final: 17 May 2021
Protocol Approved	Final: 31 July 2020

Previous Amendments Summary of Changes table:

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
2	18 April 2022	Modified end of data collection from Q1 2024 to Q4 2024. Added clarification regarding continuous enrollment gap allowance Footnote for gout added to Outcome identification algorithms *Table 3* (column 10) Added clarification to evaluate graphical distribution of RZV and conduct seasonality adjusted analysis Added sensitivity analysis of alternative definition of GCA Updated inferential analyses for the primary outcomes - Censoring events	Refer to Section 6 Section 9.2.2 Section 9.3.2 Section 9.7.6 Section 9.7.6 Section 9.7.6 Section 9.7.7 Section 9.7.8 Section 9.10 Section 9.2.2 Section 9.7.6	Section 6: Data collection updated as Q4 2024 to align with revised timelines for obtaining the report for GCA/SVT/ION. Section 9.2.2: Study inclusion / exclusion criteria updated to clarify the operational definition of continuous enrollment Sections 9.3.2, 9.7.6, 9.7.7: To clarify the analytical approach for the sensitivity HOI definitions for gout, GCA and ION as defined in Table 3 (column 10). Section 9.7.6: To clarify the seasonality adjusted SCRI analysis for gout and GBS

Amendment or update no	Date	Amendment or update	Section of study protocol	Reason
		Added sensitivity analysis of alternative definition of ION Added sensitivity analysis to evaluate the impact of COVID-19 Updated Other aspects Posting of information on publicly available clinical trial registers and publication policy		Section 9.7.6: To clarify the end of study period censoring event Section 9.7.8: Amended in response to CBER's request to evaluate the impact of the COVID-19 pandemic due to the concern that people may change their health seeking behavior due to COVID-19 and associated pandemic lock-down measures. Section 9.10: To align with policies and regulations regarding disclosure activities.
1	17 May 2021	Exposure measure Covariates Potential confounding variables and effect modifiers Descriptive analyses Inferential analyses for the primary outcomes Statistical models	Refer to Section 9.3.1 Section 9.3.3 Section 9.3.4 Section 9.7.4 Section 9.7.6 Section 9.7.8	Regulatory feedback

Detailed description of the current Protocol Amendment 3:

PASS Information

Contributing authors:	PPD

Section 3 Responsible Parties

Study Teams:	Core UMB study team members: PPD

Section 9.2.2 Study population

The study population will be comprised of all US Medicare beneficiaries who received the RZV vaccine (i.e., exposed) in 2018 through 2020 as well as a random sample of Medicare beneficiaries who did not receive the RZV vaccine but who had at least one preventive care visit ***(i.e., comparator group)***, as defined in Section 9.7.5.

Study inclusion / exclusion criteria

3. Continuous ***enrollment*** ~~eligibility~~ is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and ***enrollment*** in at least 11 of the 12 preceding months.

The requirement for continuous enrollment in Medicare Parts A, B, and D in the 365 days***, allowing one calendar month gap,*** before the RZV vaccination or preventive care visit will ensure complete data on all services covered by Medicare

9.4.1 Description of the database

Master Beneficiary Summary File (MBSF): The information in this dataset relevant to this study includes beneficiary enrollment ***each calendar month*** in Medicare Parts A, B, and D. This file will be used to obtain information on the baseline study variables, including original and current enrollment reason, eligibility, and demographic characteristics.

Section 9.7.3 ~~Subject~~ *Participant* Disposition

~~Subject~~ ***Participant*** disposition will be summarized for the overall study population and for the RZV vaccinated and RZV unvaccinated comparators with a preventive health visit by computing:

- Not continuously enrolled in Medicare Parts A, B, and D for 365 days***, allowing one calendar month gap,*** preceding the index date

Section 9.7.5 Analysis Population

Population for the Cohort Design Analysis

To ensure complete data for the baseline period preceding cohort follow-up, individuals must be continuously enrolled in Medicare Parts A, B, and D for a minimum of 365 days preceding the preventive care visit***. Continuous enrollment is determined by Medicare enrollment in the month of the preventative care visit and enrollment in at least 11 of the 12 preceding months.***

Section 9.7.6 Inferential analyses for the primary outcomes

Analysis of the SCRI Design

Additional inclusion requirements for the SCRI design analyses for new onset (i.e., incidence) primary HOIs GBS and gout include:

3. ~~Parts A, B, and D enrollment 365 days prior to the HOI;~~ ***Continuously enrolled in Medicare Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination and enrollment in at least 11 of the 12 preceding months.***

4. ***Continuous*** enrollment in Parts A and B (and in the case of gout Part D to capture gout-specific medication) through the end of the respective control interval.

Analysis of the Cohort Design

Additional inclusion requirements for the cohort design analyses for new onset (i.e., incidence) primary HOIs PMR and GCA include:

3. At least 365 days (1 year) of Parts A, B, and D ***continuous*** enrollment prior to the index date. ***Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and enrollment in at least 11 of the 12 preceding months.***

Annex 6 Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	209696 (EPI-ZOSTER-032 VS US DB)
Date of protocol amendment	Amendment 3 Final, 15 July 2022
Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Sponsor signatory	Agnes Mwakingwe-Omari, Clinical and Epidemiology Project Lead, GSK Vaccines
Signature	_____
Date	_____

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

Annex 7 Protocol Amendment 3 Pharmacovigilance Signatory Approval

eTrack study number and Abbreviated Title	209696 (EPI-ZOSTER-032 VS US DB)
Date of protocol	Amendment 3 Final: 15 July 2022
Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
QPPV signatory	PPD PPD Clinical Safety and Pharmacovigilance, GSK
Signature	_____
Date	_____

Note: In order to comply with the pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) must be involved in the review, content approval and sign off (in addition to sponsor signatory) of Post-Authorization Safety studies (PASS) protocols (GVP Module 1). This also applies to Targeted Safety Study (TSS) protocols.

Annex 8 Protocol Amendment 3 Investigator Agreement

I agree:

- **To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.**
- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of, and will comply with, ENCePP guide for methodological standards in pharmacoepidemiology, the International Society of Pharmacoepidemiology guidelines for good pharmacoepidemiology practices, and all applicable regulatory requirements.**
- **To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.**
- **To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.**
- **To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions and to implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.**
- **To have control of all essential documents and records generated under my responsibility before, during, and after the study**
- **That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.**

Hence I:

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

eTrack study number and Abbreviated Title	209696 (EPI-ZOSTER-032 VS US DB)
Date of protocol amendment	Amendment 3 Final, 15 July 2022
Title	A targeted safety study, EPI-ZOSTER-032 VS US DB, to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States.
Investigator name	Susan dos Reis, University of Maryland, Baltimore
Signature	
Date	

Annex 9 ENCePP Checklist for study protocols

Section 1: Milestones			Yes	No	N/A	Section Number
1.1	Does the protocol specify timelines for					
	1.1.1	Start of data collection[1]	☒	☐	☐	6
	1.1.2	End of data collection[2]	☒	☐	☐	6
	1.1.3	Progress report(s)	☐	☐	☒	
	1.1.4	Interim report(s)	☐	☐	☒	
	1.1.5	Registration in the EU PAS Register®	☒	☐	☐	
	1.1.6	Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question			Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:					
	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)	☒	☐	☐	7
	2.1.2	The objective(s) of the study?	☒	☐	☐	8
	2.1.3	The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2
	2.1.4	Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.7.1
	2.1.5	If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.8
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.8
3.5	Does the protocol describe the approach for the collection and reporting of AEs/adverse reactions? (e.g. AEs that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations			**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?		☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:					
	4.2.1	Study time period	☒	☐	☐	9.4.3
	4.2.2	Age and sex	☒	☐	☐	9.2.2
	4.2.3	Country of origin	☒	☐	☐	9.2.2
	4.2.4	Disease/indication	☒	☐	☐	9.2.2
	4.2.5	Duration of follow-up	☒	☐	☐	9.4.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)		☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorized 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?	☒	☐	☐	9.7.5

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
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)	☒	☐	☐	9.3.2
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.4 9.7.10
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.5
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.4.2 9.3.1 9.3.2 9.7.6

Comments:

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

Comments:

Section 9: Data sources			Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:					
	9.1.1	Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
	9.1.2	Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
	9.1.3	Covariates and other characteristics?	☒	☐	☐	9.3
9.2	Does the protocol describe the information available from the data source(s) on:					
	9.2.1	Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4.1
	9.2.2	Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.1

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.2.3	Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.1
9.3	Is a coding system described for:				
9.3.1	Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2	Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3	Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4.1

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.8
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.4
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.10
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.6

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2	Are methods of quality assurance described?	☒	☐	☐	9.8 9.10
11.3	Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	9.9
	12.1.2 Information bias?	☒	☐	☐	
	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).	☒	☐	☐	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2	Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3	Have data protection requirements been described?	☒	☐	☐	9.6 10

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9.4
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9.4

Comments:

Name of the main author of the protocol: PPD PhD, Professor, University of Maryland, Baltimore

Date: / /

Signature: _____

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

Signature Page for 209696 TMF-14833531 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 20-Jul-2022 18:26:57 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 22-Jul-2022 20:38:05 GMT+0000

Signature Page for TMF-14833531 v1.0

Statistical Analysis Plan	
Detailed Study Title:	A targeted safety study, EPI-ZOSTER-032 VS US DB to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the United States
eTrack study number and Abbreviated title	209696 (EPI-ZOSTER-032 VS US DB)
SAP version	V5.0 (Amendment 4)
Date of SAP Amendment 4	21 Jul 2022
Scope:	All data pertaining to the above study
Co-ordinating author:	PPD
Other author(s):	PPD
Reviewers:	PPD (Principal Investigator and Lead Epidemiologist) PPD (Statistics Leader, GSK) PPD PPD GSK) PPD (Epidemiology Lead, GSK)
Approved by:	PPD (Principal Investigator and Lead Epidemiologist) PPD (Statistics Leader , GSK) PPD PPD , GSK) PPD (Epidemiology Lead, GSK)

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LIST OF ABBREVIATIONS

AE	Adverse Event
CCW	Chronic Condition Warehouse
CDC	Centers for Disease Control and Prevention
CMS	Center for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CW	Control Window
DME	Durable Medical Equipment
DMP	Data Management Plan
DUA	Data Use Agreement
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration, United States
GBS	Guillain Barre Syndrome
GCA	Giant Cell Arteritis
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practices
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HOI	Health Outcome of Interest
HR	Hazard Ratio
HZ	Herpes Zoster
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
ION	Ischemic Optic Neuropathy
IPTW	Inverse Probability of Treatment Weight
MAH	Marketing Authorisation Holder
MBSF	Medicare Beneficiary Summary File
MS-DRG	Medicare Severity Diagnosis Related Group

NDC	National Drug Code
NIST	National Institute of Standards and Technology
PASS	Post-Authorisation Safety Study
PDE	Prescription Drug Event
PHSR	Pharmaceutical Health Services Research
PMR	Polymyalgia Rheumatica
PPV	Positive Predictive Value
PRC	Pharmaceutical Research Computing
RIF	Research Identifiable Files
RW	Risk Window
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SASDS	Statistical Analysis System Data Set
SCRI	Self-Controlled Risk Interval
SMD	Standardized Mean Difference
SNF	Skilled Nursing Facility
SVT	Supraventricular Tachycardia
TDAP	Tetanus, Diphtheria, and Pertussis
TIA	Transient Ischemic Attack
TSS	Targeted Safety Study
UMB	University of Maryland Baltimore
US	United States
VZV	Varicella Zoster Virus
ZVL	Zostavax Vaccine Live

1. DOCUMENT HISTORY

Date	Description	Protocol Version
11 September 2020	Final SAP V1.0	Final Protocol 18 August 2020
13 October 2020	Final Amendment 1 Change: Added Supplemental Analysis in section 9.3.8 Rationale: CBER's Request	Final Protocol 18 August 2020
20 May 2021	Final Amendment 2 Change: Removed dose number as a covariate;added variables list in appendix D; updated Table 1 column 8 Rationale: CBER's Request; Table 1 updated to align with protocol.	Final Protocol Amendment 1 17 May 2021
27 April 2022	Final Amendment 3 Change: Added footnote to Table 1 for gout, added analysis for the sensitivity HOI definitions for GCA and ION as defined in Table 1 (column 10); Timelines in table 2: Sequence of analysis updated; Clarified operational definition of continuous enrollment; Added Covid-19 sensitivity analysis; updated Appendix B and C Rationale: To clarify the analytical approach for the sensitivity HOI definitions for gout, GCA, and ION; To accurately clarify the data end date as end of the planned follow-up period and data acquisition period for each HOI; To add clarification that continuous enrollment allows one-month gap. CBER's Request; Appendix B and C updated to align with analyses	Final Protocol Amendment 2 18 April 2022
21 Jul 2022	Final Amendment 4 Change: Updated sections 8.1, 8.2.1, 8.2.2, 9.3.1 and 16.2 -Appendix B table shells 1-7 to clarify the allowable gap that defines continuous enrollment Rationale: CBER's Request	Final Protocol Amendment 3 15 July 2022

2. STUDY OBJECTIVES

This study is a targeted safety study (TSS) and a post-authorisation safety study (PASS) designed to address the question of whether there is an increased risk of new-onset Guillain-Barré syndrome (GBS), gout, polymyalgia rheumatica (PMR), giant cell arteritis (GCA), supraventricular tachycardia (SVT), or ischemic optic neuropathy (ION) within specified time periods after *Shingrix*, or recombinant zoster vaccine (RZV), vaccination in people ≥ 65 years of age in the US starting in January 2018 in Center for Medicare and Medicaid Services (CMS) Medicare data.

2.1. Primary objectives

1. To estimate the risk of new onset Guillain Barré Syndrome (GBS) within 42 days following recombinant zoster vaccine (RZV) vaccination using a self-controlled risk interval (SCRI) design
2. To estimate the risk of new onset gout within 30 days following RZV vaccination using an SCRI design
3. To estimate the risk of new onset Polymyalgia Rheumatica (PMR) within 183 days following RZV vaccination using a cohort design
4. To estimate the risk of new onset Giant Cell Arteritis (GCA) within 183 days following RZV vaccination using a cohort design

2.2. Secondary objectives

1. To estimate the risk of new onset Supraventricular Tachycardia (SVT) within 30 days following RZV vaccination using an SCRI design
2. To estimate the risk of new onset Ischemic Optic Neuropathy (ION) within 183 days following RZV using a cohort design

3. EXPOSURE OF INTEREST

Receipt of at least one dose of RZV is the exposure of interest. RZV vaccination will be identified by means of Current Procedural Terminology (CPT) code 90750, National Drug Codes (NDCs) 58160-828-01, 58160-829-01, 58160-819-12, 58160-828-03, 58160-829-03, and 58160-823-11, and the date of RZV vaccination. All dose-combined analyses as well as dose-specific analyses will be conducted.

RZV vaccination records occurring within 27 days after a previous RZV vaccination record (i.e., on days 1-27, where the day of the previous RZV record is day 0) will be considered a duplicate record and will be deleted. The participant will be retained for the analytic cohort.

For participants who receive more than two doses of RZV, even after removal of possible duplicates, we will exclude from analysis RZV doses beyond two per study participant.

4. HEALTH OUTCOMES OF INTEREST (HOI)

The health outcomes of interest (HOI) are new-onset GBS, gout, PMR, GCA, SVT, and ION. GBS, gout, PMR, and GCA are primary outcomes. SVT and ION are secondary outcomes.

4.1. Definitions for case identification

Table 1 describes the definitions for the case identification of GBS, gout, PMR, and GCA (primary HOIs) and ION and SVT (secondary HOIs). Sensitivity analyses are conducted where validated outcome identification algorithms are not available in the literature for reference.

Table 1 HOI case identification algorithms

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
GBS (SCRI)	G61.0	PPV: 50% (Inpatient visit)[1]	None	Inpatient primary position OR Diagnosis in any setting followed by an inpatient claim within 7 days	Days 1-42	1 year; inpatient; primary position only	Same as in Col.2	HOI	N/A
Gout (SCRI)	M10.x, M1A.x (chronic gout)	PPV: 61% (≥ 2 visits associated with the diagnosis) [2]	At least one gout-specific oral medication (allopurinol, colchicine, probenecid, febuxostat) prescribed within 3 months after the first date of the diagnosis.	≥ 2 outpatient claims within the follow-up window[a] OR ≥1 inpatient claim	Days 1-30	1 year; diagnosis code –all settings[b] OR At least one gout-specific oral medication (allopurinol, colchicine, probenecid, febuxostat);	Same as in Col. 2 OR Col. 4	HOI	-Exclude chronic and secondary gout codes. -Examine frequency distribution of ICD-10 codes and consider low-frequency codes such as codes for chronic gout (M1A*), lead-induced gout (M10.1*, drug-induced gout (M10.2*), and gout due to renal impairment (M10.3*) (note: this exclusion of gout codes does not apply in assessing prevalent gout)[d]
PMR (Cohort)	M35.3 – PMR M31.5 – GCA w/ PMR	Sensitivity: 99.5% Specificity: 92.2% [3] (based on the 3 methods used by Bernatsky: diagnosis in inpatient or	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone) prescriptions; The first dispensing within 6	≥2 outpatient claims within the follow up window a OR ≥1 inpatient claim	Days 1-183	1 year; all settings[b]	Same as in Col. 2	Exposure	N/A

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
		outpatient, or a visit by a rheumatologist/ internist)	months of PMR diagnosis and the second dispensing date within 6 months after the first dispensing.						
GCA (Cohort)	M31.6 (GCA), M31.5 (GCA with PMR), M31.9 (necrotizing vasculopathy unspecified)	Not available	2 oral glucocorticoids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone). The first dispensing within 6 months of GCA diagnosis and the second dispensing date within 6 months after the first dispensing.	≥2 outpatient claims within the follow up window[a] OR ≥1 inpatient claim	Days 1-183	1 year; all settings[b]	Same as in Col. 2	Exposure	-Use the primary algorithm based on the GCA diagnosis code and steroid prescription but add a requirement for a temporal artery biopsy at the time of diagnosis, as determined by a CPT code=37609
ION (Cohort)	H47.01	Not available	Exclude patients who had coronary artery bypass graft (CABG) surgery[4] or lumbar or lumbosacral spinal fusion and/or laminectomy surgery within 30 days before ION diagnosis date	≥1 claim in all settings	Days 1-183	1 year; all settings[b] ICD code only	Same as in Col. 2	Exposure	Additional criteria for arteritic: ≥ 40 mg/day of prednisone prescription ± 4 weeks of the diagnosis plus an ophthalmologist/neuro-ophthalmologist consult (if possible) and GCA diagnosis within 3 months; lookback to rule out prevalent cases will use ICD code only; all settings

1	2	3	4	5	6	7	8	9	10
Study Outcome (Study design)	**ICD-10 code(s) for case ascertainment**	**Validation Statistics**	**Other requirements[c]**	**Setting for case ascertainment**	**Risk Interval**	**Look-back period & settings to determine incidence**	**What to look back for**	**What to look back from**	**Sensitivity Analysis**
SVT (SCRI)	I47.1	Sensitivity-91.7% [5]	None	≥1 ED or inpatient claim any position	Days 1-30	1 year; all settings[b] any position	Same as in Col. 2	HOI	N/A

Definitions: GCA - Giant Cell Arteritis; GSB - Guillain-Barré Syndrome; ION - Ischemic Optic Neuropathy; PMR - Polymyalgia Rheumatica; SCRI - Self-controlled Risk Interval; SVT - Supraventricular Tachycardia;

[a] Outpatient visits are defined using ≥2 claims for consistency with methods used by CMS algorithms using the CMS CCW Medicare data to define chronic conditions, and to avoid misclassification of the outcome due to the potential for 1 visit to reflect rule-out diagnosis.

[b] Includes inpatient, emergency department, and outpatient settings

[c] Based on external expert opinion.

[d] Consistent with the study EPI-ZOSTER-030 VS US DB no analysis will be conducted for the gout sensitivity HOI definitions. These definitions are for administrative purposes only.

4.2. Medical record review validation

Not applicable for the Epi-Zoster032VSDB study.

5. STUDY DESIGN

This is an observational TSS and a PASS using SCRI and cohort designs among RZV-exposed and RZV-unexposed US adults age 65 years and older, registered in the CMS Chronic Condition Warehouse (CCW) Medicare database with enrollment in Parts A (i.e., hospital insurance), B (i.e., outpatient medical insurance), and D (i.e., prescription medication insurance) at any time from 2017 through 2021. Medicare Parts A, B, and D are the fee-for-service components of CMS Medicare.

5.1. Self-controlled risk interval (SCRI) design for GBS, gout, and SVT

An SCRI design will assess the risk of new-onset GBS, gout and SVT among individuals exposed to the RZV vaccine.[6] Individuals serve as their own control. The analysis is conditioned on the interval (or "window"), and only RZV vaccinees who experience the HOI in the risk or the control interval contribute to the analysis. The advantage of the SCRI design is the implicit control for time-fixed potential confounders such as sex, race/ethnicity and stable chronic medical conditions. An SCRI design is used because it is ideal for acute outcomes and transient exposures. This design is a special (and simpler) case of both the case-crossover[7,8] and the self-controlled case series[8,9] designs, in which the cumulative number of cases in pre-specified risk and control intervals (or "window") are compared.

We will assess any seasonal pattern of RZV vaccination graphically, and we will adjust for seasonality in secondary SCRI analyses for GBS and gout, as both of these outcomes are known to have a seasonal pattern. These season-adjusted analyses are detailed in Section 9.2.4.

5.2. Cohort design for PMR, GCA, and ION

A cohort design will be used to assess the risk of new onset PMR, GCA and ION by comparing the hazard of these HOIs among RZV-exposed individuals relative to RZV-unexposed individuals who had a preventive care visit.

6. STUDY POPULATION

The study population includes a nationally representative sample of US Medicare beneficiaries age 65 years and older who are registered in the CMS CCW Medicare database with enrollment in Parts A, B, and D any time from January 1, 2017 through December 31, 2021. This is a longitudinal cohort, so the same individuals are followed over time until they are no longer in Medicare.

6.1. Number of participants

The number of participants that will be included in the analysis is the total number of eligible individuals in the CMS CCW Medicare database acquired by the University of Maryland, Baltimore (UMB). This is estimated to be 20 million individuals.

6.2. Study period

The study population will be followed retrospectively from January 1, 2017 until the last day of follow-up on December 31, 2021.

6.3. Eligibility criteria

The study population will comprise all US Medicare beneficiaries age 65 years and older who are in the CMS CCW Medicare database during the study period and meet the criteria described in Sections 6.3.1 and 6.3.2.

6.3.1. Inclusion criteria

Each individual registered in the CMS CCW Medicare database must be:

1. Age 65 years and older, **AND**
2. Enrolled in Medicare due to age or end-stage renal disease (ESRD) as the original and current qualifying reason for enrollment, **AND**
3. Enrolled in Medicare Parts A, B, and D fee-for-service at any point during the study period.

6.3.2. Exclusion criteria

Individuals will be excluded if they are:

1. Continuously enrolled only in Medicare Part C, **OR**
2. Enrolled in Medicare due to disability as the original qualifying reason for enrollment.

7. DATA SOURCES

7.1. CMS CCW Medicare data management

7.1.1. Data extraction

CMS data require implementation of a Data Use Agreement (DUA). Contained within the DUA is a specifications workbook that details the raw files data extraction. For this study, up to 20 million Medicare beneficiaries per year will be obtained, which includes 100% of those with evidence of RZV exposure with the remaining beneficiaries unexposed.

7.1.2. Database lock

All CMS data are shipped via an encrypted external drive and loaded onto the server in a read-only format. Original data are stored in a raw data directory, are not manipulated in any way and are considered locked. The shipped media are stored in a fire-proof safe in the server room and are only accessible to the Database Administrator and the Pharmaceutical Research Computing (PRC) Director.

7.1.3. Data quality checks performed on the data

Included in the CMS data delivery are additional documents, one being dataset variable frequencies. PRC confirms that every file contains the data as expected and indicated by CMS, including but not limited to, number of records, number of variables and anticipated variable frequencies. PRC has up to 30 days to dispute data quality and obtain new cuts of data if necessary.

7.2. Overview of the CMS CCW Medicare database

CMS maintains the Medicare administrative database of all paid claims for billable healthcare services in inpatient and outpatient settings, skilled nursing facilities, hospice, home health services, and for the provision of durable medical equipment (DME) and prescription drugs for older and disabled US citizens.

The CMS Medicare data are made available through the research database, CCW, which permits linkage across all datasets, via an encrypted beneficiary identifier. This study will use the CMS CCW Medicare databases below:

- Inpatient Claims
- Outpatient Claims
- Carrier Claims
- Home Health Agency Claims
- Hospice Claims
- Skilled Nursing Facility Claims
- Durable Medical Equipment
- Master Beneficiary Summary File – Base
- Part D Events

7.2.1. Inpatient claims

The inpatient dataset contains fee-for-service claims submitted by inpatient hospital providers for reimbursement of facility costs, including hospitalizations and ED visits. Up to 25 diagnosis fields, coded as the International Classification of Disease 10th revision (ICD-10), including the admission diagnosis as well as a principal diagnosis, are available on each claim. CPT codes and the Healthcare Common Procedure Coding

System (HCPCS) for services rendered are also available on each claim and can be used to identify any laboratory tests (but not the results) that were performed as well as consultation with specialty providers.

7.2.2. Outpatient claims

The outpatient dataset contains fee-for-service claims submitted by institutional outpatient providers. Institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, Federally Qualified Health Centers and community mental health centers. The outpatient files contain up to 25 ICD-10 diagnosis fields as well as CPT and HCPCS codes.

7.2.3. Carrier claims

The carrier dataset includes fee-for-service claims submitted by professional providers, including physicians, physician assistants, clinical social workers, nurse practitioners and by organizational providers, including freestanding facilities (i.e., independent clinical laboratories), ambulance providers, freestanding ambulatory surgical centers and freestanding radiology centers. The carrier files contain up to 12 ICD-10 diagnosis fields as well as CPT and HCPCS codes.

7.2.4. Home health agency claims

The home health agency dataset contains claims submitted by Medicare home health agency providers for reimbursement of covered home health services. The home health agency files also contain up to 25 ICD-10 diagnosis fields as well as CPT and HCPCS codes.

7.2.5. Hospice claims

The hospice dataset contains claims submitted by Medicare hospice providers. The hospice files contain up to 25 ICD-10 diagnosis fields as well as CPT and HCPCS codes.

7.2.6. Skilled nursing facility claims

The skilled nursing facility (SNF) dataset includes fee-for-service claims for paid services that are submitted by SNF institutional facility providers. The SNF files contain up to 25 ICD-10 diagnosis fields as well as CPT and HCPCS codes.

7.2.7. Durable medical equipment

The DME file contains fee-for-service claims submitted by suppliers of DMEs to the DME Medicare Administrative Contractor.

7.2.8. Master beneficiary summary file

The Master Beneficiary Summary File (MBSF) dataset includes demographic information as well as information on beneficiary enrollment each calendar month in Medicare Parts A, B, C, and D.

7.2.9. Part D events

The Part D Events dataset includes all prescription medications filled at an outpatient pharmacy that have been submitted by the prescription drug plan.

8. STATISTICAL ANALYSIS COHORTS

The statistical analysis will be staggered and conducted in the following order: 1) gout; 2) PMR and GBS; and 3) GCA, SVT and ION, as shown in Table 2**.** Analytic cohorts will be constructed for each HOI, with either SCRI analysis design or cohort analysis design, separately. Descriptive tables showing the baseline demographic and health characteristics of the cohorts will be presented. Table shells are provided in Appendix B.

Table 2 Sequence of analysis for each HOI

Outcome	Target risk to detect	Data Start date (i.e. baseline)	Data End date (i.e. end of follow-up)	Data acquisition period	Statistical Analysis complete period	Report to CBER/EMA
Gout	RR of 2	1 Jan2017	29 Feb 2020	2022 – Q4	2023 – Q2	30 Jun 2027
GBS	RR of 4	1 Jan2017	25 Mar 2021	2023 - Q2	2024 – Q2	30 Jun 2027
PMR	RR of 2	1 Jan2017	31 Dec 2021	2023 - Q2	2024 – Q2	30 Jun 2027
GCA	RR of 3	1 Jan2017	31 Dec 2021	2023 - Q2	2025 – Q2	30 Jun 2027
SVT	N.a.	1 Jan2017	01 Mar 2021	2023 - Q2	2025 – Q2	30 Jun 2027
ION	N.a.	1 Jan2017	31 Dec 2021	2023 - Q2	2025 – Q2	30 Jun 2027

8.1. Inclusion criteria for GBS, gout, and SVT with the SCRI analysis design

Only the cases of new-onset gout, GBS, and SVT recorded in the RZV exposed cohort during either the risk or the control windows will be included in SCRI analysis. RZV exposure excludes duplicate doses and if participants receive more than two doses, only the first two doses will be considered in the analysis. Details of the identification of cases for each HOI is described in Section 4. Additional inclusion criteria for new-onset cases for each HOI in the SCRI analysis design include:

1. Receipt of RZV vaccination before the new-onset case of the HOI.

2. First-in-365-days case of the respective HOI in the risk or control interval (i.e., definition of an incident case)
3. Continuously enrolled in Medicare Parts A, B, and D fee-for-service for at least 365 days preceding the date of RZV vaccination. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination and enrollment in at least 11 of the 12 preceding months.
4. Continuous enrollment in Parts A and B (and in the case of gout Part D to capture gout-specific medication) from receipt of RZV vaccine through the end of the respective control interval.

8.2. Inclusion criteria for PMR, GCA, and ION with the cohort analysis design

The study population for the cohort design will comprise all RZV exposed and RZV unvaccinated comparators with a preventive care visit who satisfy the inclusion criteria listed in sections 8.2.1 and 8.2.2.

8.2.1. Exposed group

The exposed group is any individual who receives RZV during the study period. RZV exposure excludes duplicate doses and if participants receive more than two doses, only the first two doses will be considered in the analysis. The index date for the exposed group in the cohort design is the date of RZV vaccination. Details defining index date for RZV unexposed comparator is described in Section 9.3.

Inclusion criteria for the exposed group in the cohort design include:

1. RZV vaccine exposed during the study period.
2. No HOIs during the 365-day look-back period from the index date.
3. At least 365 days of Parts A, B, and D continuous enrollment prior to the index date. Continuous enrollment is determined by Medicare enrollment in the month of the RZV dose and enrollment in at least 11 of the 12 months preceding the month of the RZV dose.

8.2.2. Comparator group

A concurrent comparator group will be selected among individuals who have not received RZV at the time of selection or in the available history prior to the index date. The index date for the RZV unexposed comparator for the cohort design is the date of the randomly selected preventive care visit (see Section 9.3).

Inclusion criteria for the RZV unexposed comparator for the cohort design include:

1. At least one visit for a routine adult annual exam OR at least one preventive screening intervention performed during the study period. The ICD-10, CPT, and HCPCS codes to identify eligible preventive care visits are in Appendix A.
2. No RZV vaccination at any time in the available history prior to the index date.

3. No HOIs on or in the 365-day look-back period from the index date.
4. At least 365 days of Parts A, B, and D continuous enrollment prior to the index date. Continuous enrollment is determined by Medicare enrollment in the month of the preventative care visit and enrollment in at least 11 of the 12 preceding months.

9. STATISTICAL METHODS

9.1. Descriptive analyses

GBS, gout, and SVT will include cases only and will be analyzed using the SCRI design. The descriptive analyses will show the baseline demographic and health characteristics of each respective HOI analytic cohort. See table shells in Appendix B.

PMR, GCA, and ION will be analyzed using the cohort design and will include two groups, RZV vaccinated and RZV unvaccinated comparators. The descriptive analysis will show the baseline demographic and health characteristics of both groups. A separate descriptive analysis will be conducted for each HOI. See table shells in Appendix B.

The recommended RZV vaccination schedule in Europe is 0 and 2 months, with the option of administering Dose 2 within 2-6 months after Dose 1 if necessary. The European Medicines Agency (EMA) wishes to see whether a meaningful number of study participants receive Dose 2 within 2 months after Dose 1 in order to determine the applicability of the study results to the European context. In accordance with this request, we will report the proportion of all 2-dose recipients receiving the second dose on days 28-60 after the first dose. The descriptive analysis will show the baseline demographic and health characteristics of RZV vaccinees by a) number of doses and b) timing of doses, i.e., Dose 2 days 28-60 after Dose 1 versus Dose 2 beyond day 60 after Dose 1. See table shells in Appendix B.

Additionally, we will report on the number of GBS cases with evidence in the inpatient or outpatient claims of respiratory or gastrointestinal infection (including COVID-19) in the 60 days prior to the GBS diagnosis, noting in which post-RZV windows (risk versus control) these GBS cases occurred. If deemed appropriate by the study team, an ad hoc sensitivity SCRI analysis will be conducted like the primary SCRI analysis but with these cases excluded.

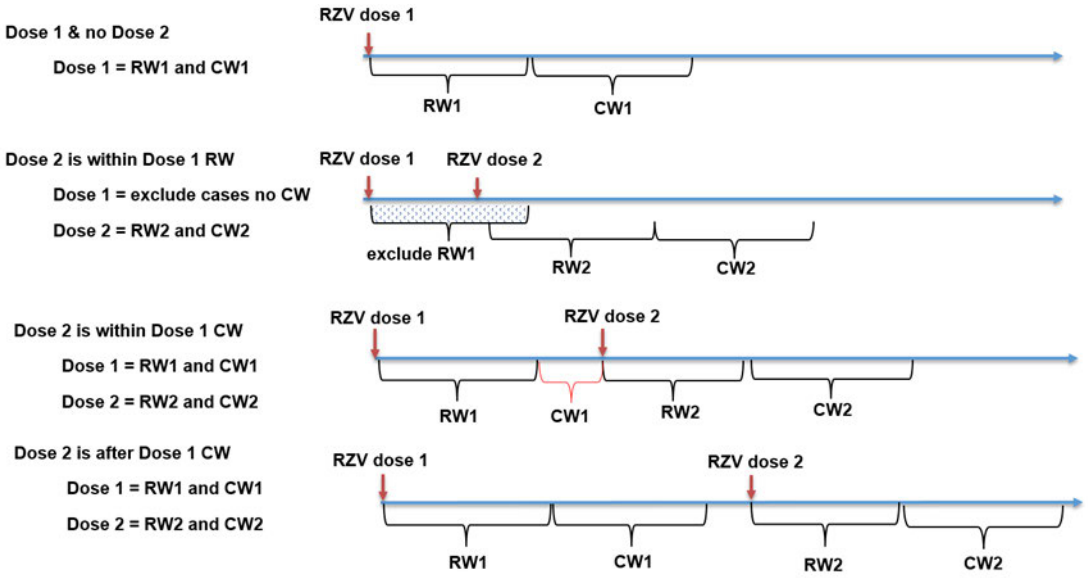
In addition, the number of cases and the incidence rate (or cumulative incidence) in vaccinated and preventative care comparators identified using the sensitivity analysis HOI definition of GCA and ION (Table 1 column 10) will be reported.

9.2. Self-controlled risk interval analyses

The SCRI analyses will be used for the study of GBS, gout, and SVT. Individuals serve as their own control. The analysis is conditioned on the interval (or “window”), and only RZV vaccinees who experience the HOI in the risk or the control interval contribute to the analysis. The SCRI design implicitly controls for time-fixed potential confounders such as sex, race/ethnicity and stable chronic medical conditions.

Per US schedule, RZV is indicated as a two-dose schedule, 2 to 6 months apart, thus it is not possible to define a consistent control interval for Dose 1. The control interval following Dose 1 will depend upon the time between doses. The potential scenarios are illustrated in Figure 1.

Figure 1 Illustration of SCRI design with variable spacing between Dose 1 and Dose 2



RW1: Risk window for dose 1; RW2: Risk window for dose 2; CW1: Control window for dose 1; CW2: Control window for dose 2;
Risk window: GBS days 1-42 following vaccination; Gout days 1-30 following vaccination
Control window (may be shorted in some scenarios): GBS days 43-84 following vaccination; Gout days 31-60 following vaccination.

Details of the primary, secondary, and sensitivity SCRI analyses are shown in Table 3 (below) and Figure 1 (above). Day 0 is the day of vaccination and will not be part of the follow-up period for any of the HOI analyses. See table shells in Appendix B.

Table 3 Planned self-controlled risk interval analyses for GBS, gout and SVT

Row	Category of analysis (short description)	Doses to include	Exclusions*	Dose 1 control interval	Risk estimate
GBS—risk window (RW) for all doses is Days 1-42 (6 wks) after the dose; control window (CW) for all doses starts on Day 43 after the dose					
1	Primary (Dose 1 CW censored at receipt of Dose 2)	1 and 2 without distinguishing	*	Maximum of Days 43-84 after Dose 1, censored at Dose 2	For any dose
2	Sensitivity (restricted to 2-dose recipients with 60-183-day dose spacing per US dosing recommendations, subset of #1)	1 and 2 without distinguishing	People not getting Dose 2 60-183 days inclusive after Dose 1	Maximum of Days 43-84 after Dose 1, censored at Dose 2	For any dose, in people who get 2 doses 60-183 days apart
3	Secondary (3-wk CW for both doses)	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 43-63 after Dose 1 (3 wks)	For any dose
4	Secondary (6-wk CW for both doses)	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 43-84 after Dose 1 (6 wks)	For any dose
5	Sensitivity (Dose 1, subset of #4)	Just Dose 1	Dose 1 CW cases if also in Dose 2 RW	Days 43-84 after Dose 1 (6 wks)	For Dose 1
6	Sensitivity (Dose 2, subset of #4)	Just Dose 2	None	N.a.	For Dose 2
Gout and SVT—risk window (RW) for all doses is Days 1-30 after the dose; control window (CW) for all doses starts on Day 31 after the dose					
7	Primary (Dose 1 CW censored at receipt of Dose 2)	1 and 2 without distinguishing	*	Maximum of Days 31-60 after Dose 1, censored at Dose 2	For any dose
8	Sensitivity (restricted to 2-dose recipients with 60-183-day dose spacing per US dosing recommendations, subset of #7)	1 and 2 without distinguishing	People not getting Dose 2 60-183 days inclusive after Dose 1	Maximum of Days 31-60 after Dose 1, censored at Dose 2	For any dose, in people who get 2 doses 60-183 days apart
9	Secondary (30-d CW for both doses)	1 and 2 without distinguishing	Dose 1 CW cases if also in Dose 2 RW	Days 31-60 after Dose 1	For any dose
10	Sensitivity (Dose 1, subset of #9)	Just Dose 1	Dose 1 CW cases if also in Dose 2 RW	Days 31-60 after Dose 1	For Dose 1
11	Sensitivity (Dose 2, subset of #9)	Just Dose 2	None	N.a.	For Dose 2

* Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist.

9.2.1. Primary SCRI analyses

The primary SCRI analyses will compare the risk of the respective HOI during the respective risk window with the risk during a control window starting the day after the risk window. The analysis will include Doses 1 and 2, without distinguishing between them for purposes of risk estimation.

For GBS, the risk window will be Days 1-42 after the respective dose; the control window will start on Day 43 and will end on Day 84 after the respective dose unless a second-dose was received during Days 44-84, in which case the control window will extend only through the day before second-dose receipt (Table 3, Row 1; Figure 1, third diagram).

For gout and SVT, the risk window will be Days 1-30 after vaccination; the control window will start on Day 31 and will end on Day 60 after vaccination unless a second dose was received during Days 32-60, in which case the control window will extend only through the day before second-dose receipt (Table 3, Row 7; Figure 1, third diagram).

In instances where the second dose is received during the first dose risk window+1 day, the first dose will be omitted from analysis, as it will have no corresponding control time (Figure 1, second diagram).

9.2.2. Secondary SCRI analyses

Secondary analyses for all three outcomes will be done without censoring the Dose 1 control window at the time of receipt of Dose 2. The purpose is to avoid the possibility of bias from informative censoring that might exist in the primary analyses.

Two secondary analyses will be conducted for GBS. Like the primary analysis, these will include Doses 1 and 2, without distinguishing between them for purposes of risk estimation. The first GBS secondary analysis will use a fixed 21-day-long control window (Table 3, Row 3), while the second GBS secondary analysis will use a fixed 42-day-long control window (Table 3, Row 4). If a case of GBS occurs during a period of overlap between the Dose 1 control window and the Dose 2 risk window, the case will not be counted as having occurred in the Dose 1 control window but will be counted as having occurred in the Dose 2 risk window.

In the case of gout and SVT, whose maximum follow-up period is only 60 days instead of 84 days, only one secondary analysis will be conducted. Like the primary analysis, it will include Doses 1 and 2, without distinguishing between them. It will use a fixed 30-day-long control window (Table 3, Row 9). If a case of the HOI occurs during a period of overlap between the Dose 1 control window and the Dose 2 risk window, the case will not be counted as having occurred in the Dose 1 control window but will be counted as having occurred in the Dose 2 risk window.

For all these secondary analyses, in instances where the second dose is received during the first-dose risk window+1 day, the first dose will be omitted from analysis (Figure 1, second diagram).

9.2.3. Sensitivity SCRI analyses

For each of the three HOIs (GBS, gout, and SVT), a sensitivity analysis will be carried out that is exactly like the primary analysis for the HOI but restricted to two-dose recipients with 60-183 days inclusive between the two doses (Table 3, Rows 2 and 8). In addition, there will be dose-specific sensitivity analyses, restricted to the respective dose.

The GBS Dose 1 sensitivity analysis will use a fixed 42-day-long control window with no censoring (Table 3, Row 5). If a case of GBS occurs during a period of overlap between the Dose 1 control window and the Dose 2 risk window, then the case will be excluded from analysis. The GBS Dose 2 sensitivity analysis will similarly use a fixed 42-day-long control window with no censoring (Table 3, Row 6). No exclusion of post-Dose 2 cases will be implemented (as long as the case is in either the risk or control window for Dose 2).

The gout and SVT Dose 1 sensitivity analyses will use a fixed 30-day-long control window with no censoring (Table 3, Row 10). If a case of the HOI occurs during a period of overlap between the Dose 1 control window and the Dose 2 risk window, the case will be excluded from the analysis. The gout and SVT Dose 2 analyses will similarly use a fixed 30-day-long control window with no censoring (Table 3, Row 11). No exclusion of post-Dose 2 cases will be implemented (as long as the case is in either the risk or control window for Dose 2).

For all the Dose 1 sensitivity analyses, if the second dose is received during the first-dose risk window+1 day, the first dose will be omitted from analysis (Figure 1, second diagram).

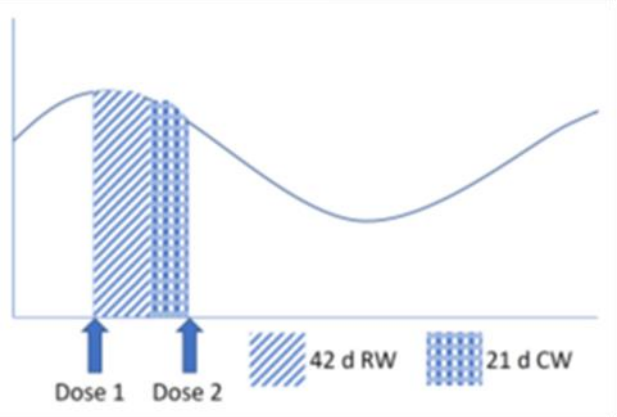
9.2.4. Secondary analyses of GBS and gout, adjusting for seasonality

Graphical description of the accumulating data could show whether or not RZV vaccination varies by time of year. We will conduct a seasonally adjusted SCRI analysis for the respective HOI, conforming to the specifications for the primary analysis (Table 3, Row 1 or 7) in all other respects.

The adjustment will be by means of an offset term, following the approach used in other SCRI studies of vaccine safety adjusted for time-varying confounding.[1-3] We will first seek counts of the HOI by month from the Healthcare Cost and Utilization Project (HCUP)'s Nationwide Inpatient Sample [https://www.hcup-us.ahrq.gov/nisoverview.jsp] and calculate the average monthly counts for the most recent three years available. We will then fit a curve to the averaged counts using a polynomial function, a sine function, and/or splines. Predicted values from the best-fitting curve, together with the length of the respective interval (e.g., for GBS, RW=42 d, CW=42 d or less if Dose 2 received within 84 days after Dose 1), will be used to calculate the area under the HOI-by-calendar-month curve. For each case, the natural log (ln) of the area under the curve for the risk interval will be the offset term for that case's risk interval, and the natural log of the area under the curve for the control interval will be the offset term for that case's control interval. The offset term thus serves to adjust for both the lengths of the risk and control intervals and the background risk of the HOI during the risk and control intervals. A hypothetical example of the relevant areas under the curve for a specific hypothetical GBS case is shown in Figure 2.

Figure 2 illustrates the hypothetical background risk of GBS over one average calendar year. The shaded areas are used to calculate offset terms for season adjusted SCRI analysis for a hypothetical post-Dose 1 GBS case who received Dose 1 during a period of high GBS background risk and Dose 2 on Day 64 after Dose 1.

Figure 2 Season-adjusted SCRI analysis



9.2.5. Models for the SCRI analyses

We will estimate the relative risk of the HOI in the post-RZV risk window relative to the comparator window using conditional Poisson regression. The dataset will contain two rows of data for each individual case (i.e., BENE_ID), one pertaining to the risk window (RW), the other pertaining to the control window (CW).

An invented example dataset follows in Table 4. The BENE_ID is a unique identification number assigned to individual Medicare beneficiaries. EXPOSURE is the variable to indicate whether the record is the risk or control window (1=risk window and 0=control window). Since the primary and secondary analyses are conducted without distinguishing dose, an exposure = 1 indicates the record is either Dose 1 or Dose 2 risk window (RW) and the exposure = 0 indicates the record is either Dose 1 or Dose 2 control window (CW). The HOI is the variable to indicate whether the case occurred (1=yes and 0=no). The variable ln_daysinterval is the log of the days in the risk or control window, which is the off-set term. In this example, rows with 3.73767 in the offset (i.e., ln_daysinterval) column have a full 42 days in the respective window. As noted above in Section 9.2.4., the natural log (ln) of the area under the HOI-by-calendar-month curve for the risk and control interval will be the offset term for the season-adjusted analysis.

Table 4 Example data structure for the SCRI analyses

BENE_ID	Exposure (1=RW, 0=CW)	HOI (1=yes, 0=no)	ln_daysinterval
PPD	1	1	3.73767
	0	0	2.89037
	1	0	3.73767
	0	1	3.61092
	1	0	3.73767
	0	1	3.73767
	1	1	3.73767
	0	0	3.40120
	1	0	3.73767
	0	1	3.73767
	1	1	3.73767
	0	0	3.04452

9.2.6. Calculation of attributable risk

If, and only if, a statistically significant elevated risk of an HOI is found, we will calculate the attributable risk as the number of excess cases of that HOI per 100,000 doses administered, according to the formula 100,000 × no. of cases in the risk window × [1 − (1 ÷ relative risk)] ÷ [no. of vaccine doses].[1]

To compute a 95% confidence interval of the attributable risk, we will transform the Wald-type confidence interval of the log relative risk from the Poisson regression model. This approach is commonly used by statistical software to obtain a 95% CI on the relative risk –i.e. exponentiating the bounds of the log-RR. Specifically, let **a1** and **a2** be the 95% Wald-type upper and lower bounds of the 95% CI for the log relative risk, then we know that, with large sample sizes, Pr(**a1** <= log(RR) <= **a2**) = 0.95. The latter is equivalent to Pr(**b1** <= AR <= **b2**) = 0.95 where

> **b1** = 100,000 × no. of cases in the risk window × [1 − (1 ÷ exp(**a1**))] ÷ [no. of vaccine doses], and
>
> **b2** = 100,000 × no. of cases in the risk window × [1 − (1 ÷ exp(**a2**))] ÷ [no. of vaccine doses]

In this case, **b1** and **b2** are a 95%CI for the AR.

9.3. Cohort analyses

9.3.1. Selection of the analytic cohorts

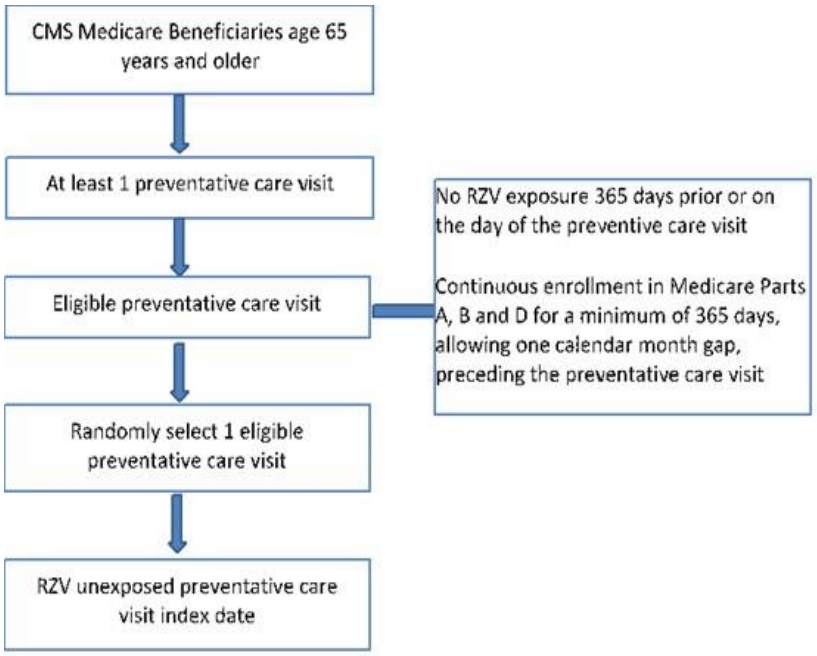
The study population for the cohort design is all RZV exposed and RZV unexposed comparators who meet the inclusion criteria listed in Section 8.2. The rationale for selecting comparators from those with a preventive care visit, as opposed to all unvaccinated individuals, is to mitigate the potential for healthy user bias stemming from differences in the overall tendency to use health services by vaccinated and unvaccinated individuals. The selection will identify individuals with at least one preventive care visit, and one eligible preventive care visit will be randomly selected. The identified cohort of RZV unexposed preventive care visit comparators will be inspected to ensure the sample is sufficient to ensure the power needed to detect the specified risk for each HOI.

Generating an index date for the RZV unexposed preventive care visit comparators.

The steps described below will be performed separately for Dose 1 and Dose 2. This is illustrated in Figure 3.

1. Create a pool of eligible comparators with at least one preventive care visit.
   - The pool of eligible comparators are unvaccinated individuals who had at least one preventive care visit, which is defined as having at least one visit for a routine adult annual exam OR at least one preventive screening intervention performed (See List of Codes in Appendix A).
   - For an individual to be eligible as a comparator, the individual must not have had RZV at any time in the available history prior to or on the day of the preventive care visit.
   - To ensure complete data for the baseline period preceding cohort follow-up, individuals must have been continuously enrolled in Medicare Parts A, B, and D for a minimum of 365 days preceding the preventive care visit. Continuous enrollment is determined by Medicare enrollment in the month of the preventative care visit and enrollment in at least 11 of the 12 preceding months.
     - Visits that do not satisfy this criterion will be excluded.
     - If an individual has multiple preventive care visits, only visits that do not meet the continuous eligibility criterion will be excluded.
     - If an individual has only one preventive care visit, the entire person will be excluded if the visit does not meet continuous eligibility criterion.
2. Select one preventive care visit at random from eligible visits.
3. The preventive care visit date serves as the index date for the RZV unexposed comparator.

Figure 3 Selection of RZV unexposed comparators with a preventive care visit



To test for the new onset (i.e., incident) primary HOIs PMR and GCA and secondary HOI ION, the analytic cohort will meet all of the following criteria:

1. Eligible RZV exposed or RZV unexposed preventive care visit comparator;
2. A 365-day look-back from the index date (i.e., vaccination with Dose 1 or Dose 2 or preventive care visit date) to exclude prevalent HOI cases prior to the index date;
3. Continuous enrollment in Parts A, B, and D in the 365 days prior to the index date. Continuous enrollment is determined by Medicare enrollment in the month of the RZV vaccination or preventative care visit and enrollment in at least 11 of the 12 preceding months.

9.3.2. Overview of the cohort analysis plan

Table 5 is a synopsis of the plan of analysis. See table shells in Appendix B.

For the sensitivity analysis of the HOI definitions for GCA and ION (Table 1; Column 10), analyses consistent with the primary (1^{o}) approach as described in Table 5 will be conducted if an appropriate number of GCA and ION cases are identified to allow meaningful inference.

Table 5 Overview of the Primary, Secondary, and Sensitivity Analyses

HOIs	Analysis Plan	Risk Interval	Risk Estimate
PMR GCA ION	1°: Separate analytic models for separate estimates of Doses 1 and 2	Days 1-183 after the index date	Separate risk estimates for Dose 1 and Dose 2
	2°: Single analytic model for the combined estimate of Dose 1 and Dose 2	Days 1-183 after the index date for each dose	Combines Dose 1 and Dose 2 into a single risk estimate
	2°: Single analytic model for separate estimate of Dose 1 and Dose 2	Days 1-183 after the index date	Separate risk estimate for each dose in a time-varying model
	Sensitivity analyses for the Dose 1 and 2 compliant subgroup	Days 1-183 after the index date	Separate and single risk estimates (mirror the two 2° analyses)

9.3.3. Primary cohort analyses

The primary analysis incorporates the same risk period after each dose. Each dose is analyzed separately and will yield two separate risk estimates, one for Dose 1 and Dose 2 (Figure 4)

Exposed: At least one dose of the RZV vaccine

Unexposed: At least one eligible preventive care visit and no prior or same day RZV exposure

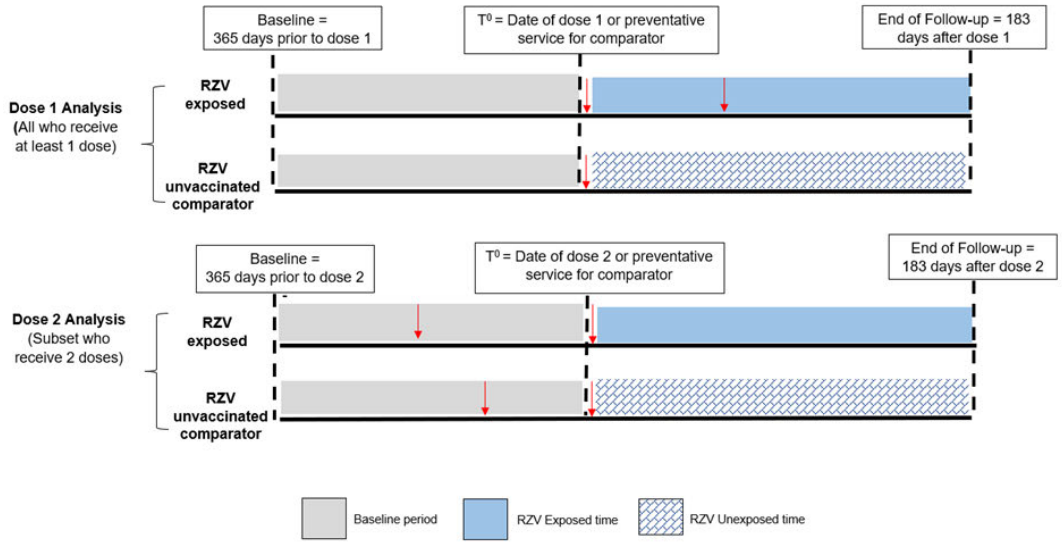
Index date for RZV exposed: Dose 1 and Dose 2 vaccination date

Index date for the RZV unexposed preventive care visit comparator: Date of the randomly selected preventive care visit

Risk period: Day 1 to 183 after the Dose 1 and Dose 2 vaccination dates for the RZV exposed and after the preventive care visit date for the RZV unexposed.

Baseline covariates and capture of incident cases: Day 1 to 365 preceding the Dose 1 and Dose 2 vaccination date for the RZV exposed and preceding the preventive care visit date for the RZV unexposed.

Figure 4 Separate analysis for Dose 1 and Dose 2



9.3.4. Secondary cohort analysis of combined doses

This analysis does not distinguish between doses and will yield a single risk estimate for the HOI in days 1 to 183 following vaccination with either Dose 1 or Dose 2. The hazard function being modeled accounts for the event time of both Dose 1 and Dose 2 and only conditions on the baseline covariate history (i.e., 365 days preceding the index date). The data structure has multiple event times for the same participant, each corresponding to a different measurement time (i.e., S2). Since individuals may contribute more than one observation in the analysis, this model allows for the repeated measures on survival. Any gap in the time between the end of the Dose 1 risk period and the Dose 2 vaccination date is not included in the analysis (shown in Figure 5 as a red circle with an ‘x’). The maximum allowable spacing between doses will be 365 days. This means that Dose 2 is not included in the analysis if it is received more than 365 days after Dose 1.

Exposed: At least one dose of the RZV vaccine

Unexposed: At least one eligible preventive care visit and no prior or same day RZV exposure

Index date for RZV exposed: Dose 1 and Dose 2 vaccination dates

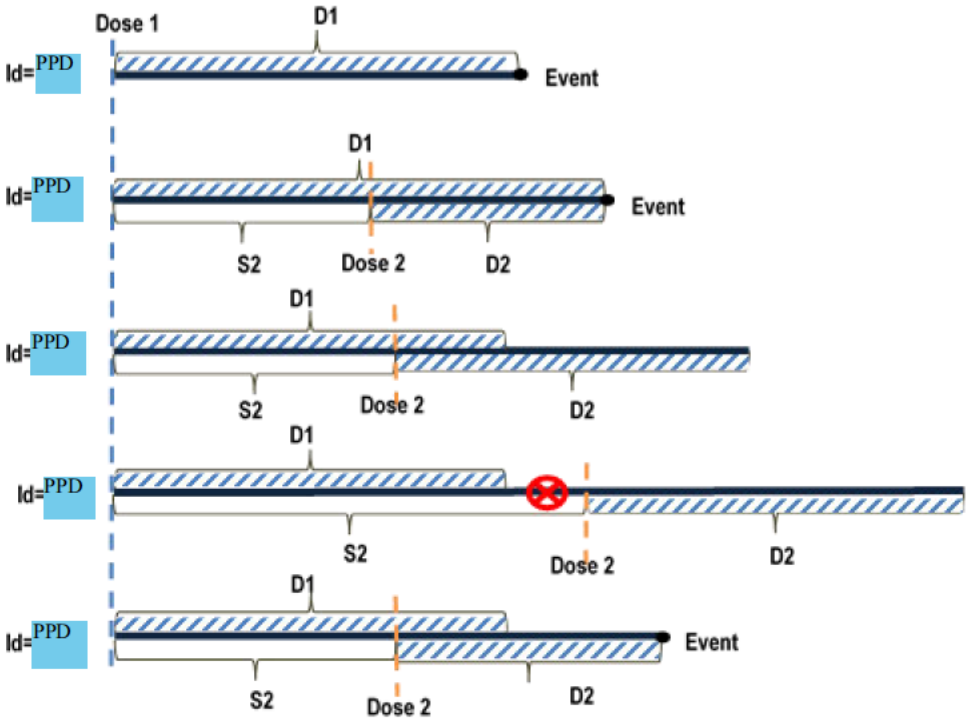
Index date for the RZV unexposed preventive care visit comparator: Date of the randomly selected preventive care visit

Risk period: Day 1 to 183 after the Dose 1 and Dose 2 vaccination dates for the RZV exposed and after the preventive care visit date for the RZV unexposed.

Baseline covariates: Day 1 to 365 preceding the Dose 1 vaccination date for the RZV exposed or preceding the preventive care visit date for the RZV unexposed.

Capture of incident cases: No record of the HOI in Day 1 to 365 preceding Dose 1 and Dose 2 vaccination dates for the RZV exposed and preceding the preventive care visit date for the RZV unexposed.

Figure 5 Combined Dose 1 and Dose 2 Analysis



9.3.5. Secondary cohort analysis of a single model for separate doses

Two separate risk estimates for Dose 1 and Dose 2 will be analyzed in a time-varying analytic model. All individuals will be followed up for 183 days from the Dose 1 or the preventive care visit (Figure 6)

Exposed: At least one dose of the RZV vaccine

Unexposed: At least one eligible preventive care visit and no prior or same day RZV exposure

Index date for RZV exposed: Dose 1 vaccination date

Index date for the RZV unexposed preventive care visit comparator: Date of the randomly selected preventive care visit

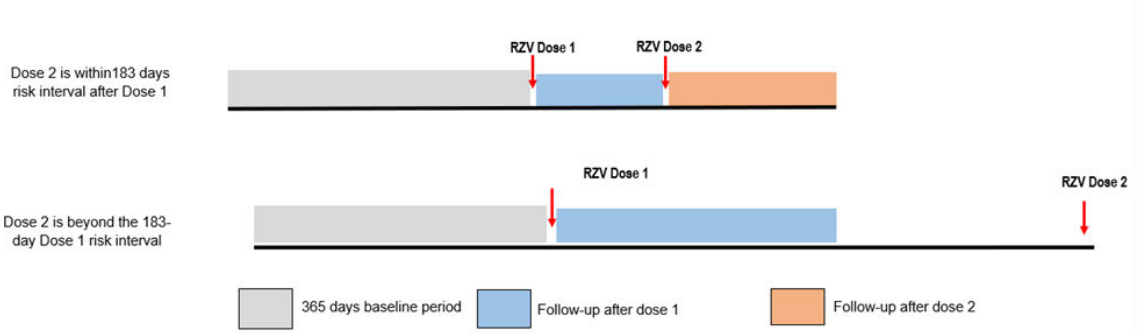
Dose 1 risk period: Day 1 after the Dose 1 vaccination date for the RZV exposed until the lesser of the Dose 2 vaccination date or day 183

Dose 2 risk period: Day 1 after the Dose 2 vaccination date for the RZV exposed until day 183 after the Dose 1 vaccination date

RZV unexposed risk period: Day 1 to 183 after the preventive care visit date

Baseline covariates and incident cases: Day 1 to 365 preceding the index date for Dose 1 and preceding the RZV unexposed preventive care visit date.

Figure 6 Time-varying Dose 1 and Dose 2 Analysis



9.3.6. Sensitivity analyses of the dose compliant cohort

As sensitivity analyses, the two secondary analyses described above will be conducted again, restricted to the sub-cohort that received Dose 1 and Dose 2 within 2-6 months apart per the US dosing schedule, i.e., dose compliant

9.3.7. Censoring events

Person-time will be defined as the period between the start of follow-up, i.e., Dose 1 or Dose 2 vaccination date for RZV exposed and the preventive care visit date for the RZV unexposed, and the earliest of the following events:

- End of study period (defined as the lesser of 183 days after the index date or December 31, 2021)
- Date of disenrollment from Medicare Parts A, B, and D
- Date of death
- Date of *Shingrix* vaccination among comparators
- Date of *Zostavax* vaccination
- Date of first diagnosis of the outcome of interest

9.3.8. Statistical models for the cohort analyses

Primary analysis of separate doses.

The primary analysis of separate doses will be conducted using a Cox proportional hazards regression model. This is a semi-parametric model in that it assumes a parametric form for the effects of the explanatory variables and a non-parametric form for the underlying survival function. The general form of a Cox proportional hazards regression model with time-independent covariates is specified by the hazard at time t in an individual i with covariate vector $\bar{x_i}$:

$$h(t, \bar{x_i}) = \lambda_0(t) \cdot exp\left[\beta_1 \cdot x_{i,1} + \cdots + \beta_k \cdot x_{i,k}\right]$$

where, h(t) is the estimated underlying hazard at time t; λ_0(t) is the baseline hazard function and represents the hazard when all predictors are equal to their population mean.

The effect estimate generated from the Cox proportional hazards model is a hazard ratio (HR). The HR is time-independent by design, but depends on the covariate vector for individual *i*, one of which is receipt of vaccine. The HR is expressed as:

$$HR(1,0,\beta) = \frac{h(x=1,\beta)}{h(x=0,\beta)} = \exp(\beta)$$

where *x* (1,0) denotes the exposure status, and β is the vector of the estimated parameter from the regression model.

The most direct and objective method to assess violations of the proportional hazard assumption is to include time-dependent covariates in the Cox model. The time-dependent variable(s) are generated as the interaction between the covariates and the log of time, i.e., log(t). In SAS, this is incorporated within PROC PHREG and the variable(s) are added in the MODEL statement to test the interaction of the covariates as a function of survival time. The TEST statement in SAS will produce a proportionality test of all the time-dependent covariates at once. The SAS output generates a Wald chi-square and p-value to assess the significance of the proportionality test. A significant p-value for the proportionality test indicates the covariates are not proportional and the proportional hazards assumption is violated. If the proportional hazard assumption is violated, we will implement measures to deal with non-proportionality, such as including the time-dependent variable in the model or exploring alternative parametric statistical models.

Table 6 is an example, using fabricated numbers, to illustrate the data structure for the Cox proportional hazards regression analysis.

Table 6 Example data structure for the Cox proportional hazards regression analysis

BENE ID	RZV exposure	Dose number (d)	Index Date	RZV1 Date	RiskInt1 End	RZV1 Time	RZV2 Date	RiskInt2 End	RZV2 Time	HOI Date	Last Follow-up Date	Event Time	HOI	Cov1	Cov2
PPD	Yes	1	10/01/2018	10/01/2018	4/02/2019	183			0	3/07/2019	3/07/2019	157	1	65	4
	Yes	1	10/01/2018	10/01/2018	4/02/2019	183			0		4/02/2019	183	0	66	2
	Yes	2	9/02/2018	9/02/2018	3/03/2019	183	2/05/2019	8/07/2019	183		8/07/2019	336	0	65	4
	Yes	2	9/02/2018	9/02/2018	3/03/2019	183	2/05/2019	8/07/2019	183	2/25/2019	2/25/2019	176	1	66	2
	No	0	10/01/2018			0					4/02/2019	183	0	66	2
	No	0	10/01/2018			0				2/12/2019	2/12/2019	134	1	66	4

Secondary analysis of combined doses.

The secondary analysis of combined doses in one risk estimate will be executed using a partly conditional survival model. This model is appropriate as it estimates the effect of longitudinal measures, in this case dose, on survival allowing for repeated measures for each individual.[4,5]

Whereas typically survival is modeled as the time from start of follow-up to the event, i.e., D_i *event time*, in a partly conditional survival analysis, regression parameters depend upon the time of measurement (S_i; i.e., dose receipt in this case) to the event. A partly conditional survival regression models the hazard function conditional on survival time from the measurement (i.e., $D_i - S_i$). As a result, there are multiple event times for each individual which corresponds with the repeated measures for each dose.

A general form of the regression model for the hazard is shown below,

$$\lambda_{ik}(t* \,|\mathbf{Z}_{ik},\, 0 \le s_{ik} \le T_i) = g[\lambda_{\,0}(t*,\, s),\, \boldsymbol{\beta}(t*,\, s)^{\mathrm{T}}\, \mathbf{Z}_{ik}]$$

where T_i is the time to event (or censor) for participant i, s_{ik} denotes measurement times for each dose, $t* = t - s_{ik}$ measures the follow-up time since dose, $g(\lambda, \eta)$ is a link function, $\lambda_0(t*, s)$, is the baseline hazard, $\beta(t*, s)$ is the regression coefficient, and Z_{ik} is a vector of covariates associated with participant i, at time s_{ik}.

The analysis will be conducted using SAS 9.4, and standard errors will be calculated using a robust sandwich estimator for repeated measures survival data.

Table 7 is an example, using fabricated numbers, to illustrate the data structure for the partly conditional survival model.

Table 7 Example data structure for the partly conditional survival model

BENE ID	RZV Exposure	Number of Doses	Index Date	HOI Date	Last Follow-up Date	Event Time HOI	
PPD	Yes	1	10/01/2018	3/07/2019	3/07/2019	157	1
	Yes	1	10/01/2018		4/02/2019	183	0
	Yes	2	9/02/2018	2/25/2019	2/25/2019	176	1
	Yes	2	2/05/2019	2/25/2019	2/25/2019	20	1
	Yes	2	9/02/2018		3/04/2019	183	0
	Yes	2	2/05/2019		8/07/2019	183	0
	Yes	2	9/02/2018		3/04/2019	183	0
	Yes	2	2/05/2019	8/01/2019	8/01/2019	177	1
	Yes	2	9/02/2018		3/04/2019	183	0
	Yes	2	5/02/2019		11/01/2019	183	0
	No	0	10/01/2018		4/02/2019	183	0
	No	0	9/02/2018		3/04/2019	183	0

Secondary analysis of a single model for separate doses.

To generate a separate risk estimate for each dose in a combined analysis, where a binary indicator defines the Dose 1 and Dose 2 risk windows, a time-varying Cox proportional hazards regression models will be used. In the time-dependent model, we allow the risk window to vary for each dose. The time after Dose 1 until Dose 2 or end of follow-up if no Dose 2 occurs defines the Dose 1 risk window, and the time from Dose 2 until end of follow-up defines the Dose 2 risk window.

A participant who receives two doses within a 183-day risk interval starting day 1 after the Dose 1 vaccination date will contribute person-time to the Dose 1 risk window and the Dose 2 risk window. In the unvaccinated comparators the time from the preventive care visit date to end of follow-up is considered unexposed time. A general form of time-dependent Cox models can be written as:

$$h_i(t,x) = \lambda_0(t) \exp[\beta_1 x_{i1} + \ldots. \beta_2 x_{i2}(t)]$$

where x_{i1} represents a time-independent variable, and x_{i2} represents the time-dependent variable. This analysis will use the full cohort and obtain estimates for both doses whereas the primary separate dose analysis either ignores dose 2 or includes only the subset of the sample who received 2 doses.

The βs are the regression coefficients, generated from the time-dependent Cox proportional hazards model. The model will generate β1, the hazard ratio for Dose 1 relative to unexposed, and β2, the hazard ratio for Dose 2 relative to unexposed. Both hazards are generated in the same model with the full cohort, using time since the Dose 1 index date or the preventive care visit.

The data structure for this analysis is the same as displayed in Table 6.

Sensitivity analyses of the dose compliant cohort.

The sensitivity analyses, to be conducted for the two secondary analyses, will be restricted to the sub-sample of individuals who receive both RZV doses spaced within 2-6 month per US label, i.e., dose compliant. The statistical models will follow the partly conditional survival model and the time-varying Cox proportional hazards model described above for the secondary analyses.

Supplemental analysis

Some individuals in the analysis may contribute person-time both to the comparison group and (subsequently) to the RZV-vaccinated group. At CBER's request, a supplemental analysis will be conducted for the primary analysis, excluding from the control arm those participants who received RZV at any point, so that each participant contributes person-time to only one arm.

9.3.9. Sensitivity analysis to evaluate the impact of the COVID-19 pandemic

Sensitivity analyses will exclude exposures from the analytical cohort for which follow-up ended after February 1, 2020. These sensitivity analyses will be conducted for each HOI and will be aligned with the primary (1°) SCRI and cohort analysis as described in Table 3 and Table 5.

For HOIs to be studied using the SCRI design (GBS, Gout, SVT), vaccinations (and their cases) for which follow-up ends after February 1, 2020 will be excluded. For GBS, any doses administered on or after November 8, 2019 (and their cases) will be excluded to allow a full 84 days of follow-up before February 1, 2020. For Gout and SVT, any doses administered on or after December 2, 2019 (and their cases) will be excluded to allow a full 60 days of follow-up before February 1, 2020.

For HOIs to be studied using the cohort design (PMR, GCA, ION), February 1, 2020 will be included as a censoring event in addition to censoring events listed in section 9.3.7. Any doses administered (or preventative care visits for comparators) on or after February 1, 2020 will be excluded. Descriptive analyses will be conducted if the exclusion of data as described above limits the ability to conduct the analysis due to one or more of the following reasons:

- Significant reduction in the sample size (or number of cases) resulting in insufficient power or lack of meaningful estimates for inferences.
- The number of HOIs are too small to allow adequate control for confounding factors or convergence of statistical models.

Descriptive analyses will include a report of the number of cases in risk and control windows (for GBS, Gout, SVT), and a report of the incidence rate (or cumulative incidence) in vaccinated and preventative care comparators for PMR, GCA, and ION.

9.3.10. Methods to control for confounding

Several methods will be used to control for confounding. These include a) covariate adjustment in a regression model, b) propensity score methods, and c) a bias analysis.

Covariate-adjusted analysis.

A multivariable model adjusted for baseline covariates will be the primary method to control for confounding. The covariates include the demographic characteristics (e.g., age, sex, race/ethnicity, US region), calendar year/month of vaccination or preventive care visit, comorbidities including immunocompromising conditions and concomitant vaccination. A detailed covariate list and definitions is provided in Appendix D**.**

The standardized mean difference (SMD) is a statistic often used to determine if the covariate distribution is balanced between two groups. The SMD is calculated using the following formulas.

For continuous variables, $\bar{X}_1$and $\bar{X}_2$ are the means for the RZV exposed and RZV unvaccinated comparator, respectively; S_1^2 and S_2^2 are the variance for the RZV exposed and RZV unvaccinated comparator, respectively.

$$SMD = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt[2]{(S_1^2 + S_2^2/2}}$$

For dichotomous variables, $\hat{p}_1$ and $\hat{p}_2$are the proportions in the RZV exposed and the RZV unvaccinated comparator, respectively; $\hat{p}_1(1-\hat{p}_1)$ and $\hat{p}_2(1-\hat{p}_2)$ are the variance for the RZV exposed and the RZV unvaccinated comparator, respectively.

$$SMD = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{[\hat{p}_1(1-\hat{p}_1) + \hat{p}_2(1-\hat{p}_2)]/2}}$$

Variables between the RZV exposed and the RZV unvaccinated comparators that differ by a standardized mean difference greater than 0.10 are considered unbalanced and will be added to the statistical models to adjust for confounding. The standardized mean difference is preferred over a p-value metric that can be influenced by large sample sizes when in fact there is little meaningful difference between groups.

Propensity score methods for the cohort design analysis.

Should we find large differences in many of the covariates between the RZV exposed and the RZV unexposed comparator, it may not be possible to use a covariate-adjusted regression model. For HOIs that are rare, this will result in too few events to estimate for each covariate and the model will not converge. Propensity score methods can be used to correct for imbalance in confounders between RZV exposed and RZV unvaccinated comparators. A logistic regression model will be used to estimate the conditional probability of receiving the RZV vaccine predicted by the baseline covariates observed in the 365 days preceding the start of follow-up, or index date (i.e., RZV exposed vaccination date or RZV unexposed preventive care visit date). The logistic regression generates a predicted probability, which is a numeric value, i.e., the propensity score. Since the propensity score is predicted from all of the covariates, this simplifies the regression model to one variable accounting for all baseline demographic and health characteristics, and thus for rare events, this eliminates the model convergence problem. Covariates entered into the propensity score estimation model are selected empirically based on a statistically significant association between the covariate and the exposure and between the covariate and the outcome. Bivariate analyses between the covariate and the exposure and between the covariate and the outcome of interest will be conducted using chi-square (or Fisher's exact tests) for categorical variables and t-tests (or Wilcoxon rank sum tests) and simple linear regression for continuous data. According to the central limit theorem, with large sample sizes, which this study will have, a two-sample t-test is robust to data that are not normally distributed.[15]

Where the bivariate analysis shows a statistically significant association between the covariate and the outcome and between the covariate and the exposure, the covariate will be retained for the propensity score estimation. A covariate that is not statistically

significantly associated with the outcome but is related to the exposure will not be included in the propensity score estimation as such variables may increase the variance of the exposure effect estimate and will not reduce bias.[16] Covariates that are weakly associated with the outcome, as determined by $0.05 < p \leq 0.10$, will be included, even if not significantly associated with the exposure, as these variables can reduce bias.[16] We will include in the propensity score estimation model covariates that may not be significantly associated with the outcome but are known confounders.

Non-overlapping areas of the propensity score distribution between the RZV exposed and RZV unvaccinated comparator cohorts will be removed. To mitigate the potential for unmeasured confounding at the tail ends of the propensity score distribution, we may consider asymmetrical trimming, as this is shown to reduce bias at the tail ends of the propensity score distribution where unmeasured confounding may be more pronounced.[17-18] Recent research demonstrates the validity of asymmetrical trimming with respect to bias, relative efficiency, and 95% confidence interval coverage.[19-20]

Although several propensity score implementation methods, including nearest neighbor matching, inverse probability of treatment weighting (IPTW), and stratification, are available, the recommended strategy for propensity score methods is to try a few of these approaches and select the one that yields the best covariate balance between the groups.21 Matching may reduce the sample size if the predicted scores differ by a specified caliper width, generally 0.2. IPTW and stratification approaches do not reduce the sample size. We will select the propensity score implementation method, such as inverse probability of treatment weighting, that yields the best covariate balance between the groups.21The analysis in this study will use the approach that yields a SMD between RZV vaccinated and RZV unvaccinated comparators less than 0.10, i.e., indicative of good confounder balance, with minimal loss of sample size.

Bias analysis to test for unmeasured confounders for the cohort design analysis.

One assumption underlying the cohort analyses is that there are no unobserved confounders related to RZV exposure and the study outcomes of interest, given the observed covariates. Unobservable factors, related to illness severity and health status, could influence RZV receipt and the outcomes of interest. The goal of the bias analysis is to estimate the magnitude of effect of an unobserved confounder needed to change the statistical inference. [16,22-27]

The method described by Ding and VanderWeele (2016)[22] demonstrates that there is a bounding factor for the true exposure-outcome relative risk. In the formula below,

$$RR_{EU} \times RR_{UD}/(RR_{EU} + RR_{UD} - 1)$$

where, RR_{EU} is the relative risk between exposure E and the unmeasured confounder U and RR_{UD} is the relative risk between the unmeasured confounder U and the outcome D.

To illustrate how the bias analysis will be applied, suppose the observed relative risk is 3. If the exposure-confounder RR_{EU}= 5 and the confounder-outcome RR_{UD} = 4, this would yield a bounding factor of 2.5 [i.e., 5x4/(5+4-1)=2.5], which is lower than the observed

relative risk of 3. Thus, in this example, even a strong unmeasured confounder (i.e., in this example RR_{EU}= 5 and RR_{UD} = 4) would not be able to explain away the observed effect. This bias analysis permits interpretation of the inferential analyses in the context of the potential bias due to unobserved cofounders.

9.4. Temporal scan statistics

Temporal scan statistics will be used as a supplemental method for assessing the possibility of an association between RZV vaccination and an HOI during the respective follow-up period. This method evaluates whether there is any statistically significant temporal clustering of cases, the existence of which may suggest, although not confirm, an association. Just as with the SCRI method (see Section 9.2), the use of a consistent, first-in-X-days definition of incident HOI cases is necessary in order to establish an equal opportunity for a case to be ascertained regardless of where in the follow-up period it might appear and to thereby avoid temporal bias. For all outcomes, the number of days after vaccination that HOI diagnoses appear in the claims will be used. See Appendix C.

Procedures for running a temporal scan for each HOI

1. Go to treescan.org and download the free TreeScan software.
2. Prepare the count file: Create a text file (i.e., with filename ending in .txt) with no headers, in the following format, where the first number in each row is the number of cases and the second number in each row represents the number of days after vaccination the cases (if any) occurred. The number of rows of data should equal the number of days of follow-up, e.g., 183 days. Example:

   0, 1

   0, 2

   1, 3

   (Etc.)

   In the example data above, there were no cases on Day 1, no cases on Day 2, and 1 case on Day 3 post vaccination.
3. Open TreeScan. Click on “Create New Session” or go to the File tab and click on “New Session.”
4. Analysis tab:
   a. Type of Scan: Choose “Time Only.”
   b. Temporal Window: OK to put 1 in left-hand boxes and 183 (or last day in follow-up period) in right-hand boxes, although default settings will further restrict the windows being evaluated (see below).
   c. Advanced tab: On Inference tab, choose 99,999 replications instead of the default 999 in order to achieve a minimum p-value of 0.00001 instead of 0.001. Leave all other defaults as are. The Temporal Window defaults stipulate a maximum temporal cluster size of one-half of the overall follow-up period, a minimum temporal cluster size of 2 days, and that only potential risk windows

where (RW Length/End of the RW) ≥ 20% will be evaluated. These restrictions on the number of potential risk windows evaluated are biologically reasonable and serve to optimize statistical power.)

5. Input tab: Click on icon to right of blank Count File space to select the count file with .txt suffix you created. An "Import File Wizard" dialogue box will appear. Click "OK."
   Put "1" for Range Start and "183" (or last day in follow-up period) for Range End.
   Output tab: Click on icon to right of blank Results File space to select a location and name for the results file.
6. To run the analysis, click on the green rightward-pointing arrow near the top of the TreeScan screen. The results will appear on the screen as well as in the results file that was set up on the Output tab. Temporal clusters detected are presented in ascending order of p-value.

To use an example, say a potential RW of Days 2-15 is being evaluated at a particular instant of the analysis. RW length = 14 days, and end of the RW = 15. 14/15 ≥ 20%, therefore that RW gets evaluated. All potential risk windows meeting the criteria of (a) a maximum temporal cluster size of one-half of the overall follow-up period, (b) a minimum temporal cluster size of 2 days, and (c) (RW Length/End of the RW) ≥ 20% are evaluated. The purpose of Criterion (4c) is to avoid evaluating biologically implausible risk windows, like Days 180-183. (Short RWs right after vaccination are biologically plausible, but short RWs toward the end of the follow-up period are not.)

9.5. Handling missing data

Based on the feasibility study using the 2006-2015 CMS CCW Medicare database, there is no missing data on age and sex in the MBSF data. Approximately 0.01% of the population has missing information for the state of residence and 1.42% report "unknown" race. We will use the MBSF for all information on demographic characteristics as this is the key dataset for this information. To address potential problems with aberrant age values or with discrepancies in gender across different records, age, gender, and race will be determined based on the information in the MBSF data at the time of the index date, which is the date of study follow-up.

Individuals may be lost to follow-up if they lose eligibility or switch to Part C and all their data will be missing, at which point they will be censored in the analysis.

Under the assumption that data are missing at random, multiple imputation will be used to impute missing values, providing that there is more than 5% missing data for a specified covariate.

Regarding the extent of missingness, if a lot of data are missing for some covariates, the values will not be imputed and the covariate(s) in question will not be included in the analysis. Should an individual have a lot of missing data on the key variables, the values will not be imputed and the individual will be excluded from the analysis.

10. DATA EXTRACTION AND CREATION OF ANALYTIC DATASETS

10.1. Validation of the programs

Data extraction and creation of analytic datasets is based on the raw data files supplied by CMS. Data quality checks are performed as described in Section 7.1. The programs associated with data extraction and analytic file creation are scrutinized by no less than 3 individuals to ensure that they are completed with quality according to the project specifications. The project manager is responsible to outlining the details of each program and dataset as per all final decisions. The first programmer is responsible for utilizing the PRC server to program all specifications and produce draft analytic datasets. The second programmer is responsible for validating the programs for completeness and accuracy. Once reviewed and clear of any errors or discrepancies, the Principal Investigator is given all datasets for team review of all outputs.

10.2. Data extraction and creation of analytic datasets

The CMS CCW Medicare data files listed in Section 7 will be used to extract the study population and to create all of the HOI analytic datasets. In each year from 2018 through 2020, the MBSF data will be used to identify all individuals age 65 years old or older as of the end of the calendar year. We will next extract individuals who had an original and current entitlement as Old Age and Survivor's Insurance (OASIS) and who had any Medicare fee-for-service Parts A, B, and D enrollment in the calendar year. This is the base population.

Procedures for data extraction and creation of the analytic datasets for each HOI will be included in a supplement to the SAP. The supplement that will accompany the SAP will contain a detailed description of the programming procedures, the variable definitions, the data sets used, and the SAS program code for each HOI analytic cohort.

11. CONDUCT OF ANALYSES

The conduct of analyses follows the sequence and anticipated timeline in Table 2. The order of the analyses was selected according to increased risks to public health. The timeline for completion accommodates the time for sample accrual, the follow-up time for detection of new cases, and the lag in acquisition of new data. It is anticipated that 2018 sample will be conservative due to supply and demand imbalances and 2020 will also be conservative due to the COVID-19 pandemic.

Prior to each of these analyses, up-to-date code lists will be checked for any new codes for RZV, HOIs, or potential confounders to be adjusted for in the respective analysis. Any new codes will be incorporated into code lists and included in the statistical models, as appropriate.

A supplement to accompany this SAP will include all of the detailed analytic models, a description of the variables, model validation procedures, and the SAS code. Operational

definitions of the covariates are provided in Appendix D**.** Upon completion of all analyses, a final comprehensive statistical analysis report (SAR) will be submitted to GSK.

12. QUALITY MANAGEMENT

Record retention.

Data files and programs will be retained on PRC secure servers for the duration of the study as stipulated in the DUA. However, a DUA may be renewed for an indefinite duration of time, depending upon the study needs.

During project closeout, project specific programs, output, data sets and documentation are archived unless stipulated otherwise. A custodial server assessment determines what, if any, resources remain after this process.

Upon completion of research activities or expiration of the DUA, data resources covered by the DUA must be destroyed to prevent breach of confidentiality. This data destruction is then certified and reported to CMS within 30 days. Additional project files may be preserved on the PRC server archive for up to 3 years following the closure of the DUA; however, the DUA may remain active for as long as needed for the study purpose and requirement to maintain the data for a specified period of time. In this study, the project files will be preserved for 15 years, per contractual agreement.

Quality assurance.

The UMB Pharmaceutical Health Services Research (PHSR) Department and PRC are guided by the management concept of Total Quality Management. PHSR and PRC highly value quality assurance measures utilizing standardized project management procedures managing projects and project files. Best practices have been established to assist in assuring outputs are as accurate as possible.

Data management.

The study team will request CMS CCW claims data for all beneficiaries who received the RZV vaccine and a random sample of beneficiaries who did not receive the RZV vaccine that will enable sample size sufficient to power the study for all HOIs. CMS provides research identifiable data that contain dates of service, date of birth, and zip code. However, to preserve anonymity and confidentiality, the data do not contain personal identifying information, such as name, address, Medicare identification number, or social security numbers. A de-identifiable beneficiary ID is used to link data files; however, CMS does not provide the key that links the de-identified beneficiary ID to personal identifying information.

The following procedures will ensure the quality and integrity of the data.

- CMS data acquisition-retrospective data collection/analysis. All claims data acquired will include year's 2017 (baseline pre-period for 2018), 2018, 2019, 2020, and 2021 (follow-up period for 2020) for beneficiaries identified for the study.

- Extraction of individual data. All data extracted for individual level analyses will undergo reviewed by a second programmer to ensure accuracy of the programming code. Programming code includes those used to identify exposed and unexposed individuals eligible for the study, to apply the inclusion and exclusion criteria to identify the study cohort and to identify individuals eligible for the planned analyses.
- Dataset check. All programs and outputted datasets will undergo a 3-person review-initial programmer, second programmer and project coordinator. The initial programmer is responsible for the first review of his/her programs and output. A second programmer, whose sole responsibility is quality control, will be responsible for secondary review of the SAP supplement task order and all SAS programs. The project coordinator who oversees the SAP supplement task order for each programming serves as the third reviewer who will be responsible for review of all output to ensure that it adheres to the protocol.
- Perform consistency checks. Files will be inspected for correct application of inclusion criteria as outlined in this document and stored in a manner consistent with DUA specifications. Once the list of inconsistencies is reviewed, discrepancies can either be confirmed or corrected, as applicable. Once completed, the data files will again be re-transferred in a secure manner, in the required format for a final check, database freeze/archival, and lock of the dataset

13. LIMITATIONS

There are potential limitations that impact the inferences that can be drawn from this study. These are discussed in the context of the likely success of efforts taken to reduce bias.

Study design.

Despite the careful selection of appropriate study designs to address the study objectives, there are some limitations. The SCRI design mitigates bias through implicit control for time-fixed confounders. A limitation is that it does not control for time-varying confounders. With the short risk windows for this study, there may be minimal change in confounders, and thus minimal bias would be introduced.

A limitation of the cohort analysis is dis-enrollment from Medicare Parts A, B, and D, which could impact the 365-day baseline period. The feasibility assessment showed that requiring more than 365 days would reduce the sample size because individuals lose Parts A, B, or D coverage. Further, individuals who receive RZV close to age 65, the age at which individuals qualify for Medicare, may not have a full year of enrollment prior to the vaccination date. Consultation with clinical experts confirmed that the 365-day baseline would be adequate to exclude prevalent cases of the HOIs. According to the sample size estimates, the large sample size in the CMS Medicare population should be sufficient, even if the sample is reduced due to less than 365 days of enrollment in Parts A, B, and D prior to the vaccination or preventive care visit date.

Limitations of the CCW Medicare data source.

Services covered by Medicare Advantage (Part C) plans are not included in the CCW Medicare data. Older adults who opt to purchase supplemental insurance are covered under the Medicare Advantage plans, or Part C. All medical encounters and services are paid for by the supplemental insurance, and thus data on these individuals are missing.

Data on clinical metrics, such as laboratory values and illness severity, that could have been used for case identification are not available in the claims data.

Analytic methods.

The analytic models selected for the analyses have minimal assumptions, and most of which can be verified through analytic tests and graphical display of the data. However, they could still have some unverifiable assumptions.

Methods to control for confounding and bias.

A primary source of confounding in this study are healthy user bias, which refers to the fact that individuals who seek preventive care service may also participate in other healthy behaviors, thus are less likely to experience an outcome. In the cohort analyses, our proposed use of a concurrent preventive care visit as the comparison group will mitigate the effects of healthy user bias on the risk estimate as both RZV vaccinated and unvaccinated will be users of preventive care services.

While other measurable confounding variables that differ between the two groups will be adjusted for in multivariable regression models and if deemed appropriate by using propensity score methods, the risk estimates could still be biased by confounders that were not measured (unmeasured confounders) or not properly measured (residual confounding). A bias analysis is planned to identify how strong an unmeasured confounder must be to explain away the observed effect estimate.

The Dose 2 analysis is conditioned on the subset of individuals who self-select to receive 2 doses within the study period. This may introduce selection bias if there are characteristic differences in measured and unmeasured factors that influence why some individuals receive two doses whereas some only receive one dose. This can underestimate the risk relative to the unvaccinated comparator.

Generalizability.

Medicare is the most comprehensive data on older adults, and so the findings will generalize to US adults aged 65 and older. We do not expect appreciable differences between those in the study and those age 65 and older who are not enrolled in Medicare Parts A, B, and D that would affect the HOI risk estimate post-vaccination with RZV.

Sources of random error.

The goal is to mitigate bias due to random error. However, it is possible that random sources of error will occur since this is an observational study using secondary claims data. All attempts have been made to ensure appropriate study designs, well-thought out case identification algorithms, appropriate confounder adjustment methods, and planned sensitivity analyses are implemented in the conduct of the study.

Temporal variation.

There may be temporal variation due to availability of the vaccine. To address variability in the timing of the vaccine and the preventive care visit, the calendar month-year will be a covariate in the analytic models.

Case ascertainment.

It will not be possible to conduct a chart review to validate HOIs. Case-finding algorithms using administrative data are rarely sensitive and specific. The algorithms used in this study are found to have high positive predictive value in published case validation studies and we consulted with experts to assure the best possible algorithm.

14. CHANGES FROM PLANNED PROTOCOL ANALYSES

Not applicable.

15. REFERENCES

1. Funch D, Holick C, Velentgas P, et al. Algorithms for identificatin of Guillain-Barre Syndrome among adolescents in claims databases. *Vaccine.* 2013;31:2075-2079.
2. Harrold LR, Saag KG, Yood RA, et al. Validity of gout diagnoses in administrative data. *Arthritis Rheum.* 2007;57(1):103-108.
3. Bernatsky S, Linehan T, Hanly JG. The accuracy of administrative data diagnoses of systemic autoimmune rheumatic diseases. *Journal of Rheumatology.* 2011;38(8):1612-1616.
4. Rubin DS, Matsumoto MM, Moss HE, Joslin CE, Tung A, Roth S. Ischemic Optic Neuropathy in Cardiac Surgery: Incidence and Risk Factors in the United States from the National Inpatient Sample 1998 to 2013. *Anesthesiology.* 2017;126(5):810-821.
5. Sidney S, Sorel M, Quesenberry CP, Jr., DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest.* 2005;128(4):2068-2075.
6. Baker MA, Lieu TA, Li L, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. *American Journal of Epidemiology.* 2015;181(8):608-618.
7. Schneeweiss S, Sturmer T, Maclure M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. *Pharmacoepidemiology and Drug Safety.* 1997;6 Suppl 3:S51-59.
8. Hallas J, Pottegard A. Use of self-controlled designs in pharmacoepidemiology. *Journal of Internal Medicine.* 2014;275(6):581-589.
9. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ.* 2016;354:i4515.

10. Yih WK, Lieu TA, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in U.S. infants. *N Engl J Med.* 2014;370(6):503-512.
11. Yih WK, Greene SK, Zichittella L, et al. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. *Vaccine.* 2016;34(1):172-178.
12. Baker MA, Baer B, Kulldorff M, et al. Kawasaki disease and 13-valent pneumococcal conjugate vaccination among young children: A self-controlled risk interval and cohort study with null results. *PLoS Med.* 2019;16(7):e1002844.
13. Gong Q, Schaubel DE. Partly conditional estimation of the effect of a time-dependent factor in the presence of dependent censoring. *Biometrics.* 2013;69(2):338-347.
14. Zheng Y, Heagerty PJ. Partly conditional survival models for longitudinal data. *Biometrics.* 2005;61(2):379-391.
15. Lumley T, Diehr P, Emerson S, Chen L. The importance of the normality assumption in large public health data sets. *Annual Review of Public Health.* 2002;23:151-169.
16. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *American Journal of Epidemiology.* 2006;163(12):1149-1156.
17. Cadarette SM, Gagne JJ, Solomon DH, Katz JN, Sturmer T. Confounder summary scores when comparing the effects of multiple drug exposures. *Pharmacoepidemiol and Drug Safety.* 2010;19(1):2-9.
18. Sturmer, T., Rothman, K.J., Avorn, J., Glynn, R.J. Treatment effects in the presences of unmeasured confounding: Dealing with observations in the tails of the propensity score distribution--A simulation study. *Am J Epidemiol*. 2010; 172:843-854.
19. Li, F, Thomas, L.E., Li, F. Addressing extreme propensity scores via the overlap weights. Erratum. *Am J Epidemiol*. 2019; 188(1): 250-257.
20. Li, F., Thomas, L.E., Li, F. RE: Addressing extreme propensity scores via the overlap weights. Erratum. *Am J Epidemiol*. 2021; 190(1): 189-190.
21. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. *Psychological Methods.* 2010;15(3):234-249.
22. Ding P, VanderWeele TJ. Sensitivity Analysis Without Assumptions. *Epidemiology.* 2016;27(3):368-377.
23. Vanderweele TJ, Arah OA. Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. *Epidemiology.* 2011;22(1):42-52.
24. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic & Clinical Pharmacology & Toxicology.* 2006;98(3):253-259.
25. Polinski JM, Kilabuk E, Schneeweiss S, Brennan T, Shrank WH. Changes in drug use and out-of-pocket costs associated with medicare part D implementation: A

systematic review. *Journal of the American Geriatrics Society.* 2010;58(9):1764-1779.

26. Polinski JM, Shrank WH, Huskamp HA, Glynn RJ, Liberman JN, Schneeweiss S. Changes in drug utilization during a gap in insurance coverage: An examination of the medicare part d coverage gap. *PLoS Medicine.* 2011;8(8).

27. Polinski JM, Alan Brookhart M, Glynn RJ, Schneeweiss S. Comparison between aggregate- and individual-level time-trend analyses to evaluate overall effects of medicare part D on use of antipsychotic medications. *Pharmacoepidemiology and Drug Safety.* 2011;20((Polinski J.M.; Glynn R.J.; Schneeweiss S.) Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, United States):S107.

28. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiology & Drug Safety.* 2006;15(5):291-303.

16. APPENDICES

16.1. Appendix A. Preventive Care Visit Codes for the Comparator Cohort

Preventive Care Visit Description	Code	Source	Type
Routine Adult Annual Exam			
Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 40-64 years	99386	CPT-4	Procedure
Initial comprehensive preventive medicine evaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, new patient; 65 years and older	99387	CPT-4	Procedure
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 40-64 years	99396	CPT-4	Procedure
Periodic comprehensive preventive medicine reevaluation and management of an individual including an age and gender appropriate history, examination, counseling/anticipatory guidance/risk factor reduction interventions, and the ordering of laboratory/diagnostic procedures, established patient; 65 years and older	99397	CPT-4	Procedure
Annual wellness visit; includes a personalized prevention plan of service (pps), initial visit	G0438	HCPCS	Procedure
Annual wellness visit, includes a personalized prevention plan of service (pps), subsequent visit	G0439	HCPCS	Procedure
Federally qualified health center (fqhc) visit, ippe or awv; a fqhc visit that includes an initial preventive physical examination (ippe) or annual wellness visit (awv) and includes a typical bundle of medicare-covered services that would be furnished per diem to a patient receiving an ippe or awv	G0468	HCPCS	Procedure
Wellness assessment, performed by non-physician	S5190	HCPCS	Procedure
Initial preventive physical examination; face-to-face visit, services limited to new beneficiary during the first 12 months of medicare enrollment	G0402	HCPCS	Procedure
Encounter for general adult medical exam without abnormal findings	Z00.00	ICD-10-CM	Diagnosis
Encounter for general adult medical examination with abnormal findings	Z00.01	ICD-10-CM	Diagnosis
Colonoscopy Preventive Screening Intervention			
Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)	45378	CPT-4	Procedure
Colorectal cancer screening; colonoscopy on individual at high risk	G0105	HCPCS	Procedure
Colorectal cancer screening; colonoscopy on individual not meeting criteria for high risk	G0121	HCPCS	Procedure
Patients greater than 85 years of age who received a routine colonoscopy for a reason other than the following: an assessment of signs/symptoms of gi tract illness, and/or the patient is considered high risk, and/or to follow-up on previously diagnosed advance lesions	G9661	HCPCS	Procedure

Preventive Care Visit Description	Code	Source	Type
Patients greater than 85 years of age who did not have a history of colorectal cancer or valid medical reason for the colonoscopy, including: iron deficiency anemia, lower gastrointestinal bleeding, crohn's disease (i.e., regional enteritis), familial adenomatous polyposis, lynch syndrome (i.e., hereditary non-polyposis colorectal cancer), inflammatory bowel disease, ulcerative colitis, abnormal finding of gastrointestinal tract, or changes in bowel habits	G9659	HCPCS	Procedure
Ca screen;flexi sigmoidscope	G0104	HCPCS	Procedure
colorecteral screeningn ca screen;barium enema	G0106	HCPCS	Procedure
colorecteral screeningRECTAL CANCER SCREENING; FECAL-OCCULT BLOOD TEST	G0107	HCPCS	Procedure
colorecteral screeningn ca scrn; barium enema	G0120	HCPCS	Procedure
colorecteral screeningn ca scrn; barium enema	G0122	HCPCS	Procedure
colorecteral screeningrectal cancer screening, fecal occult blood test,	G0328	HCPCS	Procedure
Encounter for screening for malignant neoplasm of colon	Z12.11	ICD-10-CM	Diagnosis
Mammography Preventive Screening Intervention			
Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed	77067	CPT-4	Procedure
Screening mammography, bilateral (2-view film study of each breast) Office/Freestanding (Global)	77057	CPT-4	Procedure
Screening mammography, bilateral (two view film study of each breast).	76092	CPT-4	Procedure
Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed.	G0202	HCPCS	Procedure
Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.	G0203	HCPCS	Procedure
Screening mammogram for high-risk patient	V7611	HCPCS	Procedure
Encounter for screening mammogram for malignant neoplasm of breast	V7612	HCPCS	Procedure
Diagnostic mammography, including computer-aided detection (CAD) when performed; bilateral.	G0204	HCPCS	Procedure
Diagnostic mammography, including computer-aided detection (CAD) when performed; unilateral.	G0206	HCPCS	Procedure
Encounter for screening for malignant neoplasm of breast	Z12.3	ICD-10-CM	Diagnosis
Encounter for screening mammogram for malignant neoplasm of breast	Z12.31	ICD-10-CM	Diagnosis
Encounter for other screening for malignant neoplasm of breast	Z12.39	ICD-10-CM	Diagnosis
Osteoporosis Preventive Screening Interventions			
Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine)	77080	CPT-4	Procedure
Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; appendicular skeleton (peripheral) (eg, radius, wrist, heel)	77081	CPT-4	Procedure
PERIPHERAL SKELETAL BONE MINERAL DENSITYN20030626	G0062	HCPCS	Procedure
CENTRAL SKELETAL BONE MINERAL DENSITY STN20030626	G0063	HCPCS	Procedure
SINGLE ENERGY X-RAY ABSORPTIOMETRY (SEXAN20110101: Single energy x-ray absorptiometry (sexa) bone density study, one or more sites; appendicular skeleton (peripheral) (e.g., radius, wrist, heel) (Single energy x-ray study)	G0130	HCPCS	Procedure
COMPUTERIZED TOMOGRAPHY BONE MINERAL DENN20060101	G0131	HCPCS	Procedure

Preventive Care Visit Description	Code	Source	Type
ULTRA-SOUND BONE MINERAL STUDY, ONE OR MORE SITES, APPENDICULAR SKELETON	G0132	HCPCS	Procedure
Bone mineral density	G0133	HCPCS	Procedure
Encounter screening for osteoporosis	Z13.820	ICD-10-CM	Diagnosis

16.2. Appendix B. Table and Figure Shells for Statistical Analyses

Table Shell 1. Baseline demographic and health characteristics of the Guillain-Barré Syndrome (GBS) analytic cohort for the SCRI* analyses

	All Eligible GBS Cases^		Excluding GBS Cases with Prior Respiratory or Gastrointestinal Infection^	
	N	%	N	%
Number of unique participants				
Demographics				
Mean Age at Index Date		SD:*		SD:*
Age: 65-69				
Age: 70-74				
Age: 75-79				
Age: 80-84				
Age: 85+				
Gender: Female				
Gender: Male				
Race: American Indian or Alaskan Native				
Race: Asian				
Race: Black or African American				
Race: Native Hawaiian or Other Pacific Islander				
Race: White				
Race: Unknown				
Parts A, B, D Continuous enrollment in Year Prior to Dose 1**				
Mean Days		SD:*		SD:*
Year of Vaccination				
Year: 2018				
Year: 2019				
Year: 2020				
Recorded Medical History in Year Prior to Dose 1				
Solid organ transplant (SOT)				
Stem cell transplant (SCT)				
Solid or hematologic malignancy or receipt of chemotherapy				
Diabetes mellitus				
Chronic kidney disease				
Chronic lung disease (COPD, bronchiectasis)				
Congestive heart failure				
Ischemic heart disease				
Dementia				
Chronic liver disease				

	All Eligible GBS Cases^		Excluding GBS Cases with Prior Respiratory or Gastrointestinal Infection^	
	N	%	N	%
Stroke/TIA				
At least 1 dermatology visit				
At least 1 optometry/ ophthalmology visit				
Immunocompromised Conditions				
Organ transplant				
Hematopoietic cell transplant				
Hematologic or solid malignancy w/recent receipt of chemotherapy				
HIV infection				
Rheumatoid Arthritis				
Inflammatory Bowel Disease- Crohn's Disease				
Inflammatory Bowel Disease- Colitis				
Lupus				
Multiple Sclerosis				
Psoriasis/Psoriatic Arthritis				
Recorded Service Use History in Year Prior to Dose 1				
Number of hospitalizations				
Number of emergency department visits				
Durable medical equipment				
Hospice care				
Home health care				
Skilled nursing facility care				
Concomitant Vaccine Use at Index Date				
Influenza				
Pneumococcal				
Tetanus-Diptheria-Pertussis				

*SCRI=self-controlled risk interval; SD = standard deviation;^Cell sizes will be supressed if the total number is <11;
**Allows one calendar month gap in enrollment

Table Shell 2. Baseline demographic and health characteristics of the gout analytic cohort for the SCRI* analyses

	All Eligible Gout Cases^	
	N	%
Number of unique participants		
Demographics		
Mean Age at Index Date		SD:*
Age: 65-69		
Age: 70-74		
Age: 75-79		
Age: 80-84		
Age: 85+		
Gender: Female		
Gender: Male		
Race: American Indian or Alaskan Native		
Race: Asian		

	All Eligible Gout Cases^	
	N	%
Race: Black or African American		
Race: Native Hawaiian or Other Pacific Islander		
Race: White		
Race: Unknown		
Parts A, B, D Continuous enrollment in Year Prior to Dose 1**		
Mean Days		SD:*
Year of Vaccination		
Year: 2018		
Year: 2019		
Year: 2020		
Recorded Medical History in Year Prior to Dose 1		
Solid organ transplant (SOT)		
Stem cell transplant (SCT)		
Solid or hematologic malignancy or receipt of chemotherapy		
Diabetes mellitus		
Chronic kidney disease		
Chronic lung disease (COPD, bronchiectasis)		
Congestive heart failure		
Ischemic heart disease		
Dementia		
Chronic liver disease		
Stroke/TIA		
At least 1 dermatology visit		
At least 1 optometry/ ophthalmology visit		
Immunocompromised Conditions		
Organ transplant		
Hematopoietic cell transplant		
Hematologic or solid malignancy w/recent receipt of chemotherapy		
HIV infection		
Rheumatoid Arthritis		
Inflammatory Bowel Disease- Crohn's Disease		
Inflammatory Bowel Disease- Colitis		
Lupus		
Multiple Sclerosis		
Psoriasis/Psoriatic Arthritis		
Recorded Service Use History in Year Prior to Dose 1		
Number of hospitalizations		
Number of emergency department visits		
Durable medical equipment		
Hospice care		
Home health care		
Skilled nursing facility care		
Concomitant Vaccine Use at Index Date		
Influenza		
Pneumococcal		
Tetanus- Diphtheria- Pertussis		

* SCRI=self-controlled risk interval; SD = standard deviation;^Cell sizes will be supressed if the total number is <11; N=X cases met the gout sensitivity HOI definition.**Allows one calendar month gap in enrollment

Table Shell 3. Baseline demographic and health characteristics of the Supraventricular Tachycardia (SVT) analytic cohort for the SCRI* analyses

	All Eligible SVT Cases ^	
	N	%
Number of unique participants		
Demographics		
Mean Age at Index Date		SD:*
Age: 65-69		
Age: 70-74		
Age: 75-79		
Age: 80-84		
Age: 85-+		
Gender: Female		
Gender: Male		
Race: American Indian or Alaskan Native		
Race: Asian		
Race: Black or African American		
Race: Native Hawaiian or Other Pacific Islander		
Race: White		
Race: Unknown		
Parts A, B, D Continuous enrollment in Year Prior to Dose 1**		
Mean Days		SD:*
Year of Vaccination		
Year: 2018		
Year: 2019		
Year: 2020		
Recorded Medical History in Year Prior to Dose 1		
Solid organ transplant (SOT)		
Stem cell transplant (SCT)		
Solid or hematologic malignancy or receipt of chemotherapy		
Diabetes mellitus		
Chronic kidney disease		
Chronic lung disease (COPD, bronchiectasis)		
Congestive heart failure		
Ischemic heart disease		
Dementia		
Chronic liver disease		
Stroke/TIA		
At least 1 dermatology visit		
At least 1 optometry/ ophthalmology visit		
Immunocompromised Conditions		
Organ transplant		
Hematopoietic cell transplant		
Hematologic or solid malignancy w/recent receipt of chemotherapy		
HIV infection		
Rheumatoid Arthritis		
Inflammatory Bowel Disease- Crohn's Disease		
Inflammatory Bowel Disease- Colitis		

	All Eligible SVT Cases ^	
	N	%
Lupus		
Multiple Sclerosis		
Psoriasis/Psoriatic Arthritis		
Recorded Service Use History in Year Prior to Dose 1		
Number of hospitalizations		
Number of emergency department visits		
Durable medical equipment		
Hospice care		
Home health care		
Skilled nursing facility care		
Concomitant Vaccine Use at Index Date		
Influenza		
Pneumococcal		
Tetanus- Diphtheria- Pertussis		

* SCRI=self-controlled risk interval; SD = standard deviation;^Cell sizes will be supressed if the total number is <11;
**Allows one calendar month gap in enrollment

Table Shell 4. Baseline demographic and health characteristics of the Polymyalgia Rheumatica (PMR) analytic cohort for the cohort analyses

	RZV-vaccinated*		RZV-unvaccinated comparator*		SMD
	N	%	N	%	
Number of unique participants					
Demographics					
Mean Age at Index Date		SD:*		SD:*	
Age: 65-69					
Age: 70-74					
Age: 75-79					
Age: 80-84					
Age: 85+					
Gender: Female					
Gender: Male					
Race: American Indian or Alaskan Native					
Race: Asian					
Race: Black or African American					
Race: Native Hawaiian or Other Pacific Islander					
Race: White					
Race: Unknown					
Parts A, B, D Continuous enrollment in Year Prior to Dose 1**					
Mean Days		SD:*		SD:*	
Year of Vaccination					
Year: 2018					
Year: 2019					
Year: 2020					
Recorded Medical History in Year Prior to Dose 1					
Solid organ transplant (SOT)					
Stem cell transplant (SCT)					

	RZV-vaccinated*		RZV-unvaccinated comparator*		SMD
	N	%	N	%	
Solid or hematologic malignancy or receipt of chemotherapy					
Diabetes mellitus					
Chronic kidney disease					
Chronic lung disease (COPD, bronchiectasis)					
Congestive heart failure					
Ischemic heart disease					
Dementia					
Chronic liver disease					
Stroke/TIA					
At least 1 dermatology visit					
At least 1 optometry/ ophthalmology visit					
Immunocompromised Conditions					
Organ transplant					
Hematopoietic cell transplant					
Hematologic or solid malignancy w/recent receipt of chemotherapy					
HIV infection					
Rheumatoid Arthritis					
Inflammatory Bowel Disease- Crohn's Disease					
Inflammatory Bowel Disease- Colitis					
Lupus					
Multiple Sclerosis					
Psoriasis/Psoriatic Arthritis					
Recorded Service Use History in Year Prior to Dose 1					
Number of hospitalizations					
Number of emergency department visits					
Durable medical equipment					
Hospice care					
Home health care					
Skilled nursing facility care					
Concomitant Vaccine Use at Index Date					
Influenza					
Pneumococcal					
Tetanus- Diphtheria- Pertussis					

*RZV=recombinant zoster vaccine; RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening; SD=standard deviation; SMD=standardized mean difference; Cell sizes will be supressed if the total number is <11; **Allows one calendar month gap in enrollment

Table Shell 5. Baseline demographic and health characteristics of the Giant Cell Arteritis (GCA) analytic cohort for the cohort analyses

	RZV-vaccinated*		RZV-unvaccinated comparator*		SMD
	N	%	N	%	
Number of unique participants					
Demographics					
Mean Age at Index Date		SD:*		SD:*	
Age: 65-69					
Age: 70-74					
Age: 75-79					
Age: 80-84					
Age: 85+					
Gender: Female					
Gender: Male					
Race: American Indian or Alaskan Native					
Race: Asian					
Race: Black or African American					
Race: Native Hawaiian or Other Pacific Islander					
Race: White					
Race: Unknown					
Parts A, B, D Continuous enrollment in Year Prior to Dose 1**					
Mean Days		SD:*		SD:*	
Year of Vaccination					
Year: 2018					
Year: 2019					
Year: 2020					
Recorded Medical History in Year Prior to Dose 1					
Solid organ transplant (SOT)					
Stem cell transplant (SCT)					
Solid or hematologic malignancy or receipt of chemotherapy					
Diabetes mellitus					
Chronic kidney disease					
Chronic lung disease (COPD, bronchiectasis)					
Congestive heart failure					
Ischemic heart disease					
Dementia					
Chronic liver disease					
Stroke/TIA					
At least 1 dermatology visit					
At least 1 optometry/ ophthalmology visit					
Recorded Service Use History in Year Prior to Dose 1					
Number of hospitalizations					
Number of emergency department visits					
Durable medical equipment					
Hospice care					
Home health care					
Skilled nursing facility care					
Concomitant Vaccine Use at Index Date					
Influenza					

	RZV-vaccinated*		RZV-unvaccinated comparator*		SMD
	N	%	N	%	
Pneumococcal					
Tetanus- Diphtheria- Pertussis					

*RZV=recombinant zoster vaccine; RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening SD=standard deviation; SMD=standardized mean difference; Cell sizes will be supressed if the total number is <11; **Allows one calendar month gap in enrollment

Table Shell 6. Baseline demographic and health characteristics of the Ischemic Optic Neuropathy (ION) analytic cohort for the cohort analyses.

	RZV-vaccinated*		RZV-unvaccinated comparator*		SMD
	N	%	N	%	
Number of unique participants					
Demographics					
Mean Age at Index Date		SD:*		SD:*	
Age: 65-69					
Age: 70-74					
Age: 75-79					
Age: 80-84					
Age: 85+					
Gender: Female					
Gender: Male					
Race: American Indian or Alaskan Native					
Race: Asian					
Race: Black or African American					
Race: Native Hawaiian or Other Pacific Islander					
Race: White					
Race: Unknown					
Parts A, B, D Continuous enrollment in Year Prior to Dose 1**					
Mean Days		SD:*		SD:*	
Year of Vaccination					
Year: 2018					
Year: 2019					
Year: 2020					
Recorded Medical History in Year Prior to Dose 1					
Solid organ transplant (SOT)					
Stem cell transplant (SCT)					
Solid or hematologic malignancy or receipt of chemotherapy					
Diabetes mellitus					
Chronic kidney disease					
Chronic lung disease (COPD, bronchiectasis)					
Congestive heart failure					
Ischemic heart disease					
Dementia					
Chronic liver disease					
Stroke/TIA					

	RZV-vaccinated*		RZV-unvaccinated comparator*		SMD
	N	%	N	%	
At least 1 dermatology visit					
At least 1 optometry/ ophthalmology visit					
Immunocompromised Conditions					
Organ transplant					
Hematopoietic cell transplant					
Hematologic or solid malignancy w/recent receipt of chemotherapy					
HIV infection					
Rheumatoid Arthritis					
Inflammatory Bowel Disease- Crohn's Disease					
Inflammatory Bowel Disease- Colitis					
Lupus					
Multiple Sclerosis					
Psoriasis/Psoriatic Arthritis					
Recorded Service Use History in Year Prior to Dose 1					
Number of hospitalizations					
Number of emergency department visits					
Durable medical equipment					
Hospice care					
Home health care					
Skilled nursing facility care					
Concomitant Vaccine Use at Index Date					
Influenza					
Pneumococcal					
Tetanus- Diphtheria- Pertussis					

*RZV=recombinant zoster vaccine; RZV-unvaccinated comparator had a preventive care visit defined by a routine annual exam or preventive screening; SD=standard deviation; SMD=standardized mean difference; Cell sizes will be supressed if the total number is <11; **Allows one calendar month gap in enrollment

Table Shell 7. Baseline demographic and health characteristics of RZV* vaccinees by dose number and Dose 2 timing

Characteristic	RZV* Dose 1		RZV* Dose 2		RZV* Dose 2 received 28-60 days after Dose 1		RZV* Dose 2 received >60 days after Dose 1	
	N	%	N	%	N	%	N	%
Number of unique participants								
Demographics								
Mean Age at Index Date		SD:*		SD:*		SD:*		SD:*
Age: 65-69								
Age: 70-74								
Age: 75-79								
Age: 80-84								
Age: 85+								
Gender: Female								
Gender: Male								
Race: American Indian or Alaskan Native								

Characteristic	RZV* Dose 1		RZV* Dose 2		RZV* Dose 2 received 28-60 days after Dose 1		RZV* Dose 2 received >60 days after Dose 1	
Race: Asian								
Race: Black or African American								
Race: Native Hawaiian or Other Pacific Islander								
Race: White								
Race: Unknown								
Parts A, B, D Continuous enrollment in Year Prior to Dose**								
Mean Days		SD:*		SD:*		SD:*		SD:*
Year of Vaccination								
Year: 2018								
Year: 2019								
Year: 2020								
Recorded Medical History in Year Prior to Dose 1								
Solid organ transplant (SOT)								
Stem cell transplant (SCT)								
Solid or hematologic malignancy or receipt of chemotherapy								
Diabetes mellitus								
Chronic kidney disease								
Chronic lung disease (COPD, bronchiectasis)								
Congestive heart failure								
Ischemic heart disease								
Dementia								
Chronic liver disease								
Stroke/TIA								
At least 1 dermatology visit								
At least 1 optometry/ ophthalmology visit								
Immunocompromised Conditions								
Organ transplant								
Hematopoietic cell transplant								
Hematologic or solid malignancy w/recent receipt of chemotherapy								
HIV infection								
Rheumatoid Arthritis								
Inflammatory Bowel Disease- Crohn's Disease								
Inflammatory Bowel Disease- Colitis								
Lupus								
Multiple Sclerosis								
Psoriasis/Psoriatic Arthritis								

Characteristic	RZV* Dose 1		RZV* Dose 2		RZV* Dose 2 received 28-60 days after Dose 1		RZV* Dose 2 received >60 days after Dose 1	
Recorded Service Use History in Year Prior to Dose 1								
Number of hospitalizations								
Number of emergency department visits								
Durable medical equipment								
Hospice care								
Home health care								
Skilled nursing facility care								
Concomitant Vaccine Use at Index Date								
Influenza								
Pneumococcal								
Tetanus- Diphtheria-Pertussis								

*RZV=recombinant zoster vaccine; SD=standard deviation; Cell sizes will be supressed if the total number is <11; RZV Dose 1 includes those who also got Dose 2; **Allows one calendar month gap in enrollment

Table Shell 8. Case counts and risk estimates for the SCRI of GBS*

Type of analysis	Doses included, restrictions	Dose 1 CW censored at receipt of Dose 2	CW length	No. cases in RW*	No. cases in CW*	RR* (95% CI)	AR* (95% CI)
Primary Analysis (Dose 1 CW censored at receipt of Dose 2)	Doses 1 and 2, without distinguishing	Yes	Variable Mean =				
Sensitivity, subset of Primary Analysis	Doses 1 and 2, without distinguishing, restricted to 2-dose recipients with 60-183-days between doses	Yes	Variable Mean =				
Secondary Analysis (3-wk CW for both doses)	Doses 1 and 2, without distinguishing	No	21 days				
Secondary Analysis (6-wk CW for both doses)	Doses 1 and 2, without distinguishing	No	42 days				
Sensitivity, subset of Secondary Analysis (6-wk CW Dose 1)	Dose 1 only	No	42 days				
Sensitivity, subset of Secondary Analysis (6-wk CW Dose 2)	Dose 2 only	No	42 days				
Sensitivity, subset of Primary Analysis (exclude cases of prior respiratory or gastrointestinal infection)**	Doses 1 and 2, without distinguishing	Yes	Variable Mean=				
Seasonality Adjusted Primary Analysis	Dose 1 and 2, without distinguishing	Yes	Variable Mean=				

Type of analysis	Doses included, restrictions	Dose 1 CW censored at receipt of Dose 2	CW length	No. cases in RW*	No. cases in CW*	RR* (95% CI)	AR* (95% CI)
COVID-19 Sensitivity for Primary analysis, (Excluding any doses administered on or after November. 8, 2019 [and their GBS cases])**	Doses 1 and 2, without distinguishing	Yes	Variable Mean=				

*RW is Days 1-42 after vaccination; CW starts on Day 43. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist; SCRI=self-controlled risk interval; GBS=Guillain-Barré Syndrome; RW=risk window, CW=control window, RR=relative risk, AR=attributable risk
** RR and AR will be reported if sufficient numbers remain after exclusion,otherwise only the number of cases in the RW and CW will be reported.; only the primary analysis will be conducted;

Table Shell 9. Case counts and risk estimates for the SCRI* analyses of gout

Type of analysis	Doses included, restrictions	Dose 1 CW censored at receipt of Dose 2	CW length	No. cases in RW*	No. cases in CW*	RR* (95% CI)	AR* (95% CI)
Primary Analysis (Dose 1 CW censored at receipt of Dose 2)	Doses 1 and 2, without distinguishing	Yes	Variable Mean =				
Sensitivity, subset of Primary Analysis	Doses 1 and 2, without distinguishing, restricted to 2-dose recipients with 60-183-days between doses	Yes	Variable Mean =				
Secondary Analysis (30-d CW for both doses)	Doses 1 and 2, without distinguishing	No	30 days				
Sensitivity, subset of Secondary Analysis	Dose 1 only	No	30 days				
Sensitivity, subset of Secondary Analysis	Dose 2 only	No	30 days				
Seasonality Adjusted Primary Analysis	Dose 1 and 2, without distinguishing	Yes	Variable Mean=				
COVID-19 Sensitivity for Primary analysis, (Excluding any doses administered on or after December. 2, 2019 [and their gout cases])**	Dose 1 and 2, without distinguishing	Yes	Variable Mean=				

* RW is Days 1-30 after vaccination, CW starts on Day 31. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist; SCRI=self-controlled risk interval; RW=risk window, CW=control window, RR=relative risk, AR=attributable risk
** RR and AR will be reported if sufficient numbers remain after exclusion; otherwise only the number of cases in the RW and CW will be reported ; only the primary analysis will be conducted.

Table Shell 10. Case counts and risk estimates for the SCRI analyses of SVT*

Type of analysis	Doses included, restrictions	Dose 1 CW censored at receipt of Dose 2	CW length	No. cases in RW*	No. cases in CW*	RR* (95% CI)	AR* (95% CI)
Primary Analysis (Dose 1 CW censored at receipt of Dose 2)	Doses 1 and 2, without distinguishing	Yes	Variable Mean =				
Sensitivity, subset of Primary Analysis	Doses 1 and 2, without distinguishing, restricted to 2-dose recipients with 60-183-days between doses	Yes	Variable Mean =				
Secondary Analysis (30-d CW for both doses)	Doses 1 and 2, without distinguishing	No	30 days				
Sensitivity, subset of Secondary Analysis	Dose 1 only	No	30 days				
Sensitivity, subset of Secondary Analysis	Dose 2 only	No	30 days				
COVID-19 Sensitivity for Primary analysis, (Excluding any doses administered on or after December. 2, 2019 [and their SVT cases])**	Doses 1 and 2, without distinguishing	Yes	Variable Mean =				

*RW is Days 1-30 after vaccination, CW starts on Day 31. Post-Dose 1 cases to be excluded from all analyses if Dose 2 received within Dose 1 RW+1 day—no Dose 1 CW would exist. SCRI=self-controlled risk interval; SVT=supraventricular tachycardia; RW=risk window, CW=control window, RR=relative risk, AR=attributable risk; ** RR and AR analysis will be conducted if sufficient numbers remain after exclusion; otherwise only the number of cases in the RW and CW will be reported; only the primary analysis will be conducted.

Table Shell 11. Risk estimates for cohort design analysis of GCA with a risk window of 183 days after the index date*

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Primary Analysis - Separate analysis of Dose 1	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
Primary Analysis - Separate analysis of Dose 2	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				
Sensitivity of Primary Analysis; HOI definition sensitivity - Separate analysis of Dose 1 **	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
Sensitivity of Primary Analysis; HOI definition sensitivity - Separate analysis of Dose 2**	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				
Supplemental Analysis of Primary Analysis; exclude comparators who received RZV - Separate analysis of Dose 1	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
Supplemental Analysis of Primary Analysis; exclude comparators who received RZV - Separate analysis of Dose 2	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Secondary Analysis - Combined Dose 1 and Dose 2 for a single risk estimate	Dose 1 and Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after Dose 2; days 1-183 after preventive care visit	Any RZV dose				
		Unvaccinated comparator (ref)				
Secondary Analysis- Time-varying dose analysis for separate Dose 1 and Dose 2 risk estimates	Dose 1 and Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		RZV Dose 2				
		Comparator (ref)				
Sensitivity Analysis-Subset of combined Dose 1 and Dose 2 analysis	Dose 1 and Dose 2 RZV exposed with 2-6-month dose spacing* vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 1 and Dose 2				
		Comparator (ref)				
Sensitivity Analysis – Subset of time-varying separate Dose 1 and Dose 2 analysis	Dose 1 and Dose 2 RZV exposed with 2-6-month dose spacing* vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		RZV Dose 2				
		Comparator (ref)				
COVID-19 Sensitivity for Primary analysis, (February 1, 2020 included as a censoring event) - Separate analysis of Dose 1 **	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
COVID-19 Sensitivity for Primary analysis, (February 1, 2020 included as a censoring event) - Separate analysis of Dose 2**	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				

*GCA=giant cell arteritis; RZV=recombinant zoster vaccine; index date = date of vaccination for Dose 1 and Dose 2 for RZV exposed; date of preventive care visit for unvaccinated comparator; RW=risk window; Dose compliant per US schedule of 2-6 months spacing between Dose 1 and Dose 2; ** Hazard ratio and adjusted hazard ratio will be reported if sufficient numbers remain after exclusion; Otherwise only no.of events and person years will be reported. Only the primary analysis will be conducted.

Table Shell 12. Risk estimates for cohort design analysis of PMR with a risk window of 183 days after the index date*

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Primary Analysis - Separate analysis of Dose 1	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
Primary Analysis - Separate analysis of Dose 2	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				
Supplemental Analysis of Primary Analysis; exclude comparators who received RZV - Separate analysis of Dose 1	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
Supplemental Analysis of Primary Analysis;	Dose 1 RZV exposed vs.	RZV Dose 2				

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
exclude comparators who received RZV - Separate analysis of Dose 2	unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	Unvaccinated comparator (ref)				
Secondary Analysis - Combined Dose 1 and Dose 2 for a single risk estimate	Dose 1 and Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after Dose 2; days 1-183 after preventive care visit	Any RZV dose				
		Unvaccinated comparator (ref)				
Secondary Analysis- Time-varying dose analysis for separate Dose 1 and Dose 2 risk estimates	Dose 1 and Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		RZV Dose 2				
		Comparator (ref)				
Sensitivity Analysis-Subset of combined Dose 1 and Dose 2 analysis	Dose 1 and Dose 2 RZV exposed with 2-6-month dose spacing* vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 1 and Dose 2				
		Comparator (ref)				
Sensitivity Analysis- Subset of time-varying separate Dose 1 and Dose 2 analysis	Dose 1 and Dose 2 RZV exposed with 2-6-month dose spacing* vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		RZV Dose 2				
		Comparator (ref)				
COVID-19 Sensitivity for	Dose 1 RZV exposed vs.	RZV Dose 1				

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Primary analysis, (February 1, 2020 included as a censoring event) - Separate analysis of Dose 1**	unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	Unvaccinated comparator (ref)				
COVID-19 Sensitivity for Primary analysis, (February 1, 2020 included as a censoring event) - Separate analysis of Dose 2**	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				

*PMR=polymyalgia rheumatica; RZV=recombinant zoster vaccine; index date = date of vaccination for Dose 1 and Dose 2 for RZV exposed; date of preventive care visit for unvaccinated comparator; RW=risk window; Dose compliant per US schedule of 2-6 months spacing between Dose 1 and Dose 2; ** Hazard ratio and adjusted hazard ratio will be reported if sufficient numbers remain after exclusion; Otherwise only no.of events and person years will be reported. only the primary analysis will be conducted.

Table Shell 13. Risk estimates for cohort design analysis of ION with a risk window of 183 days after the index date*

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Primary Analysis - Separate analysis of Dose 1	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
Primary Analysis - Separate analysis of Dose 2	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				
Sensitivity of Primary Analysis; HOI definition sensitivity - Separate analysis of Dose 1**	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Sensitivity of Primary Analysis; HOI definition sensitivity - Separate analysis of Dose 2**	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				
Supplemental Analysis of Primary Analysis; exclude comparators who received RZV - Separate analysis of Dose 1	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
Supplemental Analysis of Primary Analysis; exclude comparators who received RZV - Separate analysis of Dose 2	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				
Secondary Analysis - Combined Dose 1 and Dose 2 for a single risk estimate	Dose 1 and Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after Dose 2; days 1-183 after preventive care visit	Any RZV dose				
		Unvaccinated comparator (ref)				
Secondary Analysis- Time-varying dose analysis for separate Dose 1 and Dose 2 risk estimates	Dose 1 and Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		RZV Dose 2				
		Comparator (ref)				
Sensitivity Analysis-Subset of combined Dose 1 and Dose 2 analysis	Dose 1 and Dose 2 RZV exposed with 2-6-month dose spacing* vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after	RZV Dose 1 and Dose 2				
		Comparator (ref)				

Analysis Type	Comparison Groups and RW*	Comparator cohorts	No. of events	Person years of follow-up	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
	Dose 2; days 1-183 after preventive care visit					
Sensitivity Analysis- Subset of time-varying separate Dose 1 and Dose 2 analysis	Dose 1 and Dose 2 RZV exposed with 2-6-month dose spacing* vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		RZV Dose 2				
		Comparator (ref)				
COVID-19 Sensitivity for Primary analysis, (February 1, 2020 included as a censoring event) - Separate analysis of Dose 1**	Dose 1 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 1; days 1-183 after preventive care visit	RZV Dose 1				
		Unvaccinated comparator (ref)				
COVID-19 Sensitivity for Primary analysis, (February 1, 2020 included as a censoring event)- Separate analysis of Dose 2**	Dose 2 RZV exposed vs. unvaccinated comparator RW*: days 1-183 after Dose 2; days 1-183 after preventive care visit	RZV Dose 2				
		Unvaccinated comparator (ref)				

*ION=ischemic optic neuropathy; RZV=recombinant zoster vaccine; index date = date of vaccination for Dose 1 and Dose 2 for RZV exposed; date of preventive care visit for unvaccinated comparator; RW=risk window; Dose compliant per US schedule of 2-6 months spacing between Dose 1 and Dose 2; ** Hazard ratio and adjusted hazard ratio will be reported if sufficient numbers remain after exclusion; Otherwise only no.of events and person years will be reported. only the primary analysis will be conducted.

- **Figure Shell 1. Distribution of RZV Vaccination Over Time**
- **Supplemental Analysis Table Shell 14. Bias Analysis for Unmeasured Confounders, Cohort Design**

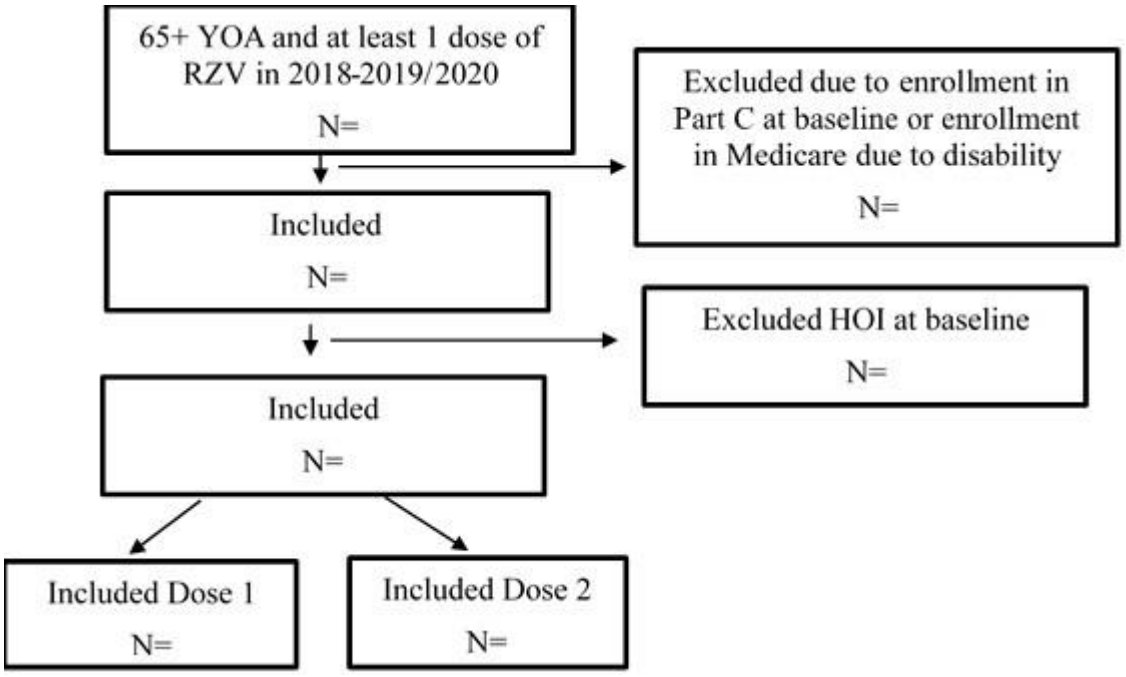
*Supplemental analysis table shell 14 will be included for PMR, GCA, ION separately

- **Supplemental Figure Shell 2. Propensity Score Distribution for each HOI, Cohort Design**

*Figure shell 2 will be included for PMR, GCA, ION separately and only if propensity score methods are implemented

- **Supplemental Figure Shells 3. Consort Flow Chart of Analytical Cohort for Each HOI and preventative care comparators**

*Figure shell 3 below will be included for each HOI separately for RZV vaccinated (and preventative care comparators in the cohort design). The structure is an example and may be updated or varied based on the criteria required for the HOI or specific analysis.



16.3. Appendix C. Temporal Scan

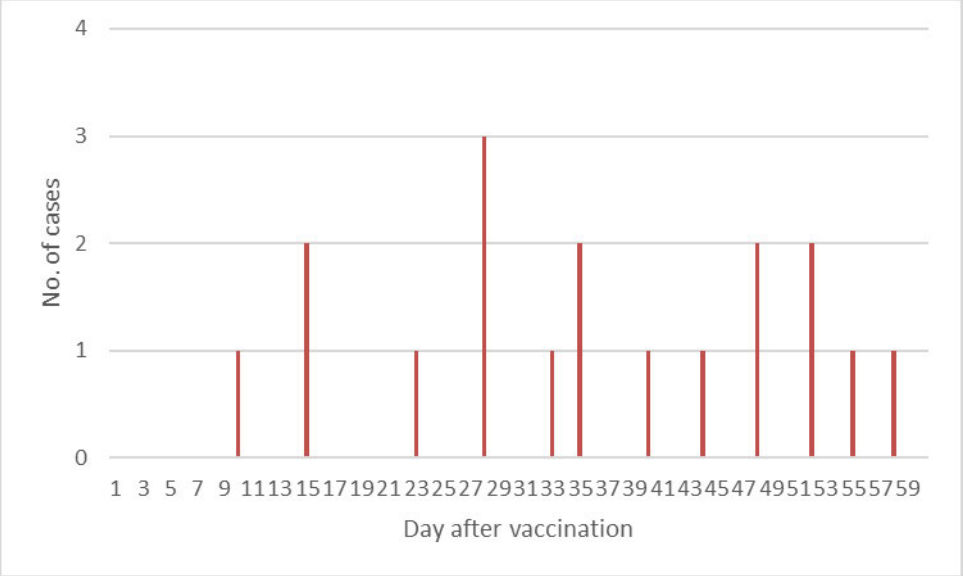
Number of cases by day after vaccination (for Dose 1 and, separately, for Doses 1 and 2 together) will be graphed for all HOIs, with the following specifics:

HOI	Event	Follow-up (length of x axis)
GBS*	Onset of symptoms	84 days
Gout	Diagnosis in administrative data	60 days
SVT*	Diagnosis in administrative data	60 days
PMR*	Diagnosis in administrative data	183 days
GCA*	Diagnosis in administrative data	183 days
ION*	Diagnosis in administrative data	183 days

*GBS=Guillain-Barre Syndrome; SVT=supraventricular tachycardia; PMR=polymyalgia rheumatica; GCA=giant cell arteritis; ION=ischemic optic neuropathy

An example for gout is shown below.

Figure Shell 1 - 6. Distribution of gout cases by day of diagnosis after vaccination with RZV Dose 1 [example only—not real data]. *This figure will be replicated in the study report for each HOI



Supplemental Analysis Table Shell 1 - 6. Temporal Scan for Clustering of all HOIs
*****This table will be replicated in the study report for each HOI

16.4. Appendix D. Operational Definitions of the Covariates

Category	Variable Description	Variables in SAP supplement	Data Source	Operational Definitions		
				Binary	Categorical	Continuous
Demographic	Age at vaccination or preventive care visit (year)	AGE_RZV_1 AGE_RZV_2 AGE_GRP_RZV_1 AGE_GRP_RZV_2 AGE_INDEX AGE_GRP_INDEX	MBSF		65-69 (1) 70-74 (2) 75-79 (3) 80-84 (4) 85+ (5)	Year of age
	Sex	SEX_IDENT_CD	MBSF	Male (1) Female (0)		
	Race and ethnicity	BENE_RACE_CD	MBSF		For descriptive analysis: White (1) Black (2) Hispanic (5) Asian (4) North American Native (6) Other (3)	
	Region of residence within US	CENSUS_REGION	MBSF		4 US regions & Other: Northeast (1) Midwest (2) South (3) West (4) Other (5)	
Health service variables	Calendar date of vaccination or preventive care visit	DT_RZV_1 DT_RZV_2 DT_INDEX	PDE file, outpatient or carrier claim			Date
	RZV dose number	RZV_NUM EXPOSED	PDE file, outpatient or carrier claim	Any exposure (1) Unexposed (0)	Dose 1 (1) Dose 2 (2) Unexposed (0)	
	Admissions to SNFs	HSU_SNF_D1 HSU_SNF_D2 HSU_SNF	SNF claim	Any use (1) No use (0)		
	No. of hospitalizations	HSU_HOSPITAL_D1 HSU_HOSPITAL_D2 HSU_HOSPITAL	Inpatient claim			Total No. (≥0)
	No. of ED visits	HSU_ED_D1 HSU_ED_D2 HSU_ED	Inpatient claim			Total No. (≥0)
	Durable Medical Equipment (DME) use	HSU_DME_D1 HSU_DME_D2 HSU_DME	SNF, inpatient, outpatient or carrier claim	Any use (1) No use (0)		

Category	Variable Description	Variables in SAP supplement	Data Source	Operational Definitions		
				Binary	Categorical	Continuous
	Hospice Use	HSU_HOSPICE_D1 HSU_ HOSPICE _D2 HSU_ HOSPICE	Hospice claim	Any use (1) No use (0)		
	Home Health use	HSU_HOMEHLTH_ D1 HSU_ HOMEHLTH _D2 HSU_ HOMEHLTH	Home Health claim	Any use (1) No use (0)		
	Dermatology visit	HSU_DERM_D1 HSU_DERM _D2 HSU_DERM	Outpatient or carrier claim	Any use (1) No use (0)		
	Ophthalmology visit	HSU_OPHTH_D1 HSU_OPHTH _D2 HSU_OPHTH	Outpatient or carrier claim	Any use (1) No use (0)		
Preventive care services	Influenza vaccine	V_FLU_D1 V_FLU_D2 V_FLU	PDE file, outpatient claim, or carrier file	Any use (1) No use (0)		
	Pneumococcal vaccine	V_PNEUMO_D1 V_ PNEUMO _D2 V_ PNEUMO	PDE file, outpatient claim, or carrier file	Any use (1) No use (0)		
	Tdap vaccine	V_TDAP_D1 V_TDAP_D2 V_TDAP	PDE file, outpatient claim, or carrier file	Any use (1) No use (0)		
General medical comorbidities	Diabetes mellitus	CHRONIC_DIBTS_ D1 CHRONIC_DIBTS_ D2 CHRONIC_DIBTS	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Alzheimer's, Related Disorders or Senile Dementia	CHRONIC_AZH_D1 CHRONIC_AZH_D2 CHRONIC_AZH	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Chronic kidney disease	CHRONIC_CKD_D 1 CHRONIC_CKD_D 2 CHRONIC_CKD	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Chronic lung disease	CHRONIC_COPD_ D1 CHRONIC_COPD_ D2 CHRONIC_COPD	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		

Category	Variable Description	Variables in SAP supplement	Data Source	Operational Definitions		
				Binary	Categorical	Continuous
	Congestive heart failure	CHRONIC_CHF_D1 CHRONIC_CHF_D2 CHRONIC_CHF	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Ischemic heart disease	CHRONIC_IHD_D1 CHRONIC_IHD_D2 CHRONIC_IHD	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Chronic liver disease	CHRONIC_CLD_D1 CHRONIC_CLD_D2 CHRONIC_CLD	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Stroke/Transient Ischemic Attack	CHRONIC_STROK_D1 CHRONIC_STROK_D1 CHRONIC_STROK	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
Immunocompromised conditions	Organ transplant	CHRONIC_OTRSPLT_D1 CHRONIC_OTRSPLT_D2 CHRONIC_OTRSPLT	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Hematopoietic cell transplant	CHRONIC_HCTRSPLT_D1 CHRONIC_HCTRSPLT_D2 CHRONIC_HCTRSPLT	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any procedure (1) No procedure (0)		
	Hematologic or solid malignancy with recent receipt of chemotherapy	CHRONIC_MALIG_D1 CHRONIC_MALIG_D2 CHRONIC_MALIG CHRONIC_CHEMO_D1 CHRONIC_CHEMO_D2 CHRONIC_CHEMO CHRONIC_CHEMO_MALIG_D1	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		

Category	Variable Description	Variables in SAP supplement	Data Source	Operational Definitions		
				Binary	Categorical	Continuous
		CHRONIC_CHEMO_MALIG_D2 CHRONIC_CHEMO_MALIG				
	HIV infection	CHRONIC_HIV_D1 CHRONIC_HIV_D2 CHRONIC_HIV	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Rheumatoid Arthritis	IMMUNO_RA_D1 IMMUNO_RA_D2 IMMUNO_RA	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Inflammatory Bowel Disease-Crohn's Disease	IMMUNO_CROHN_D1 IMMUNO_CROHN_D2 IMMUNO_CROHN	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Inflammatory Bowel Disease-Colitis	IMMUNO_COLITIS_D1 IMMUNO_COLITIS_D2 IMMUNO_COLITIS	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Lupus	IMMUNO_LUPUS_D1 IMMUNO_LUPUS_D2 IMMUNO_LUPUS	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Multiple Sclerosis	IMMUNO_MS_D1 IMMUNO_MS_D2 IMMUNO_MS	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Psoriasis/Psoriatic Arthritis	IMMUNO_PSOR_D1 IMMUNO_PSOR_D2 IMMUNO_PSOR	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		

Category	Variable Description	Variables in SAP supplement	Data Source	Operational Definitions		
				Binary	Categorical	Continuous
Specific to PMR/GCA	Gout	HOI_GOUT_PRE	Inpatient, outpatient, carrier or PDE claim	Any diagnosis (1) No diagnosis (0)		
	Checkpoint inhibitors	CHKPT_INHIB_D1 CHKPT_INHIB_D2 CHKPT_INHIB	PDE file	Any use (1) No use (0)		
Medical comorbidities specific to ION	Obstructive sleep apnea	HOI_ION_OSA	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Hypertension	HOI_ION_HTN	Inpatient, outpatient, carrier, SNF, Home Health or Hospice claim	Any diagnosis (1) No diagnosis (0)		
	Amiodarone	HOI_ION_AMIODRNE	PDE file	Any use (1) No use (0)		
	Phosphodiesterase type 5 inhibitors	HOI_ION_PHOSDINHIB	PDE file	Any use (1) No use (0)		
Specific to GBS	Respiratory or Gastrointestinal infection	HOI_GBS_RESPGI_PRE	Inpatient, outpatient or carrier claim	Any diagnosis (1) No diagnosis (0)		