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