ANNEX 2 ABSTRACT

Title	A targeted safety study, EPI-ZOSTER-030 VS US DB, to evaluate the safety of *Shingrix* in adults ≥50 years of age in the United States.
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Keywords	Recombinant zoster vaccine (RZV), herpes zoster, Guillain-Barré syndrome, gout, supraventricular tachycardia, polymyalgia rheymatica, giant cell arteritis, ischemic optic neuropathy, vaccine safety
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Rationale and background

Pooled safety analysis of clinical data from two placebo-controlled Phase 3 studies of recombinant zoster vaccine (RZV) identified numerical differences in the occurrence of gout, supraventricular tachycardia (SVT), polymyalgia rheumatica (PMR), giant cell arteritis (GCA) and ischemic optic neuropathy (ION). Other safety surveillance mechanisms detected a statistical signal for Guillain-Barré syndrome (GBS), which has since been observed among Medicare beneficiaries aged 65 years or older. Further investigation in a large data source is needed to evaluate these potential associations in the population aged 50 years and older.

Research questions and objectives

Primary objectives

- To assess the risk of new-onset GBS within 42 days after RZV vaccination
- To assess the risk of new-onset gout within 30 days after RZV vaccination

- To assess the risk of new-onset PMR within 183 days after RZV vaccination
- To assess the risk of new-onset GCA within 183 days after RZV vaccination

Secondary objectives

- To assess the risk of new-onset SVT within 30 days after RZV vaccination
- To assess the risk of new-onset ION within 183 days after RZV vaccination

Study design

We used a self-controlled risk-interval design with HOI-specific risk and control windows to assess the risk of new-onset GBS, gout, and SVT. We used a cohort design to compare the hazard of new-onset PMR, GCA, and ION (separate analyses) after RZV exposure with the hazard after preventive care visits among those who had never received RZV. Potential confounding was addressed in the cohort design using inverse probability of treatment weighting (IPTW).

Setting

The study population included US commercially-insured individuals ≥50 years of age at the time of their qualifying visit date (i.e., RZV vaccination date or preventive care visit date).

Subjects and study size, including dropouts

The primary GBS analysis included 44 claims-based GBS cases. The primary gout analysis included 302 claims-based gout cases. The primary SVT analysis included 64 confirmed SVT cases. After implementing 1% asymmetric trimming, the analytical study sample for PMR included 300,666 RZV Dose 1-exposed individuals, 166,740 Dose 2-exposed individuals, and 1,159,359 unvaccinated comparators. The analytic study sample for GCA after 1% propensity score trimming included 640,398 RZV Dose 1-exposed individuals, 439,822 RZV Dose 2, and 2,515,736 unvaccinated comparators. For ION, the analytic study sample after 1% propensity score trimming included 94,451 RZV Dose 1-exposed individuals, 71,736 RZV Dose 2, and 210,952 unvaccinated comparators.

Variables and data sources

This study was conducted using health plan data held by five Research Partners (RPs) that participate in the Food and Drug Administration (FDA's) Sentinel System. All exposure and covariate data was identified from claims, and outcomes were initially identified using claims-based algorithms. Events other than gout were adjudicated via medical record review.

Results

The analysis of GBS identified 44 GBS cases from claims, and found no evidence of an increased risk of GBS following RZV (Risk ratio [RR]=1.16, 95% CI: 0.61, 2.21). The analysis of gout identified 302 patients from claims and found no evidence of an increased risk of gout following RZV (RR= 1.03, 95% CI: 0.81, 1.29). The analysis of SVT included 64 confirmed cases, and found an elevated but not statistically significant increased risk of SVT following RZV (RR=1.66, 95% CI: 0.98, 2.89).

The analysis of PMR detected no increased risk of claims-based PMR in the 183 days following RZV versus unvaccinated comparators (Dose 1 hazard ratio [HR]=0.66 [95% CI: 0.53, 0.80], Dose 2 HR=0.54 [95% CI: 0.40, 0.71]). The analysis of GCA detected a statistically significant increase in the risk of GCA in the 183 days following RZV Dose 2 relative to the 183 days following a preventive care visit among unvaccinated comparators (HR=3.11, 95% CI: 1.23, 7.90). The effect estimate for GCA following Dose 1 was elevated but not statistically significant (HR = 1.67, 95% CI: 0.63, 4.46). The analysis of ION detected no increased risk of chart-confirmed or -probable ION in the 183 days following RZV Dose 1 (HR=0.71; 95% CI: 0.32, 1.57) or Dose 2 (HR=0.13; 95% CI: 0.03, 0.55) versus unvaccinated comparators.

Discussion

The precision of primary analysis results was limited by low case counts for most health outcome of interests (HOIs). The findings for GBS in this study in commercially insured adults ≥50 years were not statistically significant, in contrast to other studies in older (≥65 years) Medicare populations, suggesting the possibility of differing effect by age or population. GCA, SVT, and ION are less rare, but these primary analyses included only adjudicated cases. For each outcome, approximately 50% of cases had unretrievable charts, and some retrieved charts included insufficient information for adjudication, resulting in low counts of confirmed cases for analyses. The findings for the GCA, SVT, and ION analyses that included only chart-confirmed (or -probable, for ION) cases must be considered in the context of the random error introduced by availability of complete charts for only a small number of claims-based events. The findings for the claims-based PMR and gout analyses should also be considered in the context of potential outcome misclassification.

Conclusion

This study detected an increased risk of GCA following RZV Dose 2. This study did not find evidence of an increased risk of GBS or gout following RZV, with near-null, non-statistically significant, effect estimates. This study found evidence suggestive of a potential increased risk of SVT following RZV exposure, although this finding was not statistically significant. No evidence of an increased risk of PMR or ION following RZV exposure was observed.