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# Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials

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**Abstract**

**Background**: The ZOE-50 (NCT01165177) and ZOE-70 (NCT01165229) phase 3 clinical trials showed that the adjuvanted recombinant zoster vaccine (RZV) was ≥90% efficacious in preventing herpes zoster in adults. Here we present a comprehensive overview of the safety data from these studies.

**Methods**: Adults aged ≥50 (ZOE-50) and ≥70 (ZOE-70) years were randomly vaccinated with RZV or placebo. Safety analyses were performed on the pooled total vaccinated cohort, consisting of participants receiving at least one dose of RZV or placebo. Solicited and unsolicited adverse events (AEs) were collected for 7 and 30 days after each vaccination, respectively. Serious AEs (SAEs) were collected from the first vaccination until 12 months post-last dose. Fatal AEs, vaccination-related SAEs, and potential immune-mediated diseases (pIMDs) were collected during the entire study period.

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**Conclusions**: No safety concerns arose, supporting the favorable benefit-risk profile of RZV.

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# Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials ☆

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*Abbreviations:* HZ, herpes zoster; RZV, adjuvanted recombinant zoster vaccine; VZV, varicella-zoster virus; gE, VZV glycoprotein E; AE, adverse event; SAE, serious AE; pIMD, potential immune-mediated disease; D, day; M, month; Y, year; YOA, years of age; ZOE-50/70, the pivotal RZV efficacy trials in adults ≥50/≥70 YOA; MedDRA, medical dictionary for regulatory activities; SOC, system organ class; PT, preferred term; CI, confidence interval; RR, relative risk; AML, acute myeloid leukemia.

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ABSTRACT

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*Methods:* Adults aged ≥50 (ZOE-50) and ≥70 (ZOE-70) years were randomly vaccinated with RZV or placebo. Safety analyses were performed on the pooled total vaccinated cohort, consisting of participants receiving at least one dose of RZV or placebo. Solicited and unsolicited adverse events (AEs) were collected for 7 and 30 days after each vaccination, respectively. Serious AEs (SAEs) were collected from the first vaccination until 12 months post-last dose. Fatal AEs, vaccination-related SAEs, and potential immune-mediated diseases (pIMDs) were collected during the entire study period.
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*Conclusions:* No safety concerns arose, supporting the favorable benefit-risk profile of RZV.


## 1. Introduction

Herpes zoster (HZ) results from reactivation of latent varicella-zoster virus (VZV) in the dorsal root ganglia, usually years after primary VZV infection. HZ is typically characterized by a unilateral dermatomal vesicular rash, generally accompanied by pain. Its most common complication is postherpetic neuralgia, a chronic pain that can persist for months or years after the rash has resolved [1]. HZ incidence increases substantially with age, from 3 to 5 cases per 1000 person-years in the general population of all ages [2], to 4–8 cases per 1000 person-years in adults ≥50 years of age (YOA) and 8–12 cases per 1000 person-years for those ≥80 YOA [2,3].

An adjuvanted recombinant zoster vaccine, RZV (Shingrix, GSK), consisting of a truncated form of VZV glycoprotein E (gE) and the $AS01_B$ adjuvant system, is currently licensed in different regions worldwide for the prevention of HZ in adults ≥50 YOA. Two pivotal phase 3 efficacy trials (ZOE-50/70) demonstrated that RZV reduces the risk of HZ by over 90% in all age groups among adults ≥50YOA [4,5]. Although the vaccine induces transient local and systemic reactions, no safety concerns were identified during these clinical trials. In both studies, serious adverse events (SAEs) and potential immune-mediated diseases (pIMDs) were balanced between participants in the RZV and Placebo groups [4,5].

The similar enrollment criteria, study procedures, and safety follow-up period for the ZOE-50/70 trials allowed us to pool study data. We present here a comprehensive analysis of the safety data from pooled ZOE 50/70 studies.

## 2. Methods

### 2.1. Study design and participants

ZOE-50 (NCT01165177) and ZOE-70 (NCT01165229) were phase 3, randomized, placebo-controlled, observer-blinded clinical trials

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conducted concurrently at the same sites in 18 countries in Europe, North and South America, Asia and Australia. Adults aged ≥ 50 YOA (ZOE-50) or ≥ 70 YOA (ZOE-70) were randomized and vaccinated with RZV or placebo (Supplementary Fig. 1). A full list of eligibility criteria was previously presented [4,5], and is provided here in the Supplementary Material. The two studies were conducted in an identical manner, and adults ≥70 YOA were randomly enrolled to participate in either the ZOE-50 or ZOE-70 study. Additional study design details are presented in the primary publications [4,5]. The clinical study reports are available at http://www.gsk-clinicalstudyregister.com (IDs 110390 and 113077). Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

### 2.2. Study vaccines

RZV contains 50 μg of gE antigen and the GSK proprietary $AS01_B$ Adjuvant System (containing 50 μg of 3-O-desacyl-4′-monophosphoryl lipid A, 50 μg of *Quillaja saponaria* Molina, fraction 21 [licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation] and liposome). Placebo consisted of 0.5 mL 150 mM NaCl solution.

### 2.3. Collection of safety data

Solicited adverse events (AEs) were collected for 7 days (D) after each vaccination (D0-D6) in the reactogenicity sub-cohort, consisting of participants who completed diary cards; severe AEs are described in the Supplementary Material. Unsolicited AEs were collected for 30D after each vaccination and graded on a scale from 1 (mild: not interfering with everyday activities) to 3 (severe: significant at rest and preventing normal everyday activities). Unsolicited AEs comprised both SAEs and non-serious AEs, including all local and systemic reactions reported by participants who were not part of the reactogenicity sub-cohort. Unsolicited AEs with medically attended visits (defined as hospitalizations, emergency room visits, or visits to or from medical personnel), other than routine health care visits, were recorded from first vaccine dose up to 6 months (M) post-last vaccination. SAEs were collected from the first vaccine dose up to 1 year (Y) post-last vaccination. Fatal AEs, SAEs considered causally related to study vaccination by the investigators, and pIMDs (new onset and possible exacerbations) were collected during the entire study period. SAEs were defined according to standard reporting guidelines [6]. AEs were coded by Medical Dictionary for Regulatory Activities (MedDRA) dictionary both per System Organ Class (SOC) and Preferred Term (PT) [7]. Local AEs were considered related to study vaccination. Relatedness of other AEs was determined based on study investigators clinical judgment, in a blinded manner. pIMDs were defined as a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest that may or may not have an autoimmune etiology. AEs to be recorded as pIMDs were pre-defined in the study protocol (Supplementary Table 1) and, in addition, study investigators were instructed to use their medical judgment to determine whether other events could fall in this category and to record them as pIMDs [8].

### 2.4. Statistical analysis

Safety analyses were performed on the pooled total vaccinated cohort, consisting of participants who received at least one dose of RZV/placebo. Analyses of unsolicited AEs, SAEs, and pIMDs were descriptive and, for each of these, percentages of participants with at least one event were calculated with their exact 95% Confidence Intervals (CIs) both per SOC and PT. Analyses of SAEs, fatal AEs, and pIMDs were performed up to 30D and 1Y post-last dose. In addition, analyses of fatal AEs and pIMDs were also performed during the entire study period. Exploratory analyses of unsolicited AEs reported within the 30D post-vaccination period, SAEs and pIMDs reported within 1Y post-last dose assessed the relative risks (RRs) and frequencies of selected events of interest using MedDRA queries. RRs and their 95% CIs were calculated by Exact Tests conditional to the number of cases. Additional details are presented in the Supplementary Material.

## 3. Results

### 3.1. Study population

A total of 14,645 RZV and 14,660 placebo recipients were included in the pooled analysis. The median follow-up duration was 4.4Y. The mean age of the participants was 68.6Y; 58.2% of those were female. Most (73.7%) participants were white/Caucasian. Demographic characteristics were comparable between groups (Supplementary Table 2).

### 3.2. Reactogenicity

In line with previously reported reactogenicity results from the ZOE-50/70 studies [4,5], RZV was more reactogenic than placebo in the pooled reactogenicity sub-cohort. Pain was the most frequent solicited local symptom reported after 68.1% (95% CI: 67.1–69.0) of documented doses in the RZV group and after 6.9% (95% CI: 6.4–7.4) in the Placebo group. Grade 3 pain was reported after 3.8% (95% CI: 3.5–4.3) of documented doses in the RZV group and after 0.2% (95% CI: 0.1–0.3) in the Placebo group. In the RZV group, the most frequently reported solicited general symptoms were myalgia and fatigue, reported after 32.9% (95% CI: 31.9–33.8) and 32.2% (95% CI: 31.3–33.2) of doses, respectively. Grade 3 fatigue was reported after 3.0% (95% CI: 2.6–3.3) of documented doses in the RZV group and after 0.5% (95% CI: 0.4–0.7) in the placebo group (Supplementary Fig. 2). Local and general symptoms in the RZV group were mostly mild to moderate in intensity and transient (median duration was of 3 days or less for local and 2 days or less for general symptoms, including grade 3 symptoms). Overall, there were no differences in the proportions of RZV recipients reporting any grade or grade 3 solicited local events between dose 1 and dose 2. All-grade solicited general symptoms tended to be more frequent after dose 2 compared to dose 1.

### 3.3. Unsolicited adverse events

The percentage of participants reporting unsolicited AEs during 30D post-vaccination was greater for RZV than for placebo recipients (7393 [50.5%] versus 4689 [32.0%]; RR: 1.58 [95%CI:1.52–1.64]; $p < 0.0001$). RZV recipients reported unsolicited AEs more frequently, irrespective of age group, gender, or race (Table 1). Unsolicited AEs more frequently reported by RZV recipients were injection site and general symptoms that were reported as solicited reactions in the reactogenicity sub-cohort (Table 1). More RZV than placebo recipients reported unsolicited AEs during the first week (D0-D6) post-vaccination (5861 [40.0%] versus 2230 [15.2%]). Unsolicited AEs were balanced between groups during the subsequent 23D (D7-D29) post-vaccination period (3,076 [21.0%] versus 3,280 [22.4%]) (Fig. 1).

Unsolicited AEs not categorized as solicited AEs in the reactogenicity sub-cohort, those occurring in >1% of RZV recipients and more frequently than in placebo recipients were, by PT: injection site pruritus, pain, injection site warmth, pain in extremity, malaise, arthralgia, back pain, dizziness, upper respiratory tract infection, and oropharyngeal pain (Table 1).

**Table 1**
Unsolicited Adverse Events reported within 30 days after vaccination (Pooled Total Vaccinated Cohort).

| | RZV (N = 14,645) | | | | Placebo (N = 14,660) | | | | Relative Risk | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 95% CI | | | | 95% CI | | | | 95% CI | | | |
| | n | % | LL | UL | n | % | LL | UL | RR | LL | UL | |
| Unsolicited adverse events (any grade) | 7393 | 50.5 | 49.67 | 51.29 | 4689 | 32 | 31.23 | 32.75 | 1.58 | 1.52 | 1.64 | *** |
| Grade 3 | 1094 | 7.5 | 7.0 | 7.9 | 563 | 3.8 | 3.5 | 4.2 | | | | |
| Considered related | 5052 | 34.5 | 33.7 | 35.3 | 968 | 6.6 | 6.2 | 7.0 | | | | |
| *Age* | | | | | | | | | | | | |
| 50–69 YOA; N = 5887 (RZV), 5887 (Placebo) | 3027 | 51.4 | 50.1 | 52.7 | 1957 | 33.2 | 32.0 | 34.5 | | | | |
| ≥70 YOA; N = 8758 (RZV), 8773 (Placebo) | 4366 | 49.9 | 48.8 | 50.9 | 2732 | 31.1 | 30.2 | 32.1 | | | | |
| *Sex* | | | | | | | | | | | | |
| Female; N = 8498 (RZV), 8547 (Placebo) | 4578 | 53.9 | | | 2932 | 34.3 | | | | | | |
| Male; N = 6147 (RZV), 6113 (Placebo) | 2815 | 45.8 | | | 1757 | 28.7 | | | | | | |
| *Race* | | | | | | | | | | | | |
| White; N = 10,878 (RZV), 10,883 (Placebo) | 5360 | 49.3 | | | 3382 | 31.1 | | | | | | |
| Black; N = 219 (RZV), 196 (Placebo) | 77 | 35.2 | | | 50 | 25.5 | | | | | | |
| Asian; N = 2682 (RZV), 2688 (Placebo) | 1527 | 56.9 | | | 934 | 34.7 | | | | | | |
| Other; N = 866 (RZV), 893 (Placebo) | 429 | 49.5 | | | 323 | 36.2 | | | | | | |
| **Reported in > 1% of RZV recipients** | | | | | | | | | | | | |
| ***General disorders and administration site conditions*** | | | | | | | | | | | | |
| *Injection site pain*[†] | | | | | | | | | | | | |
| Any grade | 3365 | 22.98 | 22.30 | 23.67 | 252 | 1.72 | 1.51 | 1.94 | 13.37 | 11.76 | 15.25 | *** |
| Grade 3 | 212 | 1.4 | 1.3 | 1.7 | 5 | 0.0 | 0.0 | 0.1 | | | | |
| Considered related | 3362 | 23.0 | 22.3 | 23.6 | 252 | 1.7 | 1.5 | 1.9 | | | | |
| *Injection site erythema*[†] | | | | | | | | | | | | |
| Any grade | 1357 | 9.27 | 8.80 | 9.75 | 37 | 0.25 | 0.18 | 0.35 | 36.71 | 26.50 | 52.37 | *** |
| Grade 3 | 58 | 0.4 | 0.3 | 0.5 | 0.0 | 0.0 | 0.0 | 0.0 | | | | |
| Considered related | 1356 | 9.3 | 8.8 | 9.7 | 37 | 0.3 | 0.2 | 0.3 | | | | |
| *Pyrexia*[†] | | | | | | | | | | | | |
| Any grade | 1037 | 7.08 | 6.67 | 7.51 | 76 | 0.52 | 0.41 | 0.65 | 13.66 | 10.81 | 17.48 | *** |
| Grade 3 | 138 | 0.9 | 0.8 | 1.1 | 10 | 0.1 | 0.0 | 0.1 | | | | |
| Considered related | 979 | 6.7 | 6.3 | 7.1 | 31 | 0.2 | 0.1 | 0.3 | | | | |
| *Injection site swelling*[†] | | | | | | | | | | | | |
| Any grade | 1014 | 6.92 | 6.52 | 7.35 | 22 | 0.15 | 0.09 | 0.23 | 46.14 | 30.30 | 73.96 | *** |
| Grade 3 | 42 | 0.3 | 0.2 | 0.4 | 0.0 | 0.0 | 0.0 | 0.0 | | | | |
| Considered related | 1014 | 6.9 | 6.5 | 7.3 | 22 | 0.2 | 0.1 | 0.2 | | | | |
| *Fatigue*[†] | | | | | | | | | | | | |
| Any grade | 522 | 3.56 | 3.27 | 3.88 | 140 | 0.95 | 0.80 | 1.13 | 3.73 | 3.09 | 4.53 | *** |
| Grade 3 | 62 | 0.4 | 0.3 | 0.5 | 7 | 0.0 | 0.0 | 0.1 | | | | |
| Considered related | 459 | 3.1 | 2.9 | 3.4 | 83 | 0.6 | 0.5 | 0.7 | | | | |
| *Chills*[†] | | | | | | | | | | | | |
| Any grade | 516 | 3.52 | 3.23 | 3.83 | 35 | 0.24 | 0.17 | 0.33 | 14.76 | 10.47 | 21.42 | *** |
| Grade 3 | 87 | 0.6 | 0.5 | 0.7 | 2 | 0.0 | 0.0 | 0.0 | | | | |
| Considered related | 498 | 3.4 | 3.1 | 3.7 | 25 | 0.2 | 0.1 | 0.3 | | | | |
| *Injection site pruritus* | | | | | | | | | | | | |
| Any grade | 317 | 2.16 | 1.94 | 2.41 | 35 | 0.24 | 0.17 | 0.33 | 9.07 | 6.38 | 13.25 | *** |
| Grade 3 | 7 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.0 | | | | |
| Considered related | 313 | 2.1 | 1.9 | 2.4 | 35 | 0.2 | 0.2 | 0.3 | | | | |
| *Malaise* | | | | | | | | | | | | |
| Any grade | 254 | 1.73 | 1.53 | 1.96 | 43 | 0.29 | 0.21 | 0.39 | 5.91 | 4.27 | 8.37 | *** |
| Grade 3 | 25 | 0.2 | 0.1 | 0.3 | 3 | 0.0 | 0.0 | 0.1 | | | | |
| Considered related | 237 | 1.6 | 1.4 | 1.8 | 24 | 0.2 | 0.1 | 0.2 | | | | |
| *Pain* | | | | | | | | | | | | |
| Any grade | 204 | 1.39 | 1.21 | 1.60 | 34 | 0.23 | 0.16 | 0.32 | 6.01 | 4.16 | 8.91 | *** |
| Grade 3 | 30 | 0.2 | 0.1 | 0.3 | 3 | 0.0 | 0.0 | 0.1 | | | | |
| Considered related | 170 | 1.2 | 1.0 | 1.3 | 9 | 0.1 | 0.0 | 0.1 | | | | |
| *Injection site warmth* | | | | | | | | | | | | |
| Any grade | 149 | 1.02 | 0.86 | 1.19 | 5 | 0.03 | 0.01 | 0.08 | 29.83 | 12.50 | 93.22 | *** |
| Grade 3 | 4 | 0.0 | 0.0 | 0.1 | 0 | 0.0 | 0.0 | 0.0 | | | | |
| Considered related | 149 | 1.0 | 0.9 | 1.2 | 5 | 0.0 | 0.0 | 0.1 | | | | |
| ***Nervous system disorders*** | | | | | | | | | | | | |
| *Headache*[†] | | | | | | | | | | | | |
| Any grade | 954 | 6.51 | 6.12 | 6.93 | 445 | 3.04 | 2.76 | 3.33 | 2.15 | 1.92 | 2.41 | *** |
| Grade 3 | 99 | 0.7 | 0.5 | 0.8 | 27 | 0.2 | 0.1 | 0.3 | | | | |
| Considered related | 729 | 5.0 | 4.6 | 5.3 | 167 | 1.1 | 1.0 | 1.3 | | | | |
| *Dizziness* | | | | | | | | | | | | |
| Any grade | 182 | 1.24 | 1.07 | 1.44 | 113 | 0.77 | 0.64 | 0.93 | 1.61 | 1.27 | 2.06 | *** |
| Grade 3 | 22 | 0.2 | 0.1 | 0.2 | 13 | 0.1 | 0.0 | 0.2 | | | | |
| Considered related | 110 | 0.8 | 0.6 | 0.9 | 47 | 0.3 | 0.2 | 0.4 | | | | |

(*continued on next page*)

**Table 1** (*continued*)

| | RZV (N = 14,645) | | | | Placebo (N = 14,660) | | | | Relative Risk | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 95% CI | | | | 95% CI | | | | 95% CI | | | |
| | n | % | LL | UL | n | % | LL | UL | RR | LL | UL | |
| ***Infections and infestations*** | | | | | | | | | | | | |
| *Nasopharyngitis* | | | | | | | | | | | | |
| Any grade | 492 | 3.36 | 3.07 | 3.66 | 538 | 3.67 | 3.37 | 3.99 | 0.92 | 0.81 | 1.04 | |
| Grade 3 | 32 | 0.2 | 0.1 | 0.3 | 25 | 0.2 | 0.1 | 0.3 | | | | |
| Considered related | 75 | 0.5 | 0.4 | 0.6 | 36 | 0.2 | 0.2 | 0.3 | | | | |
| *Upper respiratory tract infection* | | | | | | | | | | | | |
| Any grade | 231 | 1.58 | 1.38 | 1.79 | 182 | 1.24 | 1.07 | 1.43 | 1.27 | 1.04 | 1.55 | * |
| Grade 3 | 18 | 0.1 | 0.1 | 0.2 | 16 | 0.1 | 0.1 | 0.2 | | | | |
| Considered related | 16 | 0.1 | 0.1 | 0.2 | 11 | 0.1 | 0.0 | 0.1 | | | | |
| ***Musculoskeletal and connective tissue disorders*** | | | | | | | | | | | | |
| *Myalgia*† | | | | | | | | | | | | |
| Any grade | 478 | 3.26 | 2.98 | 3.56 | 105 | 0.72 | 0.59 | 0.87 | 4.56 | 3.68 | 5.68 | *** |
| Grade 3 | 63 | 0.4 | 0.3 | 0.6 | 8 | 0.1 | 0.0 | 0.1 | | | | |
| Considered related | 431 | 2.9 | 2.7 | 3.2 | 43 | 0.3 | 0.2 | 0.4 | | | | |
| *Arthralgia* | | | | | | | | | | | | |
| Any grade | 252 | 1.72 | 1.52 | 1.94 | 171 | 1.17 | 1.00 | 1.35 | 1.48 | 1.21 | 1.80 | *** |
| Grade 3 | 27 | 0.2 | 0.1 | 0.3 | 15 | 0.1 | 0.1 | 0.2 | | | | |
| Considered related | 131 | 0.9 | 0.7 | 1.1 | 25 | 0.2 | 0.1 | 0.3 | | | | |
| *Pain in extremity* | | | | | | | | | | | | |
| Any grade | 155 | 1.06 | 0.90 | 1.24 | 107 | 0.73 | 0.60 | 0.88 | 1.45 | 1.13 | 1.87 | * |
| Grade 3 | 14 | 0.1 | 0.1 | 0.2 | 9 | 0.1 | 0.0 | 0.1 | | | | |
| Considered related | 50 | 0.3 | 0.3 | 0.4 | 10 | 0.1 | 0.0 | 0.1 | | | | |
| *Back pain* | | | | | | | | | | | | |
| Any grade | 211 | 1.44 | 1.25 | 1.65 | 186 | 1.27 | 1.09 | 1.46 | 1.14 | 0.93 | 1.39 | |
| Grade 3 | 27 | 0.2 | 0.1 | 0.3 | 22 | 0.2 | 0.1 | 0.2 | | | | |
| Considered related | 45 | 0.3 | 0.2 | 0.4 | 18 | 0.1 | 0.1 | 0.2 | | | | |
| ***Respiratory, thoracic and mediastinal disorders*** | | | | | | | | | | | | |
| *Cough* | | | | | | | | | | | | |
| Any grade | 209 | 1.43 | 1.24 | 1.63 | 210 | 1.43 | 1.25 | 1.64 | 1.00 | 0.82 | 1.21 | |
| Grade 3 | 14 | 0.1 | 0.1 | 0.2 | 16 | 0.1 | 0.1 | 0.2 | | | | |
| Considered related | 19 | 0.1 | 0.1 | 0.2 | 12 | 0.1 | 0.0 | 0.1 | | | | |
| *Oropharyngeal pain* | | | | | | | | | | | | |
| Any grade | 165 | 1.13 | 0.96 | 1.31 | 154 | 1.05 | 0.89 | 1.23 | 1.07 | 0.86 | 1.34 | |
| Grade 3 | 6 | 0.0 | 0.0 | 0.1 | 8 | 0.1 | 0.0 | 0.1 | | | | |
| Considered related | 37 | 0.3 | 0.2 | 0.3 | 20 | 0.1 | 0.1 | 0.2 | | | | |
| ***Gastrointestinal disorders*** | | | | | | | | | | | | |
| *Nausea*† | | | | | | | | | | | | |
| Any grade | 197 | 1.35 | 1.16 | 1.55 | 69 | 0.47 | 0.37 | 0.60 | 2.86 | 2.16 | 3.82 | *** |
| Grade 3 | 26 | 0.2 | 0.1 | 0.3 | 6 | 0.0 | 0.0 | 0.1 | | | | |
| Considered related | 167 | 1.1 | 1.0 | 1.3 | 32 | 0.2 | 0.1 | 0.3 | | | | |

Adverse events are presented by System Organ Class and Preferred Term, in order of most frequently reported in RZV recipients. Only adverse events reported by > 1% of RZV recipients are presented here. Significance testing on relative risks was performed on all-grade events, irrespective of relatedness.
RZV = participants receiving the adjuvanted Recombinant Zoster Vaccine; Placebo = participants receiving placebo; N = number of participants in the pooled total vaccinated cohort; n/% = number/percentage of participants reporting an event in each category; YOA = years of age; 95% CI = 95% Confidence Interval; RR = Relative Risk; LL/UL = Lower Limit/Upper Limit of 95% Confidence Interval. † denotes adverse events classified as solicited adverse events in the reactogenicity sub-cohort; Stars indicate significance of difference as expressed by the relative risk: * = $p \leq 0.05$; ** = $p \leq 0.01$; *** = $p \leq 0.001$.

The frequency of grade 3 unsolicited AEs was also higher in RZV than in placebo recipients within D0-D6 post-vaccination (Fig. 1) due to PTs covering the local and general symptoms reported by participants who were not part of the reactogenicity sub-cohort. The most frequent grade 3 unsolicited AEs in the RZV group were injection site pain, pyrexia, and headache. Injection site pain was the only PT under which grade 3 unsolicited AEs were reported by >1% of RZV recipients and had a higher frequency as compared to the Placebo group (Table 1).

Unsolicited AEs with medically attended visits were reported by 2751 (18.8%) RZV and 2774 (18.9%) placebo recipients during the 30D post-vaccination, and by 5834 (39.8) RZV and 5983 (40.8%) placebo recipients within 6 M post-last dose. The incidence of unsolicited AEs with medically attended visits was similar between the RZV and Placebo groups in both males and females, in participants of any race, and in both age cohorts within the same period; incidences were also comparable between the age cohorts (Supplementary Table 3).

### 3.4. Serious adverse events

Overall, the occurrence of SAEs was similar in both groups for all time periods analyzed. Within 30D post-last dose, 342 (2.3%) RZV and 327 (2.2%) placebo recipients reported at least one SAE. Within 1Y post-last dose, SAEs were reported by 1482 (10.1%) and 1525 (10.4%) participants in the RZV and Placebo groups, respectively (RR = 0.97 [95%CI:0.91–1.05]; p = 0.46). During the entire study period, SAEs considered causally related to vaccina-

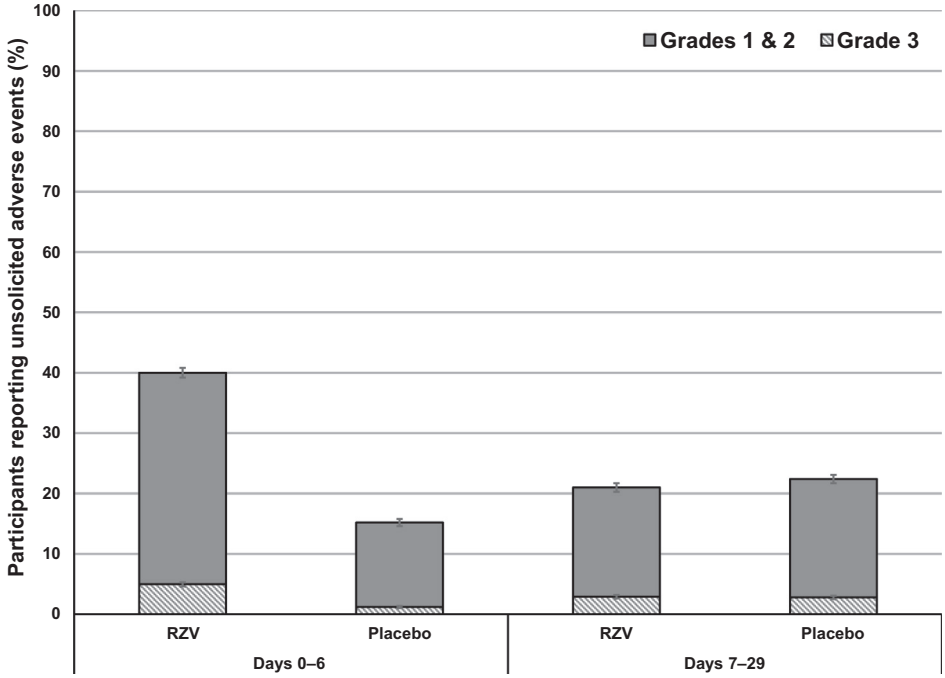


**Fig. 1.** Unsolicited Adverse Events reported in the 30 days after vaccination – days 0–6 and 7–29 post-vaccination (Pooled Total Vaccinated Cohort). RZV = participants receiving the adjuvanted Recombinant Zoster Vaccine; Placebo = participants receiving placebo. Bars present percentage of study population experiencing any unsolicited event, error bars present 95% Confidence Intervals.

tion by investigators were reported by 15 (0.1%) participants in each group (Table 2, Supplementary Table 4).

Within 1Y post-last dose, SAE incidence was similar between the RZV and Placebo groups in both age cohorts, in both males and females, and in participants of any race (Table 2). In both study groups, the most frequently reported SAEs by SOC were: infections and infestations (RZV: 299 [2.04%], Placebo: 302 [2.06%]), cardiac disorders (RZV: 290 [1.98%], Placebo: 318 [2.17%]), and neoplasms benign, malignant and unspecified (RZV: 226 [1.54%], Placebo: 225 [1.53%], Fig. 2). By PT, the most frequently reported SAEs in both groups were pneumonia (RZV: 83 [0.57%], Placebo: 66 [0.45%]) and atrial fibrillation (RZV: 55 [0.38%], Placebo: 58 [0.40%], Table 2).

Statistically significant imbalances based on the nominal unadjusted p-value ($p < 0.05$) between RZV and placebo recipients were found for four individual SAEs by PT (Table 2). Six (<0.05%) RZV recipients reported SAEs under the supraventricular tachycardia PT versus no participants in the Placebo arm. By grouping supraventricular tachycardia with other PTs that are pathophysiologically similar to or synonymous with supraventricular tachycardia (*i.e.* arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, cardiac flutter, tachyarrhythmia, and tachycardia paroxysmal), the data showed no imbalance between RZV and placebo recipients (69 [0.47%] versus 66 [0.45%]; RR = 1.05 [95%CI:0.74–1.49]; p = 0.86). PTs under which SAEs were reported more frequently in placebo than in RZV recipients, were aortic stenosis (0 [0.00%] versus 10 [0.07%]; RR = 0.00 [95% CI:0.00–0.35]; p = 0.0020), cardio-respiratory arrest (0 [0.00%] versus 6 [0.04%]; RR = 0.00 [95%CI:0.00–0.65]; p = 0.0313), and retinal detachment (1 [0.01%] versus 8 [0.05%]; RR = 0.13 [95%CI:0.00–0.93]; p = 0.0392).

### 3.5. Fatal adverse events

Overall, the percentage of participants reporting fatal AEs was similar between RZV and placebo recipients during all time periods analyzed. Within 30D post-last dose, 17 (0.1%) RZV and 21 (0.1%) placebo recipients reported fatal AEs. Within 1Y post-last dose, fatal AEs were reported by 153 (1.1%) and 168 (1.1%) participants in the RZV and Placebo groups, respectively (Table 3).

During the entire study period, fatal AEs were reported by 634 (4.3%) participants in the RZV group and by 680 (4.6%) participants in the Placebo group. The occurrence of fatal AEs was similar between groups in both age cohorts, but higher in participants ≥70 YOA compared to those 50–69 YOA (Table 3). The most frequently reported fatal AEs by SOC in each study group were neoplasms benign, malignant and unspecified (RZV: 182 [1.2%], Placebo: 177 [1.2%]), followed by cardiac disorders (RZV: 174 [1.2%], Placebo: 193 [1.3%]), and infections and infestations (RZV: 103 [0.7%], Placebo: 107 [0.7%]). The most frequently reported fatal AEs by PT were cardiac failure, pneumonia, myocardial infarction, death (with no specified cause), and cardiac arrest (Table 3).

One fatal AE was assessed as possibly vaccine-related by the investigator. A 90-year-old male study participant with a past medical history of stable immune-mediated thrombocytopenia for approximately 10Y prior to vaccination developed pancytopenia and was diagnosed, on the basis of a bone marrow biopsy, with acute myeloid leukemia (AML) 75D after receiving the first RZV dose. He was hospitalized and withdrawn from study treatment. The study participant died 97D post-dose 1 due to neutropenic sepsis.

### 3.6. Potential immune-mediated diseases

Overall, the occurrence of pIMDs (new onset and possible exacerbations) was similar between RZV and placebo recipients during all time periods analyzed. Up to 30D post-last dose, pIMDs were reported by 30 (0.2%) participants in each group. pIMDs were reported by 90 (0.6%) RZV and 105 (0.7%) placebo recipients up to 1Y post-last dose, and by 179 (1.2%) RZV and 202 (1.4%) placebo recipients during the entire study period. Up to 1Y post-last dose,

**Table 2**
Serious Adverse Events reported during the ZOE-50/70 clinical trials (Pooled Total Vaccinated Cohort).

| | RZV (N = 14,645) | | | | Placebo (N = 14,660) | | | | Relative Risk | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL | RR | LL | UL |
| *Reported within 30 days post-last dose* | | | | | | | | | | | |
| Any event | 342 | 2.3 | 2.1 | 2.6 | 327 | 2.2 | 2.0 | 2.5 | | | |
| *Reported within 1 year post-last dose* | | | | | | | | | | | |
| Any event | 1482 | 10.1 | 9.6 | 10.6 | 1525 | 10.4 | 9.9 | 10.9 | 0.97 | 0.91 | 1.05 |
| *Age* | | | | | | | | | | | |
| 50–69 YOA; N = 5887 (RZV), 5887 (Placebo) | 367 | 6.2 | 5.6 | 6.9 | 359 | 6.1 | 5.5 | 6.7 | | | |
| ≥70 YOA; N = 8758 (RZV), 8773 (Placebo) | 1115 | 12.7 | 12.0 | 13.4 | 1166 | 13.3 | 12.6 | 14.0 | | | |
| *Sex* | | | | | | | | | | | |
| Female; N = 8498 (RZV), 8547 (Placebo) | 748 | 8.8 | | | 763 | 8.9 | | | | | |
| Male; N = 6147 (RZV), 6113 (Placebo) | 734 | 11.9 | | | 762 | 12.5 | | | | | |
| *Race* | | | | | | | | | | | |
| White; N = 10,878 (RZV), 10,883 (Placebo) | 1118 | 10.3 | | | 1149 | 10.6 | | | | | |
| Black; N = 219 (RZV), 196 (Placebo) | 23 | 10.5 | | | 26 | 13.3 | | | | | |
| Asian; N = 2682 (RZV), 2688 (Placebo) | 280 | 10.4 | | | 288 | 10.7 | | | | | |
| Other; N = 866 (RZV), 893 (Placebo) | 61 | 7.0 | | | 62 | 6.9 | | | | | |
| *Reported during the entire study period* | | | | | | | | | | | |
| Considered related | 15 | 0.1 | 0.1 | 0.2 | 15 | 0.1 | 0.1 | 0.2 | | | |
| **Reported in > 0.3% of RZV recipients** | | | | | | | | | | | |
| *Cardiac disorders* | | | | | | | | | | | |
| Atrial Fibrillation | 55 | 0.38 | 0.28 | 0.49 | 58 | 0.40 | 0.30 | 0.51 | 0.95 | 0.64 | 1.4 |
| *Infections and Infestations* | | | | | | | | | | | |
| Pneumonia | 83 | 0.57 | 0.45 | 0.7 | 66 | 0.45 | 0.35 | 0.57 | 1.26 | 0.90 | 1.77 |
| **Statistically significant differences in occurrence between RZV and Placebo** | | | | | | | | | | | |
| *Vascular Disorders* | | | | | | | | | | | |
| Aortic Stenosis** | 0 | 0 | 0 | 0.03 | 10 | 0.07 | 0.03 | 0.13 | 0.00 | 0.00 | 0.35 |
| *Cardiac Disorders* | | | | | | | | | | | |
| Supraventricular Tachycardia* | 6 | 0.04 | 0.02 | 0.09 | 0 | 0 | 0 | 0.03 | INF | 1.55 | INF |
| Cardio-respiratory arrest* | 0 | 0 | 0 | 0.03 | 6 | 0.04 | 0.02 | 0.09 | 0.00 | 0.00 | 0.65 |
| *Eye Disorders* | | | | | | | | | | | |
| Retinal detachment* | 1 | 0.01 | 0 | 0.04 | 8 | 0.05 | 0.02 | 0.11 | 0.13 | 0.00 | 0.93 |

Serious adverse events are presented by System Organ Class and Preferred Term, in order of most frequently reported in RZV recipients. Only serious adverse events reported by > 0.3% of RZV recipients are presented here. Significance testing on relative risks was performed irrespective of relatedness. Details on serious adverse events considered related to vaccination by study investigators are provided in Supplementary Table 4.
RZV = participants receiving the adjuvanted Recombinant Zoster Vaccine; Placebo = participants receiving placebo; N = number of participants in the pooled total vaccinated cohort; n/% = number/percentage of participants reporting an event in each category; YOA = years of age; 95% CI = 95% Confidence Interval; RR = Relative Risk; LL/UL = Lower Limit/Upper Limit of 95% Confidence Interval; INF = estimation considered infinite.
Stars indicate significance of difference as expressed by the relative risk: * = $p \leq 0.05$; ** = $p \leq 0.01$.

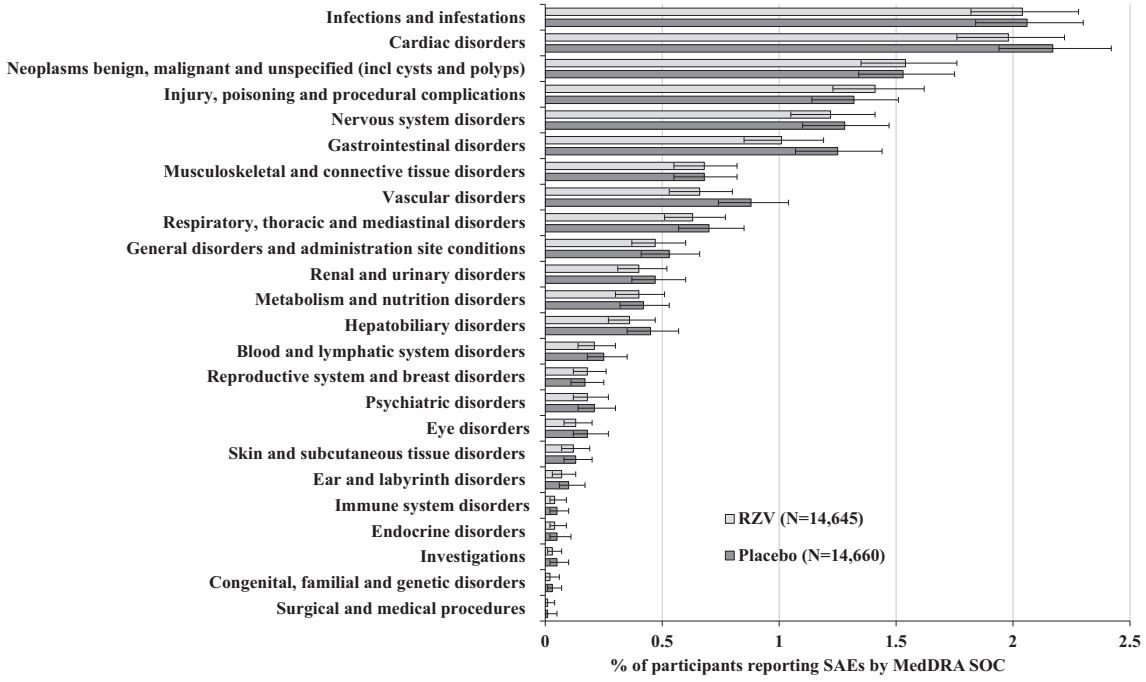


**Fig. 2.** Serious Adverse Events reported within 1 year post-last dose (Pooled Total Vaccinated Cohort). RZV = participants receiving the adjuvanted Recombinant Zoster Vaccine; Placebo = participants receiving placebo; N = number of participants in the pooled total vaccinated cohort; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class; SAE = Serious Adverse Event.

**Table 3**
Adverse Events with fatal outcome reported during the ZOE-50/70 clinical trials (Pooled Total Vaccinated Cohort).

| | RZV (N = 14,645) | | | | Placebo (N = 14,660) | | | |
|---|---|---|---|---|---|---|---|---|
| | 95% CI | | | | 95% CI | | | |
| | n | % | LL | UL | n | % | LL | UL |
| *Reported within 30 days post-last dose* | | | | | | | | |
| Any event | 17 | 0.1 | 0.1 | 0.2 | 21 | 0.1 | 0.1 | 0.2 |
| *Reported within 1 year post-last dose* | | | | | | | | |
| Any event | 153 | 1.0 | 0.9 | 1.2 | 168 | 1.1 | 1.0 | 1.3 |
| *Reported during the entire study period* | | | | | | | | |
| Any event | 634 | 4.3 | 4.0 | 4.7 | 680 | 4.6 | 4.3 | 5.0 |
| *Age* | | | | | | | | |
| 50–69 YOA; N = 5887 (RZV), 5887 (Placebo) | 95 | 1.6 | 1.3 | 2.0 | 100 | 1.7 | 1.4 | 2.1 |
| ≥70 YOA; N = 8758 (RZV), 8773 (Placebo) | 539 | 6.2 | 5.7 | 6.7 | 580 | 6.6 | 6.1 | 7.2 |
| **Reported in ≥ 0.1% of RZV recipients during the entire study period** | | | | | | | | |
| *Cardiac Disorders* | | | | | | | | |
| Cardiac failure | 42 | 0.3 | 0.2 | 0.4 | 53 | 0.4 | 0.3 | 0.5 |
| Myocardial infarction | 39 | 0.3 | 0.2 | 0.4 | 39 | 0.3 | 0.2 | 0.4 |
| Cardiac arrest | 29 | 0.2 | 0.1 | 0.3 | 23 | 0.2 | 0.1 | 0.2 |
| Acute myocardial infarction | 13 | 0.1 | 0.0 | 0.2 | 24 | 0.2 | 0.1 | 0.2 |
| Cardiac failure congestive | 11 | 0.1 | 0.0 | 0.1 | 15 | 0.1 | 0.1 | 0.2 |
| Cardiogenic shock | 9 | 0.1 | 0.0 | 0.1 | 2 | 0.0 | 0.0 | 0.0 |
| *Infections and infestations* | | | | | | | | |
| Pneumonia | 39 | 0.3 | 0.2 | 0.4 | 47 | 0.3 | 0.2 | 0.4 |
| Sepsis | 21 | 0.1 | 0.1 | 0.2 | 20 | 0.1 | 0.1 | 0.2 |
| Septic shock | 10 | 0.1 | 0.0 | 0.1 | 14 | 0.1 | 0.1 | 0.2 |
| *General disorders and administration site conditions* | | | | | | | | |
| Death | 28 | 0.2 | 0.1 | 0.3 | 44 | 0.3 | 0.2 | 0.4 |
| Sudden death | 18 | 0.1 | 0.1 | 0.2 | 11 | 0.1 | 0.0 | 0.1 |
| Multi-organ failure | 15 | 0.1 | 0.1 | 0.2 | 13 | 0.1 | 0.0 | 0.2 |
| *Neoplasms benign, malignant and unspecified* | | | | | | | | |
| Lung neoplasm malignant | 27 | 0.2 | 0.1 | 0.3 | 13 | 0.1 | 0.0 | 0.2 |
| Pancreatic carcinoma | 12 | 0.1 | 0.0 | 0.1 | 18 | 0.1 | 0.1 | 0.2 |
| Lung cancer metastatic | 8 | 0.1 | 0.0 | 0.1 | 5 | 0.0 | 0.0 | 0.1 |
| *Nervous system disorders* | | | | | | | | |
| Cerebrovascular accident | 19 | 0.1 | 0.1 | 0.2 | 23 | 0.2 | 0.1 | 0.2 |
| Cerebral infarction | 9 | 0.1 | 0.0 | 0.1 | 9 | 0.1 | 0.0 | 0.1 |
| *Respiratory, thoracic and mediastinal disorders* | | | | | | | | |
| Respiratory failure | 16 | 0.1 | 0.1 | 0.2 | 19 | 0.1 | 0.1 | 0.2 |
| Chronic obstructive pulmonary disease | 9 | 0.1 | 0.0 | 0.1 | 11 | 0.1 | 0.0 | 0.1 |
| Pneumonia aspiration | 8 | 0.1 | 0.0 | 0.1 | 6 | 0.0 | 0.0 | 0.1 |
| *Renal and urinary disorders* | | | | | | | | |
| Acute kidney injury | 14 | 0.1 | 0.1 | 0.2 | 8 | 0.1 | 0.0 | 0.1 |

Adverse events with fatal outcome are presented by System Organ Class and Preferred Term, in order of most frequently reported in RZV recipients. Only adverse events with fatal outcome reported by ≥ 0.1% of RZV recipients are presented here.
RZV = participants receiving the adjuvanted Recombinant Zoster Vaccine; Placebo = participants receiving placebo; N = number of participants in the pooled total vaccinated cohort; n/% = number/percentage of participants reporting an event in each category; YOA = years of age; 95% CI = 95% Confidence Interval; LL/UL = Lower Limit/Upper Limit of 95% Confidence Interval.

pIMDs considered related to vaccination by study investigators were reported by 15 (0.1%) participants in each group (Table 4).

Overall, occurrences of pIMDs during the entire study period were similar between RZV and placebo recipients irrespective of age cohort, gender, or race (Table 4). The most frequently reported pIMDs by PT were polymyalgia rheumatica, rheumatoid arthritis, psoriasis, and autoimmune thyroiditis (Table 4, Supplementary Table 5).

The additional analysis of participants with pre-existing pIMDs revealed that 983 (6.7%) RZV and 960 (6.5%) placebo recipients had a pre-existing pIMD at enrollment (Table 5, Supplementary Fig. 3). The most common pre-existing pIMDs at baseline by PT were psoriasis (RZV: 215 [21.9%], Placebo: 239 [24.9%]), spondyloarthropathy (RZV: 109 [11.1%], Placebo: 89 [9.3%]), and rheumatoid arthritis (RZV: 96 [9.8%], Placebo: 94 [9.8%]). Over 95% of participants with a pre-existing pIMD did not experience a possible exacerbation of a pre-existing pIMD nor an onset of a new pIMD during the study. Among participants with pre-existing pIMDs, onset of new pIMDs were reported by 16 (1.6%) RZV and 23 (2.4%) placebo recipients, and possible exacerbation of pre-existing pIMD by 27 (2.8%) of participants in each group (Table 5).

## 4. Discussion

Overall, the pooled safety data from ZOE-50/70 studies did not reveal any safety concerns. A plain language summary contextualizing the results and potential clinical research relevance and impact is displayed in the Focus on Patient Section (Supplementary Fig. 4).

Unsolicited symptoms were more frequent in RZV recipients, driven by local and systemic reactions reported during D0-D6 post-vaccination by participants who were not part of the reactogenicity sub-cohort [4,5]. Data published previously showed that RZV induces transient local and systemic reactions, such as injection site pain and, to a lesser extent, fatigue and myalgia [4,5,9–11]. In line with these findings, the pooled analysis presented here shows a similar profile of transient local and systemic reactions to the vaccine (including those of grade 3 intensity) occurring during D0-D6 post-vaccination. No clinically significant imbalance in other unsolicited AEs was observed.

The nature of the SAEs reported in the pooled ZOE-50/70 studies reflects those observed in the general older adult population [12,13], and overall, no apparent differences were observed

**Table 4**
Potential Immune-Mediated Diseases reported during the ZOE-50/70 clinical trials (Pooled Total Vaccinated Cohort).

| | RZV (N = 14,645) | | | | Placebo (N = 14,660) | | | | Relative Risk | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL | RR | LL | UL |
| *Reported within 30 days post-last dose* | | | | | | | | | | | |
| Any event | 30 | 0.2 | 0.1 | 0.3 | 30 | 0.2 | 0.1 | 0.3 | | | |
| *Reported within 1 year post-last dose* | | | | | | | | | | | |
| Any Event | 90 | 0.6 | 0.5 | 0.8 | 105 | 0.7 | 0.6 | 0.9 | 0.86* | 0.64 | 1.15 |
| Considered related | 15 | 0.1 | 0.1 | 0.2 | 15 | 0.1 | 0.1 | 0.2 | | | |
| *Reported during the entire study period* | | | | | | | | | | | |
| Any event | 179 | 1.2 | 1.1 | 1.4 | 202 | 1.4 | 1.2 | 1.6 | | | |
| *Age* | | | | | | | | | | | |
| 50–69 YOA; N = 5887 (RZV), 5887 (Placebo) | 69 | 1.2 | 0.9 | 1.5 | 84 | 1.4 | 1.1 | 1.8 | | | |
| ≥70 YOA; N = 8758 (RZV), 8773 (Placebo) | 110 | 1.3 | 1.0 | 1.5 | 118 | 1.3 | 1.1 | 1.6 | | | |
| *Sex* | | | | | | | | | | | |
| Female; N = 8498 (RZV), 8547 (Placebo) | 115 | 1.4 | | | 128 | 1.5 | | | | | |
| Male; N = 6147 (RZV), 6113 (Placebo) | 64 | 1.0 | | | 74 | 1.2 | | | | | |
| *Race* | | | | | | | | | | | |
| White; N = 10,878 (RZV), 10,883 (Placebo) | 153 | 1.4 | | | 171 | 1.6 | | | | | |
| Black; N = 219 (RZV), 196 (Placebo) | 1 | 0.5 | | | 0 | 0 | | | | | |
| Asian; N = 2682 (RZV), 2688 (Placebo) | 19 | 0.7 | | | 23 | 0.9 | | | | | |
| Other; N = 866 (RZV), 893 (Placebo) | 6 | 0.7 | | | 8 | 0.9 | | | | | |
| **Reported in ≥ 0.1% of RZV recipients** | | | | | | | | | | | |
| *Musculoskeletal and connective tissue disorders* | | | | | | | | | | | |
| Polymyalgia rheumatica | 32 | 0.2 | 0.1 | 0.3 | 29 | 0.2 | 0.1 | 0.3 | | | |
| Rheumatoid arthritis | 20 | 0.1 | 0.1 | 0.2 | 26 | 0.2 | 0.1 | 0.3 | | | |
| *Skin and subcutaneous tissue disorders* | | | | | | | | | | | |
| Psoriasis | 15 | 0.1 | 0.1 | 0.2 | 18 | 0.1 | 0.1 | 0.2 | | | |
| *Endocrine disorders* | | | | | | | | | | | |
| Autoimmune thyroiditis | 13 | 0.1 | 0.0 | 0.2 | 10 | 0.1 | 0.0 | 0.1 | | | |
| *Nervous system disorders* | | | | | | | | | | | |
| VII$^{th}$ nerve paralysis | 8 | 0.1 | 0.0 | 0.1 | 7 | 0.0 | 0.0 | 0.1 | | | |

Potential immune-mediated diseases are presented by System Organ Class and Preferred Term, in order of most frequently reported in RZV recipients. Only diseases reported by ≥ 0.1% of RZV recipients are presented. A full list of potential immune-mediated diseases reported during the clinical trials is presented in Supplementary Table 5. Significance testing on relative risks was performed irrespective of relatedness. * p = 0.3195.
RZV = participants receiving the adjuvanted Recombinant Zoster Vaccine; Placebo = participants receiving placebo; N = number of participants in the pooled total vaccinated cohort; n/% = number/percentage of participants reporting an event in each category; YOA = years of age; 95% CI = 95% Confidence Interval; RR = Relative Risk; LL/UL = Lower Limit/Upper Limit of 95% Confidence Interval.

**Table 5**
Potential Immune-Mediated Diseases reported during the ZOE-50/70 clinical trials in participants with a pre-existing potential Immune-Mediated Disease at enrolment (Total Vaccinated Cohort with pre-existing pIMD).

| | RZV (N = 983) | | | | Placebo (N = 960) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| No pre-existing pIMD exacerbation or new pIMD onset | 940 | 95.6 | | | 912 | 95.0 | | |
| ***Exacerbation of a pre-existing pIMD*** | | | | | | | | |
| Any Event | 27 | 2.8 | 1.8 | 4.0 | 27 | 2.8 | 1.9 | 4.1 |
| *Blood and lymphatic system disorders* | | | | | | | | |
| Immune thrombocytopenic purpura | 2 | 0.2 | 0.0 | 0.7 | 1 | 0.1 | 0.0 | 0.6 |
| *Endocrine disorders* | | | | | | | | |
| Basedow's disease | 2 | 0.2 | 0.0 | 0.7 | 0 | 0 | 0.0 | 0.4 |
| *Eye disorders* | | | | | | | | |
| Uveitis | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| *Gastrointestinal disorders* | | | | | | | | |
| Colitis ulcerative | 1 | 0.1 | 0.0 | 0.6 | 1 | 0.1 | 0.0 | 0.6 |
| *Metabolism and nutrition disorders* | | | | | | | | |
| Type 1 diabetes mellitus | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| *Musculoskeletal and connective tissue disorders* | | | | | | | | |
| Crest syndrome | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Polymyalgia rheumatica | 2 | 0.2 | 0.0 | 0.7 | 3 | 0.3 | 0.1 | 0.9 |
| Psoriatic arthropathy | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Rheumatoid arthritis | 3 | 0.3 | 0.1 | 0.9 | 5 | 0.5 | 0.2 | 1.2 |
| Spondyloarthropathy | 4 | 0.4 | 0.1 | 1.0 | 2 | 0.2 | 0.0 | 0.8 |
| *Nervous system disorders* | | | | | | | | |
| VII$^{th}$ nerve paralysis | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| *Respiratory, thoracic and mediastinal disorders* | | | | | | | | |
| Pulmonary fibrosis | 2 | 0.2 | 0.0 | 0.7 | 1 | 0.1 | 0.0 | 0.6 |
| *Skin and subcutaneous tissue disorders* | | | | | | | | |
| Alopecia areata | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |

**Table 5** (*continued*)

| | RZV (N = 983) | | | | Placebo (N = 960) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| Erythema nodosum | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Pemphigus | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Psoriasis | 9 | 0.9 | 0.4 | 1.7 | 4 | 0.4 | 0.1 | 1.1 |
| Vitiligo | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| *Vascular disorders* | | | | | | | | |
| Raynaud's phenomenon | 1 | 0.1 | 0.0 | 0.6 | 1 | 0.1 | 0.0 | 0.6 |
| Temporal arteritis | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| ***New onset pIMD*** | | | | | | | | |
| Any event | 16 | 1.6 | 0.9 | 2.6 | 23 | 2.4 | 1.5 | 3.6 |
| *Endocrine disorders* | | | | | | | | |
| Autoimmune thyroiditis | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Basedow's disease | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| *Gastrointestinal disorders* | | | | | | | | |
| Autoimmune pancreatitis | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| Chronic gastritis | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| Coeliac disease | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Crohn's disease | 1 | 0.1 | 0.0 | 0.6 | 1 | 0.1 | 0.0 | 0.6 |
| Oral lichen planus | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| *Metabolism and nutrition disorders* | | | | | | | | |
| Diabetes mellitus | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| *Musculoskeletal and connective tissue disorders* | | | | | | | | |
| Mixed connective tissue disease | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Polymyalgia rheumatica | 2 | 0.2 | 0.0 | 0.7 | 3 | 0.3 | 0.1 | 0.9 |
| Rheumatoid arthritis | 0 | 0 | 0.0 | 0.4 | 6 | 0.6 | 0.2 | 1.4 |
| Still's disease adult onset | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| Systemic lupus erythematosus | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| *Nervous system disorders* | | | | | | | | |
| Chronic inflammatory demyelinating polyradiculoneuropathy | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Guillain-Barré syndrome | 1 | 0.1 | 0.0 | 0.6 | 1 | 0.1 | 0.0 | 0.6 |
| Multiple sclerosis | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Neuritis cranial | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| Paraneoplastic neurological syndrome | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Radiculitis brachial | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| Trigeminal nerve paresis | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| Trigeminal neuralgia | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| *Renal and urinary disorders* | | | | | | | | |
| Glomerulonephritis | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| IgA nephropathy | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| *Respiratory, thoracic and mediastinal disorders* | | | | | | | | |
| Idiopathic pulmonary fibrosis | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| Pulmonary fibrosis | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |
| *Skin and subcutaneous tissue disorders* | | | | | | | | |
| Erythema nodosum | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| Lichen planus | 1 | 0.1 | 0.0 | 0.6 | 2 | 0.2 | 0.0 | 0.8 |
| Psoriasis | 1 | 0.1 | 0.0 | 0.6 | 0 | 0 | 0.0 | 0.4 |
| *Vascular disorders* | | | | | | | | |
| Polyarteritis nodosa | 0 | 0 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.6 |

Potential immune-mediated diseases (pIMDs) are presented by System Organ Class and Preferred Term, in alphabetical order. RZV = participants receiving the adjuvanted Recombinant Zoster Vaccine; Placebo = participants receiving placebo; N = number of participants with a pre-existing pIMD at enrolment; n/% = number/percentage of participants reporting an event in each category; 95% CI = 95% Confidence Interval; LL/UL = Lower Limit/Upper Limit of 95% Confidence Interval.
Participants with pre-existing pIMDs were identified by querying the global medical history of the participants included in the Total Vaccinated Cohort with a customized MedDRA query for pIMDs [Tavares 2013].

between the two groups during any of the time intervals assessed, irrespective of age, gender or race. Similarly, SAEs considered related to study vaccination by the investigator were balanced between groups. A descriptive analysis revealed that supraventricular tachycardia was the only SAE by PT with an increased risk in RZV recipients up to 1Y post-last vaccination. However, given the high number of comparisons, the probability of obtaining a false significant increase in the incidence of a particular event is inflated. The analysis performed considering grouped PTs referring to the same medical context of supraventricular tachyarrhythmias did not show any apparent differences between RZV and placebo recipients. In addition, no biologically plausible mechanism by which RZV could cause supraventricular tachycardia is known.

The incidence of AEs with a fatal outcome reflected the age of participants [13,14], and was balanced between RZV and placebo recipients. One fatal AE (neutropenic sepsis) that occurred more than 3M post-vaccination, was considered related to vaccination by the study investigator [4]. The neutropenia and neutropenic sepsis in this participant were likely the result of the induction chemotherapy for the treatment of AML. Additionally, there were no clustering of similar events temporally associated with vaccination. Neutropenic fever and sepsis are common AEs for therapeutic treatment [15–17].

Although concerns have been raised regarding potential associations between vaccine adjuvants and the occurrence of pIMDs [18–20], the association between vaccination and pIMDs has largely been extrapolated from isolated case reports, and large epidemiological studies and pooled analyses only showed such an association for a very limited number of vaccine and autoimmune disease combinations [21,22]. The theoretical risk of acquiring

autoimmune diseases is considered to be driven by chronic inflammation, antigen mimicry and inflammation of target organs [23]. However, pre-clinical evidence suggests that RZV is unlikely to cause long-term inflammation, as the innate immune response and activity of pro-inflammatory cytokines are transient [24]. Nonetheless, in the ZOE-50/70 studies, pIMDs were monitored through standard data collection methods and disease-specific standard questionnaires for the collection of the pIMD safety data [25]. In eligible participants with pre-existing pIMDs at study entry, exacerbations as well as new onset of other pIMDs were recorded during the entire study period. The analyses of the pooled study population presented here show no evidence for a statistical imbalance between RZV and placebo recipients. Overall, the most frequently reported pIMDs were those with the greatest prevalence in this age group [26–29]. The occurrence of new onset pIMDs was similar between groups, irrespective of time interval assessed, participant age, gender, or race. Additionally, in participants with pre-existing pIMDs, the occurrences of a possible exacerbation or a new onset of a different pIMD were also balanced between groups. Overall, these data do not show an increased risk of developing a new pIMD or exacerbating an underlying pIMD in RZV recipients $\geq$50 YOA.

The results of these pooled analyses need to be considered in the context of study strengths and weaknesses. The ZOE-50/70 clinical trials included a large and global population of relevant age, predominantly of Caucasian and Asian ancestries. The statistical power of pre-licensure clinical trials to detect very rare events is limited due to the sample size. Since incidence rates of some medical conditions, such as certain pIMDs and allergic reactions vary roughly from 1 to 20 per 100,000 person-years in the general population, these AEs will require post-licensure safety monitoring, during which a larger population will be vaccinated. In addition, some populations were excluded per protocol from the pivotal studies (*e.g.* patients with certain underlying diseases treated with high dose steroids or immune-modulators).

The pooled analyses of the phase 3 ZOE-50/70 clinical trials did not identify any safety concerns, and, along with the high vaccine efficacy demonstrated in these trials, these results support the favorable benefit-risk profile of RZV in all age-groups studied.

## 5. Potential conflicts of interest

MLF, LC, FD, MEI and FTdS are employees, and LO, TCH and HL are former employees, of the GSK group of companies. FJDL reports receiving grant support from GSK and Novartis outside the submitted work. LO is an employee of CureVac AG. LO and TCH are inventors on a patent owned by GSK and relevant to RZV. JDD reports receiving personal fees from GSK for an advisory board on a pharmacoeconomic study with Synflorix in Spain, as well as grants and personal fees from Sanofi Pasteur MSD for an epidemiological study on herpes zoster and an advisory board on Zostavax, respectively, outside the submitted work. LO, TCH, HL and FTdS hold shares or stock options from GSK as part of their current or former employee remuneration. TCH served as a paid consultant to GSK outside the submitted work. HL is a current employee of Pfizer and receives stock as part of his employee remuneration. JEM reports receiving honoraria and fees paid to her institution from GSK, Sanofi Pasteur, Merck and Pfizer, as well as travel support from GSK, Sanofi Pasteur, Merck and Pfizer outside the submitted work. SAM reports research grant from Pfizer, personal fees for continuing professional development talks on adult immunization from Pfizer and Merck, and consulting fees from Pfizer and Merck outside the submitted work, as well as grant from GSK outside the submitted work. WY reports financial support from GSK to perform the study.

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## Authors' contribution

Detailed authors' contribution is provided in the supplementary materials.

## Appendix A. Supplementary material

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