Long-term Protection Against Herpes Zoster by the Adjuvanted Recombinant Zoster Vaccine: Interim Efficacy, Immunogenicity, and Safety Results up to 10 Years After Initial Vaccination

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Approximately 10 years after vaccination with the recombinant zoster vaccine (RZV), an interim analysis of this follow-up study of the ZOE-50/70 trials demonstrated that efficacy against herpes zoster remained high. Moreover, the safety profile remained clinically acceptable, suggesting that the clinical benefit of the RZV in ≥50-year-olds is sustained up to 10 years.

Keywords. adjuvanted recombinant zoster vaccine; immune response persistence; long-term efficacy; long-term safety.

Lay summary

What is the context?

• Herpes zoster, also known as shingles, is a vaccine-preventable disease with potentially debilitating complications that greatly decrease quality of life.

• Shingrix is a vaccine indicated for the prevention of herpes zoster in adults aged 50 years or older and those 18 years or older who are at a higher risk of getting shingles.

• Published data shows that Shingrix offers a high level of protection against herpes zoster for up to eight years after vaccination.

What is new?

• Here we present the long-term protection and safety after vaccination with Shingrix in adults 50 years of age or older, up to 10 years after vaccination.

• Immune responses and the level of protection induced by RZV long-term efficacy • OFID • 1

Shingrix remain high, and the safety profile of Shingrix remains clinically acceptable.

What is the impact?

• Two doses of Shingrix offer sustained protection against herpes zoster in adults aged 50 years or older, with a clinically acceptable safety profile in the long term.

Reactivation of the varicella-zoster virus, known as herpes zoster (HZ) or shingles, occurs most frequently after the age of 50 years [1]. However, HZ and its debilitating complications, including postherpetic neuralgia, are preventable by vaccination [2–4]. The adjuvanted recombinant zoster vaccine (RZV, Shingrix, GSK) was first approved in 2017 for the prevention of HZ in ≥50-year-olds. RZV is currently licensed in >40 countries worldwide, including the United States and the European Union, where it is also approved for adults aged ≥18 years who are at increased risk of developing HZ. In the 2 pivotal prelicensure phase III randomized clinical trials (ZOE-50 and ZOE-70), RZV demonstrated 97% and 90% efficacy against HZ in adults aged ≥50 and ≥70 years over a median follow-up of 3.1 and 3.7 years, respectively [3, 4]. To evaluate the durability of the efficacy, immunogenicity, and safety of RZV, a long-term follow-up (LTFU) study (ZOE-LTFU) was initiated, which enrolled all eligible recipients of at least 1 dose of RZV from ZOE-50/70 who were willing to participate. ZOE-LTFU is planned to follow participants for 6 additional years, starting at ~5 years after vaccination with RZV [5].

In an interim analysis conducted after at least 2 years of follow-up in ZOE-LTFU, the efficacy of RZV against HZ was 84.0% for the period ranging from ~5–7 years postvaccination. When evaluated from 1 month post–second RZV dose in ZOE-50/70 up to 8 years postvaccination, efficacy was 90.9%. In addition, humoral and cell-mediated immune responses plateaued at >6-fold above prevaccination levels, and the safety profile remained clinically acceptable [5].

Here we present the results of a second interim analysis based on data collected after at least 4 years of follow-up in ZOE-LTFU and up to 10 years postvaccination in ZOE-50/70.

METHODS

Study Design and Participants

In the ZOE-50/70 parent studies (NCT01165177, NCT01165229), adults aged ≥50 and ≥70 years were randomized 1:1 to receive 2 RZV or placebo doses 2 months apart [3, 4]. Participants receiving...
at least 1 RZV dose during ZOE-50/70 were eligible to participate in ZOE-LTFU (NCT02723773), and ~50% enrolled [5].

ZOE-LTFU is an ongoing phase IIIb, open-label LTFU study of ZOE-50/70 conducted in 18 countries/regions (Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Mexico, Spain, Sweden, Taiwan, the United Kingdom, United States). The study started on April 16, 2016, and the data lock point (DLP) for this second interim analysis was on August 19, 2021, when participants had completed at least 4 additional years of follow-up and data accrual was complete through year (Y) 9. Results for Y10 are also included, although they are still incomplete at this DLP. Additional details, including a schematic representation of the study design, have been reported previously [5].

**Outcomes and Assessments**

The primary objective of the study is to assess the efficacy of RZV against HZ over the total duration of ZOE-LTFU. Other main objectives include evaluation of efficacy of RZV against HZ from 1 month post–second RZV dose in ZOE-50/70 through the end of ZOE-LTFU (overall and by year postvaccination), persistence of humoral and cell-mediated immune (CMI) responses to RZV at each year postvaccination, and safety.

For efficacy analyses, HZ cases were ascertained rigorously as described previously [3, 4]. Humoral and CMI responses were determined in terms of anti–glycoprotein E (gE) antibody concentrations (expressed in milli-International Units per milliliter [mIU/mL]) and frequencies of gE-specific CD4[2+] T cells (CD4+ T cells expressing at least 2 of the 4 activation markers assessed: interferon-γ, interleukin-2, tumor necrosis factor–α, and CD40 ligand per 10⁶ CD4+ T cells) [6]. Long-term safety was evaluated in terms of serious adverse events related to study participation and HZ-related complications (eg, postherpetic neuralgia, disseminated HZ).

**Table 1. Vaccine Efficacy in the ZOE-50/70 Studies and ZOE-LTFU After at Least 4 Additional Years of Follow-up (mTVC)**

|                | RVZ                                      | Historical Control/Placebo Group in ZOE-50/70a |
|----------------|------------------------------------------|-----------------------------------------------|
|                | N  n Sum of Follow-up (Years) Incidence (per 1000 py) | N  n Sum of Follow-up (Years) Incidence (per 1000 py) | Vaccine Efficacy (95% CI), % | P value |
| Vaccine efficacy in ZOE-LTFU – primary objective (up to the data lock point for the second interim analysis in ZOE-LTFU) | | | | |
| Overallb      | 7277 52 32673.8 1.6 7277 283 32673.8 8.7 | 81.6 (75.2–86.6) | P < .0001 |
| Vaccine efficacy from 1 month post–dose 2 – secondary objective (up to the data lock point for the second interim analysis in ZOE-LTFU) | | | | |
| Overallb      | 13881 84 85796.7 1.0 13881 765 85796.7 8.9 | 89.0 (85.6–91.3) | P < .0001 |
| Year 1b       | 13881 3 13744.5 0.2 14035 130 13823.3 9.4 | 97.7 (93.1–99.5) | P < .0001 |
| Year 2b       | 13569 10 13415.6 0.7 13564 136 13325.5 10.2 | 92.7 (86.2–96.6) | P < .0001 |
| Year 3b       | 13185 9 13016.1 0.7 13074 116 12834.0 9.0 | 92.4 (85.0–96.6) | P < .0001 |
| Year 4b       | 12757 10 12946.7 0.8 12517 95 12637.4 7.5 | 89.8 (80.3–95.2) | P < .0001 |
| Gap between ZOE-50/70 and ZOE-LTFU | | | | |
| Year 6a       | 7277 7 7210.2 1.0 7277 61 7210.2 8.5 | 88.5 (74.9–95.6) | P < .0001 |
| Year 7a       | 7100 10 6995.8 1.4 7100 60 6995.8 8.6 | 83.3 (67.2–92.4) | P < .0001 |
| Year 8a       | 6878 9 6762.9 1.3 6878 57 6762.9 8.4 | 84.2 (67.9–93.1) | P < .0001 |
| Year 9a       | 6648 15 6487.6 2.3 6648 55 6487.6 8.5 | 72.7 (51.0–85.7) | P < .0001 |
| Year 10a,c    | 6258 11 4869.1 2.3 6258 41 4869.1 8.4 | 73.2 (46.9–87.6) | P < .0001 |

Abbreviations: CI, confidence interval; mTVC, modified total vaccinated cohort; N, number of individuals included in each group; n, number of individuals with at least 1 confirmed herpes zoster episode; py, person-years; RVZ, adjuvanted recombinant zoster vaccine; ZOE-LTFU, long-term follow-up study of ZOE-50/70.

bRVZ vs matched historical controls from the placebo group in the ZOE-50/70 studies. The same N and follow-up period were considered for the historical control and vaccinated groups; n for historical controls represents the projected number of included placebo group participants from ZOE-50/70 with at least 1 confirmed herpes zoster episode based on the estimated incidence rate.

cRVZ vs placebo recipients from the ZOE-50/70 trials. The follow-up ceased at the first occurrence of a confirmed herpes zoster episode, last contact date, or data lock point for this second interim analysis. All efficacy estimates are adjusted by region.

aAt the data lock point for the second interim analysis in ZOE-LTFU, data collection for year 10 was still incomplete.

**Statistical Analyses**

Efficacy in ZOE-LTFU was evaluated in the modified total vaccinated cohort (mTVC), consisting of participants who received both RZV doses and did not develop a confirmed HZ episode before 1 month post–dose 2 in ZOE-50/70. Participants with confirmed HZ in ZOE-50/70 were censored for the efficacy analysis. In ZOE-50/70 and ZOE-LTFU, humoral and CMI responses were assessed in participant subsets. Persistence of humoral/CMI responses in ZOE-LTFU was evaluated in the according-to-protocol cohort for persistence. Long-term safety was evaluated in participants enrolled for LTFU. Detailed criteria for inclusion in these cohorts have been presented previously [5].

Because more than half of the placebo recipients from ZOE-50/70 were also vaccinated with RZV in a subsequent study [7], historical control estimates of incidence rates from the ZOE-50/70 placebo groups were used to assess vaccine efficacy during ZOE-LTFU. Additional statistical considerations have been presented previously [5].

For the previous interim efficacy analysis [5], a yearly effect was used in the model to estimate the yearly incidence rate for the placebo group from ZOE-50/70 data. As this yearly effect does not...
apply to the ZOE-LTFU data, it was removed from the model used for the present interim analysis, and the yearly incidence rate in the placebo group was considered the overall rate in the placebo group of ZOE-50/70. This change in the model resulted in slightly different efficacy estimates for the ZOE-LTFU period in this compared with the previous interim analysis [5].

RESULTS

Study Participants

Of the 7413 participants enrolled for the long-term efficacy assessment, 7277 were included in the mTVC, and 813 and 108 were included in the according-to-protocol cohorts for humoral and CMI persistence. In the mTVC, the mean age at first...
vaccination in ZOE-50/70 was 67.3 (±9.4) years; 60.7% were women, and 76.5% of participants were of European ancestry. Demographic characteristics were comparable between the different cohorts [5].

**Long-term Efficacy**

Over the ≥4-year follow-up in ZOE-LTFU, from a mean of 5.6 (±0.3) years to 9.6 (±0.3) years postvaccination, the interim analysis demonstrated 81.6% (95% confidence interval [CI], 75.2%–86.6%) efficacy of RZV against HZ (Table). When evaluated from 1 month post-dose 2 in ZOE-50/70 to a mean of 9.6 (±0.3) years postvaccination, the efficacy of RZV against HZ was 89.0% (95% CI, 85.6%–91.3%) in ZOE-LTFU participants. Annual vaccine efficacy estimates were ≥83.3% through Y8, 72.7% for Y9, and 73.2% for Y10 postvaccination.

**Immunogenicity Persistence**

The prevaccination anti-gE antibody geometric mean concentration was 1320.5 (95% CI, 1253.6–1391.0) mIU/mL, and the postvaccination geometric mean concentrations remained >5-fold over this level across Y5–Y10 postvaccination (Figure 1A). The mean geometric increases of anti-gE antibody concentrations were ≥5.8 across this interval. The median prevaccination CD4[2+] T-cell frequency (interquartile range) was 89.8 (1.0–202.4) and plateaued ≥6-fold over this level across Y5–Y10 postvaccination (Figure 1B).

**Long-term Safety**

No deaths or other serious adverse events were considered causally related to vaccination by the investigator. Since the previous interim analysis [5], 3 participants reported HZ-related complications. Two participants aged 78 and 80 years at the time of diagnosis experienced postherpetic neuralgia at >9 years postvaccination. Pain was resolving when the first participant was lost to follow-up, and at the DLP for the present interim analysis for the second participant. The third HZ-related complication was disseminated HZ, occurring in an 81-year-old participant at ∼9 years postvaccination, and had resolved by the DLP for the present interim analysis.

**DISCUSSION**

More than 95% of adults ≥20 years of age show serologic evidence of previous varicella-zoster virus infection, putting them at increasing risk for HZ and related complications throughout their lifetime [8]. Considering the increasing age-related risk, duration of protection in older adults is an important attribute; our LTFU study of >7000 adults with an average age of >67 years at vaccination showed that the efficacy against HZ remained high up to 10 years postvaccination.

The efficacy of RZV against HZ was 81.6% during the ≥4-year follow-up in ZOE-LTFU, ranging from a mean of 5.6 years up to 10 years postvaccination. When considering the period from vaccination in ZOE-50/70 up to 10 years, efficacy was 89.0%. Although vaccine efficacy plateaued from Y6 to Y8, it tended to decrease at Y9 and then remained stable through Y10.

Humoral immune responses during ZOE-LTFU plateaued through Y8, after which a decrease occurred through Y9, followed by a stabilization through Y10 at >5-fold over the prevaccination level. CMI responses remained stable at >6-fold above the prevaccination level in ZOE-LTFU through Y10. A similar trend in immune response kinetics has also been observed in adults ≥60 years of age [5, 9].

The strengths and limitations of our study have been detailed previously [5]. The limitations are related to the use of historical control group HZ incidence estimates for efficacy assessments, the fact that nearly half of ZOE-50/70 participants did not enroll in ZOE-LTFU, and the lack of data for Y5 efficacy estimations. Data accrual for Y10 is still ongoing, and precision of estimates for this time point will increase at the final analysis. The strengths include a long follow-up period (up to 10 years postvaccination at the DLP for this second interim analysis) and a more racially heterogeneous population for immunogenicity assessments compared with previous data [9].

**CONCLUSIONS**

At ∼10 years after vaccination, the efficacy of RZV against HZ remained high, and immune responses to RZV remained >5-fold above prevaccination levels. In addition, the safety profile of RZV remained clinically acceptable. These data suggest that the clinical benefit of the RZV in adults aged ≥50 years is sustained up to 10 years after vaccination, which may reassure practitioners and consequently lead to increased vaccination coverage among those who are recommended to receive RZV.

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Trademarks. Shingrix is a trademark owned by or licensed to the GSK group of companies.

Data sharing. The interim data analyzed during the current study are not available on a public registry but are available from the corresponding author on reasonable request.

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