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Translational Section

Research Article

Quality of Life Impact of an Adjuvanted Recombinant Zoster Vaccine in Adults Aged 50 Years and Older

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Abstract

Background: To determine the efficacy of an adjuvanted recombinant zoster vaccine in reducing the herpes zoster (HZ) burden of illness, HZ burden of interference with activities of daily living, and HZ impact on quality of life.

Methods: The assessments were integrated in two Phase III trials, ZOE-50 (NCT01165177) and ZOE-70 (NCT01165229). HZ burden of illness and HZ burden of interference with activities of daily living were assessed by the Zoster Brief Pain Inventory (ZBPI) instrument and quality of life by the EuroQol-5 Dimension (EQ-5D) utility index and the SF-36 health survey. We report the ZOE-50 results and a pooled analysis of patients aged 70 years and older from the trials combined.

Results: The estimated vaccine efficacy in reducing HZ burden of illness and HZ burden of interference was greater than 90% in both the ZOE-50 and the pooled ZOE-70 analysis. In confirmed HZ cases, adjuvanted recombinant zoster vaccine reduced the maximal ZBPI worst-pain score in the pooled ZOE-70 analysis (p = .032) and the maximal ZBPI average-pain scores in both the ZOE-50 (p = .049) and the pooled ZOE-70 analysis (p = .043). In breakthrough HZ cases, trends for diminished loss of quality of life compared with placebo-recipient HZ cases were observed, with differences up to 0.14 on the EQ-5D index at time points during the 4 weeks following HZ onset.

Conclusions: Adjuvanted recombinant zoster vaccine reduced the HZ burden of illness significantly, particularly due to its very high vaccine efficacy in preventing HZ. For breakthrough HZ cases, the results suggest that the adjuvanted recombinant zoster vaccine mitigated severity of HZ-related pain, burden of interference with activities of daily living, and recipients' utility loss.

Keywords: Burden of illness, Burden of interference, Activities of daily living

Herpes zoster (HZ) results from reactivation of the varicella-zoster virus (VZV). HZ typically manifests as a unilateral, painful dermatomal rash. Most cases of HZ resolve completely within about 1 month of rash onset, but 10%–20% of HZ patients develop postherpetic neuralgia, a condition of debilitating pain that may last for months or even years and is very difficult to treat (1–3).

The pain and discomfort experienced during an acute HZ episode may substantially reduce patients' health-related quality of life (QoL) by impairing their physical, emotional, and social functioning. The pain may interfere with patients' ability to perform activities of daily living (ADLs), diminish vitality, and impair physical and mental health (4–6).

The incidence of HZ increases substantially from around the age of 50 years, concurrent with the natural age-related decline of cell-mediated immunity, which is considered an important risk factor for reactivation of VZV (7). The lifetime risk of developing HZ is estimated at approximately 30%, increasing to 50% or more in people living beyond the age of 85 years (8,9).

The principal available treatments for HZ, analgesics, and antivirals have shown efficacy in the context of clinical trials but in clinical-practice patient satisfaction with their perceived effectiveness in alleviating symptoms was found to be low (9). HZ is preventable by vaccination, and an HZ vaccine containing live attenuated VZV was licensed in the United States and Europe in 2006 (10).

Adjuvanted recombinant zoster vaccine (RZV; *Shingrix*, GSK) is a two-dose adjuvanted nonlive subunit vaccine combining recombinant VZV glycoprotein E and the $AS01_B$ adjuvant system. Two multinational Phase III randomized, observer-blinded, placebo-controlled clinical trials were conducted concurrently at the same study sites using the same methods to assess the efficacy of RZV in preventing HZ in two adult populations. The ZOE-50 study (NCT01165177) included patients aged 50 years and older (11) and ZOE-70 study (NCT01165229) included patients aged 70 years and older (12). For patients developing HZ, the trials also collected data for assessing the burden of illness of HZ, its burden of interference with the patients' ADLs and its impact on their QoL.

A protocol prespecified pooled analysis of all patients aged 70 years and older from the two trials (henceforth "the pooled ZOE-70 analysis") was performed to obtain more robust estimates of the vaccine's efficacy in people aged 70 years and older. In both the ZOE-50 trial and the pooled ZOE-70 analysis, the overall vaccine efficacy (VE) of RZV in preventing HZ was estimated to be more than 90% (11,12).

In this article, using data from the ZOE study and the pooled ZOE-70 analysis, we present results showing the efficacy of RZV in preventing the burden of illness of HZ and the HZ burden of interference with ADLs, and its impact on the QoL of patients with HZ. The corresponding comparative results of the ZOE-70 analysis are presented in Supplementary Material for this article.

Methods

Study Design

The study design was described in detail in the articles presenting the efficacy and safety results of the trials (11,12).

Outcome Measures

Patients with suspected HZ were asked to attend assessment visits and to complete the Zoster Brief Pain Inventory (ZBPI) daily for 28 days after rash onset and then weekly until either the patient had been pain free for four consecutive weeks or 90 days had elapsed after rash onset (whichever came last). For all analyses of data involving HZ episodes, Day 0 was defined as the first day of HZ rash (13). If the rash had started more than 24 hours before the initial assessment, patients were asked to retrospectively complete the ZBPI for the period between rash onset and 24 hours before the first assessment day.

The ZBPI asks the patients to rate four categories of pain (least, worst, average over the last 24 hours, and now) on 11-point Likert-type scales (0–10, with 10 signifying the worst imaginable pain). The "worst pain" over the last 24 hours category is considered the most reliable indicator of pain (13) and was used to measure the VE in reducing the burden of illness related to HZ pain.

The ZBPI questionnaire also assesses the degree to which the HZ pain interferes with seven ADLs: general activity, mood, walking ability, work, relation with others, sleep, and enjoyment of life. These are all to be rated on 11-point Likert-type scales with

Table 1. HZ ZBPI Severity and Burden of Illness Scores (Based on ZBPI "Worst-Pain" Score)

	RZV				Placebo					
Age Group (YOA)	*n*	*m*	ZBPI Severity of Illness Score[a]	ZBPI Burden of Illness Score	*n*	*m*	ZBPI Severity of Illness Score[a]	ZBPI Burden of Illness Score	VE (%)	95% CI for VE (%)
ZOE-50 study										
50–59	4	3,491	0.069	0.018	103	3,523	4.179	1.056	98.3	(83.8, 100)
60–69	3	2,140	0.082	0.020	89	2,165	4.274	1.067	98.1	(79.2, 100)
≥70	2	1,709	0.069	0.019	60	1,723	6.059	1.644	98.9	(72.1, 100)
Total	9	7,340	0.073	0.019	252	7,411	4.644	1.188	98.4	(92.2, 100)
Pooled ZOE-70 analysis										
70–79	19	6,468	0.316	0.084	214	6,552	6.369	1.690	95.1	(92.5, 97.7)
≥80	6	1,782	1.222	0.344	67	1,791	6.777	1.932	82.2	(77.2, 87.2)
Total	25	8,250	0.511	0.137	281	8,343	6.457	1.739	92.1	(90.4, 93.8)

Notes: CI = confidence interval; HZ = herpes zoster; *m* = total number of patients in this group; *n* = number of HZ cases in this group; RZV = adjuvanted recombinant zoster vaccine; VE = vaccine efficacy; YOA = years of age; ZBPI = Zoster Brief Pain Inventory.

[a]ZBPI severity of illness was calculated as the area under the curve (AUC), Days 0–182, of the ZBPI "worst-pain" score for patients with confirmed HZ cases. Patients without a confirmed HZ case were allocated an AUC score of 0. The ZBPI burden of illness score was calculated as the ZBPI severity of illness score divided by the total follow-up in years. In the ZOE-50 study and pooled ZOE-70 analysis, two and three patients in the placebo groups, respectively, had a confirmed HZ episode but did not have an evaluable ZBPI score and were therefore not included in this table. Score: 0–10, with 10 signifying the worst pain.

Table 2. HZ ZBPI Severity and Burden of Interference Scores (Based on ZBPI ADL Summary Scores)

	RZV				Placebo					
Age Group (YOA)	*n*	*m*	ZBPI Severity of Interference Score[a]	ZBPI Burden of Interference Score	*n*	*m*	ZBPI Severity of Interference Score[a]	ZBPI Burden of Interference Score	VE	95% CI for VE
ZOE-50 study										
50–59	4	3,491	0.024	0.006	103	3,523	2.850	0.720	99.2	(68.0, 100)
60–69	3	2,140	0.038	0.010	89	2,165	2.823	0.705	98.7	(63.8, 100)
≥70	2	1,709	0.024	0.006	60	1,723	4.004	1.087	99.4	(37.0, 100)
Total	9	7,340	0.028	0.007	252	7,411	3.110	0.796	99.1	(86.2, 100)
Pooled ZOE-70 analysis										
70–79	19	6,468	0.180	0.048	214	6,552	4.261	1.130	95.8	(92.3, 99.3)
≥80	6	1,782	1.353	0.381	67	1,791	5.110	1.457	73.8	(69.5, 78.1)
Total	25	8,250	0.434	0.116	281	8,343	4.443	1.196	90.3	(88.5, 92.1)

Notes: ADL = activities of daily living; CI = confidence interval; HZ = herpes zoster; *m* = total number of patients in this group; *n* = number of HZ cases in this group; VE = vaccine efficacy; YOA = years of age; ZBPI = Zoster Brief Pain Inventory.

[a]ZBPI severity of interference was calculated as the area under the curve (AUC), Days 0–182, of the ZBPI ADL score for patients with confirmed HZ cases. Patients without a confirmed HZ case were allocated an AUC score of 0. The ZBPI burden of interference score was calculated as the ZBPI severity of interference score divided by the total number of years of follow-up. Score: 0–10, with 0 signifying "does not interfere" and 10 "completely interferes."

0 signifying "does not interfere" and 10 "completely interferes." A summary ADL score is calculated by averaging the scores for the seven activities.

The EuroQol-5 Dimension (EQ-5D) is a utility instrument widely used in assessments of individuals' health-related QoL. Patients are asked to grade their extent of problems (no problem, some problems, and severe problems) in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The combination of answers to the five dimensions results in 243 possible health states, each of which may be translated into a utility score ranging from less than 0 (ie, a health state worse than death) to 1 (ie, best possible health state) (14).

QoL was also assessed by the Short Form Survey (SF-36) (15). This assessment method and a short summary of the SF-36 results are described in Supplementary Material for this article. All patients were asked to complete the EQ-5D and SF-36 questionnaires at baseline (ie, Day 0, before vaccination Dose 1). Patients not developing HZ were asked to complete the questionnaires at Months 14, 26, and 38. All patients experiencing a suspected HZ episode were to complete both the EQ-5D and SF-36 at the first visit to evaluate suspected HZ and then weekly along with the ZBPI.

For patients with suspected HZ, specimens were tested centrally by polymerase chain reaction and reviewed by an adjudication committee. Only HZ cases confirmed by polymerase chain reaction or by the adjudication committee were included in the analyses (11,12).

Statistical Analyses

For each case of HZ, the maximal ZBPI "worst-pain" and "average-pain" scores during the HZ episode were calculated and compared between the RZV and placebo groups by means of the Wilcoxon nonparametric test. Clinically significant pain was defined as a ZBPI "worst-pain" score greater than or equal to 3.

A combined measure of pain intensity and duration was calculated by the area under the curve method (13). For each patient, the area under the curve was calculated by multiplying the average of two consecutive ZBPI worst-pain scores by the number of days between the scores and adding up these measures over a specified time period (13). The modified ZBPI scale was used (13), which

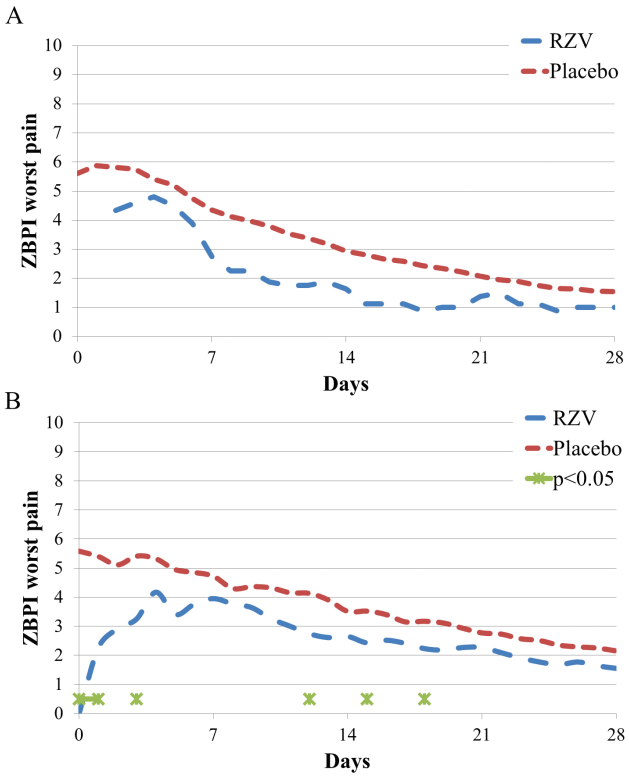

Figure 1. Mean ZBPI "worst-pain" scores per day during the first 28 days after rash onset (**A**: ZOE-50 study; **B**: pooled ZOE-70 analysis). RZV = adjuvanted recombinant zoster vaccine; ZBPI = Zoster Brief Pain Inventory. *Days with statistically significant differences (at the .05 level) in ZBPI worst-pain scores between the two groups. In the ZOE-50 study, no RZV recipient with HZ completed the ZBPI days 0 and 1.

from Day 30 onwards sets ZBPI "worst-pain" scores of less than 3 equal to 0. The ZBPI severity of illness scores were calculated as the area under the curve from the day of rash onset until Day 182. An area under the curve value of 0 was imputed for patients without confirmed HZ. The burden of illness due to pain was then estimated by aggregating the severity of illness scores over all the

patients in a group and dividing by the total number of years of patient follow-up. Consequently, this composite measure takes the incidence of HZ as well as the severity and duration of HZ pain into account.

VE was defined as the relative reduction in the burden of illness score in the RZV group as compared to the score in the placebo group and calculated as 1 minus the relative risk (ie, the burden of illness score in the RZV group divided by the burden of illness score in the placebo group). The VE in reducing the burden of interference was defined and calculated in a similar way using the combined ZBPI ADL score as the measure.

These analyses were performed on the modified total vaccinated cohort, which excluded patients who did not receive two doses or who had a confirmed HZ episode within 1 month of receiving Dose 2 and included only HZ patients who completed at least one ZBPI questionnaire. The chop-lump test (16) was used to assess the difference in ZBPI severity of illness scores and ZBPI severity of interference scores between the RZV and placebo groups in the modified total vaccinated cohort.

In a post hoc analysis, VE for reducing severe ZBPI pain (score ≥ 7 for "worst-pain") was estimated in patients in the modified total vaccinated cohort HZ evaluable subgroup which included confirmed HZ cases with a ZBPI questionnaire completed during the first 14 days after HZ onset. Standardized asymptotic binomial confidence intervals (CI) for the VE were calculated using the score method of Farrington and Manning (17).

A repeated-measures analysis of variance model was fitted to estimate the impact of HZ on EQ-5D utility scores in the placebo group only, stratified by age. There were too few patients in the RZV group with breakthrough HZ to apply this modeling approach. The model included the baseline utility scores, that is, the most recent utility assessment prior to the onset of HZ and the utility scores during the first 4 weeks of the HZ episode. The least squares mean estimates over time are presented.

Results

Flowcharts of the trials and demographic data of the patients enrolled in the two studies who developed confirmed HZ along with the various study populations are presented in Supplementary Figures S1 and S2. At the end of study analysis of the ZOE-50 study, 9 HZ cases had occurred among the 7,340 patients receiving RZV compared with 254 cases among the 7,413 patients receiving placebo. In the pooled ZOE-70 analysis, 25 HZ cases occurred among the 8,250 patients receiving RZV and 284 cases among the 8,346 patients receiving placebo (Table 1).

Table 3. Distribution of Maximal ZBPI "Worst-Pain" and ZBPI "Average-Pain" Scores Over the Duration of the Entire HZ Episode

	ZOE-50			Pooled ZOE-70		
	RZV (*N* = 8)	Placebo (*N* = 241)		RZV (*N* = 23)	Placebo (*N* = 263)	
ZBPI Scale	*n* (%)	*n* (%)	*p* Value	*n* (%)	*n* (%)	*p* Value
"Worst-pain" score						
≥3	7 (87.5)	211 (87.6)	.113	19 (82.6)	239 (90.9)	.032
0	1 (12.5)	13 (5.4)		1 (4.3)	18 (6.8)	
1	0	10 (4.1)		1 (4.3)	2 (0.8)	
2	0	7 (2.9)		2 (8.7)	4 (1.5)	
3	0	9 (3.7)		1 (4.3)	21 (8.0)	
4	2 (25.0)	13 (5.4)		4 (17.4)	14 (5.3)	
5	0	19 (7.9)		2 (8.7)	16 (6.1)	
6	1 (12.5)	13 (5.4)		2 (8.7)	8 (3.0)	
7	2 (25.0)	33 (13.7)		1 (4.3)	23 (8.7)	
8	2 (25.0)	38 (15.8)		3 (13.0)	50 (19.0)	
9	0	48 (19.9)		5 (21.7)	43 (16.3)	
10	0	38 (15.8)		1 (4.3)	64 (24.3)	
Mean	5.5	6.7		5.7	7.0	
SD	2.73	2.94		2.96	3.02	
"Average-pain" score						
0	1 (12.5)	14 (5.8)	.049	1 (4.3)	19 (7.2)	.043
1	0	13 (5.4)		2 (8.7)	8 (3.0)	
2	0	15 (6.2)		2 (8.7)	18 (6.8)	
3	2 (25.0)	13 (5.4)		4 (17.4)	18 (6.8)	
4	1 (12.5)	25 (10.4)		2 (8.7)	21 (8.0)	
5	3 (37.5)	23 (9.5)		3 (13.0)	26 (9.9)	
6	1 (12.5)	40 (16.6)		4 (17.4)	35 (13.3)	
7	0	30 (12.4)		3 (13.0)	46 (17.5)	
8	0	38 (15.8)		1 (4.3)	32 (12.2)	
9	0	17 (7.1)		0	21 (8.0)	
10	0	13 (5.4)		1 (4.3)	19 (7.2)	
Mean	3.9	5.5		4.5	5.6	
SD	1.89	2.74		2.50	2.81	

Notes: HZ = herpes zoster; *N* = number of HZ cases in each group; *n* = number of HZ cases in each category; ZBPI = Zoster Brief Pain Inventory. Includes only patients in the modified total vaccinated cohort HZ evaluable subgroup, that is, confirmed HZ cases with a ZBPI questionnaire completed during the first 14 days after HZ onset.

The mean delay between the date of rash onset and the first HZ evaluation was 4.7 and 4.8 days in the ZOE-50 and pooled ZOE-70 analysis, respectively (range 0–33 in both analyses). Completion rates for the ZBPI questionnaire were approximately 15% on Day 0, more than 60% from Day 3 onwards, and greater than or equal to 80% from Day 6 onwards. For the EQ-5D and SF-36 instruments during an ongoing HZ episode, the completion rates were approximately 50% on Day 0 and greater than or equal to 84% at all time points thereafter.

Overall VE

The estimated overall VE in reducing the ZBPI burden of illness was 98.4% in the ZOE-50 study and 92.1% in the pooled ZOE-70 analysis (Table 1). The VE in reducing burden of illness was lower in patients aged 80 years and older (ie, 82.2%). However, the absolute reduction in burden of illness score was higher in these patients compared with younger patients (ie, 1.932–0.344 ≈ 1.6 in patients aged 80 years and older compared with 1.0 in patients aged 50–69 years). The estimated overall VE in reducing the burden of interference with ADLs was 99.1% in the ZOE-50 study and 90.3% in the pooled ZOE-70 analysis (Table 2).

Outcomes for Patients Developing HZ

Figure 1 presents the mean ZBPI "worst-pain" scores per day during the first 28 days for all the confirmed HZ cases. The mean "worst-pain" scores were at all times lower in the RZV group than in the placebo group, but the differences were only statistically significant for a few days spread over the period in the pooled ZOE-70 analysis.

Table 3 presents the distribution of the individual maximal ZBPI "worst-pain" and "average-pain" scores experienced over the entire HZ episode. In the ZOE-50 study, a severe ZBPI "worst-pain" score (ie, ≥7) was reported by 50.0% in the RZV group and 65.2% in the placebo group (VE 23.3%, 95% CI = −22.4%–67.2%). The corresponding proportions reporting severe ZBPI "average pain" were 0% and 40.7%, respectively (VE 100%, 95% CI = 19.4%–100%). The median time to resolution of clinically significant pain (ie, ZBPI "worst pain" ≥ 3) was 14 days in the RZV group and 17 days in the placebo group (p = .600).

In the pooled ZOE-70 analysis, the proportions reporting severe "worst pain" were 43.5% in the RZV group and 68.4% in the placebo group (VE 36.5%, 95% CI = 6.5%–62.8%). The corresponding proportions reporting severe "average pain" were 21.7% in the RZV group and 44.9% in the placebo group (VE 51.6%, 95% CI = 4.9%–78.7%). The median time to resolution of clinically significant pain was 14 days in the RZV group versus 22 days in the placebo group (p = .409).

Figure 2 presents the mean ZBPI ADL interference scores during the first 28 days for the placebo groups only. Sleep, mood, and general activities appear to be the most affected. In both plots, the mean ADL interference scores appeared to peak at Days 3 and 4 after rash onset and gradually diminished over time.

Table 4 presents the utility loss of the HZ patients in the placebo groups over the first 28 days after rash onset, assessed using the EQ-5D instrument. The estimated utility loss was highest on Day 0 and decreased over time in all age groups as the patients recovered from HZ, but a negative impact of HZ on QoL remained until the end of Week 4.

The estimated differences over time in mean EQ-5D utility scores between the RZV and placebo groups are presented in Figure 3, suggesting that they were greatest at Day 0 (up to 0.14 in ZOE-50) and decreased over time. Using the utility assessments prior to the HZ episode as baseline, the VE in terms of reducing the patients' utility loss due to HZ over the first 28 days after rash onset was estimated to be 63.7% in the ZOE-50 study and 21.2% in the pooled ZOE-70 analysis.

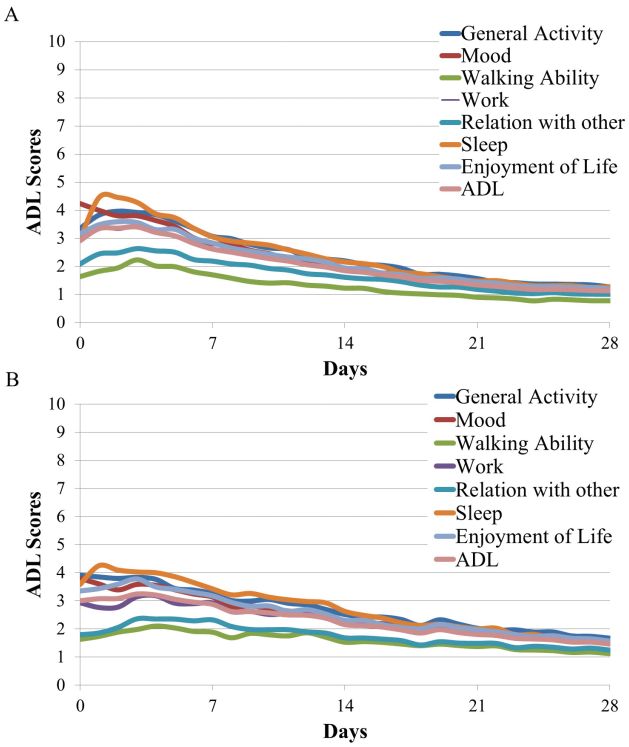

Figure 2. Mean daily ZBPI ADL scores during the first 28 days after rash onset for the placebo groups (**A**: ZOE-50 study; **B**: pooled ZOE-70 analysis). ADL = activities of daily living; ZBPI = Zoster Brief Pain Inventory.

Discussion

The overall efficacy of the RZV in reducing the burden of illness and the burden of interference in ADLs of HZ was more than 90% in both the ZOE-50 study and the pooled ZOE-70 analysis. These are mainly the results of VE in preventing HZ. However, even with the small number of breakthrough HZ cases compared with the placebo recipients, this study demonstrated that adults who developed HZ despite vaccination with RZV were less likely to have severe pain, and there was a trend for them to have a shorter duration of pain, less burden of interference in ADLs, and higher QoL scores over the first 4 weeks following rash onset. Therefore, RZV not only prevented HZ but also attenuated the severity of disease in individuals who developed HZ despite being vaccinated with RZV.

The corresponding comparative results of the ZOE-70 analysis are presented in Supplementary Material for this article. The results are in line with the ZOE-70 pooled analysis presented in the main text and also with those presented by Cunningham and colleagues (12). Note that the two clinical trials, ZOE-50 and ZOE-70, were conducted at the same sites, and patients aged 70 years and older were randomly assigned to the ZOE-50 or ZOE-70 study. This ensured that the prespecified pooled analysis could be done appropriately, leading to more robust results in all patients aged 70 years and older.

Table 4. Estimated Placebo-Group EQ-5D Scores for Utility Loss by Age Group and Time Point During the Acute HZ Period

Age Group (YOA)	Time Point	LS Means Estimate	Estimated Utility Loss	95% CI
ZOE-50 study				
50–59	Pre-HZ	0.880		
	Day 0	0.622	0.258	(0.204, 0.313)
	Week 1	0.685	0.195	(0.136, 0.254)
	Week 2	0.736	0.145	(0.081, 0.208)
	Week 3	0.821	0.059	(–0.007, 0.125)
	Week 4	0.872	0.008	(–0.060, 0.076)
60–69	Pre-HZ	0.879		
	Day 0	0.637	0.242	(0.176, 0.308)
	Week 1	0.713	0.166	(0.102, 0.230)
	Week 2	0.791	0.087	(0.020, 0.155)
	Week 3	0.800	0.078	(0.008, 0.150)
	Week 4	0.799	0.080	(0.007, 0.152)
≥70	Pre-HZ	0.800		
	Day 0	0.517	0.284	(0.209, 0.358)
	Week 1	0.610	0.190	(0.110, 0.270)
	Week 2	0.703	0.097	(0.011, 0.184)
	Week 3	0.713	0.087	(0.000, 0.175)
	Week 4	0.765	0.035	(–0.054, 0.124)
Pooled ZOE-70 analysis				
70–79	Pre-HZ	0.840		
	Day 0	0.606	0.234	(0.191, 0.277)
	Week 1	0.674	0.166	(0.121, 0.210)
	Week 2	0.686	0.153	(0.107, 0.200)
	Week 3	0.735	0.105	(0.057, 0.152)
	Week 4	0.787	0.052	(0.004, 0.100)
≥80	Pre-HZ	0.753		
	Day 0	0.542	0.211	(0.133, 0.289)
	Week 1	0.645	0.108	(0.030, 0.187)
	Week 2	0.686	0.067	(–0.017, 0.150)
	Week 3	0.682	0.071	(–0.015, 0.157)
	Week 4	0.749	0.004	(–0.083, 0.091)

Notes: CI = confidence interval; EQ-5D = EuroQol-5 Dimension; HZ = herpes zoster; LS = least squares; YOA = years of age. An EQ-5D value of 1 represents the best possible health state.

It is likely that vaccine-induced VZV-specific CD4+ T cells play a role in the attenuation of breakthrough cases for both the live attenuated vaccine and for RZV (especially as such CD4+ T cells are present in the dorsal root ganglion in natural HZ). Plausible hypotheses are that memory CD4+ T cells could have direct antiviral effects (eg, through interferon-γ) or could mobilize natural killer cells, resulting in (antibody-dependent) cytolytic responses. Thus, memory CD4+ T cells would be capable of mounting a rapid antiviral response upon reactivation of VZV. In some cases, this anamnestic immune response may not be able to prevent an HZ episode, but in vaccine recipients with breakthrough disease, the response may be sufficient to more rapidly control the reactivated virus, leading to reduced severity of disease. Observations of apparent mitigation of breakthrough disease in vaccine recipients have also been reported for a number of other vaccine-preventable diseases such as influenza, rotavirus, and pertussis (18–20).

The greatest interference of HZ-related pain on ADLs occurred during the first week following rash onset. Sleep was the most impacted activity in the placebo recipients. Another study also found that some 65% of HZ patients did not get sufficient sleep most of the time (21). As both the ZBPI pain and ADL interference scores on the day of rash onset were high, it may be hypothesized that pain started during the prodromal period. Previous studies showing that prodromal pain may last for 1–5 days or even longer before rash onset (6,22) suggest that the overall duration of clinically relevant HZ pain and utility loss was greater than we estimated.

In the placebo groups, based on the mean utility values estimated for the HZ patients during the first 4 weeks after HZ onset (Table 4) and the pre-HZ scores, the monthly values for the utility loss may be estimated at 0.140 and 0.132 (ie, 4.3 and 4.0 days of perfect health lost for each month of HZ) for the ZOE-50 and pooled ZOE-70 analysis, respectively. These values are in line with Pellissier and colleagues (23), who also reported quality-adjusted life-years losses for postherpetic neuralgia patients, in unvaccinated patients of 0.106 and 0.156 (ie, 38.7 and 56.9 days of perfect health lost during a year). Kawai and colleagues, in a literature review, estimated, based on the values from Pellissier and colleagues, that the overall quality-adjusted life-years lost due to HZ including postherpetic neuralgia was 0.021, 0.049, and 0.058 for patients aged 60–69, 70–79, and 80 years and older, respectively. Much higher values were reported by Moore and colleagues based on data from Oster and colleagues (1,24,25). Using these estimates and incidence estimates from Leung and colleagues (26), between 25,000 and 100,000 years of perfect health are lost annually in the United States in patients aged 60 years and older due to HZ.

As a consequence of the high VE against HZ, and the low number of breakthrough cases, the statistical power to identify statistically significant differences between the groups is low. We calculated, using Cohen's "*d*" effect size measure, that at the $p = .05$ level, power was only 29% for the ZOE-50 study and 63% for the pooled ZOE-70 analysis (27).

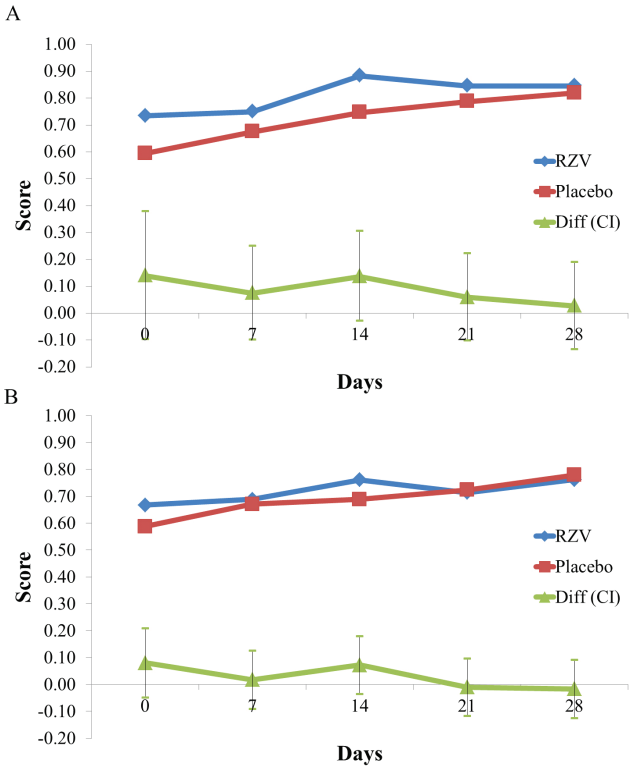

Figure 3. Mean EQ-5D utility scores during the first 28 days after rash onset (**A**: ZOE-50 study; **B**: pooled ZOE-70 analysis). CI = confidence interval; Diff. = difference; EQ-5D = EuroQol-5 Dimension; RZV = adjuvanted recombinant zoster vaccine.

To conclude, this study provided evidence that the RZV vaccine, in addition to its very high efficacy in preventing HZ, has an effect of attenuating the severity of HZ disease in breakthrough cases. This mitigation was most clearly quantified with the HZ-specific ZBPI instrument to assess the severity of pain but was also discernible as trends with the less sensitive, generic QoL instruments. Vaccination with RZV could prevent loss of quality of life associated with both HZ and postherpetic neuralgia.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Compliance With Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

J.E.M. received honoraria and fees paid to her institution from GSK, Sanofi Pasteur, Merck Sharp & Dohme, and Pfizer, as well as travel support from Sanofi Pasteur, Merck Sharp & Dohme, and Pfizer outside the submitted work. A.V. reports personal fees from Sanofi Pasteur MSD outside the submitted work. J.D.D. reports personal fees from GSK (advisory board: pharmacoeconomic study with Synflorix in Spain), grants from Sanofi Pasteur MSD (epidemiological study on herpes zoster), and personal fees from Sanofi Pasteur MSD (advisory board: Zostavax) outside the submitted work. M.J.L. received fees for serving on advisory boards from Merck Sharp & Dohme and GSK, grant support from Merck Sharp & Dohme and GSK, and royalties from a patent related to a zoster vaccine held with Merck. E.A., C.A., B.J., T.K., and E.L. have nothing to disclose. F.D.L. reports grants from GSK and Novartis outside the submitted work. He is the medical director of a company that conducts clinical trials for a large number of pharmaceutical companies in many different therapeutic areas. S.McN. reports grants and personal fees from Pfizer (continuing professional development talks on adult immunization; research grant; consulting fees), grants from GSK, personal fees from Merck Sharp & Dohme (continuing professional development talks on adult immunization and consulting fees) outside the submitted work. R.J. reports personal fees from GSK. During the conduct of the study, he also reports personal fees from Sanofi Pasteur MSD and Merck Sharp & Dohme. Outside the submitted work, he reports personal fees from Merck Sharp & Dohme and Sanofi Pasteur MSD. H.L. is a current employee of Pfizer and receives stock options as part of his employee remuneration. D.C. and L.C. are employees of the GSK group of companies. D.C. hold shares in the GSK group of companies. T.C.H., H.L., and L.O. are former employees of the GSK group of companies. T.C.H., H.L., and L.O. hold shares or stock options from GSK as part of their current or former employee remuneration. T.C.H. is a consultant for GSK and is the coinventor of a patent application related to the vaccine used in this study. S.M. is a freelance consultant working on behalf of GSK.

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