Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Infectious Disease

Recombinant Zoster Vaccine Significantly Reduces the Impact on Quality of Life Caused by Herpes Zoster in Adult Autologous Hematopoietic Stem Cell Transplant Recipients: A Randomized Placebo-Controlled Trial (ZOE-HSCT)

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Article history:
Received 17 June 2019
Accepted 28 July 2019

Keywords:
Autologous hematopoietic stem cell transplant
Herpes zoster

A B S T R A C T

Herpes zoster (HZ) can have a substantial impact on quality of life (QoL). The vaccine efficacy (VE) of a recombinant zoster vaccine (RZV) was 68.2% (95% confidence interval [CI], 55.6% to 77.5%) in a phase 3 study in adult autologous hematopoietic stem cell transplant (HSCT) recipients (NCT01610414). Herein, we report the impact of RZV on patients' QoL. Autologous HSCT recipients were randomized 1:1 to receive 2 doses of RZV or placebo, given 1 to 2 months apart. QoL was measured by the Short Form Survey-36 and Euro-QoL-5 Dimension at baseline, 1 month, and 1 year postdose 2 and during suspected HZ episodes with the Zoster Brief Pain Inventory (ZBPI). The RZV impact

Financial disclosure: See Acknowledgments on page 2480.

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https://doi.org/10.1016/j.bbmt.2019.07.036

Quality of life
Recombinant zoster vaccine
Vaccination

on ZBPI burden of illness and burden of interference scores was estimated. The 2 scores were calculated from the area under the curve (days 0 to 182) of the ZBPI worst pain and ZBPI activities of daily living scores, respectively, assuming a score of 0 for patients not having a confirmed HZ episode. The ZBPI maximum worst pain score was significantly lower in the RZV than placebo group (mean: 5.8 versus 7.1, $P = .011$). Consequently, the VE estimates for HZ burden of illness (82.5%; 95% CI, 73.6 to 91.4) and burden of interference (82.8%; 95% CI, 73.3 to 92.3) were higher than the HZ VE estimate (ie, 68.2%). RZV showed significantly better QoL scores than placebo 1 week following rash onset among patients with confirmed HZ. In addition to reducing the risk of HZ and its complications, RZV significantly reduced the impact of HZ on patients' QoL in those who developed breakthrough disease.

INTRODUCTION

Herpes zoster (HZ), which occurs following the reactivation of latent varicella zoster virus (VZV), usually presents as a painful vesicular dermatomal rash [1,2]. VZV cell-mediated immunity, which inhibits the development of HZ, can decline for a number of reasons, including increasing age and immune suppression [3,4]. Patients with malignant, chronic, or autoimmune conditions, or those receiving immunosuppressive therapies, therefore have an increased risk of developing HZ [5]. Hematopoietic stem cell transplantation is the risk factor with the highest odds ratio for developing HZ (odds ratio, 13.46) [5]. Several studies reported an increased risk of HZ among stem cell transplant recipients, with incidence rates reaching 41.7 per 1000 person years [6-10].

In addition to the increased risk of HZ in patients with various immunocompromising conditions, these individuals also experience an increased severity of disease. For example, high proportions of hematopoietic stem cell transplant (HSCT) recipients develop complications, including postherpetic neuralgia following HZ [11,12].

In a study in Canada, Drolet et al. [13] reported that individuals with an impaired immune status had HZ severity of illness scores, as measured by the Zoster Brief Pain Inventory (ZBPI), that were twice as high as individuals with normal immune function. In a study in the United States, Yawn et al. [14] reported that although 8% of HZ cases occurred among immunocompromised patients, these individuals represented 23.8% of the total HZ-related costs. Another study, based on data from the United Kingdom, demonstrated that the highest direct medical costs related to patients with HZ were observed in HSCT recipients [15].

Prevention of HZ in HSCT recipients is traditionally achieved using oral acyclovir or valacyclovir. However, as there is still a high risk of HZ once treatment is stopped, the optimal duration of prophylaxis remains unclear [8,16,17]. A live-attenuated vaccine produced by Merck (Zostavax, New Jersey, United States) is licensed to prevent HZ in immunocompetent adults aged ≥50 years. However, the vaccine is contraindicated in immunocompromised individuals, in whom administration may result in disseminated disease. Recently, a nonlive 2-dose adjuvanted recombinant zoster vaccine (RZV) produced by GlaxoSmithKline (Shingrix, United Kingdom) was licensed in adults aged ≥50 years [18]. This vaccine consists of the VZV glycoprotein E antigen and an adjuvant system ($AS01_B$). The vaccine efficacy (VE) in preventing HZ in immunocompetent individuals was 97.2% in adults ≥50 years and 91.3% in older adults ≥70 years [19,20].

This phase III ZOster Efficacy trial in HSCT recipients (NCT01610414; ZOE-HSCT) was designed to explore the impact of RZV (2 doses administered 1 to 2 months apart starting 50 to 70 days post-transplantation) on reducing the burden of HZ in autologous HSCT recipients. The efficacy, safety, and immunogenicity results of the study are published elsewhere [21]; only the quality-of-life (QoL) results are presented here. The VE of RZV in preventing HZ in adult autologous HSCT recipients was 68.2% (95% confidence interval [CI], 55.6% to 77.5%). In this article, we present further results from the ZOE-HSCT trial concerning the impact of RZV on the burden of HZ illness, the burden of HZ interference on patients' activities of daily living (ADLs), and the effect of HZ on patients' QoL.

MATERIALS AND METHODS

This randomized, placebo-controlled, phase III multicenter study assessed the efficacy, immunogenicity, and safety of RZV in autologous HSCT recipients aged ≥18 years. The study design has been described in detail in the study presenting the efficacy and safety results of the trial [21].

Outcome Measures

The ZBPI questionnaire asks the participant to rate 4 categories of pain (least, worst, and average "in the last 24 hours," in addition to "right now") on 11-point Likert-type scales (0 to 10, with 10 signifying the worst imaginable pain). The ZBPI also assesses the degree to which HZ pain interfered with 7 ADLs: general activity, mood, walking ability, work, relation with others, sleep, and enjoyment of life. These were all rated on 11-point Likert-type scales, with 0 signifying "does not interfere" and 10 "completely interferes." A summary ADL score was calculated by averaging the scores for all 7 activities.

Autologous HSCT recipients with suspected HZ were asked to complete the ZBPI at home every day from rash onset until the first visit to the site. They completed a ZBPI on site at this visit, at home for the next 28 days, and weekly thereafter until either they had been pain free for 4 consecutive weeks or 90 days had elapsed since the onset of the rash (whichever came last). For all analyses of data involving HZ episodes, day 0 was defined as the first day of HZ rash [22].

EuroQol-5 Dimension (EQ-5D) is a utility instrument widely used to assess individuals' health-related QoL. Autologous HSCT recipients were asked to grade the extent of their problems (no problem, some problems, and severe problems) in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The combination of answers to the 5 dimensions results in 243 possible health states, each of which could be translated into a utility score ranging from below 0 (a health state worse than death) to 1 (best possible health state) [23]. QoL was also assessed using the Short Form Survey-36 (SF-36) [24]. The SF-36 is a self-reported multidimensional instrument designed to assess overall health status and QoL. It consists of 36 questions covering 8 domains: physical function, physical role, general health, bodily pain, mental health, social functioning, vitality/fatigue, and emotional role. Responses from these domains are subsequently summarized into 2 component scores: physical and mental.

All autologous HSCT recipients completed the EQ-5D and SF-36 questionnaires at baseline (ie, before vaccination dose 1). Autologous HSCT recipients who did not develop HZ also completed the questionnaires at 1 month and 1 year postvaccination, whereas all those experiencing a suspected HZ episode completed both the EQ-5D and SF-36 weekly during the entire period that the ZBPI questionnaires were completed.

Statistical Analyses

For each case of HZ, the maximal ZBPI worst 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.

The ZBPI severity of illness scores were calculated as the area under the curve (AUC) of the ZBPI worst pain score from day 0 until day 182 [22]. A ZBPI severity of illness score of 0 was imputed for autologous HSCT recipients without confirmed HZ. The burden of illness due to pain was then estimated by aggregating the severity of illness scores over all the autologous HSCT recipients in a group and dividing by the total number of years of participant follow-up. Consequently, this composite measure took into account the incidence of HZ as well as the severity and duration of HZ pain.

VE was defined as the relative reduction in the burden of illness score in the RZV group compared with 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 composite ZBPI ADL score as the measure.

These analyses were performed on the modified Total Vaccinated Cohort (mTVC), which excluded autologous HSCT recipients who did not receive 2 doses or who had a confirmed HZ episode within 1 month of receiving dose 2, and included only patients with HZ who completed at least 1 ZBPI questionnaire. The Chop-Lump [25] test 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 mTVC cohort.

The VE for reducing severe ZBPI pain (score ≥7 for worst pain) was estimated in the ZBPI evaluable subgroup, which comprised autologous HSCT recipients in the mTVC with confirmed HZ cases who had completed a ZBPI questionnaire during the first 14 days after HZ onset. Standardized asymptotic binomial CIs for the VE were calculated using the score method of Farrington and Manning [26].

A repeated-measures analysis of variance model (ANOVA) was fitted including terms for region, age, sex, and a vaccine-by-time (window) interaction [27]. The least squares mean estimates for time by vaccine effects were obtained from the ANOVA model. The associated differences in least squares means and *P* values were also estimated. A multivariate rank analysis of repeated-measures ordinal categorical data was carried out using the Wei-Lachin method, which assumes that missing data are missing at random [28]. A repeated-measures ANOVA model was fitted to estimate the impact of HZ on EQ-5D utility scores in the placebo group only, stratified by age. The model included the baseline utility scores (ie, the most recent utility assessment before the onset of HZ and the utility scores during the first 4 weeks of the HZ episode).

RESULTS

Most participants in the TVC were white (78.4%), male (62.7%), and aged ≥50 years (75.1%). At a median follow-up of 21 months, 49 confirmed HZ cases had occurred among the 870 autologous HSCT recipients receiving RZV compared with 135 among the 851 receiving placebo in the mTVC (Figure 1).

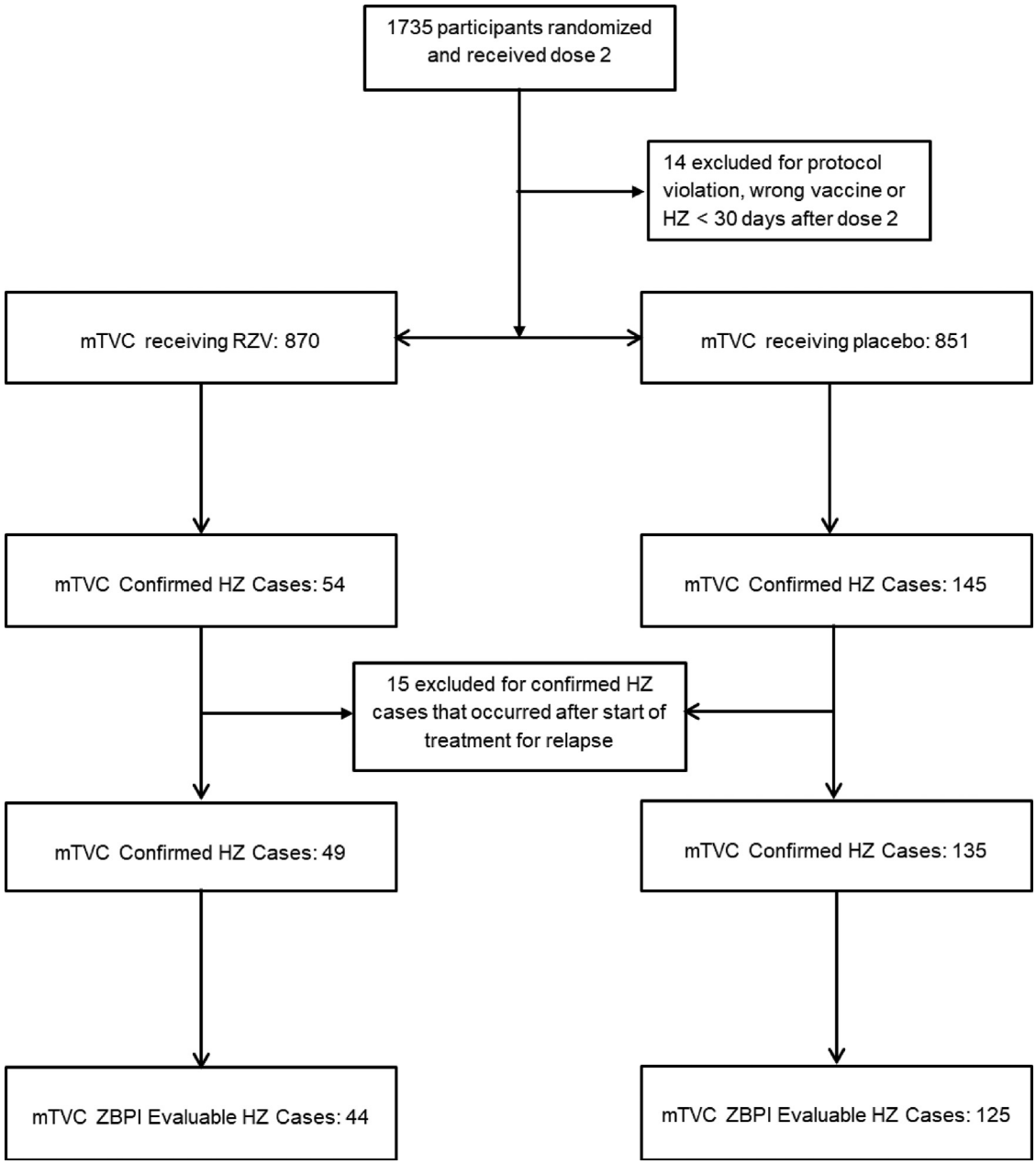

Figure 1. Flowchart for the ZOE-HSCT study. mTVC: excluded autologous HSCT recipients who did not receive 2 doses of RZV or who had a confirmed HZ episode within 1 month of receiving dose 2. mTVC ZBPI evaluable HZ cases: included HZ confirmed cases in participants who completed a ZBPI questionnaire within 14 days postrash onset.

Table 1
Demographics of the Participants Developing HZ

Characteristic	RZV (n = 49)	Placebo (n = 135)
Age, yr		
Mean	56.0	56.6
Range	24-69	23-72
Sex, n (%)		
Female	16 (32.7)	61 (45.2)
Male	33 (67.3)	74 (54.8)
Ancestry, n (%)		
African heritage/African American	0	4 (3.0)
Asian: East Asian heritage	1 (2.0)	16 (11.9)
Asian: Japanese heritage	1 (2.0)	12 (8.9)
Asian: Southeast Asian heritage	0	1 (0.7)
White: Caucasian/European heritage	45 (91.8)	99 (73.3)
Other	2 (4.1)	3 (2.2)

The demographic data of the autologous HSCT recipients who developed confirmed HZ are presented Table 1. The mean ages of both groups were similar, but there were proportionally more males and more whites in the RZV group.

The mean time between the onset of rash and first HZ evaluation was 2.8 (range, 0 to 16) and 3.4 (range, 0 to 29) days in the RZV and placebo groups, respectively. Completion rates for the ZBPI questionnaire were approximately 40% on day 0, >60% from day 3 onward, and ≥80% from day 6 onward. The mTVC HZ confirmed case–ZBPI evaluable subgroup, comprised 44 RZV and 125 placebo autologous HSCT recipients. The completion rate of the EQ-5D and SF-36 instruments during an ongoing HZ episode was approximately 50% on day 0 and ≥77% at all time points thereafter.

ZBPI

Figure 2 displays the mean ZBPI worst pain scores (Figure 2A) and ADL scores (Figure 2B) per day during the first 28 days after rash onset for the mTVC HZ confirmed case–ZBPI evaluable subgroup. The mean ZBPI worst pain and ADL scores were lower in the RZV group than in the placebo group at all time points (overall Wei-Lachin test $P = .003$ and $P = .012$, respectively). This observation was relatively consistent for all of the ZBPI ADL individual items (ie, ZBPI general activity score: $P = .009$, ZBPI mood score: $P = .067$, ZBPI walking ability score: $P = .002$, ZBPI normal work score: $P = .003$, ZBPI relations score: $P = .022$, ZBPI sleep score: $P = .018$, ZBPI enjoyment of life score: $P = .046$, data not shown).

Table 2 presents the distribution of the individual maximal ZBPI worst pain and average pain scores experienced over the entire HZ episode. A severe ZBPI worst pain score (ie, ≥7) was reported by 47.7% of the RZV group and 68.8% of placebo HZ cases (VE, 30.6%; 95% CI, 6.7% to 51.8%). The corresponding proportions reporting severe average pain were 22.7% and 44.0%, respectively (VE, 48.4%; 95% CI, 11.9% to 71.7%). The median time to resolution of clinically significant pain was 20 days in the RZV group and 31 days in the placebo group ($P = .048$).

Table 3 presents the mean AUC for the ZBPI worst pain and ADL scores. For all time periods, the AUC of the ZBPI worst pain score was statistically significantly lower in the RZV group compared with placebo ($P \leq .004$). Similarly, the AUC of the ZBPI ADL scores was statistically significantly lower in the RZV group compared with placebo ($P \leq .014$ for all time periods).

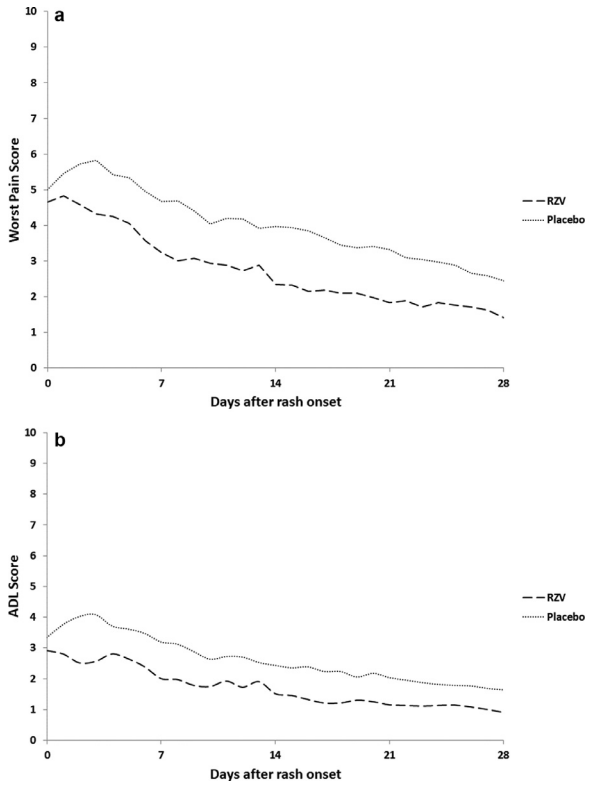

Figure 2. Mean ZBPI worst pain (A) and ADL scores (B) per day during the first 28 days after rash onset (mTVC HZ confirmed Cases–ZBPI evaluable subgroup).

Table 2
Distribution of Maximal ZBPI Worst Pain and ZBPI Average Pain Scores over the Duration of the Entire HZ Episode (mTVC Cohort HZ Confirmed Cases–ZBPI Evaluable Subgroup*)

	Worst Pain		Average Pain	
ZBPI Score	RZV (n = 44)	Placebo (n = 125)	RZV (n = 44)	Placebo (n = 125)
≥3	36 (81.8)	115 (92.0)	34 (77.3)	109 (87.2)
≥7	21 (47.7)	86 (68.8)	10 (22.7)	55 (44.0)
0	4 (9.1)	3 (2.4)	4 (9.1)	3 (2.4)
1	1 (2.3)	2 (1.6)	2 (4.5)	7 (5.6)
2	3 (6.8)	5 (4.0)	4 (9.1)	6 (4.8)
3	2 (4.5)	6 (4.8)	4 (9.1)	9 (7.2)
4	4 (9.1)	3 (2.4)	6 (13.6)	9 (7.2)
5	5 (11.4)	9 (7.2)	7 (15.9)	17 (13.6)
6	4 (9.1)	11 (8.8)	7 (15.9)	19 (15.2)
7	7 (15.9)	16 (12.8)	4 (9.1)	31 (24.8)
8	4 (9.1)	29 (23.2)	0	10 (8.0)
9	5 (11.4)	22 (17.6)	5 (11.4)	8 (6.4)
10	5 (11.4)	19 (15.2)	1 (2.3)	6 (4.8)
P value†	.0111		.0183	
Mean	5.8	7.1	4.7	5.7
SD	3.06	2.54	2.70	2.44

Values are presented as n (%) unless otherwise indicated.

* Includes only autologous HSCT recipients in the mTVC HZ confirmed case–ZBPI evaluable subgroup (ie, confirmed HZ cases with a ZBPI questionnaire completed during the first 14 days after rash onset).

† *P* value is based on the Wilcoxon test.

Table 3
Vaccine Efficacy in Reducing the HZ Disease Impact as Measured by the Worst Pain and Activities of Daily Living Scores (mTVC Confirmed Cases–HZ ZBPI Evaluable Subgroup)

	ZBPI Worst Pain Score				ZBPI ADL Score			
AUC	RZV (n = 44)	Placebo (n = 125)	P Value*	Vaccine Efficacy, %	RZV (n = 44)	Placebo (n = 125)	*P* Value*	Vaccine Efficacy, %
30 days								
Mean	77.52	115.69	.003	33.0	49.73	75.92	.012	34.5
SD	66.34	72.50			53.63	65.56		
90 days								
Mean	103.89	167.74	.004	38.1	69.52	114.06	.014	39.0
SD	123.31	150.63			97.12	126.65		
182 days								
Mean	105.28	186.94	.003	43.7	70.17	125.78	.014	44.2
SD	128.29	211.97			97.88	160.64		

mTVC: excluded autologous hematopoietic stem cell transplant recipients who did not receive 2 doses of RZV or who had a confirmed HZ episode within 1 month of receiving dose 2.
mTVC ZBPI evaluable HZ cases: included HZ confirmed cases in participants who completed a ZBPI questionnaire within 14 days after rash onset.
* *P* value is based on the Wilcoxon test.

SF-36 and EQ-5D

The QoL scores by SF-36 tended to be higher in the RZV group compared with placebo. For example, at week 1 post HZ rash onset, when the greatest differences were observed, statistically significant differences in favor of RZV ($P < .05$) were observed for the SF-36 bodily pain, social functioning, role emotional, mental health, and mental component scores (Table 4).

The estimated mean EQ-5D utility scores over time are shown in Figure 3. The differences between RZV and placebo groups were greatest at week 1 and decreased over time. At week 1, the EQ-5D utility score was significantly higher in the RZV group compared with placebo ($P = .0021$).

The estimated utility loss of autologous HSCT recipients in the placebo group, who developed HZ over the first 28 days after rash onset, is presented by age (ie, 18 to 49 and ≥50 years) in Table 5. The utility loss was highest on day 0 and decreased over time in both age groups as the autologous HSCT recipients recovered from HZ. Nevertheless, a negative impact of HZ on QoL remained until the end of week 4.

Vaccine Efficacy

As seen in Table 6, the overall VE estimate for the burden of illness score was 82.5% (95% CI, 73.6% to 91.4%) with point estimates of 83.4 and 82.4 in the 18 to 49 and ≥50 years age groups, respectively. The overall VE estimate for the burden of interference score was 82.8% (95% CI, 73.3% to 92.3%) with point estimates of 79.6 and 83.6 in the 18 to 49 and ≥50 years age groups, respectively.

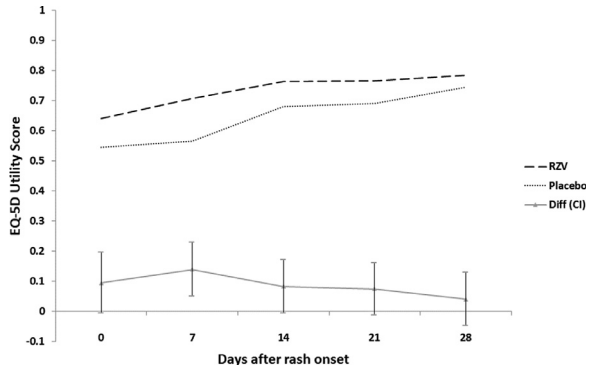

Figure 3. Estimated mean EQ-5D utility scores during the first 28 days after rash onset (mTVC HZ confirmed cases). An EQ-5D value of 1 represents the best possible health state. Diff (CI), difference (CI).

Table 4
SF-36 and EQ-5D Domains at Week 1 (mTVC HZ Confirmed Cases)

Domain	RZV* (n = 49)	Placebo* (n = 135)	Difference	Confidence Interval	*P* Value†
Physical functioning	64.21	60.41	3.80	(−5.29, 12.89)	.4122
Physical role	58.45	49.32	9.13	(−1.06, 19.32)	.0790
Bodily pain	53.18	39.85	13.33	(4.38, 22.28)	.0035
General health	47.05	48.22	−1.17	(−7.94, 5.60)	.7350
Vitality	49.76	43.92	5.84	(−2.24, 13.91)	.1566
Social functioning	68.81	55.88	12.93	(3.99, 21.87)	.0046
Role emotional	77.62	67.13	10.49	(0.99, 19.98)	.0304
Mental health	74.44	66.69	7.75	(0.59, 14.91)	.0339
PCS	41.14	39.62	1.52	(−1.51, 4.56)	.3252
MCS	49.08	44.10	4.97	(1.22, 8.73)	.0095
EQ-5D utility score	0.7075	0.5670	0.140	(0.051, 0.230)	.0021
EQ-5D VAS score	67.7	63.5	4.2	(−2.2, 10.6)	.1944

MCS indicates mental health component score; PCS, physical health component score; VAS, visual analog scale.
* Least squares means.
† *P* value is based on the difference in least squares means taken from the repeated-measures mixed-effects model.

Table 5
Estimated EQ-5D Scores for Utility Loss by Age Group in Placebo Group and Time Point during the Acute HZ Period (mTVC Confirmed Cases)

Age Group, yr	Time Point	Least Squares Means Estimate	Estimated Utility Loss	*P* Value*
18-49	Pre-HZ	.8523		
	Day 0	.5188	.3335	<.0001
	Week 1	.5316	.3206	<.0001
	Week 2	.6716	.1807	.0069
	Week 3	.7607	.0916	.1870
	Week 4	.7796	.0727	.3099
≥50	Pre-HZ	.8003		
	Day 0	.5696	.2308	<.0001
	Week 1	.5797	.2206	<.0001
	Week 2	.6856	.1147	.0016
	Week 3	.6696	.1307	.0005
	Week 4	.7359	.0644	.0939

An EQ-5D value of 1 represents the best possible health state.
* *P* value is based on the repeated-measures mixed-effects model testing the null hypothesis that the utility loss = 0.

DISCUSSION

Recipients of HSCT have both an increased incidence and severity of HZ [5-7,11,12]. In this trial, the overall efficacy of RZV in preventing HZ cases in autologous HSCT recipients was 68.2% (95% CI, 55.6% to 77.5%) [21]. In this article, it was further demonstrated that even when RZV failed to prevent HZ, vaccine recipients experienced less severe pain, had a shorter duration of pain, had less interference in ADLs, and had higher QoL scores compared with the placebo group. Therefore, RZV not only prevented HZ but also attenuated the severity of disease in RZV recipients who developed HZ during this study. Consequently, the overall efficacy of RZV in reducing the burden of illness of HZ and the burden of interference in ADLs exceeded 80%.

In the preceding ZOE-50 study and ZOE-70 pooled analysis, in older adults, only 9 of 7340 and 25 of 7413 participants developed HZ in the RZV groups, respectively, compared with 49 of 870 HSCT recipients in the current study [19-21]. The magnitude of differences in pain scores, between the RZV and placebo groups, in this present study during the acute HZ period was consistent with the ZOE-50 and the ZOE-70 pooled analysis. However, due to more individuals developing breakthrough HZ in the ZOE-HSCT study, the statistical power to detect significant differences between the groups was higher in the present study.

Although the ZBPI pain scores in the placebo group in ZOE-50, ZOE-70 pooled analysis, and ZOE-HSCT studies appeared to be similar during the first week following rash onset, there were differences in the median time to resolution of clinically significant pain (17, 22, and 31 days, respectively). The HZ burden of illness scores in the placebo group of the ZOE-50 and ZOE-70 pooled analysis were approximately 1.2 and 1.7, respectively [29], compared with 16.9 in the ZOE-HSCT study. As such, the HZ burden of illness is of a magnitude of approximately 10 times higher in autologous HSCT recipients, due to a combination of both a higher incidence and a greater severity of disease. Consequently, although the RZV VE is lower in autologous HSCT recipients compared with healthy individuals receiving RZV, the absolute reduction of HZ burden of illness is meaningfully higher in autologous HSCT recipients.

Interestingly, in the placebo group of this study, the HZ burden of illness and HZ burden of interference scores were lower in younger rather than older autologous HSCT recipients (Table 5); however, the utility losses appeared to be greater in younger compared with older autologous HSCT recipients (Table 4). As such, the reduction in HZ-related burden appears important for both the young and older autologous HSCT recipients.

The vaccine efficacy reported in this study was similar to that of a heat-inactivated varicella-zoster virus vaccine administered to a similar HSCT population [30]. However, the latter was achieved using a 4-dose schedule of the heat-inactivated vaccine compared with a 2-dose schedule of RZV. Furthermore, the first dose of the 4-dose regimen was administered 1 month before autologous HSCT, which can be logistically challenging [21].

This study has some limitations. The QoL endpoints were either secondary or exploratory endpoints within the ZOE-HSCT study, and as such, the study was not powered to show specific differences in QoL parameters between the RZV and placebo groups. Similarly, the study was not stratified or powered to draw conclusions by age groups.

This study of autologous HSCT recipients demonstrates that RZV reduces both the frequency and severity of HZ. The HZ burden of illness is dramatically higher in autologous HSCT recipients compared with healthier individuals included in the prior ZOE studies. The results from this transplant study support the findings from the previous ZOE studies in older adults and

Table 6
HZ ZBPI Severity and Burden of Illness (Based on ZBPI Worst Pain) and Interference (Based on ZBPI ADL) Scores (mTVC)

		RZV (n = 870)				Placebo (n = 851)			
Age Group, yr	n	m	ZBPI Severity of Illness	ZBPI Burden of Illness	n	m	ZBPI Severity of Illness	ZBPI Burden of Illness	VE (95% CI), %
18-49	9	213	3.779	1.911	29	212	20.769	11.544	83.4 (63.4, 100.0)
≥50	37	654	6.155	3.326	104	637	31.348	18.857	82.4 (72.5, 92.3)
Total	46	867	5.572	2.960	133	849	28.706	16.921	82.5 (73.6, 91.4)
Age Group, yr	n	m	ZBPI Severity of Interference	ZBPI Burden of Interference	n	m	ZBPI Severity of Interference	ZBPI Burden of Interference	VE (95% CI), %
18-49	9	213	3.371	1.704	29	212	15.011	8.343	79.6 (51.3, 100.0)
≥50	37	654	3.908	2.112	104	637	21.355	12.846	83.6 (73.9, 93.3)
Total	46	867	3.776	2.007	133	849	19.770	11.654	82.8 (73.3, 92.3)

Three and 2 participants in the RZV and placebo groups, respectively, had a confirmed HZ episode but did not have an evaluable ZBPI score and were therefore not included in this table. The ZBPI severity of illness and severity of interference scores were calculated as the AUC, days 0 to 182, of the ZBPI worst pain scores and ZBPI Activities of daily living scores, respectively, for participants with confirmed HZ cases. Participants without a confirmed HZ case were allocated an AUC score of 0. The ZBPI burden of illness and burden of interference scores were calculated as the sum of the ZBPI severity of illness and severity of interference scores, respectively, and divided by the total follow-up in years. Higher scores represent more burden.
m indicates number of HZ cases in each vaccination group.

suggest that the RZV vaccine, in addition to being efficacious in preventing HZ, has a benefit in attenuating the severity of HZ disease in breakthrough cases, including in transplant recipients younger than 50 years of age. In conclusion, RZV may represent an additional prophylactic intervention in the care of patients after autologous HSCT, who are at high risk for HZ.

TRADEMARK

Shingrix is a registered trademark of GSK Group of Companies. Zostavax is a trademark of Merck Sharp & Dohme Corp.

ACKNOWLEDGMENTS

The authors would like to thank the study participants, investigators, and study teams involved in this trial, as well as Anne Schuind for her comments during review and Christophe Sauboin, Camelia Marcos, and Thomas C. Heineman for the patient-reported outcome questionnaire selection (ie, ZBPI, EQ-5D, and SF-36), which was included in the ZOE-HSCT clinical trial.

Medical writing services were provided by Julia Donnelly (freelancer on behalf of GSK). Editorial assistance and publication coordination were provided by Sara Blancquaert (Modis on behalf of GSK). Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Financial disclosure: This work was funded by GlaxoSmithKline Biologicals SA. GlaxoSmithKline Biologicals SA was involved in all stages of the study and covered all costs associated with developing and publishing this manuscript.

Declaration of Competing Interest: During the conduct of the study, J.M.C. reports data monitoring board fees from the GSK group of companies. S.S. reports reimbursement for treatment and monitoring of study participants from the GSK group of companies. K.M.S. reports a grant and personal fees from the GSK group of companies and from NIAID, NIH awarded to Duke University. J.A.Y. reports reimbursement from the GSK group of companies to the University of Minnesota for participant enrollment. Outside the submitted work, A.A. reports grants from MERCK. S.D.R. reports consultant fees from Incyte, Fate Therapeutics, and Mesoblast. S.S. reports personal fees and nonfinancial support from AMGEN, Basilea Pharmaceutica, Gilead, Jazz Pharmaceuticals, MSD Sharp & Dohme, and Pfizer. K.M.S. reports personal fees from Kiadis Pharmaceutical and Roche Genentech. J.S. reports personal fees from Novartis; nonfinancial support from Pfizer, Sanofi Genzyme, and Shire; and grants, personal fees, and nonfinancial support from Alexion. F.Z. reports consultancy fees from Abbvie, Celgene, Gilead, Janssen, Novartis, Roche, and Sandoz; payment for lectures including service on speakers bureaus from Abbvie, Amgen, BMS, Celgene, Gilead, Janssen, Novartis, and Roche; payment for development of educational presentations from Novartis; and travel/accommodations/meeting expenses unrelated to activities listed (eg, consultancy) from Amgen, Celgene, Novartis, Roche, and Takeda. D.C. and M.E.I. are employees of the GSK group of companies. D.C. owns stock options, and M.E.I. owns stock from the GSK group of companies. S.M. works as a freelance consultant on behalf of the GSK group of companies. A.B. and L.O. were employees of the GSK group of companies during the conduct of the study and continue to own stock from the GSK group of companies. A.B. is an employee of Mithra Pharmaceuticals as of June 17, 2019. L.O. is an employee of CureVac AG as of March 1, 2018; continues to own stock from the GSK group of companies; and is inventor on a patent owned by the GSK group of companies and relevant to the recombinant zoster vaccine. I.B., P.H.C., M.D., I.H., S.T.M., M.B.N.M., B.P-J., D.Q., W.S., D.L.D.S., K.T., Z.A.Y., and S.-P.Y. have nothing to disclose.

Authorship statement: A.B., D.C., M.E.I., S.T.M., L.O., and K. M.S. conceived and designed the study. A.A., I.B., A.B., P.H.C., M.D., S.T.M., J.M.C., M.B.N.M., B.P.-J., D.Q., S.D.R., W.S., S.S., D. L.D.S., K.M.S., J.S., K.T., Z.A.Y., S.-P.Y., J.A.H.Y., and F.Z. collected or generated study data. A.A., A.B., P.H.C., D.C., M.D., S. T.M., J.M.C., M.B.N.M., B.P.-J., D.Q., S.D.R., W.S., S.S., D.L.D.S., K.M.S., J.S., K.T., Z.A.Y., S.-P.Y., J.A.H.Y., and F.Z. performed the study. A.B., D.C., M.D., S.D.R., W.S., D.L.D.S., K.M.S., S.-P.Y., J.A.H.Y., and F.Z. contributed materials/analysis/reagent tools. A.B., D.C., M.E.I., S.M., L.O., S.D.R., S.S., K.M.S., J.S., K.T., and F.Z. were involved in the analysis or interpretation of the data. All authors contributed to the writing/reviewing of the manuscript and approved the final version for submission. All authors vouch for the completeness and accuracy of all the data and the presented analyses.

SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online doi:10.1016/j.bbmt.2019.07.036.

REFERENCES

1. Cohen JI. Clinical practice: Herpes zoster.*N Engl J Med*. 2013;369:255–263.
2. Johnson RW, Bouhassira D, Kassianos G, Leplège A, Schmader KE, Weinke T. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. *BMC Med*. 2010;8:37.
3. Oxman MN. Zoster vaccine: current status and future prospects. *Clin Infect Dis*. 2010;51:197-213.
4. Gershon AA, Gershon MD. Pathogenesis and current approaches to control of varicella-zoster virus infections. *Clin Microbiol Rev*. 2013;26:728-743.
5. Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Langan SM. Quantification of risk factors for herpes zoster: population based case-control study. *BMJ*. 2014;348:g2911.
6. Yanni EA, Ferreira G, Guennec M, et al. Burden of herpes zoster in 16 selected immunocompromised populations in England: a cohort study in the Clinical Practice Research Datalink 2000-2012. *BMJ Open*. 2018;8: e020528.
7. Li Q, Chen SY, Burstin SJ, Levin MJ, Suaya JA. Cost of herpes zoster in patients with selected immune-compromised conditions in the United States. *Open Forum Infect Dis*. 2016;3:ofw067.
8. Sahoo F, Hill JA, Xie H, et al. Herpes zoster in autologous hematopoietic cell transplant recipients in the era of acyclovir or valacyclovir prophylaxis and novel treatment and maintenance therapies. *Biol Blood Marrow Transplant*. 2017;23:505-511.
9. Crippa F, Holmberg L, Carter RA, et al. Infectious complications after autologous CD34-selected peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant*. 2002;8:281-289.
10. Schuchter LM, Wingard JR, Piantadosi S, Burns WH, Santos GW, Saral R. Herpes zoster infection after autologous bone marrow transplantation. *Blood*. 1989;74:1424-1427.
11. Offidani M, Corvatta L, Olivieri A, et al. A predictive model of varicella-zoster virus infection after autologous peripheral blood progenitor cell transplantation. *Clin Infect Dis*. 2001;32:1414-1422.
12. Rogers JE, Cumpston A, Newton M, Craig M. Onset and complications of varicella zoster reactivation in the autologous hematopoietic cell transplant population. *Transpl Infect Dis*. 2011;13:480-484.
13. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. *CMAJ*. 2010;182:1731-1736.
14. Yawn BP, Itzler RF, Wollan PC, Pellissier JM, Sy LS, Saddier P. Health care utilization and cost burden of herpes zoster in a community population. *Mayo Clin Proc*. 2009;84:787-794.
15. Curran D, Hunjan M, El Ghachi A, El Hahi Y, Bianco V, Ferrera G. Herpes zoster related healthcare burden and costs in both immunocompromised (IC) and IC-free populations in the United Kingdom. Abstract presented at ISPOR-EU International Society for Pharmacoeconomics and Outcomes Research, 20th Annual European Congress; November 4-8, 2017; Glasgow, Scotland. Available at: https://www.valueinhealthjournal.com/article/S1098-3015(17)32630-X/fulltext. Accessed June 17, 2019.
16. Seo HM, Kim YS, Bang CH, et al. Antiviral prophylaxis for preventing herpes zoster in hematopoietic stem cell transplant recipients: a systematic review and meta-analysis. *Antiviral Res*. 2017;140:106-115.
17. Lee CJ, Savani BN, Ljungman P. Varicella zoster virus reactivation in adult survivors of hematopoietic cell transplantation: how do we best protect our patients? *Biol Blood Marrow Transplant*. 2018;24:1783-1787.

18. Symoniak MR, Farrokh P, Gandhi MA, Slish JC. Herpes zoster subunit vaccine for the prevention of herpes zoster. *Am J Health Syst Pharm*. 2018;75:861-869.
19. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372:2087-2096.
20. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med*. 2016;375:1019-1032.
21. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of a recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. *JAMA*. 2019; 322;123-133.
22. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: adaptation of the brief pain inventory. *J Pain*. 2004;5:344-356.
23. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. *Ann Med*. 2001;33:337-343.
24. Ware Jr JE. SF-36 health survey update. Spine. 2000;25:3130-3139.
25. Follmann D, Fay MP, Proschan M.Chop-lump tests for vaccine trials. *Biometrics*. 2009;65:885-893.
26. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med*. 1990;9:1447-1454.
27. Verbeke G, Molenberghs G. *Linear Mixed Models in Practice*. New York, NY: Springer-Verlag; 1997.
28. Wei LJ, Lachin JM. Two-sample asymptotically distribution-free tests for incomplete multivariate observations. *J Am Statist Assoc*. 1984;79:653-661.
29. Curran D, Oostvogels L, Heineman T, et al. Quality of life impact of a recombinant zoster vaccine in adults ≥50 years of age [e-pub ahead of print]. *J Gerontol A Biol Sci Med Sci*. doi: 10.1093/gerona/gly150.
30. Winston DJ, Mullane KM, Cornely OA, et al. Inactivated varicella zoster vaccine in autologous haematopoieitc stem-cell transplant recipients: an international, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391:2116-2127.