

ORIGINAL ARTICLE

Immunogenicity, Safety, and Tolerability of Live Attenuated Varicella-Zoster Virus Vaccine (ZOSTAVAX™) in Healthy Adults in India

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Abstract

Background: Herpes zoster (HZ) is caused by varicella-zoster virus (VZV) reactivation. In the United States, Zoster vaccine (ZOSTAVAX) is indicated for HZ prevention in patients ≥ 50 years.

Aims: To evaluate the immunogenicity, safety, and tolerability of ZOSTAVAX in healthy Indian subjects, to support its registration in India.

Methods: This open-label, single-arm study was conducted at 10 sites in India. Healthy Indians (≥ 50 years) received a single ZOSTAVAX dose. Immunogenicity was assessed by VZV-specific antibody titer using gpELISA assay. VZV-specific antibody geometric mean titers (GMT; Day 1 pre-vaccination, Week 6 post-vaccination) and geometric mean fold-rise (GMFR; Week 6 post-vaccination) were assessed. Safety was evaluated by the incidence of adverse events (AEs) and serious adverse events (SAEs) within 42 days of vaccination. Two-sided 95% confidence intervals (CIs) were evaluated using *t*-distribution with natural log-transformed values.

Results: Of the 250 subjects (mean age, 58.6 years) enrolled and vaccinated, 244 subjects completed the 6-week follow-up. Overall, subjects in the per-protocol population had GMT of 149.8 gpELISA units/mL ($n=250$; 95% CI: 132.6, 169.2) at Day 1 pre-vaccination, and 410.8 gpELISA units/mL ($n=243$; 95% CI: 373.0, 452.6) at Week 6 post-vaccination. GMFR of VZV-specific antibody from Day 1 pre-vaccination to Week 6 post-vaccination was 2.8 (95% CI: 2.5, 3.1). Overall, 67 subjects (26.8%) experienced AEs, with 48 (19.2%) reporting injection-site AEs and 38 (15.2%) reporting non-injection-site AEs. SAE—abdominal pain and bronchitis—was reported in one (0.4%) patient each. There was one death, which was unrelated to the vaccine.

Limitations: Since ZOSTAVAX introduces a new live attenuated virus, clinical reactivation of ZOSTAVAX virus and wild-type VZV will need to be differentiated.

Conclusion: In healthy Indians ≥ 50 years, ZOSTAVAX was well tolerated and resulted in expected VZV-specific antibody titer levels at 6 weeks post-vaccination.

review of 130 studies conducted in 26 countries showed that the incidence of HZ ranges between 3 and 5 per 1,000 person-years in North America, Europe, and Asia-Pacific regions. The risk of recurrence of HZ ranged from 1% to 6%, whereas the risk of developing complications such as PHN varied from 5% to more than 30%.⁵ Moreover, the risk of developing PHN increases markedly with age.^{6,7} However, the HZ Global Awareness Survey of 8,688 subjects ≥ 50 years, conducted in 22 countries, evaluated the existing levels of awareness and knowledge of HZ and reported that $< 20\%$ participants were aware of HZ and its symptoms in Turkey, Chile, and India.⁸

The live attenuated Zoster (Oka/Merck) vaccine (ZOSTAVAX) for adults can boost host immunity to VZV. It contains the same virus strain as the varicella vaccine for children, but is 14.4 times more potent (1,350 plaque-forming units [PFU] vs. 19,400 PFU).^{9,10} ZOSTAVAX is approved by the US Food and Drug Administration for prevention of HZ (shingles) in individuals ≥ 50 years,^{9,11} supported by the results of the ZOSTAVAX Efficacy and Safety Trial (ZEST)¹² and Shingles Prevention Study (SPS).¹³ In ZEST, ZOSTAVAX significantly reduced the risk of developing zoster by 69.8% in comparison to placebo and increased the VZV-specific antibody geometric mean titers (GMT) by 2.3 fold at 6 weeks post-vaccination in a random 10% subcohort.^{9,12,14} In SPS, ZOSTAVAX significantly reduced the risk of developing HZ, the burden of illness,

Introduction

Herpes zoster (HZ) is caused by the reactivation of varicella-zoster virus (VZV), which causes chickenpox. Hope-Simpson hypothesized that, in some individuals, VZV remains latent in the sensory ganglion after primary infection and reactivates or replicates, perhaps as a consequence of advancing age and waning cell-mediated immunity.¹⁻³ HZ is associated with pain, which may occur during prodrome, the acute eruptive phase,

and the postherpetic phase of the infection (postherpetic neuralgia; PHN). Serious complications, such as PHN, scarring, cranial and motor neuron palsies, encephalitis, visual impairment, hearing loss, and death can occur as a result of HZ.^{4,5} A systematic

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Received: 14.06.2017; Accepted: 16-04-2018

and PHN by 51.3%, 61.1%, and 66.5%, respectively, compared to placebo.¹³ Vaccine efficacy for the prevention of HZ declined with increasing age. Except for the increased risk of injection-site adverse events (AEs), the vaccine was considered safe in the SPS population. SPS reported a 1.7-fold (95% confidence interval [CI]: 1.6, 1.8) increase in VZV-specific antibody titers at 6 weeks post-vaccination.^{9,13} An immunogenicity study conducted on the VZV vaccine showed a comparable 1.6-fold increase in antibody titers at 6 weeks.¹⁵ Further, the increase in VZV-specific antibody titer correlated with vaccine efficacy in another study.¹⁶

The purpose of this study was to evaluate the immunogenicity, safety, and tolerability of ZOSTAVAX in otherwise healthy subjects ≥ 50 years old in India, to support registration of ZOSTAVAX in India.

Methods

Study design

This open-label, single-arm study (Clinicaltrials.gov NCT01527370; protocol number 025-00) was conducted at 10 sites in India between November 1, 2012 and April 9, 2013. Healthy Indians ≥ 50 years old received a single dose of ZOSTAVAX™ (Zoster Vaccine Live; Oka/Merck strain; Merck & Co., Inc., West Point, Pennsylvania, USA) on Day 1. The study was conducted in accordance with the Declaration of Helsinki and in compliance with the approved protocol and Good Clinical Practice Guidelines issued by the Central Drugs Standard Control Organization, Ministry of Health, of the Government of India. The study protocol was approved by the Institutional Review Boards of the respective investigational centers. All participants provided written informed consent.

Study population

Subjects ≥ 50 years, who were afebrile ($< 38.0^\circ\text{C}$ oral) on the day of vaccination and did not have underlying chronic illness were eligible for the study. Additional eligibility criteria are included in the supplemental section.

Vaccination procedure

Subjects were assigned an allocation number and received a single-dose subcutaneous injection of ~ 0.65 mL ZOSTAVAX in the deltoid region—

preferably in the nondominant arm—on Day 1. Dose was based on previously demonstrated acceptable safety and immunogenicity responses in subjects ≥ 50 years in clinical studies. ZOSTAVAX is a single-dose, sterile, lyophilized, live attenuated virus vaccine reconstituted in sterile water (without preservatives or other substances that might inactivate the vaccine) as a diluent. Study vaccine was stored at 2°C to 8°C , and the sterile diluent was stored at room temperature at 20°C to 25°C or refrigerated at 2°C to 8°C . All subjects were evaluated for safety for 42 days post-vaccination.

Assessments

Efficacy/immunogenicity

Immunogenicity endpoints included immune response measured by VZV-specific antibody titer using gpELISA assay¹⁷ (PPD Vaccines and Biologics, LLC, Wayne, PA, USA). The VZV-specific antibody GMT (Day 1 pre-vaccination and Week 6 post-vaccination) and its geometric mean fold-rise (GMFR) at Week 6 post-vaccination were assessed. Subjects were also evaluated by age category (50-59 years and ≥ 60 years). For assessing VZV-specific antibody titer, 5 mL of whole blood was collected from all subjects before vaccination (Day 1) and post-vaccination (Week 6; Days 43-49). Subjects who had protocol deviations that may have interfered with the assessment of VZV-specific antibody response, developed suspected varicella or HZ rashes before a blood sample was taken, or reported an exposure to varicella/HZ were excluded from the analysis of VZV-specific antibody responses.

Safety

All subjects who were vaccinated and had any safety follow-up were included in the safety evaluation. The primary safety endpoint was the incidence of serious adverse events (SAEs) observed within 42 days post-vaccination. Key safety measures included any adverse experience, injection-site AEs, systemic AEs, SAEs, vaccine-related SAEs, and discontinuation due to an AE within 42 days post-vaccination. A vaccination report card (VRC) was maintained by the subjects in which they recorded subject-reported safety parameters such as systemic adverse experiences, varicella-like and HZ-like rash, injection-site complaints such as redness, swelling, and pain/tenderness/soreness occurring Days

1-5 after vaccination, and elevated temperature (oral $\geq 38.0^\circ\text{C}$) during the 42-day follow-up period. The VRC was examined by study personnel between Days 43-49. Subjects reporting suspected varicella/varicella-like or HZ/HZ-like rashes were evaluated by the investigator at the study site within 72 hours of rash onset (preferably within 24 hours) for clinical evaluation, and then every 3 days for evaluation of complications and for rash and pain assessments until no new lesions appeared. Provisions were made for the administration of antiviral medication (e.g., acyclovir, famciclovir, or valacyclovir) and the clinical assessment of the rash, including collection of a lesion specimen for VZV identification by polymerase chain reaction (PCR; PPD Vaccines and Biologics, LLC, Wayne, PA, USA) to differentiate between vaccine-strain and wild-type VZV.

Statistical analysis

This was an open-label descriptive study, and no hypotheses were tested. No formal statistical considerations were employed in determining sample size. Vaccinated subjects with any safety follow-up were included in the safety evaluation. The primary immunogenicity analysis was based on the per-protocol population. For immune responses measured by VZV-specific antibody responses, if 225/250 subjects (90%) were included in the per-protocol population, the half-width of the 95% CI for the GMFR would be 0.13 in the natural log-scale, assuming the standard deviation of the natural log of the fold rise was 1.0. For example, if the observed GMFR was 2.0, then its associated 95% CI would be 1.75, 2.28, if the estimated standard deviation matched the assumption. The final observed GMFR and its 95% CI depended on actual study results. The immunogenicity of the vaccine was evaluated overall and by age group (50-59 years and ≥ 60 years). The GMT and the GMFR of VZV-specific antibody values from pre-vaccination to 6 weeks post-vaccination were summarized, along with two-sided 95% CIs, which were evaluated on the basis of a *t*-distribution with natural log-transformed values. For safety analyses, if no vaccine-related SAEs were observed among the 250 subjects, this study was expected to provide 97.5% confidence that the true vaccine-

Table 1: Summary of subject disposition

	ZOSTAVAX™ n (%)
Subjects	250
Vaccinated	250 (100.0)
Study disposition	
Completed	244 (97.6)
Discontinued	6 (2.4)
Death	1 (0.4)
Physician decision	1 (0.4)
Withdrawal by subject	4 (1.6)

Each subject is counted once for study disposition based on the latest corresponding disposition record.

related SAE rate was $\leq 1.47\%$ (1 in every 68 subjects). The incidence rate and its associated 95% CI were provided for broader safety measures. Counts and proportions on SAEs, the overall safety profile, and injection-site AEs were also provided by age category (50-59 years and ≥ 60 years).

Results

Patient disposition and baseline characteristics

Of the 250 subjects enrolled and vaccinated, 244 subjects completed the 6-week follow-up. A summary of subject disposition is presented in Table 1. Subjects (mean age, 58.6 years) were mostly men (73.6%; Table 2). The most frequently used concomitant medications were metformin (12.0%) and glimepiride (9.6%; Table 2), and the most frequently reported medical conditions were hypertension (18.8%) and diabetes mellitus (14.4%).

Immunogenicity

Overall, subjects in the per-protocol population had an estimated VZV-specific antibody GMT of 149.8 gpELISA units/mL (n=250; 95% CI: 132.6, 169.2) at Day 1 pre-vaccination, and 410.8 gpELISA units/mL (n=243; 95% CI: 373.0, 452.6) at Week 6 post-vaccination. The estimated GMFR of VZV-specific antibody from Day 1 pre-vaccination to Week 6 post-vaccination was 2.8 (95% CI: 2.5, 3.1; Figure 1). In subjects 50-59 years old, the 6-week VZV-specific antibody GMT and its GMFR were 431.7 units/mL (95% CI: 383.1, 486.5) and 2.9 (95% CI: 2.5, 3.3), respectively; the corresponding values in subjects ≥ 60 years old were 379.3 units/mL (95% CI: 321.7, 447.3) and 2.5 (95% CI: 2.2, 3.0), although the CIs overlapped between the two age groups. The reverse cumulative distribution of VZV-specific antibody

Table 2: Summary of baseline characteristics

	ZOSTAVAX™ n (%)
Subjects in population	250
Gender	
Female	66 (26.4)
Male	184 (73.6)
Age (years)	
50 to 59	153 (61.2)
≥ 60	97 (38.8)
Mean (SD)	58.6 (7.1)
Median	57.0
Range	50 to 86
Race	
Asian	250 (100.0)
Ethnicity	
Not Hispanic or Latino	250 (100.0)
Concomitant medications*	
With one or more concomitant medications	117 (46.8)
Angiotensin II Antagonists, Plain	27 (10.8)
Losartan potassium	6 (2.4)
Olmesartan medoxomil	1 (0.4)
Telmisartan	20 (8.0)
Anilides	36 (14.4)
Aceclofenac (+)	1 (0.4)
Acetaminophen	
Acetaminophen	18 (7.2)
Acetaminophen (+)	17 (6.8)
Ibuprofen	
Biguanides	36 (14.4)
Metformin	30 (12.0)
Metformin hydrochloride	6 (2.4)
Sulfonamides, Urea derivatives	26 (10.4)
Gliclazide	2 (0.8)
Glimepiride	24 (9.6)

*Reported in $\geq 10\%$ subjects. Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category.

titers and its fold increase by age group for subjects in the per-protocol population is presented in Figure 2.

Safety

Overall, 67 subjects (26.8%) experienced one or more AEs, with 48 subjects (19.2%) reporting injection-site AEs and 38 (15.2%) reporting non-injection-site AEs (systemic AEs; Table 3). SAEs were reported for 2 subjects (0.8%); these were abdominal pain and bronchitis in each subject and were not considered vaccine-related by the investigators. There was one death reported in a subject experiencing abdominal pain, but it was not considered vaccine-related.

At least one vaccine-related injection-site AE was reported in 48

(19.2%) subjects from Day 1 to 5 post-vaccination: injection-site erythema (14.0%), injection-site swelling (12.4%), and injection-site pain (8.8%), all prompted for on the VRC, were the most frequently reported (Table 4). When summarized by age, 27.5% subjects 50-59 years old and 6.2% ≥ 60 years old experienced injection-site AEs. Most injection-site AEs occurred within 5 days of vaccination. A majority of injection-site erythema (13.2%) and injection-site swelling (10.4%) measured by subjects were 0 to ≤ 1 inch in diameter.

Overall, the frequency of systemic AEs was low; 38 (15.2%) subjects experienced at least one systemic AE post-vaccination. The most frequently reported specific systemic AEs were pyrexia (4.4%) and cough (2.8%). A total of 11 (4.4%) subjects reported at least one vaccine-related systemic AE post-vaccination. The most frequently reported vaccine-related systemic AE was pyrexia (2.8%). When summarized by age, 17.0% subjects 50-59 years old and 12.4% subjects ≥ 60 years old experienced systemic AEs (Table 5). A total of 6 (2.4%) subjects reported elevated temperatures ($\geq 100.4^\circ\text{F}$ [$\geq 38^\circ\text{C}$] oral). There were no reports of varicella/varicella-like or HZ/HZ-like rashes during this study.

Discussion

Results of this phase 3 study show that ZOSTAVAX was immunogenic as measured by an increase in VZV antibody titer—149.8 gpELISA units/mL pre-vaccination to 410.8 gpELISA units/mL 6 weeks post-vaccination; GMFR at Week 6 was 2.8. The 6-week GMT and GMFR were higher in subjects 50-59 years old compared to subjects ≥ 60 years old, although the CIs overlapped between the groups. The primary safety endpoint was met, as the SAEs reported for 2 subjects (0.8%) were not vaccine-related. Overall, ZOSTAVAX was generally well tolerated. The types of AEs reported by subjects were consistent with those reported in earlier studies.^{12,13} To our knowledge, this is the first study evaluating ZOSTAVAX in an Indian population.

Immunogenicity in the current study was slightly higher than in previous studies. In SPS, involving 38,000 subjects ≥ 60 years old, GMFR was 1.7 in the ZOSTAVAX group at 6 weeks

Table 3: Overall summary of adverse events

	ZOSTAVAX™	
	n (%)	95% CI
Subjects in population with follow-up	250	
With one or more adverse events	67 (26.8)	(21.4, 32.7)
Injection-site	48 (19.2)	
Non-injection-site	38 (15.2)	
With no adverse event	183 (73.2)	(67.3, 78.6)
With vaccine-related [†] adverse events	50 (20.0)	(15.2, 25.5)
Injection-site	48 (19.2)	
Non-injection-site	11 (4.4)	
With serious adverse events	2 (0.8)	(0.1, 2.9)
With serious vaccine-related adverse events	0	(0.0, 1.5)
Who died	1 (0.4)	(0.0, 2.2)
Discontinued [‡] due to an adverse event	0	(0.0, 1.5)
Discontinued due to a vaccine-related adverse event	0	(0.0, 1.5)
Discontinued due to a serious adverse event	0	(0.0, 1.5)
Discontinued due to a serious vaccine-related adverse event	0	(0.0, 1.5)

[†]As determined by the investigator to be related to the vaccine; [‡]Adverse event checked as the reason for discontinuation in the subject disposition page; 95% CI based on exact binomial distribution; CI: confidence interval

Table 4: Subjects with injection-site adverse events (Days 1 to 42 post-vaccination)

	ZOSTAVAX™	
	n (%)	95% CI
Subjects in population with follow-up	250	
With one or more injection-site adverse events	48 (19.2)	(14.5, 24.6)
With no injection-site adverse events	202 (80.8)	(75.4, 85.5)
General disorders and administration site conditions	48 (19.2)	(14.5, 24.6)
Injection-site erythema	35 (14.0)	(9.9, 18.9)
Injection-site pain	22 (8.8)	(5.6, 13.0)
Injection-site pruritus	7 (2.8)	(1.1, 5.7)
Injection-site swelling	31 (12.4)	(8.6, 17.1)

Every subject is counted a single time for each applicable specific injection-site adverse event. A subject with multiple injection-site adverse events within a system organ class is counted a single time for that system organ class; 95% CI based on exact binomial distribution; CI: confidence interval

post-vaccination in a subset of 1,395 subjects^{9,13} compared to 2.5 for subjects ≥60 years old in this study. Similarly, in the ZEST study with 22,000 subjects 50-59 years old, a subcohort population of 1,136 reported a GMFR of 2.3 at 6 weeks post-vaccination, compared to 2.9 for subjects 50-59 years old in this study. Since the fold increase in antibody titer is a better marker for protection than absolute values of VZV-specific antibody titers at 6 weeks,¹⁶ the results of the current study are encouraging.

We report a lower rate of injection-site AEs in healthy Indian adults. Overall, 19.2% subjects reported at least one vaccine-related injection-site AE; these were more frequent in subjects 50-59 years old (27.5%), compared to subjects ≥60 years old (6.2%). The most frequently reported injection-site AEs were injection-site erythema (14.0%), swelling (12.4%), and pain (8.8%). The most frequent injection-site AEs in the

SPS AE sub study were comparatively higher and included injection-site erythema (35.8%), pain or tenderness (34.5%), swelling (26.2%), and pruritus (7.1%).¹³ The rate of injection-site AEs in the ZV group reported in ZEST was 64%.¹² In the current study, the rate of injection-site AEs was higher in subjects 50-59 years old versus ≥60 years old, which is similar to reports of the same age-specific populations in ZEST (50-59 years) and SPS (≥60 years).

Overall, we report a lower rate of systemic AEs in healthy Indian adults. In this study, 15.2% subjects experienced at least one systemic AE; pyrexia (4.4%) and cough (2.8%) were the most frequently reported. Systemic AEs occurred in 17.0% subjects 50-59 years old and 12.4% subjects ≥60 years old. In ZEST, systemic AEs were reported in approximately 35% and 34% of ZOSTAVAX and placebo recipients, respectively; vaccine-related systemic AEs were reported in 6.7% and

4.7% subjects, respectively. The most frequent systemic AE was headache (ZOSTAVAX, 9.4%; placebo, 8.2%), which was considered vaccine-related in ~3% and ~2% in the ZOSTAVAX and placebo groups, respectively.¹² The SPS reported systemic AEs in 24.7% and 23.6% subjects in the ZV and placebo groups, respectively; vaccine-related systemic AEs were reported in 6.3% and 4.9% subjects, respectively.¹³ We did not receive reports of any varicella/varicella-like or HZ/HZ-like rash during this study; however, the identification and differentiation of viral subtypes is imperative in vaccinated subjects reporting breakthrough varicella zoster.¹⁸⁻²¹

For the potential of this vaccine to be fully realized, it is important to ensure there is adequate knowledge among healthcare providers about HZ. An HZ global awareness survey, conducted in 2010 in 22 countries, reported an overall poor knowledge of the causes

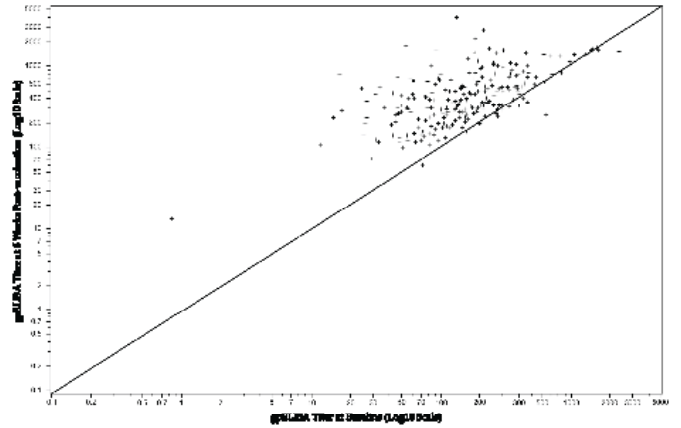


Fig. 1: Scatter plot of VZV antibody titers by gpELISA (all vaccinated subjects)

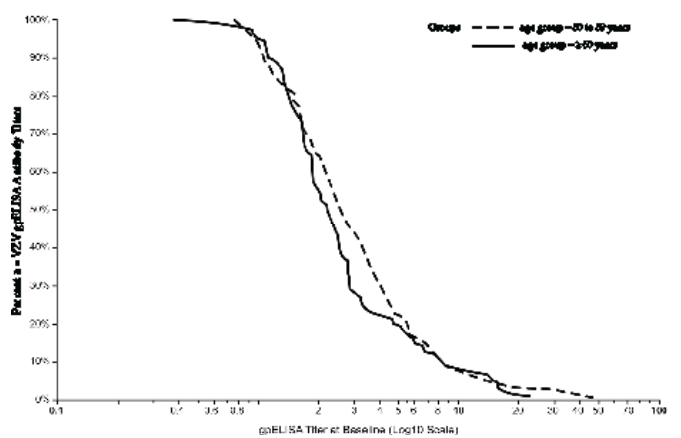


Fig. 2: Reverse cumulative distribution of gpELISA titer fold rise by age group (all vaccinated subjects)

Table 5: Systemic adverse events by system organ class (Days 1 to 42 post-vaccination)- overall and vaccine-related

	ZOSTAVAX™					
	Overall			Vaccine-Related [†]		
	n	(%)	95% CI	n	(%)	95% CI
Subjects in population with follow-up	250			250		
With one or more systemic adverse events	38	(15.2)	(11.0, 20.3)	11	(4.4)	(2.2, 7.7)
With no systemic adverse events	212	(84.8)	(79.7, 89.0)	239	(95.6)	(92.3, 97.8)
Ear and labyrinth disorders	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Vertigo	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Gastrointestinal disorders	5	(2.0)	(0.7, 4.6)	0	(0.0)	(0.0, 1.5)
Abdominal pain	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Gastritis	2	(0.8)	(0.1, 2.9)	0	(0.0)	(0.0, 1.5)
Haematemesis	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Vomiting	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
General disorders and administration site conditions	14	(5.6)	(3.1, 9.2)	8	(3.2)	(1.4, 6.2)
Chills	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Pain	3	(1.2)	(0.2, 3.5)	1	(0.4)	(0.0, 2.2)
Pyrexia	11	(4.4)	(2.2, 7.7)	7	(2.8)	(1.1, 5.7)
Infections and infestations	13	(5.2)	(2.8, 8.7)	1	(0.4)	(0.0, 2.2)
Bronchitis	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Gastroenteritis	2	(0.8)	(0.1, 2.9)	0	(0.0)	(0.0, 1.5)
Influenza	4	(1.6)	(0.4, 4.0)	0	(0.0)	(0.0, 1.5)
Rhinitis	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Upper respiratory tract infection	3	(1.2)	(0.2, 3.5)	1	(0.4)	(0.0, 2.2)
Urinary tract infection	2	(0.8)	(0.1, 2.9)	0	(0.0)	(0.0, 1.5)
Injury, poisoning and procedural complications	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Ligament sprain	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Musculoskeletal and connective tissue disorders	3	(1.2)	(0.2, 3.5)	0	(0.0)	(0.0, 1.5)
Arthralgia	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Pain in extremity	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Periarthritis	1	(0.4)	(0.0, 2.2)	0	(0.0)	(0.0, 1.5)
Nervous system disorders	3	(1.2)	(0.2, 3.5)	1	(0.4)	(0.0, 2.2)
Headache	3	(1.2)	(0.2, 3.5)	1	(0.4)	(0.0, 2.2)
Psychiatric disorders	1	(0.4)	(0.0, 2.2)	1	(0.4)	(0.0, 2.2)
Nervousness	1	(0.4)	(0.0, 2.2)	1	(0.4)	(0.0, 2.2)
Respiratory, thoracic and mediastinal disorders	7	(2.8)	(1.1, 5.7)	0	(0.0)	(0.0, 1.5)
Cough	7	(2.8)	(1.1, 5.7)	0	(0.0)	(0.0, 1.5)

A subject with multiple adverse events within a system organ class is counted a single time for that system organ class; 95% CI based on exact binomial distribution; [†]Determined by the investigator to be related to the vaccine; CI: confidence interval

and symptoms of the disease.⁸ In India, <20% individuals surveyed were aware of HZ in India compared to 97%-100% individuals in New Zealand, Brazil, and Malaysia. The survey recommended a population-wide effort to improve global awareness of HZ. Since then, immense progress has been made towards raising awareness of HZ among healthcare providers and expanding its treatment options. Since this survey was conducted before the launch of the vaccine globally, the numbers are likely to improve in countries where the vaccine is being marketed.

In conclusion, in healthy Indian subjects ≥50 years old who received ZOSTAVAX, the VZV-specific antibody titers as measured by GMT and GMFR at 6 weeks post-vaccination were consistent with what has been observed

previously in the clinical development program. The AE profile suggests that ZOSTAVAX was generally well tolerated. With greater use, ZOSTAVAX is expected to prevent the pain and suffering due to HZ disease in elderly population in India.

Acknowledgements

We acknowledge the efforts of Drs. D.N. Mishra, Anu Gaikwad, Hemant Talnikar, Neeraj Pandey, and Monica Gupta as investigators on the study. Medical writing assistance was provided by Suchita Nath-Sain, PhD, and Disha Dayal, PhD, of Cactus Communications, Mumbai, India. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The study was funded by MSD, India.

Conflicting interest

MS and SP are permanent employees of MSD, India. LS, BSC, SRR, PV, and RN have no conflicts of interest.

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