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Immunogenicity and Safety of a Live Attenuated Zoster Vaccine (ZOSTAVAX™) in Korean Adults

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A live attenuated zoster vaccine (ZOSTAVAX™, Merck & Co., Inc.) was approved by the Korea Ministry of Food and Drug Safety in 2009. However, the immunogenicity and safety of the vaccine has not been assessed in Korean population. This is multi-center, open-label, single-arm study performed with 180 healthy Korean adults ≥ 50 yr of age. The geometric mean titer (GMT) and geometric mean fold rise (GMFR) of varicella zoster virus (VZV) antibodies were measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) at 4 weeks post-vaccination. Subjects were followed for exposure to varicella or herpes zoster (HZ), the development of any varicella/varicella-like or HZ/HZ-like rashes, and any other clinical adverse experiences (AEs) for 42 days post-vaccination. For the 166 subjects included in the per-protocol population, the GMT at Day 1 was 66.9. At 4 weeks post-vaccination, the GMT for this population was 185.4, with a GMFR of 2.8 (95% CI, 2.5-3.1). Of the 180 subjects vaccinated, 62.8% experienced ≥ 1 AE, with 53.3% of subjects reporting injection-site AEs. The most frequently reported injection-site AEs were erythema (45.0%) with the majority being mild in intensity. Overall, 44 (24.4%) subjects experienced ≥ 1 systemic AE, 10 (5.5%) subjects experienced a systemic vaccine-related AE, and 3 (1.7%) subjects experienced ≥ 1 serious AE not related to vaccine. No subjects reported a VZV-like rash. There was no subject of death and no subject discontinued due to an adverse event. A single dose of zoster vaccine induced VZV-specific gpELISA antibody response and was generally well-tolerated in healthy Korean adults ≥ 50 yr of age (registry at www.clinicaltrial.gov No. NCT01556451).

Keywords: Immunology; Adverse Effects; Aged; Herpes Zoster Vaccine; Humans; Republic of Korea

INTRODUCTION

Herpes zoster (HZ) is a disease occurring after first infection by varicella-zoster virus (VZV), due to reactivation of latent viruses remaining in sensory ganglion of cranial or spinal nerves. HZ causes pain and vesicular skin lesions along the unilateral dermatome. The cumulative lifetime incidence of HZ is as high as about 10%-30% (1,2). The incidence of HZ increases with age (3-9). The incidence of complications, such as post-herpetic neuralgia (PHN), increases in the elderly (4,5,10). The occurrence of HZ considerably lowers the quality of life and exacts high socioeconomic cost (8,11-14).

A live attenuated zoster vaccine (ZOSTAVAX™, Merck & Co., Inc.) has been developed for the prevention of HZ and its complications, especially herpes zoster associated pain and PHN. The Shingles Prevention Study (SPS) performed with subjects ≥ 60 yr of age demonstrated that the use of the HZ vaccine reduced the incidence of HZ and PHN by 51.3%, and 66.5%, respectively (15). The Zostavax Efficacy and Safety Trial (ZEST) performed with subjects 50-59 yr of age showed the vaccine reduced the risk of developing zoster by 69.8% (16).

ZOSTAVAX™ was approved by the Korea Ministry of Food and Drug Safety in 2009 for the prevention of HZ in adults ≥ 60 yr of age, with an expanded indication for adults ≥ 50 yr of age in 2011. This study (NCT01556451; V211-034) evaluated the immunogenicity, safety, and tolerability of the vaccine when administered to Korean adults ≥ 50 yr of age.

MATERIALS AND METHODS

Study design

This was a multi-center (9 sites in Korea) open-label, single-arm, phase 4 study conducted from April 2012 to October 2012.

Study population

Healthy adults ≥ 50 yr of age on the day of signed informed con-

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sent were eligible. All subjects were afebrile (< 38.0°C) on the day of vaccination and any underlying chronic illness needed to be stable. All females were postmenopausal or had a negative urine pregnancy test. Subjects were excluded if they had previous vaccination with any VZV-containing vaccine, history of hypersensitivity reaction to any vaccine component, history of HZ, immunodeficiency associated with illness or medical treatments, known or suspected active untreated tuberculosis, received immunoglobulin or any blood products during the 5 months prior to vaccination or expected during 4 weeks post-vaccination period, received any other live virus vaccine within 4 weeks prior to vaccination or expected during 6 weeks post-vaccination period, received any inactivated vaccine within 7 days prior to vaccination or expected during 6 weeks post-vaccination period, or used any non-topical antiviral therapy with activity against herpes viruses. Subjects who received any pneumococcal polysaccharide vaccine within 4 weeks prior to vaccination or expected to receive any pneumococcal vaccine polyvalent during the 42-day duration of the study were also excluded.

Study procedure

Subjects were vaccinated with the zoster live vaccine (ZOSTAVAX™, Merck & Co., Inc.) on day 1 and followed for exposure to varicella or HZ or development of any varicella/varicella-like or HZ/HZ-like rashes, as well as any other clinical adverse experiences for 42 days post-vaccination. Blood samples were obtained from all subjects immediately before vaccination and at 4 weeks post-vaccination. Injection-site reactions, rashes, other adverse experiences, other concomitant medications, and concomitant vaccinations were recorded by the subject on a Vaccination Report Card (VRC). This study was supported using the Merck Research Laboratories (MRL), One Merck Drive, P.O. Box 100, Whitehouse Station, NJ 0889-0100 USA, for procedures relative to initiation, monitoring, data handling, clinical supply management, safety management, and clinical study result reporting.

Immunologic measurements

The key immunogenicity outcome measures were the geometric mean fold rise (GMFR) of subjects' VZV antibody titers from pre-vaccination to 4 weeks post-vaccination and geometric mean titer (GMT) at 4 weeks postvaccination. The VZV antibody titer was assessed by glycoprotein enzyme-linked immunosorbent assay (gpELISA) at a central laboratory. The method detected antibodies to VZV glycoprotein (gp), purified from MRC-5 cells infected with the KMcC strain of VZV by lectin affinity chromatography. The reactivity of sera to the gp antigens from uninfected MRC-5 cells, denoted as tissue culture control (TCC) wells, was substracted from the reactivity of the sera to the gp antigens purified from VZV-infected MRC-5 cells. For the gpELISA, VZV gp or TCC antigen was absorbed to polystyrene microtiter wells and used as the solid phase antigen. Experimental, control, and standard curve sera (serum sample for reference standard curve) were incubated in VZV gp-coated and TCC-coated wells. Regarding standard curve performance, a single human serum sample with a high titer was used as a standard in the gpELISA. Within each validation run, the standard was tested in nine, twofold serial dilutions, ranging in concentration from 0.3125 to 80 gpELISA units/mL. For each serum sample, a delta optical density (DOD) was calculated as the difference between the average optical density (OD) of the 2 VZV antigen wells and the average OD of the 2 TCC wells. Quantitation was performed by comparison of sample DOD with a standard curve.

Safety measurements

Safety and tolerability data was collected for all subjects for 42 days post-vaccination. Each subject was given a VRC to document injection-site adverse events (AEs), systemic clinical AEs, concomitant medications, and oral temperatures (only if feeling feverish) noted during the 42-day post-vaccination period. All serious adverse events occurring through day 42 post-vaccination were to be reported by the investigator within 24 hr of first notification to the study site personnel.

Severity of injection-site AEs except erythema and swelling, were classified as mild, moderate, and severe. Mild AE was defined as an event causing no or minimal interference with usual social and functional activities. Moderate AE was defined as an event causing greater than minimal interference with usual social and functional activities. Severe AE was defined as an event causing inability to perform usual social and functional activities. Injection site erythema and swelling was measured to establish the maximum size.

Subjects who develop suspected varicella/varicella-like or HZ/HZ-like rashes were to notify the investigator immediately. The subjects were planned to be seen by the investigator at the study site within 72 hr of rash onset (preferably within 24 hr) for clinical evaluation. Polymerase chain reaction assay was planned to detect VZV and herpes simplex virus (HSV) deoxyribonucleic acid (DNA) in specimens obtained from subjects suspected of having varicella or HZ.

Statistical methods

This study was descriptive and no hypothesis was tested. The immunologic analysis was based on a per-protocol population, which included all subjects who received the vaccine and did not have major deviations from the protocol procedure or Good Clinical Practices (GCP) violation. If 162 subjects (90% of the 180 subjects enrolled) were included in the pre-protocol population, the half-width of the 95% confidence interval (CI) for GMFR would be 0.15 in the natural log scale, assuming the standard deviation of the natural log of the fold rise was 1.0. All

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subjects who were vaccinated and had safety follow-up were included in the safety analysis. If no vaccine-related serious AEs were observed among the 180 subjects, this provided 97.5% confidence that the true vaccine-related serious AE rate was ≤ 2.03%.

Ethics statement

The study was approved by the institutional review boards at all study sites: Korea University Guro Hospital Institutional Review Board (KUGH11261-001), Korea University Ansan Hospital Institutional Review Board (AS11200), Korea University Anam Hospital Institutional Review Board (ED11308), Yonsei University Severance Hospital Institutional Review Board (4-2011-0913), Kangdong Sacred Heart Hospital Institutional Review Board/Ethics Committee (12-2-008), The Catholic University of Korea Seoul St. Mary's Hospital Institutional Review Board (XC12MSMV0011K), Hanyang University Seoul Hospital Institutional Review Board (HYUH IRB 2012-C-15), and Samsung Medical Center Institutional Review Board (2012-01-051). Written informed consent was obtained from each subject prior to any study procedure. This study was registered at www.clinicaltrial.gov as NCT01556451.

Table 1. Baseline characteristics of the study subjects

Characteristics	Total (n = 180)	
	No.	%
Gender		
Female	136	75.6
Male	44	24.4
Age (yr)		
50-59	89	49.4
≥ 60	91	50.6
≥ 70	12	6.7
Median (range)	60 (50-82)	
Underlying medical conditions	115	63.9
Vascular disorders	58	32.2
Hypertension	55	30.6
Metabolism and nutritional disorders	39	21.7
Hyperlipidemia	26	14.3
Diabetes mellitus	16	8.9
Musculoskeletal diseases	31	17.2
Osteoarthritis	5	2.8
Osteoporosis	5	2.8
Spinal stenosis	5	2.8
Gastrointestinal diseases	21	11.7
Colonic polyp	6	3.3
Gastroesophageal reflux disease	5	2.8
Gastritis	4	2.2
Nervous system disorders	14	7.8
Renal and urinary disorders	5	2.8
Cardiac disorders (excluding hypertension)	5	2.8
Respiratory disorders	4	2.2
With one or more concomitant vaccinations	2	1.1
Influenza vaccine	2	1.1

RESULTS

Characteristics of the study subjects

One hundred eighty subjects were enrolled from April 2012 to October 2012. Each study site enrolled 20 subjects. The demographic characteristics are shown in Table 1. The mean age at enrollment was 60.6 ± 6.1 yr. Among the subjects, 91 (50.6%) were ≥ 60 yr of age and 136 (75.6%) were female. Approximately 64% of subjects had one or more underlying medical conditions. The most common underlying condition was vascular disorders (32.2%), followed by metabolism and nutrition disorders (21.7%), and musculoskeletal and connective tissue disorders (17.2%). Throughout the study the most frequently reported concomitant prescription medications were analgesics (21.1%), agents acting on the renin–angiotensin system (20.0%), lipid-modifying agents (19.4%), and calcium channel blockers (13.9%). Two subjects were administered influenza vaccine between days 1 and 42.

Immunogenicity

Protocol deviation or GCP violation occurred in 14 (7.8%) subjects among the 180 subjects vaccinated. As a result, the immunologic analysis was performed with 166 subjects. The GMT at Day 1 was 66.9 (Table 2). At 4 weeks post-vaccination, the GMT for this population was 185.4, with a GMFR of 2.8 (95% CI, 2.5-3.1). The inverse cumulative distribution of VZV antibody titer is shown in Fig. 1. In subgroup analysis according to the age group, the GMT for subjects 50-59 yr of age at 4 weeks post-vaccination was 173.0, with a GMFR of 2.9 (95% CI, 2.5-3.4). The GMT for subjects ≥ 60 yr of age at 4 weeks post-vaccination was 199.2, with a GMFR of 2.6 (95% CI, 2.3-3.0). The inverse cumulative distribution of gpELISA fold rise at 4 weeks post-vaccination according to the age group is shown in Fig. 2.

Safety

Table 3 summarizes AEs that occurred during the 42 days after

Table 2. Varicella-zoster virus antibody geometric mean titers and geometric mean fold rise in the per-protocol population

Age group			No. of subjects	Results*	95% CI†
Overall	GMT (units/mL)	Day 1	166	66.9	59.2-75.5
		Week 4	166	185.4	167.0-205.9
	GMFR	Week 4	166	2.8	2.3-3.1
50-59 yr	GMT (units/mL)	Day 1	84	58.7	49.6-69.4
		Week 4	84	173.0	149.2-200.6
	GMFR	Week 4	84	2.9	2.5-3.4
≥ 60 yr	GMT (units/mL)	Day 1	82	76.4	64.1-91.2
		Week 4	82	199.2	171.5-231.3
	GMFR	Week 4	82	2.6	2.3-3.0

*Antibody measured as gpELISA units/mL; †95% CI for GMFR and GMT was computed based on the t-distribution. CI, confidence interval; GMT, geometric mean titer in gpELISA units/mL; GMFR, geometric mean fold rise.

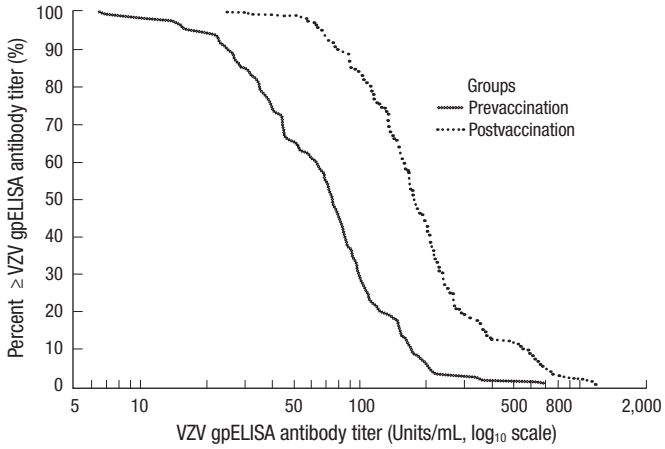

Fig. 1. Inverse Cumulative Distribution of Varicella-zoster Virus (VZV) Antibody Titer in the per-protocol (PP) group. VZV glycoprotein enzyme-linked immunosorbent assay (gpELISA) antibody titers (units/mL) were observed clearly increased after the vaccination with ZOSTAVAX™ in the PP group.

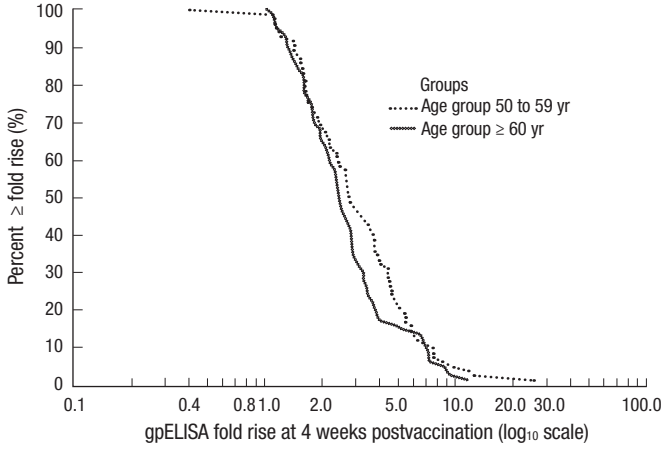

Fig. 2. Inverse cumulative distribution of glycoprotein enzyme-linked immunosorbent assay (gpELISA) fold rise at 4 weeks post-vaccination according to the age group.

Table 3. Adverse events among all study subjects

Adverse events	Total (n = 180)		
	No.	%	95% CI†
Subjects with one or more AEs	113	62.8	55.3-69.9
With one or more injection site AEs	96	53.3	
With systemic AEs	44	24.4	
Subjects with AEs related to the vaccine*	97	53.9	46.3-61.3
With one or more injection site AEs	95	52.8	
With no injection site AEs	10	5.6	
Subjects with one or more SAEs	3	1.7	0.4-4.8
Subjects with SAEs related to the vaccine	0	0.0	0.0-0.0

*As determined by the investigator to be related to the vaccine; †95% CI based on exact binomial distribution. CI, confidence interval; AE, adverse event; SAE, severe adverse event.

Table 4. Classification of adverse events among all study subjects

Adverse events	Total (n = 180)		
	No.	%	95% CI*
Subjects with one or more injection site AEs	96	53.3	45.8-60.8
Erythema	81	45.0	37.6-52.6
Swelling	68	37.8	30.7-45.3
Pain	50	27.8	21.4-34.9
Tenderness	5	2.8	0.9-6.4
Pruritus	5	2.8	0.9-6.4
Feeling hot	2	1.1	0.1-4.0
Rash	1	0.6	0.0-3.1
Sensation of heaviness	1	0.6	0.0-3.1
Subjects with one or more systemic AEs	44	24.4	18.4-31.4
General disorders and administration site conditions	50	27.8	21.4-34.9
Skin and subcutaneous tissue disorders	15	8.3	4.7-13.4
Infections and infestations	9	5.0	2.3-9.3
Gastrointestinal disorders	9	5.0	2.3-9.3
Musculoskeletal and connective tissue disorders	7	3.9	1.6-7.9
Eye disorders	3	1.7	0.4-4.8
Nervous system disorders	3	1.7	0.4-4.8
Psychiatric disorders	3	1.7	0.4-4.8
Respiratory, thoracic and mediastinal disorders	3	1.7	0.4-4.8
Injury, poisoning and procedural complications	1	0.6	0.0-3.1

*95% CI based on exact binomial distribution. CI, confidence interval.

the vaccinations. Of the 180 subjects vaccinated, 113 (62.8%) subjects experienced ≥ 1 AE, with 96 (53.3%) of subjects reporting injection-site AEs. The most frequently reported injection-site AEs were erythema (45.0%) (Table 4). All injection-site AEs except for one were determined to be related to the vaccine. Most (85.7%) of injection-site AEs were mild in intensity and there was no severe event. Most of the injection-site erythema (93.8%) and swelling (95.6%) were ≤ 3 inches in size and no case exceeded 5 inches. The injection-site AEs were more frequent in subjects 50-59 yr of age (58.4%) than those ≥ 60 yr of age (48.4%). Overall, 44 (24.4%) subjects experienced ≥ 1 systemic AE and 10 (5.5%) subjects experienced a systemic vaccine-related AE. The most frequently reported systemic AEs were rash (3.9%). The systemic AEs were slightly more frequent in subjects 50-59 yr of age (25.8%) than those ≥ 60 yr of age (23.1%). Three (1.7%) subjects experienced ≥ 1 severe adverse event (SAE): gastric polyp, anal fissure, and spinal compression fracture. None of these SAEs were classified as related to the vaccine. Most (> 90%) of the AEs, except SAEs, subsided in 2 days. No subjects reported a VZV-like rash. There were no deaths and no subjects discontinued due to an adverse event.

DISCUSSION

This study was performed to evaluate the safety, tolerability, and immunogenicity of ZOSTAVAX™ in Korean adults ≥ 50 yr of age. Because previous studies did not specifically target Korean subjects for enrollment, this is the first study to evaluate the characteristics of the zoster vaccine in Korean adults. All subjects were completely followed up for 42 days and reliable results were obtained.

In immunologic analysis performed in the per-protocol pop-

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ulation, the GMT was 66.9 at pre-vaccination and 185.4 at 4 weeks post-vaccination, with a GMFR of 2.8 (95% CI, 2.5-3.1). In subgroup analysis, the GMFR at 4 weeks post-vaccination was 2.9 (95% CI, 2.5-3.4) for subjects 50-59 yr of age and 2.6 (95% CI, 2.3-3.0) for those ≥ 60 yr of age. The GMFR observed in this study is higher than previous studies. ZEST, performed with subjects 50-59 yr of age, showed a GMFR of 2.3 (95% CI, 2.2-2.4) (16). SPS, performed with subjects ≥ 60 yr of age, showed a GMFR of 1.7 (95% CI, 1.6-1.8) (15). The most important reason for the difference is considered to be the difference between the timing of post-vaccination blood sampling. In two prior studies, the VZV-specific immune responses were measured at 6 weeks post-vaccination (15,16). Racial difference might be another reason for study differences; the previous two studies did not include Asian countries. Although this study showed that the immunogenicity of the zoster vaccine is good in Korean adults, the efficacy and the effectiveness of the vaccine for preventing zoster should be assessed with further studies.

In the safety analysis performed on all subjects, most of the AEs were due to local injection-site reactions and their intensity was mild. The safety profile of the vaccine in Korean adults was similar to previous studies.

In conclusion, a single dose of zoster vaccine induced VZV-specific gpELISA antibody response and was generally well-tolerated in healthy Korean adults ≥ 50 yr of age. These findings are consistent with data previously observed in the clinical development program.

DISCLOSURE

This work was supported by Merck Sharp & Dohme Corp. (sponsor), a subsidiary of Merck & Co., Inc. This study was designed, executed, and analyzed by the sponsor. Although the sponsor reviewed a draft, the opinions expressed are those of the authors and may not necessarily reflect those of the sponsor. All co-authors approved the final version of the manuscript.

AUTHOR CONTRIBUTION

Acquisition of data: Choi WS, Choi JH, Choi JY, Eom JS, Kim SI, Pai HJ, Peck KR, Sohn JW, and Cheong HJ. Interpretation of data: Choi WS, Cheong HJ. Writing and revision of the manuscript: Choi WS. Study supervision: Cheong HJ.

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