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-
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 nega-
tive 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 pneu-
mooccocal polysaccharide vaccine within 4 weeks prior to vacci-
nation or expected to receive any pneumococcal vaccine poly-
valent during the 42-day duration of the study were also excluded.

Study procedure
Subjects were vaccinated with the zoster live vaccine (ZOSTA-
VAX™, 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 experi-
ences for 42 days post-vaccination. Blood samples were obtain-
ed from all subjects immediately before vaccination and at 4
weeks post-vaccination. Injection-site reactions, rashes, other
adverse experiences, other concomitant medications, and con-
comitant vaccinations were recorded by the subject on a Vaccin-
ation Report Card (VRC). This study was supported using the
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Box 100, Whitehouse Station, NJ 08890-0100 USA, for procedures
relative to initiation, monitoring, data handling, clinical supply
management, safety management, and clinical study result re-
porting.

Immunologic measurements
The key immunogenicity outcome measures were the geom-
etric 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 anti-
body titer was assessed by 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 af-
finity chromatography. The reactivity of sera to the gp antigens
from uninfected MRC-5 cells, denoted as tissue culture control
(TCC) wells, was subtracted 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 polysty-
rene 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 stan-
dard was tested in nine, twofold serial dilutions, ranging in con-
centration from 0.3125 to 80 gpELISA units/mL. For each se-
rum 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 docu-
ment injection-site adverse events (AEs), systemic clinical AEs,
concomitant medications, and oral temperatures (only if feel-
ing febrish) noted during the 42-day post-vaccination period.
All serious adverse events occurring through day 42 post-vacci-
nation 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 de-
finied 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 so-
cial and functional activities. Severe AE was defined as an event
causing inability to perform usual social and functional activi-
ties. Injection site erythema and swelling was measured to es-
tablish 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) deoxy-
ribonucleic 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
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 (XC12MS-MV0011K), 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 vaccination. 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.

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

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