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Immunogenicity and safety of a new live attenuated herpes zoster vaccine (NBP608) compared to Zostavax® in healthy adults aged 50 years and older

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ABSTRACT

A multi-centre, randomised, double-blinded, active-controlled, parallel-group clinical trial was carried out to assess the immunogenicity and safety of NBP608—a newly developed live-attenuated zoster vaccine in Korea—relative to Zostavax® in healthy adults aged 50 years or older. Immune responses to the vaccine were evaluated by glycoprotein enzyme-linked immunosorbent assay (gpELISA) and enzyme-linked immunosorbent spot (ELISPOT) assays using the interferon (IFN)-γ and interleukin (IL)-2 FluoroSpot kit 6 weeks after vaccination. Safety was monitored for 26 weeks based on subjects' diaries, spontaneous reports from subjects, and history taking by the investigators. A total of 845 subjects participated in the screening, and 823 received the vaccination (413 in the NBP608 group and 411 in the comparator group). The gpELISA-determined geometric mean fold rise from baseline to post NBP608 vaccination was 2.75 [95% confidence interval, CI (2.57, 2.94)]. The gpELISA-determined adjusted geometric mean titers (GMTs) of NBP608 and the comparator were 1346.37 [95% CI (1273.99, 1422.87)] and 1674.94 [95% CI (1585.35, 1769.58)], respectively. The adjusted GMT ratio of NBP608 to the comparator was 0.80 [95% CI (0.75, 0.87)]. There was no statistically significant difference between two groups in terms of the geometric mean spot numbers determined by IFN-γ and IL-2 ELISPOT assays at 6 weeks post vaccination (P = 0.7232, 0.3844). The incidence of adverse events (AEs) within 6 weeks post vaccination was 49.82% overall (410/823, 941 cases), 50.73% (209/412, 474 cases) in the NBP608 group, and 48.91% (201/411, 467 cases) in the comparator group. The difference in AE rate between the two groups was not statistically significant (P = 0.6010). Most AEs were mild, with a rate of 83.12% in the NBP608 group and 75.37% in the comparator group. Thus, NBP608 is non-inferior to Zostavax® in terms of inducing the immune response and can be safely administered to adults aged 50 years or older.
ClinicalTrials.gov Identifier: NCT03120364.

1. Introduction

Shingles (herpes zoster, HZ) is derived from the Latin and French words for belt or girdle and refers to a girdle-like skin eruption that occurs on the body trunk. Anyone who has ever had varicella can develop HZ due to the reactivation of varicella-zoster virus (VZV) from latency at neuronal ganglia. About 10%–30% of the population experiences HZ at least once in their lifetime [1,2]. How and when the virus is reactivated is not well understood, but the probability gradually increases over time as immunity against VZV acquired from varicella infection declines [1]. The disease burden associated with HZ is greater in immunologi-

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cally compromised individuals including those with leukaemia or lymphoma and patients receiving chemotherapy or radiotherapy for malignancies, who have diseases affecting immune function, or who are taking immunosuppressants [3–7]. Approximately 10% of patients with HZ develop post-herpetic neuralgia (PHN), which is the most serious complication of HZ. The incidence of PHN increases to 25%–50% in patients who experienced HZ at or after the age of 50 years. In severe cases PHN can be incapacitating due to pain that may last for months or even years.

Zostavax®, the licensed live attenuated HZ vaccine, has been shown to reduce HZ incidence and PHN frequency in clinical trials [8,9], and Shingrix® has currently been approved claiming better efficacy across the age group of ≥50 years [10,11]. The Advisory Committee on Immunization Practices of the U.S. Center for Disease Control and Prevention 2008 guidelines recommended vaccination with Zostavax® for HZ prevention in healthy adults aged ≥60 years [12], and a supplement was announced in 2018 to recommend two doses of Shingrix® for healthy adults aged ≥ 50 years, as a preferred vaccine over Zostavax® [13]. Korea started to import the vaccine in 2012, but the supply has been limited. Recently, the incidence rate of herpes zoster has steadily been increased due to an aging population and other extrinsic factors, but supply has not expanded to meet demand globally. Korea has one of the fastest-growing elderly populations and there has been a sharp increase in the demand for the zoster vaccine, prompting the development of a new live-attenuated zoster vaccine NBP608 by SK bioscience (Andong-si, Republic of Korea). NBP608 is manufactured with the Oka virus strain using the MRC-5 cell line, same as Zostavax®, and intended to provide as comparable protection against herpes zoster as Zostavax® in order to solve an insufficient supply of the vaccine.

Previous non-clinical studies have shown that NBP608 is non-toxic in rats, beagle dogs, and guinea pigs, and has immunogenicity equivalent to the licensed varicella (Varivax®) and zoster (Zostavax®) vaccines in guinea pigs, which has been reported to the Ministry of Food and Drug Safety, Korea but has not been published. Three clinical studies of NBP608 have been performed in healthy Korean adults; the results showed that the vaccine is safe and well tolerated with an immunogenicity comparable to that of Zostavax® (ClinicalTrials.gov Identifier: NCT03121638, NCT03116594, and NCT03120364).

This investigation was carried out as a clinical study for licensing in Korea to confirm the immunogenicity and safety of NBP608 compared to Zostavax® in healthy adults aged 50 years or older.

2. Materials and methods

2.1. Study design

A multi-centre, randomised, double blinded, active controlled, parallel-group clinical trial was conducted to assess the immunogenicity and safety of NBP608 compared to Zostavax® in adults aged 50 and over at eight university hospitals in the Republic of Korea (ClinicalTrials.gov Identifier: NCT03120364). The study period was from September 9, 2015 to April 28, 2016. The primary objectives were to determine the geometric mean fold rise (GMFR) in VZV antibody titer of NBP608 by glycoprotein enzyme-linked immunosorbent assay (gpELISA) from baseline to 6 weeks post vaccination, and to evaluate the immunogenicity of NBP608 relative to the comparator drug (Zostavax®) by comparing gpELISA-determined GMFRs.

2.2. Study population

Healthy adults aged 50 and over who were available for follow-up during the study period were screened and enrolled. Female subjects had to be of non-childbearing potential or agree to use a medically accepted form of contraception for at least 6 weeks. Persons with immunocompromised conditions or who had a positive history of herpes zoster and contraindication to vaccination were excluded. Subjects who met the inclusion/exclusion criteria were randomised to NBP608 and comparator (Zostavax®) groups at a ratio of 1:1. Randomisation was stratified by age to achieve a balanced treatment assignment within age strata (≥50–< 60 [50 s], ≥ 60–< 70 [60 s], ≥ 70 [70 s]).

2.3. Intervention

The subjects were subcutaneously administered one dose of the study or comparator vaccine in the deltoid region of the upper arm. One vial of the study drug contained a 0.5-ml suspension with a minimum of 27,400 plaque-forming units (PFU) of the vaccine virus. The comparator was Zostavax® manufactured by Merck & Co. (Kenilworth, NJ, USA). Subjects were monitored for 30 min at the study site following vaccine administration.

2.4. Follow-up

Subjects were required to keep a diary to record all adverse events (AEs) occurring over a 6-week period starting from the date of injection. At 1 week post vaccination, subjects were contacted via telephone to monitor serious (S)AEs and development of rash. At 6 weeks post vaccination, subjects were required to visit the study site for post vaccination blood sampling and to return their diaries for AE evaluation and additional safety assessment. At 26 weeks post vaccination, subjects were contacted via telephone to verify the occurrence of SAEs.

2.5. Immunogenicity evaluation

The immunogenicity of NBP608 was assessed by gpELISA, which is one of the most reliable methods for measuring the protective antibody response against VZV based on the specific interaction of antibodies with their target antigen. gpELISA was performed at the Life Science Laboratory of SK bioscience using the SERION ELISA *classic* Varicella-Zoster Virus IgG kit with the sensitivity and specificity of >99% and 97.8% respectively [14]. To verify cell-mediated immunity (CMI) against VZV after vaccination, enzyme-linked immunosorbent spot (ELISPOT) assays were performed using the interferon (IFN)-γ and interleukin (IL)-2 FluoroSpot kit (Mabtech, Nacka Strand, Sweden) in 20% of the subjects at the Laboratory of Immunology and Infectious Diseases, Graduate School of Medical Science & Engineering, KAIST (Daejeon, Republic of Korea). In ELISPOT assays, PBMCs were stimulated with γ-irradiation-inactivated, semi purified VZV lysate (Microbix, Mississauga, Canada).

2.6. Safety evaluation

AE monitoring was based on spontaneous reports from subjects, subject diary review, and history taking by investigators. AEs were regularly followed for additional safety information until resolution or until follow up was no longer possible. The severity of AE was graded on a scale from 1 to 4 based on the guidelines of Korean Ministry of Food and Drug Safety and U.S. Food and Drug Administration. Causal relationships were determined by the investigators. Physical examination and other safety assessments including 12-lead electrocardiography, chest X-ray, and laboratory tests were performed before and 6 weeks after vaccination.

2.7. Statistical analysis

Demographic information for all subjects enrolled in the clinical study (intention-to-treat [ITT] set) was analysed, and descriptive statistics including the mean and standard deviation are presented.

Statistical analyses of immunogenicity assessment endpoints were performed in the per protocol set (PPS) as the primary analysis set (defined as all subjects who completed the study procedures without any major protocol violations) as well as in the full analysis set (FAS) (defined as subjects who underwent immunogenicity assessment after vaccination). Results from both datasets are presented. Safety endpoints in the safety set (defined as all subjects who were enrolled in the study and received vaccination) were statistically analysed.

Two hypotheses were sequentially tested for the primary endpoint. GMFR from baseline to 6 weeks post vaccination and the corresponding 95% confidence interval (CI) were estimated in the NBP608 group to confirm that the lower bound of the 95% CI was >1.4. The 6 weeks post-vaccination GMT ratio of NBP608 to the comparator adjusted for age, sex, and baseline GMT was estimated along with the 95% CI to confirm that the lower bound of the 95% CI was >0.67. If this threshold was met, NBP608 was to be considered as non-inferior to the comparator. Adjusted GMTs were calculated with age, sex, and baseline GMT as covariates in the analysis of covariance. For CMI response assessment, geometric mean spot numbers (GMSNs) and their 95% CIs before and after vaccination were estimated. The two-sample *t* test was used to compare the GMSNs of the test and comparator groups.

All subjects who received the vaccine were included in the safety assessments. All AEs were categorised and analysed according to severity and in terms of a causal relationship to the vaccine. The χ^2 or Fisher's exact test was used to compare AE rates between the NBP608 and comparator groups. The *t* test was used to compare means. Changes in measurements from baseline to post vaccination were evaluated with the paired *t* test and McNemar's test.

2.8. Ethics approval

The study was performed with approval of the Institutional Review Board from each of the eight participating university hospitals. Written, informed consent was obtained from all participants.

3. Results

3.1. Characteristics of the study subjects

A total of 845 subjects participated in the screening; of these, 21 failed to meet the inclusion/exclusion criteria (Fig. 1). Consequently, 824 subjects determined as eligible were enrolled (ITT set) and randomised to the NBP608 (n = 413) or the comparator (n = 411) group. A total of 823 subjects were included in the safety set, of whom 821 and 812 were included in the FAS and PPS, respectively.

Demographic characteristics and medical histories of the study population are shown in Table 1. The mean ages of the 824 subjects

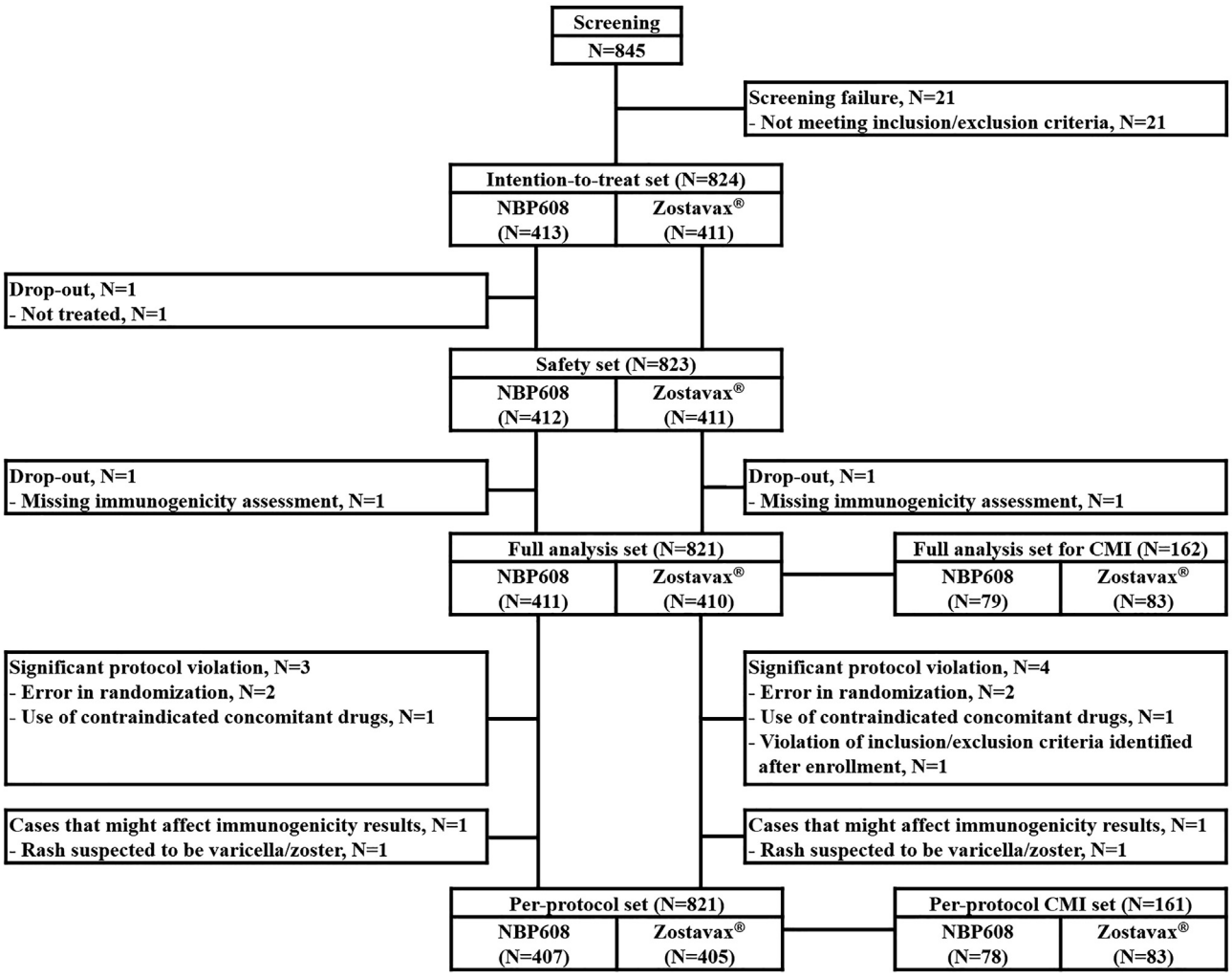

Fig. 1. Characteristics of study subjects.

in the ITT set were 60.17 ± 7.03 and 60.14 ± 7.11 years in the NBP608 and comparator groups, respectively. The percentages of females and males were 68.28% (282/413) and 31.72% (131/413), respectively, in NBP608 group, and 64.96% (267/411) and 35.04% (144/411), respectively, in the comparator group. The proportion of subjects in the NBP608 and comparator groups who had a history of cured past medical conditions within the 2 years prior to the screening visit was 16.71% (69/413) and 17.52% (72/411), respectively; the proportion who had an existing medical condition was 49.64% (205/413) and 46.96% (193/411), respectively; and the proportion who used concomitant medications during the study was 45.04% (186/413) and 43.31% (178/411), respectively. There were no statistically significant differences in demographic characteristics or medical history between the two groups.

3.2. Immunogenicity assessment

The gpELISA-determined GMT of NBP608 unadjusted was 1300.68, and GMFR of NBP608 from baseline to post vaccination was 2.75 [95% CI (2.57, 2.94)] (Fig. 2); since the lower bound of 95% CI exceeded 1.4, the immunogenicity hypothesis was satisfied. The gpELISA-determined GMTs of NBP608 and Zostavax® at 6 weeks after vaccination were adjusted for age, sex, and baseline GMT to evaluate non-inferiority of NBP608 to Zostavax®. The adjusted GMTs were 1346.37 [95% CI (1273.99, 1422.87)] and 1674.94 [95% CI (1585.35, 1769.58)], respectively. The adjusted GMT ratio of NBP608 to Zostavax® was 0.80 [95% CI (0.75, 0.87)]. The fact that the lower bound of the 95% CI exceeded 0.67 indicated that NBP608 was non-inferior to Zostavax®.

A subgroup analysis by age group was performed in the PPS for the gpELISA-determined GMFR from baseline to 6 weeks post vaccination in the NBP608 group. The adjusted GMFRs in the NBP608 and comparator groups were 2.93 [95% CI (2.70, 3.18)] and 3.79 [95% CI (3.51, 4.10)], respectively, 50 s; 2.64 [95% CI (2.42, 2.87)] and 2.87 [95% CI (2.64, 3.13)], respectively, in 60 s; and 2.38 [95% CI (2.02, 2.79)] and 3.02 [95% CI (2.58, 3.55)], respectively, in 70 s. The lower bound of the 95% CI for the GMFRs was >1.4 in all age strata. Adjusted GMT ratios between the two groups were statistically significant in 50 s and 70 s (50 s, $P < 0.0001$; 60 s, $P = 0.1329$; and 70 s, $P = 0.0378$).

IFN-γ and IL-2 ELISPOT assays were performed in 161 subjects (NBP608 group, n = 78 and comparator group, n = 83). IFN-γ ELISPOT-determined GMSNs at 6 weeks post vaccination were 95.60 spot-forming cells (SFCs)/10^6 peripheral blood mononuclear cells (PBMCs) for the NBP608 group and 91.11 SFCs/10^6 PBMCs for the comparator group (Fig. 3). The IL-2 ELISPOT-determined GMSNs at 6 weeks post vaccination was 17.37 SFCs/10^6 PBMCs for the NBP608 group and 13.59 SFCs/10^6 PBMCs for the compara-

Table 1
Baseline characteristics of the subjects.

Characteristics	NBP608 (n = 413) No./total (%)	Zostavax® (n = 411) No./total (%)	P value
Gender, male	131/413 (31.72)	144/411 (35.04)	0.3126
Age, years, mean ± SD	60.17 ± 7.03	60.14 ± 7.11	0.9462
50–59 years	214/413 (51.82)	214/411 (52.07)	0.9833
60–69 years	146/413 (35.35)	146/411 (35.52)	
≥70 years	53/413 (12.83)	51/411 (12.41)	
Body mass index, kg/m^2, mean ± SD	24.11 ± 2.97	24.08 ± 2.93	0.8805
Medical history within 2 years[1]	69/413 (16.71)	72/411 (17.52)	0.7572
Surgical history within 2 years, yes	27/413 (6.54)	25/411 (6.08)	0.7883
Current medical history[1]	205/413 (49.64)	193/411 (46.96)	0.4418
Concomitant medications[1]	186/413 (45.04)	178/411 (43.31)	0.6176

[1] Duplicate counting.

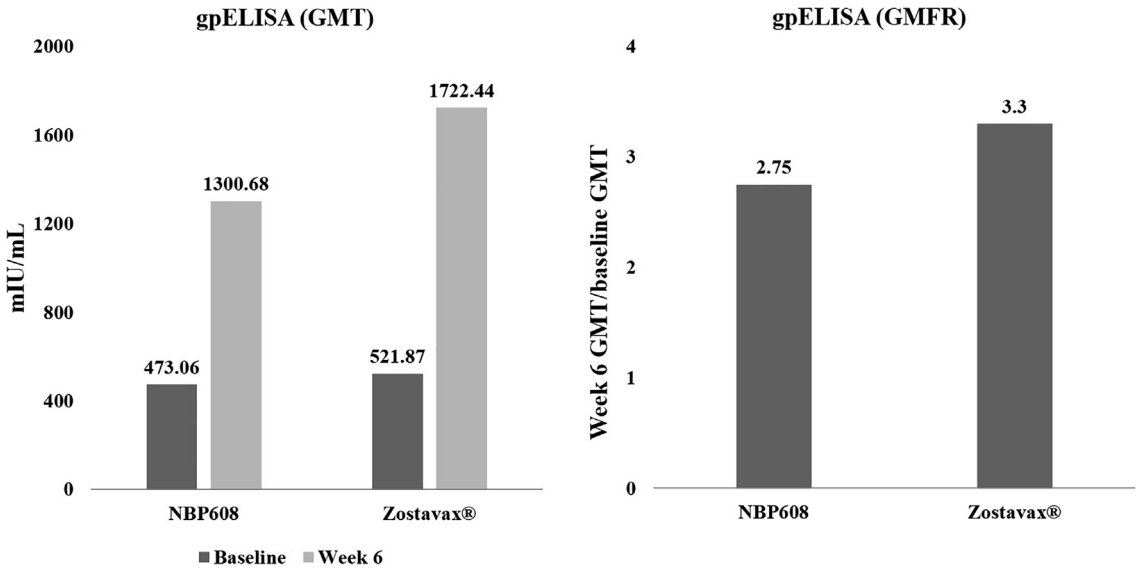

Fig. 2. Immunogenicity of NBP608 and Zostavax®. Unadjusted VZV geometric mean titer (GMT) and geometric mean fold-rise (GMFR) measured by gpELISA at 6 weeks post-vaccination are presented.

tor group. GMSN values of NBP608 were higher in both the IFN-γ and IL-2 ELISPOT analyses but the differences were not statistically significant (P = 0.7232 and 0.3844, respectively).

3.3. Safety assessment

The incidence of AEs within 6 weeks after vaccination was 49.82% (410/823, 941 cases) overall, 50.73% (209/412, 474 cases) in the NBP608 group and 48.91% (201/411, 467 cases) in the comparator group (Table 2). The difference in incidence between the two groups was not statistically significant (P = 0.6010). Most AEs (746/941, 79.28%) were mild in terms of severity: 394 [83.12%] and 352 [75.37%] cases in the NBP608 and comparator group, respectively. Severe AEs were reported in 12 cases (1.28%): four in the NBP608 group (0.84%) and eight in the comparator group (1.71%). There were no potentially life-threatening AEs.

Solicited local AEs were reported at a rate of 34.14% (281/823, 416 cases): 35.19% (145/412, 220 cases) in the NBP608 group and 33.09% (136/411, 196 cases) in the comparator group. Solicited systemic AEs were reported at a rate of 25.88% (213/823, 388 cases): 25.97% (107/412, 195 cases) in the NBP608 group and 25.79% (106/411, 193 cases) in the comparator group. Unsolicited AEs were reported at a rate of 13.37% (110/823, 137 cases): 11.65% (48/412, 59 cases) in the NBP608 group and 15.09% (62/411, 78 cases) in the comparator group. Comparisons of solicited local, solicited systemic, and unsolicited AE incidences between the two groups showed no statistically significant differences. AE incidence by age did not differ significantly between the two groups (50 s, P = 0.9528; 60 s, P = 0.1890; ≥70 s, P = 0.4470).

A total of eight SAEs (four each in the NBP608 and comparator groups) occurred within 26 weeks after vaccination, including influenza, spinal column stenosis, 7th cranial nerve paralysis, vertigo, ankle fracture, contusion, lipoma excision, and removal of internal fixation. None of the SAEs were considered as being causally related to the vaccine. Of these, two events (both in the comparator group) occurred within 6 weeks post vaccination.

The events were confirmed as varicella- or zoster-like rashes in 0.24% of the subjects (2/823, two cases): one varicella-like rash in the NBP608 group and one zoster-like rash in the comparator group. The former, which appeared on day 9 post vaccination, was of mild severity and consisted of two blisters at the site of vaccination that disappeared in 11 days after onset. A sample was analysed by PCR but the results were indeterminate because a VZV-Oka pattern was identified only in partial open reading frames; moreover, the sample was negative by PCR amplification for herpes simplex virus.

Table 2
Adverse events (AEs) reported within 26 weeks post-vaccination.

Characteristics	NBP608 (n = 412) No. (%)	Zostavax® (n = 411) No. (%)	P value
AEs within 6 weeks post-vaccination	209 (50.73)	201 (48.91)	0.6010
Solicited local AEs	145 (35.19)	136 (33.09)	0.5245
Pain	86 (20.87)	83 (20.19)	0.8094
Redness/erythema	102 (24.76)	87 (21.17)	0.2209
Induration/swelling	32 (7.77)	26 (6.33)	0.4193
Solicited systemic AEs	107 (25.97)	106 (25.79)	0.9530
Fever	2 (0.49)	2 (0.49)	1.0000
Vomiting	3 (0.73)	1 (0.24)	0.6241
Diarrhoea	11 (2.67)	9 (2.19)	0.6547
Headache	38 (9.22)	39 (9.49)	0.8959
Fatigue/malaise	65 (15.78)	65 (15.82)	0.9880
Myalgia	76 (18.45)	77 (18.73)	0.9154
Unsolicited AEs	48 (11.65)	62 (15.09)	0.1477
Infections and infestations	12 (2.91)	24 (5.84)	0.0401
Musculoskeletal and connective tissue disorders	10 (2.43)	11 (2.68)	0.8207
Gastrointestinal disorders	11 (2.67)	9 (2.19)	0.6547
Skin and subcutaneous tissue disorders	7 (1.70)	8 (1.95)	0.7908
Nervous system disorders	3 (0.73)	2 (0.49)	1.0000
Immune system disorders	2 (0.49)	3 (0.73)	0.6864
Injury, poisoning, and procedural complications	2 (0.49)	3 (0.73)	0.6864
Other disorders[1]	8 (1.94)	10 (2.43)	–
Serious adverse events			
Within 6 weeks post-vaccination	0 (0.00)	2 (0.49)	0.2491
Within 26 weeks post-vaccination	4 (0.97)	4 (0.97)	1.0000

[1] Other disorders include "General disorders and administration site conditions", "Investigations", "Eye disorders", "Respiratory, thoracic, and mediastinal disorders", "Ear and labyrinth disorders", "Blood and lymphatic system disorders", "Metabolism and nutrition disorders", "Renal and urinary disorders", and "Surgical and medical procedures", which occurred in fewer than five subjects.

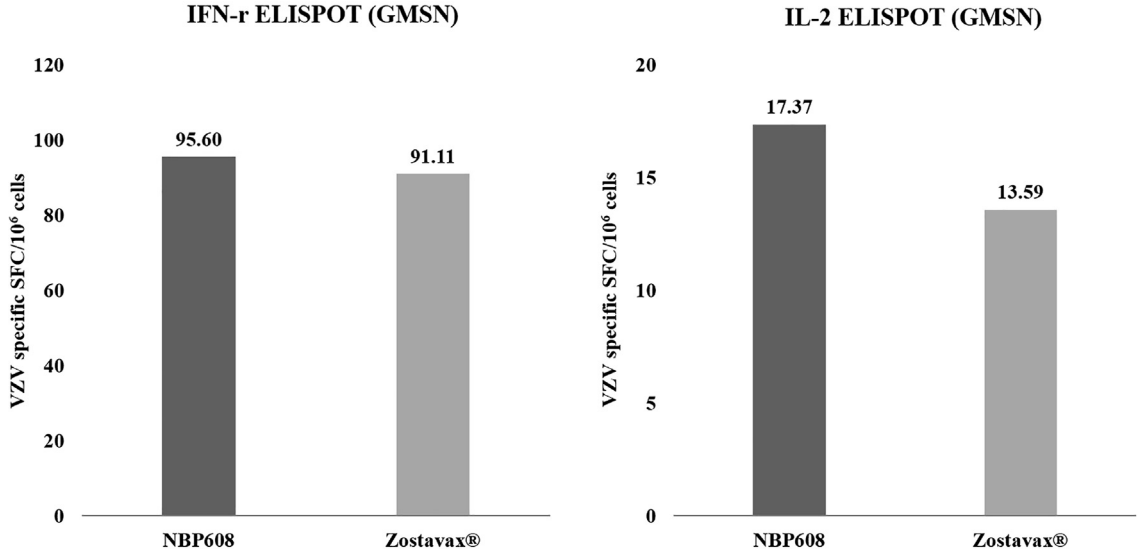

Fig. 3. CMI induced by NBP608 and Zostavax®. VZV-CMI response measured by IFN-γ and IL-2 ELISPOT is presented as the GMSNs at 6 weeks post-vaccination.

4. Discussion

This clinical study was designed to assess the immunogenicity and safety of NBP608 compared to Zostavax® after administration of a single dose in healthy adults aged 50 and older. Immunogenicity and safety were monitored for 6 and 26 weeks, respectively, after vaccination. The results revealed that NBP608 was non-inferior to Zostavax® in terms of immunogenicity, as determined by gpELISA. The immune response was generally weaker in older vaccinated patients, but our results indicate that NBP608 could induce robust immune response in the elderly. The hypotheses tested in this study correspond to the guidelines of the World Health Organization on the clinical evaluation of vaccines and criteria adopted in Zostavax® studies [15,16].

The CMI induced by vaccination was compared between the two vaccines, given that it is the most important factor in suppressing VZV reactivation. The IFN-γ and IL-2 ELISPOT-determined GMSNs at 6 weeks post vaccination showed higher tendency in subjects receiving NBP608 as compared to the comparator (Zostavax®), although the differences between the two groups were not statistically significant due to the insufficient sample size. It is presumed that the CMI might be more induced by NBP608.

Our results also showed that the safety of NBP608 was comparable to that of Zostavax®, since the overall incidence of AEs as well as the incidence of specific subgroups (solicited local, solicited systemic, and unsolicited AEs) did not differ statistically between the two groups. The severity of AEs was also similar between the groups, with most AEs being mild—i.e., 83.12% in the NBP608 group and 75.37% in the Zostavax® group, although in the latter the proportion of mild events was lower.

In the 6 weeks after vaccination, there was one case of a Zoster-like rash in comparator group and one case of a Varicella-like rash in the NBP608 group. In earlier clinical studies on Zostavax®, the incidences of Zoster- and varicella-like rashes were 0.1%–0.2% and 0.1%–0.6%, respectively [8,9]. The rate of varicella-like rash in the present study is consistent with the previous report.

The limitation of the present study is that we did not directly assess the effectiveness of NBP608 in preventing the development of herpes zoster after vaccination. Also, a long-term immunogenicity was not examined and there was no comparison with the recently developed adjuvanted subunit zoster vaccine; further research is needed in these areas.

In conclusion, the immunogenicity and safety results from the current study indicate that NBP608 was non-inferior to Zostavax® in inducing immune response against VZV, can be administered safely in adults 50 years of age and older, and can therefore meet the increasing demand for the zoster vaccine in Korea.

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Declaration of interest

None.

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