

Immunogenicity and Safety of the HZ/su Adjuvanted Herpes Zoster Subunit Vaccine in Adults Previously Vaccinated With a Live Attenuated Herpes Zoster Vaccine

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(See the major article Schwarz et al, on pages 1352–61 and editorial commentary by Oxman et al, on pages 1329–33.)

Background. Protection against herpes zoster (HZ) induced by the live attenuated zoster vaccine Zostavax (ZVL) wanes within 3–7 years. Revaccination may renew protection. We assessed whether (re)vaccination with the adjuvanted HZ subunit vaccine candidate (HZ/su) induced comparable immune responses in previous ZVL recipients and ZVL-naïve individuals (HZ-NonVac).

Methods. In an open-label, multicenter study, adults ≥65 years of age, vaccinated with ZVL ≥5 years previously (HZ-PreVac), were matched to ZVL-naïve adults (HZ-NonVac). Participants received 2 doses of HZ/su 2 months apart. The primary objective of noninferiority of the humoral immune response 1 month post-dose 2 was considered demonstrated if the upper limit of the 95% confidence interval (CI) of the adjusted anti-glycoprotein E geometric mean concentration (GMC) ratio of HZ-NonVac over HZ-PreVac was <1.5. HZ/su cellular immunogenicity, reactogenicity, and safety were also assessed.

Results. In 430 participants, humoral immune response to HZ/su was noninferior in HZ-PreVac compared with HZ-NonVac (adjusted GMC ratio, 1.04 [95% CI, .92–1.17]). Cellular immunogenicity, reactogenicity, and safety appeared to be comparable between groups. HZ/su was well-tolerated, with no safety concerns raised within 1 month post-dose 2.

Conclusions. HZ/su induces a strong immune response irrespective of prior vaccination with ZVL, and may be an attractive option to revaccinate prior ZVL recipients.

Clinical Trials Registration. NCT02581410.

Keywords. herpes zoster; HZ/su adjuvanted herpes zoster subunit vaccine; live attenuated zoster vaccine Zostavax; immune response; revaccination.

Herpes zoster (HZ) results from reactivation of latent varicella zoster virus (VZV) and usually presents as a vesicular dermatomal rash [1]. HZ can be followed by postherpetic neuralgia (PHN), chronic neuropathic pain that persists after resolution of the zoster rash [2]. A decline in VZV-specific cell-mediated immunity (CMI) increases the risk of HZ [3–5]. Because CMI naturally decreases with age [6], the risk of developing HZ, and the risk of PHN, increases as people get older. The incidence of HZ increases from <5 cases per 1000 person-years (PY) in those <50 years of age to 4–8 cases per 1000 PY in adults between 50 and 59 and >10 cases per 1000 PY in adults >70 years of age [7, 8]. Half of all HZ cases occur in adults aged >60 years, and the

lifetime risk is 50% in those surviving to 85 years of age [9]. The risk of developing PHN increases from 5% to 14% in HZ patients aged 50–59 years to >15% in those >70 years of age [10, 11].

Many HZ complications, but not PHN, can be prevented with antivirals if administered shortly after disease onset [1, 12]. Vaccination of at-risk populations is a cost-effective approach to prevent HZ and its complications [13]. The live attenuated zoster vaccine (ZVL) licensed for use in healthy adults >50 years of age (Zostavax, a trademark of Merck Sharp & Dohme Corporation) reduces HZ incidence by 70% in people between 50 and 59 years of age [14]. In the United States, vaccination is currently recommended to prevent HZ in people >60 years of age [9] and the efficacy of ZVL in this population is lower: 51% in people >60 years and 38% in people >70 years of age [15]. In adults >60 years of age, efficacy against HZ declines to 30.6% in the sixth year [16] and to 21.1% between 7 and 11 years postvaccination [17]. The vaccine efficacy against PHN wanes from 66.5% shortly after vaccination [15] to 35.4% between 7 and 11 years postvaccination [17].

HZ/su is a subunit vaccine candidate that contains the recombinant VZV glycoprotein E (gE) [18, 19], adjuvanted with the proprietary AS01 Adjuvant System (GSK Vaccines) [20, 21].

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HZ/su substantially boosts the immune response to gE [22–24]. Interestingly, the humoral immune response to the vaccine does not markedly differ between people aged 50–59 years and those >70 years of age [23], and both the humoral and cellular immune responses persist above baseline levels for at least 6 years postvaccination [25]. HZ/su has shown an efficacy of >90% for the prevention of HZ in people 50 years of age and older [26, 27]. Moreover, vaccine efficacy against HZ persisted for at least 4 years after vaccination, with 88% efficacy in the fourth year postvaccination [27].

ZVL continues to provide protection against the incidence of HZ through the first 5 years after vaccination [16], and revaccination after year 5 may therefore be beneficial [28]. A second vaccination with ZVL in previously vaccinated individuals 10 years after the initial vaccination induces a VZV-specific CMI response higher than in age-matched controls who had never been vaccinated with ZVL, showing that immune responses can be boosted by a second dose [29]. However, given HZ/su's high vaccine efficacy against HZ and PHN across all age groups, revaccinating older adults, who were previously vaccinated with ZVL, with HZ/su may be an attractive alternative to reduce the risk of HZ and PHN. This study therefore compared immunogenicity and assessed reactogenicity and safety of HZ/su in adults aged ≥ 65 years who were vaccinated with ZVL ≥ 5 years before study start and group-matched ZVL-naive adults.

METHODS

Study Design and Participants

This study is a phase 3, open-label, group-matched, multicenter study conducted in the United States. Adults ≥ 65 years of age who were previously vaccinated with ZVL (Zostavax) ≥ 5 years prior to study start (HZ-PreVac) and group-matched ZVL-naive adults (HZ-NonVac) were enrolled (for the distribution of matching criteria at vaccination, see Supplementary Table 1). The active phase of the study started in March 2016 (first vaccination) and was completed in August 2016 (1 month post-dose 2). The extended safety follow-up is expected to be completed in August 2017.

Participants in the HZ-NonVac group were group-matched to those in the HZ-PreVac group according to the predefined variables age (65–69, 70–79, ≥ 80 years), sex, race (white, African American, Hispanic, and other), and medical condition. Medical conditions were ranked in a hierarchical order (immune-mediated diseases, diabetes mellitus, current depression, pulmonary disorders, heart conditions, none of these medical conditions), and participants were matched according to the highest-ranked condition.

Study participants were men or women aged ≥ 65 years at the time of the first vaccination with HZ/su. Adults eligible for inclusion in the HZ-PreVac group had received ZVL at least 5 years prior to study start. Participants provided written informed consent before study start. Adults were excluded from participation if they had received or were scheduled to receive a live vaccine within 30 days, had received any investigational or nonregistered

drug or vaccine within 30 days, had received immunosuppressants or other immune-modifying drugs for >14 consecutive days within 180 days, or had received any long-acting immune-modifying drugs within 180 days before the first HZ/su vaccination. Adults with a history of HZ, or adults scheduled to receive a HZ vaccine other than HZ/su, as well as adults with a history of any reaction or hypersensitivity to any of the vaccine components, were excluded from participation.

The study protocol was reviewed and approved by the institutional review boards (Chesapeake institutional review board [IRB], Columbia, MD; Office of Human Research IRB, Philadelphia, PA; Kaiser Permanente, Northern California IRB, Oakland, CA; Marshfield Clinic Research Foundation IRB, Marshfield, WI). The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice, and is registered at ClinicalTrials.gov (NCT02581410) and available at <http://www.gsk-clinicalstudyregister.com> (study ID: 201198).

Study Vaccines

Study participants in both groups received 2 intramuscular doses of HZ/su 2 months apart. Participants were vaccinated in the deltoid region of the nondominant arm. Each dose of HZ/su contained 50 μg of the gE antigen and the GSK proprietary AS01_B Adjuvant System (containing 50 μg of 3-O-desacyl-4'-monophosphoryl lipid, 50 μg of *Quillaja saponaria* Molina, fraction 21 [QS21, Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Genus Inc], and liposome).

Study Objectives and Measures

Study Objectives

The co-primary objectives of the study were to compare the humoral immune responses 1 month after dose 2 of HZ/su between the HZ-PreVac and HZ-NonVac groups, and to evaluate safety and reactogenicity up to 1 month after dose 2 of HZ/su in both study groups. The secondary study objectives also presented in this manuscript were to assess the humoral and CMI responses to the HZ/su vaccine at baseline (prevaccination), and 1 month post-dose 1 and post-dose 2 in both study groups.

Assessment of Immunogenicity

Blood samples for the immunogenicity assessments were collected at baseline and at 1 month after the first and second vaccine doses (Figure 1). Anti-gE antibody concentrations were measured by anti-gE enzyme-linked immunosorbent assay. The assay cutoff was 97 mIU/mL. CMI responses were assessed by intracellular cytokine staining and flow cytometry, as detailed previously [25]. In brief, peripheral blood mononuclear cells were stimulated in vitro with gE peptides, after which frequencies of gE-specific CD4⁺ T cells expressing at least 2 activation markers (here referred to as CD4²⁺) of the 4 markers assessed (interferon- γ , interleukin 2, tumor necrosis factor- α , and CD40 ligand) were determined.

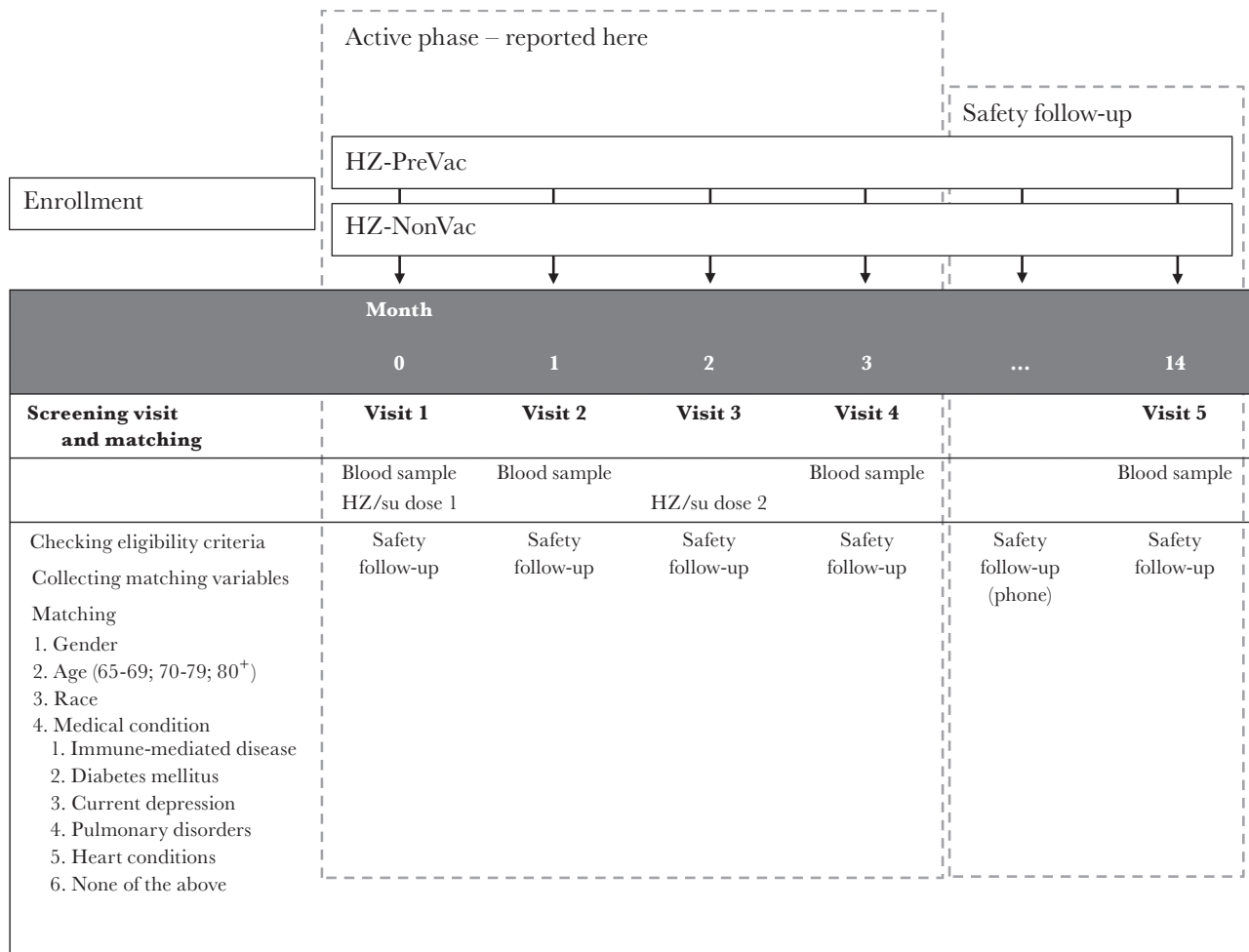


Figure 1. Study design. Before the first participant was vaccinated, potential participants were screened for eligibility and matching purposes. Matched participants were included in the study. During the active phase of the study, participants visited the study center at specified timepoints for a blood draw to determine immune parameters (months 0, 1, and 3), and to receive the study vaccine (months 0 and 2). Only data collected during the active phase of the study are reported in this manuscript. The safety follow-up was expected to continue until August 2017. During this safety follow-up, participants are being followed for safety through monthly phone calls. A final blood draw is scheduled to take place at 12 months after the second dose of study vaccine. Abbreviations: HZ-NonVac, participants who never received the live attenuated zoster vaccine; HZ-PreVac, participants who received the live attenuated zoster vaccine ≥ 5 years prior to study start; HZ/su, herpes zoster subunit candidate vaccine.

Assessment of Safety

Solicited adverse events (AEs) were reported on diary cards provided to study participants and recorded for 7 days (days 0–6) after each vaccination. Solicited AEs were recorded as local (injection site pain, redness, and swelling) or systemic (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering). Unsolicited AEs were recorded for 30 days after each vaccination, and included any AE not recorded as a solicited AE. The intensity of all AEs was graded on a scale of 1 to 3. A grade 3 (severe) unsolicited AE was defined as preventing normal activities. Solicited AEs were defined as grade 3 when preventing normal everyday activity (for pain, headache, fatigue, gastrointestinal symptoms, myalgia, shivering), when presenting a surface diameter >100 mm (for redness and swelling), or when presenting as a tympanic/oral/axillary temperature $>39.0^{\circ}\text{C}$ (for fever). All solicited local AEs were considered

causally related to vaccination. The causality of all other AEs was assessed by the investigator.

Serious adverse events (SAEs) and potential immune-mediated diseases (pIMDs) were recorded for the entire duration of the study, but only findings from the active phase of the study (first vaccination visit through 30 days post-dose 2) are presented here. A full list of pIMDs is provided in Supplementary Table 2.

Statistical Analyses

All statistical analyses were performed using the SAS software version 9.3 TS1M2 on Windows SDD 4.3.3.

Immunogenicity data were analyzed on the according to protocol cohort, which included all participants who complied with protocol-specified procedures and for whom data were available. For inferential analyses of the co-primary endpoint data, an

analysis of variance (ANOVA) model was used on log-transformed antibody concentration data and included the vaccine group and the group-matching categories as fixed effects. Adjusted means and a difference of means between both study groups were calculated together with 2-sided confidence intervals (CIs) and back-transformed to the original units to provide adjusted geometric mean concentrations (GMCs) and GMC ratio. Per protocol, noninferiority of the response was demonstrated if the upper limit of the 2-sided CI of the adjusted GMC ratio of the HZ-NonVac over the HZ-PreVac group at 1 month post-dose 2 (active phase) was <1.5. Secondary immunogenicity endpoint data, including CMI data presented here, were evaluated using descriptive analyses. For descriptive humoral immunogenicity data, the 95% CI for GMCs was obtained for each group separately. First, a 95% CI for the mean of log-transformed concentrations was obtained, under the assumption that log-transformed values were normally distributed with unknown variance. Subsequently, the 95% CI for GMCs was calculated by anti-log transformation of the previously calculated 95% CI for the mean of log-transformed concentrations. For descriptive cellular immunogenicity, the frequency of gE-specific CD4²⁺ T cells was calculated as the difference between the frequency of CD4²⁺ T cells, stimulated in vitro with the gE antigen and those stimulated with culture alone. Descriptive statistics (min, Q1, median, Q3, max) of CD4²⁺ T cells were tabulated by group at all timepoints.

Safety and reactogenicity data were evaluated using descriptive analyses. Safety data were analyzed in the total vaccinated cohort of participants who received at least 1 dose of HZ/su.

Based on variability in the anti-gE antibody response to HZ/su as seen in previous clinical trials, a sample size of 190 evaluable participants per study group would demonstrate noninferiority in humoral immunogenicity with at least 99% power.

RESULTS

Participants

A total of 822 older adults were screened for participation in this study. Of these, 215 people not previously vaccinated were matched according to prespecified criteria (age, sex, geographic ancestry, and medical condition) to 215 people who had previously been vaccinated with ZVL (Figure 2). Of the 430 vaccinated participants, 425 (98.8%) completed the active phase of the study. Demographic characteristics were comparable for participants in both study groups and are presented in Table 1. Details of participant matching are provided in Supplementary Table 1.

Immunogenicity

Prior to the first vaccination, all evaluable participants in the HZ-PreVac group and 98% of evaluable participants in the HZ-NonVac group were seropositive for anti-gE antibodies (anti-gE concentration above the assay cutoff of 97 mIU/mL). Anti-gE antibody GMCs appeared similar at baseline in both study groups and increased markedly after both vaccine doses (Figure 3A and Supplementary Table 3). Anti-gE antibody GMCs post-dose 2 were comparable for both study groups, with an adjusted GMC ratio of 1.04 (Table 2). The primary immunologic study objective was met, as the upper limit of the adjusted

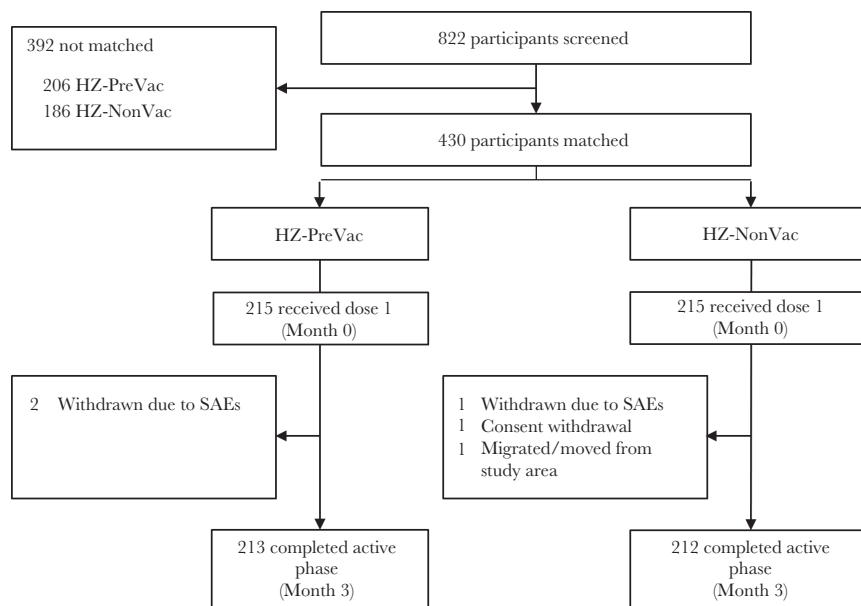


Figure 2. Participant disposition. Potential participants were first screened and matching variables were collected (see Figure 1). Only matched participants were vaccinated with herpes zoster subunit candidate vaccine (see Supplementary Table 1 for additional information on matching). Abbreviations: HZ-NonVac, participants who never received the live attenuated zoster vaccine; HZ-PreVac, participants who received live attenuated zoster vaccine ≥ 5 years prior to study start; SAE, serious adverse event.

Table 1. Characteristics of Study Participants (Total Vaccinated Cohort)

Characteristic	Total (N = 430)	HZ-NonVac (n = 215)	HZ-PreVac (n = 215)
Age, mean (SD)	70.9 (4.6)	70.8 (4.6)	71.1 (4.5)
Sex, No (%)			
Female	220 (51.2)	111 (51.6)	109 (50.7)
Male	210 (48.8)	104 (48.4)	106 (49.3)
White/European ancestry, No. (%)	430 (100)	215 (100)	215 (100)

Abbreviations: HZ-NonVac, participants who never received the live attenuated zoster vaccine; HZ-PreVac, participants who received the live attenuated zoster vaccine ≥ 5 years prior to study start; N/n, number of participants; SD, standard deviation.

GMC ratio of the HZ-NonVac group over the HZ-PreVac group was below the 1.5 cutoff (Table 2).

At baseline, the median CD4²⁺ T-cell frequency appeared similar in both groups. After dose 1, median frequencies of gE-specific CD4²⁺ T cells increased in both groups, and a more substantial overall increase was seen after dose 2 (Figure 3B and Supplementary Table 3). No difference in CD4²⁺ T-cell frequency was apparent between study groups.

Reactogenicity and Safety

The percentage of participants reporting all-grade solicited local and systemic AEs, as well as grade 3 solicited AEs, was comparable between study groups (Table 3). The most common local solicited AE reported after each HZ/su dose was pain. The most common systemic solicited AE reported after each dose was

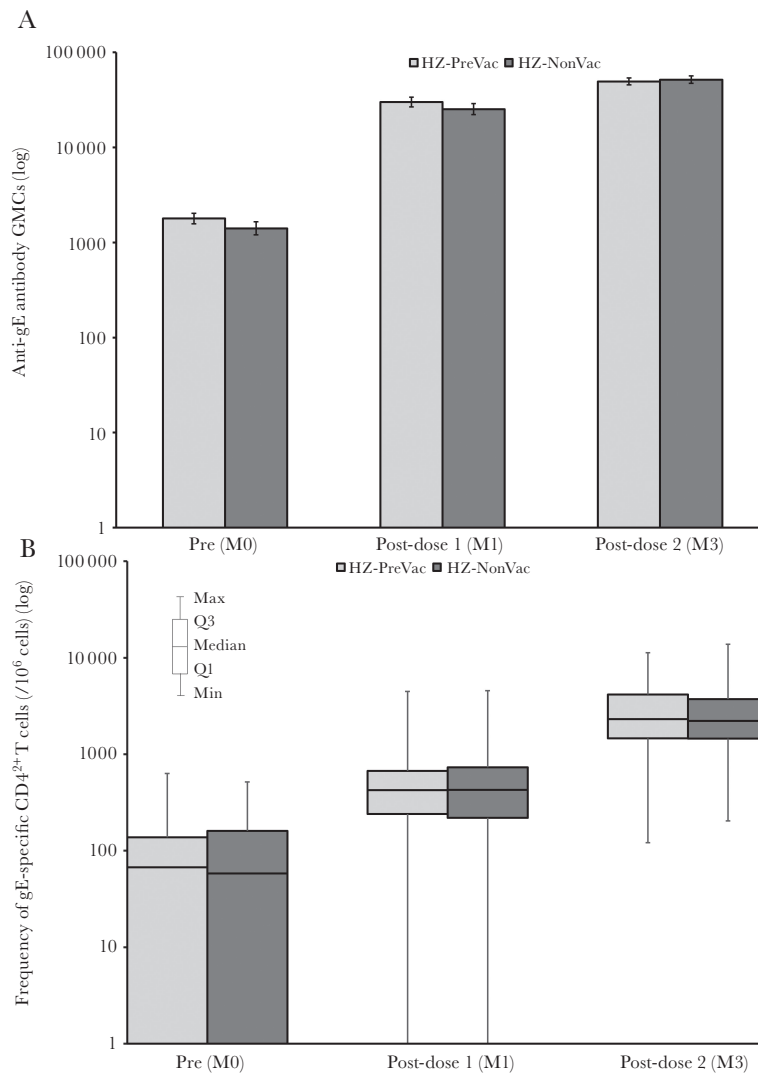


Figure 3. Humoral and cellular immune response to herpes zoster subunit candidate vaccine (HZ/su) (according to protocol cohort for immunogenicity). *A*, Humoral immune response to HZ/su vaccination. Anti-glycoprotein E (gE) antibody concentrations were determined by enzyme-linked immunosorbent assay. Data are geometric mean concentrations (GMCs [mIU/mL]) and error bars indicate 95% confidence intervals. *B*, Cellular immune response to HZ/su vaccination. The gE-specific CD4²⁺ cells expressing at least 2 activation markers (CD4²⁺) were determined by intracellular staining and flow cytometry. Data are median cell counts per 10⁶ total peripheral blood mononuclear cells. Light bars indicate participants who received the live attenuated zoster vaccine ≥ 5 years prior to study start (HZ-PreVac group); dark bars indicate participants who never received the live attenuated zoster vaccine (HZ-NonVac group). Abbreviations: M0 = pre vaccination; M1, one month post-dose 1; M3, one month post-dose 2.

Table 2. Adjusted Geometric Mean Concentrations (GMCs) and Adjusted GMC Ratio of Anti-Glycoprotein E Antibody Concentrations 1 Month Post-Dose 2 (According to Protocol Cohort for Immunogenicity)

HZ-NonVac				HZ-PreVac				GMC Ratio (HZ-NonVac/HZ-PreVac)		
No.	Adjusted GMC	95% CI ^a		No.	Adjusted GMC	95% CI ^a		Value	95% CI ^b	
		Lower Limit	Upper Limit			Lower Limit	Upper Limit		Lower Limit	Upper Limit
204	50 522.9	44 347.4	57 558.4	204	48 589.4	42 649.4	55 356.6	1.04	0.92	1.17 ^c

Abbreviations: adjusted GMC, geometric mean antibody concentration adjusted for group-matching variable; CI, confidence interval; HZ-NonVac, participants who never received the live attenuated zoster vaccine; HZ-PreVac, participants who received live attenuated zoster vaccine ≥5 years prior to study start; No., number of participants with both pre- and postvaccination results available.

^a95% confidence intervals for the adjusted GMC (analysis of variance [ANOVA] model: adjustment for group-matching variable) – pooled variance.

^b95% confidence interval for the adjusted GMC ratio (ANOVA model: adjustment for group-matching variable) – pooled variance.

^cPrimary objective considered met if <1.5.

fatigue (Figure 4). Solicited AEs were transient with a median duration of ≤3 days for local AEs and ≤2 days for systemic AEs.

Within 30 days after vaccination, 130 participants reported a total of 208 unsolicited AEs (HZ-PreVac: 125 AEs in 78 participants; HZ-NonVac: 83 AEs in 52 participants) (Table 3). At least 1 grade 3 unsolicited symptom was reported by 14 participants in the HZ-PreVac group and 5 participants in the HZ-NonVac group. No evidence of clinically relevant differences in reported unsolicited AE was observed between study groups.

From study start until 30 days after the second vaccination, a total of 9 SAEs were reported in 8 study participants (HZ-PreVac: 5 SAEs in 4 participants; HZ-NonVac: 4 SAEs in 4 participants). None of these SAEs were considered related to vaccination by

the study investigators. No deaths occurred, and no HZ cases or pIMDs were reported during the active phase of the study.

DISCUSSION

This study showed that the humoral immune response to HZ/su 1 month post-dose 2 was noninferior in adults >65 years of age who were vaccinated with the live attenuated zoster vaccine (Zostavax) >5 years ago compared with adults who never received this vaccination. Moreover, HZ/su was well-tolerated in both study groups, and no safety concerns were identified from first vaccination up to 1 month post-dose 2.

As in previous studies, HZ/su induced robust immune responses [22–24]. This study showed that prior vaccination

Table 3. Reactogenicity and Safety After Vaccination With Adjuvanted Herpes Zoster Subunit Candidate Vaccine (Total Vaccinated Cohort)

Adverse Event	HZ-NonVac (n = 214)		HZ-PreVac (n = 215)	
	No. ^a	% (95% CI)	No. ^a	% (95% CI)
Solicited AEs				
Within the 7-day (days 0–6) postvaccination period				
Participants reporting any solicited local reaction	187	87.4 (82.2–91.5)	193	89.8 (84.9–93.5)
Grade 3 solicited local reactions	21	9.8 (6.2–14.6)	21	9.8 (6.1–14.5)
Participants reporting any solicited systemic reaction	154	72.0 (65.4–77.9)	149	69.3 (62.7–75.4)
Grade 3 solicited systemic reactions	24	11.2 (7.3–16.2)	23	10.7 (6.9–15.6)
		HZ-NonVac (n = 215 ^b)		HZ-PreVac (n = 215 ^b)
Unsolicited AEs				
Within the 30-day (days 0–29) postvaccination period				
Total reported unsolicited AEs	83	—	125	—
Participants reporting any unsolicited AE	52	24.2 (18.6–30.5)	78	36.3 (29.8–43.1)
Unsolicited AEs considered related by investigator	12	5.6 (2.9–9.5)	13	6.0 (3.3–10.1)
Grade 3 unsolicited AEs	5	2.3 (.8–5.3)	14	6.5 (3.6–10.7)
SAEs				
From the first vaccination up to 30 days after last vaccination				
Total reported SAEs	4	—	5	—
Participants reporting any SAE	4	1.9 (.5–4.7)	4	1.9 (.5–4.7)
SAEs considered related by investigator	0	—	0	—
pIMDs				
From the first vaccination up to 30 days after last vaccination				
Total reported pIMDs	0	—	0	—

Abbreviations: AE, adverse event; CI, exact 2-sided confidence interval; HZ-NonVac, participants who never received the live attenuated zoster vaccine; HZ-PreVac, participants who received the live attenuated zoster vaccine ≥5 years prior to study start; n, number of participants with at least 1 administered dose and solicited adverse event symptom screen completed; pIMD, potential immune-mediated disease; SAE, serious adverse event.

^aTotal number of AEs, SAEs, pIMDs, or participants reporting at least 1 event.

^bNumber of participants with at least 1 administered dose.

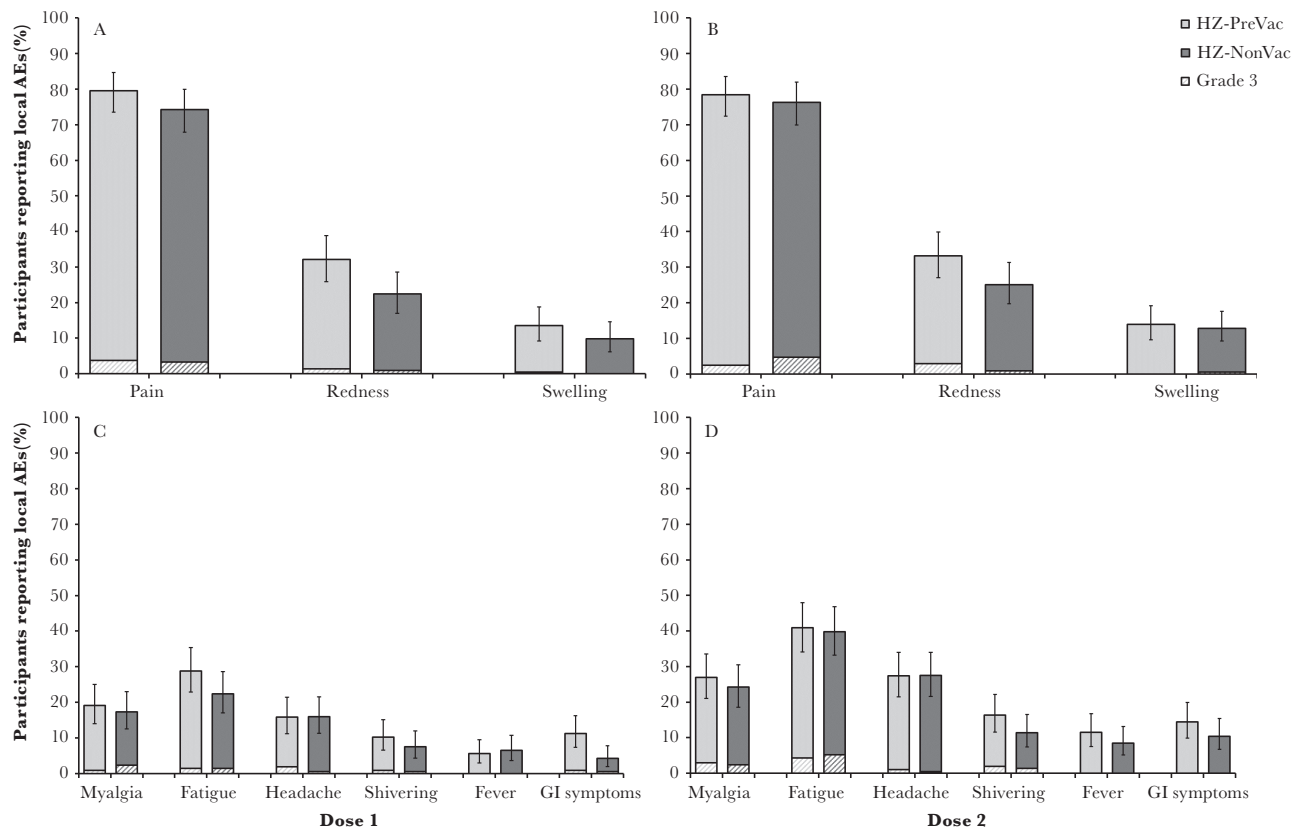


Figure 4. Solicited adverse events (AEs) after vaccination doses (total vaccinated cohort). *A*, Percentage of participants reporting local solicited AEs after herpes zoster subunit candidate vaccine (HZ/su) dose 1. *B*, Percentage of participants reporting local solicited AEs after HZ/su dose 2. *C*, Percentage of participants reporting related systemic solicited AEs after HZ/su dose 1. *D*, Percentage of participants reporting related systemic solicited AEs after HZ/su dose 2. Light bars indicate participants who received the live attenuated zoster vaccine ≥ 5 years prior to study start (HZ-PreVac group); dark bars indicate participants who never received the live attenuated zoster vaccine (HZ-NonVac group). Striped sections indicate grade 3 solicited AEs. Error bars indicate 95% confidence intervals.

with ZVL does not negatively impact the humoral immune responses to HZ/su. In addition, descriptive analyses did not reveal any apparent differences in CMI responses as assessed by CD4²⁺ T-cell frequencies, and postvaccination increases in CD4²⁺ T cell-frequencies were observed in both study groups. Altogether, these observations suggest that vaccination with HZ/su may provide protection and therefore may be an attractive candidate to revaccinate adults >65 years of age who were vaccinated with ZVL >5 years ago.

Consistent with previous findings, HZ/su recipients frequently reported the occurrence of solicited local and systemic AEs. Reactogenicity, as observed during phase 2 and phase 3 clinical trials with HZ/su [22–24, 26, 27, 30–32], was characterized by transient injection site reactions, headache, fatigue, and myalgia. The findings in the study presented here show that reactogenicity after vaccination is not exacerbated in older adults who were previously vaccinated with ZVL. As such, reactogenicity in HZ/su recipients who previously received ZVL is unlikely to differ from ZVL-naïve HZ/su recipients. Similarly, the number of SAEs reported were balanced between study groups, and no SAEs were considered related to vaccination by the study investigators. No fatal SAEs or pIMDs were reported

in either study group from first vaccination up to 1 month post-dose 2.

Our findings need to be evaluated in consideration of the strengths and limitations of the study design. The sample size was calculated to demonstrate noninferiority of the humoral immune response with 99% power, and our matching strategy aimed to ensure that the selected baseline characteristics are similar in both groups. Nonetheless, matching resulted in a study population that was fully of white heritage. In addition, as the United States was one of the few countries where ZVL coverage was sufficiently high, only US study centers participated.

In sum, we show that following vaccination with HZ/su, the humoral response in adults who were previously vaccinated with the live attenuated zoster vaccine was noninferior to that in adults without any previous vaccination against HZ. Robust cellular immune responses were observed in both groups. No clinically significant differences in safety and reactogenicity were observed between the 2 study groups. Taken together, HZ/su was well tolerated and induced a strong immune response irrespective of prior vaccination with ZVL, and may therefore be an attractive option to revaccinate prior ZVL recipients.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. GSK takes a commitment to convey a message in a way that would be easily understandable by Health Care Professionals (supplement text). L. C., M. D., T. C. H., H. L., L. O., and I. V. conceived and designed the study. K. G., N. K., L. O., and P. J. collected or generated study data. L. C., K. G., N. K., H. L., and J. P. performed the study. L. C., M. D., K. G., T. C. H., N. K., H. L., L. O., and I. V. 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.

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Potential conflicts of interest. L. C., M. D., K. G., I. V., and L. O. are employed by the GSK group of companies. I. V. and L. O. own stock options as part of their employee remuneration. T. C. H. and H. L. were employed by the GSK group of companies at the time this study was designed and received their stock as part of employee remuneration. H. L. is currently employed by Pfizer Inc. T. C. H. is coinventor of the patent application related to the vaccine used in this study and is currently a consultant for the GSK group of companies. N. K. reports receiving grants from the GSK group of companies during the conduct of this study, as well as receiving grants from Merck & Co, Pfizer Inc, Sanofi Pasteur, MedImmune, Novartis, and Protein Science for work outside of this study. J. P. reports receiving principal investigator fees from the GSK group of companies during the conduct of the study. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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