ORIGINAL ARTICLE

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

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ABSTRACT

BACKGROUND

In previous phase 1–2 clinical trials involving older adults, a subunit vaccine containing varicella–zoster virus glycoprotein E and the $AS01_B$ adjuvant system (called HZ/su) had a clinically acceptable safety profile and elicited a robust immune response.

METHODS

We conducted a randomized, placebo-controlled, phase 3 study in 18 countries to evaluate the efficacy and safety of HZ/su in older adults (≥50 years of age), stratified according to age group (50 to 59, 60 to 69, and ≥70 years). Participants received two intramuscular doses of the vaccine or placebo 2 months apart. The primary objective was to assess the efficacy of the vaccine, as compared with placebo, in reducing the risk of herpes zoster in older adults.

RESULTS

A total of 15,411 participants who could be evaluated received either the vaccine (7698 participants) or placebo (7713 participants). During a mean follow-up of 3.2 years, herpes zoster was confirmed in 6 participants in the vaccine group and in 210 participants in the placebo group (incidence rate, 0.3 vs. 9.1 per 1000 person-years) in the modified vaccinated cohort. Overall vaccine efficacy against herpes zoster was 97.2% (95% confidence interval [CI], 93.7 to 99.0; P<0.001). Vaccine efficacy was between 96.6% and 97.9% for all age groups. Solicited reports of injection-site and systemic reactions within 7 days after vaccination were more frequent in the vaccine group. There were solicited or unsolicited reports of grade 3 symptoms in 17.0% of vaccine recipients and 3.2% of placebo recipients. The proportions of participants who had serious adverse events or potential immune-mediated diseases or who died were similar in the two groups.

CONCLUSIONS

The HZ/su vaccine significantly reduced the risk of herpes zoster in adults who were 50 years of age or older. Vaccine efficacy in adults who were 70 years of age or older was similar to that in the other two age groups. (Funded by GlaxoSmithKline Biologicals; ZOE-50 ClinicalTrials.gov number, NCT01165177.)

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Herpes zoster, or shingles, results from the reactivation of latent varicella–zoster virus (VZV) in the dorsal-root or cranial-nerve ganglia, usually decades after primary infection.[1,2] Herpes zoster is characterized by a vesicular rash with a unilateral and dermatomal distribution and is almost always accompanied by pain. More than 90% of adults have been infected with VZV and are at risk for herpes zoster.[3,4] Although herpes zoster is most frequent in adults who are 50 years of age or older owing to immunosenescence, it can occur at any age, especially when cell-mediated immunity is decreased as a result of disease or drug therapy.[1,3,5] Common complications, such as postherpetic neuralgia, are more frequent and severe with increasing age.[1,4,5]

A live-attenuated vaccine against herpes zoster (Zostavax, Merck) containing the Oka VZV strain is licensed for use in adults who are 50 years of age or older.[1,6] Zostavax showed 51.3% efficacy against herpes zoster and 66.5% efficacy against postherpetic neuralgia in participants who were 60 years of age or older.[7] However, its efficacy against herpes zoster decreased with age (from 69.8% in adults between the ages of 50 and 59 years to 37.6% in those ≥70 years of age),[7,8] and it is contraindicated for use in persons with immunosuppression in whom live-attenuated vaccines may cause disease.[1,6]

Recombinant subunit vaccines are an alternative to live-attenuated vaccines and may also be suitable for persons with immunosuppression because the risk of disease resulting from replication of the vaccine virus is prevented.[9,10] An investigational recombinant subunit vaccine containing VZV glycoprotein E and the $AS01_B$ adjuvant system (called HZ/su, GlaxoSmithKline Biologicals) is being evaluated for the prevention of herpes zoster in older adults. VZV glycoprotein E was selected as a candidate vaccine antigen because it is essential for viral replication and cell-to-cell spread and is a primary target of VZV-specific immune responses.[11-15] The antigen was combined with $AS01_B$ because this adjuvant system promotes strong CD4+ T-cell and humoral immune responses against recombinant proteins.[16-20] Previous phase 1–2 clinical trials that were conducted in older adults and in persons with immunosuppression showed that HZ/su had a clinically acceptable safety profile and elicited a robust immune response that persisted for at least 3 years in older adults.[19,21-24] In light of these results, we conducted a phase 3 trial, called the Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50), to assess whether two doses of HZ/su reduce the risk of herpes zoster in adults 50 years of age or older.

METHODS

STUDY DESIGN AND OVERSIGHT

ZOE-50 is an ongoing, randomized, placebo-controlled study conducted in 18 countries in Europe, North America, Latin America, and Asia–Australia. It was designed to evaluate the efficacy, immunogenicity, and safety of the HZ/su vaccine in adults who are 50 years of age or older. The study protocol was approved by the appropriate independent ethics committee or institutional review board at each study center. Written informed consent was obtained from all participants before study entry.

The study is being conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation–Good Clinical Practice guidelines. During the course of the study, potential research compliance issues were investigated and appropriate actions were taken when needed. (Details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

The study was monitored by an independent data and safety monitoring committee, which met regularly during the course of the study to review all safety data in an unblinded manner and which identified no safety concerns. The primary efficacy end point has been reached and is reported here. Because the study is ongoing to allow for collection of data that are required to assess several secondary end points, the authors remain unaware of participant-level data at this stage of the analysis.

Therefore, all statistical analyses were performed by external statisticians. Data regarding study results were screened by a firewall team consisting of scientists employed by the sponsor, GlaxoSmithKline Biologicals, who were not involved in the conduct of the trial, and only data that would not risk participant- level unblinding were shared with the authors. (A more detailed description of the methods that are being used in the study is provided in the Supplementary

Appendix and the study protocol, available at NEJM.org.)

STUDY PARTICIPANTS

Participants who were 50 years of age or older were eligible for inclusion unless they had a history of herpes zoster, were previously vaccinated against varicella or herpes zoster, or had an immunosuppressive condition. The complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix.

RANDOMIZATION AND BLINDING

We randomly assigned participants in a 1:1 ratio to receive either vaccine or placebo using an online centralized randomization system. Participants were stratified according to region and age group (50 to 59, 60 to 69, and ≥70 years). Because the appearance of the reconstituted HZ/su vaccine differed from the placebo solution, injections were prepared and administered by study staff who did not participate in any study assessment. The investigators, participants, and those who were responsible for the evaluation of any study end point were unaware of whether vaccine or placebo had been administered.

VACCINATION

The HZ/su vaccine contains 50 μg of recombinant VZV glycoprotein E and the liposome-based $AS01_B$ adjuvant system containing 50 μg of 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL) and 50 μg of *Quillaja saponaria* Molina, fraction 21 (QS21, Antigenics, a wholly owned subsidiary of Agenus). Vaccine or placebo (0.9% saline solution) was administered (0.5 ml) into the deltoid muscle at months 0 and 2. Starting 1 month after the administration of the second dose, participants were followed for at least 30 months through monthly contacts and through annual visits, which will continue for the entire study period (which is expected to be approximately 60 months).

STUDY END POINTS

The primary objective of the study was to evaluate overall vaccine efficacy in reducing the risk of herpes zoster, as compared with placebo, in adults who were 50 years of age or older. Secondary objectives included determining the vaccine efficacy in reducing the incidence of herpes zoster in each age group (50 to 59 years, 60 to 69 years, and ≥70 years) and HZ/su safety and reactogenicity profiles. (A complete list of study objectives is provided in the Supplementary Appendix.) Vaccine efficacy, as a percentage, was defined as 1 minus the ratio of the incidence of herpes zoster in the HZ/su group to the incidence in the placebo group, multiplied by 100.

EVALUATION OF SAFETY AND REACTOGENICITY

A reactogenicity subgroup of participants recorded solicited injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) on diary cards for 7 days after each vaccination. This subgroup included all participants who were 70 years of age or older and randomly selected participants in the two other age groups (50 to 59 years and 60 to 69 years). The participants rated the intensity of the solicited reactions on a scale from 0 (absent) to 3 (preventing normal everyday activities). Unsolicited adverse events were recorded for 30 days after each dose. Serious adverse events were recorded in all participants for up to 12 months after the second dose. Such events that were considered to be related to the study vaccine or study participation, any events resulting in death, and potentially immune-mediated diseases were evaluated in all participants over the entire study period. (A full list of potentially immune-mediated diseases is provided in the Supplementary Appendix.)

SUSPECTED CASES OF HERPES ZOSTER

A suspected case of herpes zoster was defined as new unilateral rash with pain (broadly defined to include allodynia, pruritus, or other sensations) that had no alternative diagnosis. Participants were instructed on how to recognize signs and symptoms of herpes zoster and to contact their study site immediately if any developed. They were required to record their symptoms on a specific diary card. Investigators were to examine suspected cases of herpes zoster within 48 hours, if possible.

Participants were followed for at least 90 days after the onset of the episode or until the rash resolved and the participant was pain-free for 4 weeks. For each suspected case, the rash was photographed and samples were collected from three lesions to confirm the diagnosis of herpes zoster by means of real-time polymerase-chain-reaction (PCR) assay targeting VZV ORF62.[25]

The lower limit of detection was 10 VZV DNA copies per reaction. A hierarchical case-definition algorithm was used to classify each suspected case. If the PCR assay was positive for VZV, the case was confirmed. If the PCR assay was negative for VZV and positive for β-actin (internal control), the case was classified as not herpes zoster. If all three samples were negative for both VZV and β-actin, or if lesion samples were not available, the final diagnosis was determined by unanimous agreement among the five members of an ascertainment committee. The members of this committee, who were unaware of PCR results and study-group assignments, reviewed all suspected cases on the basis of available clinical information, such as rash and pain evaluations, digital photographs, and clinical progress notes.

STATISTICAL ANALYSIS

Safety was analyzed in the total vaccinated cohort, which included all participants who received at least one dose of HZ/su or placebo. Efficacy was analyzed in the total vaccinated cohort and in the modified vaccinated cohort (primary analysis); in the latter cohort, participants who

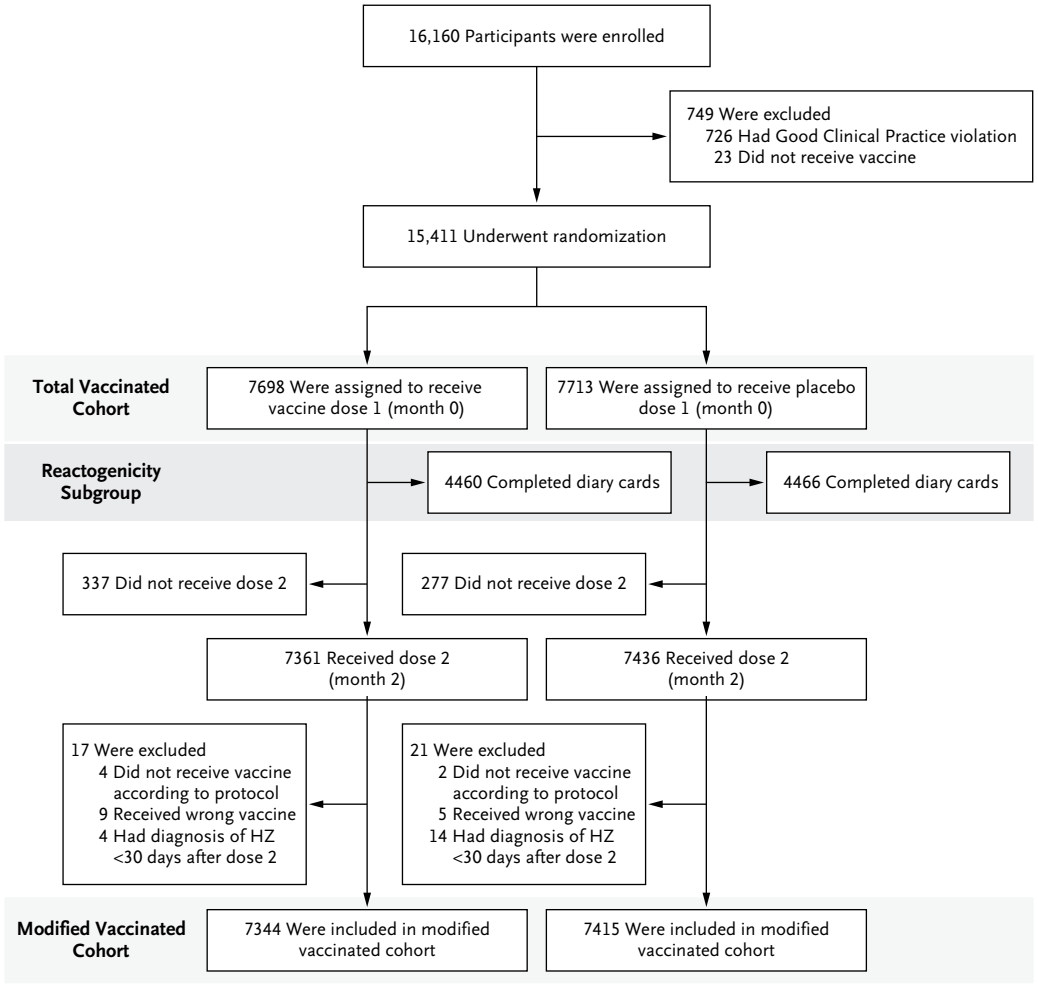

Figure 1. Enrollment and Outcomes.

During the course of the study of the herpes zoster subunit (HZ/su) vaccine, two study centers were closed because of Good Clinical Practice violations. All participants who were enrolled in these centers were excluded from the statistical analyses. Because the ongoing study remains blinded, participants who withdrew from the study after dose 2 will be included in the modified vaccinated cohort until study completion.

did not receive the second dose of vaccine or who received the diagnosis of herpes zoster within 1 month after the second dose were excluded.

All significance tests were two-tailed; a P value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute), and StatXact software, version 8.1 (Cytel).

RESULTS

STUDY POPULATION

A total of 16,160 participants were enrolled between August 2, 2010, and July 21, 2011 (Fig. 1). Of these participants, 749 were excluded from the efficacy analyses, mostly owing to deviations from Good Clinical Practice standards at two study centers (involving 726 patients). The remaining 15,411 participants constituted the total vaccinated cohort for analysis; of these participants, 14,759 (95.8%) were included in the modified vaccinated cohort. Most participants received two doses of the study vaccines (95.6% of HZ/su recipients and 96.4% of placebo recipients). A total of 8926 participants were assigned to the reactogenicity subgroup (4460 in the HZ/su group and 4466 in the placebo group).

Demographic characteristics were similar in the two study groups (Table 1). Most participants were from Europe (51.2%) and were white (71.8%) and female (61.2%). The mean age of participants at enrollment was 62.3 years.

VACCINE EFFICACY

A total of 408 participants reported suspected herpes zoster. Of these participants, 244 (59.8%) were confirmed (220 [90.2%] on PCR assay and 24 [9.8%] by the ascertainment committee) (Fig. S1 in the Supplementary Appendix). The concordance between the PCR assay results and the committee assessment was 87%.

Of the 216 confirmed cases in the modified vaccinated cohort, 6 occurred in the HZ/su group and 210 in the placebo group after a mean follow-up of 3.2 years (Table 2). The overall incidence of herpes zoster per 1000 person-years was 0.3 in the HZ/su group and 9.1 in the placebo group, for an overall vaccine efficacy of 97.2% (95% confidence interval [CI], 93.7 to 99.0; P<0.001) among participants who were 50 years of age or older. There was no significant difference in vaccine efficacy among the age groups (range, 96.6 to 97.9%). The overall vaccine efficacy was similar in the total vaccinated cohort (96.2%; 95% CI, 92.7 to 98.3; P<0.001).

SAFETY AND REACTOGENICITY

In the reactogenicity subgroup, solicited or unsolicited symptoms within 7 days after vaccination were reported in 84.4% of participants in the HZ/su group and 37.8% in the placebo group (Table 3). Most symptoms were of mild-to-moderate intensity, but 17.0% of HZ/su recipients and 3.2% of placebo recipients reported symptoms that prevented normal everyday activities (grade 3). These symptoms were mostly due to solicited injection-site reactions, which occurred in 81.5% of HZ/su recipients (grade 3 in 9.5%) and 11.9% of placebo recipients (grade 3 in 0.4%), and to systemic reactions, which occurred in 66.1% of HZ/su recipients (grade 3 in 11.4%) and 29.5% of placebo recipients (grade 3 in 2.4%). Pain was the most common injection-site reaction and was reported in 79.1% of HZ/su recipients and 11.2% of placebo recipients. Myalgia was the most common systemic reaction and was reported in 46.3% of HZ/su recipients and 12.1% of placebo recipients. Reactions were transient, with median durations ranging from 1 to 3 days for different solicited reactions among HZ/su recipients. For grade 3 reactions, the median duration was 1 day for all systemic reactions and pain and 2 days for redness and swelling. The overall frequencies of solicited reactions were similar after each dose, but grade 3 solicited systemic reactions were more frequent after the second dose (8.5%; 95% CI, 7.7 to 9.4) than after the first dose (5.9%; 95% CI, 5.2 to 6.6).

Within the first 30 days after vaccination, 231 serious adverse events (103 in HZ/su recipients and 128 in placebo recipients) were reported in 87 of 7698 HZ/su recipients (1.1%) and 97 of 7713 placebo recipients (1.3%) in the total vaccinated cohort. Among these events, 4 participants (1 HZ/su recipient and 3 placebo recipients) had a serious adverse event that was considered to be related to vaccination by the investigators: hypotension with syncope, mononeuritis, neurosensory deafness, and musculoskeletal chest pain. To date, after a mean follow-up of 3.5 years, the overall numbers and types of serious adverse events were similar in the HZ/su group (689 participants [9.0%]) and the placebo group (686

Table 1. Characteristics of the Participants at Baseline (Total Vaccinated Cohort).*

Characteristic	HZ/su Group (N=7698)	Placebo Group (N=7713)	All Participants (N=15,411)
Age			
Mean (±SD) at first dose	62.4±9.0	62.3±9.0	62.3±9.0
Age group — no. (%)			
50–59 yr	3645 (47.3)	3644 (47.2)	7,289 (47.3)
60–69 yr	2244 (29.2)	2246 (29.1)	4,490 (29.1)
70 yr or older	1809 (23.5)	1823 (23.6)	3,632 (23.6)
Sex — no. (%)			
Female	4711 (61.2)	4713 (61.1)	9,424 (61.2)
Male	2987 (38.8)	3000 (38.9)	5,987 (38.8)
Race — no. (%)†			
White	5532 (71.9)	5535 (71.8)	11,067 (71.8)
Black	140 (1.8)	130 (1.7)	270 (1.8)
Asian	1466 (19.0)	1470 (19.1)	2,936 (19.1)
Other	560 (7.3)	578 (7.5)	1,138 (7.4)
Region — no. (%)			
Asia or Australia	1642 (21.3)	1642 (21.3)	3,284 (21.3)
Europe	3941 (51.2)	3948 (51.2)	7,889 (51.2)
Latin America	772 (10.0)	779 (10.1)	1,551 (10.1)
North America	1343 (17.4)	1344 (17.4)	2,687 (17.4)

* There were no significant differences between the groups. The percentages may not total 100 because of rounding.
† Race was self-reported.

participants [8.9%]), with the most frequent events being myocardial infarction and cardiac failure (Table S1 in the Supplementary Appendix). The total numbers and types of potential immune-mediated diseases were also similar in the HZ/su group (78 participants [1.0%]) and the placebo group (97 participants [1.3%]) (Table S4 in the Supplementary Appendix). A total of 341 participants have died (167 HZ/su recipients [2.2%] and 174 placebo recipients [2.3%]) (Fig. S2 in the Supplementary Appendix).

DISCUSSION

In this phase 3 efficacy trial of a subunit vaccine against herpes zoster, two doses of HZ/su administered 2 months apart had a vaccine efficacy of 97.2%, as compared with placebo, in reducing the risk of herpes zoster in adults 50 years of age or older. The vaccine efficacy was similar among the three age groups. To date, no safety concerns have been identified, although solicited injection-site and systemic reactions were more frequent in the HZ/su group.

The efficacy findings for HZ/su, with no significant variation according to age, contrast with the results for Zostavax, which had lower efficacy among participants who were 70 years of age or older (37.6%) than among those between the ages of 50 and 59 years (69.8%).[7,8] The age-independent efficacy of HZ/su is of clinical interest, since the incidence and severity of herpes zoster are higher among older adults. HZ/su may thus provide a benefit to the population with the greatest medical need.[2] In addition, the ongoing ZOE-70 study (ClinicalTrials.gov number, NCT01165229), which includes adults who are 70 years of age or older and is being conducted at the same study centers as the ZOE-50 study, will provide an opportunity to assess vaccine efficacy against postherpetic neuralgia and other complications of herpes zoster.

Although no immunologic correlate of protection against herpes zoster has been identified,

Table 2. Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.*

Cohort and Age Group	HZ/su Group				Placebo Group				Vaccine Efficacy†
	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period ‡	Rate of Herpes Zoster	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period‡	Rate of Herpes Zoster	
			person-yr	*no./1000 person-yr*			*person-yr*	*no./1000 person-yr*	*% (95% CI)*
Modified vaccinated cohort									
All participants in cohort	7344	6	23,297.0	0.3	7415	210	23,170.5	9.1	97.2 (93.7–99.0)
50–59 yr	3492	3	11,161.3	0.3	3525	87	11,134.7	7.8	96.6 (89.6–99.3)
60–69 yr	2141	2	7,007.9	0.3	2166	75	6,952.7	10.8	97.4 (90.1–99.7)
70 yr or older	1711	1	5,127.9	0.2	1724	48	5,083.0	9.4	97.9 (87.9–100.0)
Total vaccinated cohort									
All participants in cohort	7698	9	25,584.5	0.4	7713	235	25,359.9	9.3	96.2 (92.7–98.3)
50–59 yr	3645	3	12,244.9	0.2	3644	95	12,162.5	7.8	96.9 (90.6–99.4)
60–69 yr	2244	5	7,674.1	0.7	2246	83	7,581.8	10.9	94.1 (85.6–98.1)
70 yr or older	1809	1	5,665.5	0.2	1823	57	5,615.6	10.2	98.3 (89.9–100.0)

* The total vaccinated cohort included all vaccinated participants for whom data related to efficacy end points were available. The modified vaccinated cohort excluded participants who did not receive the second dose of vaccine or who received a confirmed diagnosis of herpes zoster within 1 month after the second dose. Efficacy was calculated by means of the Poisson method.

† P<0.001 for all efficacy comparisons with placebo. Vaccine efficacy in each age group was adjusted for region. Overall vaccine efficacy was adjusted for age group and region.

‡ Data were censored at the time of the first confirmed diagnosis of herpes zoster.

CD4+ and CD8+ T cells are believed to play a central role in preventing VZV reactivation.[14,26-29] In our study, the observation that vaccine efficacy was maintained even among patients in the oldest age group, in conjunction with previous clinical data showing that HZ/su immunogenicity decreases only minimally with increasing age, suggests that HZ/su can overcome immunosenescence to provide protection against herpes zoster.[19,21,30-32] The immune response to HZ/su in both older persons and those with immunosuppression that was observed in earlier clinical studies might be attributed to the $AS01_B$ adjuvant system, which boosts VZV-specific memory immune responses.[20,33] Glycoprotein E adjuvanted with $AS01_B$ elicits higher glycoprotein-E–specific CD4+ T-cell and humoral immune responses than does unadjuvanted glycoprotein E, glycoprotein E adjuvanted with alum, or glycoprotein E adjuvanted with AS01 formulations containing lower amounts of the MPL and QS21 immunostimulants.[18,20,21] Therefore, although the small number of HZ/su recipients with herpes zoster in our study may prove insufficient to define an immunologic correlate of protection, future analyses of HZ/su immunogenicity will be of interest in explaining how an immune response targeting a single VZV antigen provides age-independent protection against herpes zoster in older adults.

HZ/su was more reactogenic than placebo. Among HZ/su recipients, 81.5% had injection-site reactions, and 66.1% had systemic reactions. The most frequent reactions were pain at the injection site and myalgia, findings that are consistent with the results of phase 1–2 studies.[19,21-24] Previous studies suggest that the antigen and the adjuvant both contribute to the difference in solicited injection-site and systemic reactions.[17,21] However, reactions were transient and mostly of mild-to-moderate intensity, and the fact that approximately 96% of the participants in the HZ/su and placebo groups received two doses of the study vaccine suggests that the reactogenicity of the HZ/su vaccine did not greatly affect participants' willingness to receive the second dose.

Table 3. Adverse Events and Reactogenicity.*

Variable	HZ/su Group		Placebo Group	
	no. of participants/total no.	*% (95% CI)*	*no. of participants/total no.*	*% (95% CI)*
Reactogenicity subgroup	4460		4466	
Within 30 days after vaccination				
Unsolicited report of adverse event	1308	29.3 (28.0–30.7)	1226	27.5 (26.1–28.8)
Grade 3 unsolicited report of adverse event†	208	4.7 (4.1–5.3)	151	3.4 (2.9–4.0)
Within 7 days after vaccination				
Solicited or unsolicited report of adverse event	3765	84.4 (83.3–85.5)	1689	37.8 (36.4–39.3)
Grade 3 solicited or unsolicited report of adverse event†	760	17.0 (15.9–18.2)	145	3.2 (2.7–3.8)
Grade 3 solicited or unsolicited report of adverse event related to vaccination	694	15.6 (14.5–16.7)	83	1.9 (1.5–2.3)
Solicited report of injection-site reaction	3571/4382	81.5 (80.3–82.6)	522/4377	11.9 (11.0–12.9)
Pain	3464/4382	79.1 (77.8–80.2)	490/4377	11.2 (10.3–12.2)
Redness	1664/4382	38.0 (36.5–39.4)	59/4377	1.3 (1.0–1.7)
Swelling	1153/4382	26.3 (25.0–27.6)	46/4377	1.1 (0.8–1.4)
Grade 3 solicited report of injection-site reaction†	417/4382	9.5 (8.7–10.4)	16/4377	0.4 (0.2–0.6)
Solicited report of systemic reaction	2894/4375	66.1 (64.7–67.6)	1293/4378	29.5 (28.2–30.9)
Myalgia	2025/4375	46.3 (44.8–47.8)	530/4378	12.1 (11.2–13.1)
Fatigue	2008/4375	45.9 (44.4–47.4)	728/4378	16.6 (15.5–17.8)
Headache	1716/4375	39.2 (37.8–40.7)	700/4378	16.0 (14.9–17.1)
Shivering	1232/4375	28.2 (26.8–29.5)	259/4378	5.9 (5.2–6.7)
Fever	939/4375	21.5 (20.3–22.7)	132/4378	3.0 (2.5–3.6)
Gastrointestinal symptoms	788/4375	18.0 (16.9–19.2)	387/4378	8.8 (8.0–9.7)
Grade 3 solicited report of systemic reaction†	498/4375	11.4 (10.5–12.4)	106/4378	2.4 (2.0–2.9)
Total vaccinated cohort	7698		7713	
Throughout study period				
Serious adverse event‡	689	9.0 (8.3–9.6)	686	8.9 (8.3–9.6)
Potential immune-mediated disease	78	1.0 (0.8–1.3)	97	1.3 (1.0–1.5)
Death	167	2.2 (1.9–2.5)	174	2.3 (1.9–2.6)
Within 30 days after vaccination				
Serious adverse event‡	87	1.1 (0.9–1.4)	97	1.3 (1.0–1.5)
Serious adverse event related to vaccination§	1	0.0 (0.0–0.1)	3	0.0 (0.0–0.1)
Death	8	0.1 (0.0–0.2)	7	0.1 (0.0–0.2)

* Additional details regarding adverse events are provided in Tables S1 through S4 and Fig. S2 in the Supplementary Appendix.
† Redness and swelling at the injection site were scored as 0 for reactions of less than 20 mm diameter, 1 for those between 20 mm and 50 mm, 2 for those of more than 50 mm to 100 mm, and 3 for those more than 100 mm. Temperature was scored as 0 for less than 37.5°C, 1 for 37.5 to 38.0°C, 2 for 38.1 to 39.0°C, and 3 for more than 39.0°C. (The preferred route for recording temperature was oral.) All other symptoms were scored as 0 for absent, 1 for easily tolerated, 2 for interfering with normal activity, and 3 for preventing normal activity.
‡ Serious adverse events were defined as events that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, and resulted in disability or incapacity.
§ The four serious adverse events that were considered to be related to vaccination by the investigators were hypotension with syncope, mononeuritis, neurosensory deafness, and musculoskeletal chest pain.

Although the interpretation of the safety data are subject to limitations resulting from the need to maintain participant-level study blinding, at present, no safety concerns have been raised by either the independent monitors who have critically reviewed and analyzed the unblinded safety data during the course of the study or the sponsor's firewall team, who reviewed and confirmed the results presented here. Exacerbation or triggering of immune-mediated diseases in susceptible persons is a hypothetical concern for vaccines containing new adjuvants such as $AS01_B$ because of their immunostimulatory effects.[16,34,35] Through careful monitoring during the course of the study, we found no evidence that immune-mediated diseases occurred more frequently among HZ/su recipients than among placebo recipients. The safety of HZ/su will continue to be monitored in the ongoing ZOE-50 and ZOE-70 studies.

In conclusion, the HZ/su vaccine significantly reduced the risk of herpes zoster among adults who were 50 years of age or older, and overall efficacy was well preserved among participants who were 70 years of age or older.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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