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Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

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ABSTRACT

BACKGROUND

A trial involving adults 50 years of age or older (ZOE-50) showed that the herpes zoster subunit vaccine (HZ/su) containing recombinant varicella–zoster virus glycoprotein E and the $AS01_B$ adjuvant system was associated with a risk of herpes zoster that was 97.2% lower than that associated with placebo. A second trial was performed concurrently at the same sites and examined the safety and efficacy of HZ/su in adults 70 years of age or older (ZOE-70).

METHODS

This randomized, placebo-controlled, phase 3 trial was conducted in 18 countries and involved adults 70 years of age or older. Participants received two doses of HZ/su or placebo (assigned in a 1:1 ratio) administered intramuscularly 2 months apart. Vaccine efficacy against herpes zoster and postherpetic neuralgia was assessed in participants from ZOE-70 and in participants pooled from ZOE-70 and ZOE-50.

RESULTS

In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from participants 70 years of age or older in ZOE-50 and ZOE-70 (16,596 participants), vaccine efficacy against herpes zoster was 91.3% (95% CI, 86.8 to 94.5; P<0.001), and vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7 to 97.1; P<0.001). Solicited reports of injection-site and systemic reactions within 7 days after injection were more frequent among HZ/su recipients than among placebo recipients (79.0% vs. 29.5%). Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two study groups.

CONCLUSIONS

In our trial, HZ/su was found to reduce the risks of herpes zoster and postherpetic neuralgia among adults 70 years of age or older. (Funded by GlaxoSmithKline Biologicals; ZOE-50 and ZOE-70 ClinicalTrials.gov numbers, NCT01165177 and NCT01165229.)

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*A complete list of investigators in the Zoster Efficacy Study in Adults 70 Years of Age or Older (ZOE-70) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Cunningham and Lal contributed equally to this article. Authors from Dr. Godeaux to Dr. Zahaf (listed alphabetically) also contributed equally, as did authors from Dr. Ahonen to Dr. Yeo (listed alphabetically).

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Herpes zoster, or shingles, results from the reactivation of latent varicella–zoster virus (VZV) and typically manifests as a vesicular, painful dermatomal rash.[1,2] The most common complication of herpes zoster, postherpetic neuralgia, manifests as chronic neuropathic pain that can greatly limit daily activities.[1,3-6]

A Quick Take is available at NEJM.org

The overall incidence of herpes zoster is 2.0 to 4.6 cases per 1000 person-years but increases with age to 10.0 to 12.8 per 1000 person-years among persons 80 years of age or older.[7-10] Similarly, the incidence of postherpetic neuralgia also increases with age.[10-13]

Antiviral therapy can reduce the duration of herpes zoster rash but has not been shown to decrease the incidence of postherpetic neuralgia.[14-17] Vaccination is therefore an attractive option to reduce the disease burden due to herpes zoster and its complications in older adults. Currently, a live attenuated herpes zoster vaccine (Zostavax, Merck) is approved for use in adults 50 years of age or older and is recommended for adults 60 years of age or older.[2,18,19]

An investigational herpes zoster subunit vaccine (HZ/su; GSK Vaccines) containing VZV glycoprotein E and the AS01$_B$ adjuvant system is being evaluated for the prevention of herpes zoster and postherpetic neuralgia in adults 50 years of age or older.[20-25] A previous trial (Zoster Efficacy Study in Adults 50 Years of Age or Older [ZOE-50]) showed that HZ/su had a vaccine efficacy against herpes zoster of 97.2%, which was consistent across all age groups.[26] Although 24% of the participants in ZOE-50 were 70 years of age or older, the trial was not intended to definitively assess vaccine efficacy against herpes zoster or postherpetic neuralgia in this age group. Therefore, in parallel with ZOE-50, we conducted a second trial involving only adults who were 70 years of age or older (Zoster Efficacy Study in Adults 70 Years of Age or Older [ZOE-70]) to assess vaccine efficacy against herpes zoster in this population; we also estimated vaccine efficacy against postherpetic neuralgia in the combined population (i.e., from ZOE-50 plus ZOE-70) of adults 70 years of age or older and adults 50 years of age or older.

Here, we present the results of ZOE-70. We also present the results of the prespecified pooled analyses of vaccine efficacy against herpes zoster and postherpetic neuralgia among participants in ZOE-70 and ZOE-50.

METHODS

STUDY DESIGN

ZOE-70 was a randomized, placebo-controlled, phase 3 trial conducted in 18 countries in Europe, North America, Latin America, and Asia–Australia to evaluate the efficacy, immunogenicity, and safety of HZ/su in adults 70 years of age or older. The investigators were unaware of the study-group assignments during the trial. This trial had the same design as ZOE-50 and was conducted concurrently at the same sites.[26]

The trial protocol, available with the full text of this article at NEJM.org, 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. ZOE-70 was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. During the study, potential research compliance issues were investigated, and appropriate actions were taken when needed. ZOE-70 was monitored by an independent data and safety monitoring committee that met regularly during the course of the study to review all safety data in an unblinded manner, as described previously for ZOE-50.[26]

Medical writing was provided by 4Clinics, France, with funding support from GlaxoSmithKline Biologicals. All the authors reviewed and approved the final submitted version of the manuscript. The last author vouches for the completeness and accuracy of all the data and the analyses presented and for the fidelity of the trial to the protocol.

ELIGIBILITY, RANDOMIZATION, AND BLINDING

Adults 70 years of age or older were eligible for inclusion in the trial unless they had a history of herpes zoster, had previously been vaccinated against varicella or herpes zoster, or had an immunosuppressive condition (see the Supplementary Appendix, available at NEJM.org, for a complete list of inclusion and exclusion criteria). Participants who were 70 years of age or older were first randomly assigned to either ZOE-50[26] or ZOE-70 and then were randomly assigned in a 1:1 ratio to either the HZ/su group or the placebo group with the use of an online centralized randomization system. Participants were stratified according to region (Asia and Australia,

Europe, Latin America, and North America) and age group (70 to 79 years vs. ≥80 years [in a 3:1 ratio]). The investigators, participants, and persons responsible for evaluating the study end points were unaware of whether HZ/su or placebo had been administered.

VACCINATION

HZ/su contains 50 μg of recombinant VZV glycoprotein E and the liposome-based $AS01_B$ adjuvant system (which contains 50 μg of 3-*O*-desacyl-4′-monophosphoryl lipid A [MPL] and 50 μg of *Quillaja saponaria* Molina, fraction 21 [QS21, licensed by GSK from Antigenics, a subsidiary of Agenus]). Vaccine or placebo (0.9% saline solution) was administered (0.5 ml) into the deltoid muscle at month 0 and month 2. Participants were to be followed for at least 30 months after the second dose through monthly contacts and annual clinic visits.

TRIAL END POINTS

The primary objective of ZOE-70 was to evaluate the efficacy of HZ/su, as compared with placebo, in reducing the risk of herpes zoster among adults 70 years of age or older. The primary objectives of the pooled analysis involving participants from ZOE-50 and ZOE-70 were to evaluate the efficacy of the vaccine, as compared with placebo, in reducing the risk of herpes zoster and the risk of postherpetic neuralgia in the overall population of participants 70 years of age or older from the two studies. The secondary objectives included the evaluation of vaccine efficacy against postherpetic neuralgia among participants 50 years of age or older and the evaluation of vaccine safety and reactogenicity. (A complete list of objectives is provided in the Supplementary Appendix.)

EVALUATION OF SAFETY AND REACTOGENICITY

In ZOE-70, a randomly selected subgroup of age-stratified participants recorded 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 injection. Redness and swelling at the injection site were scored as 0 if the affected area was less than 20 mm in diameter, 1 if the affected area was 20 to 50 mm, 2 if the affected area was more than 50 to 100 mm, and 3 if the affected area was more than 100 mm. Fever was scored as 0 for a body temperature lower than 37.5°C, 1 for 37.5°C to 38.0°C, 2 for 38.1°C to 39.0°C, and 3 for higher 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 interferes with normal activity, and 3 for prevents normal activity.

Unsolicited reports of adverse events were recorded for 30 days after each dose for all participants. All serious adverse events were recorded for all participants for 12 months after the second dose. Serious adverse events that were considered to be related to the study vaccine or to trial participation, events resulting in death, and potential immune-mediated diseases were evaluated in all participants throughout the trial.

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 abnormal sensations) that had no alternative diagnosis. Suspected cases of herpes zoster were evaluated as described previously.[26] Lesion samples were obtained from patients with suspected herpes zoster for polymerase-chain-reaction (PCR) analysis. A suspected case was confirmed as herpes zoster if the PCR assay was positive for VZV. The case was classified as not herpes zoster if the PCR assay was VZV-negative and β-actin–positive (control). If the PCR results were indeterminate (VZV-negative and β-actin–negative) or if samples were not available, the final diagnosis was determined by unanimous agreement among the five members of an ascertainment committee, the members of which were unaware of the study group assignments. If the committee opinion was not unanimous, the case was classified as inconclusive and was considered not to be herpes zoster for the purposes of the statistical analyses.

ASSESSMENT OF POSTHERPETIC NEURALGIA CASES

Participants with a suspected case of herpes zoster were asked to attend a schedule of assessment visits and to complete the Zoster Brief Pain Inventory[27] questionnaire daily for 28 days and weekly thereafter, until the participant had been pain-free for 4 weeks or for at least 90 days after the onset of the rash. The "worst pain" score (item 3: "Please rate your pain by circling the one number that best describes your pain at its

worst in the last 24 hours," rated on a scale of 0 to 10, with higher numbers indicating worse pain) was used to determine whether a participant had postherpetic neuralgia.[27] As in previous studies, postherpetic neuralgia was defined as a worst pain score of 3 or higher for pain that persisted or developed more than 90 days after the onset of herpes zoster rash.[19,28]

STATISTICAL ANALYSIS

Safety was analyzed in the total vaccinated cohort, which included all participants who could be evaluated and who had received at least one dose of HZ/su or placebo. Efficacy was analyzed in the total vaccinated cohort and in the modified vaccinated cohort (the primary cohort for the efficacy analysis), which excluded participants who did not receive the second dose or who had a confirmed herpes zoster episode within 1 month (30 days) after the second dose. All the analyses included participants 70 years of age or older, with the exception of the analysis of vaccine efficacy against postherpetic neuralgia, which included participants 50 years of age or older.

Vaccine efficacy was defined as 1 minus the ratio of herpes zoster incidence in the HZ/su group to that in the placebo group, multiplied by 100. All significance tests were two tailed. P values of 0.05 or less were considered to indicate statistical significance. All statistical analyses were performed with SAS software, version 9.3 (SAS Institute), and StatXact software, version 9.0 (Cytel).

RESULTS

STUDY POPULATION

Participants were enrolled in ZOE-70 between August 2, 2010, and July 21, 2011. The last study visit was on July 24, 2015. A total of 14,816 participants were enrolled and underwent randomization, of whom 916 were excluded from all analyses; 865 of these participants were excluded because of deviations from Good Clinical Practice standards at a study center (see the Supplementary Appendix). The remaining 13,900 participants constituted the total vaccinated cohort, 13,163 of whom (94.7%) were included in the modified vaccinated cohort (Fig. 1). Most participants (94.4% of HZ/su recipients and 95.6% of placebo recipients) received both doses. In the pooled analysis of participants from ZOE-70 and ZOE-50, 17,531 participants 70 years of age or older were included in the total vaccinated cohort, and 16,596 were included in the modified vaccinated cohort (Fig. S1 in the Supplementary Appendix).

In ZOE-70, the demographic characteristics of the participants at baseline were similar in the two groups (Table S1 in the Supplementary Appendix). A total of 54.0% of the participants were from Europe, 76.9% were white, and 54.9% were female. The mean age of the participants at study entry was 75.6 years (range, 62 to 96 years). Four participants younger than 70 years of age were erroneously enrolled in ZOE-70 (3 were 69 years of age, and 1 was 62 years of age). These participants were included in the cohort of participants 70 to 79 years of age for all analyses. Overall, 3066 participants (22.1%) were 80 years of age or older, and 76 (0.5%) were 90 years of age or older. The demographic characteristics of the participants at baseline were also similar in the two groups in the pooled population of participants 70 years of age or older from ZOE-70 and ZOE-50.[26]

VACCINE EFFICACY AGAINST HERPES ZOSTER IN ADULTS 70 YEARS OF AGE OR OLDER

In the ZOE-70 total vaccinated cohort, 432 suspected episodes of herpes zoster were reported, 270 of which were confirmed as herpes zoster (Fig. S2 in the Supplementary Appendix). Of the 270 confirmed cases, 246 occurred in the modified vaccinated cohort: 23 in HZ/su recipients and 223 in placebo recipients, after a mean follow-up period of 3.7 years (Table 1). The incidence of herpes zoster per 1000 person-years was 0.9 in the HZ/su group and 9.2 in the placebo group, for an overall vaccine efficacy of 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001). Vaccine efficacy did not differ significantly between the two age groups (90.0% among participants 70 to 79 years of age and 89.1% among participants ≥80 years of age). In a time-to-event analysis, the cumulative incidence of herpes zoster was lower in the HZ/su group than in the placebo group, in both the modified and the total vaccinated cohorts (Fig. 2A and 2C).

In the pooled analysis of participants 70 years of age or older from ZOE-70 and ZOE-50, a total

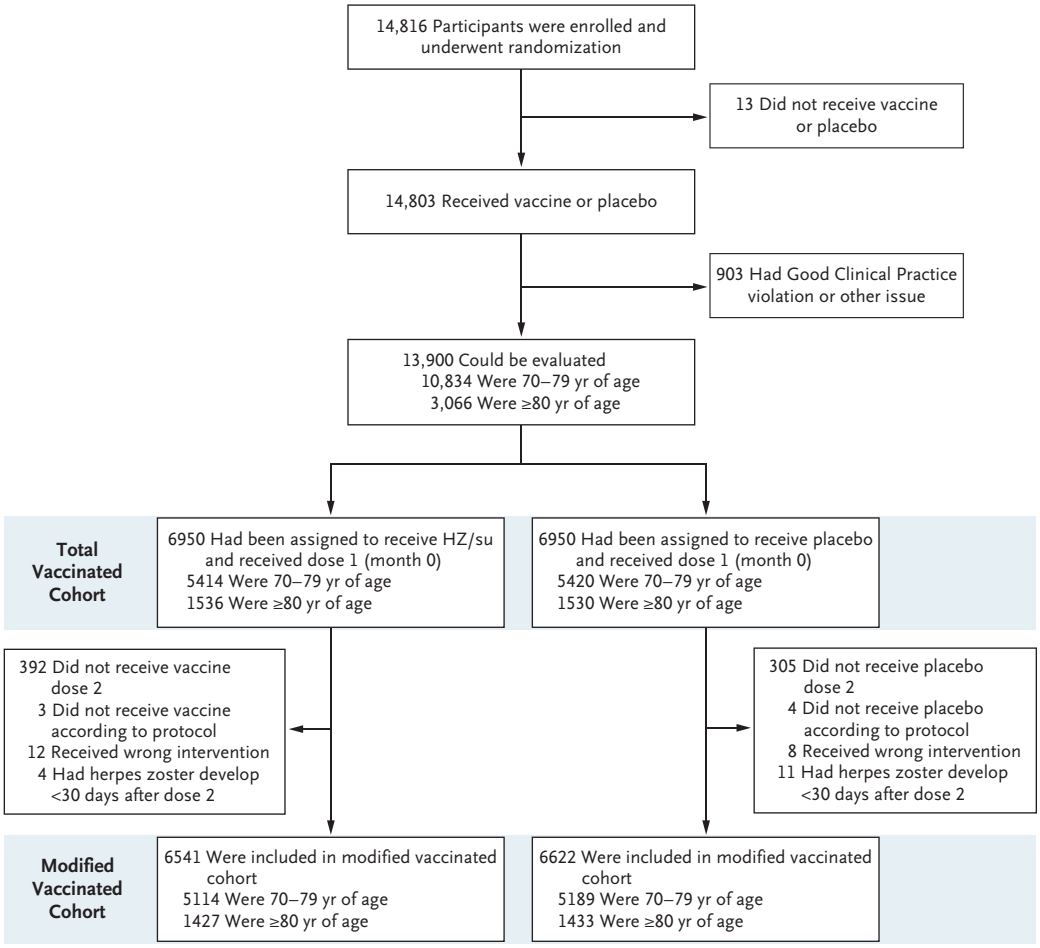


Figure 1. Enrollment and Randomization.

After enrollment, one study center was closed because of Good Clinical Practice violations, and one study center was closed for financial reasons (see the Supplementary Appendix). All participants who had been enrolled at these centers were excluded from all analyses. An additional four participants were excluded because of issues with informed consent. Some participants in the total vaccinated cohort had more than one reason for being excluded from the modified vaccinated cohort. HZ/su denotes herpes zoster subunit vaccine.

of 25 confirmed cases of herpes zoster occurred in HZ/su recipients, as compared with 284 cases in placebo recipients, which resulted in a vaccine efficacy of 91.3% against herpes zoster (95% CI, 86.8 to 94.5%) (Table 1). Vaccine efficacy did not differ significantly between the two age groups (91.3% in participants 70 to 79 years of age and 91.4% in participants ≥80 years of age); the results were similar in the total vaccinated cohort (Table S2 in the Supplementary Appendix). The cumulative incidence of herpes zoster was lower in the HZ/su group than in the placebo group (Fig. 2B and 2D). Vaccine efficacy was 97.6% during year 1, 92.0% during year 2, 84.7% during year 3, and 87.9% during year 4 after the second vaccination (Table 1).

VACCINE EFFICACY AGAINST POSTHERPETIC NEURALGIA

In the pooled modified vaccinated cohort that included all participants 50 years of age or older, postherpetic neuralgia developed in 4 of 32 HZ/su recipients and in 46 of 477 placebo recipients with herpes zoster, during a mean follow-up period

Table 1. Vaccine Efficacy against the First or Only Episode of Herpes Zoster and Postherpetic Neuralgia in the Modified Vaccinated Cohort.*

Condition and Cohort	HZ/su Group				Placebo Group				Vaccine Efficacy†
	Participants	Cases	Cumulative Follow-up Period‡	Incidence Rate	Participants	Cases	Cumulative Follow-up Period‡	Incidence Rate	
	number		*person-yr*	*cases/1000 person-yr*	*number*		*person-yr*	*cases/1000 person-yr*	*% (95% CI)*
Herpes zoster									
ZOE-70									
Age group									
Overall	6,541	23	24,405.1	0.9	6,622	223	24,167.8	9.2	89.8 (84.2 to 93.7)
70–79 yr	5,114	17	19,346.5	0.9	5,189	169	19,247.5	8.8	90.0 (83.5 to 94.4)
≥80 yr	1,427	6	5,058.5	1.2	1,433	54	4,920.3	11.0	89.1 (74.6 to 96.2)
Year§									
1	6,541	2	6,464.7	0.3	6,622	68	6,511.2	10.4	97.0 (88.8 to 99.7)
2	6,379	6	6,281.0	1.0	6,372	68	6,240.4	10.9	91.3 (79.9 to 96.9)
3	6,137	9	6,043.5	1.5	6,076	48	5,943.0	8.1	81.6 (61.9 to 92.1)
4	5,898	6	5,615.9	1.1	5,776	39	5,473.2	7.1	85.1 (64.4 to 94.9)
Pooled ZOE-70 and ZOE-50									
Age group									
Overall	8,250	25	30,725.5	0.8	8,346	284	30,414.7	9.3	91.3 (86.8 to 94.5)
70–79 yr	6,468	19	24,410.9	0.8	6,554	216	24,262.8	8.9	91.3 (86.0 to 94.9)
≥80 yr	1,782	6	6,314.6	1.0	1,792	68	6,151.9	11.1	91.4 (80.2 to 97.0)
Year§									
1	8,250	2	8,156.2	0.2	8,346	83	8,206.2	10.1	97.6 (90.9 to 99.8)
2	8,039	7	7,916.9	0.9	8,024	87	7,860.5	11.1	92.0 (82.8 to 96.9)
3	7,736	9	7,612.2	1.2	7,661	58	7,488.4	7.7	84.7 (69.0 to 93.4)
4	7,426	7	7,040.3	1.0	7,267	56	6,859.6	8.2	87.9 (73.3 to 95.4)
Postherpetic neuralgia									
Pooled ZOE-70 and ZOE-50									
≥70 yr¶	8,250	4	30,760.3	0.1	8,346	36	30,942.0	1.2	88.8 (68.7 to 97.1)
≥50 yr	13,881	4	53,171.5	0.1	14,035	46	53,545.0	0.9	91.2 (75.9 to 97.7)

Age group									
50–59 yr	3,491	0	13,789.7	0.0	3,523	8	13,928.7	0.6	100.0 (40.8 to 100.0)
60–69 yr	2,140	0	8,621.4	0.0	2,166	2	8,674.4	0.2	100.0 (–442.9 to 100.0)
70–79 yr	6,468	2	24,438.8	0.1	6,554	29	24,660.4	1.2	93.0 (72.4 to 99.2)
≥80 yr	1,782	2	6,321.5	0.3	1,792	7	6,281.6	1.1	71.2 (–51.6 to 97.1)

* The modified vaccinated cohort excluded participants who did not receive the second dose of the herpes zoster subunit vaccine (HZ/su) or placebo or who had a confirmed episode of herpes zoster within 1 month (30 days) after the second dose.
† Vaccine efficacy was calculated by means of the Poisson method. Vaccine efficacy in each age group was adjusted for region, and overall vaccine efficacy was adjusted for age group and region. P<0.001 for all comparisons of the efficacy against herpes zoster of the vaccine versus placebo. For the comparison of efficacy against postherpetic neuralgia of the vaccine versus placebo, P<0.001 in the ≥50-yr, ≥70-yr, and 70–79-yr age groups and P=0.008 in the 50–59-yr age group; the numbers of cases in the placebo group were not sufficient to obtain a significant result in the 60–69-yr (P=0.51) and ≥80-yr (P=0.18) age groups.
‡ Data were censored at the time of the first confirmed diagnosis of herpes zoster or postherpetic neuralgia.
§ Year 1 is defined as the period from 30 to 395 days after the second vaccination, year 2 as the period from 396 to 760 days after the second vaccination, year 3 as the period from 761 to 1125 days after the second vaccination, and year 4 as the period of more than 1125 days after the second vaccination to the last contact date.
¶ The assessment of vaccine efficacy for the prevention of postherpetic neuralgia in participants ≥70 years of age was the primary objective of the pooled analyses.

of 3.8 years. The incidence of postherpetic neuralgia per 1000 person-years was 0.1 in the HZ/su group and 0.9 in the placebo group, for a vaccine efficacy of 91.2% among adults 50 years of age or older (95% CI, 75.9 to 97.7%; P<0.001) (Table 1). Postherpetic neuralgia did not develop in any HZ/su recipients younger than 70 years of age. Among participants 70 years of age or older, vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7 to 97.1%; P<0.001) (Table 1, and Fig. S3 in the Supplementary Appendix). The cumulative incidence of postherpetic neuralgia was lower in the HZ/su group than in the placebo group, in both the modified and the total vaccinated cohorts (Fig. 3). The incidence of postherpetic neuralgia among HZ/su recipients with breakthrough herpes zoster did not differ significantly from that among placebo recipients (12.5% and 9.6%, respectively; P=0.54).

REACTOGENICITY

In ZOE-70, a total of 1025 participants (7.4%) were randomly assigned to the reactogenicity subgroup (512 HZ/su recipients and 513 placebo recipients). In this subgroup, solicited reports of reactions ("solicited reactions") that occurred within 7 days after each vaccination were noted in 79.0% of HZ/su recipients and in 29.5% of placebo recipients (Table 2).

Injection-site solicited reactions occurred in 74.1% of HZ/su recipients and in 9.9% of placebo recipients; most reactions were mild to moderate in intensity. Grade 3 injection-site solicited reactions were reported in 8.5% of HZ/su recipients and in 0.2% of placebo recipients. Systemic solicited reactions occurred in 53.0% of HZ/su recipients and in 25.1% of placebo recipients (grade 3 reactions were reported in 6.0% and 2.0%, respectively). In the HZ/su group, the most common injection-site reaction was pain (in 68.7% of HZ/su recipients) and the most common systemic reaction was fatigue (in 32.9%). The reactions were transient, with median durations of 2 to 3 days for injection-site reactions, 1 to 2 days for systemic reactions, and 1 to 2 days for grade 3 reactions (Table S3 in the Supplementary Appendix).

The overall frequency and severity of the solicited reactions did not increase significantly after the second dose (Fig. S4 in the Supplementary Appendix). Solicited reactions tended to be less

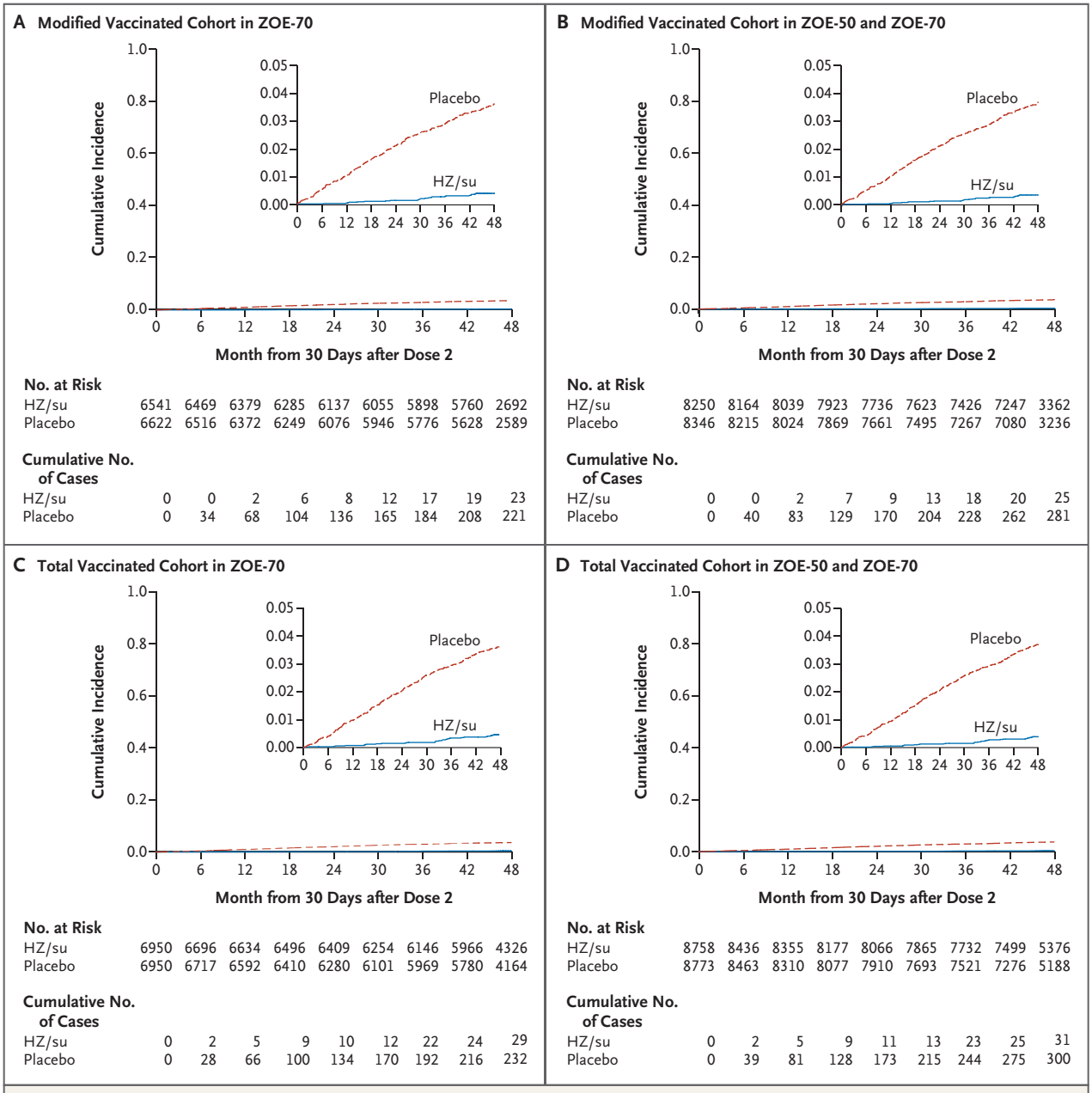


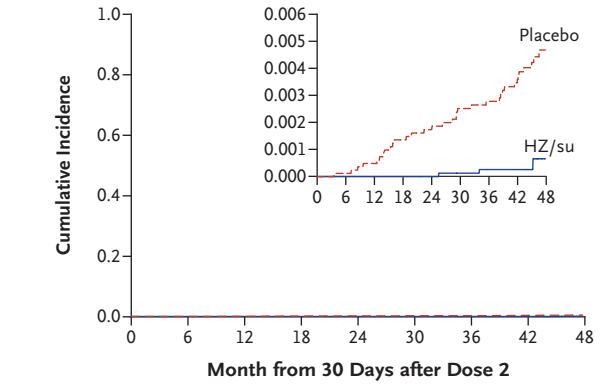
Figure 2. Risk of Development of Herpes Zoster after Vaccination.

Shown are the Kaplan–Meier estimates of the cumulative incidence (expressed as the percentage of the participants at risk) of the development of herpes zoster during the period from 30 days after receiving the second dose of HZ/su or placebo to the end of follow-up among participants 70 years of age or older. Because of the declining numbers of participants at risk, the Kaplan–Meier curves have been truncated at 48 months after the second dose of HZ/su. Some cases occurred after 48 months. In each panel, the inset shows the same data on an expanded y axis.

frequent among participants 80 years of age or older than among those 70 to 79 years of age (Table S4 in the Supplementary Appendix).

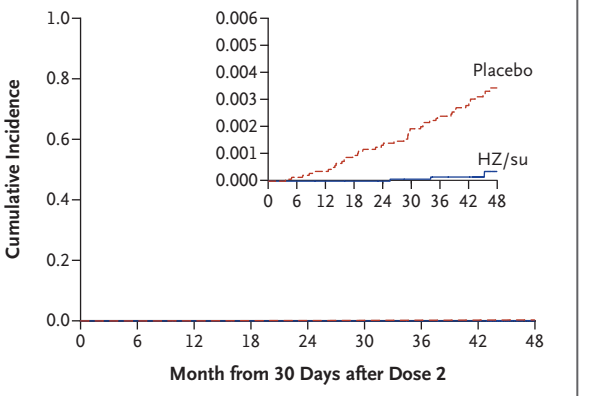
SAFETY

In ZOE-70, during a mean follow-up period of 4.0 years, the overall incidence of serious adverse



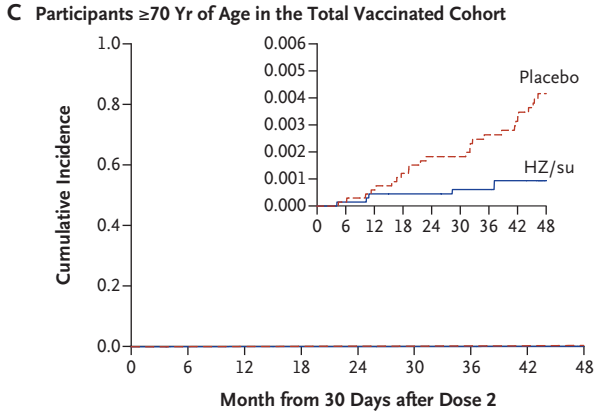
No. at Risk									
HZ/su	8250	8164	8041	7930	7745	7635	7442	7265	3369
Placebo	8346	8254	8102	7982	7808	7666	7457	7294	3340

Cumulative No. of Cases									
HZ/su	0	0	0	0	0	1	2	2	4
Placebo	0	1	4	11	14	20	22	27	34



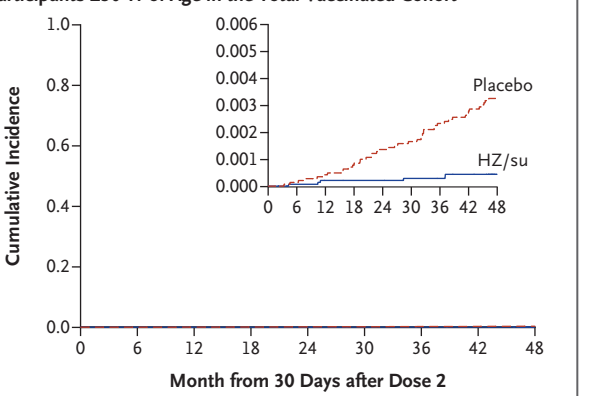
No. at Risk									
HZ/su	13,881	13,756	13,572	13,430	13,198	13,041	12,777	12,535	7128
Placebo	14,035	13,892	13,687	13,528	13,311	13,132	12,847	12,615	7104

Cumulative No. of Cases									
HZ/su	0	0	0	0	0	1	2	2	4
Placebo	0	2	5	13	18	26	32	37	44



No. at Risk									
HZ/su	8758	8437	8357	8183	8074	7874	7751	7518	5393
Placebo	8773	8500	8386	8192	8061	7878	7725	7502	5361

Cumulative No. of Cases									
HZ/su	0	1	3	3	3	4	4	6	6
Placebo	0	1	4	9	15	18	23	26	34



No. at Risk									
HZ/su	14,645	14,168	14,038	13,789	13,655	13,393	13,230	12,885	10,308
Placebo	14,660	14,250	14,104	13,817	13,659	13,432	13,241	12,902	10,292

Cumulative No. of Cases									
HZ/su	0	1	3	3	3	4	4	6	6
Placebo	0	2	6	11	19	23	32	37	45

Figure 3. Risk of Development of Postherpetic Neuralgia after Vaccination in the Pooled Population.

Shown are the Kaplan–Meier estimates of the cumulative incidence (expressed as the percentage of the participants at risk) of the development of postherpetic neuralgia during the period from 30 days after receipt of the second dose of HZ/su or placebo to the end of follow-up in the pooled ZOE-70 and ZOE-50 populations. Because of the declining numbers of participants at risk, the Kaplan–Meier curves have been truncated at 48 months after the second dose of HZ/su. Some cases occurred after 48 months. In each panel, the inset shows the same data on an expanded y axis.

events and potential immune-mediated diseases were similar in the two study groups; serious adverse events occurred in 16.6% of HZ/su recipients and in 17.5% of placebo recipients, and potential immune-mediated diseases occurred in 1.3% of HZ/su recipients and in 1.4% of placebo

recipients (Table 2). Serious adverse events that were considered by the investigators to be related to the trial intervention occurred in 12 HZ/su recipients (0.2%) and in 8 placebo recipients (0.1%). Overall, 426 participants in the HZ/su group (6.1%) and 459 participants in the placebo group (6.6%) died. One death was considered by the investigators to be related to the trial intervention: a 90-year-old participant with preexisting thrombocytopenia had acute myeloid leukemia diagnosed 75 days after the first dose of HZ/su and died from neutropenic sepsis 97 days after vaccination, without having received the second dose.

DISCUSSION

Herpes zoster and its complications, especially postherpetic neuralgia, are associated with substantial morbidity among older adults. In this phase 3 trial, two doses of HZ/su administered 2 months apart had a vaccine efficacy of 89.8%, as compared with placebo, in reducing the risk of herpes zoster among adults 70 years of age or older. A similar vaccine efficacy in reducing the risk of postherpetic neuralgia was shown in the pooled analysis.

The results of the current trial, which involved a population of adults 70 years of age or older, are consistent with those of a parallel study involving adults 50 years of age or older (ZOE-50), in which HZ/su was shown to have an efficacy of 97.9% for the prevention of herpes zoster in a smaller population of adults 70 years of age or older.[26] Vaccine efficacy for the prevention of herpes zoster in adults 70 years or age or older did not differ significantly between these two studies.

ZOE-50 and ZOE-70 were conducted in an identical manner at the same sites, and participants 70 years of age or older were randomly assigned to one of the two studies. Therefore, pooling data from both studies was justified and provided a more robust assessment of vaccine efficacy against herpes zoster; it also allowed for an analysis of vaccine efficacy against postherpetic neuralgia, an analysis that would not otherwise have been feasible given the low risk of postherpetic neuralgia among the participants in each individual study. Vaccine efficacy against herpes zoster in the pooled analysis was very similar in the two age groups studied (91.3% among participants 70 to 79 years of age and 91.4% among participants ≥80 years of age), which indicated that there was no decline in efficacy with age. This finding is consistent with the results of ZOE-50, in which vaccine efficacy against herpes zoster was found to be similar in all age groups (50 to 59, 60 to 69, and ≥70 years of age), but it contrasts with the efficacy of the approved live attenuated vaccine (Zostavax), which was found to decline with increasing age: 70% in adults 50 to 59 years of age, 64% in adults 60 to 69 years of age, 41% in adults 70 to 79 years of age, and 18% in adults 80 years of age or older.[24,25]

In the Shingles Prevention Study, the live attenuated herpes zoster vaccine appeared to provide additional protection against postherpetic neuralgia beyond preventing herpes zoster (among adults 60 years of age or older, 51% vaccine efficacy against herpes zoster vs. 67% vaccine efficacy against postherpetic neuralgia).[19] Protection against postherpetic neuralgia in our trials appeared to be driven by the lower incidence of herpes zoster (91.3% vaccine efficacy against herpes zoster vs. 88.8% vaccine efficacy against postherpetic neuralgia in the pooled population of adults ≥70 years of age); there is no evidence for additional efficacy against postherpetic neuralgia among HZ/su recipients with breakthrough herpes zoster. However, although the number of postherpetic neuralgia cases in HZ/su recipients was limited because of the high vaccine efficacy against herpes zoster, which precludes a robust assessment of HZ/su vaccine efficacy against postherpetic neuralgia among persons with breakthrough herpes zoster, our results indicate that vaccination with HZ/su substantially reduces the overall risk of postherpetic neuralgia among older adults.

The vaccine efficacy against herpes zoster was 87.9% in the fourth year after vaccination. Although the point estimate for vaccine efficacy against herpes zoster was higher in the first year after vaccination than in subsequent years, this difference was not significant. Therefore, we cannot make conclusions regarding the magnitude of a potential decline in efficacy. Additional follow-up is required to assess the persistence of HZ/su-induced protection over a longer period.

Table 2. Vaccine Reactogenicity and Safety Overall.

Time Period and Event	HZ/su Group		Placebo Group	
	no. of participants/ total no.	*% (95% CI)*	*no. of participants/ total no.*	*% (95% CI)*
Within 7 days after vaccination in the reactogenicity subgroup*				
Any reaction	399/505	79.0 (75.2–82.5)	149/505	29.5 (25.6–33.7)
Grade 3 reaction†	60/505	11.9 (9.2–15.0)	10/505	2.0 (1.0–3.6)
Injection-site reaction	374/505	74.1 (70.0–77.8)	50/505	9.9 (7.4–12.8)
Pain	347/505	68.7 (64.5–72.7)	43/505	8.5 (6.2–11.3)
Redness	198/505	39.2 (34.9–43.6)	5/505	1.0 (0.3–2.3)
Swelling	114/505	22.6 (19.0–26.5)	2/505	0.4 (0.0–1.4)
Grade 3 injection-site reaction†	43/505	8.5 (6.2–11.3)	1/505	0.2 (0.0–1.1)
Systemic reaction	267/504	53.0 (48.5–57.4)	127/505	25.1 (21.4–29.2)
Fatigue	166/504	32.9 (28.8–37.2)	77/505	15.2 (12.2–18.7)
Myalgia	157/504	31.2 (27.1–35.4)	41/505	8.1 (5.9–10.9)
Headache	124/504	24.6 (20.9–28.6)	55/505	10.9 (8.3–13.9)
Shivering	75/504	14.9 (11.9–18.3)	22/505	4.4 (2.7–6.5)
Fever	62/504	12.3 (9.6–15.5)	13/505	2.6 (1.4–4.4)
Gastrointestinal symptoms	55/504	10.9 (8.3–14.0)	40/505	7.9 (5.7–10.6)
Grade 3 systemic reaction†	30/504	6.0 (4.1–8.4)	10/505	2.0 (1.0–3.6)
Throughout the study period in the total vaccinated cohort‡				
Serious adverse event	1153/6950	16.6 (15.7–17.5)	1214/6950	17.5 (16.6–18.4)
Serious adverse event considered as related to vaccination §	12/6950	0.2 (0.1–0.3)	8/6950	0.1 (0.0–0.2)
Potential immune-mediated disease	92/6950	1.3 (1.1–1.6)	97/6950	1.4 (1.1–1.7)
Death	426/6950	6.1 (5.6–6.7)	459/6950	6.6 (6.0–7.2)

* Reports within 7 days after vaccination in the reactogenicity subgroup (a randomly selected subgroup of age-stratified participants) were solicited reports of injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering).

† Redness and swelling at the injection site were scored as 0 if the affected area was less than 20 mm in diameter, 1 if the affected area was 20 to 50 mm, 2 if the affected area was more than 50 to 100 mm, and 3 if the affected area was more than 100 mm. Fever was scored as 0 for a body temperature lower than 37.5°C, 1 for 37.5°C to 38.0°C, 2 for 38.1°C to 39.0°C, and 3 for higher 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 interferes with normal activity, and 3 for prevents normal activity. Serious adverse events were defined as events that resulted in death, were life-threatening, led to hospitalization or prolongation of existing hospitalization, resulted in disability or incapacity, or caused a congenital anomaly or birth defect in the child of a participant.

‡ Details are provided in Tables S5 through S8 in the Supplementary Appendix.

§ The serious adverse events considered by the investigator to be related to the trial intervention were lymphadenitis, acute myocardial infarction, ulcerative colitis, acute pancreatitis, administration-site erythema, administration-site pain, chills, pyrexia, allergic granulomatous angiitis, bacterial arthritis, erysipelas, herpes zoster oticus, eczema, neutropenic sepsis, and acute myeloid leukemia in the HZ/su group and polymyalgia rheumatica, gastric adenocarcinoma, cerebral infarction, cerebrovascular accident, the Guillain–Barré syndrome, loss of consciousness, syncope, and glomerulonephritis in the placebo group. Some participants had more than one event.

Solicited reports of injection-site and systemic reactions were more common among HZ/su recipients than among placebo (saline) recipients, a finding consistent with results of previous studies.[23,25,26] The reactions were generally mild-to-moderate in intensity and were transient, and neither their frequencies nor their severity increased significantly after the second dose.

Despite the higher reactogenicity observed with HZ/su, adherence to receiving the second dose was similar to that with placebo (approximately 95%). The frequency of solicited reports of injection-site and systemic reactions decreased slightly with age.

No safety concerns associated with HZ/su were identified in the current trial. The overall incidences of potential immune-mediated diseases, serious adverse events, and deaths were similar in the vaccine and placebo groups. One death in the HZ/su group was considered by the local investigator to be related to the vaccination; however, serious adverse events considered by the investigators to be related to vaccination were similar in frequency between the two study groups. In addition, reported serious adverse events were consistent with general expectations for this older population.[29] These results are consistent with those of ZOE-50, in which no safety concerns related to vaccination with HZ/su were identified.[26] Furthermore, participants from the placebo groups in ZOE-50 and ZOE-70 are currently being offered vaccination with HZ/su under a separate protocol (ClinicalTrials.gov number, NCT02690207). This open-label, single-group study will allow us to collect additional safety data.

As we found in adults 50 years of age or older,[26] the efficacy of HZ/su indicates that immune responses directed against a single VZV antigen (glycoprotein E) are capable of protecting against herpes zoster in adults 70 years of age or older. Although the immunologic basis for protection against herpes zoster is not known, VZV-specific CD4+ T cells are believed to play a central role.[30,31] Accordingly, HZ/su induces strong glycoprotein E–specific immune responses, including CD4+ T-cell responses, that are preserved with age.[20,24] Moreover, the robustness of the immune responses to glycoprotein E are attributable to the action of the $AS01_B$ adjuvant system, which has also been shown to enhance CD4+ T-cell and humoral immune responses to subunit antigens from other pathogens.[32,33] Together, these results suggest that such adjuvants have the potential to improve the efficacy of vaccines that are intended for use in older adults and other populations that may otherwise have a lower response to vaccination.

In conclusion, in ZOE-70 we found that the adjuvanted subunit HZ/su vaccine reduced the risk of herpes zoster and postherpetic neuralgia among adults 70 years of age or older, without substantial safety concerns.

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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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