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Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation
A Randomized Clinical Trial

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IMPORTANCE Herpes zoster, a frequent complication following autologous hematopoietic stem cell transplantation (HSCT), is associated with significant morbidity. A nonlive adjuvanted recombinant zoster vaccine has been developed to prevent posttransplantation zoster.

OBJECTIVE To assess the efficacy and adverse event profile of the recombinant zoster vaccine in immunocompromised autologous HSCT recipients.

DESIGN, SETTING, AND PARTICIPANTS Phase 3, randomized, observer-blinded study conducted in 167 centers in 28 countries between July 13, 2012, and February 1, 2017, among 1846 patients aged 18 years or older who had undergone recent autologous HSCT.

INTERVENTIONS Participants were randomized to receive 2 doses of either recombinant zoster vaccine (n = 922) or placebo (n = 924) administered into the deltoid muscle; the first dose was given 50 to 70 days after transplantation and the second dose 1 to 2 months thereafter.

MAIN OUTCOMES AND MEASURES The primary end point was occurrence of confirmed herpes zoster cases.

RESULTS Among 1846 autologous HSCT recipients (mean age, 55 years; 688 [37%] women) who received 1 vaccine or placebo dose, 1735 (94%) received a second dose and 1366 (74%) completed the study. During the 21-month median follow-up, at least 1 herpes zoster episode was confirmed in 49 vaccine and 135 placebo recipients (incidence, 30 and 94 per 1000 person-years, respectively), an incidence rate ratio (IRR) of 0.32 (95% CI, 0.22-0.44; $P < .001$), equivalent to 68.2% vaccine efficacy. Of 8 secondary end points, 3 showed significant reductions in incidence of postherpetic neuralgia (vaccine, n=1; placebo, n=9; IRR, 0.1; 95% CI, 0.00-0.78; $P = .02$) and of other prespecified herpes zoster–related complications (vaccine, n=3; placebo, n=13; IRR, 0.22; 95% CI, 0.04-0.81; $P = .02$) and in duration of severe worst herpes zoster–associated pain (vaccine, 892.0 days; placebo, 6275.0 days; hazard ratio, 0.62; 95% CI, 0.42-0.89; $P = .01$). Five secondary objectives were descriptive. Injection site reactions were recorded in 86% of vaccine and 10% of placebo recipients, of which pain was the most common, occurring in 84% of vaccine recipients (grade 3: 11%). Unsolicited and serious adverse events, potentially immune-mediated diseases, and underlying disease relapses were similar between groups at all time points.

CONCLUSIONS AND RELEVANCE Among adults who had undergone autologous HSCT, a 2-dose course of recombinant zoster vaccine compared with placebo significantly reduced the incidence of herpes zoster over a median follow-up of 21 months.

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Supplemental content

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Herpes zoster risk increases following autologous hematopoietic stem cell transplantation (HSCT) because of diminished T-cell immunity but declines after 2 to 3 years as immune function improves.[1-4] Antiviral prophylaxis is commonly administered to patients after HSCT to prevent such complications,[5] but the efficacy depends on adherence to treatment.[5-7] Furthermore, the duration of prophylaxis is not standardized,[5] and there is a high risk of herpes zoster occurring once prophylaxis has stopped.[6,7] Vaccination has the potential to provide long-term protection against herpes zoster, but live attenuated vaccines are contraindicated in immunocompromised individuals because of the risk of varicella resulting from spread of the vaccine strain.[8,9]

An adjuvanted recombinant zoster vaccine, consisting of the varicella-zoster virus glycoprotein E antigen and the $AS01_B$ adjuvant system, is nonlive and has no associated risk of triggering the infection in healthy adults.[10] This vaccine significantly reduced herpes zoster risk in adults aged at least 50 and at least 70 years (vaccine efficacy, 91%) and has been licensed in several countries.[11,12]

Because the immune system is immature after stem cell infusion and intensive conditioning regimens given before HSCT, patients cannot mount an adequate protective immune response to vaccines given shortly after transplantation.[13] Recently, a heat-inactivated varicella-zoster virus vaccine given in 4 doses (1 before and 3 after transplantation) was shown to have an efficacy of 64% in preventing herpes zoster in patients undergoing autologous HSCT.[14]

In a phase 1/2a study, the recombinant zoster vaccine induced strong glycoprotein E-specific humoral and cell-mediated immunity responses in patients undergoing HSCT,[15] providing a rationale to explore the efficacy of this vaccine in a randomized trial. The Zoster Efficacy Study in Patients Undergoing HSCT (ZOE-HSCT) was undertaken to assess vaccine efficacy, adverse events, and immune responses following administration of 2 doses of recombinant zoster vaccine shortly after autologous HSCT.

Key Points

Question What is the efficacy of 2 doses of the adjuvanted recombinant zoster vaccine in preventing herpes zoster in immunocompromised patients after autologous hematopoietic stem cell transplantation?

Findings In this randomized clinical trial of 1846 patients who had undergone autologous hematopoietic stem cell transplantation, the incidence of herpes zoster over a median follow-up of 21 months was 30 per 1000 person-years after 2 recombinant zoster vaccine doses vs 94 per 1000 person-years after placebo. This difference was statistically significant.

Meaning A 2-dose course of recombinant zoster vaccine reduced the incidence of herpes zoster in autologous stem cell transplant recipients.

Methods

The study was approved by site institutional review boards and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants. An independent data monitoring committee regularly reviewed all adverse event data.

Study Design and Oversight

This randomized, observer-blinded, placebo-controlled, phase 3 study was conducted in 167 centers in 28 countries between July 13, 2012, and February 1, 2017. The protocol is available in Supplement 1 and the statistical analysis plan in Supplement 2. The study design, timelines, and interventions are presented in eFigure 1 in Supplement 3.

Study Participants

Individuals aged at least 18 years who had undergone autologous HSCT in the previous 50 to 70 days were eligible. Individuals undergoing tandem autologous HSCT could participate following their second transplantation. Exclusion criteria included anticipated anti-varicella-zoster virus prophylaxis for more than 6 months, history of or vaccination against varicella or herpes zoster during the previous year, and HIV infection. Incidence data for participants experiencing a relapse of their underlying disease during the study were censored from the start of the antineoplastic treatment given for relapse. The eAppendix in Supplement 3 contains a complete list of inclusion and exclusion criteria.

Randomization and Blinding

Participants were randomized in a 1:1 ratio to receive either recombinant zoster vaccine or placebo using a centralized randomization system. A minimization procedure was applied to achieve a balanced representation of study groups across 6 different factors: age, underlying diagnosis, posttransplantation antineoplastic maintenance therapy, anticipated duration of posttransplantation antiviral prophylaxis, center, and sex (eAppendix in Supplement 3).[16,17] To maintain blinding in both study participants and investigators, reconstituted recombinant zoster vaccine, which differed slightly in appearance from placebo, was prepared and administered by study staff who did not participate in any study end-point assessments.

Vaccination

Two 0.5-mL doses of either recombinant zoster vaccine or placebo were administered into the deltoid muscle; the first dose 50 to 70 days after the date of autologous HSCT and the second dose 1 to 2 months thereafter. The dosing schedule was chosen based on the results from the phase 1/2a study.[15] Each recombinant zoster vaccine dose contained 50 µg of recombinant varicella-zoster virus glycoprotein E antigen and the liposome-based $AS01_B$ adjuvant system (containing 50 µg of 3-*O*-desacyl-4′-monophosphoryl lipid A, 50 µg of *Quillaja saponaria* Molina, fraction 21, and liposome). Each 0.5-mL dose of placebo contained lyophilized sucrose reconstituted in 0.9% saline solution.

End Points

The trial protocol lists 20 study end points (1 primary, 8 secondary, and 11 tertiary) (Supplement 1). The results of the primary, all 8 secondary, and 2 of the tertiary end points are

presented in this article. The primary end point was occurrence of confirmed herpes zoster cases between first dose and study end. The secondary and tertiary end points (descriptive and exploratory) are described in the eAppendix in Supplement 3.

Incidence Rate Assessments

The incidence rate ratio (IRR) for development of herpes zoster or herpes zoster-related complications (postherpetic neuralgia, other herpes zoster-related complications, and herpes zoster-related hospitalizations) between participants who received recombinant zoster vaccine or placebo was analyzed in the modified total vaccinated cohort, which included all participants who received 2 doses of the same investigational product. Participants who developed an episode of herpes zoster less than 1 month after receiving the second study dose were excluded from the modified total vaccinated cohort because the elapsed time since completing vaccination was considered insufficient to achieve full protection.

Immunogenicity Assessments

Blood samples were collected from all participants before dose 1 (50-70 days after transplantation) and 1 month after dose 2, with additional blood samples (1 month after dose 1 and 12 and 24 months after dose 2) collected from participants at predefined centers who comprised the humoral immunity and cell-mediated immunity subcohorts. Humoral and cell-mediated immune responses were assessed in the per-protocol immunogenicity cohorts, which included all eligible participants from the humoral immunogenicity and cell-mediated immunity subcohorts, respectively, who received both doses, adhered to the protocol, and had available immunogenicity end-point measurements. Serum anti-glycoprotein E antibody concentrations were measured using an in-house enzyme-linked immunosorbent assay (cutoff, 97 mIU/mL). The humoral immunity vaccine response rate was defined as the percentage of participants with a postvaccination anti-glycoprotein E antibody concentration of at least 4-fold the cutoff (for participants with concentrations initially below the cutoff) or at least 4-fold the prevaccination concentration (for participants with concentrations initially above the cutoff). Glycoprotein E–specific cell-mediated immunity responses, measured by intracellular cytokine staining, were expressed as the frequency of CD4 T cells expressing at least 2 of the following activation markers per 10^6 total CD4 T cells ($CD4^{2+}$ T cells): interferon γ, interleukin 2, tumor necrosis factor α, and CD40 ligand. The cell-mediated immunity vaccine response rate was defined as the percentage of participants with postvaccination $CD4^{2+}$ T-cell frequencies of at least 2-fold the threshold of 320 $CD4^{2+}$ T cells per 10^6 total CD4 T cells (for participants with concentrations initially below this threshold) or at least 2-fold the prevaccination $CD4^{2+}$ T-cell frequencies (for participants with concentrations initially above this threshold).

Adverse Events

Adverse events were analyzed in the total vaccinated cohort, which included all participants who received at least 1 dose of study vaccine or placebo. Solicited injection site reactions (pain, redness, and swelling) and general symptoms (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) were recorded on diary cards for 7 days after each dose. Unsolicited adverse events were recorded for 30 days after each dose, and serious adverse events and potentially immune-mediated diseases (eAppendix and eTable 1 in Supplement 3) were recorded for up to 12 months after dose 2. Serious adverse events considered in an investigator's clinical opinion to be related to the study vaccine, deaths, and relapses of underlying disease were recorded for the entire study period.

Herpes Zoster Case Definition

A suspected case of herpes zoster was defined as (1) a new rash characteristic of herpes zoster (eg, unilateral, dermatomal, and accompanied by pain broadly defined to include allodynia, pruritus, or other sensations) or a vesicular rash suggestive of varicella-zoster virus infection regardless of distribution, with no alternative diagnosis or (2) clinical symptoms and/or signs suggestive of varicella-zoster virus infection and specific laboratory findings, such as varicella-zoster virus-positive culture or immunohistological staining or real-time polymerase chain reaction assay in the absence of characteristic herpes zoster or varicella-zoster virus rash. Participants with any suspicion of herpes zoster were to be examined by investigators within 96 hours. Participants were followed up for at least 90 days after the onset of the rash or until the rash resolved and the participant had been pain free for 4 weeks.

Herpes zoster episodes were confirmed (positive or negative) using real-time polymerase chain reaction assay or, if not possible, by a blinded ascertainment committee (eAppendix and eFigures 2 and 3 in Supplement 3).[11,12]

Herpes Zoster–Related Pain Assessment

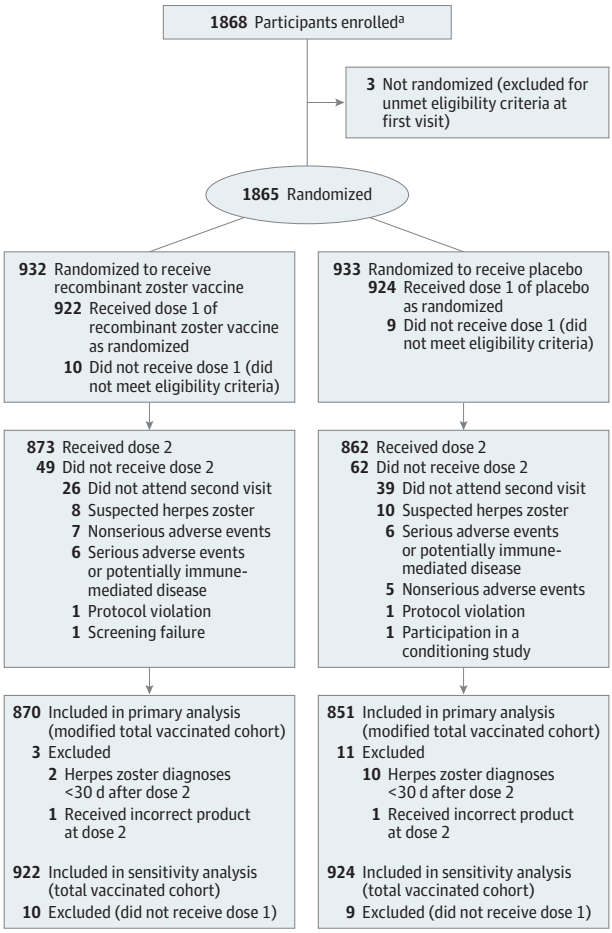
Participants were requested to complete the Zoster Brief Pain Inventory questionnaire to rate herpes zoster–associated pain as soon as the first signs suggestive of herpes zoster were noted and to continue daily questionnaire completion thereafter. Pain (least, worst, and average over the previous 24 hours) was rated on a 11-point Likert-type scale (range, 0-10, with 10 signifying the worst imaginable pain).

Statistical Analysis

The sample size was determined based on the confirmation of 125 herpes zoster cases, which provided 97% power to demonstrate an overall herpes zoster IRR significantly below 1 (ie, an upper limit of the 95% CI <1), assuming a true IRR of 0.5. This assumption was based on efficacy of the live attenuated zoster vaccine in older adults.[18] Recruitment was stopped once it was anticipated that the number of enrolled participants would accrue the required number of herpes zoster cases.

Missing or nonevaluable measurements were not replaced. The efficacy analysis included data collected from participants throughout the at-risk follow-up period. The at-risk period ceased once the data required for the analysis had been collected. Participants without an efficacy event who were lost to follow-up were censored at the time they left the study. The analysis of solicited adverse events included participants who had completed a symptom sheet. Participants who did not report any unsolicited adverse events were considered to have not had an event.

Figure 1. Participant Flow in the Zoster Efficacy Study in Patients Undergoing Hematopoietic Stem Cell Transplantation



[a] The total number of persons screened for eligibility was not recorded.

All analyses of herpes zoster and related complications used exact inference on the IRR conditional to the total number of cases and the time at risk. A sensitivity analysis was also performed on the total vaccinated cohort using a log-rank test.

The proportional hazards assumption was not met for reduction of herpes zoster incidence rate during the entire study period. Because the study was designed for a 2-year follow-up period, a post hoc analysis was performed using a piecewise Cox model considering 2 time frames (ie, within 2 years after the first month after dose 2 and after these 2 years).

A Cox proportional hazards model was used to assess the hazard rate reduction in herpes zoster–related hospitalization. The proportional hazards assumption was met using the test for nonzero slope of scaled Schoenfeld residuals. The same method was used to evaluate the reduction in duration of severe worst pain (pain scores ≥3) with the vaccine in participants who developed herpes zoster.

Anti-glycoprotein E antibody geometric mean concentrations were determined. The frequency of glycoprotein E-specific $CD4^{2+}$ T cells was calculated as the difference between the frequency of $CD4^{2+}$ T cells stimulated in vitro with glycoprotein E peptides and those stimulated with culture medium alone.

Because the inflation of the overall type I error was not controlled for the evaluated secondary and tertiary end points, findings for all analyses of secondary and tertiary end points were interpreted as exploratory. The effects of age (<50 vs ≥50 years), underlying diagnosis (multiple myeloma vs all other diagnoses), sex, or actual duration of antiviral prophylaxis therapy in the period starting 1 month after dose 2 on the vaccine effect were evaluated as post hoc analyses using the same methods as for evaluation of the primary end point. A post hoc Poisson regression model was fitted to evaluate the interaction of sex, underlying diagnosis, and age with treatment group.

All statistical tests were 2-tailed; $P<.05$ was considered statistically significant. The statistical analyses were performed using SAS version 9.3 on SDD version 4.3.4 software (SAS Institute Inc).

Results

Study Population

The total vaccinated cohort included 1846 participants who received at least the first study dose (**Figure 1**). Among the 1-dose recipients, 873 (94.7%) in the vaccine group and 862 (93.3%) in the placebo group received the second dose. Solicited adverse event data from diary cards were available for 901 vaccine recipients (98%). Injection site and general solicited adverse event data were available for 892 (97%) and 894 (97%) placebo recipients, respectively. The modified total vaccinated cohort included 1721 participants (870/922 [94%] in the vaccine group and 851/924 [92%] in the placebo group), excluding 111 participants who did not receive the second dose, 2 participants who received the incorrect product, and 12 participants who developed a herpes zoster episode within 1 month after dose 2. A total of 694 vaccine recipients (75%) and 672 placebo recipients (73%) from the total vaccinated cohort completed the study.

The study groups had similar baseline demographic characteristics (**Table 1**). Participants were predominantly male (63%) and aged at least 50 years (75%). Multiple myeloma was the most common underlying diagnosis (53%); similar percentages of participants in both groups received bortezomib after transplantation (eTable 2 in Supplement 3). In the modified total vaccinated cohort, 353 participants (20.0%) had an actual duration of antiviral prophylaxis of more than 60 days.

Primary End Point

Over a median at-risk follow-up of 21 months starting 1 month after dose 2, 184 confirmed herpes zoster cases occurred in the modified total vaccinated cohort (49 vaccine recipients and 135 placebo recipients) (**Table 2** and **Figure 2**). The overall incidences of herpes zoster were 30 and 94 per 1000 person-years in the vaccine and placebo groups, respectively, and the IRR of first herpes zoster episode was 0.32 (95% CI, 0.22-0.44; $P < .001$). At the end of follow-up, the overall cumulative incidence of herpes zoster was significantly lower in the vaccine group (10%) than in the placebo group (20%; log-rank $P < .001$) (Figure 2).

In the total vaccinated cohort (sensitivity analysis), the median at-risk follow-up period for occurrence of herpes zoster

cases was 25 months, during which 242 confirmed cases were reported (eFigure 3 in Supplement 3), resulting in an IRR of 0.36 (95% CI, 0.27-0.48; $P < .001$) (Table 2).

Secondary and Tertiary End Points

Herpes Zoster and Herpes Zoster–Related Complications

The number of participants with herpes zoster-related complications was low. In the modified total vaccinated cohort, IRRs for the vaccine group vs the placebo group, respectively, were 0.22 (95% CI, 0.04-0.81; $P = .02$; 1.6 vs 7.1 cases per 1000 person-years) for herpes zoster-related complications excluding postherpetic neuralgia and 0.11 (95% CI, 0.00-0.78; $P = .02$; 0.5 vs 4.9 cases per 1000 person-years) for postherpetic neuralgia, and the hazard ratio of hospitalizations was 0.15 (95% CI, 0.03-0.68; $P = .01$; 1.1 vs 7.1 cases per 1000 person-years). The hazard ratio for reduction of duration of worst herpes zoster-associated pain during disease episodes was 0.62 (95% CI, 0.42-0.89; $P = .01$; 892.0 days with vaccine vs 6275.0 days with placebo) (eTable 3 in Supplement 3).

Humoral Immunogenicity

In the vaccine group, humoral vaccine response rate was 67% 1 month after dose 2 and 45% 24 months after dose 2 (**Figure 3**A). The highest anti-glycoprotein E geometric mean concentrations were recorded 1 month after dose 2 and, despite a substantial decline, they remained above baseline 24 months after dose 2 (Figure 3B). In the placebo group, the humoral response was highest 24 months after dose 2 with no increase observed for anti-glycoprotein E antibody concentrations at any postvaccination time point compared with before vaccination (Figure 3).

Cell-Mediated Immunity

In the vaccine group, the vaccine cell-mediated immunity responses were 93% 1 month after dose 2 and 71% 24 months after dose 2; the frequency of glycoprotein E–specific $CD4^{2+}$ T cells was highest 1 month after dose 2 (median, 6644.9 [range, 1.0-73143.3] per 10^6 total $CD4^{2+}$ T cells) and subsequently declined but remained higher than before vaccination 24 months after dose 2. In the placebo group, the cell-mediated immunity response was highest 24 months after dose 2, with no increase observed for $CD4^{2+}$ T-cell frequencies at any postvaccination time point compared with before vaccination (**Figure 4**).

Adverse Events

Solicited injection site reactions and general symptoms occurring within 7 days of vaccination were more frequent in vaccine recipients (90%) than in placebo recipients (53%), mainly due to injection site reactions, which occurred in 86% of vaccine recipients and 10% of placebo recipients (**Table 3**). The incidences of grade 3 injection site reactions were 14% and 0%, respectively. Pain was the most common injection site symptom, occurring in 84% of vaccine recipients (grade 3, 11%) and 9% of placebo recipients (grade 3, 0%). The overall frequency of solicited general symptoms within 7 days after vaccination was 75% after vaccine and 51% after placebo (grade 3, 13% and 6%, respectively). Overall, the incidence of solicited symptoms was similar after both vaccine doses (injection site reactions after dose 1, 79%,

Table 1. Participant Characteristics

Characteristics	Recombinant Zoster Vaccine	Placebo
Total Vaccinated Cohort (Vaccine: n=922; Placebo: n=924)		
Age, mean (SD) [range], y	54.8 (11.7) [18-78]	55.1 (11.4) [18-75]
Age group, y, No. (%)		
18-49	230 (24.9)	229 (24.8)
≥50	692 (75.1)	695 (75.2)
Sex, No. (%)		
Male	580 (62.9)	578 (62.6)
Female	342 (37.1)	346 (37.4)
Region, No. (%)		
Asia/Australia	187 (20.3)	193 (20.9)
Europe and South Africa	581 (63.0)	572 (61.9)
North America	149 (16.2)	153 (16.6)
South America	5 (0.5)	6 (0.6)
Underlying diagnosis, No. (%)		
Multiple myeloma	490 (53.1)	493 (53.4)
Non-Hodgkin B-cell lymphoma	257 (27.9)	273 (29.5)
Hodgkin lymphoma	82 (8.9)	66 (7.1)
Non-Hodgkin T-cell lymphoma	48 (5.2)	45 (4.9)
Acute myeloid leukemia	21 (2.3)	20 (2.2)
Other[a]	24 (2.6)	27 (2.9)
Time from transplantation to first dose, d		
Mean (SD)	60.7 (6.2)	60.8 (6.3)
Median (IQR)	61.0 (56.0-66.0)	61.0 (56.0-66.0)
Time between doses, d		
Mean (SD)	41.0 (8.9)	40.6 (8.8)
Median (IQR)	38.0 (35.0-48.0)	37.0 (34.0-47.0)
Time between transplantation and herpes zoster episode, mo		
Mean (SD)	13.3 (10.3)	11.0 (7.9)
Median (IQR)	11.0 (5.0-18.0)	8.0 (5.0-15.5)
Time between transplantation and postherpetic neuralgia case, mo		
Mean (SD)	15.3 (11.9)	15.5 (8.1)
Median (IQR)	14.5 (5.0-25.5)	13.0 (9.5-23.5)
Follow-up at-risk period, mo		
Mean (SD)	26.3 (12.3)	23.4 (13.1)
Median (IQR)	27.3 (17.7-35.7)	23.7 (13.7-33.4)
Modified Total Vaccinated Cohort (Vaccine: n=870; Placebo: n=851)		
Follow-up at-risk period, mo		
Mean (SD)	22.5 (12.2)	20.2 (12.6)
Median (IQR)	22.0 (13.4-32.4)	19.9 (10.0-29.9)
Actual duration of antiviral prophylaxis, d[b]		
No. (%)		
0	454 (52.2)	426 (50.1)
1-60	226 (26.0)	262 (30.8)
>60	190 (21.8)	163 (19.2)
Mean (SD)[c]	115.1 (160.7)	100.4 (168.3)
Median (IQR)[c]	57.0 (34.5-104.5)	53.0 (31.0-84.0)

Abbreviation: IQR, interquartile range.

[a] Underlying diagnosis of any other diseases including solid malignancies and autoimmune diseases.

[b] Per inclusion and exclusion criteria, any antiviral treatment with activity against varicella-zoster virus either as prophylaxis against herpes zoster or prophylaxis against any other infection, such as cytomegalovirus or herpes simplex virus, was considered antiviral prophylactic therapy (no specific doses were applied).

[c] Calculated among participants who received antiviral prophylaxis.

Table 2. Incidence Rates and Incidence Rate Ratios for First or Only Herpes Zoster Episode During the Study

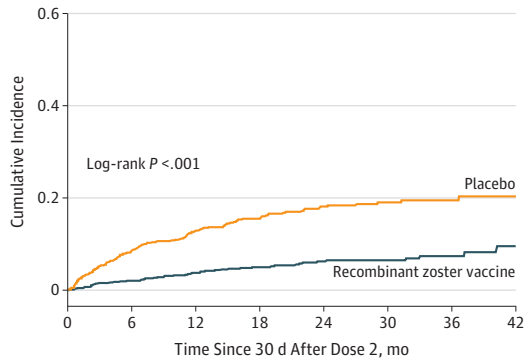
	Recipients, No.	Confirmed Cases, No.	Cumulative Follow-up Period, y[a]	Herpes Zoster Incidence Rate Per 1000 Person-Years	Incidence Rate Ratio (95% CI)[b]
Modified Total Vaccinated Cohort (Primary End Point)[c]					
Recombinant zoster vaccine	870	49	1633.1	30.0	0.32 (0.22-0.44)
Placebo	851	135	1431.9	94.3	
Total Vaccinated Cohort (Sensitivity Analysis for Primary End Point)[c]					
Recombinant zoster vaccine	922	70	2017.5	34.7	0.36 (0.27-0.48)
Placebo	924	172	1798.8	95.6	

[a] Cumulative follow-up period is the sum of follow-up periods (censored at the first occurrence of a confirmed herpes zoster episode and at the occurrence of treatment for relapse [modified total vaccinated cohort only]). For any participant who developed herpes zoster, subsequent follow-up data were excluded from analysis. Participants were followed up for herpes zoster episodes from the first vaccine dose to a minimum of 13 months after the second dose.

[b] $P < .001$ (2-sided; conditional to the number of cases); no adjustments were made.

[c] The total vaccinated cohort included all participants who received at least the first study dose. The modified total vaccinated cohort included all participants who received 2 doses of the same study vaccine; participants developing a herpes zoster episode sooner than 1 month after receiving the second vaccine dose were excluded from the analysis.

Figure 2. Cumulative Incidence of Herpes Zoster Overall (Modified Total Vaccinated Cohort)



No. at risk								
Placebo	851	704	604	464	337	209	112	40
Recombinant zoster vaccine	870	779	682	537	396	268	141	49
No. with ≥1 herpes zoster episode								
Placebo	0	69	100	117	130	133	134	135
Recombinant zoster vaccine	0	17	30	38	44	45	47	49

On the x-axis, 0 corresponds to 1 month after study dose 2; ie, 5 to 6 months after hematopoietic stem cell transplantation. Cumulative incidence at 42 months since 30 days after dose 2 was 20.3% in the placebo group and 9.5% in the recombinant zoster vaccine group. The median follow-up time at risk was 22.0 (interquartile range, 13.4-32.4) months in the recombinant zoster vaccine group and 19.9 (interquartile range, 10.0-29.9) months in the placebo group.

and after dose 2, 78%; general symptoms after dose 1, 59%, and after dose 2, 66%). However, some of the local and general solicited symptoms, including injection site redness and swelling, as well as headache, shivering, and fever, were higher after the second dose. Solicited injection site reactions and general symptoms were transient in nature, having a median duration of up to 3 days (grade 3, up to 2 days).

Within 30 days of vaccination, the incidence of unsolicited adverse events was similar in the vaccine and placebo groups; the most frequent unsolicited events were infections (eTables 5 and 6 in Supplement 3). Serious adverse events within 30 days after last vaccination occurred in 7% of both vaccine and placebo recipients and in 28% and 26%, respectively, during the 1-year follow-up after last vaccination; the most frequent serious adverse events were neoplasms (eTable 7 in Supplement 3). Three participants in the vaccine group reported 5 serious adverse events (neutropenia, immune thrombocytopenic purpura, cutaneous vasculitis, arthralgia, and atrial fibrillation) that were considered to be related to vaccination; 4 participants in the placebo group reported 4 such events (constipation, herpes zoster, disseminated cutaneous herpes zoster, and skin eruption) (Table 3). Fatal serious adverse events occurred in 242 participants (vaccine group, n=118; placebo group, n=124) during the entire study and were mainly due to recurring malignancy and non-herpes zoster-related infections (eFigure 4 in Supplement 3).

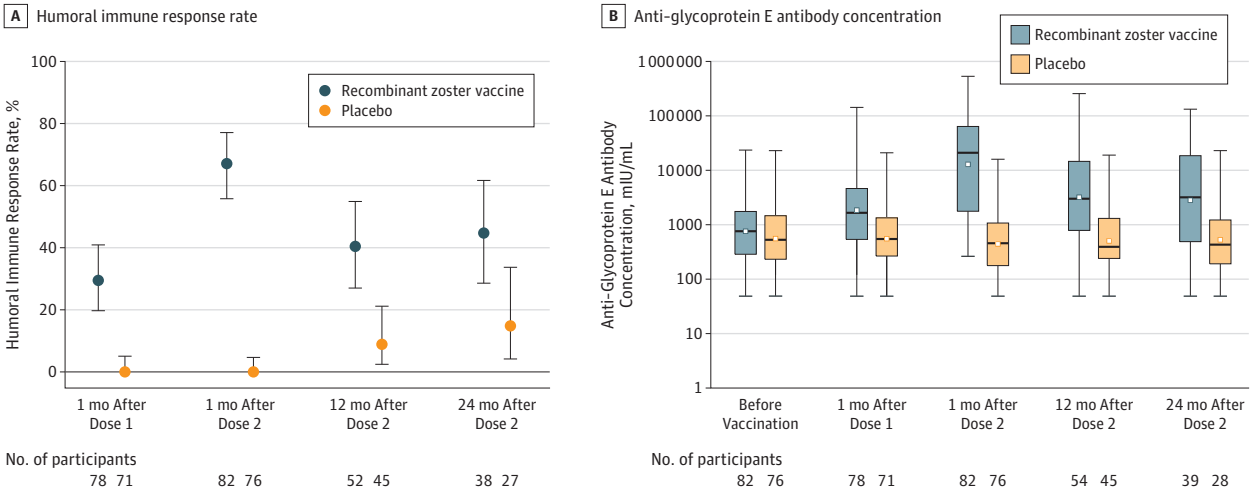
In the year following last vaccination, 13 vaccine recipients and 8 placebo recipients reported at least 1 event of potentially immune-mediated disease (eTable 8 in Supplement 3); the most frequently reported events were psoriasis (2 events in vaccine recipients) and interstitial lung disease (2 events in placebo recipients). During the entire study, 26% of vaccine recipients and 27% of placebo recipients had a malignancy relapse (eFigure 5 in Supplement 3).

Exploratory and Post Hoc End Points

A post hoc analysis using a piecewise Cox model resulted in hazard ratios for first herpes zoster episode of 0.31 (95% CI, 0.22-0.43; $P < .001$) within 2 years after the first month after dose 2 and 0.79 (95% CI, 0.23-2.72; $P < .71$) after these 2 years.

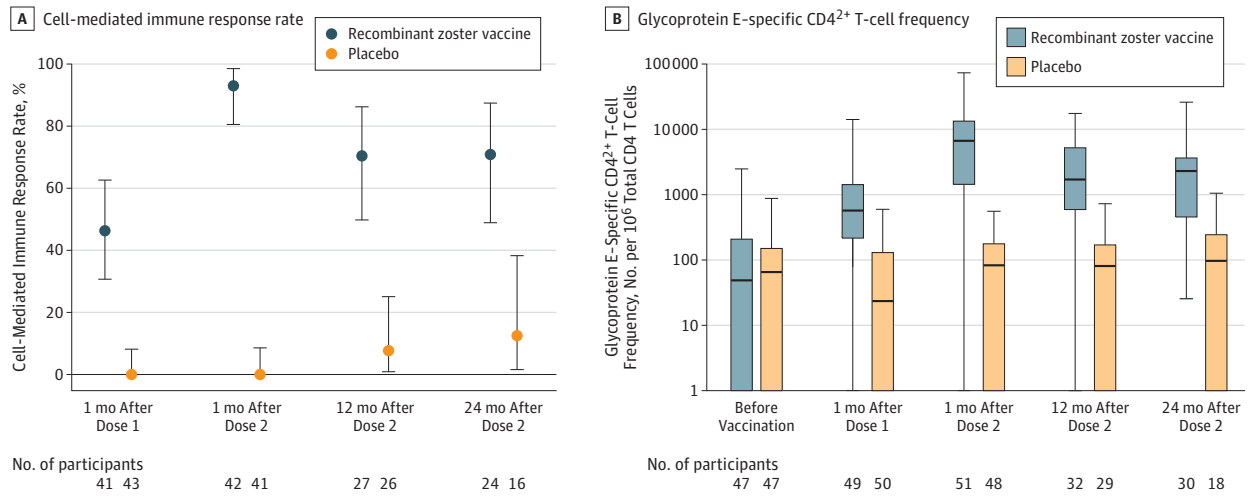
Incidence rate ratios for first herpes zoster episode were no more than 0.40 ($P < .001$) irrespective of age (<50 vs ≥50 years), underlying diagnosis (multiple myeloma vs all other diagnoses), or sex (eTable 4 and eFigure 6 in Supplement 3). The post hoc Poisson regression analysis did not show any significant interaction of these effects ($P = .58$, $P = .37$, and $P = .08$, respectively) with the study treatment. A post hoc IRR analysis taking into account the actual duration of antiviral prophylaxis therapy received in the period between 1 month after dose 2 and study end resulted in IRRs for first herpes zoster episode of 0.27 (95% CI, 0.17-0.43; $P < .001$) in participants who received no antiviral prophylaxis and 0.28

Figure 3. Humoral Immunogenicity Results (Per-Protocol Cohort for Humoral Immunogenicity/Persistence)



In panel A, error bars indicate 95% confidence intervals. In panel B, error bars indicate ranges; bar tops and bottoms, interquartile ranges; horizontal middle lines, medians; and white squares, geometric means.

Figure 4. Cell-Mediated Immunogenicity Results (Per-Protocol Cohort for Cell-Mediated Immunity/Persistence)



In panel A, error bars indicate 95% confidence intervals. In panel B, error bars indicate ranges; bar tops and bottoms, interquartile ranges; and horizontal middle lines, medians. Panel B data are for CD4 T cells expressing at least 2 of 4 assessed activation markers (interferon γ, interleukin 2, tumor necrosis factor α, and CD40 ligand).

(95% CI, 0.12-0.56; $P < .001$) in those taking antiviral prophylaxis for up to 60 days. Among participants who received more than 60 days of antiviral prophylaxis, the incidence rate was not statistically different between the 2 groups (eTable 4 in Supplement 3).

Discussion

Two doses of recombinant zoster vaccine administered to adults who had recently undergone autologous HSCT significantly reduced the incidence of herpes zoster.

The observed herpes zoster IRR of 0.32 (95% CI, 0.22-0.44) in study participants who completed the 2-dose course would be equivalent to a vaccine efficacy in preventing herpes zoster (estimated as 1 minus the IRR for herpes zoster multiplied by 100) of 68.2% (95% CI, 55.6-77.5). The IRR of 0.36 (95% CI, 0.27-0.48) in participants who received at least 1 dose would be equivalent to a 63.7% (95% CI, 51.8-72.9) vaccine efficacy.

The efficacy in this transplant population was lower than in nontransplant populations aged 50 years or older (91%),[11,12] which may reflect a weaker immune response due to underlying hematologic disease[15] and the high-dose preparative regimens given prior to autologous HSCT. Nevertheless, the overall

Table 3. Adverse Events (Total Vaccinated Cohort)[a]

Adverse Events	No. (%) [95% CI] Recombinant Zoster Vaccine	Placebo
Solicited adverse events within 7 d of vaccination		
Injection site adverse events	n=901	n=892
All types		
Any	773 (85.8) [83.3-88.0]	93 (10.4) [8.5-12.6]
Grade 3	128 (14.2) [12.0-16.7]	3 (0.3) [0.1-1.0]
Pain		
Any	756 (83.9) [81.3-86.2]	83 (9.3) [7.5-11.4]
Grade 3	99 (11.0) [9.0-13.2]	3 (0.3) [0.1-1.0]
Redness		
Any	301 (33.4) [30.3-36.6]	9 (1.0) [0.5-1.9]
>100 mm	28 (3.1) [2.1-4.5]	0 (0.0) [0.0-0.4]
Swelling		
Any	168 (18.6) [16.2-21.3]	9 (1.0) [0.5-1.9]
>100 mm	13 (1.4) [0.8-2.5]	0 (0.0) [0.0-0.4]
General adverse events	n=901	n=892
All types		
Any	678 (75.2) [72.3-78.0]	455 (50.9) [47.6-54.2]
Grade 3	119 (13.2) [11.1-15.6]	54 (6.0) [4.6-7.8]
Fatigue		
Any	508 (56.4) [53.1-59.6]	340 (38.0) [34.8-41.3]
Grade 3	66 (7.3) [5.7-9.2]	31 (3.5) [2.4-4.9]
Gastrointestinal[b]		
Any	238 (26.4) [23.6-29.4]	183 (20.5) [17.9-23.3]
Grade 3	18 (2.0) [1.2-3.1]	17 (1.9) [1.1-3.0]
Headache		
Any	302 (33.5) [30.4-36.7]	166 (18.6) [16.1-21.3]
Grade 3	26 (2.9) [1.9-4.2]	10 (1.1) [0.5-2.0]
Myalgia		
Any	484 (53.7) [50.4-57.0]	234 (26.2) [23.3-29.2]
Grade 3	56 (6.2) [4.7-8.0]	19 (2.1) [1.3-3.3]
Shivering		
Any	237 (26.3) [23.5-29.3]	115(12.9) [10.7-15.2]
Grade 3	35 (3.9) [2.7-5.4]	7 (0.8) [0.3-1.6]
Fever		
Any	183 (20.3) [17.7-23.1]	50 (5.6) [4.2-7.3]
>39.5°C	3 (0.3) [0.1-1.0]	1 (0.1) [0.0-0.6]
Unsolicited adverse events within 30 d after vaccination	n=922	n=924
Any grade	360 (39.0) [35.9-42.3]	353 (38.2) [35.1-41.4]
Grade 3	60 (6.5) [5.0-8.3]	47 (5.1) [3.8-6.7]
Serious adverse events and deaths within 30 d of last vaccination	n=922	n=924
Serious adverse events[c]	68 (7.4) [5.8-9.3]	66 (7.1) [5.6-9.0]
Serious adverse events related to vaccination[d]	1 (0.1) [0.0-0.6]	3 (0.3) [0.1-0.9]
Deaths	20 (2.2) [1.3-3.3]	19 (2.1) [1.2-3.2]
Serious adverse events, deaths, and events of interest within 365 d of last vaccination	n=922	n=924
Serious adverse events[c]	263 (28.5) [25.6-31.6]	241 (26.1) [23.3-29.0]
Serious adverse events related to vaccination[e]	3 (0.3) [0.1-0.9]	4 (0.4) [0.1-1.1]
Potentially immune-mediated diseases	13 (1.4) [0.8-2.4]	8 (0.9) [0.4-1.7]
Potentially immune-mediated diseases related to vaccination	3 (0.3) [0.1-0.9]	0 (0.0) [0.0-0.4]
Relapse of malignancy	145 (15.7) [13.4-18.2]	149 (16.1) [13.8-18.7]
Deaths	77 (8.4) [6.6-10.3]	79 (8.5) [6.8-10.5]

[a] Additional details regarding adverse events are available in eTables 5 to 8 and eFigure 4 in Supplement 3. The causal relationship of adverse events with vaccination was assessed by study investigators. Grading of injection site redness and swelling: grade 0, affected area <20 mm; grade 1, 20 to 50 mm; grade 2, >50 to 100 mm; and grade 3, >100 mm. Grading of fever: grade 0, temperature (preferably oral) <37.5°C; grade 1, 37.5°C to 38.0°C; grade 2, 38.1°C to 39.0°C; and grade 3, >39.0°C. Grading of all other symptoms including pain: grade 0, absent/none; grade 1, easily tolerated; grade 2, interferes with normal activity; grade 3, prevents normal activity.

[b] Gastrointestinal symptoms included nausea, vomiting, diarrhea, and abdominal pain.

[c] Serious adverse events were defined as events that resulted in death, were life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability or incapacity, or were a congenital anomaly/birth defect in offspring of a participant.

[d] The 4 serious adverse events related to vaccination were neutropenia in the recombinant zoster vaccine group and constipation, herpes zoster, and toxic skin eruption in the placebo group.

[e] The 5 serious adverse events related to vaccination that occurred between 30 and 365 days after dose 2 were immune thrombocytopenic purpura and cutaneous vasculitis co-reported with arthralgia and atrial fibrillation in the recombinant zoster vaccine group and herpes zoster (cutaneous disseminated) in the placebo group.

efficacy in participants who received at least 1 dose appeared very similar to that of a heat-inactivated varicella-zoster virus vaccine administered to a similar population.[14] However, this level of protection was achieved by a 4-dose schedule of the heat-inactivated vaccine compared with a 2-dose schedule of the recombinant zoster vaccine. Moreover, the first dose of the 4-dose regimen was administered 1 month before autologous HSCT, which can be logistically challenging.[19] A pretransplantation vaccine dose may generate immune memory, resulting in earlier peak immune responses, as described previously for pneumococcal vaccination.[20] Cell-mediated immunity responses in the current study were comparable with those in immunocompetent adults aged 50 years or older, while humoral immune responses were lower.[21] Vaccination before transplantation might be considered to improve such humoral immune responses. However, the clinical significance

of this potential improvement remains unclear, as cell-mediated immunity is believed to be the main mechanism for protection against herpes zoster.[22]

An advantage of the short 2-dose posttransplantation schedule is that more patients might complete the vaccination program. For instance, while the 4-dose schedule of the heat-inactivated herpes zoster vaccine was completed by 453 (81.8%) of 554 vaccinated HSCT recipients in the main treatment group of the study evaluating its efficacy,[14] 873 (94.7%) of 922 recombinant zoster vaccine recipients completed the 2-dose vaccination schedule in this study. The recombinant zoster vaccine also showed a reduction in the incidence of herpes zoster–related hospitalizations and complications, including postherpetic neuralgia, and reduced the duration of worst herpes zoster–associated pain during disease episodes.

The recombinant zoster vaccine induced strong humoral and cellular immune responses, which were significantly higher than in the placebo group, consistent with previous observations.[15] One month after dose 2, all recombinant zoster vaccine recipients had detectable glycoprotein E–specific antibodies, and although the levels subsequently decreased, as previously observed in older adults,[21,23] they remained higher than baseline 24 months after dose 2. Although anti-glycoprotein E antibody concentrations and $CD4^{2+}$ T-cell frequencies remained close to baseline levels, both humoral and cell-mediated immunity vaccine response rates increased incrementally up to 24 months after dose 2 in placebo recipients. This increase is likely due to subclinical varicella-zoster virus reactivation, which is a common event in individuals undergoing HSCT.[24]

In trials of immunocompetent populations, injection site pain, fatigue, and myalgia were the most common symptoms after recombinant zoster vaccine vaccination.[11,12,23] The relatively high incidence of these symptoms has been previously linked to the addition of an adjuvant system, which enhances the vaccine immune response and efficacy.[25,26] In this study, the vaccinations were generally well tolerated, and most symptoms were mild and transient and did not substantially deter participants from receiving their second dose. There is a hypothetical concern of adjuvant systems triggering exacerbations or onset of immune-mediated diseases.[27] This was not observed in the current study, which is in line with previous findings.[11,12] Overall, the adverse events reported in this study were consistent with the underlying and/or concurrent medical conditions or treatments for underlying disease, including infections and neoplasms.

Limitations

This study has several limitations. First, the study was not powered to compare incidences of herpes zoster–related complications excluding postherpetic neuralgia, postherpetic neuralgia, and hospitalizations. Second, long-term protection beyond the second year was not assessed in this study and merits further consideration. However, such a long-term study may prove complex because of intercurrent malignancy and comorbidities. Third, no data on pretransplantation varicella-zoster virus serology were collected.

Conclusions

Among adults who had undergone autologous HSCT, a 2-dose course of recombinant zoster vaccine compared with placebo significantly reduced the incidence of herpes zoster over a median follow-up of 21 months.

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