Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis

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Summary

Background The adjuvanted recombinant zoster vaccine (Shingrix) can prevent herpes zoster in older adults and autologous haemopoietic stem cell transplant recipients. We evaluated the safety and immunogenicity of this vaccine in adults with haematological malignancies receiving immunosuppressive cancer treatments.

Methods In this phase 3, randomised, observer-blind, placebo-controlled study, done at 77 centres worldwide, we randomly assigned (1:1) patients with haematological malignancies aged 18 years and older to receive two doses of the adjuvanted recombinant zoster vaccine or placebo 1–2 months apart during or after immunosuppressive cancer treatments, and stratified participants according to their underlying diseases. The co-primary objectives of the study were the evaluation of safety and reactogenicity of the adjuvanted recombinant zoster vaccine compared with placebo from the first vaccination up to 30 days after last vaccination in all participants; evaluation of the proportion of participants with a vaccine response in terms of anti-glycoprotein E humoral immune response to the adjuvanted recombinant zoster vaccine at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia; and evaluation of the anti-glycoprotein E humoral immune responses to the vaccine compared with placebo at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia. We assessed immunogenicity in the per-protocol cohort for immunogenicity and safety in the total vaccinated cohort. The study is registered with ClinicalTrials.gov, number NCT01767467, and with the EU Clinical Trials Register, number 2012-003438-18.

Findings Between March 1, 2013, and Sept 10, 2015, we randomly assigned 286 participants to adjuvanted recombinant zoster vaccine and 283 to placebo. 283 in the vaccine group and 279 in the placebo group were vaccinated. At month 2, 119 (80·4%, 95% CI 73·1–86·5) of 148 participants had a humoral vaccine response to adjuvanted recombinant zoster vaccine, compared with one (0·8%, 0·0–4·2) of 130 participants in the placebo group, and the adjusted geometric mean anti-glycoprotein E antibody concentration was 23132·9 mIU/mL (95% CI 16642·8–32153·9) in the vaccine group and 777·6 mIU/mL (702·8–860·3) in the placebo group (adjusted geometric mean ratio 29·75, 21·09–41·96; p<0·0001) in all patients, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia. Humoral and cell-mediated immune responses persisted above baseline until month 13 in all strata and, as expected, vaccine was more reactogenic than placebo (within 7 days after vaccination pain was reported by 221 [79·5%] of 278 vaccine group participants and 45 [16·4%] of 274 placebo group participants; fatigue was reported by 162 [58·3%] of 278 vaccine group participants and 102 [37·2%] of 274 placebo group participants). Incidences of unsolicited or serious adverse events, potential immune-mediated diseases, disease-related events, and fatal serious adverse events were similar between the groups.

Interpretation The immunocompromised adult population with haematological malignancies is at high risk for herpes zoster. The adjuvanted recombinant zoster vaccine, which is currently licensed in certain countries for adults aged 50 years and older, is likely to benefit this population.

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Introduction

After primary infection, varicella zoster virus establishes latency in sensory nerve ganglia.[1] Reactivation of the virus can lead to herpes zoster, a typically unilateral, vesicular, dermatomal rash, usually accompanied by pain.[2] The most common complication of herpes zoster, postherpetic neuralgia, can last for months or years.[1,3]

Research in context

Evidence before this study

Adjuvanted recombinant zoster vaccine was highly immunogenic and more than 90% efficacious against herpes zoster in individuals aged 50 years and older. The adjuvanted recombinant zoster vaccine has also been reported to be immunogenic and well-tolerated in several immunocompromised populations, as well as efficacious against herpes zoster in autologous haemopoietic stem cell transplant recipients.

Added value of this study

This study assessed the adjuvanted recombinant zoster vaccine in patients with haematological malignancies who were receiving immunosuppressive treatments. The vaccine induced robust and persistent humoral and cell-mediated immune responses in our population of adults aged 18 years and older with various haematological malignancies. Cell-mediated immunity, considered to play a key part in protection against herpes zoster, was similar to that observed in otherwise generally healthy adults aged 50 years and older.

Implications of all the available evidence

Taken together with results of previous clinical trials, the results of our study show that the adjuvanted recombinant zoster vaccine is immunogenic in populations that are at an increased risk of herpes zoster infection, either due to older age or because of underlying conditions and their associated immunosuppressive treatments. This immunocompromised adult population is likely to benefit from vaccination with the adjuvanted recombinant zoster vaccine, which is licensed in Australia, Canada, Japan, USA, China, and the EU for adults aged 50 years and older.

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See **Online** for appendix

The risk of herpes zoster increases with age, particularly after age 50 years, because of waning cell-mediated immunity.[1] Immunocompromised people, particularly those with impaired cell-mediated immunity due to either underlying disease or immunosuppressive thera-pies,[4–9] are also at an increased risk of herpes zoster. The incidence of herpes zoster in individuals with haematological malignancies receiving immunosuppressive cancer treatments is up to ten times higher than in the overall population (31 per 1000 person-years *vs* 3·2 per 1000 person-years).[3,10] Herpes zoster occurs in up to a quarter of patients with multiple myeloma,[11–14] Hodgkin lymphoma,[4,15,16] and chronic lymphocytic leukaemia,[6,7,16] and in more than 6% of patients with non-Hodgkin lymphoma receiving immunosuppressive cancer treatments.[15]

Vaccination is an effective approach in the prevention of infectious diseases. Two vaccines are approved for prevention of herpes zoster in adults aged 50 years and older—the live-attenuated varicella zoster virus vaccine (Zostavax; Merck Sharp & Dohme Corp) and the adjuvanted recombinant zoster vaccine (Shingrix; GlaxoSmithKline Biologicals SA).

Zostavax is a live virus vaccine and is contraindicated in people with immunodeficiency due to malignancy or immunosuppressive therapy because of potential virulence in those with substantially impaired immunity.[17–20]

Although usually not as immunogenic as live vaccines, inactivated vaccines can be used in immunocompromised populations.[17,18] An investigational inactivated varicella zoster vaccine administered on a four-dose schedule has been shown to be generally safe, immunogenic, and efficacious in autologous haematopoietic stem cell transplant recipients and patients with solid tumour malignancies receiving chemotherapy.[21,22,23] However, this vaccine was not found to be efficacious in patients with haematological malignancies and evaluation of efficacy in this group was terminated early because of evidence of futility.[23]

Shingrix is an adjuvanted non-live subunit vaccine, consisting of the truncated form of varicella zoster virus glycoprotein E and the $AS01_B$ adjuvant system. This vaccine was highly immunogenic and more than 90% efficacious against herpes zoster in individuals older than 50 years.[24–26] Shingrix was also immunogenic in immunocompromised populations aged 18 years and older, including in autologous haemopoietic stem cell transplant recipients, renal transplant recipients, patients with solid tumours, and people with HIV.[27–32] Two doses of Shingrix showed 68% efficacy in preventing herpes zoster in patients who had undergone autologous haemopoietic stem cell transplantation.[32] In this population, 873 (94·7%) of 922 Shingrix recipients completed the two-dose vaccination schedule.[32]

This study aimed to evaluate the immunogenicity and safety of two doses of the adjuvanted recombinant zoster vaccine (Shingrix) in adults aged 18 years and older with haematological malignancies who were undergoing or had just finished immunosuppressive cancer treatments.

Methods

Study design and participants

This was a phase 3, randomised, observer-blind, placebo-controlled study done at 77 centres in Australia, Belgium, Canada, the Czech Republic, Finland, France, Hong Kong, Italy, South Korea, New Zealand, Pakistan, Panama, Poland, Russia, Singapore, Spain, Sweden, Taiwan, Turkey, the UK, and the USA.

Patients with haematological malignancies aged 18 years and older were eligible for the study if, at vaccination, they had a life expectancy of 12 months or longer and were receiving or had just finished immunosuppressive cancer treatments. Participants were vaccinated during a cancer therapy course (each dose at least 10 days before and after

any cancer therapy) or after the full cancer therapy course (first dose of the study vaccine between 10 days and 6 months after therapy). Eligible treatment included direct immunosuppressive cancer therapies (chemotherapy or immunotherapy) or immunosuppressive therapies administered as part of cancer treatment or to avoid or treat complications of cancer treatment (eg, steroids at high immunosuppressive doses, ciclosporin, or tacrolimus). Radiotherapy was allowed only in combination with either chemotherapy or immunotherapy. Antiviral prophylaxis according to local standards was permitted during the study. Female participants of childbearing potential had to practice adequate contraception from 30 days before vaccination until 2 months after dose two and had to have a negative pregnancy test on the days of both vaccinations. All participants provided written informed consent before study entry.

Patients with haematological malignancies were excluded from participation if they had chronic lymphocytic leukaemia that was treated only with oral chemotherapy, were scheduled for haemopoietic stem cell transplantation during the study or had haemopoietic stem cell trans-plantation within 50 days before the first dose of study vaccine, had a clinical history of HIV infection, had used any investigational or non-registered product other than the study vaccine within 30 days preceding the first dose of study vaccine or planned use during the study period, had been vaccinated within the 12 months preceding the first dose of study vaccine or planned to be vaccinated during the study with a (non-study) vaccine against herpes zoster or varicella zoster virus, had a clinical history of a varicella zoster virus or herpes zoster episode within the 12 months preceding the first dose of study vaccine, had a history of any reaction or hypersensitivity likely to be exacerbated by any vaccine component, had received or planned to receive a live vaccine in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose of study vaccine, or had received or planned to receive a non-replicating vaccine within 8 days before or within 14 days after either dose of study vaccine.

The study protocol was reviewed and approved by the relevant institutional review boards or independent ethics committees. The study was done in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol is available online.

For the **trial protocol** see https://www.gsk-studyregister.com/study/4728

Randomisation and masking

We randomly assigned participants (1:1) using an online centralised randomisation system to receive two doses of the adjuvanted recombinant zoster vaccine or placebo 1–2 months apart. We stratified participants according to their underlying disease, as follows: non-Hodgkin B-cell lymphoma; chronic lymphocytic leukaemia; and multi-ple myeloma, non-Hodgkin T-cell lymphoma, Hodgkin lymphoma, and other haematological malignancies. We will refer to the third stratum as all excluding non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia. Similarly, the stratum referred to as all excluding non-Hodgkin B-cell lymphoma consists of the listed second and third strata. Within each of these strata, we used a minimisation procedure in the randomisation algorithm to account for the underlying disease (non-Hodgkin B-cell lymphoma, chronic lymphocytic leukaemia, multiple myeloma, non-Hodgkin T-cell lymphoma, Hodgkin lymphoma, and other haematological malignancies), age (18–49 years or ≥50 years), sex, region (Asia, Europe, Latin America, North America, and other regions), country, study centre, and timing of study vaccination (during immunosuppressive cancer treatment or after immunosuppressive cancer treatment).

Investigator site staff accessed an online centralised randomisation system and provided the patient age and sex, the underlying disease category, the cancer therapy course, and the identification number for each participant, after which the system generated the treatment number to be used for the first dose. For the second dose, upon provision of the subject identification number to the online centralised randomisation system by study personnel, the system provided a treatment number consistent with the allocated study group.

Data were collected in an observer-blind manner—study participants, those evaluating study endpoints, laboratory personnel, and the sponsor were all unaware of the treatment administered. Vaccine or placebo preparation and administration were done by unmasked authorised medical personnel who did not participate in the clinical evaluations.

Glycoprotein E-specific cell-mediated immunity was assessed in a subset of participants (hereafter referred to as the cell-mediated immunity sub-cohort) comprised of the first participants enrolled at designated sites until a country target was reached. The designated sites had to have access to peripheral blood mononuclear cell processing facilities within 24 h from collection time.

Procedures

Study participants received two doses of adjuvanted recombinant zoster vaccine or placebo in the deltoid muscle of their non-dominant arm. Each 0·5 mL dose of vaccine contained 50 µg of the glycoprotein E antigen and the GSK proprietary $AS01_B$ adjuvant system (containing 50 µg of 3-*O*-desacyl-4′-monophosphoryl lipid A, 50 µg of *Quillaja saponaria* Molina, fraction 21 [licensed by GSK from Antigenics, a wholly owned subsidiary of Agenus Inc, a Delaware, USA corporation], and liposome). Each 0·5 mL dose of placebo contained 20 mg lyophilised sucrose reconstituted with 150 mM NaCl solution.

We assessed humoral and cell-mediated immune responses from blood samples (approximately 8 mL and 30 mL, respectively) collected from participants at month 0 (pre-vaccination), month 1 (1 month after dose one), month 2 (1 month after dose two), and month 13

(12 months after dose two). We also used the blood samples collected at month 0 and month 2 for assessment of the correlation of vaccine-induced humoral immune responses with protection against herpes zoster.

We measured anti-glycoprotein E antibody concentrations by ELISA with a seropositivity cutoff of 97 mIU/mL.[26] We measured the frequencies of glycoprotein E-specific CD4[2+] T cells (CD4 T cells expressing at least two of the following four evaluated activation markers: interferon-γ, interleukin-2, tumour necrosis factor-α, and CD40 ligand) by intracellular cytokine staining after in-vitro stimulation with a pool of peptides covering the entire glycoprotein E ectodomain and detection by flow cytometry, as described previously.[26] The cutoff for the vaccine response assessment was 320 CD4[2+] T cells per 10^6 CD4 T cells counted.

We recorded herpes zoster cases prospectively. A suspected case of herpes zoster was defined as a new unilateral, dermatomal rash accompanied by pain (broadly defined to include allodynia, pruritus, or other sensations), or a vesicular rash suggestive of varicella zoster virus infection regardless of the distribution, and no alternative diagnosis; or a clinical presentation and specific laboratory findings (varicella zoster virus-positive PCR, culture, or immunohistochemical staining) specific to varicella zoster virus infection in the absence of characteristic herpes zoster or varicella zoster virus rash. Herpes zoster cases were confirmed by PCR on samples collected from lesions or by a herpes zoster ascertainment committee (HZAC) if the case could not be confirmed or excluded by PCR. The HZAC comprised three physicians with expertise in infectious diseases and haematology or oncology who were masked to treatment assignments and PCR results. Each member classified the reviewed cases as herpes zoster or non-herpes zoster based on the available clinical information from the study site (eg, summary of the rash and pain evaluations, digital photographs of the patient's rash, and clinical progress notes). A suspected case was considered herpes zoster if the HZAC members concurred unanimously; otherwise, it was classified as non-herpes zoster.

Outcomes

The co-primary objectives of the study were the evaluation of the safety and reactogenicity of the adjuvanted recombinant zoster vaccine compared with placebo from the first vaccination up to 30 days after last vaccination in all participants; evaluation of the proportion of participants with a vaccine response in terms of anti-glycoprotein E humoral immune response to the adjuvanted recombinant zoster vaccine at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia; and evaluation of the anti-glycoprotein E humoral immune responses to the vaccine compared with placebo at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia. The first co-primary objective was purely descriptive. The second co-primary objective was considered met if the lower limit of the 95% CI of the proportion of participants with a humoral vaccine response at month 2 in the vaccine group was 60% or more. The third co-primary objective was considered met if the lower limit of the 95% CI of the geometric mean ratio (vaccine over placebo) for adjusted anti-glycoprotein E ELISA antibody concentrations at month 2 was greater than 3.

Secondary objectives of the study were evaluation of the safety of the adjuvanted recombinant zoster vaccine compared with placebo from first vaccination up to 6 months after dose two in at least 50% of the total vaccinated cohort; evaluation of the safety of the vaccine compared with placebo from 30 days after last vaccination up to study end in all participants; evaluation of the proportion of participants with a humoral vaccine response at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma; evaluation of anti-glycoprotein E humoral immune responses to the vaccine compared with placebo at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma; evaluation of the incidence of confirmed herpes zoster cases in all participants; characterisation of anti-glycoprotein E humoral immune responses at month 0 (pre-vaccination), month 1, month 2, and month 13 in the vaccine and placebo groups overall and by underlying disease strata; characterisation of glycoprotein E-specific CD4 T-cell mediated immune responses at month 0, month 1, month 2, and month 13 within the vaccine and placebo groups overall (in the cell-mediated immunity sub-cohort) and by underlying disease strata; and assessment of the correlation between vaccine-induced humoral immune responses and the protection against herpes zoster in all participants. Secondary objectives were descriptive except for the third and fourth. The third secondary objective was considered met if the lower limit of the 95% CI of the proportion of participants with a humoral vaccine response at month 2 in the vaccine group was 60% or more, and the fourth objective was considered met if the lower limit of the 95% CI of the geometric mean ratio (vaccine over placebo) for adjusted anti-glycoprotein E ELISA antibody concentrations at month 2 was greater than 3.

The rationale for exclusion of patients with chronic lymphocytic leukaemia and non-Hodgkin B-cell lymphoma from the strata in which confirmatory objectives were evaluated is provided in the appendix (p 1).

We assessed confirmatory objectives (primary objectives two and three, and secondary objectives three and four) in a hierarchical order. Secondary confirmatory objectives could only be assessed if the co-primary confirmatory immunogenicity objectives were met; otherwise, interpretation of their assessment remained descriptive.

Solicited and unsolicited adverse events were recorded on diary cards for 7 days (day 0 to day 6) and 30 days

(day 0 to day 29) after each dose of study vaccine. Any medication or vaccine received within the 30-day post-vaccination period was also recorded. Solicited adverse events were categorised as local (injection site reactions: pain, redness, and swelling) or general (fever [body temperature ≥37·5°C], headache, fatigue, gastrointestinal symptoms [nausea, vomiting, diarrhoea, and abdominal pain], myalgia, and shivering). Adverse events were graded on a scale from 1 (mild) to 3 (severe). Grade 3 solicited adverse events were defined as preventing normal activity (for headache, fatigue, gastrointestinal symptoms, myalgia, and shivering), substantial pain at rest and preventing normal everyday activities (for injection site pain), having a surface diameter greater than 100 mm (for injection site redness and swelling), or body temperature greater than 39·0°C (for fever). Grade 3 unsolicited adverse events were defined as preventing normal daily activities. Adverse events were coded by Medical Dictionary for Regulatory Activities (MedDRA).

Serious adverse events, potential immune-mediated diseases, disease-related events (relapse or progression of the original haematological malignancy), pregnancies, and intercurrent medical conditions were recorded from first vaccination until study end (12 months after last dose). Intercurrent medical conditions were conditions with onset during the study period that could confound the immune response to the study vaccine. Serious adverse events related to study participation were collected from the time of consent to participate until discharge from the study.

All solicited local adverse events were considered causally related to vaccination. For other adverse events, the causal relationship to vaccination was assessed by the investigator.

Statistical analysis

In the all, excluding non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia stratum, between 140 and 158 evaluable participants were needed in each study group to assess the primary confirmatory objectives of the study. This sample size provided at least 99% power to show a proportion of participants with a humoral vaccine response to adjuvanted recominant zoster vaccine significantly greater than 60% and at least 91% power to show an anti-glycoprotein E antibody concentration geometric mean ratio (vaccine over placebo) significantly greater than 3. Assuming non-evaluability of 30%, between 200 and 226 participants needed to be enrolled in this stratum per study group.

In each of the non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia strata, between 20 and 30 evaluable participants were targeted per study group (appendix p 2). Assuming non-evaluability of 20%, between 25 and 38 participants needed to be enrolled in the non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia strata per treatment study group.

In the all, excluding non-Hodgkin B-cell lymphoma stratum, 170 evaluable participants in each study group provided at least 95% power to show a proportion of participants with a humoral vaccine response to adjuvanted recombinant zoster vaccine significantly greater than 60% and at least 90% power to show an anti-glycoprotein E antibody concentration geometric mean ratio (vaccine over placebo) significantly greater than 3.

Additional details on assumptions and power calculations, as well as other statistical considerations are provided in the appendix (p 2).

We defined the proportion of participants with a vaccine response in terms of anti-glycoprotein E humoral responses as the percentage of participants with anti-glycoprotein E antibody concentration after vaccination four or more times the cutoff (for initially seronegative participants) or anti-glycoprotein E antibody concentration after vaccination four or more times the pre-vaccination concentration (for initially seropositive participants).

For descriptive analyses, we tabulated geometric mean concentrations and proportions of participants with a humoral vaccine response for each study group with their exact 95% CIs. For comparative analyses, we calculated geometric means of antibody concentrations at month 2 conditionally to the means of the log-transformed concentrations before vaccination calculated across the treatment groups. We calculated adjusted means and the difference in adjusted means between the vaccine and placebo group together with two-sided 95% CIs and back-transformed to the original units to provide adjusted geometric mean concentrations and adjusted geometric mean ratios.

We defined the proportion of participants with a vaccine response in terms of CD4[2+] T-cell response as the percentage of participants with glycoprotein E-specific CD4[2+] T-cell frequencies after vaccination two or more times the cutoff (for participants initially below the cutoff of 320 CD4[2+] T cells per 10^6 CD4 T cells counted) or two or more times the glycoprotein E-specific CD4[2+] T-cell frequencies before vaccination (for participants initially above the cutoff).

We tabulated CD4[2+] T-cell frequencies (minimum, first quartile, median, third quartile, and maximum) and proportions of participants with a cell-mediated immunity vaccine response with exact 95% CIs for each study group at each timepoint.

We descriptively assessed correlation of vaccine-induced humoral immune responses with protection against herpes zoster by estimating anti-glycoprotein E antibody geometric mean concentration at month 2 and anti-glycoprotein E antibody concentration mean geometric increase from month 0 in participants with confirmed herpes zoster episodes versus participants with no confirmed herpes zoster episodes during the 1-year follow-up period in both the vaccine and placebo groups.

For each treatment group, we tabulated the number of participants at risk, follow-up period, number of

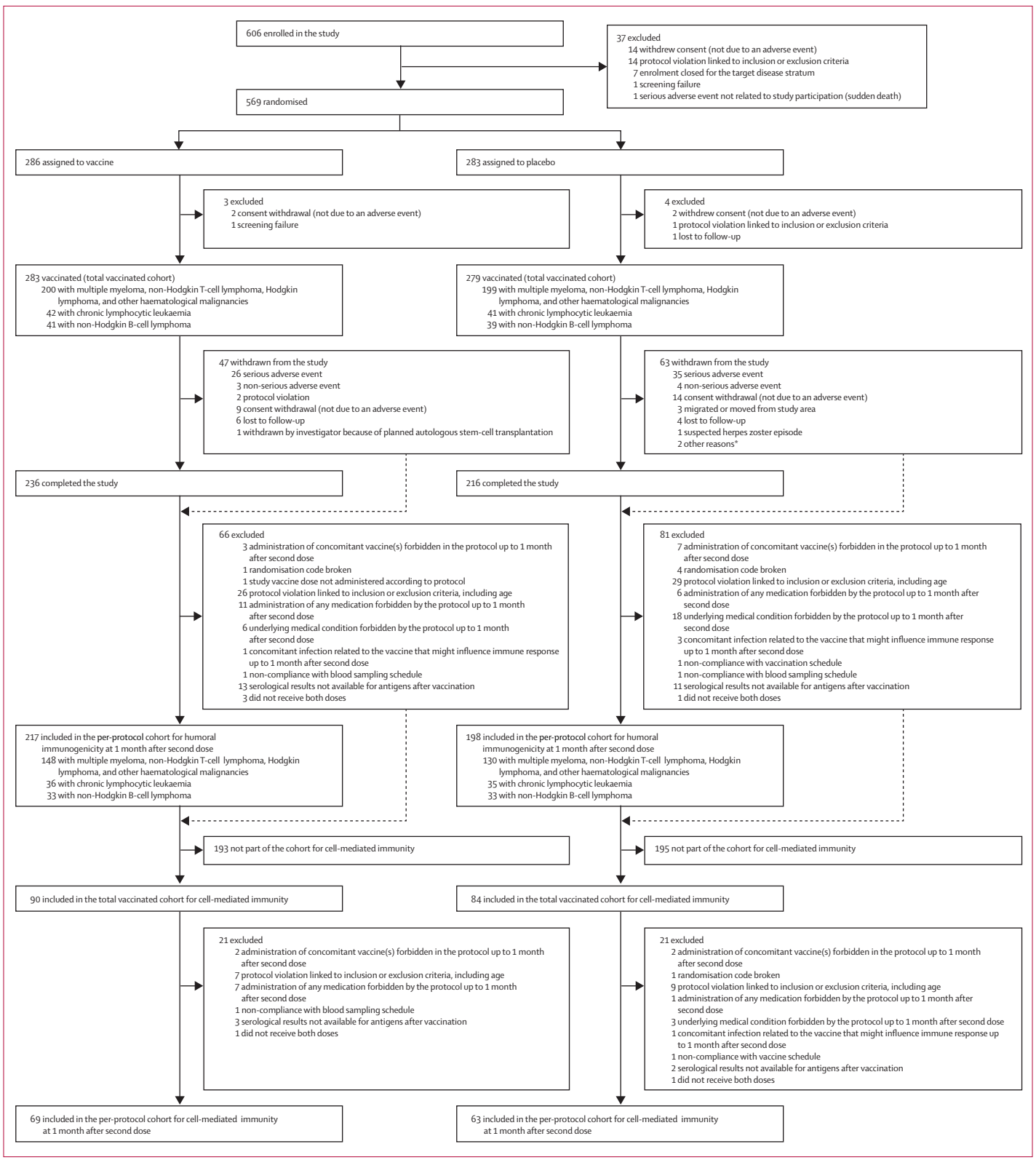

Figure 1: **Trial profile**

*One patient withdrew as they were followed up for their allograft in another hospital and one patient withdrew because they felt well.

participants reporting at least one confirmed herpes zoster case, and incidence of confirmed herpes zoster cases. We calculated post-hoc vaccine efficacy with the Poisson method, without stratification adjustment. The per-protocol cohort for immunogenicity included all participants who received both doses of vaccine or placebo, complied with the protocol, and for whom immunogenicity data were available. The total vaccinated cohort for the evaluation of safety included all participants who received at least one dose of vaccine or placebo. We included all participants from the total vaccinated cohort with at least one solicited local or general symptom documented as either present or absent in a reactogenicity analysis. We assessed correlation of vaccine-induced humoral immune responses with protection against herpes zoster in all participants who received two doses of vaccine or placebo and excluded participants who developed confirmed herpes zoster before month 2 blood sampling. This cohort will be referred to hereafter as the cohort for the assessment of the correlation of vaccine-induced humoral immune responses with protection against herpes zoster (CCP). We assessed post-hoc efficacy in the modified total vaccinated cohort, which included all participants from the total vaccinated cohort, except those who did not receive the second dose or who developed a confirmed case of herpes zoster before 30 days after dose two.

Administration of rituximab or a rituximab-containing regimen or alemtuzumab or an alemtuzumab-containing regimen within the period between 6 months before vaccination and 1 month after dose two and administration of prophylactic antiviral therapy during the study were evaluated post-hoc.

All statistical analyses were done with SAS version 9.3, Drug Development version 4.3.4. An independent data monitoring committee consisting of an independent statistician and seven clinical experts was appointed to monitor and follow-up the safety of the adjuvanted recombinant zoster vaccine.

The study is registered with ClinicalTrials.gov, number NCT01767467, and with the EU Clinical Trials Register, number 2012-003438-18.

Role of the funding source

This study was sponsored by GlaxoSmithKline Biologicals SA, which was involved in the study design, data collection, data analysis and interpretation, and writing the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between March 1, 2013, and Sept 10, 2015, we enrolled 606 participants in the study. 286 were randomly assigned to the adjuvanted recombinant zoster vaccine, 283 were randomly assigned to placebo, and 37 were not randomised. 562 (98·8%) of 569 randomised patients were vaccinated (total vaccinated cohort; 283 in the vaccine group and 279 in the placebo group). We included 174 (31·0%; 90 in the vaccine group and 84 in the placebo group) of 562 vaccinated participants in the cell-mediated immunity sub-cohort, and 452 (80·4%; 236 in the vaccine group and 216 in the placebo group) completed the study (figure 1). 516 patients received both doses (259 [91·5%] in the vaccine group and 257 [92·1%] in the placebo group). Most participants were Caucasian, and the most common malignancy was multiple myeloma, followed by Hodgkin lymphoma (table 1).

At baseline, a third of the study population was restricted in physically strenuous activity but was ambulatory and able to carry out light or sedentary work. 102 (36·0%) of 283 participants in the vaccine group were vaccinated during immunosuppressive cancer treatments and 181 (64·0%) were vaccinated after immunosuppressive cancer treatments. 106 (38·0%) of 279 participants in the placebo group were vaccinated during immunosuppressive cancer treatments and 173 (62·0%) participants were vaccinated after immunosuppressive cancer treatments. Demographic characteristics were similar between study groups (table 1).

The pre-vaccination anti-glycoprotein E antibody geometric mean concentration was 964·0 mIU/mL (95% CI 814·5–1140·8) in the vaccine group and 883·7 mIU/mL (749·9–1041·4) in the placebo group (appendix p 6). At month 2, the anti-glycoprotein E antibody geometric mean concentration was 13 445·6 mIU/mL (10158·9–17795·6) in the vaccine group and 832·0 mIU/mL (701·1–987·3) in the placebo group, and 142 (65·4%, 95% CI 58·7–71·7) of 217 participants in the vaccine group and one (0·5%, 0·0–2·8) of 198 participants in the placebo group had a humoral vaccine response (appendix pp 6–7). In all participants, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia at month 2, 119 (80·4%, 73·1–86·5) of 148 participants had a humoral vaccine response to adjuvanted recombinant zoster vaccine, compared with one (0·8%, 0·0–4·2) of 130 participants in the placebo group. The adjusted geometric mean anti-glycoprotein E antibody concentration was 23 132·9 mIU/mL (16642·8–32153·9) in the vaccine group and 777·6 mIU/mL (702·8–860·3) in the placebo group, and the adjusted geometric mean ratio (vaccine over placebo) was 29·75 (21·09–41·96; p<0·0001). Therefore, both co-primary immunogenicity objectives were met (figure 2). In a complementary analysis, the success criteria were also met for both co-primary immunogenicity objectives when evaluated in the total vaccinated cohort (appendix p 4). In all participants, excluding those with non-Hodgkin B-cell lymphoma at month 2, 127 (69·0%, 95% CI 61·8–75·6) of 184 had a humoral vaccine response to adjuvanted recombinant zoster vaccine, compared with one (0·6%, 0·0–3·3) of 165 participants in the placebo group. The adjusted geometric mean anti-glycoprotein E antibody concentrations were 7722·0 mIU/mL (5355·6 –11133·9) in the

vaccine group and 856·0 mIU/mL (775·7–944·5) in the placebo group, and the adjusted geometric mean ratio (vaccine over placebo) was 9·02 (6·18–13·17; p<0·0001), meeting the predefined criteria for both secondary confirmatory objectives (figure 2).

At month 13 in the vaccine group, the anti-glycoprotein E antibody geometric mean concentration was 5202·7 mIU/mL (95% CI 4074·8–6642·8) and 86 (52·1%, 95% CI 44·2–59·9) of 165 participants in the vaccine group had a humoral vaccine response, compared with five (3·6%, 1·2–8·1) of 140 participants in the placebo group. Across the timepoints after vaccination, the proportion of participants with a humoral vaccine response and anti-glycoprotein E antibody geometric mean concentration point estimates were higher in participants in the vaccine group, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia, than in participants in the vaccine group with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia (appendix pp 6–7). The proportion of participants with a humoral vaccine response and anti-glycoprotein E antibody geometric mean concentration point estimates were higher in participants in the vaccine group who were vaccinated after their course of immunosuppressive cancer treatments compared with those who were vaccinated during their course of immunosuppressive cancer treatments (appendix p 8).

Median CD4[2+] T-cell frequencies before vaccination were 77·5 (IQR 1·0–191·4) in the vaccine group and 101·2 (1·0–193·1) in the placebo group (appendix p 9). At month 2, median CD4[2+] T-cell frequencies were 3081·9 (1766·2–7413·6) in the vaccine group and 99·1 (1·0–268·3) in the placebo group, and 36 (83·7%, 95% CI 69·3–93·2) of 43 participants in the vaccine group and three (6·8%, 1·4–18·7) of 44 participants in the placebo group had a vaccine response in terms of glycoprotein E-specific CD4[2+] T-cell frequency (appendix p 9). At month 13 in the vaccine group, the median CD4[2+] T-cell frequency was 1006·7 (IQR 416·0–3284·5) and 22 (66·7%, 95% CI 48·2–82·0) of 33 participants in the vaccine group had a cell-mediated immunity vaccine response, compared with two (6·5%, 0·8–21·4) of 31 participants in the placebo group (appendix p 9).

At month 1, we observed cell-mediated immune responses in participants in the vaccine group from all three disease strata (appendix p 13), and in those vaccinated both during and after their course of immunosuppressive cancer treatments (appendix pp 10–11). Cell-mediated immune responses increased at month 2 and remained above pre-vaccination levels at month 13.

Herpes zoster episodes were confirmed in two participants in the vaccine group and 12 participants in the placebo group from the CCP. The two participants in the vaccine group with confirmed herpes zoster received rituximab or a rituximab-containing regimen within the interval between 6 months before vaccination and 1 month after dose two and neither of them met the

	Adjuvanted recombinant zoster vaccine (n=283)	Placebo (n=279)
Age at first vaccination (years)	56·8 (15·5)	57·8 (14·9)
Age group (years)		
18–49	74 (26·1%)	73 (26·2%)
≥50	209 (73·9%)	206 (73·8%)
Sex		
Male	169 (59·7%)	165 (59·1%)
Female	114 (40·3%)	114 (40·9%)
Ethnicity		
American Hispanic or Latino	11 (4·0%)	15 (5·6%)
Not American Hispanic or Latino	261 (96·0%)	253 (94·4%)
Missing	11	11
Geographic ancestry		
African heritage or African American	1 (0·4%)	1 (0·4%)
American Indian or Alaska native	0	1 (0·4%)
Asian—central or south Asian heritage	5 (1·8%)	6 (2·2%)
Asian—east Asian heritage	57 (21·0%)	60 (22·4%)
Asian—southeast Asian heritage	4 (1·5%)	1 (0·4%)
White—Arabic or north African heritage	0	1 (0·4%)
White—Caucasian or European heritage	198 (72·8%)	186 (69·4%)
Other	7 (2·6%)	12 (4·5%)
Missing	11	11
Timing of study vaccination		
During cancer therapy course—both doses at least 10 days before and after a chemotherapy cycle	102 (36·0%)	106 (38·0%)
10 days to 6 months after the full cancer therapy course	181 (64·0%)	173 (62·0%)
Haematological malignancy		
Chronic lymphocytic leukaemia	42 (14·8%)	41 (14·7%)
Hodgkin lymphoma	49 (17·3%)	47 (16·8%)
Multiple myeloma	67 (23·7%)	65 (23·3%)
Non-Hodgkin B-cell lymphoma	41 (14·5%)	39 (14·0%)
Non-Hodgkin T-cell lymphoma	13 (4·6%)	16 (5·7%)
Other haematological malignancies	71 (25·1%)	71 (25·4%)
Acute lymphoblastic leukaemia	7 (9·9%)	5 (7·0%)
Acute myeloid leukaemia	44 (62·0%)	37 (52·1%)
Myelodysplastic syndrome	12 (16·9%)	18 (25·4%)
Other	8 (11·3%)	11 (15·5%)
Patients who had undergone autologous haemopoietic stem cell transplantation before vaccination (post-hoc analysis)	28 (9·9%)	26 (9·3%)
Patients who had undergone allogeneic haemopoietic stem cell transplantation before vaccination (post-hoc analysis)	19 (6·7%)	21 (7·5%)
Graft-versus-host disease*	3 (15·8%)	4 (19·0%)
Eastern Cooperative Oncology Group performance status		
Fully active†	177 (63·7%)	175 (64·3%)
Restricted in physically strenuous activity‡	94 (33·8%)	89 (32·7%)
Ambulatory and capable of all selfcare§	6 (2·2%)	7 (2·6%)
Capable of only restricted selfcare¶	1 (0·4%)	1 (0·4%)
Missing	5	7

Data are mean (SD), n (%), or n. *None of the events were considered related to vaccination by the investigator and most of the events were mild or moderate in intensity. †Able to carry on all pre-disease performance without restriction. ‡Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature—for example, light house work or office work. §Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. ¶Capable of only restricted selfcare and confined to bed or a chair more than 50% of waking hours.

Table 1: **Demographic characteristics of the total vaccinated cohort**

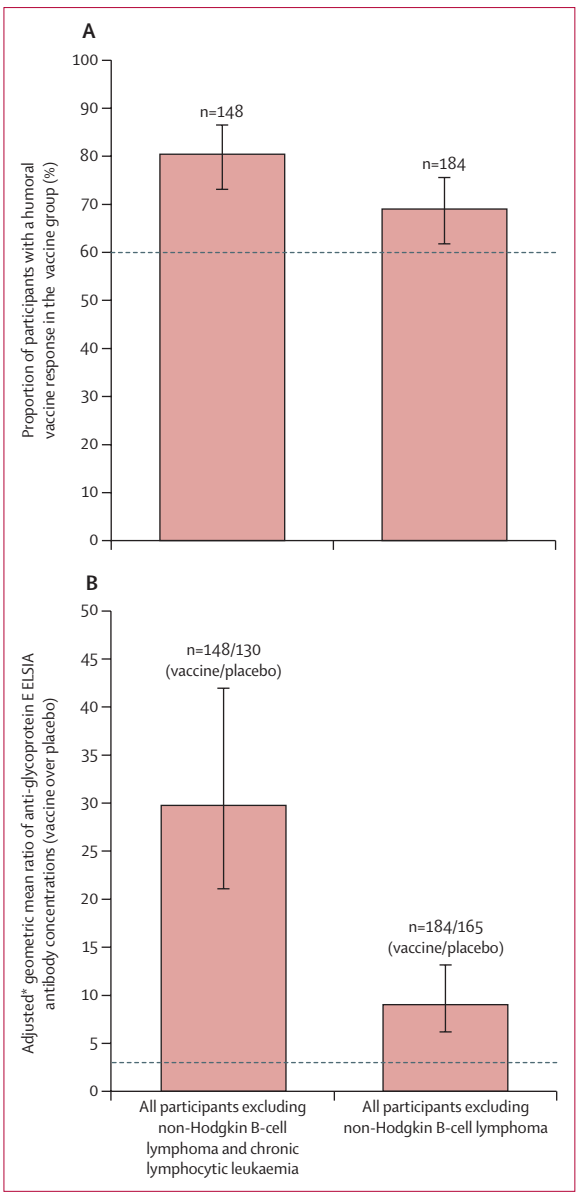

Figure 2: **Evaluation of immunogenicity objectives with predefined success criteria (1 month after dose two, per-protocol cohort for immunogenicity)**
Dashed horizontal lines represent the following predefined success criteria: the lower limit of the 95% CI of the proportion of participants with a humoral vaccine response ≥60%, and the lower limit of the 95% CI of adjusted geometric mean ratio (vaccine over placebo) for anti-glycoprotein E ELISA antibody concentrations >3. *Adjusted for baseline values.

predefined criterion for humoral vaccine response at month 2. 70 (27·2%) of 257 participants in the vaccine group who never developed herpes zoster received rituximab or a rituximab-containing regimen within the interval between 6 months before vaccination and 1 month after dose two. The two participants in the vaccine group who developed herpes zoster and 77 (30·0%) of 257 participants in the vaccine group who did not develop herpes zoster, received prophylactic antiviral therapy during the study. In the CCP, the month 2 anti-glycoprotein E antibody geometric mean concentration was 184·0 mIU/mL (95% CI 0·0–4·2×10⁹) in participants in the vaccine group who later developed herpes zoster and 12 517·4 mIU/mL (9662·0–16 216·6) in participants in the vaccine group who did not develop herpes zoster. The anti-glycoprotein E antibody concentration mean geometric increase at month 2 from baseline was 1·6 (0·0–565·5) in participants in the vaccine group with confirmed herpes zoster and 13·1 (9·9–17·2) in participants in the vaccine group without confirmed herpes zoster (appendix p 14).

Solicited injection site symptoms were reported by 233 (83·8%) of 278 participants in the vaccine group and 48 (17·5%) of 274 participants in the placebo group. 37 (13·3%) of 278 participants in the vaccine group reported grade three events, compared with no participants in the placebo group (table 2). Pain was the most common solicited injection site symptom, reported by 221 (79·5%) of 278 vaccine group participants and 45 (16·4%) of 274 placebo group participants. Grade 3 pain was reported by 29 (10·4%) participants in the vaccine group, compared with no participants in the placebo group (appendix p 12). The median duration of all-grade injection site symptoms was 3 days or less in the vaccine group and 4 days or less in the placebo group after each dose during the solicited 7-day post-vaccination period.

Solicited general symptoms were reported by 206 (74·1%) of 278 vaccine group participants and 134 (48·9%) of 274 placebo group participants. 43 (15·5%) vaccine group participants and 17 (6·2%) placebo group participants reported grade 3 events (table 2). The most common solicited general symptom was fatigue, reported by 162 (58·3%) vaccine group participants and 102 (37·2%) placebo group participants. Grade 3 fatigue was reported by 23 (8·3%) vaccine group participants and ten (3·6%) placebo group participants (appendix p 12). The median duration of all-grade general symptoms was 3·5 days or less in the vaccine group and 6 days or less in the placebo group after each dose during the solicited 7-day post vaccination period.

During the 30-day post-vaccination period, unsolicited adverse events were reported by 134 (47·3%) of 283 vaccine group participants and 128 (45·9%) of 279 placebo group participants (table 2). The most frequent unsolicited adverse events by MedDRA Preferred Term were nausea (11 [3·9%] vaccine group participants and six [2·2%] placebo group participants), pyrexia (ten [3·5%] vaccine group participants and five [1·8%] placebo group participants), and oropharyngeal pain (ten [3·5%] vaccine group parti-cipants and three [1·1%] placebo group participants). 19 (6·7%) of 283 participants in the vaccine group and five (1·8%) of 279 participants in the placebo group reported unsolicited adverse events considered causally related to vaccination by investigators (table 2). In the vaccine group, the most frequent of these adverse events by MedDRA Preferred Term were injection site

pruritus, reported by four (1·4%) participants, and injection site bruising, malaise, and arthralgia, each reported by two (0·7%) participants.

During the entire study period, serious adverse events were reported by 66 (23·3%) of 283 participants in the vaccine group and 82 (29·4%) of 279 participants in the placebo group. The incidence of serious adverse events was similar between the study groups during all time periods evaluated (table 2). In both study groups, the most frequent serious adverse events by MedDRA Preferred Term were febrile neutropenia (14 [4·9%] vaccine group participants and 11 [3·9%] placebo group participants) and pneumonia (11 [3·9%] in each study group). No clusters of similar serious adverse events were identified.

From first vaccination until study end, fatal serious adverse events were reported in 29 (10·2%) of 283 participants in the vaccine group and 37 (13·3%) of 279 participants in the placebo group (table 2). The death of a neonate whose mother was exposed to the last vaccine dose around 34 days before her last menstrual period was assessed as possibly related to vaccination by the investigator. The baby was born at 36 weeks' gestation with no apparent congenital anomalies and died a few minutes after birth because of breathing difficulties. Delivery details were scarce, and no autopsy was done.

During the entire study period, potential immune-mediated diseases were reported in three (1·1%) of 283 participants in the vaccine group and two (0·7%) of 279 participants in the placebo group (table 2). These diseases by MedDRA Preferred Term were autoimmune pancytopenia, gout, and erythema nodosum in the vaccine group, and autoimmune haemolytic anaemia and Guillain-Barré syndrome in the placebo group. From first vaccination until study end, relapse or progression of the original haematological malignancy (disease-related events) was reported in 45 (15·9%) participants in the vaccine group and 58 (20·8%) participants in the placebo group (table 2).

In the modified total vaccinated cohort, two confirmed episodes of herpes zoster occurred in the vaccine group and 14 occurred in the placebo group. Both cases in the vaccine group and six cases in the placebo group occurred in participants who received antiviral prophylaxis for any duration between first dose and study conclusion (post-hoc assessment). Confirmation of suspected herpes zoster cases in the modified total vaccinated cohort is described in detail in the appendix (p 5). A post-hoc analysis revealed that the incidence of herpes zoster was 8·5 per 1000 person-years in the vaccine group and 66·2 per 1000 person-years in the placebo group, resulting in 87·2% (95% CI 44·3–98·6; p=0·0021) efficacy against herpes zoster. Median follow-up was 11·1 months (IQR 10·3–12·2) from 30 days after dose 2.

Post-hoc analyses showed balanced antiviral prophylaxis and rituximab and alemtuzumab use. Between first dose and study conclusion, antiviral prophylaxis was administered to 79 (30·5%) of 259 participants in the vaccine group and 73 (28·5%) of 256 participants in the placebo group included in the modified total vaccinated cohort. Within the interval between 6 months before vaccination and 1 month after dose two, treatment with rituximab or a rituximab-containing regimen was administered to most participants with chronic lymphocytic leukaemia (29 [80·6%] of 36 vaccine group participants and 33 [94·3%] of 35 placebo group participants) and non-Hodgkin B-cell lymphoma (32 [97·0%] of 33 vaccine group participants and 32 [97·0%] of 33 placebo group participants), but to only a few participants in the all, excluding non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia stratum (two [1·4%] of 148 vaccine group participants and one [0·8%] of 130 placebo group participants; per-protocol cohort for humoral immunogenicity, month 2). In the total vaccinated cohort, alemtuzumab or an alemtuzumab-containing regimen was administered to

	Adjuvanted recombinant zoster vaccine		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)
Within 7 days after vaccination*				
Any solicited injection site symptom	233/278	83·8% (78·9–87·9)	48/274	17·5% (13·2–22·5)
Grade 3 solicited injection site symptom	37/278	13·3% (9·5–17·9)	0/274	0·0% (0·0–1·3)
Any solicited general symptom	206/278	74·1% (68·5–79·1)	134/274	48·9% (42·8–55·0)
Grade 3 solicited general symptom	43/278	15·5% (11·4–20·3)	17/274	6·2% (3·7–9·7)
Within 30 days after vaccination				
Any unsolicited adverse event	134/283	47·3% (41·4–53·3)	128/279	45·9% (39·9–51·9)
Considered related by investigator	19/283	6·7% (4·1–10·3)	5/279	1·8% (0·6–4·1)
Grade 3 unsolicited adverse event	25/283	8·8% (5·8–12·8)	28/279	10·0% (6·8–14·2)
Considered related by investigator	5/283	1·8% (0·6–4·1)	0/279	0·0% (0·0–1·3)
From first vaccination up to 30 days after last vaccination				
Any serious adverse event	17/283	6·0% (3·5–9·4)	29/279	10·4% (7·1–14·6)
Considered related by investigator	0/283	0·0% (0·0–1·3)	0/279	0·0% (0·0–1·3)
Any potential immune-mediated disease	1/283	0·4% (0·0–2·0)	0/279	0·0% (0·0–1·3)
From first vaccination up to 6 months after last vaccination				
Any serious adverse event	50/283	17·7% (13·4–22·6)	60/279	21·5% (16·8–26·8)
Considered related by investigator	0/283	0·0% (0·0–1·3)	1/279	0·4% (0·0–2·0)
Any potential immune-mediated disease	3/283	1·1% (0·2–3·1)	1/279	0·4% (0·0–2·0)
From first vaccination until study end				
Any serious adverse event	66/283	23·3% (18·5–28·7)	82/279	29·4% (24·1–35·1)
Considered related by investigator	1/283	0·4% (0·0–2·0)	1/279	0·4% (0·0–2·0)
Any potential immune-mediated disease	3/283	1·1% (0·2–3·1)	2/279	0·7% (0·1–2·6)
Any disease-related event†	45/283	15·9% (11·8–20·7)	58/279	20·8% (16·2–26·0)
Any fatal serious adverse event	29/283	10·2% (7·0–14·4)	37/279	13·3% (9·5–17·8)
Considered related by investigator	1‡/283	0·4% (0·0–2·0)	0/279	0·0% (0·0–1·3)

Data are the number of participants reporting an adverse event at least once out of the total vaccinated cohort. *N for solicited adverse events included all participants from the total vaccinated cohort with at least one solicited local or general symptom documented as either present or absent. †Relapse or progression of the original haematological malignancy. ‡Death, neonatal in the offspring of a lymphoma patient vaccinated before estimated pregnancy onset.

Table 2: **Safety analysis of the adjuvanted recombinant zoster vaccine**

three (1·1%) of 283 participants in the vaccine group and five (1·8%) of 279 participants in the placebo group within the interval between 6 months before vaccination and 1 month after dose two.

Discussion

The adjuvanted recombinant zoster vaccine is approved in several countries worldwide for the prevention of herpes zoster in adults aged 50 years and older and is not contraindicated for immunocompromised people. In this study, we showed that two doses of vaccine was immunogenic in adult patients with haematological malignancies aged 18 years and older who had been receiving immunosuppressive cancer treatments. All predefined success criteria for immunogenicity of the adjuvanted recombinant zoster vaccine at 1 month after dose two were met. Two doses of vaccine induced robust humoral and cell-mediated immune responses that persisted at 1 year after vaccination. Although anti-glycoprotein E antibody geometric mean concentrations and the proportion of participants with a humoral vaccine response to the adjuvanted recombinant zoster vaccine were lower, glycoprotein E-specific CD4[2+] T-cell frequencies and the proportion of participants with a cell-mediated immunity vaccine response to adjuvanted recombinant zoster vaccine were similar to those observed in immunocompetent adults aged 50 years and older.[26]

Humoral immune responses were lower in participants with non-Hodgkin B-cell lymphoma or chronic lymphocytic leukaemia compared with the all, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia stratum, probably because of B-cell depletion induced by therapy with anti-CD20 monoclonal antibody (ie, rituximab), which is commonly given to patients with chronic lymphocytic leukaemia and non-Hodgkin B-cell lymphoma.[33,34] This decreased humoral response to the adjuvanted recombinant zoster vaccine in patients with non-Hodgkin B-cell lymphoma has been observed previously.[29] Treatment with anti-CD20 monoclonal antibody has been shown to negatively affect antibody response in patients with lymphoma after influenza A H1N1 2009 vaccination.[35]

Cell-mediated immune responses, which are thought to be the main mechanistic driver of protection against herpes zoster,[36] were similar across patients with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia, and participants excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia. However, when interpreting this finding, the small number of participants in each disease stratum of the cell-mediated immunity sub-cohort should be considered. Additionally, in the absence of a universally accepted correlate of protection on the basis of glycoprotein E-specific immune responses, we cannot hypothesise the extent of protection offered by the elicited T-cell responses in patients with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia.

Our study shows that the adjuvanted recombinant zoster vaccine is able to induce robust glycoprotein E-specific humoral and cellular immune responses, both when administered during immunosuppressive cancer treatments and up to 6 months after immunosuppressive cancer treatments.

Although the sample size in our study did not allow us to assess a correlate of protection, the two adjuvanted recombinant zoster vaccine recipients that had a breakthrough herpes zoster episode during the 1-year follow-up period did not mount a humoral response to two doses of the vaccine. The clinical significance of this finding remains unclear because of the small number of confirmed herpes zoster cases and the imbalance in rituximab use between vaccine recipients who developed herpes zoster and those who did not.

A post-hoc analysis in our study revealed a vaccine efficacy of 87·2% against herpes zoster in this population of immunocompromised adults aged 18 years and older. Although we could not estimate efficacy in each disease stratum because of the small number of herpes zoster cases, our post-hoc efficacy assessment was based on all study participants, including patients with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia. The adjuvanted recombinant zoster vaccine can induce robust protection against herpes zoster in older adults by overcoming immunoscenescence,[24,25] and in adults under major immunosuppressive conditions.[27–32] Efficacy is well preserved even under the immunosuppressive conditions of the current study in a population at increased risk of herpes zoster,[3,10] and appears to be higher than in autologous haemopoietic stem cell transplant recipients.[32] However, the small number of herpes zoster cases and short follow-up period leading to broad CIs in our study should be considered when interpreting this post-hoc finding. Nevertheless, findings in this study show the consistency of the efficacy of the adjuvanted recombinant zoster vaccine across different types of populations,[24,25,32,37] which was not the case for the inactivated investigational varicella zoster vaccine administered on a four-dose schedule.[22,23]

As described previously,[24,25] the adjuvanted recombinant zoster vaccine is more reactogenic than is placebo. Nonetheless, second dose compliance was high and comparable between study groups. The occurrence of unsolicited adverse events was similar between study groups and the adverse events reported were consistent with the underlying diseases, known complications of the diseases, and the concomitant therapies. Vaccine recipients reported unsolicited adverse events causally related to vaccination by investigator assessment more frequently than did placebo recipients. Most of these adverse events were local injection site reactions. The incidences of serious adverse events, fatal serious adverse events, and potential immune-mediated diseases were similar between study groups. The death of a newborn infant of a woman with haematological malignancy was assessed by the

investigators as causally related to adjuvanted recombinant zoster vaccine. We consider that the event of early neonatal death was more likely to be associated with perinatal asphyxia or hypoxia or infection rather than medications received by the mother (including chemotherapy and vaccination) before pregnancy.

There are limitations to our study. The study population was mostly composed of ambulatory patients with haematological malignancies. 52 (26·0%) of 200 participants in the vaccine group and 69 (34·7%) of 199 participants who received placebo in the stratum used for evaluation of the primary objectives were excluded from the per-protocol cohort for immuno-genicity. Therefore, a total of 121 (30·3%) of 399 participants were excluded from the analysis. Although we assumed non-evaluability of 30·0%, the statistical power to reach the primary objectives was not affected.

No stratification or minimisation was done according to disease stage or number of treatment lines received but, because of random assignment, these characteristics were probably evenly distributed between the study groups. Although confirmed herpes zoster cases were collected prospectively and subjected to robust case ascertainment, this study was not designed to evaluate efficacy. Because of the short follow-up period, our findings might not reflect long-term efficacy. Nonetheless, both immune responses and efficacy were assessed after administering adjuvanted recombinant zoster vaccine during or shortly after treatment, when the risk of herpes zoster is the greatest. Other strengths of this study are the geographical diversity and broad age range of the study population, and the inclusion of patients with a range of haematological malignancies who received immunosuppressive cancer treatments at different stages. Despite having severe underlying disease, a high percentage of initially enrolled participants completed the study.

In conclusion, the adjuvanted recombinant zoster vaccine elicited robust and persistent humoral and cell-mediated immune responses and showed an acceptable safety profile in adults with haematological malignancies when administered during or up to 6 months after immunosuppressive cancer treatment. A post-hoc analysis of confirmed herpes zoster cases suggests that the vaccine is efficacious in preventing herpes zoster. This immunocompromised adult population, which is at high risk of herpes zoster, is likely to benefit from the adjuvanted recombinant zoster vaccine, which is currently licensed in certain countries for adults aged 50 years and older.

Contributors

TCH, LO, and MEI were involved in the conception or design of the study. MA, SB, LC, T-JC, AFD, JdlS, J-YK, W-SL, ML-F, SAM, SM, JM, MBNM, DQ, SKS, DW, OI, GRM, EDP, and BS contributed to data collection or data generation. PVdS, MEI, LO, MA, LC, AFD, JdlS, ML-F, SAM, SM, GRM, AS, EDP, and BS contributed to data analysis or data interpretation. All authors reviewed the draft critically, approved the final version to be submitted, and take accountability for all aspects of the published work.

Declaration of interests

AFD, LC, EDP, MEI, ML-F, AS, PVdS, BS, TCH, and LO were employees of the GSK group of companies at the time this study was designed, initiated, and conducted. AFD, LC, EDP, MEI, ML-F, AS, PVdS, and BS are employed by GSK. LO is an employee of CureVac as of March 1, 2018, and is inventor on a patent application related to the vaccine used in this study. TCH was a paid consultant for GSK during the development of this manuscript and is the co-inventor of a patent application related to the vaccine used in this study. AS, AFD, EDP, LC, MEI, PVdS, LO, TCH, and BS hold shares or stock options in GSK as part of their current or former employee remuneration. SAM declares that her institution has a clinical trial contract with Novartis and has received research grants for conduct of clinical trials by GSK, Merck, Pfizer, and Sanofi Pasteur. SAM received honoraria for participation in scientific advisory boards from GSK, Pfizer, Sanofi Pasteur, and Merck, and for provision of accredited continuing medical education to health-care professionals on adult immunisation and zoster vaccines. JM reports grants from GSK during the conduct of the study and personal fees for participation in Roche Pharmaceuticals advisory boards. JM has received grants from Novartis and Chugai to support meeting attendance. All other authors declare no competing interests.

Data sharing

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com (study ID 116428).

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