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Immunogenicity, reactogenicity and safety of 2 doses of an adjuvanted herpes zoster subunit vaccine administered 2, 6 or 12 months apart in older adults: Results of a phase III, randomized, open-label, multicenter study

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ABSTRACT

Background: In phase III trials, 2 doses of a herpes zoster (HZ) subunit vaccine (HZ/su; 50 μg varicella-zoster virus glycoprotein E [gE] and AS01$_B$ Adjuvant System) administered 2-months apart in older adults (≥50 and ≥70 years) demonstrated >90% efficacy in preventing HZ and had a clinically acceptable safety profile. Here we report immunogenicity, reactogenicity and safety following administration of 2 HZ/su doses at intervals longer than 2 months.

Methods: In this Phase III, open-label trial conducted in the US and Estonia, 354 adults ≥50 years were randomized 1:1:1 to receive 2 HZ/su doses 2, 6, or 12 months apart. gE-specific humoral immune responses were evaluated at pre-vaccination, 1 and 12 months post-dose 2. Co-primary objectives were to compare immune responses to HZ/su 1 month post-dose 2 when given 6-months or 12-months apart to those administered 2-months apart. For each participant, safety information was collected from dose 1 to 12 months post-dose 2.

Results: 346 participants completed the study and 343 were included in the according-to-protocol cohort for immunogenicity. One month post-dose 2, vaccine response rates were 96.5% (97.5% confidence interval [CI]: 90.4; 99.2) and 94.5% (97.5% CI: 87.6; 98.3) for the 0, 6- and 0, 12-month schedules, respectively, both schedules meeting the pre-defined criterion. Non-inferiority of anti-gE geometric mean concentrations was demonstrated for HZ/su administered on 0, 6-month compared to a 0, 2-month schedule; however, HZ/su administered on a 0, 12-month schedule did not meet the non-inferiority criterion. Injection site pain was the most commonly reported solicited adverse event (AE). 26 participants each reported at least 1 serious AE; none were assessed as related to vaccination.

Conclusions: Immune responses to HZ/su administered at 0, 6-month were non-inferior to those elicited by a 0, 2-month schedule. HZ/su exhibited a clinically acceptable safety profile for all dosing intervals.
Clinical Trials Registration: Clinicaltrials.gov (NCT01751165).

1. Introduction

Herpes zoster (HZ; shingles) is caused by reactivation of latent varicella-zoster virus (VZV) and typically manifests as a localized, dermatomal rash [1,2]. Immunosenescence (age-dependent decrease in immunological competence) and immunodeficiency (caused by disease or medication) are the most important risk factors for developing HZ. The incidence of HZ at 50–59 years of age (YOA) is about 5 cases per 1000 persons per year, and it increases to 10 cases per 1000 persons per year in people ≥60 YOA [3,4]. Half of all HZ cases occur in people over 60 YOA, and it is estimated that

Abbreviations: VZV, varicella-zoster virus; gE, glycoprotein E; HZ, herpes zoster; HZ/su, HZ subunit vaccine containing 50 μg VZV gE and AS01$_B$ Adjuvant System; YOA, years of age; VE, vaccine efficacy; Gr, group; ELISA, enzyme-linked immunosorbent assay; mIU, milli-International Units; GMC, geometric mean concentration; VRR, vaccine response rate; CI, confidence interval; LL, lower limit; AE, adverse event; SAE, serious AE; pIMDs, potential immune-mediated diseases; TVC, total vaccinated cohort; ATP, according-to-protocol.

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individuals who live to be 85 years old have a 50% chance of having HZ during their lifetime [3].

In phase II studies, GSK's HZ subunit vaccine (HZ/su) was shown to be immunogenic when administered to adults ≥50 YOA as 2 doses, 2 months apart. Immune responses were higher after the second HZ/su dose than after the first dose in these trials [5,6]. In addition, humoral and cellular immune responses to HZ/su persisted substantially above pre-vaccination levels for 6 years [7].

In recent phase III clinical trials, the administration of 2 doses of HZ/su 2 months apart, significantly reduced the risk of HZ in adults ≥50 (ZOE-50) and ≥70 (ZOE-70) YOA. Vaccine efficacy (VE) in preventing HZ was 97.2% in adults ≥50 YOA (ZOE-50) and 91.3% in adults ≥70 YOA (pooled ZOE-50 and ZOE-70 data). In both trials VE was similar across age strata [8,9]. In all completed phase II and phase III studies, HZ/su was well tolerated and had a clinically acceptable safety profile [5–8].

For both the vaccine recipients and healthcare providers, the ability to increase the interval between doses provides more flexibility to complete the 2-dose schedule. Therefore, the current study assessed the immunogenicity, reactogenicity and safety of 2 doses of HZ/su administered to adults ≥50 YOA at 6- and 12-month intervals.

2. Methods

2.1. Study design and participants

This was a phase III, randomized, multicenter, open-label study (NCT01751165) conducted in the United States and Estonia between 12 March 2013 and 08 April 2015 (study overview in Fig. S1).

Adults ≥50 YOA were eligible for inclusion in the study. Female participants had to be of non-child bearing potential or have a negative pregnancy test on the day of vaccination and meet the contraceptive requirements as outlined in the protocol. Adults were excluded from participation in the study if they had taken any investigational or non-registered product other than the study vaccine, were administered or planned to receive a live or non-replicating vaccine for the protocol-specified time period, had a history of HZ, received previous vaccination against varicella or HZ, or had a history of reaction or hypersensitivity likely to be exacerbated by any component of the vaccine. Chronic administration of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose, or any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy also resulted in exclusion.

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol, amendments, and informed consent forms were reviewed and approved by Independent Ethics Committees.

2.2. Study vaccine

HZ/su contains 50 μg of the VZV recombinant purified glycoprotein E (gE) 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 LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation] and liposomes). Study participants received 2 HZ/su doses of 0.5 mL each by intramuscular injection.

2.3. Randomization and masking

This was an open-label study. Enrolled participants were randomized 1:1:1, to receive 2 doses of HZ/su according to a 0, 2-month (group [Gr] 0–2), 0, 6-month (Gr 0–6) or 0, 12-month (Gr 0–12) schedule, using an online centralized randomization system. The enrollment was age-stratified to ensure a balanced distribution of participants across three age strata (50–59 years, 60–69 years and ≥70 years).

2.4. Outcomes

The first co-primary objective of the study was to evaluate the vaccine response rates (VRRs) for anti-gE humoral immune responses at 1 month post-dose 2 in study groups Gr 0–6 and Gr 0–12, in participants ≥50 YOA. The objective for the 0, 6-month schedule was met if the lower limit (LL) of the 97.5% confidence interval (CI) of the VRR for anti-gE enzyme-linked immunosorbent assay (ELISA) antibody concentrations at 1 month post-dose 2 was ≥60%. Once met, this would allow analysis of the second co-primary objective: to assess the non-inferiority of anti-gE ELISA responses (based on geometric mean concentrations [GMCs]) for the Gr 0–6 study group. Non-inferiority was established if the upper limit of the 97.5% CI for the anti-gE ELISA GMC ratio (Gr 0–2 over Gr 0–6) at 1 month post-dose 2 was <1.5.

Similarly, the success criterion for the 0, 12-month schedule was met if the LL of the 97.5% CI of the VRR for anti-gE antibody concentrations at 1 month post-dose 2 was ≥60%. In that case the next second co-primary objective, non-inferiority based on the GMC ratio, could also be assessed for the 0, 12-month schedule; assessment was done in the same manner as for Gr 0–6.

Secondary objectives included the characterization of anti-gE humoral immune responses for all study groups at all sampling time points and the evaluation of safety and reactogenicity following administration of HZ/su.

2.5. Immunogenicity assessment

Blood samples for the assessment of the humoral immune responses to HZ/su (anti-gE antibody concentrations) were collected at baseline, 1 month post-dose 2 and for persistence at 12 months post-dose 2 (Fig. S1).

Anti-gE antibody concentrations were measured using an ELISA assay developed by GSK, with an assay cut-off of 97 milli-International Units (mIU)/mL. Participants with anti-gE antibody concentrations ≥97 mIU/mL were considered seropositive.

The VRR for anti-gE was defined as the percentage of study participants who had a ≥4-fold increase in the post-dose 2 anti-gE antibody concentration as compared to the pre-vaccination concentration (for initially seropositive participants) or as compared to the anti-gE antibody cut-off value for seropositivity (for initially seronegative participants).

2.6. Safety and reactogenicity assessment

Solicited local and general symptoms occurring within 7 days after each vaccination, and unsolicited adverse events (AEs), occurring within 30 days after each vaccination, were recorded. For all AEs, the Medical Dictionary for Regulatory Activities classification was used. All events were reported by the study participants on diary cards, which they had to return after completion.

The intensity of all AEs was graded on a scale from 1 to 3. Grade 3 solicited symptoms were defined as "preventing normal everyday activity" (pain, headache, fatigue, gastrointestinal symptoms, myalgia, shivering); surface diameter >100 mm (redness/swelling); tympanic/oral/axillary temperature >39.0 °C (fever). Grade 3 unsolicited AEs were also defined as "preventing normal, everyday activities".

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