Vaccine 35 (2017) 6700–6706

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A randomized lot-to-lot immunogenicity consistency study of the candidate zoster vaccine HZ/su

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ARTICLE INFO

Article history:
Received 13 July 2017
Received in revised form 5 October 2017
Accepted 6 October 2017
Available online 24 October 2017

Keywords:
Varicella-zoster virus
Recombinant subunit vaccine
Glycoprotein E
Lot consistency
Immunogenicity
Safety

ABSTRACT

Background: The risk of developing herpes zoster (HZ) increases with age and is thought to be associated with a decrease in cell-mediated immunity in older adults. The adjuvanted varicella-zoster virus (VZV) glycoprotein E (gE) recombinant subunit vaccine (HZ/su) showed >90% efficacy in the prevention of HZ when administered in adults ≥50 years of age. Here we aim to evaluate immunogenicity consistency of 3 different HZ/su vaccine lots and to assess safety of these lots.

Methods: This multicenter, phase III, double-blind, randomized study (NCT02075515), assessed lot-to-lot consistency in terms of immunogenicity of HZ/su and also assessed safety of these lots. Participants aged 50 years or older were randomized (1:1:1) to receive 2 doses of HZ/su, 2 months apart, from 1 out of 3 randomized HZ/su lots (Lots A, B and C). Humoral immunogenicity was assessed pre-vaccination and 1 month post-second vaccination by anti-gE antibody enzyme-linked immunosorbent assay. Lot-to-lot consistency was demonstrated if the 2-sided 95% confidence intervals of the anti-gE geometric mean concentration ratio between all lot pairs were within 0.67 and 1.5. Solicited symptoms were recorded within 7 days and unsolicited adverse events (AEs) within 30 days after each vaccination. Serious AEs (SAEs) and potential immune-mediated diseases (pIMDs) were reported until study end (12 months post-second vaccination).

Results: Of 651 participants enrolled in the study, 638 received both doses of the HZ/su vaccine and 634 completed the study. Humoral immune responses were robust and consistency between 3 manufacturing lots was demonstrated. The incidence of solicited symptoms, unsolicited AEs and SAEs was comparable between all lots. Three fatal SAEs, 1 in each lot, were reported, none of which were considered vaccine-related by investigator assessment. Two out of the 8 reported pIMDs were considered vaccine-related by the investigator.

Conclusion: The three HZ/su manufacturing lots demonstrated consistent immunogenicity. No safety concerns were identified.

Clinical trial registry number: NCT02075515 (ClinicalTrials.gov).

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; ATP, according-to-protocol; CI, confidence interval; CMI, cell-mediated immunity; ELISA, enzyme-linked immunosorbent assay; gE, glycoprotein E; GMC, geometric mean concentration; HZ, herpes zoster; HZ/su, recombinant subunit herpes zoster vaccine; PHN, postherpetic neuralgia; pIMD, potential immune-mediated disease; SAE, serious adverse event; TVC, total vaccinated cohort; VRR, vaccine response rate; VZV, varicella-zoster virus; YOA, years of age.

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https://doi.org/10.1016/j.vaccine.2017.10.017
0264-410X/

Focus on the patient section

What is the context?

Varicella-zoster virus, the virus that causes chickenpox, remains life-long in the body after the initial infection. Although it may remain silent, it can also reactivate later in life and present itself as the disease known as herpes zoster (shingles), which patients typically experience as a painful rash. The risk of shingles increases with age and more substantially as of 50 years of age. A non-live herpes zoster (HZ) candidate vaccine (HZ/su) against shingles has recently been developed and the regulatory registration file is currently being assessed by a number of regulatory agencies worldwide.

What is new?

This clinical study was conducted to evaluate consistency of humoral immune responses in different HZ/su manufacturing lots. In participants aged 50 years or older the three HZ/su vaccine lots demonstrated acceptable safety profile and consistent humoral immune responses.

What is the impact?

In conjunction with technical comparability studies indicating that commercial manufacturing of HZ/su is largely similar to clinical manufacturing, this data suggests that HZ/su lots can be consistently manufactured.

1. Introduction

Herpes zoster (HZ) results from symptomatic reactivation of latent varicella-zoster virus (VZV) and typically manifests as a painful vesicular rash in a single unilateral dermatome [1]. The risk of HZ increases with age from 2–4 cases per 1000 person-years in adults under 50 years of age (YOA) [2] to 3–9 cases per 1000 person-years in adults 50–59 YOA, 6–12 cases per 1000 person-years in adults 60–69 YOA, 7–14 cases per 1000 person-years in adults 70–79 YOA and 8–15 cases per 1000 person-years in adults over 80 YOA [2,3]. Postherpetic neuralgia (PHN), the most common complication of HZ, is defined as a clinically significant pain that persists after the resolution of the HZ rash [4]. PHN lasts up to 2 years in 15% of HZ patients and 22–46% of HZ patients report PHN lasting between 2 and 10 years after resolution of HZ [2,5].

Protection from VZV reactivation is thought to be primarily driven by cell-mediated immunity (CMI) [6]. The adjuvanted VZV glycoprotein E (gE) recombinant subunit vaccine (HZ/su) has shown 97.2% efficacy against HZ in adults 50 years and older and 91.3% in adults over 70 YOA [7,8]. Moreover, no safety concerns have been identified [7–11]. Effective vaccination can boost VZV-specific CMI and vaccination with HZ/su might therefore be a cost-effective strategy to prevent HZ [12].

For regulatory approval, manufacturing consistency of the HZ/su candidate has to be demonstrated [13,14]. Although vaccine efficacy is most likely driven by the CMI responses to HZ/su, humoral response to HZ/su can be used in comparative studies because it provides highly reproducible results by well-established methods. CMI assays yield highly variable results and are therefore not well-suited for consistency evaluation. Moreover, CMI testing on large scale is logistically challenging to perform because it requires large volumes of blood and complicated preparation, storage and laboratory analyses. Antibody responses have thus been previously proposed as suitable immunogenicity marker for comparative studies of a zoster vaccine [15].

In this phase III study, we therefore assessed lot-to-lot consistency of 3 lots of the HZ/su candidate vaccine in terms of anti-gE immune responses 1 month after the second vaccine dose and safety of all 3 lots was assessed during the entire study period (12 months after the second vaccine dose).

2. Methods

2.1. Study design and participants

A phase III, double-blind, randomized, multicenter, lot-to-lot consistency study with 3 parallel groups was conducted in Belgium, Canada and the United States.

Study participants were aged 50 years or older at the time of the first vaccination.

A complete list of exclusion criteria is presented in Supplement A and includes participants who used or were planning to use any investigational or non-registered product other than the study vaccine within 30 days before the first dose of study vaccine, who were administered or expected administration of immunosuppressants for more than 14 consecutive days or other immune-modifying drugs within 6 months prior to the first vaccine dose or during the study period, or who were administered or planned administration of a live vaccine 30 days prior to the first dose of study vaccine and 30 days after the last dose of study vaccine.

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 national/regional Independent Ethics Committees.

The study is registered at ClinicalTrials.gov (NCT02075515) and available at http://www.gsk-clinicalstudyregister.com (study ID: 117177).

2.2. Study vaccines

Study participants received 2 intramuscular doses of HZ/su, 2 months apart (Month 0 and 2).

Each dose of HZ/su contains 50 μg of the VZV gE antigen and the GSK proprietary $AS01_B$ Adjuvant System (containing 50 μg of 3-O-desacyl-4′-monophosphoryl lipid, 50 μg of *Quillaja saponaria Molina*, fraction 21 [QS-21, Licensed by GSK from Antigenics LLC, a wholly owned 167 subsidiary of Agenus Inc., a Delaware, USA corporation] and liposome).

Three lots of HZ/su (Lot A, Lot B, Lot C) were manufactured from 3 consecutive $AS01_B$ adjuvant lots randomly combined with 1 of 3 consecutive gE antigen lots.

2.3. Randomization and masking

Enrolled participants were randomized (1:1:1), using a web-based central randomization system, to receive 2 doses from 1 out of the 3 lots (Lot A, Lot B, Lot C).

The randomization algorithm accounted for study center and participant age (50–59 years, 60–69 years and ≥70 years) to ensure equal distribution.

2.4. Outcomes

The primary objective of the study was to demonstrate lot-to-lot consistency of 3 HZ/su lots, as measured by anti-gE geometric mean concentrations (GMCs) 1 month after the second dose (Month 3) and was considered met if the 2-sided 95% confidence intervals (CIs) of the GMC ratio between all lot pairs were within 0.67 and 1.5.

The secondary objectives for this study were to demonstrate lot-to-lot consistency of 3 HZ/su lots, as measured by anti-gE antibody vaccine response rates (VRRs), to characterize the anti-gE antibody response for all lots at Months 0 and 3, and to evaluate the safety and reactogenicity of the HZ/su. Lot-to-lot consistency in VRRs was considered demonstrated if the 2-sided 95% CIs on the difference in VRRs for all lot pairs at Month 3 were within −10% and 10%.

2.5. Immunogenicity assessment

Blood samples were taken from participants at pre-vaccination and 1 month post-dose 2.

Serum anti-gE antibody concentrations were measured by an in-house enzyme-linked immunosorbent assay (ELISA) with a cut-off of 97 mIU/mL. A participant with an antibody concentration greater than or equal to the cut-off value was considered VZV 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 (pain, redness, swelling) and general symptoms (fatigue, fever [oral temperature ≥37.5 °C], gastrointestinal symptoms [nausea, vomiting, diarrhea, and/or abdominal pain], headache, myalgia, shivering) were recorded up to 7 days (days 0–6) after each HZ/su vaccination. Grade 3 solicited symptoms were defined as AEs preventing normal activity. All solicited local (injection site) reactions were considered causally related to vaccination. Causality of all other AEs was assessed by the investigator.

Unsolicited adverse events (AEs) were recorded up to 30 days (days 0–29) post-vaccination.

Serious adverse events (SAEs) and potential immune-mediated diseases (pIMDs), were recorded from first receipt of study vaccine until study end (12 months post-dose 2).

Suspected HZ was defined as a new rash characteristic of HZ (unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations). A suspected HZ case was clinically diagnosed and based on investigator judgment.

Complications of HZ were also collected throughout the study. At day 0, all participants were informed of the signs and symptoms of typical HZ.

The occurrence of HZ and/or HZ complications constituted an AE/SAE as appropriate.

2.7. Statistical analyses

The statistical analyses were performed using the SAS version 9.2 on Windows and StatXact-8.1 procedure for SAS.

The primary analysis was based on the according-to-protocol (ATP) cohort for immunogenicity. If, in any vaccine group, the percentage of vaccinated participants with serological results excluded from the ATP cohort for immunogenicity was 5% or more, a second analysis based on total vaccinated cohort (TVC) was performed to complement the ATP analysis.

To assess the primary objective (lot-to-lot consistency in terms of GMC), 95% CIs of the GMC ratios of anti-gE antibodies 1 month post-dose 2 were computed for each pair of vaccine lots (Lot A vs Lot B, Lot A vs Lot C, Lot B vs Lot C), using an analysis of covariance (ANCOVA) model on the $\log_{10}$ transformation of the anti-gE concentrations. The ANCOVA model included the vaccine group as fixed effect and the pre-vaccination $\log_{10}$-transformed concentration as the regressor. Lot-to-lot consistency in terms of VRR was assessed by computing the asymptotic standardized 95% CIs for the pair-wise VRR differences of anti-gE antibodies 1 month post-dose 2.

Safety and reactogenicity were analyzed in all participants who received at least one vaccine dose. Demographic characteristics, cohort description, withdrawal status were summarized by group using descriptive statistics.

Information regarding the determination of sample size is presented as supplementary material (Supplement B).

3. Results

3.1. Demographics

This study was conducted between August 13, 2014 and April 25, 2016 and enrolled 651 adults, of whom 638 (98.0%) received both vaccinations and 634 completed the study (Fig. 1). The second dose compliance was similar among the groups.

There were more female (360; 55%) than male participants (291; 45%), but the female:male ratio did not substantially differ between treatment arms. The mean age of participants at first vaccination was 64.5 years, most participants were of white Caucasian heritage (93.7%) and demographic characteristics were comparable between groups. A complete summary of demographic characteristics is provided in Table 1.

3.2. Immunogenicity

Anti-gE antibody concentrations increased markedly after vaccination with any of the HZ/su lots (Table 2). As a result of the lower anti-gE antibody GMCs in Lot B at pre-vaccination while post-vaccination GMCs were similar between groups, the mean geometric increase was higher in that group (Table 2).

VRR for anti-gE antibody ELISA concentrations at 1 month post-dose 2 for all 3 lots were between 95.7–97.6% and are presented in Table 3.

Lot consistency based on humoral immunogenicity was demonstrated, as the 95% CIs of the GMC ratios of anti-gE antibody concentrations 1 month after the second dose were between 0.67 and 1.5 for all treatment pairs (Table 4), and the 2-sided 95% CIs for VRRs on the lot differences were within the −10% to 10% range (Table 4).

As 6.5% (≥5%) of the participants were excluded from the ATP cohort for immunogenicity in Lot C, comparison of humoral immune responses was also done on the TVC. The results were consistent with the ATP analyses (data not shown).

3.3. Safety and reactogenicity

The percentage of participants with solicited symptoms in the 7-day period following vaccination was comparable between lots (Table 5).

Injection site pain was the most frequently (86.0–90.3%) reported solicited local symptom following vaccination with all 3 lots of HZ/su. Myalgia was the most frequently (52.3–59.0%) reported solicited general symptom. The median duration of symptoms was 3 days or less for local symptoms and 2 days or less for general symptoms. The percentage of participants reporting unsolicited AEs within the 30-day post-vaccination period was also comparable between the 3 lots (Table 5).

During the study, 86 SAEs were reported by 47 participants. In Lot A, 13 (6.0%) participants reported 26 SAEs. One fatal SAE (acute myocardial infarction) was reported 23 days post-dose 1. In Lot B,

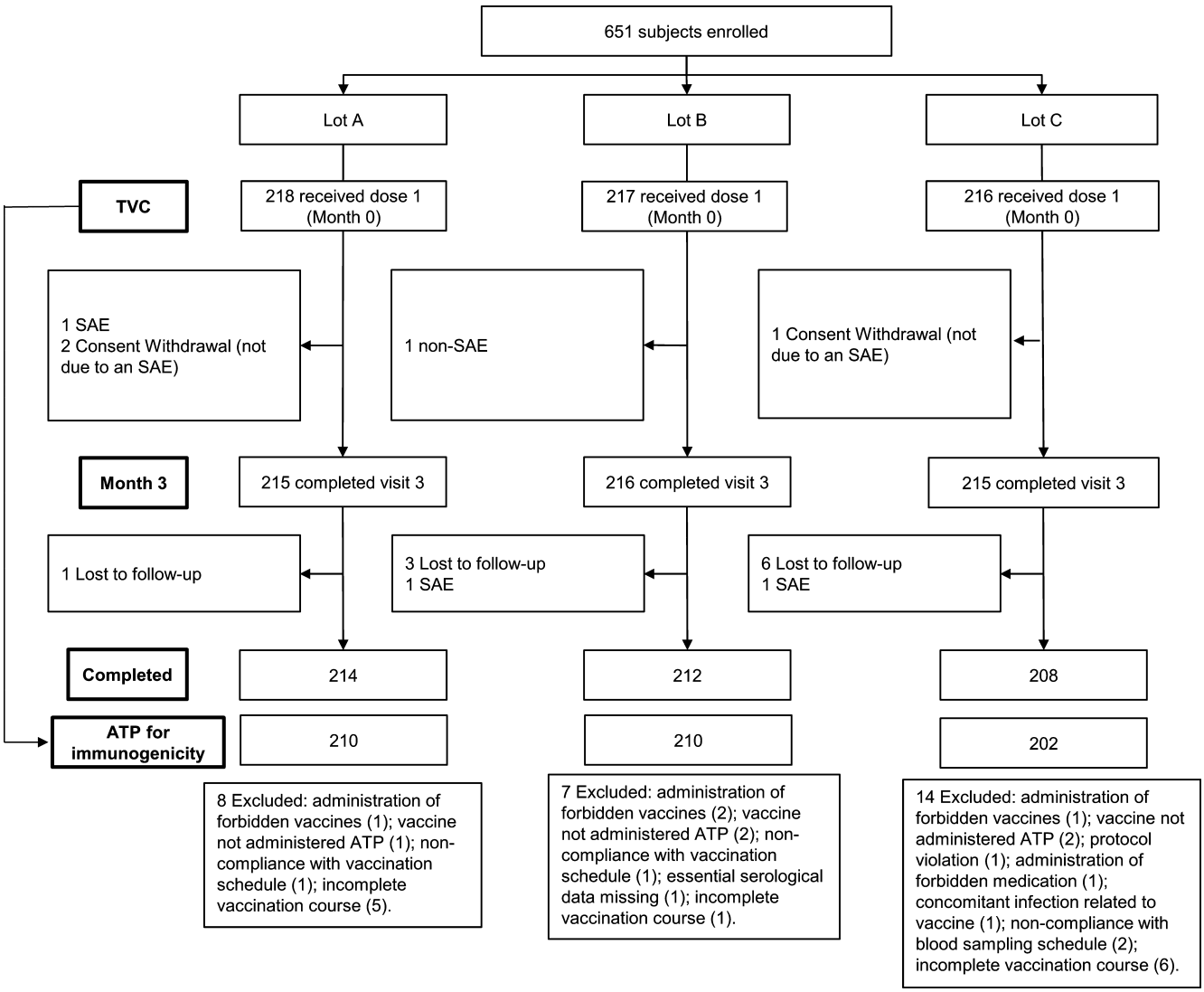

Fig. 1. Flow of participants[1].

14 (6.5%) participants reported 30 SAEs, with 1 fatal SAE (attributed to Parkinson's disease, 160 days post-dose 2). In Lot C, 20 (9.3%) participants reported 30 SAEs, with 1 fatal SAE (necrotizing pancreatitis, 300 days post-dose 1). No SAE was considered related to vaccination by the investigator.

During the study 8 pIMDs were reported by 8 participants (Table 5). One pIMD, a case of neuromyelitis optica spectrum disorder, in a participant receiving Lot C, was considered as SAE. This SAE was not considered related to vaccination by the study investigator. All other reported pIMDs were not considered serious. Two pIMDs reported in participants receiving Lot A were considered related to vaccination by the investigator. A detailed description of all pIMDs is provided in Supplementary Table S1.

One case of suspected HZ was reported 4 days after the second vaccination in a participant receiving Lot C. The case was considered vaccine-related by the investigator and resolved after 31 days.

4. Discussion

In this phase III double-blind, randomized, multicenter study, we demonstrate that 3 lots of the HZ/su vaccine produced consistent humoral immune responses following 2 doses of the vaccine.

The primary objective of the study was met as the 95% CIs of the adjusted anti-gE antibody GMC ratio between lots were within the pre-specified range showing that the HZ/su vaccine immunogenicity is consistent between the lots. The data indicate that vaccine lots can be consistently manufactured, which is a regulatory requirement for provision of vaccines.

Post-vaccination anti-gE antibody concentrations were greatly increased over pre-vaccination concentrations in recipients of all lots, and increases were of a magnitude comparable to another trial [10]. The goal of our study was to demonstrate immunological consistency, and as such it was justified to assess the humoral rather than the CMI response, since the anti-gE ELISA is a highly reproducible method and does not require the more complicated sample preparation needed to assess the CMI response.

There were no safety concerns in this study and reactogenicity was comparable between vaccine lots. In addition, the incidence of solicited reactions after vaccination was comparable to data from previous clinical trials, with injection site pain [8–10] and myalgia [9,10] as the most frequently reported local and systemic reactions, respectively. Reactions were transient, less than 3 days for local symptoms and less than 2 days for general symptoms. The compliance with the second vaccine dose was high. The frequency of SAEs

[1] Footnote: TVC, total vaccinated cohort; ATP; According-to-protocol; SAE, serious adverse event.

Table 1
Demographic characteristics (total vaccinated cohort).

Characteristics	Lot A (N = 218)	Lot B (N = 217)	Lot C (N = 216)	Total (N = 651)
Age (years)				
Mean (SD)	64.8 (8.8)	64.3 (9.4)	64.4 (8.8)	64.5 (9.0)
Median (min, max)	65.0 (50.0–89.0)	65.0 (50.0–91.0)	65.0 (49.0–87.0)	65.0 (49.0–91.0)
Gender, n (%)				
Female	116 (53.2)	130 (59.9)	114 (52.8)	360 (55.3)
Ethnicity, n (%)				
Not American, Hispanic or Latino	217 (99.5)	214 (98.6)	213 (98.6)	644 (98.9)
American, Hispanic or Latino	1 (0.5)	3 (1.4)	3 (1.4)	7 (1.1)
Geographic ancestry, n (%)				
White Caucasian/European Heritage	206 (94.5)	202 (93.1)	202 (93.5)	610 (93.7)
African Heritage/African American	5 (2.3)	8 (3.7)	4 (1.9)	17 (2.6)
Asian-South East Asian Heritage	7 (3.2)	4 (1.8)	8 (3.7)	19 (2.9)
Other	–	3 (1.4)	2 (0.9)	5 (0.8)

Footnote: SD, standard deviation; min, minimum; max, maximum; N, number of participants per lot/total; n (%), number (percentage) of participants in a given category.

Table 2
Anti-gE antibody concentrations before and after vaccination with HZ/su (ATP cohort for immunogenicity).

HZ/su	N	Month 0 (Pre)		Month 3		MGI	LL–UL
		GMC	LL–UL	GMC	LL–UL		
Lot A	210	1378.4	1180.0–1610.0	59556.1	54587.6–64976.7	43.2	36.6–51.0
Lot B	210	1166.5	1005.5–1353.4	60733.8	55995.2–65873.3	52.1	44.1–61.4
Lot C	202	1381.2	1190.9–1601.9	62058.3	57422.3–67068.7	44.9	38.3–52.7

Footnote: ATP, According-to-protocol; Month 0 (Pre), pre-vaccination results; Month 3, 1 month post-dose 2, post-vaccination results; HZ/su, Herpes Zoster subunit vaccine; N, number of participants with pre and post-vaccination results available; GMC, geometric mean concentration; MGI, mean geometric increase (M3/M0 [Pre]); LL, lower limit; UL, upper limit.
Immunogenicity assessment was done on the ATP cohort for all lots, a TVC analysis, which was consistent with the ATP cohort for immunogenicity analysis, was also performed because in Lot C ≥5% of the participants were excluded from ATP (data not shown).

Table 3
Vaccine response rates for anti-gE antibody ELISA concentrations at 1 month post-dose 2 (ATP cohort for immunogenicity).

HZ/su	N	Vaccine response		
		n	%	95% CI (LL–UL)
Lot A	210	201	95.7	92.0–98.0
Lot B	210	205	97.6	94.5–99.2
Lot C	202	197	97.5	94.3–99.2

Footnote: ATP, According-to-protocol; ELISA, enzyme-linked immunosorbent assay; N, number of participants with both pre- and post-vaccination results available; n/%, number/percentage of responders; CI, confidence interval.

Table 4
Lot-to-lot comparisons for adjusted anti-gE antibody concentrations and vaccine response rates in terms of the anti-gE antibody ELISA concentrations at 1 month post-dose 2 (ATP cohort for immunogenicity).

	Adjusted GMC ratio (95% CI)		VRR difference (95% CI)
Lot A/Lot B	0.97 (**0.86–1.09**)	Lot A–Lot B	−1.90 (−**5.86 to 1.72**)
Lot A/Lot C	0.96 (**0.85–1.08**)	Lot A–Lot C	−1.81 (−**5.79 to 1.92**)
Lot B/Lot C	0.99 (**0.88–1.10**)	Lot B–Lot C	0.09 (−**3.30 to 3.58**)

Footnote: ELISA, enzyme-linked immunosorbent assay; ATP, According-to-protocol; GMC, geometric mean concentration; CI, confidence interval; VRR, vaccine response rate.
Immunogenicity assessment was done on the ATP cohort for all lots, a TVC analysis, which was consistent with the ATP analysis, was also performed because in Lot C ≥5% of the participants were excluded from ATP (data not shown).
Note: The adjusted GMC ratios are calculated using the ANCOVA model including the vaccine group as fixed effect and the pre-vaccination $\log_{10}$ transformed concentration as regressor. Bolded values indicate the non-inferiority criterion was met.

reported in this study did not differ between recipients of the different vaccine lots, and none were considered vaccine-related by the investigator.

There are theoretical concerns regarding potential associations between vaccine adjuvants and pIMDs [16], although only limited empirical support exists for an association [17]. The frequency of pIMDs reported in the phase III ZOE trials did not differ between HZ/su and saline placebo-recipients and pIMDs frequency as well as percentage of participants reporting pIMDs in this study were similar with data reported in ZOE trials [8].

The study was well-powered to show immunological consistency of the vaccine lots, and the randomization of both the antigen and adjuvant lots to the different lots adds to the validity of our findings.

In conclusion, this study demonstrates lot-to-lot consistency of HZ/su vaccine lots, with the vaccine inducing a strong and

Table 5
Percentage of participants reporting solicited AEs (7 days post-vaccination), unsolicited AEs (30 days post-vaccination), SAEs and pIMDs (from first vaccination until study end) (total vaccinated cohort).

		Lot A % (95% CI)		Lot B % (95% CI)		Lot C % (95% CI)
Solicited AEs	n	N = 217	n	N = 217	n	N = 216
Any	200	92.2 (87.8–95.4)	200	92.2 (87.8–95.4)	195	90.3 (85.5–93.9)
Grade 3	48	22.1 (16.8–28.2)	40	18.4 (13.5–24.2)	33	15.3 (10.8–20.8)
Local AEs		N = 217		N = 217		N = 215
Injection site pain						
Any	188	86.6 (81.4–90.9)	196	90.3 (85.6–93.9)	185	86.0 (80.7–90.4)
Grade 3	22	10.1 (6.5–14.9)	16	7.4 (4.3–11.7)	13	6.0 (3.3–10.1)
Redness						
Any	52	24.0 (18.4–30.2)	68	31.3 (25.2–38.0)	62	28.8 (22.9–35.4)
Grade 3	4	1.8 (0.5–4.7)	3	1.4 (0.3–4.0)	3	1.4 (0.3–4.0)
Swelling						
Any	38	17.5 (12.7–23.2)	44	20.3 (15.1–26.2)	39	18.1 (13.2–24.0)
Grade 3	3	1.4 (0.3–4.0)	1	0.5 (0.0–2.5)	2	0.9 (0.1–3.3)
General AEs		N = 217		N = 217		N = 216
Fatigue						
Any	114	52.5 (45.7–59.3)	109	50.2 (43.4–57.1)	107	49.5 (42.7–56.4)
Grade 3	18	8.3 (5.0–12.8)	11	5.1 (2.6–8.9)	10	4.6 (2.2–8.3)
Gastrointestinal symptoms						
Any	46	21.2 (16.0–27.2)	45	20.7 (15.5–26.7)	50	23.1 (17.7–29.4)
Grade 3	3	1.4 (0.3–4.0)	2	0.9 (0.1–3.3)	9	4.2 (1.9–7.8)
Headache						
Any	101	46.5 (39.8–53.4)	108	49.8 (42.9–56.6)	89	41.2 (34.6–48.1)
Grade 3	13	6.0 (3.2–10.0)	13	6.0 (3.2–10.0)	9	4.2 (1.9–7.8)
Myalgia						
Any	128	59.0 (52.1–65.6)	119	54.8 (48.0–61.6)	113	52.3 (45.4–59.1)
Grade 3	24	11.1 (7.2–16.0)	12	5.5 (2.9–9.5)	10	4.6 (2.2–8.3)
Shivering						
Any	80	36.9 (30.4–43.7)	67	30.9 (24.8–37.5)	60	27.8 (21.9–34.3)
Grade 3	12	5.5 (2.9–9.5)	7	3.2 (1.3–6.5)	7	3.2 (1.3–6.6)
Temperature						
Any	59	27.2 (21.4–33.6)	49	22.6 (17.2–28.7)	43	19.9 (14.8–25.9)
Grade 3	2	0.9 (0.1–3.3)	0	0.0 (0.0–1.7)	1	0.5 (0.0–2.6)
Unsolicited AEs		N = 218		N = 217		N = 216
Any	72	33.0 (26.8–39.7)	69	31.8 (25.7–38.4)	76	35.2 (28.8–42.0)
Grade 3	13	6.0 (3.2–10.0)	15	6.9 (3.9–11.1)	9	4.2 (1.9–7.8)
Related to vaccination	23	10.6 (6.8–15.4)	22	10.1 (6.5–14.9)	27	12.5 (8.4–17.7)
Grade 3-related to vaccination*	6	2.8 (1.0–5.9)	3	1.4 (0.3–4.0)	3	1.4 (0.3–4.0)
		N = 218		N = 217		N = 216
SAEs	13	6.0 (3.2–10.0)	14	6.5 (3.6–10.6)	20	9.3 (5.7–13.9)
pIMDs	5	2.3 (0.7–5.3)	0	0.0 (0.0–1.7)	3	1.4 (0.3–4.0)

Footnote: N, number of participants per lot; n, number of participants in a given category; %, percentage of participants in a given category; CI, confidence interval; AE, adverse event; SAE, serious adverse event; pIMD, potential immune-mediated disease. Grade 3 redness and swelling was a surface diameter >100 mm, grade 3 temperature was considered >39.0 °C. *By investigator assessment.

consistent humoral immune response after 2 doses of HZ/su. No safety concerns were identified.

Funding

GlaxoSmithKline Biologicals SA was the funding source and was involved in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals SA also took responsibility for all costs associated with the development and publishing of the present manuscript.

Author's contributions

HL, IV, OG, and TCH conceived and designed the study. AS, GLR, HL, MLF, NA, OG, PVD, TCH collected or generated study data. AS, GLR, HL, NA, OG, PVD, TCH performed the study. AS, CVA, GLR, HL, IV, MLF, PVD, TCH were involved in the analyses or interpretation of the data. All authors contributed to the writing/reviewing of the paper and approved the final version for submission.

Conflict of interest

AS, CVA, IV and MLF are GSK employees. AS and IV own stock options as part of their employee remuneration. HL, OG and TCH were employed by GSK at time of study conduct. HL and TCH received stock as part of their employee remuneration. TCH is co-inventor of the patent application related to the vaccine used in this study and is currently a consultant for the GSK group of companies. OG owns shares in GSK. GLR and PVD report that their institutes received grants from GSK to compensate study costs. PVD is

also an investigator in other vaccine trials from several vaccine companies for which his institute receives research grants. NA has nothing to disclose.

Acknowledgments

The authors would like to thank all study participants as well as the contribution of Aerssens Annelies, De Boever Fien and Maes Cathy (Ghent University, Ghent, Belgium), Campora Laura (GSK, Wavre, Belgium), De Coster Ilse and Suykens Leen (University of Antwerp, Antwerp, Belgium), Elsafy Fatiha (GSK, Rockville, US), Girard Ginette (Diex Research Sherbrook, Sherbrook, Canada), Guerra-Karekides Helena Denise (GSK, Ciudad Panama, Panama), Galgani Ilaria (GSK, Siena, Italy), McCloskey Natali (GSK, New Jersey, US), Poling Terry (Heartland Research Associates, Kansas, Wichita, US), Puopolo Anthony (Milford Emergency Associates, Inc., Massachusetts, Milford, US), Ramachandran Girish (Tata Consultancy Services on behalf of GSK), Shu Daniel (Gain Medical Center, British Columbia, Canada).

Medical writing services were provided by Jarno Jansen and Maria Cornelia Maior (XPE Pharma & Science on behalf of GSK). Editorial assistance and publication coordination were provided by Sara Blancquaert (XPE Pharma & Science on behalf of GSK).

Previous Publications: The results of this study were not presented previously.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2017.10.017.

References

[1] Cohen JI. Clinical practice: herpes zoster. N Engl J Med 2013;369:255–63.
[2] Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open 2014;4.
[3] Pinchinat S, Cebrian-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis 2013;13:170.
[4] Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007: S1–S26.
[5] Johnson RW, Rice ASC. Postherpetic neuralgia. N Engl J Med 2014;371:1526–33.
[6] Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol 2010;48(Suppl 1):S2–7.
[7] Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015;372:2087–96.
[8] Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Diez-Domingo J, et al. Efficacy of the Herpes Zoster subunit vaccine in adults 70 years of age or older. N Engl J Med 2016;375:1019–32.
[9] Chlibek R, Bayas JM, Collins H, de la Pinta ML, Ledent E, Mols JF, et al. Safety and immunogenicity of an AS01-adjuvanted varicella-zoster virus subunit candidate vaccine against herpes zoster in adults ≥50 years of age. J Infect Dis 2013;208:1953–61.
[10] Chlibek R, Smetana J, Pauksens K, Rombo L, Van den Hoek JAR, Richardus JH, et al. Safety and immunogenicity of three different formulations of an adjuvanted varicella-zoster virus subunit candidate vaccine in older adults: a phase II, randomized, controlled study. Vaccine 2014;32:1745–53.
[11] Leroux-Roels I, Leroux-Roels G, Clement F, Vandepapeliere P, Vassilev V, Ledent E, et al. A phase 1/2 clinical trial evaluating safety and immunogenicity of a varicella zoster glycoprotein e subunit vaccine candidate in young and older adults. J Infect Dis 2012;206:1280–90.
[12] Weinberg A, Zhang JH, Oxman MN, Johnson GR, Hayward AR, Caulfield MJ, et al. Varicella-Zoster Virus–specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. J Infect Dis 2009;200:1068–77.
[13] European Medicine Agency Products. Committee for human medicinal products. Note for guidance on the clinical evaluation of vaccines Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003875.pdf> [accessed January 10, 2017].
[14] World Health Organization. Clinical considerations for evaluation of vaccines for prequalification. Available at: <http://www.who.int/entity/immunization_standards/vaccine_quality/clinical_considerations_oct10.pdf> [accessed January 10, 2017]
[15] Levin MJ, Schmader KE, Gnann JW, McNeil SA, Vesikari T, Betts RF, et al. Varicella-Zoster Virus–specific antibody responses in 50–59-year-old recipients of zoster vaccine. J Infect Dis 2013;208:1386–90.
[16] Agmon-Levin N, Kivity S, Shoenfeld Y. Influenza vaccine and autoimmunity. Isr Med Assoc J 2009;11:183–5.
[17] Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? Int Rev Immunol 2010;29:247–69.