IMMUNOGENICITY AND SAFETY OF 2 DOSES OF A CANDIDATE HERPES ZOSTER SUBUNIT VACCINE ADMINISTERED 2, 6 OR 12 MONTHS APART IN ADULTS 50 YEARS AND OLDER: RESULTS OF A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER TRIAL

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BACKGROUND AND AIM

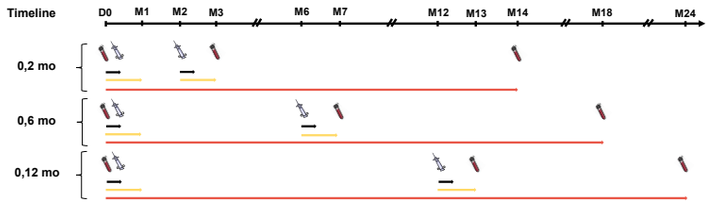
- Herpes zoster (HZ) is caused by the reactivation of latent varicella-zoster virus (VZV) and typically occurs as a localized, dermatomal rash.[1,2]
- HZ incidence increases from 50 years of age (YOA), presumably due to age-related decline in VZV-specific cellular immunity.[1,2]
- Two doses of GSK Vaccines' candidate HZ subunit vaccine (HZ/su, containing recombinant VZV glycoprotein E [gE] and $AS01_B$ Adjuvant System) administered 2 months apart in adults ≥50 YOA demonstrated >89% efficacy in preventing HZ and had a clinically acceptable safety profile.[3,4]
- Here, we report the results of a study conducted to evaluate the immunogenicity and safety of two HZ/su doses administered 6 and 12 months apart. We also report the formal non-inferiority comparison between the extended schedules versus the standard 2 months apart vaccine administration schedule.

METHODS

Study design and participants

- In this phase III, open-label trial (NCT01751165) conducted in the United States and Estonia, adults ≥50 YOA were randomized 1:1:1 to receive two intramuscular doses of HZ/su administered 2, 6 or 12 months apart (0,2-mo; 0,6-mo; 0,12-mo groups) (**Figure 1**).

Figure 1. Study design



D, day; **M**, month; **0,2-mo, 0,6-mo, 0,12-mo groups**, subjects vaccinated according to a 0,2-; 0,6-; or 0,12-month schedule; , blood sampling for immunogenicity assessment; , HZ/su vaccination; ➡, solicited adverse events (AEs) reporting (within 7 days after each vaccination); ⇒, unsolicited AEs reporting (within 30 days after each vaccination); ➡, serious AEs and potential immune-mediated diseases reporting (from first dose vaccination up to 12 months post-dose 2)

Vaccine composition

- Each HZ/su dose contained 50 µg of VZV gE and AS01B Adjuvant System (containing 50 µg of 3-*O*-desacyl-4'-monophosphoryl lipid A [MPL, produced by GSK], 50 µg of *Quillaja saponaria* Molina, fraction 21 [QS-21, licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation] and liposomes).

Study objectives

Co-primary:

- To evaluate the vaccine response rate (VRR) for anti-gE humoral immune responses 1 month post-dose 2 in the 0,6-mo and 0,12-mo groups. *Criterion*: lower limit (LL) of the 97.5% confidence interval (CI) of VRR ≥60%.
  - ➤ If the objective was met for the 0,6-month schedule:
    - To demonstrate non-inferiority in terms of anti-gE humoral immune responses 1 month post-dose 2 in the 0,6-mo versus 0,2-mo group. *Criterion*: upper limit (UL) of the 97.5% CI of geometric mean concentration (GMC) ratio (0,2-mo over 0,6-mo schedule) <1.5.
  - ➤ If the objective was met for the 0,12-month schedule:
    - To demonstrate non-inferiority in terms of anti-gE humoral immune responses 1 month post-dose 2 in the 0,12-mo versus 0,2-mo group. *Criterion*: UL of the 97.5% CI of GMC ratio (0,2-mo over 0,12-mo schedule) <1.5.

Secondary:

- To characterize anti-gE humoral immune responses for all groups at all timepoints.
- To evaluate HZ/su safety and reactogenicity.

Immunogenicity assessment

- Blood samples for the assessment of humoral immune responses to the HZ/su vaccine (anti-gE enzyme-linked immunosorbent assays [ELISA]) were collected at pre-vaccination, 1 month post-dose 2 and 12 months post-dose 2.
- Anti-gE VRR was defined as the percentage of subjects with a ≥4-fold increase in the anti-gE antibody concentration at 1 month post-dose 2 as compared to the pre-vaccination concentration (for initially seropositive subjects) or ≥4-fold increase as compared to the seropositivity cut-off (97 mIU/mL) (for initially seronegative subjects).

Safety and reactogenicity assessment

- Solicited and unsolicited adverse events (AEs) were recorded between days 0-6 and 0-29 post-each dose, respectively.
- Serious AEs (SAEs) and potential immune-mediated diseases (pIMDs) were reported from dose 1 up to 12 months post-dose 2.

RESULTS

Study participants

- Of the 354 vaccinated subjects, 343 were included in the according-to-protocol (ATP) cohort for immunogenicity at 1 month post-dose 2 and 342 in the ATP cohort for persistence at 12 months post dose 2, respectively.
- A total of 99.2% (0,2-mo and 0,6-mo groups) and 96.6% (0,12-mo group) of subjects received both vaccine doses.
- Demographic characteristics were similar among study groups (**Table 1**).

Table 1. Demographic characteristics (TVC)

Characteristics		0,2-mo (N=119)	0,6-mo (N=119)	0,12-mo (N=116)
Mean age (years) at vaccine dose 1 (SD)		64.5 (8.9)	64.0 (8.6)	64.1 (9.2)
Gender, n (%)	Female	90 (75.6)	77 (64.7)	79 (68.1)
	Male	29 (24.4)	42 (35.3)	37 (31.9)
Geographic ancestry, n (%)	White - Caucasian / European	116 (97.5)	118 (99.2)	116 (100)
	African / African American	3 (2.5)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	1 (0.8)	0 (0.0)

TVC, total vaccinated cohort; **N**, total number of subjects in each group; **SD**, standard deviation; **n/%**, number / percentage of subjects in a given category

Immunogenicity

- One month post-dose 2, the pre-defined success criterion was met: the LL of the 97.5% CI of VRR was ≥60% for both 0,6-mo and 0,12-mo groups (**Table 2**).

Table 2. Humoral VRRs by anti-gE ELISA 1 month post-dose 2 (ATP cohort for immunogenicity)

Study group	N	VRR		
		%	97.5% CI	
			LL	UL
0,6-mo	114	96.5	**90.4**	99.2
0,12-mo	110	94.5	**87.6**	98.3

VRR, vaccine response rate; **ELISA**, enzyme-linked immunosorbent assays; **gE**, glycoprotein E; **ATP**, according-to-protocol; **N**, number of subjects with both pre- and post-vaccination results available; **%**, percentage of responders; **CI**, confidence interval; **LL**, lower limit; **UL**, upper limit

- Subsequently, non-inferiority of the anti-gE immune response in terms of antibody GMC was assessed for both 0,6-mo and 0,12-mo groups against the 0,2-mo schedule (**Table 3**).
- While the non-inferiority of the anti-gE immune response in terms of antibody GMC against the 0,2-mo was demonstrated for the 0,6-mo schedule (UL of 97.5% CI: 1.39 [<1.5]), it was not demonstrated for the 0,12-mo schedule (UL of 97.5% CI: 1.53) (**Table 3**).

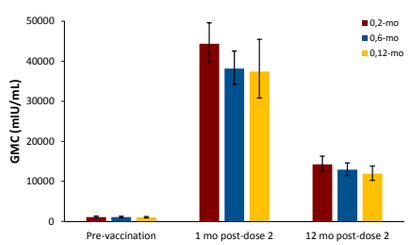
Table 3. Adjusted anti-gE GMC ratios 1 month post-dose 2 (ATP cohort for immunogenicity)

0,2-mo / 0,6-mo			0,2-mo / 0,12-mo		
GMC ratio	97.5% CI		GMC ratio	97.5% CI	
	LL	UL		LL	UL
1.16	0.98	**1.39**	1.19	0.93	1.53

Adjusted GMC, geometric mean antibody concentration adjusted for baseline concentration; **gE**, glycoprotein E; **GMC**, geometric mean concentration; **ATP**, according-to-protocol; **CI**, confidence interval; **LL**, lower limit; **UL**, upper limit

- At baseline, ≥99.1% of subjects were seropositive for VZV based on anti-gE antibody concentrations.
- One month post-dose 2, HZ/su elicited robust anti-gE immune responses regardless of the vaccination schedule (**Figure 2**).
- Anti-gE immune responses remained at least 11.6-fold above pre-vaccination levels 12 months post-dose 2 in all study groups.

Figure 2. Anti-gE antibody GMCs (adapted ATP cohort for immunogenicity)

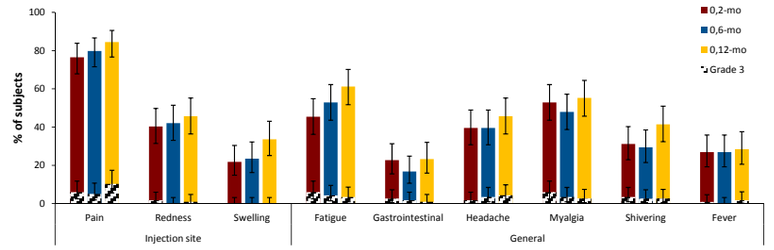


gE, glycoprotein E; **GMC**, geometric mean concentration; **ATP**, according-to-protocol; **mo**, month(s). **Adapted ATP cohort**: pre-vaccination and 1 month post-dose 2 results from the ATP cohort for immunogenicity; 12 months post-dose 2 results from the ATP cohort for persistence. Error bars depict 95% confidence intervals

Reactogenicity and safety

- Solicited injection site and general AEs were reported at similar rates among the 3 study groups, by 89.9%, 89.1%, and 92.2% of subjects in the 0,2-mo, 0,6-mo and 0,12-mo groups, respectively. Reactions were transient (median duration: 1–4 days) and mostly mild to moderate.
- Injection site pain, myalgia and fatigue were the most frequently reported solicited AEs (**Figure 3**).

Figure 3. Incidence of solicited local and general AEs reported within 7 days post-vaccination (TVC, overall/subject)



AEs, adverse events; **TVC**, total vaccinated cohort; **%,** percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; **fever**, oral, axillary or tympanic temperature ≥37.5°C. **Grade 3**: >100 mm diameter (redness, swelling); temperature >39.0°C (fever); preventing normal activity (all other AEs). Error bars depict 95% confidence intervals

- Unsolicited AEs were reported at similar rates among the 3 study groups: 22.7% (95% CI: 15.5; 31.3) (0,2-mo and 0,6-mo groups); 19.8% (13.0; 28.3) (0,12-mo group).
- No pIMDs were reported throughout the study.
- SAEs were reported for 26 subjects, but none were considered as vaccine-related by the investigator (**Table 4**).

Table 4. Number of subjects reporting SAEs from first vaccination until 12 months post-dose 2 (TVC)

Number of subjects reporting ≥1 SAE	0,2-mo	0,6-mo	0,12-mo
Number of months of recording SAEs	14	18	24
All	5	9	12
Fatal	1	0	1
Vaccine-related	0	0	0

SAEs, serious adverse events; **TVC**, total vaccinated cohort

CONCLUSIONS

- For both 0,6-mo and 0,12-mo groups the pre-defined success criterion for VRR was met, while the subsequent non-inferiority for anti-gE immune response GMCs versus the 0,2-mo schedule was only demonstrated in the 0,6-mo group.
- HZ/su elicited robust anti-gE immune responses that persisted for up to 12 months post-dose 2 in all study groups.
- HZ/su demonstrated an acceptable reactogenicity and safety profile regardless of the vaccination schedule.

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DISCLOSURES

GlaxoSmithKline Biologicals SA funded this study and the development of the abstract and poster presentation.

Brecht Geeraerts, Himal Lal, Lidia Oostvogels, Carline Vanden Abeele and Thomas C. Heineman are employees of the GSK group of companies. BG and LO also hold shares in the GSK group of companies as part of their employee remuneration. In addition, TCH is co-inventor of the candidate vaccine used in this study, for which a patent is pending. Airi Poder has no conflict of interest to declare.

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