RANDOMIZED, PHASE III CLINICAL TRIAL TO ASSESS THE IMMUNOGENICITY AND SAFETY OF A CANDIDATE SUBUNIT ADJUVANTED HERPES ZOSTER VACCINE CO-ADMINISTERED WITH A SEASONAL QUADRIVALENT INACTIVATED INFLUENZA VACCINE IN ADULTS AGED 50 YEARS AND OLDER

Presenting author: Tino F Schwarz
Address: Central Laboratory and Vaccination Center, Stiftung Juliusspital, Juliuspromenade 19, Wuerzburg, Germany
Email: tinoschwarz@googlemail.com
Tel: +49 177 753 6634

Tino F Schwarz[1], Naresh Aggarwal[2], Beate Moeckesch[3], Isabelle Schenkenberger[4], Carine Claeys[5], Olivier Godeaux[6]*, Katrijn Grupping[5], Thomas C Heineman[7]**, Lidia Oostvogels[5], Peter Van den Steen[5] and Himal Lal[7]***

[1]Central Laboratory and Vaccination Center, Stiftung Juliusspital, Wuerzburg, Germany; [2]Aggarwal And Associates Limited, Brampton, Ontario, Canada; [3]Gemeinschaftspraxis Dr. Michael und Dr. Beate Möckesch, Weinheim, Germany; [4]Klinische Forschung, Berlin, Germany; [5]GSK, Wavre, Belgium; [6]Janssen Vaccines & Prevention B.V., Leiden, the Netherlands; [7]GSK, King of Prussia, PA, USA
Current affiliations: *Janssen Vaccines & Prevention B.V., Leiden, the Netherlands; **Genocea Biosciences, Cambridge, MA, USA; ***Pfizer, Collegeville, PA, USA

INTRODUCTION

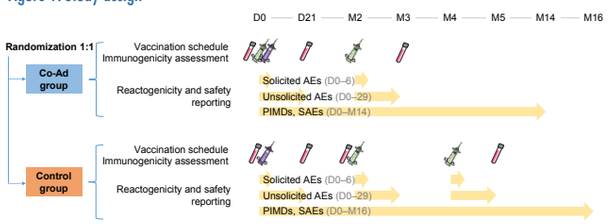
- Herpes zoster (HZ) occurs following reactivation of latent varicella-zoster virus (VZV).[1,2]
- The overall incidence of HZ varies from 3 to 5 cases/1000 person-years, with an estimated lifetime risk of developing HZ of approximately 30%.[3]
- HZ incidence increases from 50 years of age (YOA),[3] presumably due to a decline in VZV-specific cellular immunity.[2]
- GSK (Wavre, Belgium)'s candidate HZ subunit vaccine (HZ/su) containing recombinant VZV glycoprotein E (gE) and $AS01_B$ Adjuvant System has ≥90% efficacy against HZ and a clinically acceptable safety profile when administered as 2 doses to adults ≥50 YOA.[4-6]
- Seasonal influenza is a worldwide health burden, with epidemics estimated to cause around 3–5 million cases of severe illness and 250,000–500,000 deaths every year.[7]
- Here we report immunogenicity and safety data of HZ/su and GSK (Wavre, Belgium)'s quadrivalent inactivated split virion influenza vaccine (IIV4) containing two A and two B virus strains, when IIV4 is co-administered with the first HZ/su vaccine dose compared to separate administration.

METHODS

Study design

- Phase III, randomized, open-label trial in Canada, Germany and the United States (ClinicalTrials.gov: NCT01954251).
- Adults ≥50 YOA were randomized 1:1 during the 2013 northern hemisphere influenza vaccination season to receive intramuscularly either (1) HZ/su and IIV4, co-administered at Day (D) 0, and HZ/su administered at Month (M) 2 (Co-Ad group), or (2) IIV4 administered at D0, and HZ/su at M2 and M4 (Control group) (**Figure 1**).

Figure 1. Study design



D, day; M, month. M14 (Co-Ad group), M16 (Control group), 12 months after last dose. , HZ/su vaccine, composed of 50 µg of VZV gE and $AS01_B$ Adjuvant System (50 µg 3-*O*-desacyl-4′-monophosphoryl lipid A, MPL [produced by GSK], 50 µg *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 liposome); , IIV4, manufactured in Dresden (Germany) and containing 15 µg hemagglutinin of each: A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata) and B/Brisbane/60/2008 (Victoria) (strains chosen in accordance with the WHO recommendations issued for the northern hemisphere season 2013–2014); , blood sampling for immunogenicity assessment; AE, adverse event; SAE, serious AE; pIMD, potential immune-mediated disease

Study objectives

Co-primary objectives:

- To evaluate the HZ/su vaccine response rate (VRR) in terms of anti-gE antibodies measured by the enzyme-linked immunosorbent assay (ELISA) 1 month after the last vaccine dose in the Co-Ad group
  - *Success criterion*: the lower limit (LL) of the 95% confidence interval (CI) of VRR ≥60%
- To demonstrate non-inferiority of HZ/su co-administered with IIV4 *versus* HZ/su given alone in terms of geometric mean concentrations (GMCs) 1 month after the last vaccine dose
  - *Success criterion*: upper limit (UL) of the 95% CI of the Control/Co-Ad GMC ratio <1.5
- To demonstrate non-inferiority of IIV4 co-administered with HZ/su *versus* IIV4 given alone in terms of geometric mean titers (GMTs) of influenza hemagglutinin inhibition (HI) antibodies 21 days post-vaccination
  - *Success criterion*: UL of 95% CI of the Control/Co-Ad GMT ratio <1.5 for all IIV4 strains.

Secondary objectives:

- To demonstrate non-inferiority of IIV4 co-administered with HZ/su *versus* IIV4 given alone in terms of seroconversion rates (SCRs) 21 days post-vaccination
  - *Success criterion*: UL of 95% CI of the Control–Co-Ad SCR difference <10% for all IIV4 strains
- To assess IIV4 GMTs, seroprotection rates (SPRs), SCRs and mean geometric increases 21 days post-vaccination *versus* pre-vaccination as per CBER (Center for Biologics Evaluation and Research)'s *criteria*: LL of 95% CI for SPRs ≥70% in subjects 50–64 YOA; ≥60% in those ≥65 YOA; LL of 95% CI for SCRs ≥40% in subjects 50–64 YOA; ≥30% in those ≥65 YOA
- To evaluate safety and reactogenicity following administration of HZ/su and IIV4 up to 1 month post-vaccination, and during the whole follow-up period (**Figure 1**).

RESULTS AND DISCUSSION

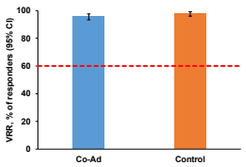
Study participants

- Of the 828 vaccinated subjects (Co-Ad: 413; Control: 415), 781 were included in the according-to-protocol cohort for immunogenicity (Co-Ad: 386; Control: 395).
- The mean age in the total vaccinated cohorts was 63.4 years in both groups; the percentage of female subjects was 51.1% and 52.5% in the Co-Ad and Control groups, respectively; 92.3% and 91.8% of subjects in the Co-Ad and Control groups, respectively, were of white heritage.

Immunogenicity

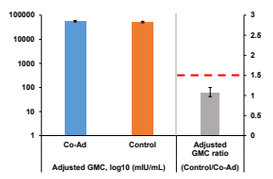
- Humoral immune responses to HZ/su and IIV4 antigens were substantial and comparable when co-administered *versus* given as separate doses (**Figures 2–6**).
- All co-primary objectives were met:
  - 1 month post-second HZ/su vaccination, LL of 95% CI anti-gE VRR in the Co-Ad group was 93.3% *(success criterion met: ≥60%)* (**Figure 2**).
  - 1 month post-second HZ/su vaccination, UL of 95% CI anti-gE Control/Co-Ad GMC ratio was 1.2 *(non-inferiority criterion met: <1.5)* (**Figure 3**).
  - 21 days post-IIV4 vaccination, UL of 95% CI IIV4 Control/Co-Ad GMT ratio was 1.1–1.2 *(non-inferiority criterion met: <1.5)* (**Figure 4**).
- Some of the secondary objectives were not met 21 days post-IIV4 vaccination:
  - UL of 95% CI IIV4 Control–Co-Ad SCR difference was <10% for all strains, except B (Victoria) (**Figure 5B**).
  - The CBER criterion for SPR was reached for both age groups, in both treatment groups, for all vaccine strains, as the LL of 95% CI was >70% and >60% for subjects 50–64 YOA and for those ≥65 YOA, respectively (**Figure 6**).
  - The CBER criterion for SCR was reached for the H1N1 strain for both age groups and in both treatment groups, as the LL of 95% CI was >40% and >30% in subjects 50–64 YOA and ≥65 YOA, respectively; the criterion was also reached for the B Victoria strain in the Control group and for the B Yamagata strain in the Co-Ad group, both in subjects 50–64 YOA (**Figure 5A**).
- The fact that several CBER criteria for SCR were not reached is probably related to the high influenza pre-exposure rate in the study population, as reflected by the high SPR at baseline and the high rate of previous influenza vaccination.
- The results of the secondary objectives should be interpreted with caution, since no type I error adjustment was made for multiple endpoints.

Figure 2. Vaccine response rates for anti-gE antibody concentrations 1 month after last HZ/su vaccination (ATP cohort for immunogenicity)



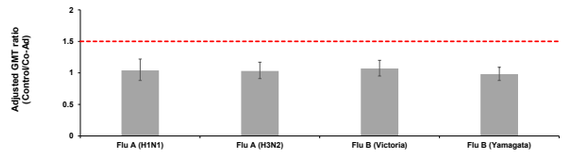
ATP, according-to-protocol; VRR, vaccine response rate, defined as (i) for subjects initially seronegative for anti-gE antibodies, antibody concentration at post-vaccination ≥4-fold the cut-off (97 mIU/mL); (ii) for subjects initially seropositive for anti-gE antibodies, antibody concentration at post-vaccination ≥4-fold the pre-vaccination antibody concentration. Red line depicts a success criterion for HZ/su and IIV4 co-administration: lower limit of the 95% confidence intervals (CIs) ≥60%. Error bars depict 95% CIs. Number of subjects analyzed (with pre- and post-vaccination results available): Co-Ad: 382; Control: 388

Figure 3. Anti-gE antibody geometric mean concentrations (GMCs, adjusted for baseline) and adjusted GMC ratios (Control/Co-Ad) 1 month after last HZ/su vaccination (ATP cohort for immunogenicity)



ATP, according-to-protocol; GMC, geometric mean concentration. Red line depicts a non-inferiority criterion for HZ/su and IIV4 co-administration: upper limit of the 95% confidence intervals (CIs) of GMC ratio <1.5. Error bars depict 95% CIs. Number of subjects analyzed (with pre- and post-vaccination results available): Co-Ad: 382; Control: 388

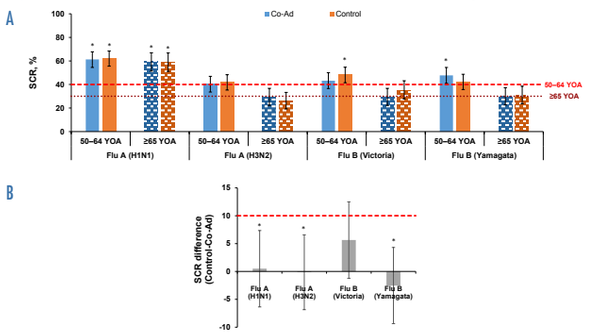
Figure 4. Influenza HI antibody adjusted geometric mean titer (GMT) ratios (Control/Co-Ad), corresponding GMTs (adjusted for baseline) and mean geometric increases 21 days post-IIV4 vaccination (ATP cohort for immunogenicity)



		Flu A (H1N1)	Flu A (H3N2)	Flu B (Victoria)	Flu B (Yamagata)
Adjusted GMT (95% CI)	Co-Ad	187.5 (166.7; 210.8)	63.7 (58.3; 69.7)	170.2 (156.1; 185.6)	423.5 (392.0; 457.5)
	Control	194.3 (173.0; 218.1)	65.9 (60.3; 72.0)	181.6 (166.7; 197.8)	413.9 (383.4; 446.8)
MGI (D21/D0) (95% CI)	Co-Ad	6.8 (5.9; 7.8)	3.4 (3.0; 3.7)	3.4 (3.0; 3.8)	3.4 (3.0; 3.7)
	Control	7.7 (6.7; 9.0)	3.5 (3.2; 4.0)	3.8 (3.4; 4.3)	3.3 (3.0; 3.7)

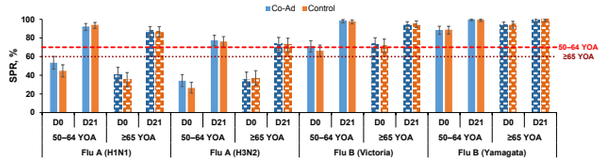
HI, hemagglutinin inhibition; ATP, according-to-protocol; GMT, geometric mean titer; MGI, mean geometric increase, defined as the geometric mean of the within subject ratios of the 21 days post-vaccination (D21) reciprocal HI titer to the Day 0 (D0) reciprocal HI titer; Flu A (H1N1), Flu A/California/7/2009 H1N1; Flu A (H3N2), Flu A/Texas/50/2012 H3N2; Flu B (Victoria), Flu B/Brisbane/60/2008 Victoria; Flu B (Yamagata), Flu B/Massachusetts/2/2012 Yamagata. Red line depicts a non-inferiority criterion for HZ/su and IIV4 co-administration: upper limit of the 95% confidence interval (CIs) of GMT ratio <1.5. Error bars depict 95% CIs. Number of subjects analyzed (with available results at the two considered time points): Co-Ad: 384; Control: 394

Figure 5. Influenza HI antibody seroconversion rates (SCRs) (A) and SCR differences (Control–Co-Ad, adjusted for baseline) 21 days post-IIV4 vaccination (B) (ATP cohort for immunogenicity)



HI, hemagglutinin inhibition; ATP, according-to-protocol; YOA, years of age; SCR, seroconversion rate, defined as the percentage of vaccinees with either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a ≥4-fold increase in post-vaccination titer; Flu A (H1N1), Flu A/California/7/2009 H1N1; Flu A (H3N2), Flu A/Texas/50/2012 H3N2; Flu B (Victoria), Flu B/Brisbane/60/2008 Victoria; Flu B (Yamagata), Flu B/Massachusetts/2/2012 Yamagata. Red lines depict: (A) CBER criteria for HZ/su and IIV4 co-administration: lower limit of 95% confidence intervals (CIs) ≥40% for subjects 50–64 YOA and ≥30% for those ≥65 YOA; (B) a non-inferiority criterion for HZ/su and IIV4 co-administration: upper limit of the SCR difference <10%; *criteria were met. Error bars depict 95% CIs. Number of subjects analyzed (with available results): Co-Ad: 222 (50–64 YOA), 162 (≥65 YOA); Control: 235 (50–64 YOA), 159 (≥65 YOA)

Figure 6. Influenza HI antibody seroprotection rates (ATP cohort for immunogenicity)

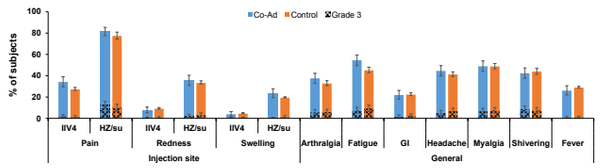


HI, hemagglutinin inhibition; ATP, according-to-protocol; YOA, years of age; D0, Day 0 (pre-vaccination); D21, Day 21 post-vaccination; SPR, seroprotection rate, defined as the percentage of vaccinees with a serum HI titer ≥1:40; Flu A (H1N1), Flu A/California/7/2009 H1N1; Flu A (H3N2), Flu A/Texas/50/2012 H3N2; Flu B (Victoria), Flu B/Brisbane/60/2008 Victoria; Flu B (Yamagata), Flu B/Massachusetts/2/2012 Yamagata. Red lines depict CBER criteria for HZ/su and IIV4 co-administration: lower limit of 95% confidence intervals (CIs) ≥70% for subjects 50–64 YOA and ≥60% for those ≥65 YOA. Error bars depict 95% CIs. Number of subjects analyzed (with available results): Co-Ad: 222, 223 (50–64 YOA), 162, 163 (≥65 YOA); Control: 235 (50–64 YOA), 159, 160 (≥65 YOA)

Reactogenicity and safety

- Solicited adverse events (AEs) were reported at similar rates (overall/subject) in the Co-Ad and Control groups, except for several general AEs, which tended to be reported at slightly higher rates when HZ/su was co-administered with IIV4 (**Figure 7**).
- Solicited AEs were mostly mild or moderate (**Figure 7**) and transient (median duration: 1–3 days during the solicited period).
- Solicited injection site AEs were much more common in response to HZ/su compared to IIV4 injection (**Figure 7**).

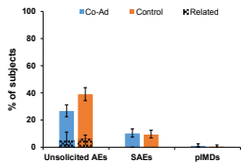
Figure 7. Incidence of solicited injection site (for each vaccine) and solicited general adverse events within 7 days post-vaccination (total vaccinated cohort, overall/subject)



GI, gastrointestinal symptoms; grade 3, significant pain at rest, preventing normal everyday activities (pain), diameter >100 mm (redness/swelling), preventing normal everyday activities (arthralgia, fatigue, GI, headache, myalgia, shivering), oral temperature >39.0°C (fever); any fever, oral temperature ≥37.5°C. Error bars depict 95% confidence intervals. Number of subjects analyzed (with ≥1 documented dose): Co-Ad: 410, 411; Control: 405–413

- The percentage of subjects reporting unsolicited AEs was higher in the Control group, however, this should be interpreted with caution due to the difference in follow-up time (2*30 days in the Co-Ad group; 3*30 days in the Control group [30 days after each vaccination]). For AEs considered as vaccine-related by the investigator, percentages were comparable between the Co-Ad and Control groups (**Figure 8**).
- 8 subjects died (Co-Ad: 3; Control: 5), 73 reported non-fatal serious AEs (SAEs) (Co-Ad: 39; Control: 34) and 6 experienced potential immune-mediated diseases (pIMDs) (Co-Ad: 4 [rheumatoid arthritis, myasthenia gravis, VIIth nerve paralysis and psoriasis]; Control: 2 [colitis ulcerative and vocal cord paralysis]) throughout the study. None of the SAEs (including fatalities) or pIMDs were considered as vaccine-related by the investigator (**Figure 8**).

Figure 8. Incidence of unsolicited adverse events (AEs) within 30 days post-vaccination, serious AEs and potential immune-mediated diseases reported until study end (total vaccinated cohort)



AE, adverse event; SAE, serious AE; pIMD, potential immune-mediated disease. Error bars depict 95% confidence intervals. Number of subjects analyzed (with ≥1 administered dose): Co-Ad: 413; Control: 415

CONCLUSIONS

- No immunological interference was observed between the HZ/su vaccine and IIV4 when IIV4 was co-administered with the first HZ/su dose.
- The reactogenicity of HZ/su was similar when the first HZ/su dose was co-administered with IIV4 and when the 2 vaccines were administered separately. The co-administration of HZ/su and IIV4 did not raise any safety concerns.

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DISCLOSURES

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