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Session: 152. Herpes Zoster Vaccine
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Background. We conducted a phase 1, randomized, double-blind, placebo-controlled trial of a replication-defective HSV-2 vaccine, HSV529 (deleted for UL5 and UL29), in 60 healthy adults aged 18 to 40 years.

Methods. Subjects were enrolled in groups of 20 from 3 serogroups: HSV1+ or -/HSV2+ (group 1), HSV1+/HSV2- (group 2), and HSV1-/HSV2- (group 3). At months 0, 1, and 6, 15 subjects in each group received HSV529 intramuscularly and 5 subjects received placebo. The primary endpoint was the frequency of solicited injection site and systemic reactions from day 0 to 7 after each vaccination and unsolicited adverse events up to 6 months after the last dose.

Results. 89% of vaccine recipients experienced a mild to moderate solicited injection site reaction vs. 47% of placebo recipients ($P = 0.006$, 95% CI 0.129, 0.676) that did not preclude additional doses. 64% of vaccine recipients experienced solicited systemic reactions vs. 53% of placebo recipients ($P = 0.44$, 95% CI -0.179, 0.402). Two serious adverse events occurred in 2 participants and were assessed as unrelated to HSV529 administration. Serum neutralizing antibody titers significantly increased from baseline after 3 doses of HSV529 compared with placebo in group 3 only ($P < 0.001$). This increase persisted up to 6 months after the third dose of vaccine ($P < 0.001$). Serum and vaginal antibodies to HSV2 glycoprotein D (gD) also significantly increased after 3 doses of vaccine in group 3 subjects ($P < 0.001$ and $P = 0.012$, respectively). The mean vaginal gD titer after 3 doses was about one-third of the mean serum gD titer. In addition, the vaccine induced significant levels of HSV2-specific antibody dependent cellular cytotoxicity (ADCC) after 3 doses in group 3 subjects compared with placebo ($P < 0.001$). Vaccine-induced CD4 T-cell responses were detected in 46%, 27%, and 36% of subjects in groups 1, 2, and 3, respectively, one month after the third dose of vaccine. CD8 T-cell responses were detected in 8%, 18%, and 14% of subjects in groups 1, 2, and 3, respectively, at the same time point.

Conclusion. The HSV529 vaccine was safe, well-tolerated, and immunogenic, eliciting significant neutralizing, gD, and ADCC-mediating antibodies, and modest cellular immune responses in HSV seronegative individuals. NCT01915212

Disclosures. L. Dropulic, sanofi pasteur: Collaborator, Research support; K. Wang, sanofi pasteur: Collaborator, Research support; M. Oestreich, sanofi pasteur: Collaborator, Research support; H. Pietz, sanofi pasteur: Collaborator, Research support; D. Garabedian, sanofi pasteur: Collaborator, Research support; K. Dowdell, sanofi pasteur: Collaborator, Research support; H. Nguyen, sanofi pasteur: Collaborator, Research support; K. Laing, sanofi pasteur: Research Contractor, payment for conducting T cell assays; D. Koelle, sanofi pasteur: Research Contractor, payment for conducting T cell assays; A. Azose, sanofi pasteur: Research Contractor, payment for conducting T cell assays; A. Chen, sanofi pasteur: Employee, Salary; L. J. Chang, sanofi pasteur: Employee, Salary; S. Phogat, sanofi pasteur: Employee, Salary

1346. Results of a Safety Pooled Analysis of an Adjuvanted Herpes Zoster Subunit Vaccine in More than 14,500 Participants Aged 50 Years or Older

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Background. The recombinant herpes zoster (HZ) subunit vaccine (HZ/su) has shown efficacy against HZ in adults ≥ 50 and ≥ 70 years of age (YOA), in two pivotal Phase III clinical trials (NCT01165177, NCT01165229). A pooled safety analysis of data from these two efficacy studies was performed, including a comparative analysis on HZ/su vs. placebo groups, to provide a comprehensive understanding of the HZ/su safety profile.

Methods. Two pivotal, randomized, placebo-controlled Phase III studies, assessed the efficacy, reactogenicity and safety of HZ/su, administered intramuscularly according to a 0, 2-month schedule. Solicited and unsolicited adverse events (AEs) were collected for 7 and 30 days after each dose, respectively; serious AEs (SAEs) for 1 year after last dose; fatal and related SAEs and potential immune-mediated diseases (pIMDs) during the entire study period. Reactogenicity was assessed in a subset of participants; safety was assessed in all vaccinated participants.

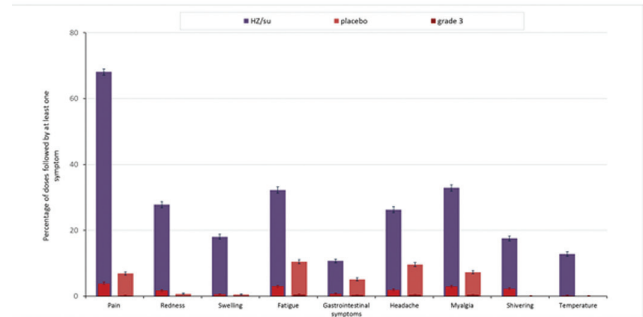
Results. 29,305 participants ≥ 50 YOA (HZ/su: 14,645; placebo: 14,660) were included in the pooled analysis. HZ/su was more reactogenic than placebo. Local

reactions were mostly mild to moderate in intensity and transient (median duration = 3 days); the percentages of participants reporting SAEs, fatal SAEs and pIMDs were similar in both groups, at 30 days and 1 year after last dose (Figures 1 and 2). Percentages of fatal SAEs ranged between 4.3% (95% Confidence Interval [CI]: 4.0–4.7) and 4.6% (95% CI: 4.3–5.0) and pIMDs between 1.2% (95% CI: 1.1–1.4) and 1.4% (95% CI: 1.2–1.6), in HZ/su and placebo groups, respectively. In both groups, the most frequent causes of death were neoplasms, cardiac disorders, and respiratory tract infections and infestations, and most frequent pIMDs were polymyalgia rheumatica, rheumatoid arthritis and psoriasis.

Conclusion. No safety concern was identified. Together with the high efficacy against HZ (97.2% [95% CI: 93.7–99.0],¹ 91.3% [95% CI: 86.8–94.5]²), the safety data supports a favorable benefit/risk profile of HZ/su in participants ≥ 50 YOA.

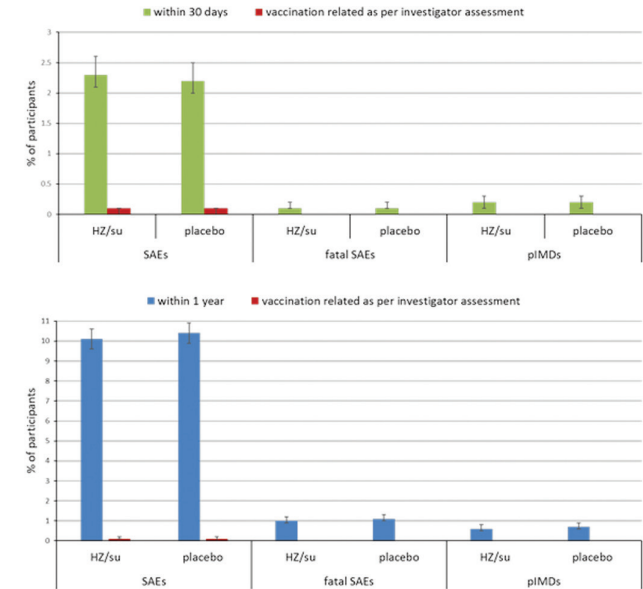
Funding. GlaxoSmithKline Biologicals SA

Figure 1: Incidence of solicited symptoms reported during the 7-day after vaccination period



Temperature is defined on oral, axillary, rectal or tympanic; Error bars depict 95% confidence intervals (CIs).

Figure 2: Overview of SAEs, fatal SAEs and pIMDs within 30 days and 1 year after last vaccination, respectively



SAEs: serious adverse events; pIMDs: potential immune-mediated diseases; Error bars depict 95% confidence intervals (CIs).

Disclosures. M. López-Fauqued, GSK Biologicals: Employee, Salary; L. Campora, GSK Biologicals: Employee, Salary; F. Delannois, GSK Vaccines: Employee, Salary; M. El Idrissi, GSK Vaccines: Employee, Salary; E. Ledent, GSK Vaccines: Employee, Salary; J. Diez-Domingo, GSK Vaccines: Consultant and Investigator, Educational support and Research grant; J. McElhaney, GSK Vaccines: Scientific Advisor, Speaker honorarium; S. McNeil, GSK/Merck: Grant Investigator, Investigator and Scientific Advisor, Consulting fee, Grant recipient, Research grant, Research support and Speaker honorarium; F. De Looze, GSK Vaccines: Investigator and Research Contractor, Research support; F. Tavares Da Silva, GSK Vaccines: Employee, restricted shares and Salary

1347. A Cost-Effectiveness Analysis of an Adjuvanted Subunit Vaccine for the Prevention of Herpes Zoster and Post-Herpetic Neuralgia

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Background. Herpes zoster (HZ) develops in up to 50% of unvaccinated individuals who live to 85 years of age, accounting for more than 1 million cases of HZ annually in the United States. A live attenuated vaccine (LAV) for HZ is U.S. FDA approved for persons 50 years or older, though CDC Advisory Committee on Immunization Practices (ACIP) recommendations are only for persons beginning at age 60 years. LAV efficacy at preventing HZ is ~70% for persons 50–59 years of age, with lower efficacy in older adults, and it is efficacious in preventing post-herpetic neuralgia (PHN) beyond the HZ prevention. The efficacy of LAV after vaccination wanes over time. A new adjuvanted HZ subunit vaccine (SUV), administered as a two-dose series, has greater than 95% efficacy against HZ in persons 50–69 years of age. SUV efficacy remains greater than 90% in persons vaccinated at age 70 years and older, including the subgroup older than 80 years of age. Overall efficacy of SUV against PHN approaches 90%. The waning rate of efficacy after SUV vaccination is unknown.

Methods. To estimate the relative cost-effectiveness of SUV, LAV and no vaccination (NV) strategies, a Markov model was developed based on published trials and data on vaccine efficacy persistence, quality of life, resource utilization, costs and disease epidemiology. The perspective was U.S. societal, and the cycle length was one year with a lifelong time horizon. SUV efficacy was estimated for the base case to wane at the same rate as LAV, all persons were assumed to receive both doses of SUV, and the cost of SUV included both doses.

Results. For individuals vaccinated at age 50 years the incremental cost-effectiveness ratio (ICER) for LAV vs. NV was \$142,811 per quality-adjusted life-year (QALY); at age 60 years the ICER dropped to \$59,482 per QALY. The cost-effectiveness ratio of SUV approached that of LAV when the SUV cost approached \$500 for persons vaccinated at age 50 years and when the cost was \$400 for those vaccinated at age 60 years. The SUV cost that would result in achieving an ICER target of \$100,000 per QALY for SUV vaccination vs. NV at age 50 years was \$316; at age 60 years the cost was \$638.

Conclusion. Vaccination at age 60 years with SUV was more cost-effective than LAV when SUV cost was ~\$450 or less. Vaccination with SUV at age 50 years appeared to be cost-effective if SUV cost was ~\$315 or less.

Disclosures. All authors: No reported disclosures.

1348. Immunogenicity and Safety of a Candidate Subunit Adjuvanted Herpes Zoster Vaccine (HZ/su) in Adults Post Renal Transplant: a Phase III Randomized Clinical Trial

Peter Vink, MD; GSK, Rockville, Maryland

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Background. The incidence rate of herpes zoster (HZ) in individuals with solid organ transplants (SOTs) is estimated as 8–9 times higher than the rate in the overall US population (3.2/1000 person-years). No vaccine is currently available to prevent HZ in immunocompromised individuals. GSK's HZ/su candidate vaccine, containing varicella-zoster virus glycoprotein E (gE) and AS01_b Adjuvant System, has shown >90% efficacy for HZ prevention in immunocompetent adults ≥50 years of age (YOA). We performed a study to determine immunogenicity and safety of HZ/su in adult renal transplant (RT) recipients (RTR) on chronic immunosuppressive therapy; RT was chosen as it can be representative of SOTs due to the nature of administered immunosuppressive therapies.

Methods. In this phase III, observer-blind, multicenter study (NCT02058589), RTRs ≥18 YOA were randomized 1:1 to receive 2 doses of HZ/su or placebo intramuscularly 1–2 months apart. gE-specific vaccine response rates (VRRs) and geometric means (GMs) were assessed for humoral and CD4⁺ cell-mediated immune (CMI) responses 1 month post dose 2 (M2). Solicited adverse events (AEs) were recorded for 7 days and unsolicited AEs and medically-attended AEs (MAEs) for 30 days after each dose. Solicited general and unsolicited AEs were also collected for 7 days prior to dose 1. Potential immune-mediated diseases (pIMDs) and serious AEs (SAEs) were recorded until 1 year post dose 2. Data from dose 1 through M2 is presented.

Results. At M2, 240 subjects (121 HZ/su; 119 placebo) were included in the humoral immunogenicity according-to-protocol (ATP) cohort. All immunogenicity success criteria were met at M2 (Table 1). VRRs for ATP humoral immune cohort and CMI sub-cohort (72 subjects: 36 HZ/su; 36 placebo) were higher in HZ/su groups. Humoral GM concentrations and CMI GM frequencies were significantly higher in HZ/su compared with placebo groups. The frequency of AEs was higher in HZ/su vs. placebo groups for solicited local AEs, but similar for solicited general AEs, unsolicited AEs, MAEs and SAEs. No pIMDs, vaccine-related SAEs or transplant rejections were reported (Table 2).

Conclusion. HZ/su was highly immunogenic in adults with RT at M2. No safety concerns were identified.

Funding. GlaxoSmithKline Biologicals SA

Table 1. VRRs, GMs and GM ratios for anti-gE antibody ELISA concentrations and gE-specific CD4⁺ T cell frequencies at M2 (ATP cohorts for humoral immunogenicity and CMI, respectively)

	HZ/su		Placebo		Adjusted ratio HZ/su:placebo
	N	Value	N	Value	
Humoral immune response (anti-gE antibody ELISA concentration)					
VRR, % (95% CI)	121	80.2% (71.9; 86.9)	119	4.2% (1.4; 9.5)	—
Adjusted* GMC, mIU/ml (95% CI)	121	19983.3 (15779.7; 25306.7)	119	1427.3 (1310.0; 1555.2)	14.00 (10.90; 17.99) p<0.0001
CMI response (gE-specific CD4⁺ T cell frequencies)**					
VRR, % (95% CI)	28	71.4% (51.3; 86.8)	28	0.0% (0.0; 12.3)	—
Adjusted* GM, events/10 ⁶ CD4 ⁺ T cells (95% CI)	28	1440.5 (1044.4; 1959.6)	28	83.5 (8.6; 181.5)	17.25 (5.92; 50.36) p<0.0001

VRR, vaccine response rate; GMC, geometric mean (concentration); M2, month 2 (1 month after last vaccination); ATP, according-to-protocol; N, number of subjects with available results; CI, confidence interval; IU, international units.
*adjusted for baseline values; **for the inferential analysis, the frequency of CD4⁺ T cells producing at least two activation markers (IFN-γ, IL2, TNFα, and CD40 Ligand) upon in vitro stimulation with the antigen (induction condition) is calculated, by adding an offset of 0.5 to the number of activated CD4⁺ T cells (numerator) divided by the total number of CD4⁺ T cells involved (denominator).
*VRR: (i) for humoral immune response: (a) in initially seronegative subjects, the post-vaccination antibody concentration ≥4-fold the cut-off for anti-glycoprotein E (gE) (4x97 mIU/ml); (b) in initially seropositive subjects, the post-vaccination antibody concentration ≥4-fold the pre-vaccination antibody concentration; (ii) for cell-mediated immunogenicity (CMI): (a) in subjects with initial pre-vaccination T cell frequencies below the cut-off (320/10⁶ CD4⁺ T cells), the post-vaccination T cell frequencies ≥2-fold the cut-off (≥2x320/10⁶ CD4⁺ T cells); (b) in subjects with initial pre-vaccination T cell frequencies above the cut-off, the post-vaccination T cell frequencies ≥2-fold the pre-vaccination T cell frequencies.
Bolded values indicate that immunogenicity success criteria of primary objective (lower limit of 95% CI ≥60% for VRR – humoral) and secondary objectives (lower limit of 95% CI ≥50% for VRR – CMI, ≥3 for GM ratio – humoral, >1 for GM ratio – CMI) were met.

Table 2. Overall incidence of AEs (TVC)

AEs	Reporting period	n (% (95% CI))	
		HZ/su N=132 ^a	Placebo N=132
Solicited local	D0–6 after each dose	114	10
		87.0% (80.0–92.3)	7.6% (3.7–13.5)
Solicited general	7D pre-dose 1	90	73
		68.7% (60.0–76.5)	55.3% (46.4–64.0)
Unsolicited	D0–29 after each dose	9	5
		6.8% (3.2–12.5)	5.3% (2.2–10.6)
MAEs	Dose 1 through 30 days post-dose 2	51	44
		38.6% (30.3–47.5)	33.3% (25.4–42.1)
pIMDs	All	34	29
		25.8% (18.5–34.1)	22.0% (15.2–30.0)
SAEs	Vaccine-related	0	0
		0% (0.0)	0% (0.0)
	Biopsy confirmed allograft rejection	6	5
		4.5% (1.7–9.6)	3.8% (1.2–8.6)
		0	0
		0% (0.0)	0% (0.0)
		0	0
		0% (0.0)	0% (0.0)

AEs, adverse events; TVC, total vaccinated cohort; n (%), number (percentage) of subjects with the respective AE; CI, confidence interval; MAEs, AEs with medically-attended visits; pIMDs, potential immune-mediated diseases; SAEs, serious AEs; D, day, N, number of subjects documented with ≥1 administered dose; *131 for the incidence of solicited local and general AEs.

Disclosures. P. Vink, GSK group of companies: Employee, Salary and stock options and stock granted

1349. Immunogenicity and Safety of a Candidate Subunit Adjuvanted Herpes Zoster Vaccine in Adults with Solid Tumors Vaccinated Before or During Immunosuppressive Chemotherapy Treatment: A Phase II/III, Randomized Clinical Trial

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Background. No herpes zoster (HZ) vaccine for immunosuppressed individuals is currently available. GSK's candidate HZ vaccine containing recombinant varicella zoster virus glycoprotein E (gE) subunit and AS01_b Adjuvant System (HZ/su) showed >90% efficacy for HZ prevention in immunocompetent adults aged ≥50 years. The HZ incidence in individuals with solid tumors (ST) receiving immunosuppressive chemotherapy (chemo) is estimated as 3–4 times higher than in the overall US population (3.2/1000 person-years). We present HZ/su immunogenicity and safety in ST adults aged ≥18 years.

Methods. In this phase II/III, observer-blind, multicenter study (NCT01798056), ST adults received 2 doses of HZ/su or placebo intramuscularly 1–2 months apart and were randomized 4:4:1:1 to receive a first dose 8–30 days (D) pre-chemo (HZ/su – HZ/su-PreC group, placebo – Pl-PreC) or on chemo start (±1 D) (HZ/su-OnC, Pl-OnC). Vaccine response rates (VRRs) and geometric means (GMs)/means were evaluated for gE humoral immune and gE-specific CD4⁺ cell-mediated immune (CMI) responses 1 month (M2) and 12 months (M13) post-dose 2. Solicited adverse events (AEs) were recorded for 7 D and unsolicited and medically-attended AEs (MAEs) for 30 D post each dose. Potential immune-mediated diseases (pIMDs) and serious AEs (SAEs) were recorded until study end.

Results. 185 subjects (65 HZ/su-PreC, 78 Pl-PreC, 22 HZ/su-OnC, 20 Pl-OnC) were included in the according-to-protocol (ATP) cohort for humoral immunogenicity and 58 (27 HZ/su-PreC, 31 Pl-PreC) in the ATP sub-cohort for CMI. The most common ST were breast tumors (54% HZ/su, 49% placebo), followed by colorectal, lung, then other. Humoral and CMI VRRs were higher in HZ/su than Pl groups at M2 and M13. GM concentration (GMC) was highest at M2 in HZ/su-PreC. M13 GMCs were similar in the HZ/su-PreC and HZ/su-OnC groups (Table 1). The frequency of local solicited AEs was higher in HZ/su than Pl groups (Table 2); that of general solicited, unsolicited AEs, MAEs and SAEs was similar among groups (Table 3). 1 pIMD (Pl-OnC) and 23 fatal SAEs were reported. No SAE was considered vaccine-related by investigators.

Conclusion. HZ/su was highly immunogenic in ST adults receiving chemo. No safety concerns were raised.

Funding. GlaxoSmithKline Biologicals SA