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Session: 152. Herpes Zoster Vaccine
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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.

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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

Session: 152. Herpes Zoster Vaccine
Friday, October 6, 2017: 12:30 PM

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.

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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	44
		6.8% (3.2–12.5)	5.3% (2.2–10.6)
MAEs	Dose 1 through 30 days post-dose 2	34	29
		25.8% (18.5–34.1)	22.0% (15.2–30.0)
pIMDs	Dose 1 through 30 days post-dose 2	0	0
		0% (0.0)	0% (0.0)
SAEs	Dose 1 through 30 days post-dose 2	6	5
		4.5% (1.7–9.6)	3.8% (1.2–8.6)
Vaccine-related	Dose 1 through 30 days post-dose 2	0	0
		0% (0.0)	0% (0.0)
Biopsy confirmed allograft rejection	Dose 1 through 30 days post-dose 2	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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Friday, October 6, 2017: 12:30 PM

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

Table 1. Humoral and cellular immune responses (ATP cohort for humoral immunogenicity and ATP sub-cohort for CMI, respectively)

	Time point	HZ/su-PreC (HZ/su)		PI-PreC (placebo)		HZ/su-OnC (HZ/su)		PI-OnC (placebo)	
		N	Value	N	Value	N	Value	N	Value
Humoral immune responses (ATP cohort for humoral immunogenicity)									
VRR* , % (95% CI)	M2	65	93.8 (85.0–98.3)	76	0.0 (0.0–4.7)	22	63.6 (40.7–82.8)	18	0.0 (0.0–18.5)
	M13	51	52.9 (38.5–67.1)	55	0.0 (0.0–6.5)	17	47.1 (23.0–72.2)	14	0.0 (0.0–23.2)
GMC , mIU/ml (95% CI)	M2	65	22974.3 (19080.0–27663.5)	78	1120.9 (903.9–1390.0)	22	9328.0 (4492.5–19368.2)	20	854.6 (534.1–1367.2)
	M13	51	4563.0 (3532.8–5893.7)	56	1178.9 (923.3–1505.1)	17	4229.5 (2073.8–8626.0)	14	708.5 (376.9–1331.8)
Adjusted** GMC ratio (HZ/su:placebo) (95% CI)	M2		23.2 (17.9–30.0) p<0.0001						
CMI responses (ATP sub-cohort for CMI)									
VRR* , % (95% CI)	M2	22	50.0 (28.2–71.8)	27	0.0 (0.0–12.8)				
	M13	17	17.6 (3.8–43.4)	16	0.0 (0.0–20.6)				
Freq. , 95% CI	M2	22	781.8 (535.2–1110.4)	27	78.7 (13.7–162.9)				
	M13	18	523.83	19	125.78				
Adjusted** GM frequency ratio (HZ/su:placebo) (95% CI)	M2		9.94 (3.63–27.19) p<0.0001						

ATP, according-to-protocol; CMI, cell-mediated immunogenicity; HZ/su-PreC, first of 2 HZ/su vaccinations at 8–30 days prior to the start of a chemotherapy cycle; PI-PreC, first of 2 placebo administrations at 8–30 days prior to the start of a chemotherapy cycle; HZ/su-OnC, first of 2 HZ/su vaccinations at the start of a chemotherapy cycle (±1 day); PI-OnC, first of 2 placebo administrations at the start of a chemotherapy cycle (±1 day); N, number of subjects with available results; VRR, vaccine response rate; GMC, geometric mean; GM, geometric mean anti-gE antibody ELISA concentration; Freq., frequency of gE-specific CD4(+) T-cells (per 10⁶ total CD4+ T-cells); %, percentage of subjects; CI, confidence interval; IU, international unit; M2, Month 2, 1 month post-dose 2; M13, Month 13, 12 months post-dose 2. The p-value is relative to the null hypothesis H₀: HZ/su:placebo ratio = 1.0. Bolded values indicate that immunogenicity success criteria of the primary objective (lower limit [LL] of 95% CI for GMC HZ/su:placebo ratio ≥ 200% = humoral immunogenicity) and secondary objectives (LL of 95% CI for VRR ≥ 23 = humoral immunogenicity and for GM frequency HZ/su:placebo ratio ≥ 1 = CMI) were met.
*Humoral VRR, percentage of subjects with vaccine response; for initially seronegative subjects (anti-gE antibody concentration below the cut-off [97 mIU/ml]), at least a 2-fold increase as compared to the cut-off; for initially seropositive subjects (anti-gE antibody concentration above the cut-off), at least a 4-fold increase as compared to the pre-vaccination antibody concentration. CMI VRR, percentage of subjects with vaccine response; for subjects with pre-vaccination T-cell frequencies below the threshold (330 gE-specific CD4(+) T-cells/10⁶ CD4+ T-cells), at least a 2-fold increase as compared to the threshold; for subjects with pre-vaccination T-cell frequencies above the threshold, at least a 2-fold increase as compared to pre-vaccination T-cell frequencies. **, adjusted for baseline values.

Table 2. Overall frequency of solicited AEs (Days 0–6 post each dose) per subject (TVC)

AE	HZ/su-PreC		PI-PreC		HZ/su-OnC		PI-OnC	
	% (95% CI)	N=86	% (95% CI)	N=86	% (95% CI)	N=26	% (95% CI)	N=24
Local	Pain	83.7% (74.2–90.8)	4.7% (1.3–11.5)	69.2% (48.2–85.7)	12.5% (2.7–32.4)			
	Redness	39.5% (29.2–50.7)	0% (0.0–4.2)	23.1% (9.0–43.6)	0% (0.0–14.2)			
	Swelling	17.4% (10.1–27.1)	1.2% (0.0–6.3)	11.5% (2.4–30.2)	0% (0.0–14.2)			
General	Fatigue	66.3% (55.3–76.1)	60.5% (49.3–70.8)	80.8% (60.6–93.4)	66.7% (44.7–84.4)			
	GI	38.4% (28.1–49.5)	39.5% (29.2–50.7)	69.2% (48.2–85.7)	62.5% (40.6–81.2)			
	Headache	34.9% (24.9–45.9)	30.2% (20.8–41.1)	50.0% (29.9–70.1)	58.3% (36.6–77.9)			
	Myalgia	58.1% (47.0–68.7)	25.6% (16.8–36.1)	38.5% (20.2–59.4)	37.5% (18.8–59.4)			
	Shivering	33.7% (23.9–44.7)	18.6% (11.0–28.4)	38.5% (20.2–59.4)	37.5% (18.8–59.4)			
	Fever	17.4% (10.1–27.1)	2.3% (0.3–8.1)	19.2% (6.6–39.4)	12.5% (2.7–32.4)			

TVC, total vaccinated cohort; AEs, any grade adverse events; N, number of subjects with ≥1 documented dose; %, percentage of subjects with the respective AE; CI, confidence interval; HZ/su-PreC, first of 2 HZ/su vaccinations at 8–30 days prior to the start of a chemotherapy cycle; PI-PreC, first of 2 placebo administrations at 8–30 days prior to the start of a chemotherapy cycle; HZ/su-OnC, first of 2 HZ/su vaccinations at the start of a chemotherapy cycle (±1 day); PI-OnC, first of 2 placebo administrations at the start of a chemotherapy cycle (±1 day); GI, gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea); fever, temperature ≥37.5°C.

Table 3. Overall frequency of AEs per subject (TVCC)

AEs	Reporting period	HZ/su-PreC		PI-PreC		HZ/su-OnC		PI-OnC	
		% (95% CI)	N=86	% (95% CI)	N=86	% (95% CI)	N=26	% (95% CI)	N=24
Solicited local	D0–6 after each dose	88.4% (79.7–94.3)	4.7% (1.3–11.5)	69.2% (48.2–85.7)	12.5% (2.7–32.4)				
		79.1% (69.0–87.1)	65.1% (54.1–75.1)	88.5% (69.8–97.6)	70.8% (48.9–87.4)				
Unsolicited MAEs	D0–29 after each dose	82.2% (72.7–89.5)	89.0% (80.7–94.6)	96.3% (81.0–99.9)	91.7% (73.0–99.0)				
		21.1% (13.2–31.0)	30.8% (21.5–41.3)	44.4% (25.5–64.7)	20.8% (7.1–42.2)				
piMDs	Dose 1 to study end	0% (0.0–4.0)	0% (0.0–4.0)	0% (0.0–12.8)	4.2% (0.1–21.1)				
		30.0% (20.8–40.6)	37.4% (27.4–48.1)	33.3% (16.5–54.0)	33.3% (15.6–55.3)				
Fatal SAEs		10.0% (4.7–18.1)	11.0% (5.4–19.3)	11.1% (2.4–29.2)	4.2% (0.1–21.1)				

TVC, total vaccinated cohort; AEs, any grade adverse events; %, percentage of subjects with the respective AE; CI, confidence interval; HZ/su-PreC, first of 2 HZ/su vaccinations at 8–30 days prior to the start of a chemotherapy cycle; PI-PreC, first of 2 placebo administrations at 8–30 days prior to the start of a chemotherapy cycle; HZ/su-OnC, first of 2 HZ/su vaccinations at the start of a chemotherapy cycle (±1 day); PI-OnC, first of 2 placebo administrations at the start of a chemotherapy cycle (±1 day); MAEs, medically-attended AEs; piMDs, potential immune-mediated diseases; SAEs, serious AEs; D, day; N, number of subjects with ≥1 documented (solicited AEs) or administered (other AEs) dose.

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1350. Vaccination Response to an Ongoing Meningitis Outbreak: Uptake and Attitudes among Men Who Have Sex with Men in Los Angeles, CA
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Session: 152. Herpes Zoster Vaccine
Friday, October 6, 2017: 12:30 PM

Background. Men who have sex with men (MSM) are at high risk for invasive meningococcal disease (IMD). Following a 2016 IMD outbreak in Southern California, public health officials issued an advisory that urged at-risk adult gay and bisexual men, and all people with HIV, to obtain immunizations. Despite public health efforts to increase MCV4 coverage, uptake and acceptance among MSM remains unknown. Thus, our study sought to: (1) estimate reported MCV4 immunization among MSM in Los Angeles, CA; and (2) document the facilitators and barriers to the newest vaccination recommendation following the recent outbreak.

Methods. From November 2016 through February 2017, we used venue-based sampling to recruit MSM in Los Angeles (N = 513). Eligible participants completed a 30-minute iPad survey that included items on MCV4 status, sexual behavior, vaccination knowledge and behaviors among other factors. Chi-square and independent sample t-tests were used to determine bivariate associations. Statistically significant variables from bivariate analyses were included in a multivariate logistic regression model predicting MCV4 uptake.

Results. Participants were young (M=33, SD=10) and racially/ethnically diverse: White (35.7%), Black/African American (14.6%), Hispanic (36.5%), Asian/Pacific Islander (4.1%), Other (9.2%). Reported MCV4 immunization among MSM (25.4%) and MSM living with HIV (37.7%) was low. Statistically significant correlates of MCV4 uptake in our multivariate model included: younger age (aOR=2.51), prior STI diagnosis (aOR=2.21), believing MCV4 vaccination was important (aOR=3.45), having confidence in the MCV4 vaccine (aOR=5.43), and knowing someone who had received the vaccination (aOR=5.79).

Conclusion. MSM's perceived health risk, vaccine confidence, and knowledge of someone who received the MCV4 vaccine were important indicators of meningitis immunization in this outbreak context. Provider and public health education efforts may be enhanced by messages that emphasize personal health risks, the safety and efficacy of MCV4, and the importance of meningococcal vaccines for men's health. Popular opinion leader programs facilitated by someone who had been vaccinated are warranted to enhance MCV4 uptake.

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1351. Bivalent Norovirus VLP Vaccine Candidate in Older Adults: Impact of MPL and a Second Dose in a Randomized, Controlled, Double-Blind Clinical Trial
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Session: 152. Herpes Zoster Vaccine
Friday, October 6, 2017: 12:30 PM

Background. Acute norovirus (NoV) gastroenteritis may cause significant morbidity in healthy adults and can prove fatal in older subjects. We investigated the safety and immunogenicity in older adults of one or two doses of an intramuscular bivalent virus-like particle (VLP) vaccine candidate (genotypes GI.1 and multivalent consensus GII.4c) formulated with alum and with and without MPL (3-O-deacyl-4-monomethylphosphoryl lipid A) adjuvant.

Methods. In a phase II, double-blind, controlled trial, 294 healthy adults ≥ 60 years of age randomized to 4 equal groups received one or two immunizations 28 days apart. One dose groups received placebo (saline) on Day 1. Vaccine formulations contained 500µg Al(OH)₃ adjuvant with 15µg GI.1 and 50µg GII.4c VLP antigens, with or without 15µg MPL adjuvant. A fifth group of 26 healthy 18–49 year-olds received one dose of MPL-free vaccine. Humoral immunity was assessed as ELISA pan-Ig and histo-blood group antigen blocking (HBGA) antibody titers at Days 1, 8, 29 and 57. Cell-mediated immunity (CMI) and avidity indices (AI) were also measured. Safety was assessed as solicited local and systemic adverse events (AE) for 7 days, and unsolicited AEs until Day 28 after each vaccination.

Results. Marked increases in pan-Ig and HBGA to both genotypes occurred by Day 8 after first vaccination. Geometric mean titers were similar in magnitude in all groups and persisted at similar levels through Day 56. No increases were observed with a second vaccine dose on Day 29 or with the formulations containing MPL. Responses were similar in magnitude when assessed by age groups (60–74, 75–84 and ≥ 85 years of age) and when compared with those to a single vaccine dose in 18–49 year-olds. No clinically relevant differences in CMI responses or changes in antibody avidity were observed between formulations. Both formulations were generally well tolerated, the most frequent reaction being mild pain at the injection site. No vaccine-related SAEs were reported.

Conclusion. Older adults aged over 60 years displayed immune responses to NoV VLP vaccines that were similar to those in younger adults with no apparent signs of immunosenescence. These data support the further development of the MPL-free vaccine candidate in older adults.

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