Human Papillomavirus (HPV)-16/18 AS04-adjuvanted Vaccine: Immunological Superiority of the 2-dose Schedule Versus 2-dose and 3-dose Schedules of HPV-6/11/16/18 Vaccine; Results of a Randomised, Multicentre, Immunogenicity Trial Up to Month 24

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Background/Objective: 2 doses (2D) of GSK Vaccines' human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine induced superior anti-HPV-16/18 antibody response compared to 2D or 3D of Merck's HPV-6/11/16/18 vaccine 1 month (M) after last vaccination, as demonstrated in this phase IIIB, randomised, observer-blind trial (NCT01462357). Here, we present immunogenicity and safety results up to 18M after last vaccination (M24).

Method: 1078 healthy 9-14-year-old girls were enrolled and randomised (1:1:1) to receive 2D of HPV-16/18 AS04-adjuvanted vaccine (HPV-16/18[2D], N=360) or HPV-6/11/16/18 vaccine (HPV-6/11/16/18[2D], N=359) at M0,6 or 3D of HPV-6/11/16/18 vaccine at M0,2,6 (HPV-6/11/16/18[3D], N=359); 355, 344 and 349 girls, respectively, returned for the M24 visit. Non-inferiority and superiority in terms of immunogenicity (by enzyme-linked immunosorbent assay [ELISA]) of HPV-16/18[2D] versus HPV-6/11/16/18[2D] and HPV-6/11/16/18[3D] were sequentially evaluated in the M24 according-to-protocol immunogenicity cohort (ATP-I; N=968) and M24 total vaccinated cohort (TVC; N=1048), respectively. HPV-16/18-specific T-cell- and B-cell-mediated immune responses and safety were also assessed.

Result: At M24, anti-HPV-16/18 ELISA responses in the HPV-16/18[2D] group were non-inferior and superior to those in HPV-6/11/16/18[2D] and HPV-6/11/16/18[3D] groups (Table); geometric mean titres were ≥2.06-fold (HPV-16) and ≥3.49-fold (HPV-18) higher for HPV-16/18[2D] versus HPV-6/11/16/18[2D] and HPV-6/11/16/18[3D] (TVC). CD4+ T-cell responses in HPV-16/18[2D] appeared higher than HPV-6/11/16/18[2D], while not being statistically significant, and similar to HPV-6/11/16/18[3D] for both antigens; memory B-cell responses appeared similar across groups. Safety was in line with the known safety profiles of both vaccines.

Conclusion: The superior anti-HPV-16/18 antibody response elicited after 2D of the HPV-16/18 AS04-adjuvanted vaccine versus 2D or 3D of the HPV-6/11/16/18 vaccine administered in 9-14-year-old girls was maintained up to M24. Cell mediated immune responses appeared similar or higher after HPV-16/18 vaccination than after HPV-6/11/16/18 vaccination.

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Table: Non-inferiority (A) and superiority (B) of anti-HPV-16/18 antibody responses in HPV-16/18[2D] versus HPV-6/11/16/18[2D] and HPV-6/11/16/18[3D], and immunogenicity results (C), (ELISA), 18 months after last vaccination (secondary sequential endpoint)

Comparison	A. Non-inferiority (ATP-I, initially seronegative subjects)		B. Superiority* (TVC)
Antibody	SCR difference % (95% CI)	GMT ratio (95% CI)	GMT ratio (95% CI)
HPV-16/18[2D] vs HPV-6/11/16/18[2D]	**HPV-6/11/16/18[2D] minus HPV-16/18[2D]**	**HPV-6/11/16/18[2D] divided by HPV-16/18[2D]**	**HPV-16/18[2D] divided by HPV-6/11/16/18[2D]**
Anti-HPV-16	-0.32 (-1.79; **0.88**)	0.39 (0.34; **0.46**)	2.49 (**2.16**; 2.88)
Anti-HPV-18	-6.94 (-10.29; **-4.63**)	0.17 (0.15; **0.20**)	5.79 (**4.95**; 6.77)
HPV-16/18[2D] vs HPV-6/11/16/18[3D]	**HPV-6/11/16/18[3D] minus HPV-16/18[2D]**	**HPV-6/11/16/18[3D] divided by HPV-16/18[2D]**	**HPV-16/18[2D] divided by HPV-6/11/16/18[3D]**
Anti-HPV-16	0.00 (-1.22; **1.20**)	0.48 (0.43; **0.55**)	2.06 (**1.81**; 2.35)
Anti-HPV-18	-3.41 (-6.00; **-1.91**)	0.29 (0.25; **0.34**)	3.49 (**2.97**; 4.10)

	C. Immunogenicity results (ATP-I, initially seronegative subjects; ELISA)					
	SCR % (95% CI)					
Antibody	N	**HPV-16/18[2D]**	N	**HPV-6/11/16/18[2D]**	N	**HPV-6/11/16/18[3D]**
Anti-HPV-16	318	100 (98.8; 100)	313	99.7 (98.2; 100)	312	100 (98.8; 100)
Anti-HPV-18	321	100 (98.9; 100)	317	93.1 (89.7; 95.6)	323	96.6 (94.0; 98.3)
	GMT (95% CI)					
Antibody	N	**HPV-16/18[2D]**	N	**HPV-6/11/16/18[2D]**	N	**HPV-6/11/16/18[3D]**
Anti-HPV-16	318	1304.3 (1201.0; 1416.4)	313	514.5 (456.2; 580.4)	312	631.9 (571.1; 699.1)
Anti-HPV-18	321	626.9 (567.4; 692.8)	317	107.1 (94.1; 122.0)	323	181.6 (159.0; 207.3)

Bolded values indicate that non-inferiority/superiority criteria were met. *Non-inferiority criteria: the upper limit (UL) of the 95% confidence intervals (CI) for SCR difference <5%, and the UL of 95% CI for GMT ratio <2, for both anti-HPV-16 and -18 antibodies. Superiority criteria: the lower limit of the 95% CI for the GMT ratio >1.* The 2-sided 95% CIs of GMT ratios between groups were computed using an analysis of variance (ANOVA) model.

*p-value=0.0001. ELISA, enzyme-linked immunosorbent assay (cut-off: 19 EL.U/ml for HPV-16 and 18 EL.U/ml for HPV-18); ATP-I, according-to-protocol cohort for immunogenicity; TVC, total vaccinated cohort; SCR, seroconversion rate; GMT, geometric mean titre; D, dose; N, number of subjects with available results.