Sustained Non-inferiority of the Human Papillomavirus (HPV)-16/18 AS04-adjuvanted Vaccine when Given as 2-dose Schedules in 9–14-year-old Girls Versus Standard 3-dose Schedule in 15–25-year-old Women: A Randomized Trial

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Background/Objective
This phase-III, multicentre, randomized, open-label trial (NCT01381575) recently demonstrated that HPV-16/18 AS04-adjuvanted vaccine is immunologically non-inferior following 2-dose schedule (2D) administration in adolescent girls versus 3-dose schedule (3D) in young women, until month (M) 18 post-dose 1. Immunogenicity and safety results until M24 are presented here.

Method
Healthy 9-14-year-old girls were randomized 1:1 to receive 2D of HPV-16/18 AS04-adjuvanted vaccine at M0,6 (N=550) or M0,12 (N=415); healthy 15-25-year-old women received 3D at M0,1,6 (N=482). Anti-HPV-16/18 antibodies were measured by enzyme-linked immunosorbent assay (ELISA) and pseudovirion-based neutralization assay. Cell-mediated immune responses were measured at M24 in sub-cohorts receiving last dose at M6. Safety outcomes were recorded.

Result
In the M24 according-to-protocol cohort for immunogenicity (initially seronegative subjects), the non-inferiority of anti-HPV-16/18 immune response following 2D(M0,6) versus 3D(M0,1,6) was demonstrated 18 months after last dose; immune response following 2D(M0,12) was non-inferior versus 3D(M0,1,6) and 2D(M0,6) 12 months after last dose (Table). Anti-HPV-16/18 neutralizing antibody levels were generally comparable across all groups 12 months after last dose, and between 2D(0,6) and 3D(0,1,6) 18 months after last dose. For both vaccine types, T-cell- and B-cell-mediated immune responses were comparable between groups 18 months after last dose. In the M24 total vaccinated cohort, serious adverse events (AEs) were reported for 14 (2.6%), 17 (4.2%) and 20 (4.4%) subjects receiving 2D(M0,6) (N=537), 2D(M0,12) (N=401) and 3D(0,1,6) (N=453), respectively; none were vaccine-related. Medically significant AEs were reported for 114 (21.2%), 70 (17.5%) and 133 (29.4%) subjects, respectively.

Conclusion
The non-inferiority of the HPV-16/18 immune response (ELISA) elicited following 2D administration (at M0,6 and M0,12) of HPV-16/18 AS04-adjuvanted vaccine in adolescent girls versus standard 3D schedule in young women was maintained until M24, with an acceptable safety profile. 2D schedule option may facilitate implementation of immunization programmes, improve compliance and reduce costs. Funding: GlaxoSmithKline Biologicals SA

Table: Anti-HPV-16 and anti-HPV-18 antibody responses (ELISA) and non-inferiority results at M24 following 2-dose and 3-dose vaccination schedules (initially seronegative subjects, ATP-I)

Comparison/ Antibody	N	Seroconversion rate, % (95% CI)	GMT, EU/mL (95% CI)	N	Seroconversion rate, % (95% CI)	GMT, EU/mL (95% CI)	Seroconversion difference*, % (95% CI)	GMT ratio** (95% CI)
2D(M0,12) vs 3D(M0,1,6) 12M after last vaccination	**2D(M0,12)**			**3D(M0,1,6)**			**3D–2D(M0,12)**	**3D/2D(M0,12)**
Anti-HPV-16	346	100 (98.9, 100)	2183.6 (1998.9, 2385.5)	332	100 (98.9, 100)	1956.6 (1754.2, 2182.4)	0.00 (-1.15, **1.10**)	0.90 (0.78, **1.03**)
Anti-HPV-18	360	100 (99.0, 100)	1188.0 (1080.2, 1306.6)	361	100 (99.0, 100)	837.1 (749.0, 935.7)	0.00 (-1.05, **1.06**)	0.70 (0.61, **0.82**)
2D(M0,12) vs 2D(M0,6) 12M after last vaccination	**2D(M0,12)**			**2D(M0,6)**			**2D(M0,6)–2D(M0,12)**	**2D(M0,6)/2D(M0,12)**
Anti-HPV-16	346	100 (98.9, 100)	2183.6 (1998.9, 2385.5)	466	100 (99.2, 100)	1743.1 (1623.0, 1872.1)	0.00 (-0.82, **1.10**)	0.80 (0.71, **0.89**)
Anti-HPV-18	360	100 (99.0, 100)	1188.0 (1080.2, 1306.6)	470	99.8 (98.8, 100)	870.9 (800.4, 947.6)	-0.21 (-1.20, **0.85**)	0.73 (0.65, **0.83**)
2D(M0,6) vs 3D(M0,1,6) 18M after last vaccination	**2D(M0,6)**			**3D(M0,1,6)**			**3D–2D(M0,6)**	**3D/2D(M0,6)**
Anti-HPV-16	468	100 (99.2, 100)	1488.4 (1388.9, 1595.1)	334	100 (98.9, 100)	1594.9 (1433.0, 1775.1)	0.00 (-1.14, **0.82**)	1.07 (0.95, **1.21**)
Anti-HPV-18	472	99.8 (98.8, 100)	715.8 (659.2, 777.1)	362	100 (99.0, 100)	664.0 (592.2, 744.5)	0.21 (-0.84, **1.19**)	0.93 (0.81, **1.06**)

*Non-inferiority for seroconversion rates was met if, for both HPV-16 and HPV-18, the upper limit of the 95% CI for the seroconversion difference was <5%. **Non-inferiority for GMT was met if, for both HPV-16 and HPV-18, the upper limit of the 95% CI for the GMT ratio was <2. Numbers in bold signify the non-inferiority criterion was met. 2D=2-dose schedule; 3D=3-dose schedule; ATP-I=M24 according-to-protocol cohort for immunogenicity including 519 subjects in 2D(0,6) group, 385 in 2D(0,12) and 407 in 3D(0,1,6); CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; EU=ELISA units; GMT=geometric mean titre; M=month; N=number of subjects with available results.