The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 106001 (HPV-035)

Title: A phase IIIb, double-blind, randomized, controlled study to evaluate the immunogenicity and safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP AS04 vaccine, administered intramuscularly according to a 0, 1, 6 month schedule in healthy female subjects aged 18 – 35 years.
HPV-16/18 L1 VLP AS04 (HPV): GSK Biologicals' human papillomavirus (HPV) vaccine containing HPV 16/18 virus-like particles (VLPs) and adjuvant AS04.

Rationale: The aim of the study was to evaluate the immunogenicity and safety of the HPV vaccine in female subjects of Chinese origin aged 18 – 35 years residing in Hong Kong.

Phase: IIIb

Study Period: 27 March 2006 to 16 June 2007

Study Design: Double-blind, randomized (1:1) and controlled multi-centre study with 2 parallel groups.

Centers: 4 study centers in Hong-Kong.

Indication: Immunization of healthy females of Chinese origin residing in Hong Kong aged 18-35 years against HPV-16 and HPV-18.

Treatment: The study groups were as follows:

- HPV Group received the HPV vaccine
- ALU Group received the control Aluminum Hydroxide [$Al(OH)_3$]

Both study groups received 3 doses of either the HPV vaccine or the control by intramuscular injection into the deltoid region of the non-dominant arm according to a 0, 1, 6 month schedule.

Objectives:

- To evaluate antibody responses against HPV-16 and HPV-18 (by enzyme-linked immunosorbent assay [ELISA]) in all HPV vaccine recipients at Month 7.

Primary Outcome/Efficacy Variable(s):

- Seroconversion rates to HPV-16 and HPV-18 as assessed by ELISA at Month 7.

Seroconversion was defined as the appearance of anti-HPV-16 or anti-HPV-18 antibodies (i.e. HPV-16 antibody titer $\geq$ 8 EL.U/mL and HPV-18 antibody titer $\geq$ 7 EL.U/mL) in the sera of subjects seronegative before vaccination.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

- Anti-HPV-16/18 antibody titers (by ELISA) at Month 0 and Month 7.

Safety

- Occurrence of serious adverse events (SAEs) throughout the study period (up to Month 7).
- Occurrence, intensity and relationship to vaccination of solicited general symptoms, and occurrence and intensity of solicited local symptoms during the 7 days (Days 0 – 6) after each and any vaccination.
- Occurrence, intensity and causal relationship to vaccination of unsolicited symptoms within 30 days (Days 0 – 29) after any vaccination.
- Occurrence of new onset chronic diseases (NOCDs) (e.g. autoimmune disorders, asthma, type I diabetes, allergies, etc) and other medically significant conditions throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity.
  Medically significant conditions were defined as: adverse events (AEs) prompting emergency room or physician visits that were not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that were not related to common diseases. Common diseases included: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

Statistical Methods:

The analyses were done on the Total Vaccinated Cohort and the According-to-Protocol (ATP) cohort for immunogenicity.
The Total Vaccinated Cohort included all subjects with at least one vaccine administration documented.
The ATP cohort for immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity measures were available.
Analysis of immunogenicity

The analysis of immunogenicity was based on the ATP cohort for immunogenicity.
For each group, at each time point that a blood sample result was available, seroconversion/seropositivity rates for anti-HPV-16 and anti-HPV-18 antibodies (with exact 95% confidence interval [CI]) and Geometric mean titers (GMTs) with 95% CI were calculated. Antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.
Analysis of safety
The analysis of safety was based on the Total Vaccinated Cohort.
The incidence of any and Grade 3 solicited local symptoms during the 7-day (Day 0-6) follow-up period and its exact 95% CI was summarized by vaccine group, by dose and across doses. The incidence of any, Grade 3 and related solicited general symptoms during the 7-day (Day 0-6) follow-up period and its exact 95% CI was summarized by vaccine group, by dose and across doses. The percentage of subjects with at least one report of NOCDs and medically significant AEs classified by MedDRA and reported during the entire study period were tabulated with exact 95% CI. The percentage of subjects reporting any unsolicited AEs, Grade 3 AEs and related AEs occurring within 30 days following vaccination (Day 0-29) was summarized by vaccine group according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The occurrence of SAEs was assessed throughout the study period and classified by the MedDRA preferred terms.

Study Population: Healthy female subjects of Chinese origin, residing in Hong Kong, aged between and including 18 and 35 years at the time of the first vaccination, free of obvious health problems as established by medical history and clinical examination before entering into the study and having a negative urine pregnancy test were enrolled. Subjects had to be of non-childbearing potential or, if of childbearing potential, had to be abstinent or using effective birth control methods for 30 days prior to vaccination and had to agree to continue such precautions for 2 months after completion of vaccination series. Subjects with a previous administration of MPL or AS04 adjuvant, a previous vaccination against HPV or planned administration of any HPV vaccine other than that foreseen by the study protocol during the study period were excluded. Written informed consent was obtained from the subject before entry into the study.

Number of subjects	**HPV Group**	**ALU Group**
Planned, N	150	150
Randomized, N (Total Vaccinated Cohort)	150	150
Completed, n (%)	148 (98.7)	146 (97.3)
Total Number Subjects Withdrawn, n (%)	2 (1.3)	4 (2.7)
Withdrawn due to Adverse Events n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not applicable	Not applicable
Withdrawn for other reasons n (%)	2 (1.3)	4 (2.7)
Demographics	**HPV Group**	**ALU Group**
N (Total Vaccinated Cohort)	150	150
Female: Male	150: 0	150: 0
Mean Age, years (SD)	26.0 (4.24)	26.0 (4.66)
Chinese, n (%)	150 (100)	150 (100)

Primary Efficacy Results:
Seropositivity and GMTs for anti-HPV-16 antibodies by pre-vaccination status (ATP cohort for immunogenicity)

Group	**Pre-vaccination status**	**Timing**	**N**	**≥ 8 EL.U/mL**				**GMT (EL.U/mL)**		
				n	**%**	**95% CI**		**Value**	**95% CI**	
						LL	**UL**		**LL**	**UL**
HPV	S-	PRE	87	0	0.0	0.0	4.2	4.0	4.0	4.0
		PIII(M7)	87	87	100	95.8	100	10421.8	8729.5	12442.2
	S+	PRE	18	18	100	81.5	100	36.8	22.3	60.7
		PIII(M7)	18	18	100	81.5	100	6511.1	4490.8	9440.2
	Total	PRE	105	18	17.1	10.5	25.7	5.9	4.9	7.0
		PIII(M7)	105	105	100	96.5	100	9614.4	8182.4	11297.0
ALU	S-	PRE	90	0	0.0	0.0	4.0	4.0	4.0	4.0
		PIII(M7)	90	2	2.2	0.3	7.8	4.3	3.8	4.8
	S+	PRE	10	10	100	69.2	100	29.7	15.3	57.6
		PIII(M7)	10	9	90.0	55.5	99.7	20.6	9.2	46.1
	Total	PRE	100	10	10.0	4.9	17.6	4.9	4.3	5.6
		PIII(M7)	100	11	11.0	5.6	18.8	5.0	4.3	5.8

S- = seronegative subjects (antibody titer < 8 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 8 EL.U/mL) prior to vaccination
N = number of subjects with pre-vaccination results available

n(%) = number(percentage) of subjects with titers within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M7) = Post Dose 3, Month 7
PRE = Pre-Vaccination

Primary Efficacy Results:
Seropositivity and GMTs for anti-HPV-18 antibodies by pre-vaccination status (ATP cohort for immunogenicity)

Group	Pre-vaccination status	Timing	N	≥7 EL.U/mL				GMT (EL.U/mL)		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
HPV	S-	PRE	88	0	0.0	0.0	4.1	3.5	3.5	3.5
		PIII(M7)	88	88	100	95.9	100	4648.8	3974.8	5437.0
	S+	PRE	16	16	100	79.4	100	15.1	10.5	21.7
		PIII(M7)	16	16	100	79.4	100	4054.7	2981.4	5514.3
	Total	PRE	104	16	15.4	9.1	23.8	4.4	3.9	4.9
		PIII(M7)	104	104	100	96.5	100	4552.0	3960.4	5232.0
ALU	S-	PRE	90	0	0.0	0.0	4.0	3.5	3.5	3.5
		PIII(M7)	89	3	3.4	0.7	9.5	3.6	3.5	3.7
	S+	PRE	8	8	100	63.1	100	23.7	11.7	47.9
		PIII(M7)	8	6	75.0	34.9	96.8	23.0	6.8	78.5
	Total	PRE	98	8	8.2	3.6	15.5	4.1	3.6	4.6
		PIII(M7)	97	9	9.3	4.3	16.9	4.2	3.7	4.8

S- = seronegative subjects (antibody titer < 7 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 7 EL.U/mL) prior to vaccination
N = number of subjects with pre-vaccination results available
n(%) = number(percentage) of subjects with titers within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M7) =Post Dose 3, Month 7
PRE =Pre-Vaccination

Secondary Outcome Variables:
Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

Symptom	Intensity	HPV Group					ALU Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Dose 1											
Pain	Any	149	142	95.3	90.6	98.1	148	108	73.0	65.1	79.9
	Grade 3	149	12	8.1	4.2	13.6	148	2	1.4	0.2	4.8
Redness	Any	149	70	47.0	38.8	55.3	148	46	31.1	23.7	39.2
	> 50 mm	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
Swelling	Any	149	72	48.3	40.1	56.6	148	34	23.0	16.5	30.6
	> 50 mm	149	2	1.3	0.2	4.8	148	0	0.0	0.0	2.5
Dose 2											
Pain	Any	147	121	82.3	75.2	88.1	147	82	55.8	47.4	64.0
	Grade 3	147	13	8.8	4.8	14.6	147	2	1.4	0.2	4.8
Redness	Any	147	78	53.1	44.7	61.3	147	40	27.2	20.2	35.2
	> 50 mm	147	2	1.4	0.2	4.8	147	0	0.0	0.0	2.5
Swelling	Any	147	74	50.3	42.0	58.7	147	32	21.8	15.4	29.3
	> 50 mm	147	3	2.0	0.4	5.8	147	0	0.0	0.0	2.5
Dose 3											
Pain	Any	143	108	75.5	67.6	82.3	146	85	58.2	49.8	66.3
	Grade 3	143	8	5.6	2.4	10.7	146	1	0.7	0.0	3.8
Redness	Any	143	68	47.6	39.1	56.1	146	37	25.3	18.5	33.2
	> 50 mm	143	0	0.0	0.0	2.5	146	0	0.0	0.0	2.5
Swelling	Any	143	75	52.4	43.9	60.9	146	36	24.7	17.9	32.5
	> 50 mm	143	3	2.1	0.4	6.0	146	0	0.0	0.0	2.5
Across doses											

Pain	Any	149	144	96.6	92.3	98.9	148	122	82.4	75.3	88.2
	Grade 3	149	25	16.8	11.2	23.8	148	4	2.7	0.7	6.8
Redness	Any	149	101	67.8	59.6	75.2	148	66	44.6	36.4	53.0
	> 50 mm	149	2	1.3	0.2	4.8	148	0	0.0	0.0	2.5
Swelling	Any	149	109	73.2	65.3	80.1	148	59	39.9	31.9	48.2
	> 50 mm	149	7	4.7	1.9	9.4	148	0	0.0	0.0	2.5

N = number of subjects with a documented dose
n(%) = number(percentage) of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = any solicited local symptom irrespective of intensity grade
Grade 3 pain = Pain that prevented normal activity

Secondary Outcome Variables:
Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

Symptom	**Intensity / relationship**	**HPV Group**					**ALU Group**				
		N	**n**	**%**	**95% CI**		**N**	**n**	**%**	**95% CI**	
					LL	**UL**				**LL**	**UL**
Dose 1											
Arthralgia*	Any	149	15	10.1	5.7	16.1	148	13	8.8	4.8	14.6
	Grade 3	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
	Related	149	9	6.0	2.8	11.2	148	7	4.7	1.9	9.5
Fatigue	Any	149	74	49.7	41.4	58.0	148	54	36.5	28.7	44.8
	Grade 3	149	2	1.3	0.2	4.8	148	2	1.4	0.2	4.8
	Related	149	56	37.6	29.8	45.9	148	36	24.3	17.7	32.1
Fever (axillary)	≥ 37.5°C	149	8	5.4	2.3	10.3	148	10	6.8	3.3	12.1
	> 39.0°C	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
	Related	149	4	2.7	0.7	6.7	148	1	0.7	0.0	3.7
Gastrointestinal	Any	149	25	16.8	11.2	23.8	148	22	14.9	9.6	21.6
	Grade 3	149	1	0.7	0.0	3.7	148	2	1.4	0.2	4.8
	Related	149	10	6.7	3.3	12.0	148	5	3.4	1.1	7.7
Headache	Any	149	45	30.2	23.0	38.3	148	35	23.6	17.1	31.3
	Grade 3	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
	Related	149	24	16.1	10.6	23.0	148	12	8.1	4.3	13.7
Myalgia	Any	149	68	45.6	37.5	54.0	148	48	32.4	25.0	40.6
	Grade 3	149	2	1.3	0.2	4.8	148	1	0.7	0.0	3.7
	Related	149	52	34.9	27.3	43.1	148	32	21.6	15.3	29.1
Rash	Any	149	2	1.3	0.2	4.8	148	3	2.0	0.4	5.8
	Grade 3	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
	Related	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
Urticaria	Any	149	4	2.7	0.7	6.7	148	4	2.7	0.7	6.8
	Grade 3	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
	Related	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
Dose 2											
Arthralgia*	Any	147	14	9.5	5.3	15.5	147	12	8.2	4.3	13.8
	Grade 3	147	1	0.7	0.0	3.7	147	0	0.0	0.0	2.5
	Related	147	9	6.1	2.8	11.3	147	6	4.1	1.5	8.7
Fatigue	Any	147	63	42.9	34.7	51.3	147	49	33.3	25.8	41.6
	Grade 3	147	0	0.0	0.0	2.5	147	2	1.4	0.2	4.8
	Related	147	54	36.7	28.9	45.1	147	35	23.8	17.2	31.5
Fever (axillary)	≥ 37.5°C	147	13	8.8	4.8	14.6	147	8	5.4	2.4	10.4
	> 39.0°C	147	1	0.7	0.0	3.7	147	0	0.0	0.0	2.5
	Related	147	4	2.7	0.7	6.8	147	1	0.7	0.0	3.7
Gastrointestinal	Any	147	22	15.0	9.6	21.8	147	10	6.8	3.3	12.2
	Grade 3	147	0	0.0	0.0	2.5	147	0	0.0	0.0	2.5
	Related	147	10	6.8	3.3	12.2	147	5	3.4	1.1	7.8
Headache	Any	147	34	23.1	16.6	30.8	147	25	17.0	11.3	24.1

	Grade 3	147	1	0.7	0.0	3.7	147	1	0.7	0.0	3.7
	Related	147	22	15.0	9.6	21.8	147	15	10.2	5.8	16.3
Myalgia	Any	147	55	37.4	29.6	45.8	147	30	20.4	14.2	27.8
	Grade 3	147	2	1.4	0.2	4.8	147	2	1.4	0.2	4.8
	Related	147	48	32.7	25.2	40.9	147	23	15.6	10.2	22.5
Rash	Any	147	5	3.4	1.1	7.8	147	1	0.7	0.0	3.7
	Grade 3	147	0	0.0	0.0	2.5	147	0	0.0	0.0	2.5
	Related	147	1	0.7	0.0	3.7	147	0	0.0	0.0	2.5
Urticaria	Any	147	4	2.7	0.7	6.8	147	1	0.7	0.0	3.7
	Grade 3	147	1	0.7	0.0	3.7	147	0	0.0	0.0	2.5
	Related	147	0	0.0	0.0	2.5	147	0	0.0	0.0	2.5
Dose 3											
Arthralgia*	Any	143	12	8.4	4.4	14.2	146	7	4.8	1.9	9.6
	Grade 3	143	2	1.4	0.2	5.0	146	0	0.0	0.0	2.5
	Related	143	8	5.6	2.4	10.7	146	3	2.1	0.4	5.9
Fatigue	Any	143	58	40.6	32.4	49.1	146	34	23.3	16.7	31.0
	Grade 3	143	2	1.4	0.2	5.0	146	1	0.7	0.0	3.8
	Related	143	48	33.6	25.9	41.9	146	29	19.9	13.7	27.3
Fever (axillary)	≥ 37.5°C	143	12	8.4	4.4	14.2	146	12	8.2	4.3	13.9
	> 39.0°C	143	0	0.0	0.0	2.5	146	0	0.0	0.0	2.5
	Related	143	3	2.1	0.4	6.0	146	1	0.7	0.0	3.8
Gastrointestinal	Any	143	13	9.1	4.9	15.0	146	11	7.5	3.8	13.1
	Grade 3	143	2	1.4	0.2	5.0	146	0	0.0	0.0	2.5
	Related	143	6	4.2	1.6	8.9	146	4	2.7	0.8	6.9
Headache	Any	143	29	20.3	14.0	27.8	146	23	15.8	10.3	22.7
	Grade 3	143	1	0.7	0.0	3.8	146	0	0.0	0.0	2.5
	Related	143	20	14.0	8.8	20.8	146	13	8.9	4.8	14.7
Myalgia	Any	143	51	35.7	27.8	44.1	146	34	23.3	16.7	31.0
	Grade 3	143	3	2.1	0.4	6.0	146	1	0.7	0.0	3.8
	Related	143	40	28.0	20.8	36.1	146	25	17.1	11.4	24.2
Rash	Any	143	2	1.4	0.2	5.0	146	2	1.4	0.2	4.9
	Grade 3	143	0	0.0	0.0	2.5	146	0	0.0	0.0	2.5
	Related	143	1	0.7	0.0	3.8	146	0	0.0	0.0	2.5
Urticaria	Any	143	1	0.7	0.0	3.8	146	2	1.4	0.2	4.9
	Grade 3	143	0	0.0	0.0	2.5	146	0	0.0	0.0	2.5
	Related	143	0	0.0	0.0	2.5	146	0	0.0	0.0	2.5
Across doses											
Arthralgia*	Any	149	26	17.4	11.7	24.5	148	25	16.9	11.2	23.9
	Grade 3	149	3	2.0	0.4	5.8	148	0	0.0	0.0	2.5
	Related	149	12	8.1	4.2	13.6	148	10	6.8	3.3	12.1
Fatigue	Any	149	94	63.1	54.8	70.8	148	75	50.7	42.3	59.0
	Grade 3	149	4	2.7	0.7	6.7	148	4	2.7	0.7	6.8
	Related	149	63	42.3	34.2	50.6	148	41	27.7	20.7	35.7
Fever (axillary)	≥ 37.5°C	149	26	17.4	11.7	24.5	148	23	15.5	10.1	22.4
	> 39.0°C	149	1	0.7	0.0	3.7	148	0	0.0	0.0	2.5
	Related	149	6	4.0	1.5	8.6	148	2	1.4	0.2	4.8
Gastrointestinal	Any	149	41	27.5	20.5	35.4	148	33	22.3	15.9	29.9
	Grade 3	149	3	2.0	0.4	5.8	148	2	1.4	0.2	4.8
	Related	149	12	8.1	4.2	13.6	148	6	4.1	1.5	8.6
Headache	Any	149	67	45.0	36.8	53.3	148	54	36.5	28.7	44.8
	Grade 3	149	2	1.3	0.2	4.8	148	1	0.7	0.0	3.7
	Related	149	30	20.1	14.0	27.5	148	19	12.8	7.9	19.3
Myalgia	Any	149	88	59.1	50.7	67.0	148	61	41.2	33.2	49.6
	Grade 3	149	5	3.4	1.1	7.7	148	2	1.4	0.2	4.8
	Related	149	58	38.9	31.1	47.2	148	35	23.6	17.1	31.3
Rash	Any	149	8	5.4	2.3	10.3	148	6	4.1	1.5	8.6

	Grade 3	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5
	Related	149	1	0.7	0.0	3.7	148	0	0.0	0.0	2.5
Urticaria	Any	149	8	5.4	2.3	10.3	148	5	3.4	1.1	7.7
	Grade 3	149	1	0.7	0.0	3.7	148	0	0.0	0.0	2.5
	Related	149	0	0.0	0.0	2.4	148	0	0.0	0.0	2.5

N = number of subjects a documented dose
n(%) = number(percentage) of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = incidence of a specified general symptom irrespective of intensity grade and relationship to vaccination
Grade 3 = symptom that prevented normal activity
Grade 3 urticaria = urticaria distributed on at least 4 body areas
Related= symptoms considered by the investigator to be causally related to the vaccination
*Arthralgia (joint pain): only in joints which were distal from the injection site.

Secondary Outcome Variables:
Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (GSK assessment) classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (Total Vaccinated Cohort)

NOCDs	**HPV N = 150**				**ALU N = 150**			
			95% CI				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	8	5.3	2.3	10.2	4	2.7	0.7	6.7
Allergy to animal	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Hypersensitivity	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Arthritis	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Asthma	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Dermatitis allergic	4	2.7	0.7	6.7	2	1.3	0.2	4.7
Urticaria	2	1.3	0.2	4.7	0	0.0	0.0	2.4

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variables:
Percentage of subjects reporting the occurrence of medically significant AEs classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (Total vaccinated cohort)

Medically significant AEs	**HPV N = 150**				**ALU N = 150**			
			95% CI				**95% CI**	
	n	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	42	28.0	21.0	35.9	24	16.0	10.5	22.9
Hyperprolactinaemia	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Conjunctivitis	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Abdominal discomfort	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Abdominal distension	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Abdominal pain upper	1	0.7	0.0	3.7	1	0.7	0.0	3.7
Constipation	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Diarrhea	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Dyspepsia	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Enteritis	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Gastritis	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Gastrointestinal disorder	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Hemorrhoids	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Irritable bowel syndrome	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Influenza like illness	2	1.3	0.2	4.7	0	0.0	0.0	2.4
Mass	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Allergy to animal	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Allergy to arthropod bite	1	0.7	0.0	3.7	0	0.0	0.0	2.4

Hypersensitivity	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Bronchitis	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Candidiasis	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Gingival infection	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Influenza	11	7.3	3.7	12.7	9	6.0	2.8	11.1
Otitis media	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Pelvic inflammatory disease	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Skin infection	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Accidental needle stick	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Animal bite	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Limb injury	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Arthritis	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Back pain	2	1.3	0.2	4.7	1	0.7	0.0	3.7
Myalgia	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Dizziness	4	2.7	0.7	6.7	1	0.7	0.0	3.7
Headache	2	1.3	0.2	4.7	0	0.0	0.0	2.4
Hyperaesthesia	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Menorrhagia	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Oligomenorrhoea	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Vaginal hemorrhage	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Vulvovaginal pruritus	2	1.3	0.2	4.7	0	0.0	0.0	2.4
Cough	6	4.0	1.5	8.5	5	3.3	1.1	7.6
Pharyngolaryngeal pain	5	3.3	1.1	7.6	0	0.0	0.0	2.4
Rhinorrhea	0	0.0	0.0	2.4	1	0.7	0.0	3.7
Acne	2	1.3	0.2	4.7	0	0.0	0.0	2.4
Dermatitis allergic	3	2.0	0.4	5.7	1	0.7	0.0	3.7
Rash	2	1.3	0.2	4.7	1	0.7	0.0	3.7
Rash pruritic	1	0.7	0.0	3.7	0	0.0	0.0	2.4
Urticaria	1	0.7	0.0	3.7	0	0.0	0.0	2.4

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Safety Results: Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort)

Most frequent adverse events - On-Therapy (occurring within Day 0-29 following vaccination)	**HPV Group N = 150**	**ALU Group N = 150**
Subjects with any AE(s), n (%)	87 (58.0)	66 (44.0)
Subjects with grade 3* AE(s), n (%)	13 (8.7)	7 (4.7)
Subjects with related** AE(s), n (%)	11 (7.3)	9 (6.0)
Influenza	17 (11.3)	13 (8.7)
Nasopharyngitis	12 (8.0)	13 (8.7)
Headache	8 (5.3)	8 (5.3)
Pharyngolaryngeal pain	10 (6.7)	6 (4.0)
Dizziness	8 (5.3)	5 (3.3)
Dysmenorrhea	8 (5.3)	5 (3.3)
Cough	6 (4.0)	6 (4.0)
Gastroenteritis	4 (2.7)	5 (3.3)
Abdominal pain upper	4 (2.7)	3 (2.0)
Dermatitis allergic	4 (2.7)	-
Diarrhea	-	3 (2.0)
Injection site reaction	-	3 (2.0)
Insomnia	-	3 (2.0)

* Grade 3 AE: AE that prevented normal activity
**Related AE: AE considered by the investigator to be causally related to the study vaccination
- : Adverse event absent or not meeting the selection rule.

Detail of rule: display 10 most frequent primary preferred terms		
Safety Results: Number (%) of subjects with serious adverse events (Total Vaccinated Cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	**HPV Group N = 150**	**ALU Group N = 150**
Subjects with any SAE(s), n (%) [n related]	3 (2.0) [0]	1 (0.7) [0]
Abdominal pain upper	1 (0.7) [0]	0 (0.0) [0]
Dizziness	1 (0.7) [0]	0 (0.0) [0]
Headache	1 (0.7) [0]	0 (0.0) [0]
Irritable bowel syndrome	1 (0.7) [0]	0 (0.0) [0]
Pelvic inflammatory disease	0 (0.0) [0]	1 (0.7) [0]
Fatal SAEs	**HPV Group N = 150**	**ALU Group N = 150**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]

Conclusions: At Month 7, all subjects in the HPV Group had seroconverted for both anti-HPV-16 and anti-HPV-18 antibodies with GMTs of 9614.4 and 4552.0, respectively. Across doses and groups, pain and fatigue were the most frequently reported solicited local and general symptoms, respectively. Unsolicited AEs were reported by 87 (58%) and 66 (44%) of the subjects in the HPV and the ALU groups, respectively. Of these unsolicited AEs, 13 (8.7%) and 7 (4.7%) were rated grade 3 in the HPV Group and the ALU Group, respectively and 11 (7.3%) and 9 (6.0%) were considered by the investigators as related to the vaccination in the HPV Group and the ALU Group, respectively. The occurrence of NOCDs was reported by 8 (5.3%) and 4 (2.7%) subjects in the HPV and the ALU groups, respectively. The occurrence of medically significant AEs was reported by 42 (28.0%) and 24 (16.0%) subjects in the HPV and the ALU groups, respectively. SAEs were reported by 3 subjects in the HPV Group and 1 subject in the ALU Group. None of the reported SAEs were considered by the investigators to be causally related to the study vaccination. No fatal SAEs were reported Please refer also to the publication below.

Publications:

Verstraeten T et al. (2008) Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines. Vaccine. 26(51):6630–6638.
Ngan HY et al. (2010) Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. Hong Kong Med J. 16(3): 171-179.

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