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.: 104951 (HPV-033)

Title: A phase III, 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 10–14 years.
HPV-16/18 L1 VLP AS04 vaccine (HPV): GSK Biologicals' prophylactic human papillomavirus (HPV) vaccine that contains HPV-16 and HPV-18 L1 proteins (which assemble into virus-like particles (VLP)) formulated with AS04 adjuvant.

Rationale: The aim of the study was to evaluate the immunogenicity and safety of the HPV-16/18 L1 VLP AS04 vaccine in pre-teen and adolescent female subjects aged 10–14 years. A control group received Havrix.
Havrix (HAV): GlaxoSmithKline Biologicals' hepatitis A vaccine.

Phase: III

Study Period: 11 November 2005 to 25 August 2006.

Study Design: Multi-centre, double-blind*, randomized (1:1) and controlled study with 2 parallel groups.
*Due to differences in the appearance of the HPV and HAV vaccines, the study was conducted in an observer-blind manner.

Centers: Eight study centers in South Korea.

Indication: Active immunization of females from the age of 10 years onwards to prevent persistent HPV-16 and HPV 18 infection and HPV-16 and HPV-18 associated cervical neoplasia.

Treatment: The study groups were as follows:

- One group received 3 doses of HPV vaccine (HPV Group).
- One control group received 3 doses of HAV vaccine (HAV Group).

All vaccines were administered intramuscularly into the deltoid 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 ELISA) in all HPV vaccine recipients at Month 7.

Primary Outcome/Efficacy Variable:
Seroconversion rates to HPV-16 and HPV-18 as assessed by ELISA at Month 7.
Seroconversion was defined as the appearance of antibodies (i.e.anti-HPV-16 titer $\geq$ 8 EL.U/mL, anti-HPV-18 titer $\geq$ 7 EL.U/mL) in the serum of subjects who were seronegative before vaccination.

Secondary Outcome/Efficacy Variables:
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 (Day 0–6) after each and any vaccination.
- Occurrence, intensity and causal relationship to vaccination of unsolicited adverse events (AEs) within 30 days (Day 0–29) after any vaccination.
- Occurrence of clinically relevant abnormalities in biochemical and hematological parameters assessed at Months 0 and 7.
- Occurrence of new onset of chronic diseases (NOCD) and other medically significant conditions, defined as AEs prompting emergency room or physician visits that were not related to common diseases or routine visits for physical examination or vaccination* throughout the study period (up to Month 7), regardless of causal relationship to vaccination and intensity.

* During the course of the study, this definition was changed into: 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 include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

Statistical Methods:
The analyses were performed on the Total Vaccinated Cohort and on 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 and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity measures were available.

Analysis of immunogenicity

The analysis was performed on the ATP cohort for immunogenicity.

For each time point that serological results were available, seroconversion/seropositivity rates with exact 95% confidence interval (CI) and geometric mean titers (GMTs) with 95% CI for anti-HPV-16, anti-HPV-18 and anti-HAV antibodies were calculated. Antibody titers 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 was performed on the Total Vaccinated Cohort.

For each group, the percentage of subjects reporting each individual solicited local and general symptom during the 7-day solicited follow-up period (Day 0–6) was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 symptoms and for solicited general symptoms with causal relationship to vaccination. At Month 7, the percentage of subjects with values outside the normal ranges was calculated for biochemistry parameters, including creatinine and alanine aminotransferase (ALT), and hematological parameters including hematocrit, red blood cell, platelet and white blood cell counts. The percentage of subjects with NOCD reported during the entire study period (up to Month 7) was tabulated with exact 95% CI, according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The percentage of subjects with a medically significant AE reported during the entire study period (up to Month 7) was tabulated with exact 95 %CI, according to the MedDRA preferred terms. The percentage of subjects with unsolicited AEs reported during the 30-day (Day 0-29) follow-up period after any vaccination was tabulated according to the MedDRA preferred terms. The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs with a causal relationship to vaccination. The occurrence of SAEs during the entire study period was tabulated according to the MedDRA preferred terms.

Study Population: Healthy female subjects between 10 and 14 years of age, free of obvious health problems as established by medical history and clinical examination, and having a negative urine pregnancy test. 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 the vaccination series. Written informed assent was obtained from the subject and written informed consent was obtained from the legally acceptable representative, the parent or guardian of the subject before entry into the study.

Number of subjects	**HPV Group**	**HAV Group**
Planned, N	150	150
Randomized, N (Total Vaccinated Cohort)	160	161
Completed, n (%)	158 (98.8)	161 (100)
Total Number Subjects Withdrawn, n (%)	2 (1.3)	0 (0.0)
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)	0 (0.0)
Demographics	**HPV Group**	**HAV Group**
N (Total Vaccinated Cohort)	160	161
Males:Females	0:160	0:161
Mean Age, Years (SD)	12.0 (1.42)	11.8 (1.39)
Asian – South East Asian, n (%)	120 (75.0)	119 (73.9)

Primary Efficacy Results:

Seroconversion/seropositivity rates 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	112	0	0.0	0.0	3.2	4.0	4.0	4.0
		PIII(M7)*	112	112	100	96.8	100	19619.8	17188.6	22394.8
	S+	PRE	7	7	100	59.0	100	24.7	15.1	40.1
		PIII(M7)	7	7	100	59.0	100	20778.6	13383.8	32259.2
	Total	PRE	119	7	5.9	2.4	11.7	4.5	4.1	4.8
		PIII(M7)	119	119	100	96.9	100	19686.1	17356.8	22328.1
HAV	S-	PRE	120	0	0.0	0.0	3.0	4.0	4.0	4.0

		PIII(M7)*	120	8	6.7	2.9	12.7	4.8	4.2	5.5
	S+	PRE	8	8	100	63.1	100	27.4	11.0	68.1
		PIII(M7)	8	6	75.0	34.9	96.8	34.4	3.7	316.5
	Total	PRE	128	8	6.3	2.7	11.9	4.5	4.1	5.0
		PIII(M7)	128	14	10.9	6.1	17.7	5.4	4.5	6.6

S- = seronegative subjects (antibody titers < 8 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody titers ≥ 8 EL.U/mL) prior to vaccination
N = number of subjects with available results
n (%) = number (percentage) of subjects with antibody titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII(M7) = post-Dose 3, Month 7
*Primary efficacy results

Primary Efficacy Results:
Seroconversion/seropositivity rates 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	115	0	0.0	0.0	3.2	3.5	3.5	3.5
		PIII(M7)*	115	115	100	96.8	100	9894.5	8674.1	11286.6
	S+	PRE	5	5	100	47.8	100	10.8	6.7	17.5
		PIII(M7)	5	5	100	47.8	100	9097.1	6155.6	13444.0
	Total	PRE	120	5	4.2	1.4	9.5	3.7	3.5	3.8
		PIII(M7)	120	120	100	97.0	100	9859.9	8687.9	11189.9
HAV	S-	PRE	119	0	0.0	0.0	3.1	3.5	3.5	3.5
		PIII(M7)*	119	9	7.6	3.5	13.9	4.7	3.8	5.9
	S+	PRE	9	9	100	66.4	100	19.5	11.1	34.0
		PIII(M7)	9	6	66.7	29.9	92.5	10.1	4.4	23.6
	Total	PRE	128	9	7.0	3.3	12.9	3.9	3.6	4.3
		PIII(M7)	128	15	11.7	6.7	18.6	5.0	4.0	6.1

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

Secondary Outcome Variable(s):
Seroconversion/seropositivity rates and GMTs for anti-HAV antibodies by pre-vaccination status (ATP cohort for immunogenicity)

Group	Pre-vaccination status	Timing	N	≥ 15 mIU/mL				GMT (mIU/mL)		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
HPV	S-	PRE	105	0	0.0	0.0	3.5	7.5	7.5	7.5
		PIII(M7)	105	11	10.5	5.3	18.0	8.9	7.9	10.1
	S+	PRE	15	15	100	78.2	100	46.5	26.1	82.9
		PIII(M7)	15	11	73.3	44.9	92.2	84.9	28.2	255.5
	Total	PRE	120	15	12.5	7.2	19.8	9.4	8.3	10.7
		PIII(M7)	120	22	18.3	11.9	26.4	11.8	9.6	14.6
HAV	S-	PRE	115	0	0.0	0.0	3.2	7.5	7.5	7.5
		PIII(M7)	115	115	100	96.8	100	1828.0	1557.6	2145.3
	S+	PRE	13	13	100	75.3	100	69.4	18.5	259.8
		PIII(M7)	13	13	100	75.3	100	3363.6	1801.6	6279.6
	Total	PRE	128	13	10.2	5.5	16.7	9.4	8.0	11.1

		PIII(M7)	128	128	100	97.2	100	1944.8	1661.7	2276.1

S- = seronegative subjects (antibody titers < 15 mIU/mL) prior to vaccination
S+ = seropositive subjects (antibody titers ≥ 15 mIU/mL) prior to vaccination
N = number of subjects with available results
n (%) = number (percentage) of subjects with antibody titers within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII(M7) = post-Dose 3, Month 7

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

Symptom	Intensity	HPV Group					HAV Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Dose 1											
Pain	Any	158	109	69.0	61.2	76.1	161	69	42.9	35.1	50.9
	Grade 3	158	1	0.6	0.0	3.5	161	0	0.0	0.0	2.3
Redness	Any	158	39	24.7	18.2	32.2	161	23	14.3	9.3	20.7
	> 50 mm	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
Swelling	Any	158	37	23.4	17.1	30.8	161	10	6.2	3.0	11.1
	> 50 mm	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
Dose 2											
Pain	Any	158	93	58.9	50.8	66.6	161	43	26.7	20.1	34.2
	Grade 3	158	1	0.6	0.0	3.5	161	0	0.0	0.0	2.3
Redness	Any	158	41	25.9	19.3	33.5	161	15	9.3	5.3	14.9
	> 50 mm	158	1	0.6	0.0	3.5	161	0	0.0	0.0	2.3
Swelling	Any	158	33	20.9	14.8	28.1	161	10	6.2	3.0	11.1
	> 50 mm	158	3	1.9	0.4	5.4	161	0	0.0	0.0	2.3
Dose 3											
Pain	Any	158	84	53.2	45.1	61.1	161	35	21.7	15.6	28.9
	Grade 3	158	1	0.6	0.0	3.5	161	0	0.0	0.0	2.3
Redness	Any	158	39	24.7	18.2	32.2	161	16	9.9	5.8	15.6
	> 50 mm	158	4	2.5	0.7	6.4	161	0	0.0	0.0	2.3
Swelling	Any	158	29	18.4	12.7	25.3	161	7	4.3	1.8	8.8
	> 50 mm	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
Across Doses											
Pain	Any	158	135	85.4	79.0	90.5	161	87	54.0	46.0	61.9
	Grade 3	158	3	1.9	0.4	5.4	161	0	0.0	0.0	2.3
Redness	Any	158	77	48.7	40.7	56.8	161	37	23.0	16.7	30.3
	> 50 mm	158	5	3.2	1.0	7.2	161	0	0.0	0.0	2.3
Swelling	Any	158	64	40.5	32.8	48.6	161	20	12.4	7.8	18.5
	> 50 mm	158	3	1.9	0.4	5.4	161	0	0.0	0.0	2.3

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

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

Symptom	Intensity / relationship	HPV Group					HAV Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Dose 1											
Arthralgia	Any	158	12	7.6	4.0	12.9	161	10	6.2	3.0	11.1
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3

	Related	158	5	3.2	1.0	7.2	161	5	3.1	1.0	7.1
Fatigue	Any	158	36	22.8	16.5	30.1	161	39	24.2	17.8	31.6
	Grade 3	158	0	0.0	0.0	2.3	161	1	0.6	0.0	3.4
	Related	158	16	10.1	5.9	15.9	161	10	6.2	3.0	11.1
Fever (axillary)	≥ 37.5°C	158	3	1.9	0.4	5.4	161	3	1.9	0.4	5.3
	> 39.0°C	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
Gastrointestinal	Any	158	8	5.1	2.2	9.7	161	17	10.6	6.3	16.4
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	4	2.5	0.7	6.4	161	8	5.0	2.2	9.6
Headache	Any	158	27	17.1	11.6	23.9	161	43	26.7	20.1	34.2
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	13	8.2	4.5	13.7	161	17	10.6	6.3	16.4
Myalgia	Any	158	30	19.0	13.2	26.0	161	16	9.9	5.8	15.6
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	16	10.1	5.9	15.9	161	8	5.0	2.2	9.6
Rash	Any	158	7	4.4	1.8	8.9	161	4	2.5	0.7	6.2
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	2	1.3	0.2	4.5	161	4	2.5	0.7	6.2
Urticaria	Any	158	1	0.6	0.0	3.5	161	4	2.5	0.7	6.2
	Grade 3	158	0	0.0	0.0	2.3	161	1	0.6	0.0	3.4
	Related	158	0	0.0	0.0	2.3	161	1	0.6	0.0	3.4
Dose 2											
Arthralgia	Any	158	3	1.9	0.4	5.4	161	5	3.1	1.0	7.1
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	2	1.3	0.2	4.5	161	1	0.6	0.0	3.4
Fatigue	Any	158	21	13.3	8.4	19.6	161	28	17.4	11.9	24.1
	Grade 3	158	0	0.0	0.0	2.3	161	1	0.6	0.0	3.4
	Related	158	9	5.7	2.6	10.5	161	9	5.6	2.6	10.3
Fever (axillary)	≥ 37.5°C	158	3	1.9	0.4	5.4	161	3	1.9	0.4	5.3
	> 39.0°C	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	0	0.0	0.0	2.3	161	2	1.2	0.2	4.4
Gastrointestinal	Any	158	8	5.1	2.2	9.7	161	10	6.2	3.0	11.1
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	2	1.3	0.2	4.5	161	3	1.9	0.4	5.3
Headache	Any	158	18	11.4	6.9	17.4	161	18	11.2	6.8	17.1
	Grade 3	158	0	0.0	0.0	2.3	161	1	0.6	0.0	3.4
	Related	158	4	2.5	0.7	6.4	161	6	3.7	1.4	7.9
Myalgia	Any	158	28	17.7	12.1	24.6	161	14	8.7	4.8	14.2
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	18	11.4	6.9	17.4	161	7	4.3	1.8	8.8
Rash	Any	158	4	2.5	0.7	6.4	161	4	2.5	0.7	6.2
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	3	1.9	0.4	5.4	161	1	0.6	0.0	3.4
Urticaria	Any	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
Dose 3											
Arthralgia	Any	158	11	7.0	3.5	12.1	161	3	1.9	0.4	5.3
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	3	1.9	0.4	5.4	161	2	1.2	0.2	4.4
Fatigue	Any	158	33	20.9	14.8	28.1	161	20	12.4	7.8	18.5
	Grade 3	158	1	0.6	0.0	3.5	161	0	0.0	0.0	2.3
	Related	158	16	10.1	5.9	15.9	161	3	1.9	0.4	5.3
Fever (axillary)	≥ 37.5°C	158	7	4.4	1.8	8.9	161	1	0.6	0.0	3.4

	> 39.0°C	158	1	0.6	0.0	3.5	161	0	0.0	0.0	2.3
	Related	158	2	1.3	0.2	4.5	161	0	0.0	0.0	2.3
Gastrointestinal	Any	158	8	5.1	2.2	9.7	161	6	3.7	1.4	7.9
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	2	1.3	0.2	4.5	161	1	0.6	0.0	3.4
Headache	Any	158	17	10.8	6.4	16.7	161	15	9.3	5.3	14.9
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	5	3.2	1.0	7.2	161	4	2.5	0.7	6.2
Myalgia	Any	158	21	13.3	8.4	19.6	161	10	6.2	3.0	11.1
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	10	6.3	3.1	11.3	161	4	2.5	0.7	6.2
Rash	Any	158	8	5.1	2.2	9.7	161	1	0.6	0.0	3.4
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	5	3.2	1.0	7.2	161	0	0.0	0.0	2.3
Urticaria	Any	158	4	2.5	0.7	6.4	161	1	0.6	0.0	3.4
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	2	1.3	0.2	4.5	161	0	0.0	0.0	2.3
Across Doses											
Arthralgia	Any	158	18	11.4	6.9	17.4	161	14	8.7	4.8	14.2
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	7	4.4	1.8	8.9	161	6	3.7	1.4	7.9
Fatigue	Any	158	59	37.3	29.8	45.4	161	52	32.3	25.2	40.1
	Grade 3	158	1	0.6	0.0	3.5	161	2	1.2	0.2	4.4
	Related	158	30	19.0	13.2	26.0	161	20	12.4	7.8	18.5
Fever (axillary)	≥ 37.5°C	158	13	8.2	4.5	13.7	161	6	3.7	1.4	7.9
	> 39.0°C	158	1	0.6	0.0	3.5	161	0	0.0	0.0	2.3
	Related	158	2	1.3	0.2	4.5	161	2	1.2	0.2	4.4
Gastrointestinal	Any	158	20	12.7	7.9	18.9	161	26	16.1	10.8	22.8
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	6	3.8	1.4	8.1	161	10	6.2	3.0	11.1
Headache	Any	158	44	27.8	21.0	35.5	161	53	32.9	25.7	40.8
	Grade 3	158	0	0.0	0.0	2.3	161	1	0.6	0.0	3.4
	Related	158	17	10.8	6.4	16.7	161	22	13.7	8.8	20.0
Myalgia	Any	158	49	31.0	23.9	38.8	161	29	18.0	12.4	24.8
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	29	18.4	12.7	25.3	161	16	9.9	5.8	15.6
Rash	Any	158	14	8.9	4.9	14.4	161	7	4.3	1.8	8.8
	Grade 3	158	0	0.0	0.0	2.3	161	0	0.0	0.0	2.3
	Related	158	9	5.7	2.6	10.5	161	5	3.1	1.0	7.1
Urticaria	Any	158	5	3.2	1.0	7.2	161	5	3.1	1.0	7.1
	Grade 3	158	0	0.0	0.0	2.3	161	1	0.6	0.0	3.4
	Related	158	2	1.3	0.2	4.5	161	1	0.6	0.0	3.4

N = number of subjects with a documented dose
n (%) = number (percentage) of subjects reporting the symptom at least once
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
Related = symptoms considered by the investigator to have a causal relationship to study vaccination
Grade 3 = symptom that prevented normal activity
Grade 3 urticaria = urticaria distributed on at least 4 body areas
Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain
Arthralgia (joint pain): only joints distal from the injection site

Secondary Outcome Variable(s):
Number and percentage of subjects outside the normal ranges for hematology and biochemistry (Total Vaccinated Cohort)

Laboratory test	Pre-	Timing	Parameters or	HPV Group	HAV Group	Total

	vaccination		Categories	n	%	n	%	n	%
Alanine amino transferase	Normal	PIII(M7)	N	154	-	156	-	310	-
			Normal	149	97.4	155	99.4	304	98.4
			Below	2	1.3	1	0.6	3	1.0
			Above	2	1.3	0	0.0	2	0.6
			Missing	1	-	0	0.0	1	-
	Below	PIII(M7)	N	3	-	4	-	7	-
			Normal	1	33.3	1	25.0	2	28.6
			Below	2	66.7	3	75.0	5	71.4
			Above	0	0.0	0	0.0	0	0.0
Basophils	Normal	PIII(M7)	N	158	-	159	-	317	-
			Normal	150	99.3	152	99.3	302	99.3
			Below	0	0.0	0	0.0	0	0.0
			Above	1	0.7	1	0.7	2	0.7
			Missing	7	-	6	-	13	-
	Above	PIII(M7)	N	0	-	2	-	2	-
			Normal	0	0.0	2	100	2	100
			Below	0	0.0	0	0.0	0	0.0
			Above	0	0.0	0	0.0	0	0.0
Creatinine	Normal	PIII(M7)	N	133	-	127	-	260	-
			Normal	130	98.5	126	99.2	256	98.8
			Below	2	1.5	1	0.8	3	1.2
			Above	0	0.0	0	0.0	0	0.0
			Missing	1	-	0	0.0	1	-
	Below	PIII(M7)	N	24	-	33	-	57	-
			Normal	8	33.3	20	60.6	28	49.1
			Below	16	66.7	13	39.4	29	50.9
			Above	0	0.0	0	0.0	0	0.0
Eosinophils	Normal	PIII(M7)	N	141	-	140	-	281	-
			Normal	128	94.1	129	96.3	257	95.2
			Below	2	1.5	1	0.7	3	1.1
			Above	6	4.4	4	3.0	10	3.7
			Missing	5	-	6	-	11	-
	Below	PIII(M7)	N	6	-	5	-	11	-
			Normal	2	50.0	2	50.0	4	50.0
			Below	2	50.0	2	50.0	4	50.0
			Above	0	0.0	0	0.0	0	0.0
			Missing	2	-	1	-	3	-
	Above	PIII(M7)	N	11	-	16	-	27	-
			Normal	7	63.6	6	37.5	13	48.1
			Below	0	0.0	0	0.0	0	0.0
			Above	4	36.4	10	62.5	14	51.9
Hematocrit	Normal	PIII(M7)	N	108	-	110	-	218	-
			Normal	95	90.5	94	85.5	189	87.9
			Below	10	9.5	16	14.5	26	12.1
			Above	0	0.0	0	0.0	0	0.0
			Missing	3	-	0	0.0	3	-
	Below	PIII(M7)	N	32	-	32	-	64	-
			Normal	10	31.3	9	28.1	19	29.7
			Below	22	68.8	23	71.9	45	70.3
			Above	0	0.0	0	0.0	0	0.0
	Above	PIII(M7)	N	18	-	19	-	37	-
			Normal	0	0.0	1	5.3	1	2.7
			Below	0	0.0	0	0.0	0	0.0
			Above	18	100	18	94.7	36	97.3

Lymphocytes	Normal	PIII(M7)	N	132	-	133	-	265	-
			Normal	110	87.3	121	93.1	231	90.2
			Below	2	1.6	0	0.0	2	0.8
			Above	14	11.1	9	6.9	23	9.0
			Missing	6	-	3	-	9	-
	Below	PIII(M7)	N	3	-	4	-	7	-
			Normal	3	100	4	100	7	100
			Below	0	0.0	0	0.0	0	0.0
			Above	0	0.0	0	0.0	0	0.0
	Above	PIII(M7)	N	23	-	24	-	47	-
			Normal	10	45.5	15	75.0	25	59.5
			Below	0	0.0	0	0.0	0	0.0
			Above	12	54.5	5	25.0	17	40.5
			Missing	1	-	4	-	5	-
Monocytes	Normal	PIII(M7)	N	131	-	139	-	270	-
			Normal	116	93.5	124	92.5	240	93.0
			Below	6	4.8	6	4.5	12	4.7
			Above	2	1.6	4	3.0	6	2.3
			Missing	7	-	5	-	12	-
	Below	PIII(M7)	N	9	-	10	-	19	-
			Normal	4	44.4	6	60.0	10	52.6
			Below	5	55.6	4	40.0	9	47.4
			Above	0	0.0	0	0.0	0	0.0
	Above	PIII(M7)	N	18	-	12	-	30	-
			Normal	14	77.8	11	100	25	86.2
			Below	0	0.0	0	0.0	0	0.0
			Above	4	22.2	0	0.0	4	13.8
			Missing	0	0.0	1	-	1	-
Neutrophils	Normal	PIII(M7)	N	123	-	121	-	244	-
			Normal	97	82.2	103	85.8	200	84.0
			Below	19	16.1	16	13.3	35	14.7
			Above	2	1.7	1	0.8	3	1.3
			Missing	5	-	1	-	6	-
	Below	PIII(M7)	N	34	-	36	-	70	-
			Normal	18	56.3	14	45.2	32	50.8
			Below	14	43.8	17	54.8	31	49.2
			Above	0	0.0	0	0.0	0	0.0
			Missing	2	-	5	-	7	-
	Above	PIII(M7)	N	1	-	4	-	5	-
			Normal	1	100	4	100	5	100
			Below	0	0.0	0	0.0	0	0.0
			Above	0	0.0	0	0.0	0	0.0
Platelets	Normal	PIII(M7)	N	148	-	150	-	298	-
			Normal	141	96.6	148	98.7	289	97.6
			Below	0	0.0	0	0.0	0	0.0
			Above	5	3.4	2	1.3	7	2.4
			Missing	2	-	0	0.0	2	-
	Below	PIII(M7)	N	0	-	1	-	1	-
			Normal	0	0.0	1	100	1	100
			Below	0	0.0	0	0.0	0	0.0
			Above	0	0.0	0	0.0	0	0.0
	Above	PIII(M7)	N	10	-	10	-	20	-
			Normal	6	66.7	6	60.0	12	63.2
			Below	0	0.0	0	0.0	0	0.0
			Above	3	33.3	4	40.0	7	36.8

			Missing	1	-	0	0.0	1	-
Red blood cells	Normal	PIII(M7)	N	143	-	143	-	286	-
			Normal	129	92.8	131	91.6	260	92.2
			Below	7	5.0	10	7.0	17	6.0
			Above	3	2.2	2	1.4	5	1.8
			Missing	4	-	0	0.0	4	-
	Below	PIII(M7)	N	11	-	13	-	24	-
			Normal	5	45.5	4	30.8	9	37.5
			Below	6	54.5	9	69.2	15	62.5
			Above	0	0.0	0	0.0	0	0.0
	Above	PIII(M7)	N	4	-	5	-	9	-
			Normal	1	25.0	5	100	6	66.7
			Below	0	0.0	0	0.0	0	0.0
			Above	3	75.0	0	0.0	3	33.3
White blood cells	Normal	PIII(M7)	N	146	-	142	-	288	-
			Normal	132	92.3	129	90.8	261	91.6
			Below	7	4.9	11	7.7	18	6.3
			Above	4	2.8	2	1.4	6	2.1
			Missing	3	-	0	0.0	3	-
	Below	PIII(M7)	N	4	-	10	-	14	-
			Normal	4	100	6	60.0	10	71.4
			Below	0	0.0	4	40.0	4	28.6
			Above	0	0.0	0	0.0	0	0.0
	Above	PIII(M7)	N	8	-	9	-	17	-
			Normal	7	87.5	8	88.9	15	88.2
			Below	1	12.5	1	11.1	2	11.8
			Above	0	0.0	0	0.0	0	0.0

N = total number of subjects
n = number of subjects in a given category
% = n / number of subjects with available results x 100
PIII(M7) = Month 7 post-vaccination

Secondary Outcome Variable(s):
Percentage of subjects with new onset of chronic diseases (GSK assessment) reported during the entire study period (Total Vaccinated Cohort)

New Onset Chronic Diseases	**HPV Group N = 160**				**HAV Group N = 161**			
	n	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**
At least one symptom	3	1.9	0.4	5.4	2	1.2	0.2	4.4
Dermatitis atopic	1	0.6	0.0	3.4	2	1.2	0.2	4.4
Dermatitis contact	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Urticaria	1	0.6	0.0	3.4	0	0.0	0.0	2.3

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

Secondary Outcome Variable(s):
Percentage of subjects with medically significant AEs reported during the entire study period (Total Vaccinated Cohort)

New Onset Chronic Diseases	**HPV Group N = 160**				**HAV Group N = 161**			
	n	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**
At least one symptom	11	6.9	3.5	12.0	10	6.2	3.0	11.1
Abdominal pain	2	1.3	0.2	4.4	0	0.0	0.0	2.3
Attention deficit/hyperactivity disorder	2	1.3	0.2	4.4	0	0.0	0.0	2.3
Dermatitis atopic	1	0.6	0.0	3.4	1	0.6	0.0	3.4

Abdominal pain upper	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Anal fissure	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Benign neoplasm of skin	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Bronchitis acute	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Chillblains	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Cough	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Cyst	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Dandruff	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Dermatitis contact	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Diarrhoea	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Ear pain	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Enteritis	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Epistaxis	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Foot fracture	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Joint sprain	0	0.0	0.0	2.3	1	0.6	0.0	3.4
Leukopenia	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Pyrexia	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Urticaria	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Vaginal discharge	1	0.6	0.0	3.4	0	0.0	0.0	2.3
Xerophthalmia	1	0.6	0.0	3.4	0	0.0	0.0	2.3

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with an administered dose
n (%) = number (percentage) of subjects reporting the symptom at least once
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 = 160**	**HAV Group N = 161**
Subjects with any AE(s), n (%)	47 (29.4)	33 (20.5)
Subjects with any Grade 3** AE(s), n (%)	0 (0.0)	1 (0.6)
Subjects with any related*** AE(s), n (%)	10 (6.3)	2 (1.2)
Upper respiratory tract infection	15 (9.4)	10 (6.2)
Nasopharyngitis	7 (4.4)	5 (3.1)
Rhinitis	5 (3.1)	6 (3.7)
Dizziness	5 (3.1)	3 (1.9)
Injection site pruritus	4 (2.5)	0 (0.0)
Abdominal pain	2 (1.3)	0 (0.0)
Cough	1 (0.6)	1 (0.6)
Dermatitis atopic	1 (0.6)	1 (0.6)
Dysmenorrhea	1 (0.6)	1 (0.6)
Epistaxis	0 (0.0)	2 (1.2)
Musculoskeletal pain	2 (1.3)	0 (0.0)
Pharyngolaryngeal pain	2 (1.3)	0 (0.0)
Pyrexia	1 (0.6)	1 (0.6)
Abdominal pain upper	0 (0.0)	1 (0.6)
Acute tonsillitis	1 (0.6)	0 (0.0)
Anal fissure	0 (0.0)	1 (0.6)
Attention deficit/hyperactivity disorder	1 (0.6)	0 (0.0)
Back pain	1 (0.6)	0 (0.0)
Benign neoplasm of skin	0 (0.0)	1 (0.6)
Chillblains	1 (0.6)	0 (0.0)
Cyst	1 (0.6)	0 (0.0)
Dandruff	1 (0.6)	0 (0.0)
Dermatitis contact	1 (0.6)	0 (0.0)
Diarrhea	1 (0.6)	0 (0.0)
Ear pain	0 (0.0)	1 (0.6)

Enteritis	0 (0.0)	1 (0.6)
Eye pain	0 (0.0)	1 (0.6)
Flushing	0 (0.0)	1 (0.6)
Foot fracture	0 (0.0)	1 (0.6)
Injection site anesthesia	1 (0.6)	0 (0.0)
Injection site nodule	1 (0.6)	0 (0.0)
Joint sprain	0 (0.0)	1 (0.6)
Myalgia	0 (0.0)	1 (0.6)
Nasal congestion	1 (0.6)	0 (0.0)
Otitis externa	0 (0.0)	1 (0.6)
Paresthesia	1 (0.6)	0 (0.0)
Pruritus	1 (0.6)	0 (0.0)
Rash	1 (0.6)	0 (0.0)
Urticaria	1 (0.6)	0 (0.0)
Varicella	1 (0.6)	0 (0.0)
Xerophthalmia	1 (0.6)	0 (0.0)
* More than 30 subjects/treatment group and ≤ 3 groups: the most frequent 10 events in each treatment group are presented. ** Grade 3 AE: AE that prevented normal activity *** Related AE: AE considered by the investigator to be causally related to the study vaccination		
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 = 160**	**HAV Group N = 161**
Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]	1 (0.6) [0]
Gastroenteritis	0 (0.0) [0]	1 (0.6) [0]
Fatal SAEs	**HPV Group N = 160**	**HAV Group N = 161**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: One month after Dose 3, all subjects in the HPV Group had seroconverted for anti-HPV-16 and anti-HPV-18 antibodies**;** GMTs for anti-HPV-16 and anti-HPV-18 antibodies were 19686.1 and 9859.9, respectively. Across doses, pain at the injection site was the most frequently reported solicited local symptom for both treatment groups and fatigue & headache were the most frequently reported solicited general symptoms in the HPV Group and the HAV Group, respectively. New onset of chronic diseases was reported by 3 (1.9%) subjects in the HPV Group and 2 (1.2%) in the HAV Group. Medically significant AEs were reported for 11 (6.9%) subjects in the HPV Group and 10 (6.2%) in the HAV Group. Unsolicited AEs were reported by 47 (29.4%) subjects in the HPV Group and 33 (20.5%) in the HAV Group. One of the AEs reported in the HAV Group was rated as Grade 3; the investigators considered the AEs reported by 10 (6.3%) subjects in the HPV Group and by 2 (1.2%) subjects in the HAV Groups to be related to the study vaccination. During the study period up to Month 7, one subject in the HAV Group reported an SAE that was considered by the investigator not to be related to the study vaccination. No fatal SAEs were reported throughout the study period.

Date Updated: 10-July-2014