25 July 2011
EMA/251548/2013
Committee for Medicinal Products for Human Use (CHMP)

Cervarix

(human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed))

Procedure No. EMEA/H/C/000721/P46/054

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. RECOMMENDATION

Based on the review of the paediatric data on safety and immunogenicity collected in study HPV-021 the Rapporteur considers that the benefit-risk balance for the above mentioned product remains unchanged and therefore does not require further regulatory action on the marketing authorisation for Cervarix. The SmPC and PIL remain unchanged.

With the submission of the final study results of study HPV-021 FUM054 can be considered as being fulfilled.

2. SCIENTIFIC DISCUSSION

The current study was designed to assess the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine in female subjects enrolled from multiple countries in Africa.

Ideally, HPV vaccination should be performed before onset of sexual activity, since studies have shown that acquisition of high-risk HPV occurs soon after sexual debut. Study HPV-021 was therefore designed to evaluate the HPV vaccine in subjects aged 10 to 25 years of age. This study report presents the analysis of final immunogenicity, reactogenicity and safety data collected up to Visit 8 (Month 12) for all subjects enrolled from Senegal and Tanzania. The study was conducted from 1 October 2007 till 26 July 2010. Data lock point: 10 November 2010.

2.1. STUDY METHODOLOGY

2.1.1. Objectives

Co-primary objectives

To evaluate antibody responses (ELISA) against HPV-16 and HPV-18 at Month 7 in subjects 15-25 years of age and subjects 10 - 14 years of age.

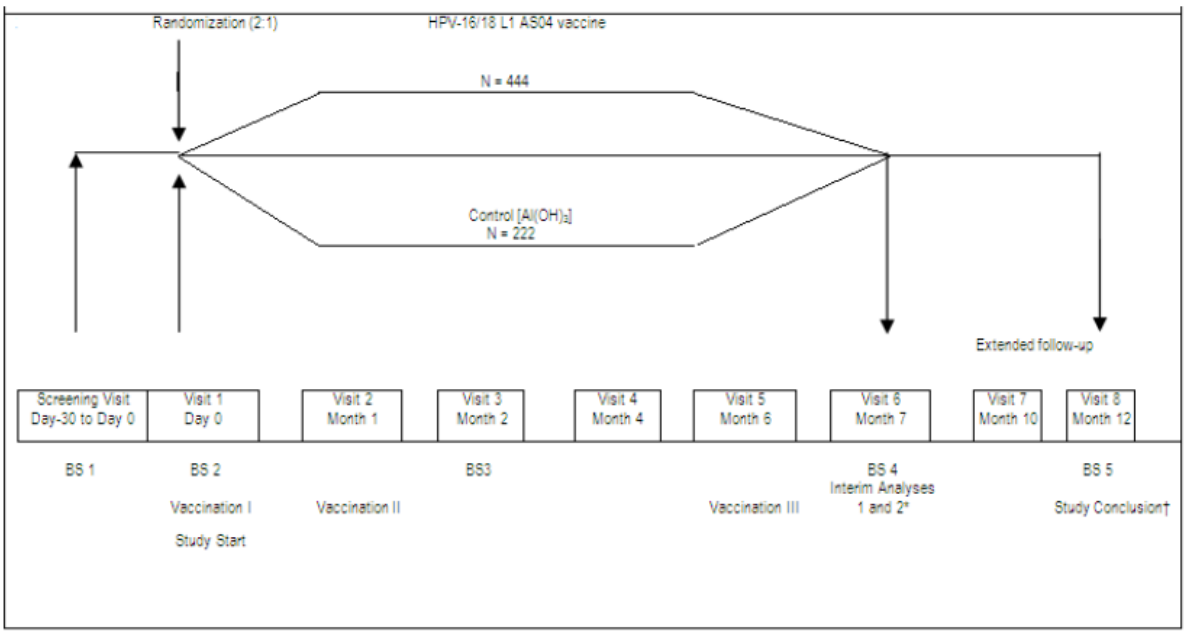
Secondary objectives

To evaluate antibody responses (ELISA) against HPV-16 and HPV-18 in all subjects at Month 2 and Month 12.

To evaluate the safety and reactogenicity of the study vaccine in all subjects throughout the entire study period.

2.1.2. Design

The study design is shown in the figure below.



BS: Blood sample

Two interim analyses (1 and 2) were planned: the first when all subjects in Senegal had completed Visit 6 (presented in the Interim Report 1 dated 22 January 2010) and the second when all subjects in Tanzania had completed Visit 6 (presented in the Interim Report 2 dated 29 November 2010).
The final analyses were performed when all subjects completed Visit 8 (Month 12) and are presented in the current report.
†Pregnancies were to be followed until delivery (even if the delivery occurred after the end of the study).
N = Number of subjects planned to be enrolled.

- Phase IIIb, controlled, randomized (2:1), double blind, multicentre trial with two parallel groups:

  Cervarix and Aluminium Hydroxide $Al(OH)_3$ as control. Two study centres in Dakar (Senegal) and Mwanza (Tanzania).

- Treatment groups: Enrolment into each treatment group was age-stratified, with two age strata (15 - 25 years of age and 10 - 14 years of age) with approximately one third of the total number of subjects enrolled in the second age stratum as follows:

Vaccines	HPV-16/18 L1 VLP AS04	Control	Total
Number of subjects planned to be enrolled	444	222	666
15 - 25 years stratum	296	148	444
10- 14 years stratum	148	74	222

- Vaccination schedule: three doses of vaccine/control according to a 0, 1, 6 month schedule.

- Within thirty days before administration of the first vaccine/control dose, subjects were invited to a screening visit. The following study procedures were performed during this visit:
    - Informed consent was obtained from the subject.
    - Review of medical history
    - General physical examination
    - Pregnancy test
    - If the pregnancy test was negative, a blood sample was to be collected to perform Human Immunodeficiency Virus (HIV) testing and hematological and biochemical parameters measurements.

After the screening visit, only eligible subjects, based on the inclusion and exclusion criteria, were enrolled in the study.

- Blood samples were collected at Visits 1, 3, 6 and 8, i.e., at Day 0, Months 2, 7 and 12), to test hematological and biochemical parameters and to perform HIV testing (at Day -30, Visits 6 and 8, i.e., at Months 7 and 12).
- Urine pregnancy tests were performed before administration of each vaccine dose.
- A behavioral questionnaire was completed by interview at screening and Month 7 to collect information on marital status, smoking history, sexual and reproductive history and contraception status.
- Safety and reactogenicity information were monitored as follows:
    - Solicited signs and symptoms were recorded on Day 0 and on the 6 subsequent days (Days 1 - 6).
    - Unsolicited signs and symptoms were reported within 30 days (Days 0 - 29) after each vaccination.
    - Serious adverse events (SAEs) were recorded in all subjects throughout the study (up to Month 12).
    - New onset of chronic diseases (NOCDs) and other medically significant conditions (i.e., 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) were reported throughout the entire study (up to Month 12) regardless of causal relationship to vaccination and intensity.
    - Pregnancies and pregnancy outcome were to be recorded throughout the study period (up to Month 12) and subjects were to be followed until delivery (even if the delivery occurs after the end of the study).

      Assessor's note: with respect to the assessment of safety variables, please refer to the clinical study report. The methodology for classifying the severity of adverse events was similar to the methodology of other GSK sponsored studies.

The data of the first interim analysis was presented in the Interim Report 1 dated 22 January 2010. The data of the second interim analysis was presented in the Interim Report 2 dated 29 November 2010. *Assessor's note: it remains unclear whether the interim reports were submitted to CHMP*.

2.1.3. Laboratory assays and time-points

Assessor's note:

Serological assays were performed at GSK Biologicals laboratories, Rixensart, Belgium. The assays have extensively been described in the initial registration dossier and not repeated here. Biochemical and hematological assays were performed by BIO-24 Laboratory, Dakar, Senegal and by the National Institute for Medical Research, Mwanza and Duke University KCMC Collaboration laboratories, Moshi, Tanzania. Further details are available in the final clinical study report.

2.1.4. Determination of sample size

The first primary objective of this study was to evaluate antibody responses against HPV-16 and HPV-18 (by ELISA) at Month 7 in HPV vaccine recipients aged 15-25 years. The second co-primary objective was to evaluate antibody responses against HPV- 16 and HPV-18 (by ELISA) at Month 7 in 10-14 year old HPV recipients.

Approximately 666 subjects were to be enrolled in the trial. Using a 2:1 randomization ratio, 444 subjects were to receive the HPV vaccine and 222 were to receive the control. The enrolment was also age-stratified, with approximately one third of the total number of subjects enrolled in the second age stratum (10-14 year olds). Assuming that 30% of subjects enrolled in this study would be non-evaluable at the time of the analysis (e.g., drop-outs, initially seropositive for HPV-16 and/or HPV-18, etc.) it was expected that there would be 309 evaluable subjects in the HPV vaccine group (206 evaluable subjects aged 15-25 years and 103 evaluable subjects aged 10-14 years).

Table 10 shows the power to demonstrate a lower limit of the 95% confidence interval (CI) for the seroconversion rate above 90% when the true seroconversion rate was 98%. The power was 99% in 15-25 year olds and 94% in 10-14 year olds. Calculations were performed using Power and sample size (PASS) 2005, using a two-sided exact test for one binomial proportion (Proportion - 1 group), type I error of 5%.

Table 10 Power calculations for immunogenicity analyses

Analysis	Enrolled subjects	Evaluable subjects[1]	Seroconversion rate that could have been excluded	Exact power[2]
Overall study				
Overall ages	444	309		
15-25 years	296	206	90%	99%
10-14 years	148	103	90%	94%
Per country				
Overall ages	222	154		
15-25 years	148	103	90%	94%
10-14 years	74	51	86%	91%

[1] Assuming 30% non-evaluable subjects due to dropout, initially seropositive for HPV-16 and/or HPV-18, etc.
[2] Assuming a true seroconversion rate of 98%

2.1.5. Study cohorts / data sets analyzed

According To Protocol (ATP) cohort for immunogenicity

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 endpoint measures were available. These included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination. The ATP cohort for immunogenicity was based on data up to Month 7 while the ATP cohort for immunogenicity Month 12 was based on data up to Month 12.

Total Vaccinated cohort

The Total Vaccinated cohort included all vaccinated subjects. Thus, the Total Vaccinated cohort for analysis of safety included all subjects with at least one vaccine administration documented and the Total Vaccinated cohort for analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The Total Vaccinated cohort Month 12 was limited to subjects for whom Month 12 data were available. The Total Vaccinated cohort analysis was performed per treatment actually administered.

According-To-Protocol (ATP) cohort for safety: all subjects:

- who had received three doses of study vaccine/control according to their random assignment
- for whom administration site of study vaccine was known
- who had not received a vaccine not specified or forbidden in the protocol
- for whom the randomization code had not been broken.

2.1.6. Protocol amendments

There were two amendments to the study protocol dated 30 June 2006. A summary of the major changes introduced by each amendment is given below. The major changes were as follows:

Amendment 1 (dated 5 July 2007)

- The global sample size was decreased from 999 to 666 subjects, as only two countries participated in the study.
- The temperature monitoring devices used during storage of the vaccine were changed.
- Medical history was updated to include information concerning contraception and smoking. The medical history collection was also added at Visit 1, in addition to the screening visit, and it was clarified that medical history information was to be recorded in the eCRF.

Amendment 2 (dated 12 December 2008)

- Two interim analyses (1 and 2) were added to be performed when: (1) all subjects enrolled in Senegal had completed Visit 6 (Month 7) and (2) all subjects in Tanzania had completed Visit 6 (Month 7).
- The list of study procedures, study design overview and statistical considerations were updated to include the two interim analyses.

Other changes

- This study was conducted according to protocol amendment 2, dated 12 December 2008, and the RAP dated 10 November 2009 with the following exceptions:
- The secondary endpoints of the protocol state that the analysis of SAEs, NOCDs, other medically significant conditions and pregnancies (and their outcome) from Month 7 through the Month 12 follow-up visit will be presented in a separate annex report. As part of the changes in protocol amendment 2, the analysis of safety endpoints from Month 7 to Month 12 are presented in this final clinical report.
- In the definition of the ATP cohort for safety, the criteria in the protocol “who have received at least one dose of study vaccine/control according to their random assignment” and “with sufficient data to perform an analysis of safety (at least one dose with safety follow-up)” were replaced by “subjects who have received three doses of study vaccine/control according to their random assignment”, to be in line with other HPV study protocols.
- In the eCRF, missing confirmed values for solicited symptoms on Day 0 to 6 following vaccination had to be recorded by default as “yes” in reply to the question “Has the subject experienced any of the following signs/symptoms at the administration site during the solicited period?” This resulted in an overestimation of the number of subjects with solicited symptoms reported. As a result, two separate analyses of solicited symptoms were performed, i.e. one on data including missing confirmed values and one on data excluding missing confirmed values.
- An additional analysis of solicited and unsolicited symptoms by age stratum (10-14 years and 15-25 years) was performed for the Month 7 analysis.

2.2. STUDY RESULTS

A total of 676 subjects were enrolled and vaccinated in the study. Subjects were enrolled at two study centers in Senegal and Tanzania. Of the 676 subjects enrolled in the study, 450 subjects were enrolled in the HPV group and 226 subjects in the Control group. The number of subjects enrolled by center, per group and age strata is presented in Table 11.

Table 11 Number of subjects by center, per group and age strata (Total Vaccinated cohort)

	HPV group			Control group			Total					
	10-14	15-25	Total	10-14	15-25	Total	10-14		15-25		Total	
Center	n	n	n	n	n	n	n	%	n	%	n	%
Senegal (35453)	81	148	229	39	74	113	120	51.7	222	50.0	342	50.6
Tanzania (54027)	74	147	221	38	75	113	112	48.3	222	50.0	334	49.4
All	155	295	450	77	149	226	232	100	444	100	676	100

HPV = HPV-16/18 L1 VLP AS04
Control = Aluminum [$Al(OH)_3$]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years
n = number of subjects included in each group or in total for a given center or for all centers
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Center = GSK Biologicals assigned center number

Of the 676 subjects enrolled and vaccinated in the study, 623 subjects completed the study. Fifty-three subjects were withdrawn from the study due to the following reasons (Table 12):

Table 12 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at Month 12 (Total Vaccinated cohort)

	HPV group	Control group	Total
Number of subjects vaccinated	450	226	676
Number of subjects completed	418	205	623
Number of subjects withdrawn	32	21	53
Reasons for withdrawal:			
Serious Adverse Event	0	0	0
Non-Serious Adverse Event	0	0	0
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	16	11	27
Migrated/moved from study area	7	3	10
Lost to follow-up (subjects with incomplete vaccination course)	4	5	9
Lost to follow-up (subjects with complete vaccination course)	5	2	7

Demographic characteristics

The demographic characteristics of the ATP cohort for immunogenicity are summarized in Table 16.

Table 16 Summary of demographic characteristics per group and age strata (ATP cohort for immunogenicity)

		HPV group						Control group						Total					
		10-14 N = 143		15-25 N = 238		Total N = 381		10-14 N = 66		15-25 N = 114		Total N = 180		10-14 N = 209		15-25 N = 352		Total N = 561	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years)	Mean	11.7	-	19.7	-	16.7	-	11.7	-	19.3	-	16.5	-	11.7	-	19.6	-	16.6	-
	SD	1.39	-	2.57	-	4.46	-	1.39	-	2.35	-	4.18	-	1.39	-	2.51	-	4.37	-
	Median	11.0	-	19.0	-	18.0	-	12.0	-	19.0	-	18.0	-	12.0	-	19.0	-	18.0	-
	Minimum	10	-	15	-	10	-	10	-	15	-	10	-	10	-	15	-	10	-
	Maximum	14	-	25	-	25	-	14	-	25	-	25	-	14	-	25	-	25	-
Race	African / African American	137	95.8	226	95.0	363	95.3	65	98.5	110	96.5	175	97.2	202	96.7	336	95.5	538	95.9
	Other	6	4.2	12	5.0	18	4.7	1	1.5	4	3.5	5	2.8	7	3.3	16	4.5	23	4.1
Height (cm)	Mean	146.0	-	162.0	-	156.0	-	147.1	-	162.3	-	156.7	-	146.3	-	162.1	-	156.2	-
	SD	10.53	-	7.24	-	11.58	-	9.02	-	6.83	-	10.65	-	10.07	-	7.10	-	11.28	-
	Median	146.0	-	161.5	-	157.0	-	148.5	-	163.0	-	158.0	-	147.0	-	162.0	-	157.0	-
Weight (kg)	Mean	35.6	-	54.3	-	47.3	-	35.9	-	54.7	-	47.8	-	35.7	-	54.4	-	47.4	-
	SD	9.02	-	10.49	-	13.45	-	7.89	-	8.19	-	12.14	-	8.66	-	9.79	-	13.04	-
	Median	34.0	-	53.0	-	49.0	-	35.5	-	53.0	-	48.8	-	35.0	-	53.0	-	49.0	-
BMI (kg/m²)	Mean	16.5	-	20.7	-	19.1	-	16.4	-	20.8	-	19.2	-	16.4	-	20.7	-	19.1	-
	SD	2.66	-	3.74	-	3.95	-	2.22	-	3.44	-	3.71	-	2.53	-	3.64	-	3.87	-
	Median	15.8	-	20.3	-	18.8	-	15.9	-	20.2	-	18.9	-	15.9	-	20.3	-	18.8	-

HPV = HPV-16/18 L1 VLP/AS04
Control = Aluminum [$Al(OH)_3$]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years
N = total number of subjects
n (%) = number (percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Immunogenicity results

Seropositivity to anti-HPV-16/18 at baseline, per group and age strata is presented in Table 20.

Table 20 Seropositivity status at baseline per group and age strata (ATP cohort for immunogenicity)

		HPV group						Control group					
		10-14 (N = 143)		15-25 (N = 238)		Total (N = 381)		10-14 (N = 66)		15-25 (N = 114)		Total (N = 180)	
Anti-HPV-16	Anti-HPV-18	n	%	n	%	n	%	n	%	n	%	n	%
Positive	Positive	4	2.9	9	3.8	13	3.5	3	4.6	7	6.2	10	5.6
Positive	Negative	8	5.7	36	15.4	44	11.8	3	4.6	9	8	12	6.7
Positive	MISSING	0	-	2	-	2	-	0	-	0	-	0	-
Negative	Positive	8	5.7	14	6	22	5.9	6	9.2	8	7.1	14	7.9
Negative	Negative	120	85.7	175	74.8	295	78.9	53	81.5	89	78.8	142	79.8
Negative	MISSING	2	-	1	-	3	-	0	-	0	-	0	-
MISSING	Positive	1	-	0	-	1	-	1	-	1	-	2	-
MISSING	Negative	0	-	1	-	1	-	0	-	0	-	0	-

HPV = HPV-16/18 L1 VLP/AS04
Control = Aluminum [$Al(OH)_3$]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years
PRE = pre-vaccination

Anti-HPV-16/18 seropositivity rates and GMTs at Months 2 and 7

An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibody titers by baseline serostatus per group and age strata is presented in Table 21 and Table 22, respectively.

At Month 2, i.e. one month after the second dose of the study vaccine all initially seronegative subjects in the HPV group had seroconverted for anti-HPV-16 and anti- HPV-18 antibodies. Anti-HPV-16 and anti-HPV-18 antibody titers at Month 2 in initially seronegative subjects were approximately 1.5 fold higher in the 10-14 years age group than in the 15-25 years age group.

An increase in GMTs was observed from the Month 2 to the Month 7 time points. Anti-HPV-16 and anti-HPV-18 antibody titers at Month 7 in initially seronegative subjects were approximately 1.7 fold higher in the 10-14 years age group than in the 15-25 years age group. This is also demonstrated by the reverse cumulative distribution curves for anti-HPV-16 and anti-HPV-18 antibodies, which are more to the right for subjects in the 10-14 years age group when compared to the 15-25 years age group (Figure 1 and Figure 2, respectively).

Table 21 Seropositivity rates and GMTs for anti-HPV-16 antibody titers by serostatus at baseline per group and age strata (ATP cohort for immunogenicity)

						≥ 8 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-HPV-16	HPV	10-14	S-	PRE	130	0	0.0	0.0	2.8	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	130	130	100	97.2	100	5279.8	4742.7	5877.8	638.0	57868.0
				PIII(M7)	130	130	100	97.2	100	18422.8	16184.8	20970.4	546.0	114564.0
			S+	PRE	12	12	100	73.5	100	20.3	12.4	33.1	9.0	131.0
				PII(M2)	12	12	100	73.5	100	6039.7	4220.2	8643.5	2729.0	12326.0
				PIII(M7)	12	12	100	73.5	100	20518.0	12821.7	32834.1	8351.0	90498.0
			Total	PRE	142	12	8.5	4.4	14.3	4.6	4.2	5.0	<8.0	131.0
				PII(M2)	142	142	100	97.4	100	5340.2	4823.7	5912.0	638.0	57868.0
				PIII(M7)	142	142	100	97.4	100	18591.3	16433.0	21033.1	546.0	114564.0
		15-25	S-	PRE	190	0	0.0	0.0	1.9	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	190	190	100	98.1	100	3525.9	3239.3	3837.8	853.0	21730.0
				PIII(M7)	190	190	100	98.1	100	10683.0	9566.7	11929.5	1341.0	97643.0
			S+	PRE	47	47	100	92.5	100	27.1	20.0	36.6	8.0	526.0
				PII(M2)	47	47	100	92.5	100	4699.7	3723.3	5932.2	1246.0	48370.0
				PIII(M7)	47	47	100	92.5	100	10587.7	8490.7	13202.6	1912.0	56392.0
			Total	PRE	237	47	19.8	15.0	25.5	5.8	5.2	6.5	<8.0	526.0
				PII(M2)	237	237	100	98.5	100	3732.6	3436.6	4054.1	853.0	48370.0
				PIII(M7)	237	237	100	98.5	100	10664.0	9668.5	11762.0	1341.0	97643.0
		Total	S-	PRE	320	0	0.0	0.0	1.1	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	320	320	100	98.9	100	4154.3	3874.5	4454.4	638.0	57868.0
				PIII(M7)	320	320	100	98.9	100	13330.2	12199.5	14565.7	546.0	114564.0
			S+	PRE	59	59	100	93.9	100	25.5	19.8	33.0	8.0	526.0
				PII(M2)	59	59	100	93.9	100	4945.7	4062.6	6020.9	1246.0	48370.0
				PIII(M7)	59	59	100	93.9	100	12112.7	9858.8	14881.9	1912.0	90498.0
			Total	PRE	379	59	15.6	12.1	19.6	5.3	4.9	5.8	<8.0	526.0
				PII(M2)	379	379	100	99.0	100	4268.7	3994.9	4561.2	638.0	57868.0
				PIII(M7)	379	379	100	99.0	100	13132.9	12109.6	14242.7	546.0	114564.0
	Control	10-14	S-	PRE	59	0	0.0	0.0	6.1	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	59	1	1.7	0.0	9.1	4.2	3.8	4.5	<8.0	39.0
				PIII(M7)	59	4	6.8	1.9	16.5	4.4	4.0	4.9	<8.0	23.0
			S+	PRE	6	6	100	54.1	100	15.8	8.6	29.1	8.0	31.0
				PII(M2)	5	3	60.0	14.7	94.7	10.7	3.3	34.5	<8.0	27.0
				PIII(M7)	6	3	50.0	11.8	88.2	10.3	3.3	32.8	<8.0	37.0
			Total	PRE	65	6	9.2	3.5	19.0	4.5	4.1	5.1	<8.0	31.0
				PII(M2)	64	4	6.3	1.7	15.2	4.5	4.0	5.0	<8.0	39.0
				PIII(M7)	65	7	10.8	4.4	20.9	4.8	4.2	5.5	<8.0	37.0
		15-25	S-	PRE	97	0	0.0	0.0	3.7	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	96	3	3.1	0.6	8.9	4.2	4.0	4.4	<8.0	21.0
				PIII(M7)	97	5	5.2	1.7	11.6	4.4	4.0	4.8	<8.0	67.0
			S+	PRE	16	16	100	79.4	100	20.5	12.9	32.6	8.0	164.0
				PII(M2)	16	10	62.5	35.4	84.8	12.4	6.6	23.0	<8.0	206.0
				PIII(M7)	15	13	86.7	59.5	98.3	18.4	10.6	31.9	<8.0	202.0
			Total	PRE	113	16	14.2	8.3	22.0	5.0	4.5	5.7	<8.0	164.0
				PII(M2)	112	13	11.6	6.3	19.0	4.9	4.3	5.5	<8.0	206.0
				PIII(M7)	112	18	16.1	9.8	24.2	5.3	4.6	6.1	<8.0	202.0
		Total	S-	PRE	156	0	0.0	0.0	2.3	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	155	4	2.6	0.7	6.5	4.2	4.0	4.3	<8.0	39.0

						≥ 8 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
				PIII(M7)	156	9	5.8	2.7	10.7	4.4	4.1	4.7	<8.0	67.0
			S+	PRE	22	22	100	84.6	100	19.1	13.4	27.2	8.0	164.0
				PII(M2)	21	13	61.9	38.4	81.9	11.9	7.3	19.7	<8.0	206.0
				PIII(M7)	21	16	76.2	52.8	91.8	15.6	9.7	24.9	<8.0	202.0
			Total	PRE	178	22	12.4	7.9	18.1	4.9	4.5	5.3	<8.0	164.0
				PII(M2)	176	17	9.7	5.7	15.0	4.7	4.3	5.1	<8.0	206.0
				PIII(M7)	177	25	14.1	9.4	20.1	5.1	4.6	5.7	<8.0	202.0

HPV = HPV-16/18 L1 VLP/AS04
Control = Aluminum [$Al(OH)_3$]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years
S- = seronegative subjects (antibody concentration < 8 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 8 EL.U/mL) prior to vaccination
GMT = geometric mean antibody titers calculated on all subjects
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = pre-vaccination
PII(M2) = Post Dose 2, Month 2
PIII(M7) = Post Dose 3, Month 7

Table 22 **Seropositivity rates and GMT for anti-HPV-18 antibody titers by serostatus at baseline per group and age strata (ATP cohort for immunogenicity)**

						≥ 7 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-HPV-18	HPV	10-14	S-	PRE	128	0	0.0	0.0	2.8	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	128	128	100	97.2	100	3018.9	2662.0	3423.7	203.0	41836.0
				PIII(M7)	128	128	100	97.2	100	6487.3	5589.7	7529.1	461.0	85686.0
			S+	PRE	13	13	100	75.3	100	12.0	10.0	14.4	7.0	25.0
				PII(M2)	13	13	100	75.3	100	2994.6	1942.9	4615.6	980.0	11112.0
				PIII(M7)	13	13	100	75.3	100	5694.4	3372.7	9614.6	1810.0	23410.0
			Total	PRE	141	13	9.2	5.0	15.3	3.9	3.7	4.2	<7.0	25.0
				PII(M2)	141	141	100	97.4	100	3016.7	2677.4	3398.9	203.0	41836.0
				PIII(M7)	141	141	100	97.4	100	6409.8	5563.4	7385.0	461.0	85686.0
		15-25	S-	PRE	212	0	0.0	0.0	1.7	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	212	212	100	98.3	100	2009.4	1824.3	2213.2	214.0	20339.0
				PIII(M7)	212	212	100	98.3	100	3742.7	3400.2	4119.8	488.0	102428.0
			S+	PRE	23	23	100	85.2	100	14.0	10.6	18.6	7.0	91.0
				PII(M2)	23	23	100	85.2	100	2337.7	1738.8	3142.7	770.0	10368.0
				PIII(M7)	23	23	100	85.2	100	2925.6	2442.9	3503.6	1469.0	8316.0
			Total	PRE	235	23	9.8	6.3	14.3	4.0	3.8	4.3	<7.0	91.0
				PII(M2)	235	235	100	98.4	100	2039.3	1861.3	2234.4	214.0	20339.0
				PIII(M7)	235	235	100	98.4	100	3653.6	3343.9	3991.9	488.0	102428.0
		Total	S-	PRE	340	0	0.0	0.0	1.1	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	340	340	100	98.9	100	2342.2	2164.0	2535.0	203.0	41836.0
				PIII(M7)	340	340	100	98.9	100	4603.8	4222.8	5019.2	461.0	102428.0
			S+	PRE	36	36	100	90.3	100	13.3	11.0	16.0	7.0	91.0
				PII(M2)	36	36	100	90.3	100	2556.4	2019.9	3235.4	770.0	11112.0
				PIII(M7)	36	36	100	90.3	100	3721.0	2949.1	4694.9	1469.0	23410.0
			Total	PRE	376	36	9.6	6.8	13.0	4.0	3.8	4.2	<7.0	91.0
				PII(M2)	376	376	100	99.0	100	2361.9	2191.8	2545.1	203.0	41836.0
				PIII(M7)	376	376	100	99.0	100	4510.9	4159.2	4892.4	461.0	102428.0
	Control	10-14	S-	PRE	56	0	0.0	0.0	6.4	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	55	1	1.8	0.0	9.7	3.6	3.4	3.7	<7.0	8.0
				PIII(M7)	56	2	3.6	0.4	12.3	3.6	3.5	3.8	<7.0	9.0
			S+	PRE	10	10	100	69.2	100	9.3	7.5	11.5	7.0	16.0
				PII(M2)	10	7	70.0	34.8	93.3	7.0	4.9	10.0	<7.0	14.0
				PIII(M7)	10	5	50.0	18.7	81.3	5.8	3.8	8.7	<7.0	14.0
			Total	PRE	66	10	15.2	7.5	26.1	4.1	3.7	4.4	<7.0	16.0
				PII(M2)	65	8	12.3	5.5	22.8	3.9	3.6	4.3	<7.0	14.0
				PIII(M7)	66	7	10.6	4.4	20.6	3.9	3.6	4.2	<7.0	14.0
		15-25	S-	PRE	98	0	0.0	0.0	3.7	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	98	4	4.1	1.1	10.1	3.8	3.5	4.2	<7.0	67.0
				PIII(M7)	98	5	5.1	1.7	11.5	3.9	3.5	4.2	<7.0	166.0
			S+	PRE	16	16	100	79.4	100	17.7	9.5	33.0	7.0	669.0
				PII(M2)	14	13	92.9	66.1	99.8	17.5	9.0	33.9	<7.0	434.0
				PIII(M7)	16	12	75.0	47.6	92.7	13.9	6.9	28.0	<7.0	393.0
			Total	PRE	114	16	14.0	8.2	21.8	4.4	3.9	5.0	<7.0	669.0
				PII(M2)	112	17	15.2	9.1	23.2	4.6	4.0	5.3	<7.0	434.0
				PIII(M7)	114	17	14.9	8.9	22.8	4.6	4.0	5.3	<7.0	393.0

						≥ 7 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
		Total	S-	PRE	154	0	0.0	0.0	2.4	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	153	5	3.3	1.1	7.5	3.7	3.5	3.9	<7.0	67.0
				PIII(M7)	154	7	4.5	1.8	9.1	3.8	3.5	4.0	<7.0	166.0
			S+	PRE	26	26	100	86.8	100	13.8	9.3	20.5	7.0	669.0
				PII(M2)	24	20	83.3	62.6	95.3	11.9	7.7	18.4	<7.0	434.0
				PIII(M7)	26	17	65.4	44.3	82.8	9.9	6.2	15.9	<7.0	393.0
			Total	PRE	180	26	14.4	9.7	20.4	4.3	3.9	4.7	<7.0	669.0
				PII(M2)	177	25	14.1	9.4	20.1	4.4	4.0	4.8	<7.0	434.0
				PIII(M7)	180	24	13.3	8.7	19.2	4.3	3.9	4.8	<7.0	393.0

HPV = HPV-16/18 L1 VLP/AS04
Control = Aluminum [$Al(OH)_3$]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years
S- = seronegative subjects (antibody concentration < 7 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 7 EL.U/mL) prior to vaccination
GMT = geometric mean antibody titers calculated on all subjects
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = pre-vaccination
PII(M2) = Post Dose 2, Month 2
PIII(M7) = Post Dose 3, Month 7

Figure 1 Reverse cumulative distribution curve for anti-HPV-16 antibodies for initially seronegative subjects per group and age strata (Post Dose III, Month 7) (ATP cohort for immunogenicity)

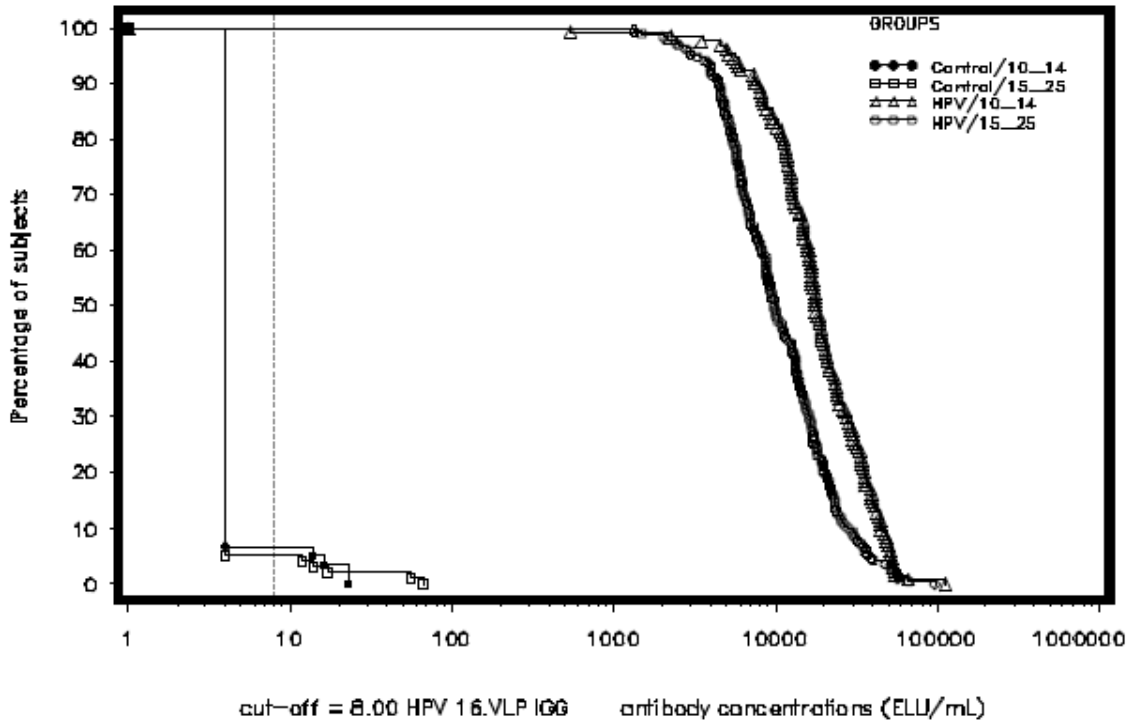
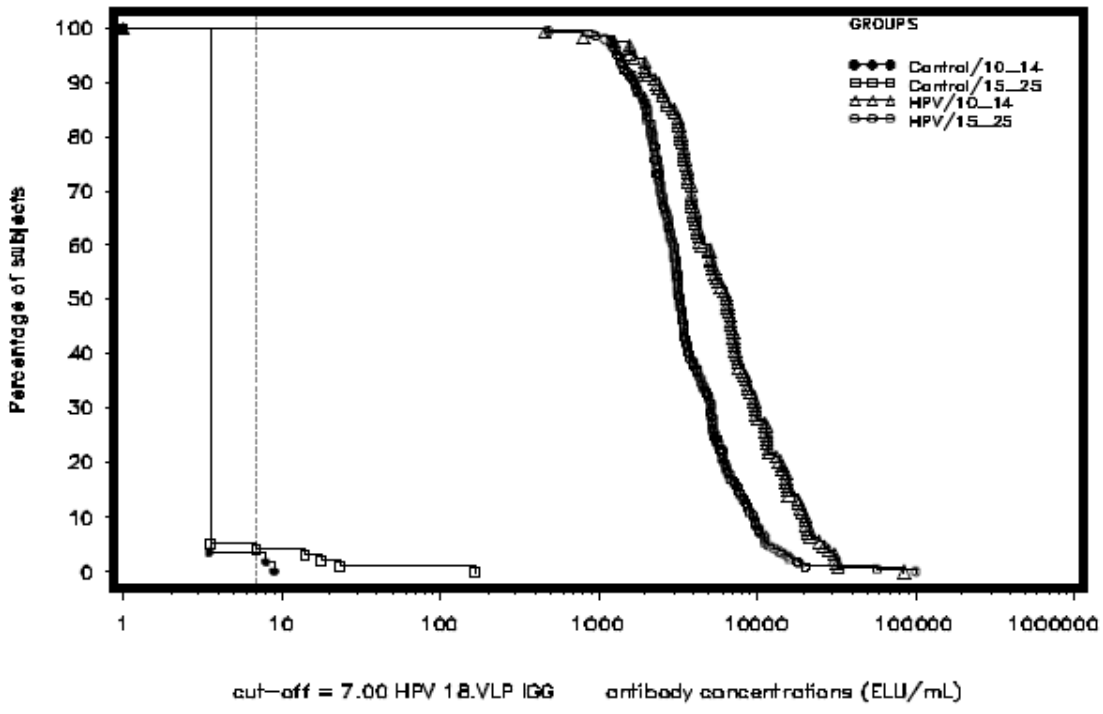


Figure 2 Reverse cumulative distribution curve for anti-HPV-18 antibodies for initially seronegative subjects per group and age strata (Post Dose III, Month 7) (ATP cohort for immunogenicity)



Comparison of anti-HPV-16/18 titers at Month 7 by age stratum to those obtained in study HPV-012

GMTs were compared to those observed in Study HPV-012 at Month 7 (Figure 3 and Figure 4). Study-012 was a phase III, double-blind, randomized study to evaluate the immunogenicity and safety of Cervarix in females aged 10-25 years from various countries in Europe (Pedersen et al. J Adoles Health 2007; 40: 564-571). GMTs observed in the current study are in the same range for subjects aged 10-14 years as those observed in subjects of similar age in Study HPV-012. GMTs observed for anti-HPV-16 antibodies for subjects aged 15-25 years were higher than those observed in Study HPV-012.

Figure 3 **Comparison of GMTs for anti-HPV-16 antibodies for initially seronegative subjects with GMTs from Study 580299/012 (HPV-012, NCT00169494) by age stratum (Post Dose III, Month 7) (ATP cohort for immunogenicity)**

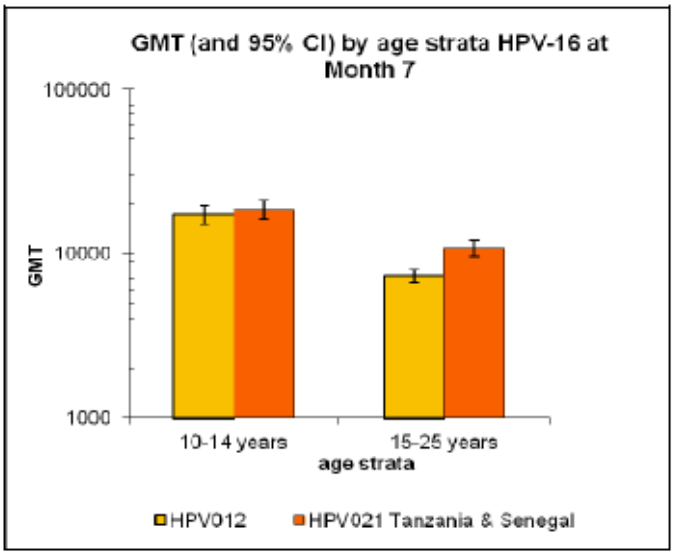
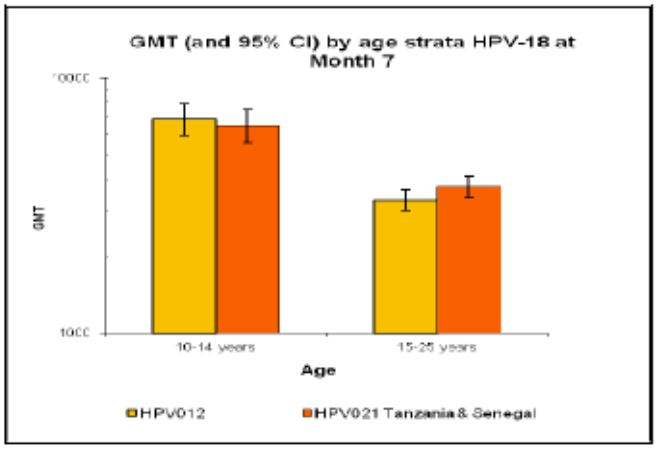


Figure 4 **Comparison of GMTs for anti-HPV-18 antibodies for initially seronegative subjects with GMTs from Study 580299/012 (HPV-012, NCT00169494) by age stratum (Post Dose III, Month 7) (ATP cohort for immunogenicity)**



According-to-protocol analysis for Month 12

Seropositivity status to anti-HPV-16/18 at baseline, per group and age strata is presented in Table 23. The anti-HPV-16/18 seropositivity status at baseline in the ATP cohort for immunogenicity Month 12 was comparable to that observed in the ATP cohort for immunogenicity for Month 7.

Anti-HPV-16/18 seropositivity rates and GMTs (Month 12)

An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibody titers, by baseline serostatus per group and age strata is presented in Table 24 and Table 25, respectively.

At Month 12, i.e. six months after completion of the three-dose vaccination course, all initially seronegative subjects in both the age strata remained seropositive for anti-HPV-16 antibodies and all except one subject remained seropositive for anti-HPV-18 antibodies. A decline in the anti-HPV-16 and anti-HPV-18 antibody titers was observed in initially seronegative subjects at Month 12 following a peak antibody response at Month 7. GMTs remained higher in the 10-14 years age group than in the 15-25 years age group. This is also demonstrated by the reverse cumulative distribution curves for anti-HPV-16 and anti-HPV-18 antibodies (Assessor's note: the RCC are not shown here).

Anti-HPV-16 antibody titers at Month 12 in initially seronegative subjects were approximately 1.7 fold higher in the 10-14 years age group than in the 15-25 years age group. Anti-HPV-18 antibody titers at Month 12 in initially seronegative subjects were approximately 1.6 fold higher in the 10-14 years age group than in the 15-25 years age group.

Table 23 Seropositivity status at baseline per group and age strata (ATP cohort for immunogenicity Month 12)

		HPV/10-14 (N = 140)		HPV/15-25 (N = 230)		HPV/Total (N = 370)		Control/10-14 (N = 66)		Control/15-25 (N = 111)		Control/Total (N = 177)		Total/10-14 (N = 206)		Total/15-25 (N = 341)		Total/Total (N = 547)	
Anti-HPV-16	**Anti-HPV-18**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Positive	Positive	3	2.2	9	4	12	3.3	3	4.6	7	6.4	10	5.7	6	3	16	4.8	22	4.1
Positive	Negative	8	5.8	34	15	42	11.6	3	4.6	9	8.2	12	6.9	11	5.4	43	12.8	54	10
Positive	MISSING	0	-	2	-	2	-	0	-	0	-	0	-	0	-	2	-	2	-
Negative	Positive	8	5.8	13	5.8	21	5.8	6	9.2	7	6.4	13	7.4	14	6.9	20	6	34	6.3
Negative	Negative	118	86.1	170	75.2	288	79.3	53	81.5	87	79.1	140	80	171	84.7	257	76.5	428	79.6
Negative	MISSING	2	-	1	-	3	-	0	-	0	-	0	-	2	-	1	-	3	-
MISSING	Positive	1	-	0	-	1	-	1	-	1	-	2	-	2	-	1	-	3	-
MISSING	Negative	0	-	1	-	1	-	0	-	0	-	0	-	0	-	1	-	1	-

HPV = HPV-16/18 L1 VLP/AS04
Control = Aluminum [$Al(OH)_3$]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years

Table 24 **Seropositivity rates and GMTs for anti-HPV-16 antibody titers by serostatus at baseline per group and age strata (ATP cohort for immunogenicity Month 12)**

						≥ 8 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-HPV-16	HPV	10-14	S-	PRE	128	0	0.0	0.0	2.8	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	128	128	100	97.2	100	5339.6	4793.9	5947.3	638.0	57868.0
				PIII(M7)	128	128	100	97.2	100	18494.0	16223.7	21081.9	546.0	114564.0
				PIII(M12)	128	128	100	97.2	100	4010.2	3276.0	4909.1	14.0	32161.0
			S+	PRE	11	11	100	71.5	100	20.6	12.0	35.4	9.0	131.0
				PII(M2)	11	11	100	71.5	100	6351.6	4352.1	9269.6	2729.0	12326.0
				PIII(M7)	11	11	100	71.5	100	20320.7	12070.7	34209.4	8351.0	90498.0
				PIII(M12)	11	11	100	71.5	100	4086.4	2409.2	6931.0	2108.0	28853.0
			Total	PRE	139	11	7.9	4.0	13.7	4.6	4.2	4.9	<8.0	131.0
				PII(M2)	139	139	100	97.4	100	5413.4	4885.2	5998.7	638.0	57868.0
				PIII(M7)	139	139	100	97.4	100	18632.3	16434.2	21124.4	546.0	114564.0
				PIII(M12)	139	139	100	97.4	100	4016.2	3323.3	4853.7	14.0	32161.0
		15-25	S-	PRE	184	0	0.0	0.0	2.0	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	184	184	100	98.0	100	3465.5	3182.1	3774.2	853.0	21730.0
				PIII(M7)	184	184	100	98.0	100	10473.7	9360.2	11719.7	1341.0	97643.0
				PIII(M12)	184	184	100	98.0	100	2357.1	2073.2	2679.9	308.0	17270.0
			S+	PRE	45	45	100	92.1	100	27.8	20.3	38.0	8.0	526.0
				PII(M2)	45	45	100	92.1	100	4916.5	3890.2	6213.4	1246.0	48370.0
				PIII(M7)	45	45	100	92.1	100	10614.0	8432.7	13359.6	1912.0	56392.0
				PIII(M12)	45	45	100	92.1	100	2955.0	2273.6	3840.5	395.0	20847.0
			Total	PRE	229	45	19.7	14.7	25.4	5.9	5.2	6.6	<8.0	526.0
				PII(M2)	229	229	100	98.4	100	3712.0	3414.1	4035.9	853.0	48370.0
				PIII(M7)	229	229	100	98.4	100	10501.1	9499.7	11608.2	1341.0	97643.0
				PIII(M12)	229	229	100	98.4	100	2464.2	2196.5	2764.5	308.0	20847.0
		Total	S-	PRE	312	0	0.0	0.0	1.2	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	312	312	100	98.8	100	4138.0	3855.5	4441.2	638.0	57868.0
				PIII(M7)	312	312	100	98.8	100	13225.3	12081.9	14476.8	546.0	114564.0
				PIII(M12)	312	312	100	98.8	100	2931.3	2611.9	3289.8	14.0	32161.0
			S+	PRE	56	56	100	93.6	100	26.2	20.1	34.3	8.0	526.0
				PII(M2)	56	56	100	93.6	100	5170.1	4235.8	6310.5	1246.0	48370.0
				PIII(M7)	56	56	100	93.6	100	12058.3	9722.8	14954.7	1912.0	90498.0
				PIII(M12)	56	56	100	93.6	100	3149.3	2501.9	3964.1	395.0	28853.0
			Total	PRE	368	56	15.2	11.7	19.3	5.3	4.9	5.8	<8.0	526.0
				PII(M2)	368	368	100	99.0	100	4280.6	4002.0	4578.6	638.0	57868.0
				PIII(M7)	368	368	100	99.0	100	13040.7	12001.5	14169.8	546.0	114564.0
				PIII(M12)	368	368	100	99.0	100	2963.5	2672.0	3286.8	14.0	32161.0
	Control	10-14	S-	PRE	59	0	0.0	0.0	6.1	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	59	1	1.7	0.0	9.1	4.2	3.8	4.5	<8.0	39.0
				PIII(M7)	59	4	6.8	1.9	16.5	4.4	4.0	4.9	<8.0	23.0
				PIII(M12)	59	2	3.4	0.4	11.7	4.2	3.9	4.5	<8.0	32.0
			S+	PRE	6	6	100	54.1	100	15.8	8.6	29.1	8.0	31.0
				PII(M2)	5	3	60.0	14.7	94.7	10.7	3.3	34.5	<8.0	27.0
				PIII(M7)	6	3	50.0	11.8	88.2	10.3	3.3	32.8	<8.0	37.0
				PIII(M12)	6	5	83.3	35.9	99.6	13.8	6.4	30.1	<8.0	34.0
			Total	PRE	65	6	9.2	3.5	19.0	4.5	4.1	5.1	<8.0	31.0
				PII(M2)	64	4	6.3	1.7	15.2	4.5	4.0	5.0	<8.0	39.0

						≥ 8 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
				PIII(M7)	65	7	10.8	4.4	20.9	4.8	4.2	5.5	<8.0	37.0
				PIII(M12)	65	7	10.8	4.4	20.9	4.7	4.2	5.3	<8.0	34.0
		15-25	S-	PRE	94	0	0.0	0.0	3.8	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	93	3	3.2	0.7	9.1	4.2	4.0	4.4	<8.0	21.0
				PIII(M7)	94	5	5.3	1.7	12.0	4.4	4.0	4.8	<8.0	67.0
				PIII(M12)	94	7	7.4	3.0	14.7	4.6	4.1	5.1	<8.0	343.0
			S+	PRE	16	16	100	79.4	100	20.5	12.9	32.6	8.0	164.0
				PII(M2)	16	10	62.5	35.4	84.8	12.4	6.6	23.0	<8.0	206.0
				PIII(M7)	15	13	86.7	59.5	98.3	18.4	10.6	31.9	<8.0	202.0
				PIII(M12)	15	12	80.0	51.9	95.7	19.8	9.2	42.7	<8.0	446.0
			Total	PRE	110	16	14.5	8.5	22.5	5.1	4.5	5.8	<8.0	164.0
				PII(M2)	109	13	11.9	6.5	19.5	4.9	4.3	5.5	<8.0	206.0
				PIII(M7)	109	18	16.5	10.1	24.8	5.4	4.7	6.2	<8.0	202.0
				PIII(M12)	109	19	17.4	10.8	25.9	5.6	4.7	6.6	<8.0	446.0
		Total	S-	PRE	153	0	0.0	0.0	2.4	4.0	4.0	4.0	<8.0	<8.0
				PII(M2)	152	4	2.6	0.7	6.6	4.2	4.0	4.3	<8.0	39.0
				PIII(M7)	153	9	5.9	2.7	10.9	4.4	4.1	4.7	<8.0	67.0
				PIII(M12)	153	9	5.9	2.7	10.9	4.4	4.1	4.8	<8.0	343.0
			S+	PRE	22	22	100	84.6	100	19.1	13.4	27.2	8.0	164.0
				PII(M2)	21	13	61.9	38.4	81.9	11.9	7.3	19.7	<8.0	206.0
				PIII(M7)	21	16	76.2	52.8	91.8	15.6	9.7	24.9	<8.0	202.0
				PIII(M12)	21	17	81.0	58.1	94.6	17.9	10.2	31.3	<8.0	446.0
			Total	PRE	175	22	12.6	8.0	18.4	4.9	4.5	5.3	<8.0	164.0
				PII(M2)	173	17	9.8	5.8	15.3	4.7	4.3	5.2	<8.0	206.0
				PIII(M7)	174	25	14.4	9.5	20.5	5.1	4.7	5.7	<8.0	202.0
				PIII(M12)	174	26	14.9	10.0	21.1	5.2	4.7	5.9	<8.0	446.0

HPV = HPV-16/18 L1 VLP AS04
Control = Aluminum [$Al(OH)_3$]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years
S- = seronegative subjects (antibody concentration < 8 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 8 EL.U/mL) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = pre-vaccination
PII(M2) = Post Dose 2, Month 2
PIII(M7) = Post Dose 3, Month 7
PIII(M12) = Post Dose 3, Month 12

Table 25 Seropositivity rates and GMTs for anti-HPV-18 antibody titers by serostatus at baseline per group and age strata (ATP cohort for immunogenicity Month 12)

						≥ 7 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-HPV-18	HPV	10-14	S-	PRE	126	0	0.0	0.0	2.9	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	126	126	100	97.1	100	3041.4	2677.6	3454.7	203.0	41836.0
				PIII(M7)	126	126	100	97.1	100	6575.8	5660.0	7639.8	461.0	85686.0
				PIII(M12)	126	125	99.2	95.7	100	1403.5	1140.7	1726.8	<7.0	36109.0
			S+	PRE	12	12	100	73.5	100	11.8	9.7	14.3	7.0	25.0
				PII(M2)	12	12	100	73.5	100	3164.4	2004.9	4994.6	980.0	11112.0
				PIII(M7)	12	12	100	73.5	100	5431.2	3090.1	9545.9	1810.0	23410.0
				PIII(M12)	12	12	100	73.5	100	1633.3	866.5	3078.7	326.0	8427.0
			Total	PRE	138	12	8.7	4.6	14.7	3.9	3.7	4.1	<7.0	25.0
				PII(M2)	138	138	100	97.4	100	3051.9	2703.7	3445.0	203.0	41836.0
				PIII(M7)	138	138	100	97.4	100	6467.3	5603.0	7465.0	461.0	85686.0
				PIII(M12)	138	137	99.3	96.0	100	1422.1	1170.0	1728.4	<7.0	36109.0
		15-25	S-	PRE	205	0	0.0	0.0	1.8	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	205	205	100	98.2	100	2011.3	1824.5	2217.3	214.0	20339.0
				PIII(M7)	205	205	100	98.2	100	3764.2	3409.5	4155.9	488.0	102428.0
				PIII(M12)	205	205	100	98.2	100	855.5	762.0	960.5	87.0	21567.0
			S+	PRE	22	22	100	84.6	100	13.8	10.3	18.5	7.0	91.0
				PII(M2)	22	22	100	84.6	100	2184.6	1662.1	2871.5	770.0	5399.0
				PIII(M7)	22	22	100	84.6	100	2842.7	2377.8	3398.5	1469.0	8316.0
				PIII(M12)	22	22	100	84.6	100	859.7	633.2	1167.3	277.0	3144.0
			Total	PRE	227	22	9.7	6.2	14.3	4.0	3.8	4.2	<7.0	91.0
				PII(M2)	227	227	100	98.4	100	2027.5	1850.4	2221.6	214.0	20339.0
				PIII(M7)	227	227	100	98.4	100	3663.2	3343.2	4013.8	488.0	102428.0
				PIII(M12)	227	227	100	98.4	100	855.9	768.3	953.5	87.0	21567.0
		Total	S-	PRE	331	0	0.0	0.0	1.1	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	331	331	100	98.9	100	2354.2	2173.1	2550.4	203.0	41836.0
				PIII(M7)	331	331	100	98.9	100	4654.8	4261.4	5084.5	461.0	102428.0
				PIII(M12)	331	330	99.7	98.3	100	1032.9	926.1	1152.0	<7.0	36109.0
			S+	PRE	34	34	100	89.7	100	13.0	10.7	15.8	7.0	91.0
				PII(M2)	34	34	100	89.7	100	2489.8	1972.2	3143.4	770.0	11112.0
				PIII(M7)	34	34	100	89.7	100	3572.5	2816.4	4531.5	1469.0	23410.0
				PIII(M12)	34	34	100	89.7	100	1078.3	800.0	1453.2	277.0	8427.0
			Total	PRE	365	34	9.3	6.5	12.8	4.0	3.8	4.1	<7.0	91.0
				PII(M2)	365	365	100	99.0	100	2366.5	2194.5	2552.1	203.0	41836.0
				PIII(M7)	365	365	100	99.0	100	4541.4	4179.0	4935.3	461.0	102428.0
				PIII(M12)	365	364	99.7	98.5	100	1037.0	936.1	1148.9	<7.0	36109.0
	Control	10-14	S-	PRE	56	0	0.0	0.0	6.4	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	55	1	1.8	0.0	9.7	3.6	3.4	3.7	<7.0	8.0
				PIII(M7)	56	2	3.6	0.4	12.3	3.6	3.5	3.8	<7.0	9.0
				PIII(M12)	56	0	0.0	0.0	6.4	3.5	3.5	3.5	<7.0	<7.0
			S+	PRE	10	10	100	69.2	100	9.3	7.5	11.5	7.0	16.0
				PII(M2)	10	7	70.0	34.8	93.3	7.0	4.9	10.0	<7.0	14.0
				PIII(M7)	10	5	50.0	18.7	81.3	5.8	3.8	8.7	<7.0	14.0
				PIII(M12)	10	3	30.0	6.7	65.2	4.8	3.3	6.9	<7.0	13.0
			Total	PRE	66	10	15.2	7.5	26.1	4.1	3.7	4.4	<7.0	16.0
				PII(M2)	65	8	12.3	5.5	22.8	3.9	3.6	4.3	<7.0	14.0

						≥ 7 EL.U/mL				GMT				
								95% CI			95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
				PIII(M7)	66	7	10.6	4.4	20.6	3.9	3.6	4.2	<7.0	14.0
				PIII(M12)	66	3	4.5	0.9	12.7	3.7	3.5	3.9	<7.0	13.0
		15-25	S-	PRE	96	0	0.0	0.0	3.8	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	96	4	4.2	1.1	10.3	3.8	3.5	4.2	<7.0	67.0
				PIII(M7)	96	5	5.2	1.7	11.7	3.9	3.5	4.3	<7.0	166.0
				PIII(M12)	96	6	6.3	2.3	13.1	3.9	3.5	4.2	<7.0	139.0
			S+	PRE	15	15	100	78.2	100	18.7	9.7	36.1	7.0	669.0
				PII(M2)	13	12	92.3	64.0	99.8	17.5	8.5	35.9	<7.0	434.0
				PIII(M7)	15	11	73.3	44.9	92.2	13.9	6.6	29.4	<7.0	393.0
				PIII(M12)	15	12	80.0	51.9	95.7	14.8	7.1	30.8	<7.0	314.0
			Total	PRE	111	15	13.5	7.8	21.3	4.4	3.8	5.0	<7.0	669.0
				PII(M2)	109	16	14.7	8.6	22.7	4.6	4.0	5.3	<7.0	434.0
				PIII(M7)	111	16	14.4	8.5	22.4	4.6	4.0	5.3	<7.0	393.0
				PIII(M12)	111	18	16.2	9.9	24.4	4.6	4.0	5.4	<7.0	314.0
		Total	S-	PRE	152	0	0.0	0.0	2.4	3.5	3.5	3.5	<7.0	<7.0
				PII(M2)	151	5	3.3	1.1	7.6	3.7	3.5	3.9	<7.0	67.0
				PIII(M7)	152	7	4.6	1.9	9.3	3.8	3.5	4.0	<7.0	166.0
				PIII(M12)	152	6	3.9	1.5	8.4	3.7	3.5	4.0	<7.0	139.0
			S+	PRE	25	25	100	86.3	100	14.2	9.4	21.3	7.0	669.0
				PII(M2)	23	19	82.6	61.2	95.0	11.7	7.5	18.4	<7.0	434.0
				PIII(M7)	25	16	64.0	42.5	82.0	9.8	6.0	15.9	<7.0	393.0
				PIII(M12)	25	15	60.0	38.7	78.9	9.4	5.7	15.4	<7.0	314.0
			Total	PRE	177	25	14.1	9.4	20.1	4.3	3.9	4.7	<7.0	669.0
				PII(M2)	174	24	13.8	9.0	19.8	4.3	3.9	4.8	<7.0	434.0
				PIII(M7)	177	23	13.0	8.4	18.9	4.3	3.9	4.8	<7.0	393.0
				PIII(M12)	177	21	11.9	7.5	17.6	4.2	3.9	4.7	<7.0	314.0

HPV = HPV-16/18 L1 VLP AS04
Control = Aluminum [Al(OH)3]
10-14 = 10-14 age stratum
15-25 = 15-25 age stratum
Total = 10-14 years/ 15-25 years
S- = seronegative subjects (antibody concentration < 7 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 7 EL.U/mL) prior to vaccination
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = pre-vaccination
PII(M2) = Post Dose 2, Month 2
PIII(M7) = Post Dose 3, Month 7
PIII(M12) = Post Dose 3, Month 12

Total Vaccinated cohort analysis

Assessor's note: the immunogenicity results obtained in the Total Vaccinated cohort were consistent with those obtained in the ATP cohort for immunogenicity and are not shown here.

Safety results

Data sets analyzed

The primary analysis of data up to Month 7 was based on the Total Vaccinated cohort. A second analysis based on the ATP cohort was performed to supplement the primary analysis. The analysis of data up to Month 12 was based on the Total Vaccinated cohort. A safety analysis was also performed on the Total Vaccinated cohort Month 12.

Total Vaccinated cohort analysis

Month 0 to Month 7 safety analysis on the Total Vaccinated cohort.

The number and percentage of subjects who received the study vaccine doses per group is presented in Table 26.

All subjects in the Total Vaccinated cohort had received at least one dose of the HPV vaccine or control. Majority (90.4%) of the subjects in both groups received 3 doses of the HPV vaccine or control.

Table 26 Number and percentage of subjects who received study vaccine doses (Total Vaccinated cohort)

	HPV group N = 450		Control group N = 226		Total N = 676	
Total number of doses received	n	%	n	%	n	%
1	13	2.9	9	4.0	22	3.3
2	26	5.8	17	7.5	43	6.4
3	411	91.3	200	88.5	611	90.4
Any	450	100	226	100	676	100

HPV = HPV-16/18 L1 VLP AS04
Control = Aluminum [$Al(OH)_3$]
N = number of subjects in each group or in total included in the considered cohort
n (%) = number (percentage) of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Overall incidence of adverse events

Incidence and nature of symptoms (solicited only) reported during the 7-day (Days 0 - 6) post-vaccination period following each dose and overall is presented in Table 27 (analysis included missing confirmed values).

Table 27 Incidence and nature of symptoms (solicited only) reported during the 7-day (Days 0 - 6) post-vaccination period following each dose and overall (Total Vaccinated cohort)*

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	HPV	450	369	82.0	78.1	85.4	450	175	38.9	34.4	43.6	450	309	68.7	64.2	72.9
	Control	226	160	70.8	64.4	76.6	226	91	40.3	33.8	47.0	226	116	51.3	44.6	58.0
Dose 2	HPV	437	313	71.6	67.1	75.8	437	151	34.6	30.1	39.2	437	266	60.9	56.1	65.5
	Control	217	124	57.1	50.3	63.8	217	74	34.1	27.8	40.8	217	95	43.8	37.1	50.7
Dose 3	HPV	411	253	61.6	56.7	66.3	411	130	31.6	27.2	36.4	411	200	48.7	43.7	53.6
	Control	200	106	53.0	45.8	60.1	200	61	30.5	24.2	37.4	200	66	33.0	26.5	40.0
Overall/dose	HPV	1298	935	72.0	69.5	74.5	1298	456	35.1	32.5	37.8	1298	775	59.7	57.0	62.4
	Control	643	390	60.7	56.8	64.5	643	226	35.1	31.5	39.0	643	277	43.1	39.2	47.0
Overall/subject	HPV	450	419	93.1	90.4	95.3	450	274	60.9	56.2	65.4	450	375	83.3	79.6	86.7
	Control	226	202	89.4	84.6	93.1	226	147	65.0	58.4	71.2	226	166	73.5	67.2	79.1

HPV = HPV-16/18 L1 VLP AS04

Control = Aluminum [$Al(OH)_3$]

For each dose and overall/subject:

N= number of subjects with at least one documented dose

n (%) = number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

N= number of documented doses

n (%) = number (percentage) of doses followed by at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

*This analysis took into account the missing confirmed values, i.e. missing confirmed values were considered as the symptom being reported.

Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0 - 29) post-vaccination period following each dose and overall is presented in Table 28 (analysis included missing confirmed values).

During the 30-day post-vaccination period, the incidence of any symptom (solicited and unsolicited) considered by the investigator to be related to vaccination was higher in the HPV group (following 65.9% of doses) than in the Control group (following 51.6% of doses).

The incidence of grade 3 symptoms (solicited and unsolicited) reported was low in both groups (following 0.6% of doses in the HPV group and following 0.2% of doses in the Control group). Two of the grade 3 symptoms (i.e. pain at the injection site) reported were considered by the investigator to be related to vaccination.

Table 28 Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0 - 29) post-vaccination period following each dose and overall (Total Vaccinated cohort)*

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	HPV	450	389	86.4	82.9	89.5	450	240	53.3	48.6	58.0	450	309	68.7	64.2	72.9
	Control	226	174	77.0	70.9	82.3	226	123	54.4	47.7	61.0	226	116	51.3	44.6	58.0
Dose 2	HPV	437	341	78.0	73.9	81.8	437	218	49.9	45.1	54.7	437	266	60.9	56.1	65.5
	Control	217	148	68.2	61.6	74.3	217	112	51.6	44.8	58.4	217	95	43.8	37.1	50.7
Dose 3	HPV	411	286	69.6	64.9	74.0	411	199	48.4	43.5	53.4	411	200	48.7	43.7	53.6
	Control	200	127	63.5	56.4	70.2	200	97	48.5	41.4	55.7	200	67	33.5	27.0	40.5
Overall/dose	HPV	1298	1016	78.3	75.9	80.5	1298	657	50.6	47.9	53.4	1298	775	59.7	57.0	62.4
	Control	643	449	69.8	66.1	73.4	643	332	51.6	47.7	55.6	643	278	43.2	39.4	47.2
Overall/subject	HPV	450	433	96.2	94.0	97.8	450	351	78.0	73.9	81.7	450	375	83.3	79.6	86.7
	Control	226	216	95.6	92.0	97.9	226	193	85.4	80.1	89.7	226	166	73.5	67.2	79.1

HPV = HPV-16/18 L1 VLP AS04
Control = Aluminum [$Al(OH)_3$]
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n (%) = number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of documented doses
n (%) = number (percentage) of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
*This analysis took into account the missing confirmed values, i.e. missing confirmed values were considered as the symptom being reported.

Solicited local adverse events

The incidence of solicited local symptoms reported during the 7-day (Days 0 - 6) postvaccination period following each dose and overall is presented in Table 29.

Only two doses (i.e. 0.2%) of the HPV vaccine were followed by grade 3 pain. Both these events were reported in the HPV group after the first vaccine dose. Swelling at the injection site (≤ 50.0 mm) was reported following 0.5% of the doses in the HPV group. None of these events were assessed as grade 3 in intensity. There were no reports of swelling at the injection site in the Control group. None of the subjects reported urticaria/rash within 30 minutes of vaccination in either group.

Table 29 **Incidence of solicited local symptoms reported during the 7-(Days 0 - 6) post-vaccination period following each dose and (Total Vaccinated cohort)**

		HPV group					Control group				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	All*	450	309	68.7	64.2	72.9	226	116	51.3	44.6	58.0
	Grade 1*2*3 **	450	299	66.4	61.9	70.8	226	109	48.2	41.6	55.0
	Grade 3	450	2	0.4	0.1	1.6	226	0	0.0	0.0	1.6
Swelling (mm)	All*	450	15	3.3	1.9	5.4	226	7	3.1	1.3	6.3
	[0.1 - ...**	450	3	0.7	0.1	1.9	226	0	0.0	0.0	1.6
	> 50.0	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Dose 2											
Pain	All*	437	265	60.6	55.9	65.3	217	95	43.8	37.1	50.7
	Grade 1*2*3 **	437	241	55.1	50.3	59.9	217	82	37.8	31.3	44.6
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Swelling (mm)	All*	437	45	10.3	7.6	13.5	217	15	6.9	3.9	11.1
	[0.1 - ...**	437	3	0.7	0.1	2.0	217	0	0.0	0.0	1.7
	> 50.0	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Dose 3											
Pain	All*	411	200	48.7	43.7	53.6	200	66	33.0	26.5	40.0
	Grade 1*2*3 **	411	185	45.0	40.1	50.0	200	58	29.0	22.8	35.8
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Swelling (mm)	All*	411	26	6.3	4.2	9.1	200	10	5.0	2.4	9.0
	[0.1 - ...**	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	> 50.0	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Overall/dose											
Pain	All*	1298	774	59.6	56.9	62.3	643	277	43.1	39.2	47.0
	Grade 1*2*3 **	1298	725	55.9	53.1	58.6	643	249	38.7	34.9	42.6
	Grade 3	1298	2	0.2	0.0	0.6	643	0	0.0	0.0	0.6
Swelling (mm)	All*	1298	86	6.6	5.3	8.1	643	32	5.0	3.4	7.0
	[0.1 - ...**	1298	6	0.5	0.2	1.0	643	0	0.0	0.0	0.6
	> 50.0	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Overall/subject											
Pain	All*	450	375	83.3	79.6	86.7	226	166	73.5	67.2	79.1
	Grade 1*2*3 **	450	360	80.0	76.0	83.6	226	151	66.8	60.3	72.9
	Grade 3	450	2	0.4	0.1	1.6	226	0	0.0	0.0	1.6
Swelling (mm)	All*	450	74	16.4	13.1	20.2	226	27	11.9	8.0	16.9
	[0.1 - ...**	450	6	1.3	0.5	2.9	226	0	0.0	0.0	1.6
	> 50.0	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6

HPV = HPV-16/18 L1 VLP AS04

Control = Aluminum [$Al(OH)_3$]

For each dose and overall/subject:

N= number of subjects with at least one documented dose

n (%) = number (percentage) of subjects reporting at least once the symptom

For Overall/dose:

N= number of documented doses

n (%) = number (percentage) of doses followed by at least one type of symptom

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

*This analysis took into account the missing confirmed values, i.e. missing confirmed values were considered as the symptom being reported.
** This analysis did not take into account the missing confirmed values, i.e., missing confirmed values were considered as no symptom reported.
All = Any solicited local symptom reported irrespective of intensity grade
Grade 3 pain = Pain that prevented normal activity

Solicited general adverse events

The incidence of solicited general symptoms reported during the 7-day (Days 0 - 6) postvaccination period following each dose and overall is shown in Table 30 and discussed below.

The most frequently reported solicited general symptoms in both groups were headache and fever followed by gastrointestinal symptoms:

- Headache was reported by 33.3% and 38.9% of the subjects in the HPV and Control groups, respectively, following 14.7% and 17.0% of doses. Vaccine-related headache was reported by 22.4% and 20.4% of the subjects following 8.7% and 8.6% of doses in the HPV and Control groups, respectively.
- Fever was reported by 24.7% and 25.2% of the subjects in the HPV and Control groups, respectively, following 13.4% of doses in both groups. Vaccine-related fever was reported by 12.7% and 11.9% of subjects following 5.6% and 5.3% of doses in the HPV and Control groups, respectively.
- Gastrointestinal symptoms were reported by 13.3% and 13.7% of the subjects in the HPV and Control groups, respectively, following 5.3% and 5.4% of doses. Vaccinerelated gastrointestinal symptoms were reported by 6.9% and 7.5% of subjects following 2.6% and 3.0% of doses in the HPV and Control groups, respectively.

Fatigue, myalgia, arthralgia, rash and urticaria were reported less frequently in both groups (≤ 4.0% of the doses in the HPV group and ≤ 3.0 of the doses in the Control group). None of the solicited general symptoms were assessed as grade 3 in intensity.

Table 30 **Incidence of solicited general symptoms reported during the 7-day (Days 0 - 6) post-vaccination period following each dose and overall (Total Vaccinated cohort)**

		HPV group					Control group				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Arthralgia	All*	450	19	4.2	2.6	6.5	226	10	4.4	2.1	8.0
	Grade 1*2*3 **	450	8	1.8	0.8	3.5	226	3	1.3	0.3	3.8
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	7	1.6	0.6	3.2	226	2	0.9	0.1	3.2
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Fatigue	All*	450	34	7.6	5.3	10.4	226	12	5.3	2.8	9.1
	Grade 1*2*3 **	450	23	5.1	3.3	7.6	226	5	2.2	0.7	5.1
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	21	4.7	2.9	7.0	226	3	1.3	0.3	3.8
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Fever/(Axillary) (°C)	All*	450	72	16.0	12.7	19.7	226	43	19.0	14.1	24.8
	[37.5 - 41.1[**	450	62	13.8	10.7	17.3	226	38	16.8	12.2	22.3
	[39.1 - 41.1[	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	34	7.6	5.3	10.4	226	17	7.5	4.4	11.8
	Rel*[39.1 - 41.1[	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Gastrointestinal symptoms	All*	450	34	7.6	5.3	10.4	226	21	9.3	5.8	13.9
	Grade 1*2*3 **	450	23	5.1	3.3	7.6	226	14	6.2	3.4	10.2
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	14	3.1	1.7	5.2	226	8	3.5	1.5	6.9
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Headache	All*	450	89	19.8	16.2	23.8	226	56	24.8	19.3	30.9
	Grade 1*2*3 **	450	82	18.2	14.8	22.1	226	50	22.1	16.9	28.1
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	51	11.3	8.6	14.6	226	25	11.1	7.3	15.9
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Myalgia	All*	450	35	7.8	5.5	10.7	226	16	7.1	4.1	11.2
	Grade 1*2*3 **	450	24	5.3	3.4	7.8	226	9	4.0	1.8	7.4
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	22	4.9	3.1	7.3	226	7	3.1	1.3	6.3
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Rash	All*	450	14	3.1	1.7	5.2	226	8	3.5	1.5	6.9
	Grade 1*2*3 **	450	3	0.7	0.1	1.9	226	1	0.4	0.0	2.4
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	1	0.2	0.0	1.2	226	0	0.0	0.0	1.6
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Urticaria	All*	450	12	2.7	1.4	4.6	226	7	3.1	1.3	6.3
	Grade 1*2*3 **	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Dose 2											
Arthralgia	All*	437	47	10.8	8.0	14.0	217	17	7.8	4.6	12.2
	Grade 1*2*3 **	437	4	0.9	0.2	2.3	217	3	1.4	0.3	4.0
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	4	0.9	0.2	2.3	217	2	0.9	0.1	3.3
	Rel*Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Fatigue	All*	437	62	14.2	11.1	17.8	217	25	11.5	7.6	16.5

		HPV group					Control group				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
	Grade 1*2*3 **	437	21	4.8	3.0	7.3	217	10	4.6	2.2	8.3
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	17	3.9	2.3	6.2	217	4	1.8	0.5	4.7
	Rel*Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Fever/(Axillary) (°C)	All*	437	82	18.8	15.2	22.7	217	33	15.2	10.7	20.7
	[37.5 - 41.1[**	437	51	11.7	8.8	15.1	217	21	9.7	6.1	14.4
	[39.1 - 41.1[	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	19	4.3	2.6	6.7	217	8	3.7	1.6	7.1
	Rel*[39.1 - 41.1[	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Gastrointestinal symptoms	All*	437	66	15.1	11.9	18.8	217	26	12.0	8.0	17.1
	Grade 1*2*3 **	437	27	6.2	4.1	8.9	217	11	5.1	2.6	8.9
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	15	3.4	1.9	5.6	217	6	2.8	1.0	5.9
	Rel*Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Headache	All*	437	96	22.0	18.2	26.1	217	49	22.6	17.2	28.7
	Grade 1*2*3 **	437	62	14.2	11.1	17.8	217	34	15.7	11.1	21.2
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	40	9.2	6.6	12.3	217	18	8.3	5.0	12.8
	Rel*Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Myalgia	All*	437	50	11.4	8.6	14.8	217	17	7.8	4.6	12.2
	Grade 1*2*3 **	437	9	2.1	0.9	3.9	217	3	1.4	0.3	4.0
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	9	2.1	0.9	3.9	217	3	1.4	0.3	4.0
	Rel*Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Rash	All*	437	44	10.1	7.4	13.3	217	15	6.9	3.9	11.1
	Grade 1*2*3 **	437	1	0.2	0.0	1.3	217	0	0.0	0.0	1.7
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	1	0.2	0.0	1.3	217	0	0.0	0.0	1.7
	Rel*Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Urticaria	All*	437	43	9.8	7.2	13.0	217	14	6.5	3.6	10.6
	Grade 1*2*3 **	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Related	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
	Rel*Grade 3	437	0	0.0	0.0	0.8	217	0	0.0	0.0	1.7
Dose 3											
Arthralgia	All*	411	28	6.8	4.6	9.7	200	10	5.0	2.4	9.0
	Grade 1*2*3 **	411	2	0.5	0.1	1.7	200	0	0.0	0.0	1.8
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Rel*Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Fatigue	All*	411	34	8.3	5.8	11.4	200	13	6.5	3.5	10.9
	Grade 1*2*3 **	411	8	1.9	0.8	3.8	200	3	1.5	0.3	4.3
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	4	1.0	0.3	2.5	200	3	1.5	0.3	4.3
	Rel*Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Fever/(Axillary) (°C)	All*	411	81	19.7	16.0	23.9	200	33	16.5	11.6	22.4
	[37.5 - 41.1[**	411	61	14.8	11.5	18.7	200	27	13.5	9.1	19.0
	[39.1 - 41.1[	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	20	4.9	3.0	7.4	200	9	4.5	2.1	8.4
	Rel*[39.1 - 41.1[	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Gastrointestinal symptoms	All*	411	43	10.5	7.7	13.8	200	19	9.5	5.8	14.4

		HPV group					Control group				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
	Grade 1*2*3 **	411	19	4.6	2.8	7.1	200	10	5.0	2.4	9.0
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	5	1.2	0.4	2.8	200	5	2.5	0.8	5.7
	Rel*Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Headache	All*	411	71	17.3	13.7	21.3	200	33	16.5	11.6	22.4
	Grade 1*2*3 **	411	47	11.4	8.5	14.9	200	25	12.5	8.3	17.9
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	22	5.4	3.4	8.0	200	12	6.0	3.1	10.2
	Rel*Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Myalgia	All*	411	28	6.8	4.6	9.7	200	10	5.0	2.4	9.0
	Grade 1*2*3 **	411	3	0.7	0.2	2.1	200	0	0.0	0.0	1.8
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	1	0.2	0.0	1.3	200	0	0.0	0.0	1.8
	Rel*Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Rash	All*	411	26	6.3	4.2	9.1	200	12	6.0	3.1	10.2
	Grade 1*2*3 **	411	0	0.0	0.0	0.9	200	2	1.0	0.1	3.6
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Rel*Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Urticaria	All*	411	26	6.3	4.2	9.1	200	11	5.5	2.8	9.6
	Grade 1*2*3 **	411	0	0.0	0.0	0.9	200	1	0.5	0.0	2.8
	Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Related	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
	Rel*Grade 3	411	0	0.0	0.0	0.9	200	0	0.0	0.0	1.8
Overall/dose											
Arthralgia	All*	1298	94	7.2	5.9	8.8	643	37	5.8	4.1	7.8
	Grade 1*2*3 **	1298	14	1.1	0.6	1.8	643	6	0.9	0.3	2.0
	Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	11	0.8	0.4	1.5	643	4	0.6	0.2	1.6
	Rel*Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Fatigue	All*	1298	130	10.0	8.4	11.8	643	50	7.8	5.8	10.1
	Grade 1*2*3 **	1298	52	4.0	3.0	5.2	643	18	2.8	1.7	4.4
	Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	42	3.2	2.3	4.3	643	10	1.6	0.7	2.8
	Rel*Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Fever/(Axillary) (°C)	All*	1298	235	18.1	16.0	20.3	643	109	17.0	14.1	20.1
	[37.5 - 41.1[**	1298	174	13.4	11.6	15.4	643	86	13.4	10.8	16.3
	[39.1 - 41.1[	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	73	5.6	4.4	7.0	643	34	5.3	3.7	7.3
	Rel*[39.1 - 41.1[	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Gastrointestinal symptoms	All*	1298	143	11.0	9.4	12.8	643	66	10.3	8.0	12.9
	Grade 1*2*3 **	1298	69	5.3	4.2	6.7	643	35	5.4	3.8	7.5
	Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	34	2.6	1.8	3.6	643	19	3.0	1.8	4.6
	Rel*Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Headache	All*	1298	256	19.7	17.6	22.0	643	138	21.5	18.3	24.8
	Grade 1*2*3 **	1298	191	14.7	12.8	16.8	643	109	17.0	14.1	20.1
	Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	113	8.7	7.2	10.4	643	55	8.6	6.5	11.0
	Rel*Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Myalgia	All*	1298	113	8.7	7.2	10.4	643	43	6.7	4.9	8.9
	Grade 1*2*3 **	1298	36	2.8	1.9	3.8	643	12	1.9	1.0	3.2

		HPV group					Control group				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
	Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	32	2.5	1.7	3.5	643	10	1.6	0.7	2.8
	Rel*Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Rash	All*	1298	84	6.5	5.2	7.9	643	35	5.4	3.8	7.5
	Grade 1*2*3 **	1298	4	0.3	0.1	0.8	643	3	0.5	0.1	1.4
	Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	2	0.2	0.0	0.6	643	0	0.0	0.0	0.6
	Rel*Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Urticaria	All*	1298	81	6.2	5.0	7.7	643	32	5.0	3.4	7.0
	Grade 1*2*3 **	1298	0	0.0	0.0	0.3	643	1	0.2	0.0	0.9
	Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Related	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
	Rel*Grade 3	1298	0	0.0	0.0	0.3	643	0	0.0	0.0	0.6
Overall/subject											
Arthralgia	All*	450	77	17.1	13.7	20.9	226	32	14.2	9.9	19.4
	Grade 1*2*3 **	450	13	2.9	1.5	4.9	226	6	2.7	1.0	5.7
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	10	2.2	1.1	4.0	226	4	1.8	0.5	4.5
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Fatigue	All*	450	111	24.7	20.8	28.9	226	42	18.6	13.7	24.3
	Grade 1*2*3 **	450	47	10.4	7.8	13.6	226	16	7.1	4.1	11.2
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	39	8.7	6.2	11.7	226	9	4.0	1.8	7.4
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Fever/(Axillary) (°C)	All*	450	147	32.7	28.3	37.2	226	70	31.0	25.0	37.4
	[37.5 - 41.1[**	450	111	24.7	20.8	28.9	226	57	25.2	19.7	31.4
	[39.1 - 41.1[	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	57	12.7	9.7	16.1	226	27	11.9	8.0	16.9
	Rel*[39.1 - 41.1[	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Gastrointestinal symptoms	All*	450	118	26.2	22.2	30.5	226	56	24.8	19.3	30.9
	Grade 1*2*3 **	450	60	13.3	10.3	16.8	226	31	13.7	9.5	18.9
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	31	6.9	4.7	9.6	226	17	7.5	4.4	11.8
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Headache	All*	450	189	42.0	37.4	46.7	226	109	48.2	41.6	55.0
	Grade 1*2*3 **	450	150	33.3	29.0	37.9	226	88	38.9	32.5	45.6
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	101	22.4	18.7	26.6	226	46	20.4	15.3	26.2
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Myalgia	All*	450	90	20.0	16.4	24.0	226	36	15.9	11.4	21.4
	Grade 1*2*3 **	450	31	6.9	4.7	9.6	226	11	4.9	2.5	8.5
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	27	6.0	4.0	8.6	226	9	4.0	1.8	7.4
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Rash	All*	450	71	15.8	12.5	19.5	226	30	13.3	9.1	18.4
	Grade 1*2*3 **	450	4	0.9	0.2	2.3	226	3	1.3	0.3	3.8
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Related	450	2	0.4	0.1	1.6	226	0	0.0	0.0	1.6
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
Urticaria	All*	450	68	15.1	11.9	18.8	226	27	11.9	8.0	16.9
	Grade 1*2*3 **	450	0	0.0	0.0	0.8	226	1	0.4	0.0	2.4
	Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6

		HPV group					Control group				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
	Related	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6
	Rel*Grade 3	450	0	0.0	0.0	0.8	226	0	0.0	0.0	1.6

HPV = HPV-16/18 L1 VLP AS04
Control = Aluminum [$Al(OH)_3$]
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n (%) = number (percentage) of subjects reporting at least once the symptom
For Overall/dose:
N= number of documented doses
n (%) = number (percentage) of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
*This analysis took into account the missing confirmed values, i.e. missing confirmed values were considered as the symptom being reported.
** This analysis did not take into account the missing confirmed values, i.e., missing confirmed values were considered as no symptom reported.
[37.5 - 41.1[= ≥ 37.5 °C
[39.1 - 41.1[= > 39.0 °C
All = Any solicited general symptom reported irrespective of intensity grade and causal relationship to vaccination
Grade 3 symptom = symptom that prevented normal activity
Grade 3 urticaria = urticaria distributed on at least 4 body areas
Related = Symptoms considered by the investigator to be related to vaccination
Rel*Grade 3 = Grade 3 symptoms which were considered by the investigator to be related to vaccination

Unsolicited adverse events

Assessor's note: a global summary of unsolicited signs and symptoms reported within the 30-day (Days 0-29) post-vaccination period is presented in Tables 31, 32 and 33 of the Clinical Study report, which are not shown here. During the 30-day post-vaccination period, 52.2% and 62.8% of subjects reported at least one unsolicited symptom following 25.3% and 30.2% of doses in the HPV and Control groups, respectively (see Table 31).

Table 31 Global Summary of unsolicited signs and symptoms reported within the 30-day (Days 0 - 29) post-vaccination period (Total Vaccinated cohort)

	Group		
	HPV	Control	Total
Number of subjects with at least one unsolicited symptom reported	235 (52.2%)	142 (62.8%)	377
Number of doses followed by at least one unsolicited symptom	329 (25.3%)	194 (30.2%)	523
Number of unsolicited symptoms classified by MedDRA Preferred Term*	413	228	641
Number of unsolicited symptoms reported	420	229	649

HPV = HPV-16/18 L1 VLP AS04
Control = Aluminum [$Al(OH)_3$]
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term were counted once

Serious adverse events

Fatal events

No fatal SAEs were reported during the active phase of the study (up to Month 7).

Non-fatal events

During the active phase of the study (i.e. up to Month 7) a total of 33 SAEs were reported by 22 subjects (20 SAEs were reported by 12 subjects in the HPV group and 13 SAEs were reported by ten subjects in the Control group). None of the SAEs were considered by the investigator to be related to vaccination.

Adverse events leading to premature discontinuation of study vaccine and/or study

None.

Other significant adverse events

Medically significant adverse events

The percentage of subjects reporting at least one medically significant AE during the active phase of the study (up to Month 7) was similar in the two groups (64.2% of subjects in the HPV group and 71.2% of subjects in the Control group). The most commonly reported medically significant AEs were malaria, headache and abdominal pain and were reported by a similar percentage of subjects in both groups.

New Onset Chronic Diseases

The percentage of subjects reporting at least one NOCD during the active phase of the study (up to month 7) was similar in the two groups (2.2% of subjects in the HPV group and 3.5% of subjects in the Control group). The most commonly reported NOCDs were eye pain in the HPV group and allergic conjunctivitis in the Control group, and were reported by 0.7% and 1.3% of the subjects, respectively. No NOCDs were reported based on the investigator's assessment during the active phase of the study (up to Month 7).

Concomitant medications /vaccinations

The use of concomitant medication was similar in the two groups (following 43.0% of doses in the HPV group and following 42.5% of doses in the Control group). Antipyretic medication was administered following 29.1% of doses in the HPV group and 27.2% of doses in the Control group. Prophylactic antipyretic was administered to one subject (0.2%) in the Control group.

Clinical laboratory evaluations

Mean values for hematology parameters (hematocrit, red and white blood cell counts, white blood cell differential counts), were similar in HPV and Control groups and no notable differences between pre-vaccination and post-vaccination (Month 7) time-points were observed.

Safety analysis stratified by age

The incidence of solicited general symptoms reported during the 7-day post-vaccination period was lower in subjects aged 10-14 years (following 24.9% of doses in the HPV group) than in subjects aged 15-25 years (following 40.7% of doses in the HPV group). The incidence of solicited local symptoms within 7 days post-vaccination was similar in both age groups. The incidence of solicited and unsolicited symptoms within the 30-day post-vaccination period were reported following 73.1% of doses in the HPV group in subjects aged 10-14 years and following 81.1% of doses in the HPV group in subjects aged 15-25 years.

According-to-protocol cohort analysis

Safety and reactogenicity data obtained from the analysis of the ATP cohort for safety were consistent with those obtained from the analysis of safety and reactogenicity on the Total Vaccinated cohort.

Total Vaccinated cohort Month 12 analysis

Month 7 to Month 12 safety analysis on the Total Vaccinated cohort Month 12: the results are comparable with those observed at Month 7.

3. DISCUSSION AND MAH'S OVERALL CONCLUSIONS (summary)

The primary objectives of this study were to evaluate the antibody responses (by ELISA) against HPV-16 and HPV-18 at Month 7, i.e., one month after completion of the three dose vaccination course, in two age strata consisting of subjects aged 15 - 25 years of age and subjects aged 10 -14 years of age.

All initially seronegative subjects had seronconverted at Month 2 for both anti-HPV-16 and anti-HPV-18 antibodies and remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies up to Month 7. GMTs observed at Month 7 were 441-fold and 200-fold above those associated with natural infections for anti-HPV-16 and anti-HPV-18 antibodies respectively. As previously observed in another study, anti-HPV-16 and anti-HPV-18 antibody titers at Month 7 were higher for subjects aged 10-14 years when compared to subjects aged 15-25 years of age.

The GMT values observed for the two age strata at Month 7 in this study were compared with values reported in subjects of similar age and who received similar vaccine lots (Hi-5 Rix4446 vaccine formulation produced at industrial scale) in study HPV-012, a study evaluating the immunogenicity and safety of Cervarix in female subjects aged 10-25 years in a European setting. GMTs observed in study HPV-21 were similar to those observed in study HPV-012 for subjects aged 10-14 years. For subjects aged 15-25 years GMTs were similar (for anti-HPV-16 antibodies) or higher (for anti-HPV-18 antibodies) than those observed in study HPV-012.

A secondary objective of this study was to evaluate the antibody responses (by ELISA) against HPV-16 and HPV-18 at Month 12, six month after completion of the three-dose vaccination course, in both age strata. The persistence of antibodies against both HPV-16 and HPV-18 in this study followed the expected pattern, i.e. after a peak response at Month 7, a decline in antibody titers was observed at Month 12. At Month 12, all initially seronegative subjects in the HPV group remained seropositive for anti-HPV-16 antibodies and all except one subject remained seropositive for anti-HPV-18 antibodies. As was observed at the Month 7 time-point, anti-HPV-16 and anti-HPV-18 antibody titers at Month 12 were higher for subjects aged 10-14 years when compared to subjects aged 15-25 years of age.

Overall, the reactogenicity and safety profile of the vaccine was similar in the HPV and Control groups, except for pain at the injection site for which a higher incidence was observed in the HPV group. Only two (first) doses of HPV vaccine were followed by grade 3 injection site pain. No impact on compliance for completion of the three-dose vaccination schedule was observed. No withdrawals due to AEs or SAEs were reported. A total of 50 non-fatal SAEs (mainly malaria) were reported by 31 subjects; none of these SAEs were considered by the investigator to be related to vaccination. No clinically significant abnormalities in biochemical and hematological parameters were observed at the Month 7 and Month 12 time points in either group when compared to baseline values observed at Month 0.

During the quarterly review of the safety data, the Independent Data Monitoring Committee supervising this study expressed that there were no serious safety concerns based on the safety data available. Taken together, the results of this study demonstrate that vaccination of adolescents and young women aged 10-25 years in Senegal and Tanzania with the HPV-16/18 L1 AS04 vaccine is highly immunogenic and generally well tolerated up to 12 months post the first vaccination dose.

4. RAPPORTEUR's CONCLUSION

The MAH's conclusion is endorsed.

5. REQUEST FOR SUPPLEMENTARY INFORMATION

None