24 June 2010
EMA/CHMP/498994/2010
Evaluation of Medicines for Human Use

CHMP variation assessment report

Type II variation EMEA/H/C/000721/II/0011

Invented name/name:	Cervarix
International non-proprietary name/common name:	human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)

Indication summary (as last approved):	prevention of cervical cancer
Marketing authorisation holder:	GlaxoSmithKline Biologicals S.A.

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

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1. Scope of the variation and changes to the dossier

Scope of the variation:	**Update of Summary of Product Characteristics, Annex II and Package Leaflet** To update sections 4.1, 4.4, 4.6 and 5.1 of the SmPC with the final analysis of pivotal study HPV-008. The PL was revised accordingly. Annex II was revised with the updated risk management plan approved.
Rapporteur: Co-Rapporteur:	Pieter Neels Christian Schneider
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1, 2 and 5
Product Information affected:	Summary of Product Characteristics, Annex II and Package Leaflet

2. Steps taken for the assessment

Step	Step date
Submission date:	7 April 2009
Start of procedure:	26 April 2009
Rapporteur's preliminary assessment report circulated on:	02 June 2009
Rapporteur's updated assessment report circulated on:	17 July 2009
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 July 2009
MAH's responses submitted to the CHMP on:	13 October 2009
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	06 November 2009
Rapporteur's updated assessment report on the MAH's responses circulated on:	16 November 2009
Follow-on Request for supplementary information and extension of timetable adopted by the CHMP on:	19 November 2009
MAH's responses submitted to the CHMP on:	15 January 2010
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	01 March 2010
Rapporteur's updated assessment report on the MAH's responses circulated on:	10 March 2010
Follow-on Request for supplementary information and extension of timetable adopted by the CHMP on:	18 March 2010
MAH's responses submitted to the CHMP on:	21 May 2010

Step	Step date
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	04 June 2010
Rapporteur's updated assessment report on the MAH's responses circulated on:	19 June 2010
CHMP opinion:	24 June 2010

3. Scientific discussion

3.1. Introduction

Cervarix was registered in the European Union on 20 September 2007. The vaccine is currently licensed for use in more than 100 countries worldwide. Cervarix is indicated for the prevention of premalignant cervical lesions and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18. The indication is based on demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years. The vaccination course consists of three doses administered according to a 0, 1, 6 month schedule via intramuscular injection.

The MAH has submitted data from the final analysis of study HPV-008, to support the present variation. On the basis of these data the MAH proposes to update section 4.1 of the SmPC to include persistent infection and to further update sections 4.4, 4.6 and 5.1 of the SmPC.

The study report of study HPV-008 should be considered final for the histopathological primary and secondary endpoints (CIN1+, CIN2+). The MAH performed the final analysis of study HPV-008 once the number of subjects required for the statistical analysis of the composite endpoint was reached. At that time point the majority of subjects had not yet reached the study endpoint that was fixed at Month 48 and therefore several analyses were still pending. The MAH expects to provide this information in an annex report that is expected by the end of 2010 (FUM23).

3.2. Clinical efficacy

3.2.1. Study HPV 008

HPV-008 is a controlled, double blinded Phase III randomised clinical trial performed in Asia Pacific, Europe, Latin America and North America. HPV-008 has been conducted under the supervision of an Independent Data Monitoring Committee (IDMC) with duration of 48 months of follow-up.

The (event-driven) interim analysis was performed when 23 cases of CIN2+ associated with HPV-16 or HPV-18 were detected in the Total Vaccinated Cohort (TVC).

The final analysis of all histopathological and virological endpoints had to be performed when at least 36 evaluable cases of CIN2+ associated with HPV-16 or HPV-18 infection, including at least 15 cases of CIN2+ associated with HPV-18 infection were detected in the According to Protocol (ATP) cohort of efficacy. The submitted final analysis was performed when 60 CIN2+ cases were identified (Data Lock Point of 31st August 2008).

3.2.1.1. Methods

Study participants and sample sizes

A total of 18729 subjects were enrolled in the study. The study is conducted in 135 centres in 14 countries spread across four study regions: Asia Pacific, Europe, Latin America and North America. The target was to enrol approximately 18 000 unscreened women aged 15 to 25 years.

Inclusion Criteria

The inclusion and exclusion criteria were selected to allow enrolment of a broad population of women, including both those previously uninfected with HPV (HPV naïve) and those previously or currently infected with HPV (HPV non-naïve). No HPV serological testing, HPV DNA screening or cervical cytological screening was performed prior to enrolment.

A woman between, and including, 15 and 25 years of age at the time of the first vaccination.
Subject must be free of obvious health problems as established by medical history and clinical examination before entering into the study.

Subject must have a negative urine pregnancy test.

Subject must be of non-childbearing potential (e.g. surgically sterilized) or, if of childbearing potential, she must be abstinent or must be using adequate contraceptive precautions for 30 days prior to the first vaccination and must agree to continue such precautions for two months after completion of the vaccination series.

Subject has had no more than 6 lifetime sexual partners prior to enrolment. This criterion may not be applicable in subjects less than 18 years of age, according to local regulatory/ethical requirements.
Subject must have intact cervix (e.g. no history of cauterization or surgical treatment involving damage to the transformation zone of the cervix).

Main Exclusion Criteria

Pregnant or breastfeeding. Women must be at least 3 months post-pregnancy and not breastfeeding to enter the study.

A woman planning to become pregnant or planning to discontinue contraceptive precautions during approximately the first nine months of the study (Months 0-8).

Previous administration of monophosphoryl lipid A (MPL) or AS04 adjuvant.

Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. Inhaled and topical steroids were allowed.

Planned administration of a vaccine not foreseen by the study protocol within 30 days before and 30 days after (i.e. days 0-29) each dose of vaccine.

History of having had colposcopy or has planned a colposcopy to evaluate an abnormal cervical cytology (Pap smear) test.

Received immunoglobulins and/or blood product within 90 days preceding enrolment. Enrolment will be deferred until the subject is outside of specified window.

Study cohorts/data sets analysed

At the final analysis, the ATP cohort for efficacy was the primary cohort for all endpoints, except for endpoints evaluated in HPV DNA positive women at Month 0.

Analysis of safety is performed on the Total Vaccinated cohort (primary analysis) and on the ATP cohort for safety.

Analysis of immunogenicity is performed on the ATP cohort for immunogenicity (primary analysis) and on the Total Vaccinated cohort.

According-to-protocol (ATP) cohort for analysis of efficacy
The ATP cohort for analysis of efficacy includes all valuable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination violations) for whom data concerning efficacy endpoint measures are available and have a normal or low-grade cytology (i.e. negative or ASCUS or Low-grade Squamous Intraepithelial Lesion (LSIL)) at Month 0. In addition, subjects must be negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type considered in the analysis (i.e. HPV type associated with the efficacy endpoint). For this cohort, the follow-up time for a subject started at the day after Dose 3. For all stratified efficacy endpoints, the principal analysis is performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type considered in the analysis. At the final analysis, the ATP cohort for efficacy was the primary cohort for all endpoints, except for endpoints evaluated in HPV DNA positive woman at Month 0.

Total Vaccinated cohort for efficacy 1 (TVC-1)
The total vaccinated cohort for efficacy-1 (TVC-1) included all vaccinated subjects who had received at least one dose, for whom data concerning efficacy endpoint measures were available and who had a normal or low-grade cytology (defined as negative, or ASCUS or LSIL) at Month 0. For this cohort, the follow-up time for a subject started the day after Dose 1.

In addition, subjects had to be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type in the analysis (i.e., the HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0. At the final analysis, TVC-1 was the primary cohort for all endpoints evaluated in HPV DNA positive women at Month 0.

For all stratified efficacy endpoints, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type.

Total Vaccinated cohort for efficacy 2 (TVC-2)
The total vaccinated cohort for efficacy 2 (TVC-2) included all vaccinated subjects who had received at least one dose and for whom data concerning efficacy endpoint measures were available, and who had a normal cytology at Month 0. For this cohort, the follow up-time for a subject started the day after Dose 1.

In addition, subjects had to be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type in the analysis (i.e., the HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0.

For all stratified efficacy endpoints, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type.

The TVC-2 analysis complements the TVC-1 analysis for efficacy and was only performed on primary, secondary endpoints and selected exploratory endpoints.

Total vaccinated cohort for efficacy (TVC)
The TVC for efficacy included all vaccinated subjects who had received at least one dose and for whom data were available for the analysis of efficacy endpoints. For this cohort, the follow-up time for a subject started the day after Dose 1. Unless otherwise specified, the results for the TVC cohort are provided in the Supplements to the clinical study report.

ATP cohort for analysis of immunogenicity
The ATP cohort for analysis of immunogenicity includes all valuable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. This includes subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination. Subjects who acquire either HPV-16 or HPV-18 infection during the trial are excluded from the ATP cohort for immunogenicity.

Treatments

The candidate HPV vaccine and hepatitis A control vaccine were administered (0.5 ml dose) intramuscularly into the deltoid of the non-dominant arm according to a 0, 1, 6-month schedule.
For the immunogenicity subset blood samples were drawn from all subjects at Months 0, 7 and 24 for HPV-16/18 serology testing by ELISA. Exit colposcopy was performed within 30 days after cytology results of the Month 48 visit depending on the cytological results.

Objectives

The primary objective of study HPV-008 was to demonstrate, that Cervarix protects individuals from histopathologically confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 and/or 18 serostatus (by ELISA). CIN2+ is defined as CIN2, CIN3, adenocarcinoma in-situ (AIS) and invasive cervical cancer.

Secondary objectives included the prevention of cervical intraepithelial neoplasia (CIN) 1, protection against persistent infection with HPV-16 and/or HPV-18 and the immunological response to vaccination.

Outcomes/endpoints

The primary endpoint for the interim analysis was protection against CIN2+ lesions associated with HPV-16 and/or HPV-18 among subjects who are negative for HPV DNA (by PCR) at baseline for the corresponding HPV type.

Secondary Endpoints included

Protection against persistent infection (6-month and 12-month definition) with HPV-16 or HPV-18 among subjects who are negative for HPV DNA at baseline for the corresponding HPV type.

Protection against persistent infection (6-month definition) with the following oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

Protection against CIN2+ and CIN1+ associated with HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

Immune response in a subset of subjects from selected study sites and immune correlates of protection against persistent infection.

Statistical methods

Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline have been calculated using the conditional exact method.

3.2.1.2. Results

Primary endpoint: CIN2+ associated with HPV-16/18

At the time of the final analysis there were 60 cases of the primary endpoint in the ATP cohort for efficacy (48 cases associated with HPV-16, 17 cases associated with HPV-18 and 5 cases associated with both HPV-16 and HPV-18) in subjects who were HPV DNA negative at Month 0 and 6, and seronegative at Month 0, for the corresponding type found in the lesion.

Vaccine efficacy (VE) against CIN3, adenocarcinoma in situ (AIS) and invasive cervical cancer (CIN3+) was to be evaluated as an exploratory endpoint if there were a sufficient number of CIN3+ cases.

Vaccine efficacy against HPV-16/18 CIN2+
Statistically significant VE was observed for CIN2+ associated with HPV-16, HPV-18 and HPV-16/HPV-18 (see Table 1). The primary objective was met.

Table 1 - Vaccine efficacy against CIN2+ associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline (ATP cohort for efficacy)

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	7344	4	17689.60	0.02	0.01	0.06	92.9	79.9	98.3	<0.0001
	HAV	7312	56	17663.32	0.32	0.24	0.42	-	-	-	-
HPV-16	HPV	6303	2	15193.63	0.01	0.00	0.05	95.7	82.9	99.6	<0.0001
	HAV	6165	46	14911.49	0.31	0.22	0.42	-	-	-	-
HPV-18	HPV	6794	2	16377.95	0.01	0.00	0.05	86.7	39.7	98.7	0.0013
	HAV	6746	15	16310.82	0.09	0.05	0.16	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or ICC
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group

T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Of the 60 cases of CIN2+, there were 12 cases of CIN3+ (9 cases of CIN3, 2 cases of AIS and 1 case of both CIN3 and AIS) with 2 cases in the HPV group and 10 cases in the HAV group. As there were sufficient cases of CIN3+ identified, an additional exploratory analysis was performed of VE against CIN3+ associated with HPV-16/18. VE against CIN3+ associated with HPV-16/18 was statistically significant at 80.0% [96.1% CI: 0.3, 98.1], p=0.0221 with 2 cases in the HPV group versus 10 cases in the HAV group in the ATP cohort for efficacy.

Similar results were observed in TVC-1. Vaccine-efficacy against CIN2+ associated with HPV-16/18 was 94.5% [96.1% CI: 86.2, 98.4], p<0.0001 with 5 cases in the HPV group versus 91 cases in the HAV group in TVC-1.

Vaccine efficacy against HPV-16/18 CIN2+ in HPV DNA negative and seronegative subjects (exploratory HPV TAA)

The pre-specified analysis of the VE against HPV-16/18 CIN2+ shown in Table 1 was based only on the detection of viral DNA by Polymerase Chain Reaction (PCR) in the biopsy sample without considering whether or not the HPV type(s) detected were likely to be causally responsible for the development of the lesion. This is important since further investigation identified that multiple oncogenic HPV types are frequently detected in cervical lesions.

A high proportion of the 60 CIN2+ cases in the primary analysis of the ATP cohort had more than one HPV type detected in the lesion (36 cases with another HPV type of which 33 were with non-vaccine oncogenic HPV types). A review of the HPV DNA detected in biopsies and preceding cytological specimens showed that in 6 of these cases in the ATP cohort for efficacy (3 cases in the HPV group and 3 in the HAV group) multiple HPV types were identified in the lesion without preceding infection with the vaccine type. For each of these cases, another oncogenic HPV type was also detected in the lesion and there was evidence of long standing infection with the other oncogenic HPV type (in each case infection with the other type was present at study entry). These data strongly suggested that the 3 cases in the HPV group were not vaccine breakthrough cases, but were likely to be causally associated with a non-vaccine HPV type. The exploratory analysis based on HPV TAA is shown in Table 2.

Table 2 - Vaccine efficacy against CIN2+ associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline (ATP cohort for efficacy/HPV TAA)

					Person-year rate			VE			
Event Type	**Group**	**N**	**N**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	7344	1	17695.52	0.01	0.00	0.03	98.1	88.4	100	<0.0001
	HAV	7312	53	17666.23	0.30	0.22	0.40	-	-	-	-
HPV-16	HPV	6303	0	15197.83	0.00	0.00	0.03	100	91.0	100	<0.0001
	HAV	6165	45	14911.61	0.30	0.22	0.41	-	-	-	-
HPV-18	HPV	6794	1	16379.68	0.01	0.00	0.04	92.3	45.7	99.9	0.0009
	HAV	6746	13	16313.61	0.08	0.04	0.14	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or ICC
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)

n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits; P-value=Two-sided Fisher Exact test

When the HPV TAA was applied to the analysis of CIN3+ related to HPV-16/18 in the ATP cohort for efficacy, VE was significant at 100% [96.1% CI: 36.4, 100], p=0.0038 with 0 cases in the HPV group versus 8 cases in the HAV group.

Similar results were seen in TVC-1 using the HPV TAA for this analysis. Vaccine-efficacy against CIN2+ associated with HPV-16/18 was 97.7% [96.1% CI: 91.0, 99.8], p<0.0001 with 2 cases in the HPV group versus 87 cases in the HAV group in TVC-1.

Vaccine efficacy against HPV-16/18 CIN2+ in HPV DNA negative subjects at baseline, regardless of initial serostatus

At enrolment, 13.9% of subjects were HPV DNA negative and seropositive for HPV-16 and 10.6% of subjects were HPV DNA negative and seropositive for HPV-18.

In subjects HPV DNA negative at baseline, regardless of initial serostatus, VE against CIN2+ associated with HPV-16/18 was statistically significant in both the ATP cohort for efficacy and TVC-1.

Vaccine efficacy against HPV-16/18 CIN2+ in HPV DNA negative and seropositive subjects

There were fewer cases of histopathological and virological endpoints associated with HPV-16/18 in the smaller population of subjects who were HPV DNA negative but seropositive for the corresponding type at baseline.

There were 8 cases of CIN2+ associated with HPV-16 and no cases with HPV-18 (2 cases in the HPV group and 6 cases in the HAV group) in the ATP cohort for efficacy. Of these 8 cases, there were 3 cases of CIN3, all in the HAV group. Multiple HPV types were detected in the majority of lesions. In TVC-1 there were 13 cases of the CIN2+, all associated with HPV-16 (3 in the HPV group and 10 in the HAV group). VE against CIN2+ associated with HPV-16/18 in the ATP cohort for efficacy and TVC-1 was therefore not statistically significant.

Based on the exploratory analysis using the HPV TAA, vaccine efficacy was not statistically significant in the ATP cohort for efficacy, but was statistically significant in TVC-1 (VE=88.5% [96.1% CI: 10.8, 99.8], p=0.0215), with 1 case in the HPV group versus 9 cases in the HAV group.

When these cohorts were analysed using the HPV TAA, VE against CIN2+ associated with HPV-16 was not statistically significant in the ATP cohort for efficacy (VE=100% [96.1% CI: -22.1, 100], p=0.0623), with 0 cases in the HPV group versus 5 cases in the HAV group, but was statistically significant in TVC-1 (VE=88.5% [96.1% CI: 10.8, 99.8], p=0.0215), with 1 case in the HPV group versus 9 cases in the HAV group.

However, statistically significant VE was observed for both 6M and 12M-persistent infections with HPV-16/18 and for other clinical endpoints (ASC-US+ and CIN1+) associated with HPV-16/18 in subjects that were HPV DNA negative and seropositive at baseline in TVC-1.

Secondary endpoints associated with HPV-16/18

Persistent infection, 12-month definition

VE in HPV DNA negative and seronegative subjects is displayed in table 3. VE against 12-month persistent infection with HPV-16/HPV-18 was statistically significant 91.4% [96.1% CI: 86.1, 95.0],

Table 3 - Vaccine efficacy against 12M persistent infection with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline (ATP-cohort for efficacy)

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	7035	20	17535.68	0.11	0.07	0.18	91.4	86.1	95.0	<0.0001
	HAV	6984	227	17185.48	1.32	1.15	1.51	-	-	-	-
HPV-16	HPV	6052	17	15088.65	0.11	0.06	0.18	90.4	83.8	94.7	<0.0001
	HAV	5903	171	14557.58	1.17	1.00	1.37	-	-	-	-
HPV-18	HPV	6508	3	16260.51	0.02	0.00	0.06	95.5	85.7	99.2	<0.0001
	HAV	6440	66	16073.81	0.41	0.31	0.53	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group Subjects have at least 10 months of follow-up after Month 12
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3 n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

In the analysis of HPV DNA negative and seronegative subjects in TVC-1, the VE against 12-month persistent infection with HPV-16/HPV-18 was statistically significant 85.3% [96.1% CI: 79.9, 89.4].

Persistent infection, 6-month definition

Vaccine efficacy against 6-month persistent infection with HPV-16/18 in HPV DNA negative and seronegative subjects is displayed in table 4.

Table 4 - Vaccine efficacy against 6M persistent infection with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline (ATP-cohort for efficacy)

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	7177	29	17713.52	0.16	0.11	0.24	94.3	91.5	96.3	<0.0001
	HAV	7122	488	17058.94	2.86	2.60	3.14	-	-	-	-
HPV-16	HPV	6163	22	15228.06	0.14	0.09	0.22	93.8	90.2	96.3	<0.0001
	HAV	6018	337	14519.10	2.32	2.07	2.60	-	-	-	-
HPV-18	HPV	6642	7	16433.32	0.04	0.02	0.09	96.3	91.9	98.6	<0.0001
	HAV	6567	184	16086.08	1.14	0.98	1.33	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
Subjects have at least 5 months of follow-up after Month 12
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding

HPV type For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type) n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL, UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Similar results were seen in TVC-1. VE against 6-month persistent infection with HPV-16/HPV-18 was 90.2% [96.1% CI: 87.3, 92.6].

Vaccine efficacy against CIN1+ associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline

Vaccine efficacy against CIN1+ associated with HPV-16/18 was 91.7% [96.1% CI: 82.4, 96.7], p<0.0001 in the ATP cohort and 91.8% [96.1% CI: 84.5, 96.2], p<0.0001 in the TVC-1 cohort.

In the exploratory HPV type assignment analysis vaccine efficacy against CIN1+ associated with HPV-16/18 was 97.8% [96.1% CI: 91.4, 99.8], p<0.0001 in the ATP cohort and 96.1% [96.1% CI: 90.3, 98.8], p<0.0001 in the TVC-1 cohort.

Secondary endpoints associated with oncogenic HPV types

Vaccine efficacy against 6-month persistent infection associated-with oncogenic HPV in subjects HPV DNA negative for the corresponding type at baseline, regardless of initial serostatus.

Results are presented in table 5 below.

Table 5 - Vaccine efficacy against 6-month persistent infection associated-with oncogenic HPV in subjects HPV DNA negative for the corresponding type at baseline, regardless of initial serostatus.

ATP			
HPV type	**6 month persistent infection**		
	Cervarix	**Control**	**% Efficacy (96.1% CI)**
	n	**n**	
HPV-16 related types (A9 species)			
HPV-31	45	199	77.5% (68.3;84.4)
HPV-33	55	100	45.1% (21.7;61.9)
HPV-35	55	43	-28.4% (<0;17.2)
HPV-52	293	315	7.4% (<0;22.0)
HPV-58	111	101	-10.3% (<0;17.7)
HPV-18 related types (A7 species)			
HPV-39	147	149	1.0% (<0;22.7)
HPV-45	19	79	76.1% (59.1;86.7)
HPV-59	56	59	4.8% (<0;36.4)
HPV-68	138	134	-3.1% (<0;20.3)
Other types			
HPV-51	304	354	14.5% (<0;27.4)
HPV-56	182	174	-5.0% (<0;16.1)
HPV-66	168	178	5.7% (<0;24.9)

n= number of cases

For oncogenic HPV types other than HPV-16 and HPV-18, VE against 6-month persistent infection was statistically significant for HPV-31, HPV-33 and HPV-45 in the ATP cohort for efficacy. Similar results were seen in TVC-1, the VE against HPV-51 was also significant.

Vaccine efficacy against CIN2+ associated with oncogenic HPV in subjects HPV DNA negative for the corresponding type at baseline, regardless of initial serostatus

VE against CIN2+ associated with High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (HR-HPV) in subjects HPV DNA negative for the corresponding HPV type at baseline, regardless of serostatus was statistically significant. VE against CIN2+ associated with All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 (High-risk (oncogenic) HPV types: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (HRW-HPV) was also statistically significant. However, it should be noted that the analyses of HRW-HPV may include lesions with multiple HPV types which, although associated with another oncogenic type besides HPV-16/18, may also contain HPV-16 or HPV-18 within the lesion (as these two types are ignored in the case definition). Therefore, the analysis of VE for histopathological endpoints with HRW-HPV may still be partially confounded by the presence of HPV-16 and/or HPV-18 (Table 6).

Statistically significant efficacy was observed against CIN2+ associated with high-risk types combined, excluding HPV-16 and HPV-18 (VE=54.0% [96.1% CI: 34.0;68.4] in the ATP cohort and VE=46.0% [96.1% CI: 27.0;60.3] in the TVC-1 cohort).

For the oncogenic HPV types other than HPV-16/18, statistically significant VE was observed for HPV-31, HPV-51 and HPV-58 in the ATP cohort. The point estimate for VE against HPV-45 was 100%, but this analysis did not reach statistical significance due to few cases (0 cases in the HPV group versus 4 cases in the HAV group).

Table 6 - Vaccine efficacy of CIN2+ associated with oncogenic HPV types in HPV DNA negative subjects at baseline (ATP cohort for efficacy)

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16	**HPV**	**7372**	**4**	**17726.34**	**0.02**	**0.01**	**0.06**	**92.7**	**79.3**	**98.2**	**<0.0001**
	HAV	7276	54	17520.68	0.31	0.23	0.41	-	-	-	-
HPV-18	**HPV**	**7645**	**2**	**18388.48**	**0.01**	**0.00**	**0.04**	**87.6**	**44.1**	**98.8**	**0.0007**
	HAV	7583	16	18312.59	0.09	0.05	0.15	-	-	-	-
HPV-31	**HPV**	**7583**	**2**	**18220.46**	**0.01**	**0.00**	**0.04**	**92.0**	**66.0**	**99.2**	**<0.0001**
	HAV	7599	25	18339.26	0.14	0.09	0.20	-	-	-	-
HPV-33	HPV	7720	12	18546.95	0.06	0.03	0.12	51.9	-2.9	78.9	0.0332
	HAV	7706	25	18596.46	0.13	0.08	0.20	-	-	-	-
HPV-35	HPV	7768	1	18674.74	0.01	0.00	0.03	83.3	-49.1	99.7	0.0702
	HAV	7764	6	18761.90	0.03	0.01	0.07	-	-	-	-
HPV-39	HPV	7609	3	18291.41	0.02	0.00	0.05	69.8	-24.2	95.2	0.0921
	HAV	7614	10	18414.11	0.05	0.02	0.10	-	-	-	-
HPV-45	HPV	7782	0	18715.82	0.00	0.00	0.02	100.0	-67.8	100.0	0.0619
	HAV	7745	4	18732.22	0.02	0.01	0.06	-	-	-	-
HPV-51	**HPV**	**7363**	**10**	**17691.42**	**0.06**	**0.03**	**0.11**	**62.9**	**18.0**	**84.7**	**0.0050**
	HAV	7352	27	17732.77	0.15	0.10	0.23	-	-	-	-
HPV-52	HPV	7461	12	17934.23	0.07	0.03	0.12	14.3	-108.1	65.4	0.7000
	HAV	7414	14	17925.16	0.08	0.04	0.13	-	-	-	-
HPV-56	HPV	7646	4	18388.52	0.02	0.01	0.06	59.9	-47.1	91.5	0.1181
	HAV	7638	10	18457.65	0.05	0.02	0.10	-	-	-	-
HPV-58	**HPV**	**7709**	**6**	**18512.03**	**0.03**	**0.01**	**0.07**	**64.5**	**1.5**	**89.2**	**0.0225**
	HAV	7702	17	18607.82	0.09	0.05	0.15	-	-	-	-
HPV-59	HPV	7720	1	18558.42	0.01	0.00	0.03	74.9	-178.6	99.6	0.3749
	HAV	7723	4	18663.51	0.02	0.01	0.06	-	-	-	-
HPV-66	HPV	7592	4	18249.66	0.02	0.01	0.06	60.0	-46.7	91.6	0.1176
	HAV	7564	10	18268.55	0.05	0.03	0.10	-	-	-	-
HPV-68	HPV	7633	5	18352.82	0.03	0.01	0.07	54.4	-49.8	88.4	0.1428
	HAV	7614	11	18396.00	0.06	0.03	0.11	-	-	-	-
HRW-HPV	**HPV**	**7863**	**50**	**18848.93**	**0.27**	**0.19**	**0.35**	**54.0**	**34.0**	**68.4**	**<0.0001**
	HAV	7853	109	18897.20	0.58	0.47	0.70	-	-	-	-
HR-HPV	**HPV**	**7863**	**54**	**18842.44**	**0.29**	**0.21**	**0.38**	**61.9**	**46.7**	**73.2**	**<0.0001**
	HAV	7853	142	18871.92	0.75	0.63	0.89	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
CIN2+ = CIN2, CIN3, AIS or ICC
For single type: Subjects DNA negative for the corresponding HPV type at Month 0 and Month 6
For combined types: Subjects DNA negative for at least one HPV type at Month 0 and Month 6 (subjects were in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event were DNA negative for the corresponding HPV type at Month 0 and Month 6
HRW-HPV = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HR-HPV= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

For the oncogenic HPV types other than HPV-16/18, statistically significant VE against CIN2+ was observed for HPV-31, HPV-33, HPV-35 and HPV-51 in TVC-1. In contrast to the results in the ATP cohort for efficacy, statistically significant VE was observed for HPV-33 and HPV-35, but not for HPV-58 in TVC-1.

In the TAA analysis, vaccine efficacy against CIN2+ associated with high-risk HPV types combined, excluding HPV-16 and HPV-18, was 53.9% [96.1% CI: 32.6;69.0]).

Following CHMP request to provide all available evidence that 6-month and 12-month persistent infections due to non-HPV16/18 types are surrogate markers that are equivalent to CIN2+ lesions in predicting cervical cancer the MAH has submitted table 7 below summarising all the relevant results obtained.

Table 7: Vaccine efficacy for cross-protection against individual non-vaccine, oncogenic HPV types (ATP cohort for efficacy, TVC-1, TVC and TVC- naïve)

Type	Endpoint	ATP				TVC-1				TVC				TVC-naïve			
		n HPV/ n HAV	%	96.1% CI	P-value	n HPV/ n HAV	%	96.1% CI	P-value	n HPV/ n HAV	%	96.1% CI	P-value	n HPV/ n HAV	%	96.1% CI	P-value
HPV-31	6M	45/199	77.5*	68.3, 84.4	<0.0001	93/264	64.9*	54.8, 72.9	<0.0001	93/266	65.2	55.2, 73.1	<0.0001	32/128	75.3	62.7, 84.2	<0.0001
	12M	17/87	80.5*	66.1, 89.5	<0.0001	48/122	60.6*	43.6, 72.9	<0.0001	48/123	60.9	44.1, 73.1	<0.0001	16/54	70.6	46.5, 84.8	<0.00 01
	CIN1+	6/49	87.7	70.2, 95.9	<0.0001	20/65	69.0	46.9,82.8	<0.0001	20/66	69.5	47.8, 83.0	<0.0001	3/30	90.0	66.5, 98.2	<0.00 01
	CIN2+	2/25	92.0	66.0, 99.2	<0.0001	11/34	67.4	32.0,85.7	0.0008	11/35	68.4	34.2, 86.1	0.0005	0/20	100	78.3, 100	<0.00 01
HPV-33	6M	55/100	45.1*	21.7, 61.9	0.0003	83/142	41.6*	21.8, 56.6	<0.0001	88/144	38.9	18.6, 54.3	0.0003	47/80	41.8	13.9, 61.1	0.0031
	12M	23/39	41.0	-4.0, 67.3	0.0422	39/62	37.0*	2.5, 59.8	0.0276	41/62	33.8	-1.9, 57.4	0.0475	24/35	31.9	-21.0, 62.4	0.1525
	CIN1+	21/34	38.1	-13.0, 66.9	0.0806	28/46	38.9	-2.3,64.2	0.0469	30/48	37.2	-3.5, 62.6	0.0530	8/21	62.0	7.2, 86.2	0.0159
	CIN2+	12/25	51.9	-2.9, 78.9	0.0332	16/32	49.8	2.9,75.2	0.0291	17/34	49.8	4.8. 74.6	0.0239	5/18	72.3	19.1, 92.5	0.0065
HPV-45	6M	19/79	76.1*	59.1, 86.7	<0.0001	30/107	72.0*	56.9, 82.4	<0.0001	30/109	72.6	57.7, 82.7	<0.0001	10/56	82.3	63.9, 92.3	<0.0001
	12M	8/20	60.0*	1.5, 85.5	0.0236	17/35	51.4*	8.3, 75.3	0.0125	17/35	51.4	8.3, 75.3	0.0125	3/17	82.5	36.3, 97.0	0.0014
	CIN1+	1/12	91.7	39.3, 99.9	0.0018	1/15	93.3	53.8,99.9	0.0005	1/17	94.1	60.1, 99.9	0.0001	1/10	90.0	25.1, 99.8	0.0063
	CIN2+	0/4	100	-67.8, 100	0.0619	0/5	100	-20.2,100	0.0625	0/6	100	7.0, 100	0.0312	0/5	100	-19.5, 100	0.0310
HPV-51	6M	304/354	14.5	-0.8, 27.4	0.0418	401/475	15.8*	3.0, 27.0	0.0112	405/476	15.2	2.3, 26.4	0.0153	217/294	27.2	12.1, 39.8	0.0004
	12M	102/139	26.8*	3.5, 44.6	0.0161	150/204	26.6*	7.9, 41.6	0.0037	152/204	25.7	6.8, 40.8	0.0053	71/119	41.0	18.9, 57.3	0.0004
	CIN1+	42/57	26.1	-14.4, 52.7	0.1316	48/82	41.4	13.7, 60.6	0.0035	48/82	41.4	13.7, 60.6	0.0035	18/47	61.9	32.1, 79.8	0.0003
	CIN2+	10/27	62.9	18.0, 84.7	0.0050	12/39	69.2	38.0, 85.9	0.0002	12/39	69.2	38.0,85.9	0.0002	2/17	88.3	47.9, 98.9	0.0004
HPV-58	6M	111/101	-10.3	-48.0, 17.7	0.5337	145/135	-8.1	-39.4, 16.1	0.5470	147/135	-9.6	-41.2, 14.9	0.4713	70/70	0.5	-43.1, 30.8	1.0000
	12M	41/35	-17.7	-95.1, 28.6	0.5656	61/48	-28.0	-94.8, 15.5	0.2128	62/48	-30.1	-97.8, 13.9	0.1816	27/23	-16.8	-119.9, 37.4	0.6712

	CIN1+	11/34	67.5	32.2, 85.8	0.0005	21/41	48.4	8.3, 71.9	0.0150	21/42	49.7	10.8, 72.5	0.0110	6/21	71.5	23.9, 91.2	0.0036
	CIN2+	6/17	64.5	1.5, 89.2	0.0225	10/20	49.6	-17.1, 79.9	0.0985	10/20	49.6	-17.1, 79.9	0.0985	3/11	72.8	-8.9, 95.6	0.0348

* n=number of subjects reporting at least one event in each group (HPV group/HAV group).
HPV = HPV group; HAV = HAV group
ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type (HPV-16 or HPV-18)
TVC-1: includes women who received at least one dose of vaccine for whom data concerning efficacy endpoint measures were available and who had a normal or low-grade cytology (i.e. negative or ASC-US or LSIL) at Month 0. Subjects had to be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type considered in the analysis (i.e. HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0. The follow-up time for subjects started the day after Dose 1
TVC: includes all women who received at least one dose of vaccine, irrespective of their HPV DNA status, cytology and serostatus at baseline. This cohort included women with or without current and/or prior HPV infection. Case counting for the TVC started on day 1 after the first dose.
TVC-naïve: is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.

Exploratory endpoints associated with oncogenic HPV types

Vaccine efficacy against vulvar and vaginal intraepithelial neoplasia (VIN/VaIN1+) associated with HPV-16/18 in HPV DNA negative and seronegative subjects

Statistically significant vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 was observed in both cohorts: 80.0% (96.1% CI: 0.3;98.1) in the ATP cohort and 83.2% (96.1% CI: 20.2 ;98.4) in the TVC-1 cohort.

Efficacy in women previously infected with the other vaccine type

Persistent infection (6-month definition) with HPV-16/18 in women previously infected with the other vaccine type is presented in Table 8.

Table 8 - Vaccine efficacy against persistent infection (6-month definition) with HPV-16/18 in subjects with a history of HPV infection with one vaccine type and HPV DNA negative and seronegative for the other-vaccine type at baseline (TVC-1)

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	1617	16	4683.38	0.34	0.19	0.57	81.9	68.2	90.4	<0.0001
	HAV	1656	89	4708.87	1.89	1.50	2.35	-	-	-	-
HPV-16	HPV	554	8	1594.53	0.50	0.21	1.02	80.8	57.3	92.6	<0.0001
	HAV	570	42	1603.88	2.62	1.85	3.59	-	-	-	-
HPV-18	HPV	1063	8	3088.86	0.26	0.11	0.53	82.9	62.2	93.4	<0.0001
	HAV	1086	47	3104.99	1.51	1.09	2.04	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
Subjects have at least 5 months of follow-up after Month 6
HPV-16: Subjects DNA positive or seropositive for HPV-18 at Month 0 and DNA negative and seronegative for HPV-16 at Month 0
HPV-18: Subjects DNA positive or seropositive for HPV-16 at Month 0 and DNA negative and seronegative for HPV-18 at Month 0
HPV-16/18: Subjects DNA positive or seropositive for either HPV-16 or HPV-18 at Month 0 and DNA negative and seronegative for the other type at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

CIN2+ associated with HPV-16/18 in women previously infected with the other vaccine type is a post-hoc analysis performed to complement the equivalent analysis for 6-month persistent infection. Analyses were performed in TVC-1 in subjects who were HPV DNA negative at baseline for the corresponding type assessed in the analysis and with a history of infection with the other vaccine type (Table 9).

Table 9 - Vaccine efficacy against CIN2+ associated with HPV-16/18 in-subjects with a history of infection with the other vaccine type (HPV DNA positive and/or seropositive) and HPV DNA negative and seronegative for the corresponding vaccine type at baseline (TVC-1)

					Person-year rate			VE			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	1643	2	4705.92	0.04	0.00	0.16	81.3	8.9	98.2	0.0224
	HAV	1690	11	4852.29	0.23	0.11	0.42	-	-	-	-
HPV-16	HPV	560	1	1602.03	0.06	0.00	0.37	79.2	-102.2	99.7	0.2179
	HAV	578	5	1667.88	0.30	0.09	0.72	-	-	-	-
HPV-18	HPV	1083	1	3103.89	0.03	0.00	0.19	82.9	-52.3	99.7	0.1246
	HAV	1112	6	3184.41	0.19	0.07	0.42	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN2+ = CIN2, CIN3, AIS or ICC
N=number of subjects included in each group
HPV-16: Subjects DNA positive or seropositive for HPV-18 at Month 0 and DNA negative and seronegative for HPV-16 at Month 0 HPV-18: Subjects DNA positive or seropositive for HPV-16 at Month 0 and DNA negative and seronegative for HPV-18 at Month 0 HPV-16/18: Subjects DNA positive or seropositive for either HPV-16 or HPV-18 at Month 0 and DNA negative and seronegative for the other type at Month 0
n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Efficacy against HPV types in women irrespective of the presence of a current or previous HPV 16/18 infection

Results for TVC and TVC naïve populations are presented in table 10.

Table 10 - Vaccine efficacy against HPV-16/18 endpoints

	HPV		**HAV**		**% Efficacy (96.1% CI)**
	N	**n**	**N**	**n**	
HPV-16/18 CIN3+					
Prophylactic Efficacy[1]	5,449	0	5,436	13	100 (64.7, 100)
Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18[2]	8,667	43	8,682	65	33.6 (-1.1, 56.9)
HPV-16/18 CIN2+					
Prophylactic Efficacy[1]	5,449	1	5,436	63	98.4 (90.4, 100.0)
Regardless of Current Infection or Prior Exposure to HPV-16 or HPV-18[2]	8,667	82	8,682	174	52.8 (37.5, 64.7)

[1] TVC naïve which includes all vaccinated subjects (who received at least one dose of vaccine) who had normal cytology, were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline
[2] TVC which includes all vaccinated subjects (who received at least one dose of vaccine) irrespective of HPV DNA status and serostatus at baseline. Case counting started on day 1 after the first dose.
N = number of subjects included in each group.
n = number of cases.
ASC-US+ = any cytological abnormality (ASC-US, LSIL, HSIL, ASC-H and AGC)
CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer.
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
CIN3+ = CIN3, AIS or invasive cervical cancer

Vaccine efficacy against virological endpoints associated with HPV-16/18 for TVC population (includes all vaccinated subjects (who received at least one dose of vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline) is 56.5% (96.1 % CI: 51.4;61.1) for 6 month persistent infection and 47.5% (96.1 % CI: 39.5;54.6) for 12 month persistent infection.

Overall vaccine efficacy against CIN2+ in subjects irrespective of HPV type in the lesion, stratified according to a subjects' baseline HPV DNA status

Vaccine efficacy against all CIN2+, (prophylactic efficacy) irrespective of HPV DNA results, in subjects DNA negative for all oncogenic HPV types at baseline, regardless of initial serostatus (TVC-1) was 63.8% (96.1% CI: 49.0;74.7)

Vaccine efficacy against all CIN2+, (overall efficacy) irrespective of HPV DNA results, in all subjects irrespective of baseline HPV DNA and serostatus (TVC-1) was 30.9% (96.1% CI: 16.4;43.0)

In the broader Total Vaccinated Cohort (TVC) which included all vaccinated women, overall efficacy against CIN2+ was 30.4% (96.1% CI: 16.4;42.1) and prophylactic efficacy in women negative for 14 oncogenic types was 70.2% (96.1% CI: 54.7;80.9).
Vaccine efficacy against CIN3+ irrespective of HPV DNA results in all subjects, irrespective of their baseline HPV DNA and serostatus (TVC-1) was 37.7% (96.1% CI: 12.6;55.9) with 64 CIN3+ cases in the vaccine group versus 103 CIN3+ cases in the control group.

In the broader Total Vaccinated Cohort (TVC) which included all vaccinated women, overall efficacy against CIN3+ was 33.4% (96.1% CI: 9.1;51.5) and prophylactic efficacy in women negative for 14 oncogenic types was 87.0% (96.1% CI: 54.9;97.7).

Reduction of local cervical therapy

Cervarix reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 68.8% (96.1% CI: 50.0;81.2) in TVC naïve and by 24.7% (96.1% CI: 7.4;38.9) in TVC.

Vaccine efficacy against HPV-16/18 in HPV DNA positive subjects at baseline

Results for vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 in subjects who were HPV DNA positive at baseline were not statistically significant. The lack of efficacy in subjects infected at baseline with the type considered in the analysis indicated the lack of therapeutic effect in the presence of active infection.

Vaccine efficacy against CIN2+ associated with HPV-16/18 in HPV DNA positive and seronegative subjects at baseline in TVC-1 was 37.8% [96.1% CI: -20.9, 68.8], p=0.1216, with 18 cases in the HPV group versus 27 cases in the HAV group. The majority of cases in this analysis were associated with HPV-16 (41 cases) and only 5 cases were associated with HPV-18.

Vaccine effect on viral clearance of HPV-16/18 infection in HPV DNA positive subjects at baseline (TVC-1)

The analyses were performed on subjects that were HPV DNA positive for the corresponding type at baseline. Clearance was defined as the first negative sample for HPV DNA (by PCR) for the corresponding HPV type after Month 0, after which no positive samples occur, i.e. subjects had to be negative at the last visit for which a DNA result was available.

No significant differences were observed between the HPV and HAV group in terms of clearance of HPV infection present at the study start (Table 11).

Table 11 - Vaccine efficacy in clearance of HPV-16/18 in HPV DNA positive and seronegative subjects at baseline (TVC-1)

					Person-year rate			*VE*			
Event Type	**Group**	**N**	**n**	**T(year)**	**n/T (Per 100)**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HPV-16/18	HPV	311	260	871.08	29.85	26.15	33.91	0.9	-53.0	35.7	0.9132
	HAV	292	243	829.28	29.30	25.55	33.44	-	-	-	-
HPV-16	HPV	219	165	612.65	26.93	22.78	31.61	-25.8	-98.7	19.7	0.2435
	HAV	202	162	570.86	28.38	23.97	33.36	-	-	-	-
HPV-18	HPV	115	108	320.50	33.70	27.35	41.07	49.4	-42.9	83.9	0.1075
	HAV	104	91	301.18	30.21	24.04	37.48	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
For single type: Subjects DNA positive and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA positive and seronegative for at least one HPV type at Month 0 (subjects were in the analysis of at least one single type)
n=number of subjects who cleared the infection in each group
T(years)=sum of follow-up period (total follow-up time) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

3.2.1.3. Discussion

The prophylactic efficacy of Cervarix in female adolescents and young adult women is fully confirmed by the longer follow-up (approximately 39 months) and the generation of more robust efficacy data in the final analysis of study HPV-008. Since vaccine efficacy in the follow-up period essentially evaluates prevention of newly acquired infections and associated lesions, the proportion of new lesions in the control group acquired after study entry increased over time. As a consequence, vaccine efficacy at the final analysis was higher than at the interim analysis.

Although the young adolescent / pre-adolescent female population remains the primary focus for universal mass vaccination programmes, women who have previously been exposed to HPV through sexual activity can still benefit from prophylactic vaccination with Cervarix. Vaccine efficacy against CIN2+ associated with HPV-16/18, regardless of baseline serostatus, was indicative of prophylactic vaccine efficacy in a general population of women, unscreened for serology. Individuals already infected with one vaccine type prior to vaccination were protected from clinical disease caused by the other vaccine type.

The overall impact of vaccination in subjects irrespective of the HPV DNA in the lesion, regardless of serostatus, against CIN2+ demonstrated statistically significant efficacy in the broader Total Vaccinated Cohort 30.4% (96.1% CI: 16.4;42.1) and was consistent with the overall reduction of local cervical therapy (24.7%). The prophylactic efficacy against CIN2+ in women who were negative for 14 oncogenic HPV types at baseline (representative of an HPV naïve population), irrespective of the HPV DNA type in the lesion and regardless of initial serostatus, was statistically significant (VE=70.2% (96.1% CI: 54.7;80.9) in TVC.

Cervarix has demonstrated a level of efficacy beyond the vaccine types HPV-16 and HPV-18. Disease endpoints such as CIN2+ are the most relevant endpoints when considering the potential public health benefit of cross-protection with combined oncogenic HPV types. Statistically significant efficacy was observed against CIN2+ associated with high-risk types combined, excluding HPV-16 and HPV-18

(VE=54.0% [96.1% CI: 34.0;68.4] in the ATP cohort and VE=46.0% [96.1% CI: 27.0;60.3] in the TVC-1 cohort).

Statistically significant vaccine efficacy against CIN2+ was observed for HPV types -31, -51 and -58 in the ATP cohort and for HPV types -31, -33, -35 and -51 in the TVC-1 cohort.

For the evaluation of specific high-risk (oncogenic) types, persistent infection overcomes the possible confounding effect of multiple infections in CIN lesions. Statistically significant vaccine efficacy against 6-month persistent infection was observed for HPV types -31, -33 and -45 in the ATP cohort and for HPV types -31, -33, -45 and -51 in the TVC-1 cohort. Vaccine efficacy against 6-month persistent infection with specific oncogenic HPV types is consistent with the efficacy against clinical endpoints and strengthens the data package. However, to better support this claim the MAH was requested to provide all available evidence that 6-month and 12-month persistent infections due to HPV 16/18 as well as non-HPV16/18 types are surrogate markers that are equivalent to CIN2+ lesions in predicting cervical cancer.

Furthermore the CHMP requested an ad hoc expert meeting on HPV vaccines to address the relevance of persistent infection as surrogate markers for cervical cancer. The meeting took place on 3 December 2009 and addressed the CHMP list of questions reaching the below conclusions.

Data for HPV vaccines demonstrate the appropriateness of using HPV 16/18 persistent infection as a surrogate endpoint to show efficacy of a given vaccine. Persistent infection can be used as a surrogate endpoint for cervical cancer for the non-vaccine HPV types, provided that high efficacy estimates against persistent infection are obtained. Furthermore persistent infection can be used to replace CIN2+ as a primary efficacy endpoint for the individual non-vaccine types. However, the clinical endpoint CIN2+ should continue to be followed as a secondary endpoint. Persistent infection predicts clinical benefit irrespective of duration of persistence, i.e. 6-, 12- or 18-months.

Additional data provided by the MAH (see table 7) shows that HPV 31 is the only non-vaccine HPV type for which robust and consistent cross-protection has been demonstrated, i.e. in all study populations and for all endpoints (CIN 2/3, 6M PI and 12M PI).

For the other relevant non-vaccine HPV types inconsistent results were seen, as detailed below:
For HPV 33, only cross-protection against 6M PI reached statistical significance in all study populations However, VE against 6M PI (45.7%) in the ATP cohort cannot be considered high, which was a provision for acceptance of this endpoint as concluded by the Ad Hoc Expert HPV Group meeting (see conclusions above). Moreover, no efficacy against CIN 2/3 (primary endpoint evaluated first in the hierarchical approach) and 12M PI could be shown in the ATP analysis. The ATP cohort represents the primary efficacy population and it is also the only population for which the efficacy results of non-vaccine HPV types are presented in the SmPC.

With respect to HPV 51, only in the CIN 2/3 endpoint statistically significant cross-protection across all study populations was obtained, whereas for 6M PI a non-significant result was obtained in the primary efficacy population. The modest cross-protection effect for HPV 51 can be questioned since the 96.1% CIs for 6 Month PI and 12 Month PI were very wide in all study populations. The reliability of the results observed for this non-vaccine HPV type is questioned.

With respect to HPV 45 and 58 no convincing cross-protection has been demonstrated based on the data provided.

Furthermore, the CHMP requested the MAH to address the long term efficacy and the concern of possible type replacement. In response the MAH has proposed to perform a collaboration with HPA to complement study HPV-27.

HPV-27 study is designed to evaluate the long-term impact of Cervarix on the occurrence of cervical cancers and precancerous lesions (CIN3+) using a passive, cancer registry-based follow-up. Subjects enrolled in the HPV-027 are those who participated in the HPV-008 study, enrolled from Finland. In addition, a parallel cohort of unvaccinated subjects was enrolled at the same time of the HPV-008 subjects. Since the sample size is limited this study will not allow the assessment of type replacement. Collaboration with HPA: the HPA's Centre for Infections has developed a two-phase national HPV surveillance program to evaluate the impact of the routine HPV vaccination with Cervarix introduced in the UK in September 2008 for girls aged 12-13 years along with a catch-up programme targeted to girls aged up to 17 years. The HPA protocol was submitted within this application. Phase 1 (2009-2014) is primarily focused on HPV infection surveillance, Phase 2 (2015 onwards), which is still under development, will shift the focus on HPV disease surveillance. The HPA has agreed to provide their HPV surveillance report to the MAH and the MAH has committed to provide reports to the CHMP every two years under confidentiality. See letter of undertaking.

The CHMP agrees with the MAH proposal to have a mixed approach of clinical trial follow-up and health authority follow-up of mass vaccinated cohorts. See letter of undertaking.

During the procedure the MAH has provided a reanalysis of the data and background for the changes for the final HPV008 data results. The CHMP agreed that the study conclusions remained unchanged after this reanalysis.

Based on the data submitted, on the conclusions of the ad hoc expert meeting and further to the MAH commitment to perform the above mentioned studies monitoring long-term duration of cross-protection against CIN 2/3 and cancer, as well as type replacement the CHMP endorsed the update of the product information as detailed in section 3.7.

3.3. Immunogenicity

3.3.1. Data sets analysed

Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and the Total Vaccinated Cohort. Analysis of antibody kinetics was performed on subjects in the ATP cohort for immunogenicity who had an ELISA/PBNA result available at all timepoints. At the final analysis, only results from the anti-HPV-16 and anti-HPV-18 ELISA and Pseudovirion-Based Neutralisation Assay (PBNA) (neutralising antibodies) testing were available. No data were available for the monoclonal inhibition enzyme immunoassays (V5/J4-monoclonal antibodies). The anti-hepatitis A ELISA will only be performed at the end of the study.

3.3.2. Results

Immune response to natural infection measured by ELISA (Total Vaccinated Cohort)

The antibody titres associated with naturally acquired HPV-16 or HPV-18 infection and successful immunological clearance of infection are presented in Table 12. The calculation of Geometric Mean

Titer (GMT)s was performed on subjects who were seropositive for HPV-16 or HPV-18 at Month 0 and who were HPV DNA negative for the antigen considered (i.e. who had successfully “cleared” the infection and mounted an immune response). Selection of this population was considered to be the most relevant to indicate GMTs that may reflect protective immune responses against natural infection.

Subjects who had cleared HPV-16 infection had GMTs of 29.8 EL.U/ml [28.6; 31.0]. Subjects who had cleared HPV-18 infection had GMTs of 22.6 EL.U/ml [21.6; 23.6].

Table 12 - GMTs for anti-HPV-16 and anti-HPV-18 antibodies in seropositive and HPV DNA negative subjects at Month 0 (Total Vaccinated cohort)

		GMT				
			95%CI			
Antibody	N	Value	LL	UL	Min	Max
HPV 16.VLP IgG	2560	29.8	28.6	31.0	8.0	2805.0
HPV 18.VLP IgG	1956	22.6	21.6	23.6	7.0	2282.0

GMT = geometric mean antibody titre calculated on subjects seropositive and HPV DNA negative for the corresponding HPV type
N = number of subjects with available results
95% CI = 95% confidence interval; LL= lower limit; UL = upper limit
Min/max: Minimum/Maximum

Immune response induced by vaccine

The immunogenicity subset included a subset of subjects from study sites selected to collect blood samples at Months 0, 6, 7, 12, 24, 36 and 48. The ATP cohort for immunogenicity included subjects from this immunogenicity subset with at least one ELISA result available after completion of the full three-dose vaccination course (N=1,933). At the final analysis, anti-HPV-16 and anti-HPV-18 ELISA results were available for Months 0, 6, 7, 12, 24 and 36. A further subset of 100 subjects had blood samples taken at Months 0, 7, 12 and 24 to be tested for anti-HPV-16 and anti-HPV-18 PBNA.

The MAH has not provided within the submitted pack the immune responses at Month 48. The annex report is expected by the end of 2010 (FUM23).

Anti-HPV-16 and anti-HPV-18 ELISA (ATP cohort for immunogenicity)

The MAH has not provided within the submitted pack the immune responses at Month 48. The annex report is expected by the end of 2010.

One month post Dose 3 (at Month 7), 99.5% of the subjects in the HPV group had seroconverted for anti-HPV-16 and anti-HPV-18 antibodies and at least 99.8 % of the subjects remained seropositive up to Month 36, i.e., up to 30 months after completion of the full vaccination course.

A substantial increase (approximately 10-fold) in GMTs for both antibodies was observed from Month 6 (post Dose 2) to Month 7 (post Dose 3). After a gradual decline from Month 7 through Month 24, GMTs reached a plateau between Month 24 and Month 36.

Overall, the immune responses after vaccination were comparable for subjects initially seronegative or seropositive for HPV-16. At Month 7, GMTs were higher in initially seronegative subjects, but at Month 12 GMTs were comparable between subjects initially seronegative and initially seropositive for HPV-16. For HPV-18, the immune responses were similar between subjects initially seronegative for HPV-18 and subjects initially seropositive for HPV-18 at all assessed timepoints. Similar immune responses

were also observed between subjects initially seronegative for both antigens and subjects initially seropositive for either antigen.

3.3.3. Discussion

The interpretation of the low GMT values observed in the immune response to natural infection in comparison with the values observed in subjects vaccinated remains unclear since there is no recognised serological correlate for clinical protection.

The immune responses data at Month 48 are waited. The annex report is expected by the end of 2010 (FUM23).

3.4. Clinical safety

At the time of the final analysis, a total of eight non-serious adverse events (AEs) leading to premature discontinuation of the study were reported, of which five in the HPV group and three in the HAV group.

At the time of the final analysis, 17 deaths were reported (9 in the HPV group, 8 in the HAV group). None of the fatal events was assessed as possibly related to vaccination.

At the time of final analysis, 1724 serious adverse events (SAE) were reported in 1400 subjects (701 in HPV group, 699 in HAV group). The number of doses followed by one or more SAEs and the number of events experienced were similar between the two groups. The most common non-fatal SAE under the SOC of infections and infestations was appendicitis (0.4% in the HPV group, 0.5% in the HAV group).

Overall, medically significant conditions were reported in a similar percentage of subjects in the HPV and HAV groups: 31.8% and 32.4%, respectively. The percentage of subjects reporting medically significant conditions classified by Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class and Preferred Term during the entire follow-up period is presented in the clinical study report.

The most common medically significant conditions were gynaecological Chlamydia infection, genito-urinary tract gonococcal infection and depression, all of which were reported in similar percentages of subjects in the HPV and HAV groups:

- Gynaecological chlamydia infection was reported in 911 (9.8%) subjects in the HPV group and 957 (10.3%) subjects in the HAV group.
- Genito-urinary tract gonococcal infection was reported in 144 (1.5%) subjects in the HPV group and 162 (1.7%) subjects in the HAV group.
- Depression was reported in 142 (1.5%) subjects in the HPV group and 137 (1.5%) subjects in the HAV group.

The MAH noted that the high incidence of gynaecological chlamydia infection and genito-urinary tract gonococcal infection was expected as Chlamydia trachomatis and Neisseria gonorrheae testing was included in the study procedures on a yearly basis.

Overall, the number of subjects experiencing a new onset of chronic diseases (NOCD) was similar in the HPV and HAV groups: 251 (2.7%) and 268 (2.9%) subjects, respectively.

The most common NOCDs were asthma, urticaria, hypersensitivity, hypothyroidism and seasonal allergy, all of which were reported with a similarly low incidence in both groups. Other events were reported at an incidence of 0.1% subjects or lower in either group.

Overall, the number of subjects experiencing an new onset autoimmune diseases (NAOD) was similar in the HPV and HAV groups: 78 (0.8%) and 77 (0.8%) subjects, respectively.

During the entire follow-up period, 3606 pregnancies were reported (1804 in the HPV group and 1802 in the HAV group) for 3091 subjects (1538 in the HPV group and 1553 in the HAV group). During the entire follow-up period, no major differences in the rates of any specific pregnancy outcome were observed between the HPV and HAV groups.

In conclusion, no clinically meaningful differences in overall safety outcomes have been identified and compliance with the full vaccination course was equally high between treatment groups.

Furthermore, the cumulative safety data accounted for in the Periodic Safety Update Report (PSUR) (period covered 18.05.2008 to 17.11.2008) provided information about the most frequently reported postmarketing adverse events. The MAH will continue to monitor hypersensitivity reactions including anaphylaxis, other allergic reactions (e.g. angio-oedema) and vasovagal syncope. The CHMP endorsed an Opinion in October 2009 to update section 4.4 of the SmPC to include a warning on syncope and to update section 4.8 of the SmPC to include allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema and syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements.

3.5. Pharmacovigilance system

3.5.1. Risk Management Plan

The MAH submitted a revised risk management plan, version 5, presented in Module 1.8.2 of the Marketing Authorisation application.

The summary of the EU risk management plan is presented in table 13 below.

Table 13: Summary of the EU risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk		
None identified	-	-
Important potential risk		
Theoretical risk of acquiring vaccine-induced autoimmune disease (AID) after vaccination.	Close monitoring of AIDs in: • ongoing clinical trials • routine pharmacovigilance	-
Important missing information		
Use of HPV-16/18 vaccine in HIV-infected women or subjects with known immune deficiencies	Data is currently being generated in HIV positive women.	Warning for use in the absence of data in this population (Section 4.4 of the EU SmPC).
Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine.	Close monitoring of pregnancies and pregnancy outcomes in: • ongoing clinical trials • routine pharmacovigilance • Pregnancy Registry	Not recommended for use in pregnant women (Section 4.6 of the EU SmPC)

3.6. Overall discussion and benefit-risk assessment

The prophylactic efficacy of Cervarix in female adolescents and young adult women is confirmed by the longer follow-up (approximately 39 months) and the generation of more robust efficacy data in the final analysis of study HPV-008.

Cervarix has demonstrated a level of efficacy beyond the vaccine types HPV-16 and HPV-18. Statistically significant efficacy was observed against CIN2+ associated with high-risk types combined, excluding HPV-16 and HPV-18 in the ATP cohort and in the TVC-1 cohort. Statistically significant vaccine efficacy against CIN2+ was observed for HPV types -31, -51 and -58 in the ATP cohort and for HPV types -31, -33, -35 and -51 in the TVC-1 cohort. Vaccine efficacy against 6 and 12 month persistent infection with specific oncogenic HPV types is consistent with the efficacy against clinical endpoints. However, HPV 31 is the only non-vaccine HPV type for which robust and consistent cross-protection has been demonstrated, i.e. in all study populations and for all endpoints.

The ad hoc expert meeting on HPV vaccines requested by the CHMP to address the relevance of persistent infection as surrogate markers for cervical cancer acknowledged the appropriateness of using persistent infection as a surrogate endpoint to show efficacy of a given vaccine.

Although persistent infection is acknowledged as a surrogate marker, the CHMP considered that it has not by itself a direct clinically meaningful objective for physicians and women. Therefore, it should not be mentioned in the indication. This should rather be mentioned in section 5.1.

The CHMP agrees with the MAH proposal to address long term efficacy and the concern of possible type replacement to have a mixed approach of clinical trial follow-up and health authority follow-up of mass vaccinated cohorts. See letter of undertaking.

The immune responses data at Month 48 are waited by the end of 2010 (FUM23).
No clinically meaningful differences in overall safety outcomes have been identified between treatment groups.

Based on the data submitted, on the conclusions of the ad hoc expert meeting and further to the MAH commitment to perform the above mentioned studies monitoring long-term duration of cross-

protection against CIN 2/3 and cancer, as well as type replacement the CHMP agreed with the update of the product information as detailed below.

3.7. Changes to the product information

Further to the assessment of the different proposals of the MAH to amend the Product Information and in the light of the assessment of the submitted data, the Product Information was revised as follows:

Summary of Product Characteristics

Section 4.1 "Therapeutic indication"
The MAH's applied to include persistent infection in the indication, based on the final analysis of study HPV-008.

The CHMP considered that the wording of the indication should only mention the events which are, by themselves, direct clinically meaningful objectives of the vaccination for physicians and women. Therefore the indication should mention cancer as the major objective (demonstrated through surrogates) and lesions clinical surrogates (they are of direct clinical relevance because they lead to surgical resection).

Persistent infection is acknowledged as a surrogate, but it has not by itself a direct clinically meaningful objective for physicians and women. Therefore, should not be mentioned in the indication. This should rather be mentioned in section 5.1.

Furthermore the CHMP took the opportunity of this variation to revise the indication to be harmonised between the HPV vaccines and the vaccine HPV types were replaced by "certain oncogenic HPV types" since for these vaccines some cross protection against related non-vaccine HPV types have been demonstrated. The CHMP included the word "certain" to make prescribers aware that the vaccine does not protect against all HPV oncogenic types. The information on the different HPV types is covered by a cross reference to section 5.1 where these data are presented. Further to cross reference to section 5.1 a cross reference to section 4.4 was added for important information on the data that support this indication.

Therefore the first paragraph of the indication was revised as follows:
"Cervarix is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication."

Section 4.4 "Special warnings and precautions for use"
A sentence was introduced at the beginning of this section to alert prescribers that the decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination. Furthermore this section was fully revised to be in line with the other HPV vaccines.

Section 4.6 "Pregnancy and lactation"
The number of pregnancies in the clinical development program was updated.

Section 5.1 "Pharmacodynamic properties"
This section was updated with the final results and data on cross protection was included. Furthermore this section was fully revised to be harmonised with the other HPV vaccines.

Package Leaflet
Section 1 of the package leaflet was updated accordingly.

Annex II
Annex II was updated with the updated version 5 of the risk management plan.

4. Conclusion

On 24 June 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.