21 November 2013
EMA/789820/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cervarix

International non-proprietary name: HUMAN PAPILLOMAVIRUS VACCINE [TYPES 16, 18] (RECOMBINANT, ADJUVANTED, ADSORBED)

Procedure No. EMEA/H/C/000721/II/0048

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals submitted to the European Medicines Agency on 7 August 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**Common name:**	**Presentations:**
Cervarix	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 16, 18] (RECOMBINANT, ADJUVANTED, ADSORBED)	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH proposed the update of section 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) for Cervarix to allow for administration of the vaccine according to an alternative 2-dose schedule (0, 6 months) in females aged 9-14 years old. The MAH took the opportunity to add Croatia to the list of representatives. The Package Leaflet was proposed to be updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Daniel Brasseur

1.2. Steps taken for the assessment

Submission date:	7 August 2013
Start of procedure:	25 August 2013
Rapporteur's preliminary assessment report circulated on:	23 September 2013
Rapporteur's updated assessment report circulated on:	18 October 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	29 October 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	6 November 2013
CHMP opinion:	21 November 2013

2. Scientific discussion

2.1. Introduction

The purpose of this variation is to propose an update of the Summary of Product Characteristics (SmPC) for Cervarix to allow for administration of the vaccine according to an alternative 2-dose schedule (0, 6 months) in females aged 9-14 years old.

The MAH has performed a first evaluation of the feasibility of a 2-dose schedule for Cervarix in the proof-of-concept study HPV-048. Immunogenicity results have shown that a 2-dose schedule of Cervarix administered at 0, 6 months in 9-14 years old females was non-inferior to the standard 3-dose schedule in females aged 15-25 years at all time-points evaluated up to Month 48.

Since the conduct of new efficacy studies is not feasible in 9-14 years old girls for ethical and practical reasons, the MAH designed a pivotal phase III confirmatory immunobridging study (study HPV-070).

In addition, these immunogenicity data were complemented by efficacy data in subjects receiving 2-doses of Cervarix in 2 large phase III studies (studies HPV-008 and HPV-009). Effectiveness results (follow-up period of 4 years) on Cervarix obtained from the surveillance of HPV-specific infection after introduction of the National HPV Immunisation Program in the UK in girls aged 12-13 years as performed by the Health Protection Agency were part of the submission data package.

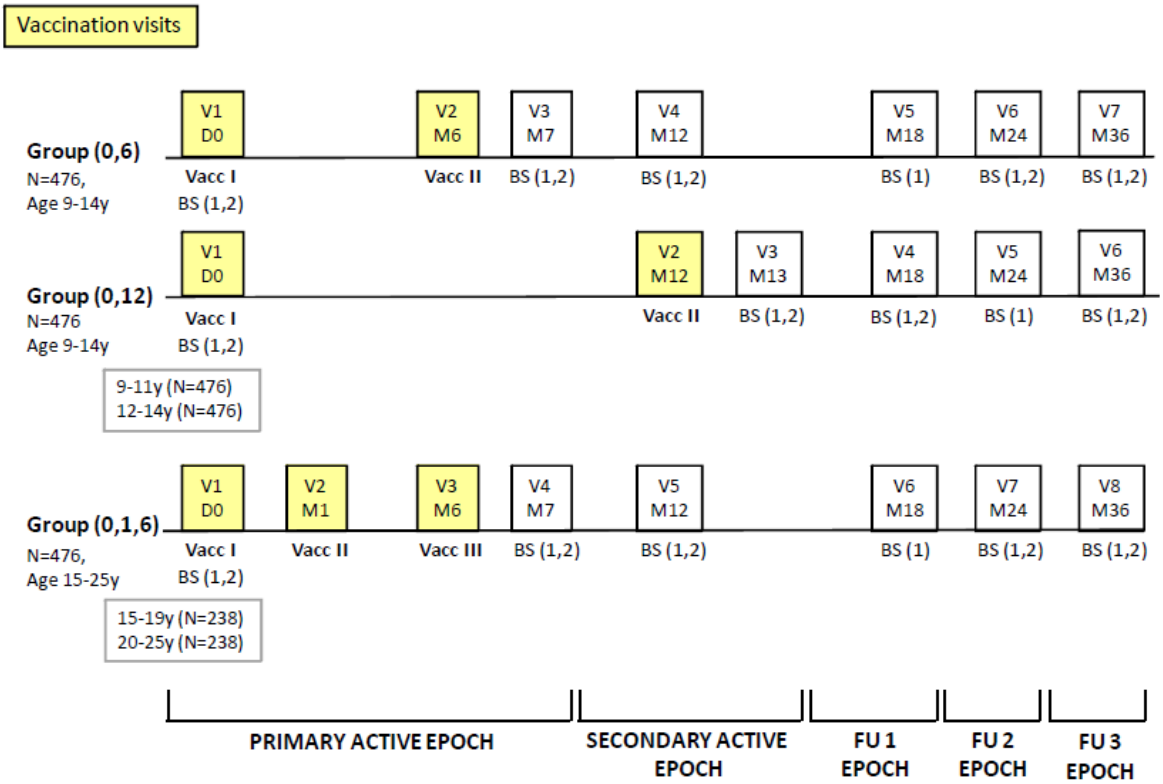
2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

2.2.1.1. Pivotal study HPV-070

Study HPV-070 is an ongoing phase IIIb, open-label, randomized, age-stratified, multi-centre trial (Canada, Germany, Italy, Taiwan and Thailand). The study design is shown in Figure 1.

Figure 1 Study HPV-070: Overall study design



N = number of subjects, **y**= years , **V**= Visit, **D**= Day, **M**= Month
Vacc = vaccination
BS(1) = blood sample for immunogenicity, **BS(2)** = blood sample for Cell-Mediated Immune (CMI) response
FU = follow-up

Treatment groups: 3 parallel groups in 2 age strata (9-14 or 15-25 years of age)

- Group (0,6): females aged 9-14 years receiving 2 doses of Cervarix at Day 0 and at Month 6, respectively.
- Group (0,12): females 9-14 years receiving 2 doses of Cervarix at Day 0 and at Month 12, respectively.
- Group (0,1,6): females aged 15-25 years receiving 3 doses of Cervarix at Day 0, at Month 1 and at Month 6, respectively.

To ensure equal distribution of the population, enrolment was stratified by age as follows:

- 9-14 years: stratification into 9-11 years (~50%) and 12-14 years (~50%).
- 15-25 years: stratification into 15-19 years (~50%) and 20-25 years (~50%).

If non-inferiority of the 2-dose schedule (0, 6 months) versus the standard 3-dose schedule (0, 1, 6 months) is not demonstrated 1 month after the last dose of study vaccine or at any further timepoint, a 3rd vaccine dose will be offered to the subjects of Group (0,6) at the end of the study, according to local prescribing information.

If non-inferiority of the 2-dose schedule (0, 12 months) versus the standard 3-dose schedule (0, 1, 6 months) is not demonstrated 1 month after the last dose of study vaccine or at any further timepoint, a 3rd vaccine dose will be offered to the subjects of Group (0, 12) at the end of the study, according to local prescribing information.

Table 1. Study HPV-070 - Treatment groups and vaccination schedule

Treatment name	Vaccine/Product name	Study Groups	Vaccination schedule (months)	Age strata (years)
HPV-16/18	HPV-16/18 L1 VLP AS04	(0,6)	0,6	9-11
				12-14
HPV-16/18	HPV-16/18 L1 VLP AS04	(0,12)	0,12	9-11
				12-14
HPV-16/18	HPV-16/18 L1 VLP AS04	(0,1,6)	0,1,6	15-19
				20-25

Treatment allocation:

- Subjects 9-14 years of age were stratified according to age and country and randomised (1:1) between the Group (0,6) and the Group (0,12).
- Subjects 15-25 years of age were stratified according to age and country. Those subjects were not randomised.

Duration of the study for each subject enrolled is approximately 36 months from Visit 1:

- Primary active epoch: starting at Day 0 and ending at Month 7.
- Secondary active epoch: starting after Month 7 and ending at Month 13.
- Follow-up 1 epoch: starting after Month 13 and ending at Month 18.
- Follow-up 2 epoch: starting after Month 18 and ending at Month 24.
- Follow-up 3 epoch: starting after Month 24 and ending at Month 36.

Table 2. Study HPV-070 - Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age Min -Max (years)	Epochs				
			primary active	secondary active	follow-up 1	follow-up 2	follow-up 3
(0,6)	476	9 - 14	x	x	x	x	x
(0,12)	476	9 - 14	x	x	x	x	x
(0,1,6)	476	15 - 25	x	x	x	x	x

Study visits: Depending on the group to which the subject is assigned, there are:

- Group (0,6): 7 study visits.
- Group (0,12): 6 study visits.
- Group (0,1,6): 8 study visits.

Blood samples for antibody determination are drawn from:

- Group (0,6) and Group (0,1,6) at Day 0, Month 7, 12, 18, 24 and 36.
- Group (0,12) at Day 0, Month 13, 18, 24 and 36.

Blood samples for Cell-Mediated Immune (CMI) response measurement are drawn from:

- A sub-cohort of Group (0,6) and Group (0,1,6) at Day 0, Month 7, 12, 24 and 36.

- A sub-cohort of Group (0,12) at Day 0, Month 13, 18 and 36.

Safety monitoring:

- Occurrence, intensity and relationship to vaccination of solicited signs and symptoms occurring during the 7-day period following each vaccination (Days 0-6) are self-reported for all subjects by use of Diary Cards.
- Occurrence, intensity and relationship to vaccination of unsolicited signs and symptoms occurring during the 30-day period following each vaccination (Days 0-29) are self-reported reported for all subjects by use of Diary Cards.
- All potential immune-mediated diseases (pIMDs) occurring from first vaccination up to 6 months after the last vaccine dose are reported for all subjects.
- All medically significant conditions (MSCs) and serious adverse events (SAEs) occurring throughout the study period (from Day 0 up to Month 36) are reported for all subjects.
- Pregnancies and pregnancy outcomes occurring throughout the study period (from Day 0 up to Month 36) are reported for all subjects.

Laboratory Evaluations

Assays for immunogenicity analysis on serum samples that were used in Studies HPV-070 and HPV-048 are summarised in Table 3 below.

Table 3. Laboratory assays and immunogenicity evaluations

Study	Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
All subjects							
HPV-070 HPV-048	Quantitative	Anti-HPV-16	ELISA†	GSK Biologicals	EL.U/mL	8	CEVAC GSK Biologicals
HPV-070 HPV-048	Quantitative	Anti-HPV-18	ELISA†	GSK Biologicals	EL.U/mL	7	CEVAC GSK Biologicals
HPV-070	Quantitative	Anti-HPV-16	PBNA§	NCI methodology adapted by GSK	ED_{50}	40	GSK Biologicals
HPV-070	Quantitative	Anti-HPV-18	PBNA§	NCI methodology adapted by GSK	ED_{50}	40	GSK Biologicals
HPV-070 HPV-048°	Quantitative	Anti-HPV-31	ELISA†	GSK Biologicals	EL.U/mL	59	GSK Biologicals
HPV-070 HPV-048°	Quantitative	Anti-HPV-45	ELISA†	GSK Biologicals	EL.U/mL	59	GSK Biologicals
Sub-cohort for CMI							
HPV-070	Quantitative	Cytokine-positive CD-4 or CD-8 T-cells (anti-HPV-16)	CFC	GSK Biologicals	Frequency of specific CD4/CD8 cells per 10^6 of CD4/CD8+ T-cells	ND	GSK Biologicals
HPV-070	Quantitative	Cytokine-positive CD-4 or CD-8 T-cells (anti-HPV-18)	CFC	GSK Biologicals	Frequency of specific CD4/CD8 cells per 10^6 of CD4/CD8+ T-cells	ND	GSK Biologicals
HPV-070	Quantitative	Cytokine-positive CD-4 or CD-8 T-cells (anti-HPV-45)	CFC	GSK Biologicals	Frequency of specific CD4/CD8 cells per 10^6 of CD4/CD8+ T-cells	ND	GSK Biologicals
HPV-070	Quantitative	Cytokine-positive CD-4 or CD-8 T-cells (anti-HPV-31)	CFC	GSK Biologicals	Frequency of specific CD4/CD8 cells per 10^6 of CD4/CD8+ T-cells	ND	GSK Biologicals
HPV-070	Quantitative	Specific Memory B-cell (anti-HPV-16)	B-cell Elispot	GSK Biologicals	Frequency of specific memory B-cells per 10^6 of memory B-cells	ND	GSK Biologicals
HPV-070	Quantitative	Specific Memory B-cell (anti-HPV-18)	B-cell Elispot	GSK Biologicals	Frequency of specific memory B-cells per 10^6 of memory B-cells	ND	GSK Biologicals
HPV-070	Quantitative	Specific Memory B-cell (anti-HPV-45)	B-cell Elispot	GSK Biologicals	Frequency of specific memory B-cells per 10^6 of memory B-cells	ND	GSK Biologicals
HPV-070	Quantitative	Specific Memory B-cell (anti-HPV-31)	B-cell Elispot	GSK Biologicals	Frequency of specific memory B-cells per 10^6 of memory B-cells	ND	GSK Biologicals

ELISA = Enzyme Linked Immunosorbent Assay; PBNA = Pseudovirion-Based Neutralization Assay; CFC = Cytokine Flow Cytometry; CEVAC= Centre for Vaccinology
ED50 = Estimated Dose: serum dilution giving a 50% reduction of the signal compared to a control without serum; ND = Not Defined
° In Study HPV-048, anti-HPV-31 and anti-HPV-45 antibodies were only measured by ELISA in subjects aged 9-14 years in the 20/20 M0,6 2-dose group (N=50) and in subjects aged
15-25 years in the standard 3-dose HPV group (N=55) at Month 48 for the Months 0, 7, 12, 18, 24, 36 and 48 time points.
† ELISA testing based on methodology developed by MedImmune Inc, Gaithersburg, MD, USA and modified by GSK Biologicals.
§ PBNA testing based on methodology developed by (Pastrana, 2004) at the National Cancer Institute (NCI).

Endpoints

Primary endpoint: anti-HPV-16/18 seroconversion rates and antibody titres (by ELISA) 1 month after the last dose of study vaccine, in the group (0,6) and the group (0,1,6).

Secondary endpoints

Immunogenicity

- Anti-HPV-16/18 seroconversion rates and antibody titres (by ELISA) at Day 0 and Months 7, 12, 18, 24 and 36 (for subjects having received their last vaccine dose at Month 6) or at Day 0 and Months 13, 18, 24 and 36 (for subjects having received their last vaccine dose at Month 12) in all subjects.
- Anti-HPV-16/18 antibody titres by the pseudovirion-based neutralization assay (PBNA) at Day 0 and Months 7, 12, 18, 24 and 36 (for subjects having received their last vaccine dose at Month 6) or at Day 0 and Months 13, 18, 24 and 36 (for subjects having received their last vaccine dose at Month 12) in a subset of subjects.
- Anti HPV-16/18 specific T and B-cell-mediated immune responses (frequency of cytokine-positive CD4 or CD8 T-lymphocytes and frequency of memory B-cells) at Day 0, Months 7, 12, 24 and 36 (for subjects having received their last vaccine dose at Month 6) or at Day 0, Months 13, 18 and 36 (for subjects having received their last vaccine dose at Month 12) in a sub-cohort of subjects.
- Anti-HPV-31/45 antibody titres by ELISA at Day 0 and Months 7, 12, 18, 24 and 36 in a subset of subjects in the group (0,6) and the group (0,1,6).
- Anti-HPV-31/45 specific T and B-cell response (frequency of cytokine-positive CD 4 or CD8 T-lymphocytes and frequency of memory B-cells) at Day 0 and Months 7, 12, 24 and 36 (for subjects having received their last vaccine dose at Month 6) or at Day 0 and Months 13, 18 and 36 (for subjects having received their last vaccine dose at Month 12), in a sub-cohort of subjects.

Safety

- The occurrence and intensity of solicited local symptoms during the 7-day period (day 0-6) following each vaccination in all groups.
- The occurrence, intensity and relationship to vaccination of solicited general symptoms during the 7-day period (day 0-6) following each vaccination in all groups.
- The occurrence, intensity and relationship to vaccination of unsolicited symptoms during the 30-day period (day 0-29) following each vaccination in all groups.
- The occurrence of pIMDs from first vaccination to 6 months after the last vaccine dose in all groups.
- The occurrence of MSCs throughout the study period (from Day 0 up to Month 36) in all groups.
- The occurrence of SAEs throughout the study period (from Day 0 up to Month 36) in all groups.
- The occurrence of SAEs related to the investigational product, to study participation, to GSK concomitant products or any fatal SAE throughout the study period (from Day 0 up to Month 36) in all groups.
- The occurrence of pregnancy and pregnancy outcomes throughout the study period (from Day 0 up to Month 36) in all groups.
- The percentage of subjects completing the vaccination schedule in all groups.

Study cohorts

The primary analysis on immunogenicity was based on the *according to protocol cohort* (ATP) for analysis of immunogenicity. A second analysis based on the *total vaccinated cohort* (TVC) was performed to complement the ATP analysis.

The ATP cohort for analysis of immunogenicity included all evaluable subjects from the ATP cohort for safety:

- Who met all eligibility criteria
- Who complied with the procedures and intervals defined in the protocol
- Who were within the allowed interval as defined in the protocol
- Who did not meet any of the criteria for elimination from an ATP analysis during the study.
- Who did not present, during the study, with a condition that had the capability of altering their immune response (e.g. leukaemia or splenectomised child) or were confirmed to have an immunodeficiency condition (specific for Study HPV-070)
- 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 TVC-naïve included all vaccinated subjects (i.e., who received at least one dose) for whom data concerning efficacy endpoint measures were available and who had a normal cytology at Month 0.

In addition, subjects were to be HPV DNA negative for all 14 oncogenic (high risk) HPV types (by PCR) at Month 0 and seronegative (by ELISA) at Month 0 for both anti-HPV- 16 and anti-HPV-18 antibodies.

For this cohort, the follow-up time for subjects started at the day after Dose 1.

Statistical methods and sample size calculation

The primary objective of this study was to demonstrate that the immunogenicity (as determined by [enzyme-linked immunosorbent assay] ELISA) of HPV-16/18 vaccine administered according to a 2-dose schedule of 0,6 months in 9-14 year old females was non-inferior to that administered according to the standard 3-dose schedule of 0,1,6 months in 15-25 year old females, 1 month after the last dose of study vaccine.

The following criteria for non-inferiority were assessed sequentially:

- Non-inferiority with respect to seroconversion was demonstrated if, 1 month after the last dose, for both anti-HPV-16 and anti-HPV-18, the upper limit of the 95% CI for the difference (HPV [0,1,6] schedule minus HPV [0,6] schedule) was below 5%.
- Non-inferiority with respect to GMT was demonstrated if, 1 month after the last dose, for both anti-HPV-16 and anti-HPV-18, the upper limit of 95% CI for the GMT ratio (HPV [0,1,6] schedule divided by HPV [0,6] schedule) was below 2.

Sample size for the primary objective:

The sample size of approximately 952 enrolled subjects (760 evaluable subjects) in HPV (0,6) schedule and HPV (0,1,6) schedule group was to rule out a difference of more than 5% in terms of seroconversion rates and more than two fold difference in terms of GMTs (HPV-16 and 18 ELISA titers) one month after last dose with 98% and 100% power, respectively ($\alpha = 0.025$ for each HPV-16 and 18).

The statistical test that was used to evaluate the difference in GMTs between the two groups was an ANOVA model on the log10 transformation of the titers. The ANOVA model includes the vaccine group as fixed effect.

Within group assessment: PBNA (pseudovirion-based neutralisation assay) and ELISA.

For each group at each time point for which a blood sample result was available, the following analyses were conducted:

- Seroconversion and seropositivity rates for each antigen (with exact 95% CI) per pre-vaccination status.
- GMTs with 95% CI and range of antibody titres were tabulated for antibodies for each antigen per pre-vaccination status.
- The distribution of antibody titres for each antigen were displayed using reverse cumulative distribution curves for the sub-cohort of initially seronegative subjects.

Between-group assessment:

Between-group comparisons were performed in the ATP cohort for immunogenicity.

Cellular mediated immunity

CD4+/CD8+ T-cell response by ICS (Intracellular Cytokine Staining)

This assay provides information on the frequency of CD4+ and CD8+ T-cells responding to the antigens (HPV-16 and HPV-18 and HPV-31 and HPV-45) and producing:

at least CD40L and another cytokine (IFNγ, IL-2, TNFα) (d-CD40L);

at least IL-2 and another cytokine (CD40L, TNFα, IFNγ) (d-IL-2);

at least TNFα and another cytokine (CD40L, IL-2, IFNγ) (d-TNFα);

at least IFNγ and another cytokine (IL-2, TNFα, CD40L) (d-IFNγ);

at least two different cytokines (CD40L, IL-2, TNFα, IFNγ) (all doubles).

The threshold for HPV-16/18/31/45-specific CD4+ and CD8+ T-cell responses are presented in Table 4.

Table 4. Study HPV-070: Threshold for HPV-16/18/31/45-specific CD4+ and CD8+ T-cell response by treatment group (ATP cohort for immunogenicity)

	Thresholds used	
	Group (0,6)	**Group (0,1,6)**
HPV-16		
CD4-ALL DOUBLES	247 HPV-16 specific CD4+ T-cells per million CD4+ T-cells	394 HPV-16 specific CD4+ T-cells per million CD4+ T-cells
CD8-ALL DOUBLES	91 HPV-16 specific CD8+ T-cells per million CD8+ T-cells	99 HPV-16 specific CD4+ T-cells per million CD8+ T-cells
HPV-18		
CD4-ALL DOUBLES	207 HPV-18 specific CD4+ T-cells per million CD4+ T-cells	314 HPV-18 specific CD4+ T-cells per million CD4+ T-cells
CD8-ALL DOUBLES	55 HPV-18 specific CD8+ T-cells per million CD8+ T-cells	73 HPV-18 specific CD8+ T-cells per million CD8+ T-cells
HPV-31		
CD4-ALL DOUBLES	237 HPV-31 specific CD4+ T-cells per million CD4+ T-cells	438 HPV-31 specific CD4+ T-cells per million CD4+ T-cells
CD8-ALL DOUBLES	61 HPV-31 specific CD8+ T-cells per million CD8+ T-cells	76 HPV-31 specific CD8+ T-cells per million CD8+ T-cells
HPV-45		
CD4-ALL DOUBLES	263 HPV-45 specific CD4+ T-cells per million CD4+ T-cells	330 HPV-45 specific CD4+ T-cells per million CD4+ T-cells
CD8-ALL DOUBLES	63 HPV-45 specific CD8+ T-cells per million CD8+ T-cells	77 HPV-45 specific CD8+ T-cells per million CD8+ T-cells

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6

Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Month 1 and Month 6

B-cell response

Frequencies of memory B-cells for each stimulant (HPV-16/18/31/45) at each time point (at Day 0 and at Month 7) were summarized for each group by the number of values (N), the number of missing values, minimum, 1st quartile, median, 3rd quartile, maximum and geometric mean (Gmean). Values of 0 were given an arbitrary value of 1 for the purpose of Gmean calculation.

Primary objective

The primary objective was to demonstrate that the immunogenicity (as determined by ELISA) of Cervarix administered according to a 2-dose schedule of 0,6 months in 9-14 year old females was non-inferior to that administered according to the standard 3-dose schedule of 0,1,6 months in 15-25 year old females, 1 month after the last dose of study vaccine.

Secondary objectives

The secondary objectives of Study HPV-070 evaluated at Month 7, one month after the last dose in Group (0,6) and Group (0,1,6) were:

- To demonstrate that the immunogenicity of Cervarix (as determined by ELISA if the primary objective is reached), administered according to a 2-dose schedule of 0 ,6 months in 9-14 year old females is

non-inferior to that administered according to the standard 3-dose schedule of 0,1,6 months in 15-25 year old females, 6, 12, 18 and 30 months after the last dose of study vaccine.

Criteria for non-inferiority

- To demonstrate the non-inferiority of the 0,12 months schedule in 9-14 years old girls versus the 0,1,6 months schedule in 15-25 years old females
- To evaluate if the immunogenicity of Cervarix (as determined by ELISA) according to a 2-dose schedule of 0,12 months in 9-14 year old females is non-inferior to that administered according to a 2-dose schedule of 0,6 months in 9-14 year old females, 1, 6 and 12 months after the last dose of study vaccine.

The following criteria for non-inferiority will be assessed sequentially:

Non-inferiority with respect to seroconversion will be shown if 1 month/ 6 months/ 12 months after the last dose for both anti-HPV-16 and anti-HPV-18 the upper limit of the 95% CI (confidence interval) for the difference (HPV [0,6] schedule minus HPV [0,12] schedule) is below 5%.

Non-inferiority with respect to GMT will be shown if, 1 month/ 6 months/ 12 months after the last dose, for both anti-HPV-16 and anti-HPV-18, the upper limit of 95% CI for the GMT ratio (HPV [0,6] schedule divided by HPV [0,12] schedule) is below 2.

2.2.1.2. Supportive study HPV-048

Study HPV-048 is a phase I/II randomized, partially blind, multicentre, age-stratified, dose-range study to assess the safety and immunogenicity of an alternate dosing of the HPV-16/18 vaccine when administered according to a 2-dose schedule (0, 2 months or 0, 6 months) vs. the standard dosing schedule at 0, 1, 6 months up to Month 60. The study was conducted in 960 healthy females aged 9-25 years in North America (Canada) and Europe (Germany). Subjects were allocated to 4 different treatment groups, receiving the HPV-16/18 vaccine at different dosages (20 µg or 40 µg of each HPV antigen), on different schedules (40 µg of each HPV antigen at 0, 2 months or 0, 6 months), or receiving the HPV-16/18 vaccine (20 µg of each HPV antigen) at 0, 1, 6 months. The study is ongoing and study results up to Month 48 were submitted.

Primary immunogenicity objective To evaluate the immunogenicity of the HPV-16/18vaccine (hereafter referred to as HPV-16/18 vaccine) one month after the last dose when administered at different dosages (20 or 40 µg of each HPV antigen) and on different schedules (0,2- or 0,6-months) compared with the standard HPV-16/18 vaccine administered on a 3-dose schedule (0,1,6-months).

Secondary Immunogenicity objectives

The three following objectives were assessed sequentially:

1. To demonstrate the non-inferiority of the antibody response to the 2-dose schedule of the HPV-16/18 vaccine in the 9-14 year age stratum when administered at different dosages (20 or 40 µg of each HPV antigen) and on different schedules (0-2 and 0-6 months) as compared to the standard 3-dose schedule in subjects 15 - 25 years of age (the age group in which efficacy has been demonstrated), one month after the last dose of vaccine.

Criterion: Non-inferiority was demonstrated if the upper limit of the 95% confidence interval (CI) for the geometric mean titer (GMT) ratio between the standard 3-dose schedule of HPV-16/18 vaccine in subjects 15-25 years of age over the 2-dose schedules in the 9-14 year age stratum was below 2.

2. To demonstrate the non-inferiority of the antibody response to the 2-dose schedule of the HPV-16/18 vaccine in the 15-19 year age stratum when administered at different dosages (20 or 40 µg of each HPV antigen) and on different schedules (0,2- or 0,6- months) as compared to the standard 3-dose schedule in subjects 15-25 years of age, one month after the last dose of vaccine.

Criterion: Non-inferiority was demonstrated if the upper limit of the 95% CI for the GMT ratio between the standard 3-dose schedule of HPV-16/18 vaccine in subjects 15-25 years of age over the 2-dose schedules in the 15-19 year age stratum was below 2.

3. To demonstrate the non-inferiority of the antibody response to the 2-dose schedule of the HPV-16/18 vaccine in the 20-25 year age stratum when administered at different dosages (20 or 40 µg of each HPV antigen) and on different schedules (0,2- or 0,6- months) as compared to the standard 3-dose schedule in subjects 15-25 years of age, one month after the last dose of vaccine.

Criterion: Non-inferiority was demonstrated if the upper limit of the 95% CI for the GMT ratio between the standard 3-dose schedule of HPV-16/18 vaccine in subjects 15-25 years of age over the 2-dose schedules in the 20-25 year age stratum was below 2.

If any of the above secondary objectives for immunogenicity were not demonstrated, the following objectives were to be evaluated:

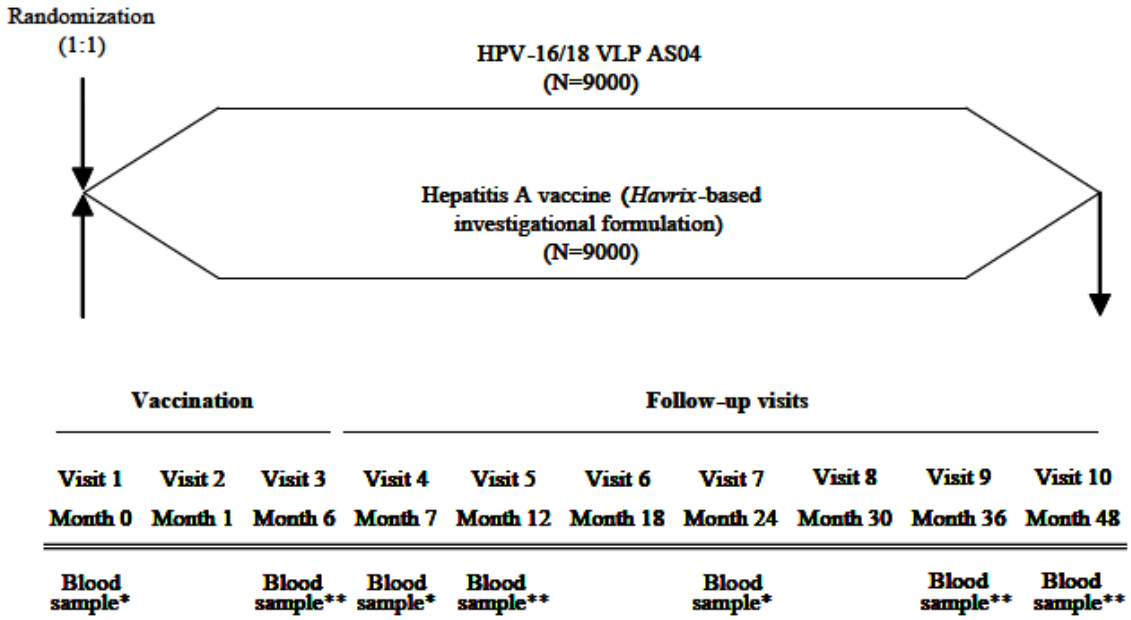
1. To examine pair wise comparisons of the antibody response between each 2-dose schedule group and the standard 3-dose schedule, one month after the last dose of vaccine within each age stratum.

2. To evaluate the antibody response to all dose schedules and dosages of the HPV-16/18 vaccine in each age stratum during the extended follow-up period (at Month 12, Month 18, Month 24, Month 36, Month 48 and Month 60).

2.2.1.3. Supportive study HPV-008

Study HPV-008 is a phase III, double-blind, randomised, and controlled multi-centre efficacy study in healthy females aged between 15 and 25 years. The study enrolled 18,729 healthy women 15-25 years of age in multiple regions of the world (North America, Latin America, Europe, Australia and Asia) and is completed and reported. Inclusion/exclusion criteria allowed the enrolment of a broad population of women, including women who were previously uninfected with HPV and women who were previously or currently infected with HPV, i.e., subjects enrolled in the study were vaccinated regardless of their baseline cytology and HPV serological and DNA status. A schematic of the study design is provided in Figure 2. The study had two parallel groups receiving either Cervarix or a Hepatitis A control vaccine (randomised according to a 1:1 ratio). Each subject was to receive three doses of vaccine or control according to a 0, 1, 6-month schedule.

Figure 2 Study HPV-008: Overview of the study design



N= planned number of subjects
* All subjects had blood drawn at these time points.
** A subset of subjects from selected study sites (immunogenicity subset) had additional blood samples taken at these time points.

The vaccine efficacy against incident infection and persistent infection (6-month definition) with HPV-16/18 in subjects who received only two doses of the study vaccine were evaluated as exploratory objectives. In this submission, the results in the Total Vaccinated cohort of HPV-naïve women, i.e., subjects who were DNA negative for all oncogenic HPV types, seronegative for HPV-16 and HPV-18 and normal cytology at baseline (TVC-naïve) at the end-of-study analysis (Month 48), are presented. This cohort is representative for the target population of this 2-dose schedule variation, i.e., girls aged 9-14 years before their sexual debut.

2.2.1.4. Supportive study HPV-009

Study HPV-009 was a phase III, double-blind, randomised, controlled study designed to evaluate the efficacy, safety and immunogenicity of the HPV-16/18 vaccine in healthy women aged 18 to 25 years. This community-based study was conducted in a single centre with 7 satellite sites, all located in Costa Rica, Guanacaste Province and adjacent areas in collaboration with the US NCI. The MAH agreed to provide their HPV-16/18 vaccine under a clinical trial agreement (CTA) with NCI for the study and the NCI was responsible for the conduct of the trial. Subjects enrolled in the study were vaccinated regardless of their baseline cytology and HPV serological and DNA status. The population studied can be considered as representative of the sexually active female young adult population. A total of 24,467 women identified via a census were screened, of which 7,466 were enrolled and randomised (1:1) to one of the 2 parallel groups receiving either the HPV-16/18 vaccine (N=3,727) or a Hepatitis A control vaccine (same Havrix-based investigational formulation as in Study HPV-008; N=3,739). The median follow-up time at the end of Study HPV-009 was 4.2 years.

The primary objective of the study was to demonstrate the efficacy of Cervarix against CIN2+ associated with HPV-16 or HPV-18 post Dose 3 in subjects who were HPV DNA negative at Months 0 and 6 for the corresponding HPV type. No objectives were pre-specified for the endpoints that were evaluated in an

ancillary post-hoc analysis by the NCI. The objective of this proof-of-principle evaluation was to assess the efficacy of fewer than 3 doses of Cervarix administered in Study HPV-009. Vaccine efficacy was evaluated in each dosage group by determination, via HPV DNA testing, of the number of newly detected HPV-16 or HPV-18 infections that persisted in visits that were 10 or more months apart (12-month persistent infection definition) or 4 or more months apart (6-month persistent infection definition).

2.2.2. Results

2.2.2.1. Pivotal study HPV-070

Number of subjects

A total of 1032 subjects were enrolled, vaccinated and included in the analyses (i.e., TVC) at Month 7, (Table 5).

Table 5. Number of subjects enrolled, vaccinated, completed and included in each cohort

	Group (0,6)	Group (0,1,6)	Total
Number of subjects planned	476	476	952
Number of subjects vaccinated (TVC)	550	482	1032
Number of subjects completed primary active epoch (Month 7)	548	472	1020
Number of subjects included in ATP cohort for safety	544	458	1002
Number of subjects included in ATP cohort for immunogenicity	542	434	976

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6
Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Month 1 and Month 6
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit

A summary of demographic characteristics in the Total vaccinated cohort is presented in Table 6.

Table 6. Summary of demographic characteristics (Total vaccinated cohort)

		Group (0,6) N = 550		Group (0,1,6) N = 482		Total N = 1032	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	11.6	-	19.6	-	15.3	-
	SD	1.59	-	3.05	-	4.67	-
	Median	12.0	-	20.0	-	14.0	-
	Minimum	9	-	15	-	9	-
	Maximum	14	-	25	-	25	-
Gender	Female	550	100	482	100	1032	100
Geographic Ancestry	African heritage / african american	6	1.1	3	0.6	9	0.9
	American indian or alaskan native	0	0.0	0	0.0	0	0.0
	Asian - central/south asian heritage	1	0.2	1	0.2	2	0.2
	Asian - east asian heritage	141	25.6	105	21.8	246	23.8
	Asian - japanese heritage	0	0.0	0	0.0	0	0.0
	Asian - south east asian heritage	108	19.6	106	22.0	214	20.7
	Native hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0
	White - arabic / north african heritage	1	0.2	0	0.0	1	0.1
	White - caucasian / european heritage	288	52.4	263	54.6	551	53.4
	Other	5	0.9	4	0.8	9	0.9

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6
Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Month 1 and Month 6
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Other includes European/African-American/Guyanese, Trinidadian, African heritage/Caucasian, African heritage/Caucasian, Caucasian/African heritage, European/Chinese/African, white/Pilipino, Scottish/Japanese, white Caucasian/east Asian heritage

Non-inferiority analysis on primary objective

The non-inferiority assessment of seroconversion rates is presented in Table 7, non-inferiority assessment of anti-HPV-16 and anti-HPV-18 antibody GMT as measured by ELISA is presented in Table 8.

Table 7. Non-Inferiority assessment of anti HPV-16 and anti- HPV-18 seroconversion rates (Group [0, 1, 6] vs Group [0, 6]) one month after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)

							Difference in seropositivity rate (Group (0,1,6) minus Group (0,6))			
									95 % CI	
Antibody	Group description	N	%	Group description	N	%	Difference	%	LL	UL
HPV-16	Group (0,6)	488	100	Group (0,1,6)	352	100	Group (0,1,6) - Group (0,6)	0.00	-1.08	0.78
HPV-18	Group (0,6)	493	100	Group (0,1,6)	382	100	Group (0,1,6) - Group (0,6)	0.00	-1.00	0.77

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6
Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Month 1 and Month 6
N = number of subjects with available results
% = percentage of subjects with HPV 16 Ab concentration ≥ 8 EL.U/ml/ HPV 18 Ab concentration ≥ 7 EL.U/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 8. Non-Inferiority assessment of immune response to HPV-16 and HPV-18 (Group [0, 1, 6] vs Group [0, 6]) one month after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)

							GMT ratio			
									95% CI	
Antibody	Group description	N	GMT	Group description	N	GMT	Ratio order	Value	LL	UL
HPV-16	Group (0,1,6)	352	10234.5	Group (0,6)	488	9400.1	Group (0,1,6)/Group (0,6)	1.09	0.97	1.22
HPV-18	Group (0,1,6)	382	5002.6	Group (0,6)	493	5909.1	Group (0,1,6)/Group (0,6)	0.85	0.76	0.95

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6
Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Month 1 and Month 6
GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

Immunogenicity evaluation

HPV-16/18 serostatus at baseline

The HPV-16/18 serostatus at baseline as measured by ELISA in the ATP cohort for immunogenicity is presented in Table 9.

Table 9. Study HPV-070: Seropositivity status at baseline (ATP cohort for immunogenicity)

		Group (0,6) (N = 542)		Group (0,1,6) (N = 434)		Total (N = 976)	
HPV 16.VLP Ab.IgG	HPV 18.VLP Ab.IgG	n	%	n	%	n	%
Positive	Positive	9	1.7	23	5.3	32	3.3
Positive	Negative	42	7.9	57	13.3	99	10.3
Positive	MISSING	1	-	0	-	1	-
Negative	Positive	34	6.4	26	6	60	6.2
Negative	Negative	449	84.1	324	75.3	773	80.2
Negative	MISSING	5	-	2	-	7	-
MISSING	Positive	0	-	1	-	1	-
MISSING	Negative	2	-	1	-	3	-

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6
Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0,Month 1 and Month 6

Overall anti-HPV-16 and anti-HPV-18 antibody response within 2-dose (0,6) and 3-dose (0,1,6) groups as measured by ELISA

Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibody titres as measured by ELISA in the ATP cohort for immunogenicity are presented in Table 10. At Month 7, all initially seronegative subjects in both Group (0,6) and Group (0,1,6) seroconverted for both anti-HPV-16 and anti-HPV-18 antibodies.

In initially seronegative subjects, GMTs for anti-HPV-16 and anti-HPV-18 antibodies were 9400.1 EL.U/ml and 5909.1 EL.U/ml in Group (0,6) and 10234.5 EL.U/ml and 5002.6 EL.U/ml in Group (0,1,6), respectively, at Month 7.

Table 10. Study HPV-070: Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies as measured by ELISA (ATP cohort for immunogenicity)

					≥ cut-off value				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-HPV-16	Group (0,6)	S-	PRE D0	488	0	0.0	0.0	0.8	4.0	4.0	4.0	<8.0	<8.0
			POS 2 M7	488	488	100	99.2	100	9400.1	8818.3	10020.4	266.0	58139.0
		S+	PRE D0	52	52	100	93.2	100	23.4	16.9	32.4	8.0	2437.0
			POS 2 M7	52	52	100	93.2	100	9538.0	7642.0	11904.4	1824.0	60090.0
		Total	PRE D0	540	52	9.6	7.3	12.4	4.7	4.5	5.0	<8.0	2437.0
			POS 2 M7	540	540	100	99.3	100	9413.3	8853.4	10008.7	266.0	60090.0
	Group (0,1,6)	S-	PRE D0	352	0	0.0	0.0	1.0	4.0	4.0	4.0	<8.0	<8.0
			POS 3 M7	352	352	100	99.0	100	10234.5	9258.3	11313.6	136.0	211235.0
		S+	PRE D0	80	80	100	95.5	100	40.8	30.3	54.9	8.0	1174.0
			POS 3 M7	80	80	100	95.5	100	8888.4	7403.0	10672.0	908.0	77851.0
		Total	PRE D0	432	80	18.5	15.0	22.5	6.1	5.6	6.8	<8.0	1174.0
			POS 3 M7	432	432	100	99.1	100	9970.7	9128.3	10890.9	136.0	211235.0
anti-HPV-18	Group (0,6)	S-	PRE D0	493	0	0.0	0.0	0.7	3.5	3.5	3.5	<7.0	<7.0
			POS 2 M7	493	493	100	99.3	100	5909.1	5508.9	6338.4	162.0	63598.0
		S+	PRE D0	43	43	100	91.8	100	15.7	11.5	21.4	7.0	822.0
			POS 2 M7	43	43	100	91.8	100	6697.5	5236.0	8567.0	1248.0	30102.0
		Total	PRE D0	536	43	8.0	5.9	10.7	3.9	3.8	4.1	<7.0	822.0
			POS 2 M7	536	536	100	99.3	100	5968.8	5580.3	6384.3	162.0	63598.0
	Group (0,1,6)	S-	PRE D0	382	0	0.0	0.0	1.0	3.5	3.5	3.5	<7.0	<7.0
			POS 3 M7	382	382	100	99.0	100	5002.6	4572.6	5473.1	310.0	127709.0
		S+	PRE D0	50	50	100	92.9	100	27.4	19.1	39.3	7.0	566.0
			POS 3 M7	50	50	100	92.9	100	4039.1	3175.0	5138.4	954.0	68716.0
		Total	PRE D0	432	50	11.6	8.7	15.0	4.4	4.1	4.8	<7.0	566.0
			POS 3 M7	432	432	100	99.1	100	4880.3	4486.4	5308.8	310.0	127709.0

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6
Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Month 1 and Month 6
S- = seronegative subjects (antibody concentration < 8 EL.U/ml for HPV-16/< 7 EL.U/ml for HPV-18) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 8 EL.U/ml for HPV-16/□ 7 EL.U/ml for HPV-18) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with concentration equal to or above the cut-off value (≥8 EL.U/ml for HPV-16 and ≥7 EL.U/ml for HPV-18)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit, MIN/MAX = Minimum/Maximum, PRE D0 =Pre-vaccination at Day 0; POS 2 M7 = Post Dose 2 at Month 7; POS 3 M7 =Post Dose 3 at Month 7

Immune response in 2-dose (0,6) group with flexibility around administration of the second dose

According to the protocol-specified HPV-070 study design, some flexibility was allowed for the administration of the second dose of the vaccine. For Group (0,6), the maximum interval allowed for the administration of the second dose was [150-210] days after the first dose. In an additional post-hoc analysis, the anti-HPV-16 and anti-HPV-18 antibody response after the second dose as measured by ELISA was stratified according to the following intervals: [150-164], [165-194] and [195-210] days after the first dose. Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibody titres as measured by ELISA in Group (0,6) as stratified by time interval between the first and second dose in the ATP cohort for immunogenicity are presented in Table 11.

Table 11. Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies as measured by ELISA by time interval of second dose administration (ATP cohort for immunogenicity)

						≥ cut-off value				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	Group (0,6)	[150-164]	S-	PRE D0	143	0	0.0	0.0	2.5	4.0	4.0	4.0	<8.0	<8.0
				POS 2 M7	143	143	100	97.5	100	9597.9	8490.7	10849.4	266.0	44301.0
			S+	PRE D0	11	11	100	71.5	100	17.7	11.8	26.6	9.0	47.0
				POS 2 M7	11	11	100	71.5	100	8102.7	4983.6	13173.8	2267.0	23202.0
			Total	PRE D0	154	11	7.1	3.6	12.4	4.4	4.2	4.8	<8.0	47.0
				POS 2 M7	154	154	100	97.6	100	9482.5	8429.8	10666.6	266.0	44301.0
		[165-194]	S-	PRE D0	286	0	0.0	0.0	1.3	4.0	4.0	4.0	<8.0	<8.0
				POS 2 M7	286	286	100	98.7	100	9477.1	8705.4	10317.1	987.0	58139.0
			S+	PRE D0	37	37	100	90.5	100	26.8	17.3	41.3	8.0	2437.0
				POS 2 M7	37	37	100	90.5	100	9745.4	7426.5	12788.2	1824.0	60090.0
			Total	PRE D0	323	37	11.5	8.2	15.4	5.0	4.6	5.4	<8.0	2437.0
				POS 2 M7	323	323	100	98.9	100	9507.4	8768.9	10308.1	987.0	60090.0
		[195-210]	S-	PRE D0	59	0	0.0	0.0	6.1	4.0	4.0	4.0	<8.0	<8.0
				POS 2 M7	59	59	100	93.9	100	8591.3	7345.2	10048.8	2489.0	27579.0
			S+	PRE D0	4	4	100	39.8	100	14.6	3.9	55.2	9.0	51.0
				POS 2 M7	4	4	100	39.8	100	12241.6	2772.5	54051.4	5648.0	37690.0
			Total	PRE D0	63	4	6.3	1.8	15.5	4.3	4.0	4.8	<8.0	51.0
				POS 2 M7	63	63	100	94.3	100	8786.6	7511.0	10279.0	2489.0	37690.0

						≥ cut-off value				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	Group (0,6)	[150-164]	S-	PRE D0	138	0	0.0	0.0	2.6	3.5	3.5	3.5	<7.0	<7.0
				POS 2 M7	138	138	100	97.4	100	6076.2	5261.7	7016.8	162.0	35665.0
			S+	PRE D0	14	14	100	76.8	100	11.5	8.7	15.3	7.0	32.0
				POS 2 M7	14	14	100	76.8	100	7020.7	4895.5	10068.4	3142.0	21023.0
			Total	PRE D0	152	14	9.2	5.1	15.0	3.9	3.7	4.1	<7.0	32.0
				POS 2 M7	152	152	100	97.6	100	6157.6	5385.7	7040.2	162.0	35665.0
		[165-194]	S-	PRE D0	299	0	0.0	0.0	1.2	3.5	3.5	3.5	<7.0	<7.0
				POS 2 M7	299	299	100	98.8	100	6019.5	5526.5	6556.4	348.0	36622.0
			S+	PRE D0	21	21	100	83.9	100	21.7	12.0	39.2	8.0	822.0
				POS 2 M7	21	21	100	83.9	100	7553.7	4950.3	11526.1	1248.0	30102.0
			Total	PRE D0	320	21	6.6	4.1	9.9	3.9	3.7	4.2	<7.0	822.0
				POS 2 M7	320	320	100	98.9	100	6109.8	5617.4	6645.4	348.0	36622.0
		[195-210]	S-	PRE D0	56	0	0.0	0.0	6.4	3.5	3.5	3.5	<7.0	<7.0
				POS 2 M7	56	56	100	93.6	100	4997.7	3986.9	6264.6	1165.0	63598.0
			S+	PRE D0	8	8	100	63.1	100	11.3	7.4	17.1	8.0	33.0
				POS 2 M7	8	8	100	63.1	100	4497.5	2610.1	7749.6	2034.0	10044.0
			Total	PRE D0	64	8	12.5	5.6	23.2	4.1	3.6	4.5	<7.0	33.0
				POS 2 M7	64	64	100	94.4	100	4932.2	4020.3	6051.0	1165.0	63598.0

Group (0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0 and Month 6
Group (0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Month 1 and Month 6
[150-164] = 150-164 days
[165-194] = 165-194 days
[195-210] = 195-210 days
S- = seronegative subjects (antibody concentration < 8 EL.U/ml for HPV-16/< 7 EL.U/ml for HPV-18) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 8 EL.U/ml for HPV-16/□ 7 EL.U/ml for HPV-18) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with concentration equal to or above the cut-off value (≥8 EL.U/ml for HPV-16 and ≥7 EL.U/ml for HPV-18)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE D0 =Pre-vaccination at Day 0; POS 2 M7 = Post Dose 2 at Month 7; POS 3 M7 =Post Dose 3 at Month 7

Anti-HPV-16 and anti-HPV-18 antibody response as measured by PBNA

Pseudovirion-based neutralization assays (PBNA) for measurement of anti-HPV-16 and anti-HPV-18 neutralising antibodies were performed on a subset of ~100 subjects in each group. The subjects in this subset were the same subjects as in the sub-cohort for cellular-mediated immunity (CMI) testing.

At Month 7, all initially seronegative subjects in both Group (0,6) and Group (0,1,6) seroconverted for both anti-HPV-16 and anti-HPV-18 antibodies.

In initially seronegative subjects, GMTs for anti-HPV-16 and anti-HPV-18 neutralising antibodies were 77625.4 ED50 and 23005.7 ED50 in Group (0,6) and 31206.4 ED50 and 13958.1 ED50 in Group (0,1,6), respectively, at Month 7.

Anti-HPV-31 and anti-HPV-45 antibody response as measured by ELISA

Anti-HPV-31 and anti-HPV-45 antibody response by ELISA were measured on a subset of ~100 subjects in each group. The subjects in this subset were the same subjects as in the sub-cohort for CMI testing. At Month 7, all initially seronegative subjects, except one subject in Group (0,1,6) seroconverted for anti-HPV-31 antibodies, respectively, and all subjects in both groups seroconverted for anti-HPV-45 antibodies.

In initially seronegative subjects, GMTs for anti-HPV-31 and anti-HPV-45 antibodies were 1680.9 EL.U/ml and 1798.0 EL.U/ml in Group (0,6) and 1224.9 EL.U/ml and 1073.0 EL.U/ml in Group (0,1,6), respectively, at Month 7.

HPV-16/18/31/45 specific T-cell response

In pre-selected sites, the first ~50 subjects in each age stratum (9-11 and 12-14 years and 15-19 and 20-25 years) in each group were assigned to the CMI sub-cohort, in which the HPV-16/18/31/45 specific T-cell responses were assessed.

CD4+ and CD8+ T-cells specific to HPV-16 and HPV-18 (vaccine HPV types) and HPV- 31 and HPV-45 (non-vaccine HPV types) were evaluated at baseline (Month 0) and at one month following the last dose of vaccine (Month 7) in Group (0,6) and Group (0,1,6) using a T-cell Intracellular Cytokine Staining (ICS).

At one month after the last vaccination (Month 7), there was a substantial increase in median frequencies of HPV-16/18/31/45 specific CD4+ T-cells expressing two or more immune markers among the cytokines CD40L, IL-2, TNF-α, and IFN-γ (all doubles) in both Group (0,6) and Group (0,1,6). No HPV-16/18/31/45 specific CD8+ T-cell response was detected.

HPV-16/18/31/45 specific T-cell response by pre-vaccination serostatus

In Group (0,6), no clear trend was observed between initially seronegative and seropositive subjects in terms of median frequencies of HPV-16/18/31/45 specific CD4+ T-cells expressing two or more immune markers among the cytokines CD40L, IL-2,TNF-α, and IFN-γ (all doubles) at Month 7. In Group (0,1,6), median frequencies of HPV-16/18/31/45 specific CD4+ T-cells expressing two or more immune markers among the cytokines CD40L, IL-2, TNF-α, and IFN-γ (all doubles) were higher in initially seronegative than in initially seropositive subjects at Month 7.

HPV-16/18/31/45 specific memory B-cell response

In pre-selected sites, the first ~50 subjects in each age stratum (9-11 and 12-14 years and 15-19 and 20-25 years) in each group were assigned to the CMI sub-cohort, in which the HPV-16/18/31/45 specific memory B-cell responses were assessed.

The HPV-16/18/31/45 specific memory B-cell responses were calculated as median frequency of HPV-16/18/31/45 specific memory B-cells at baseline and at Month 7. At one month after the last vaccination (Month 7), there was a substantial increase in median frequencies of HPV-16/18/31/45 memory B-cells in both Group (0,6) and Group (0,1,6).

HPV-16/18/31/45 specific memory B-cell response by pre-vaccination status

At pre-vaccination, median frequencies of HPV-16/18/31/45 specific memory B-cells were ≤ 1, except for HPV-16 specific memory B-cells in Group (0,1,6) and HPV-45 specific memory B-cells in both Group (0,6) and Group (0,1,6).

In Group (0,6), median frequencies of HPV-16/18/31/45 specific memory B-cells were lower in initially seronegative than in initially seropositive subjects at Month 7. In Group (0,1,6), median frequencies of HPV-16/18/31/45 specific memory B-cells were higher in initially seronegative than in initially seropositive subjects at Month 7.

2.2.2.2. Supportive study HPV-048

A total of 960 subjects were vaccinated in study HPV-048, i.e., 240 subjects in the 40/40 M0,2 group, 241 subjects in the 40/40 M0,6 group, 240 subjects in the 20/20 M0,6 group and 239 subjects in the HPV group.

Primary immunogenicity objective

HPV-16

The two-way ANOVA model that was applied using titers (log10) as response variable revealed that the group-by-age interaction was not statistically significant (p=0.195). The effect of group and age was significant (p<0.0001) (Table 12).

Table 12. Comparison for anti-HPV-16 titers between the different groups and age strata of the study (ATP cohort for immunogenicity)

SOURCE	DF	SS	MS	F-Value	P-Value
GROUP	3	14.52	4.84	34.88	<.0001
AGE STRATA	2	10.43	5.21	37.56	<.0001
GROUP * AGE STRATA	6	1.20	0.20	1.44	0.1952

A two-way ANOVA has been used
DF = degree of freedom, SS = sum of square, MS = mean square, F = Fisher-Snedecor, P = statistical probability.

Pair wise comparisons were done between each 2-dose schedule group and the standard schedule using the Dunnett's test. The standard schedule was to be considered superior to a 2-dose formulation/schedule if the lower limit of the 95%CI of the GMR was below 0.5 (2-fold difference). The standard HPV-16/18 vaccine was found superior to the 40/40 M0,2 but not to 40/40 M0,6 and 20/20 M0,6 (Table 13).

Table 13. Pair wise comparisons between each 2-dose schedule group and the 3-dose standard schedule group for anti-HPV-16 antibody titers (ATP cohort for immunogenicity)

GROUP	N	Adjusted GMT	LL	UL	GROUP	N	Adjusted GMT	LL	UL	GMR	LL	UL
V40_02	201	5692.17	5148.24	6293.56	HPV	178	13164.78	11833.99	14645.23	0.43	0.36	0.52
V40_06	173	11203.54	10049.40	12490.23	HPV	178	13164.78	11833.99	14645.23	0.85	0.70	1.03
V20_06	178	8092.90	7275.41	9002.25	HPV	178	13164.78	11833.99	14645.23	0.61	0.51	0.74

V40_02 = HPV-16/18(40,40) AS04 0,2 m
V40_06 = HPV-16/18(40,40) AS04 0,6 m
V20_06 = HPV-16/18(20,20) AS04 0,6 m
HPV = HPV-16/18(20,20) AS04 0,1,6 m
GMR = Geometric Mean Ratio
LL/UL = Lower and Upper Limits of the 95% confidence interval
Adjusted GMT = GMT adjusted on age strata HPV-18

The two-way ANOVA model that was applied using titers (log10) as response variable revealed that the group-by-age interaction was not statistically significant (p=0.435). The effect of group and age was significant (p<0.0001) (Table 14).

Table 14. Comparison for anti-HPV-18 titers between the different groups and age strata of the study (ATP cohort for immunogenicity)

SOURCE	DF	SS	MS	F-Value	P-Value
GROUP	3	5.48	1.83	12.43	<.0001
AGE STRATA	2	8.17	4.08	27.81	<.0001
GROUP * AGE STRATA	6	0.87	0.14	0.98	0.4351

A two-way ANOVA has been used
DF = degree of freedom, SS = sum of square, MS = mean square, F = Fisher-Snedecor, P = statistical probability.

The standard schedule was not found superior to any of the three 2-dose groups, the lower limit of the 95% CI of the GMR being higher than 0.50 (Table 15)

Table 15. Pair wise comparisons between each 2-dose schedule group and the 3-dose standard schedule group for anti-HPV-18 antibody titers (ATP cohort for immunogenicity

GROUP	N	Adjusted GMT	LL	UL	GROUP	N	Adjusted GMT	LL	UL	GMR	LL	UL
V40_02	192	3468.22	3120.68	3854.46	HPV	182	5088.91	4566.64	5670.92	0.68	0.56	0.82
V40_06	184	5968.26	5358.51	6647.39	HPV	182	5088.91	4566.64	5670.92	1.17	0.97	1.42
V20_06	176	4638.79	4154.06	5180.09	HPV	182	5088.91	4566.64	5670.92	0.91	0.75	1.11

V40_02 = HPV-16/18(40,40) AS04 0,2 m
V40_06 = HPV-16/18(40,40) AS04 0,6 m
V20_06 = HPV-16/18(20,20) AS04 0,6 m
HPV = HPV-16/18(20,20) AS04 0,1,6 m
GMR = Geometric Mean Ratio
LL/UL = Lower and Upper Limits of the 95% confidence interval
Adjusted GMT = GMT adjusted on age strata

Inferential analysis on secondary immunogenicity objectives

HPV-16 per age stratum

For each age stratum, the non-inferiority assessment was performed for anti-HPV-16 antibody response elicited in the different 2-dose groups compared to that of the standard schedule in subjects 15–25 years of age (Table 16).

Table 16. Non-inferiority of the anti-HPV-16 antibody response to the 2-dose schedule of the HPV-16/18 vaccine by age stratum when administered at different dosages and on different schedules compared to the standard 3-dose schedule in subjects 15–25 years of age, one month after the last dose of active vaccine (ATP cohort for immunogenicity)

GROUP	N	GMT	GROUP	N	GMT	GMR	LL	UL
9-14 years								
HPV	111	10322.0	V40_02	75	7441.9	1.39	1.03	1.87
HPV	111	10322.0	V40_06	61	15304.2	0.67	0.49	0.92
HPV	111	10322.0	V20_06	65	11066.9	0.93	0.68	1.28
15-19 years								
HPV	111	10322.0	V40_02	70	5153.3	2.00	1.47	2.73
HPV	111	10322.0	V40_06	66	11060.9	0.93	0.68	1.28
HPV	111	10322.0	V20_06	62	8442.3	1.22	0.89	1.69
20-25 years								
HPV	111	10322.0	V40_02	56	4809.1	2.15	1.53	3.00
HPV	111	10322.0	V40_06	46	8307.4	1.24	0.86	1.79
HPV	111	10322.0	V20_06	51	5673.2	1.82	1.27	2.61

V40_02 = HPV-16/18(40,40) AS04 0,2 m
V40_06 = HPV-16/18(40,40) AS04 0,6 m
V20_06 = HPV-16/18(20,20) AS04 0,6 m
HPV = HPV-16/18(20,20) AS04 0,1,6 m
GMT = geometric mean antibody titer
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance);
LL = lower limit, UL = upper limit

HPV-18 per age strata

Non-inferiority assessment is shown in Table 17.

Table 17. Non-inferiority of the anti-HPV-16 antibody response to the 2-dose schedule of the HPV-16/18 vaccine by age stratum when administered at different dosages and on different schedules compared to the standard 3-dose schedule in subjects 15–25 years of age, one month after the last dose of active vaccine (ATP cohort for immunogenicity)

GROUP	N	GMT	GROUP	N	GMT	GMR	LL	UL
9-14 years								
HPV	114	4261.5	V40_02	70	5095.4	0.84	0.64	1.09
HPV	114	4261.5	V40_06	62	8155.4	0.52	0.40	0.69
HPV	114	4261.5	V20_06	64	5509.8	0.77	0.59	1.01
15-19 years								
HPV	114	4261.5	V40_02	68	2986.4	1.43	1.07	1.90
HPV	114	4261.5	V40_06	69	6161.9	0.69	0.52	0.91
HPV	114	4261.5	V20_06	63	5141.9	0.83	0.64	1.08
20-25 years								
HPV	114	4261.5	V40_02	54	2741.5	1.55	1.12	2.15
HPV	114	4261.5	V40_06	53	4230.4	1.01	0.74	1.36
HPV	114	4261.5	V20_06	49	3523.3	1.21	0.86	1.71

V40_02 = HPV-16/18(40,40) AS04 0,2 m
V40_06 = HPV-16/18(40,40) AS04 0,6 m
V20_06 = HPV-16/18(20,20) AS04 0,6 m
HPV = HPV-16/18(20,20) AS04 0,1,6 m
GMT = geometric mean antibody titer
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance);
LL = lower limit, UL = upper limit

Persistence of immune responses to 2 doses up to 48 Months after the first vaccination

The persistence of antibodies against both HPV-16 and HPV-18 in the 40/40 M0,6 and 20/20 M0,6 vaccine groups followed a similar pattern as that observed in the standard HPV-16/18 vaccine group, i.e. after a peak response at Month 7, a gradual decline in antibody titres was observed until Month 24. Afterwards, GMTs reached a plateau between Month 24 and Month 48. In the 40/40 M0,2 group, GMTs had reached a peak response at Month 3 and evolved into a plateau from Month 18 up to Month 48.

In the absence of a correlate of protection, the relevance of GMT levels for anti-HPV-16 and anti-HPV-18 antibodies at all time-points assessed during this study was evaluated considering the following two benchmarks:

- Antibody titres from subjects evaluated in study HPV-008 (aged 15-25 years at time of enrolment) who had acquired a natural infection and presumed to clear it prior to enrolment, i.e. subjects who were HPV DNA negative and seropositive at baseline. This is considered as the benchmark for the minimum level of antibodies that may be required for protection. Subjects who had cleared HPV-16 infection had GMTs of 29.8 EL.U/mL [95% CI: 28.5-31.1] and subjects who had cleared HPV-18 infection had GMTs of 22.7 EL.U/mL [95% CI: 21.7-23.7] in TVC (total vaccinated cohort).
- Antibody titres from subjects in study HPV-001/007 (aged 15-25 years at time of enrolment in HPV-001) at the plateau phase. The GMTs at the plateau level in study HPV-001/007 (Month 45-50 time point in HPV-007) were 397.8 EL.U/mL [95% CI: 344.7-459.1] and 297.3 EL.U/mL [95% CI: 258.2-342.2] for anti-HPV-16 and anti-HPV-18 antibodies in the Total cohort, respectively. This second benchmark was defined based on the finding that the antibody levels reached at the Month 45-50 plateau were associated with demonstrated protection against HPV-16 and HPV-18 infection and associated cytological and histopathological lesions.

It is assumed that if a correlate of protection is identified, it will be between these two benchmarks.

At Month 48 in initially seronegative subjects, GMTs for antibodies against HPV-16 were 21.6-, 43.5-, 32.5- and 61.3-fold higher than those elicited by natural infection in study HPV-048 in the 40/40 M0,2, 40/40 M0,6, 20/20 M0,6 and standard HPV-16/18 vaccine groups, respectively and GMTs for anti-HPV-18 antibodies were 11.3-, 26.9-, 23.4- and 31.9-fold higher in the respective groups. When compared to the plateau level of study HPV-001/007 (Month 45-50), GMTs were 1.6- to 4.6-fold higher for anti-HPV-16 antibodies. For anti-HPV-18 antibodies, GMTs were slightly below the plateau level in the 40/40 M0,2 group (256.0 EL.U/mL) and 1.8- to 2.0-fold higher in the 40/40 M0,6, 20/20 M0,6 and standard HPV-16/18 vaccine groups. As observed at previous time points, the 40/40 M0,2 formulation and vaccination schedule appeared to result in lower anti-HPV-16 and anti-HPV-18 antibody titres at Month 48 than the other formulations/schedules evaluated in this study.

Immunogenicity by age

The persistence of the antibody response in subjects aged 9-14 years in the 20/20 M0,6 group was consistent with that observed in subjects aged 15-25 years in the standard 3-dose HPV-16/18 vaccine group. GMTs for antibodies against HPV-16 were 44.2- and 47.6-fold higher than those elicited by natural infection in study HPV-008 in the 9-14 age stratum of the 20/20 M0,6 group and in subjects aged 15-25 years in the HPV group, respectively. GMTs for anti- HPV-18 antibodies were 23.9- and 26.6-fold higher in the respective age ranges and vaccine groups. When compared to the plateau level of study HPV-001/007 (Month 45-50), GMTs were 3.3-and 3.6-fold higher for anti-HPV-16 antibodies and 1.8- and 2.0-fold higher for anti-HPV-18 antibodies in the 9-14 age stratum of the 20/20 M0,6 group and in subjects aged 15-25 years in the HPV group, respectively.

Exploratory non-inferiority analysis of 2-doses in subjects 9-14 years vs. 3 doses in subjects 15-25 years at Month 48

At Month 48, the non-inferiority assessment for subjects aged 9-14 years receiving the HPV-16/18 vaccine according to different 2 dose schedules and formulations vs. subjects aged 15-25 years receiving the standard 3-dose schedule of Cervarix as performed at Month 7 was repeated as an exploratory analysis, confirming previous results.

Cross-reactive immune response to non-vaccine HPV types HPV-31 and HPV-45

The responses to the non-vaccine types HPV-31 and HPV-45 across the 2-dose HPV-16/18 (20/20 M0,6) vaccine group aged 9-14 years and in the standard 3-dose HPV group aged 15-25 years appeared similar in terms of seroconversion and GMTs up to Month 48.

At Month 48, the GMTs in initially seronegative subjects for anti-HPV-31 antibodies were 195.5 EL.U/mL in subjects aged 9-14 years in the 2-dose (20/20 M0,6) vaccine group and were 241.7 EL.U/mL in subjects aged 15-25 years in the standard 3-dose HPV vaccine group. The GMTs for anti-HPV-45 antibodies were 156.6 EL.U/mL in subjects aged 9-14 years in the 2-dose (20/20 M0,6) vaccine group and were 147.2 EL.U/mL in subjects aged 15-25 years in the standard 3-dose HPV vaccine group.

Statistical modelling up to Month 48 for predicting long-term persistence of HPV-16/18 antibody response

The statistical model was built using real life data from subjects aged 15-25 years who participated in study HPV-001/007 (the study was conducted in Brazil, Canada and United States). The study provided data with up to 6.4 years of follow-up after first vaccination. The model was applied on data from study HPV-048 at month 48 (78 subjects in the HPV-048 2-dose 20/20, M0,6 group in the 9-14 age stratum and 157 subjects the HPV-048 standard 3-dose group in the 15-25 age stratum). The model estimated that vaccination of subjects aged 9-14 years with 2-dose of the vaccine would provide a similar duration of immune response to that of subjects aged 15-25 years vaccinated with the standard 3-dose schedule.

To further substantiate the model, the MAH has plotted real life 9.4 years GMTs from study HPV-023 (Brazilian cohort of the HPV-001/007 study where subjects were followed up with a mean of 8.9 years and a maximum of 9.4 years).

For both HPV-16 and HPV-18, GMTs and the 95% confidence intervals observed in study HPV-023 fit well with the model. As observed in study HPV- 048, kinetics of the immune response with only 2-doses of the vaccine given at 0,6 month in subjects aged 9-14 years are similar to that of subjects aged 15-25 years receiving 3- doses of the vaccine (as in HPV-001/007/023).

2.2.2.3. Supportive study HPV-008

The results presented are restricted to those from the analysis performed in initially HPV-naïve subjects (TVC-naïve).

The majority (91.9%) of subjects received all 3 vaccine doses, only 5.2% (977 subjects) received 2 doses.

Due to either lack of follow-up information or unsuitability for inclusion in these exploratory efficacy analyses, only 258 subjects who received 2 doses could be evaluated for efficacy against incident infection and only 235 subjects for efficacy against 6-month persistent infection. At Month 48, vaccine

efficacy against HPV-16/18 incident infection was 84.5% [31.7, 98.3], and vaccine efficacy against 6-month persistent infection was 100% [33.1, 100].

2.2.2.4. Supportive study HPV-009

Of the 7,466 subjects included in the TVC, 313 subjects (155 in the HPV group and 158 in the HAV group) were excluded from the post-hoc analysis because they were HPV-16 and HPV-18 DNA positive at baseline or they had no post-vaccination visits. Of the 7,153 remaining subjects, 83.4% (82.7% HPV vs. 84.1% HAV) of women received 3 vaccine doses, 11.2% (11.8% HPV vs. 10.6% HAV) women received 2 doses, and 5.4% (5.5% HPV vs. 5.3% HAV) women received one dose

Table 18 presents the vaccine efficacy against 12-month persistent infection with HPV-16/18 in subjects who received 3, 2 and 1 doses of the study vaccine in Study HPV-009.

Table 18. Study HPV-009: Estimated vaccine efficacy against 12-month persistent infection with HPV-16/18 in women who received 1, 2, and 3 doses of study vaccine

Doses, No.	Group	Women, No.	Events, No.	Proportion of women with 12-month persistent HPV-16 or HPV-18 infections, % (95% CI)*	HPV vaccine efficacy, % (95% CI)*	Efficacy relative to 3-dose regimen, % (95% CI)*
3 (standard regimen)†	HAV	3010	133	4.4% (3.7% to 5.2%)	80.9% (71.1% to 87.7%)	Referent
	HPV	2957	25	0.85% (0.56% to 1.2%)		
2‡	HAV	380	17	4.5% (2.7% to 6.9%)	84.1% (50.2% to 96.3%)	104% (69.3% to 129%)
	HPV	422	3	0.71% (0.18% to 1.9%)		
1	HAV	188	10	5.3% (2.7% to 9.3%)	100% (66.5% to 100%)	124%§
	HPV	196	0	0.0% (0.0% to 1.5%)		

HPV = HPV-16/18 vaccine; HAV = Hepatitis A vaccine
* Human papillomavirus = HPV; 95% CI = 95% confidence interval.
† The distribution of the time at diagnosis of the case patients in the HPV and control arms was qualitatively assessed to determine whether the protection afforded by two doses may be short lived compared with that of three doses. Twenty (80.0%) of 25 breakthrough 1-year persistent HPV infections in the vaccine arm were first detected in the first year of follow-up (suggesting missed prevalent infections at enrollment) compared with 40 (30.1%) of 133 infections detected in the control arm. Sixteen (64.0%) of 25 breakthrough infections occurred among women who were HPV16 seropositive at enrollment.
‡ One of the three breakthrough infections was detected in each of the first 3 years of the study compared with 0%, 64.7%, 23.5%, and 11.8% of the 17 infections in years 1, 2, 3, and 4 of the study, respectively. One (33.3%) of the three breakthrough infections occurred in a woman who was HPV16 seropositive at enrollment.
§ No bootstrap confidence interval could be estimated due to the presence of zero events in the HPV arm after one dose of vaccine.

In addition, vaccine efficacy was evaluated against 12-month persistent infection with HPV-31/33/45 (combined endpoint), and although cross-protection was observed in subjects who received the standard 3-dose regimen (VE=41.3% [18.9, 57.9], with 57 and 99 events in the HPV and HAV groups, respectively, there was no evidence of HPV-31/33/45 cross-protection in women who received only 2 doses (VE=-25.9% [-334%, 61.1%], with 7 and 5 events in the HPV and HAV groups, respectively. The small number of total events (n=7) limited the ability to evaluate cross-protection against HPV-31/33/45 among women who received only 1 dose.

2.2.2.5. Effectiveness results from Surveillance from the UK Health Protection Agency

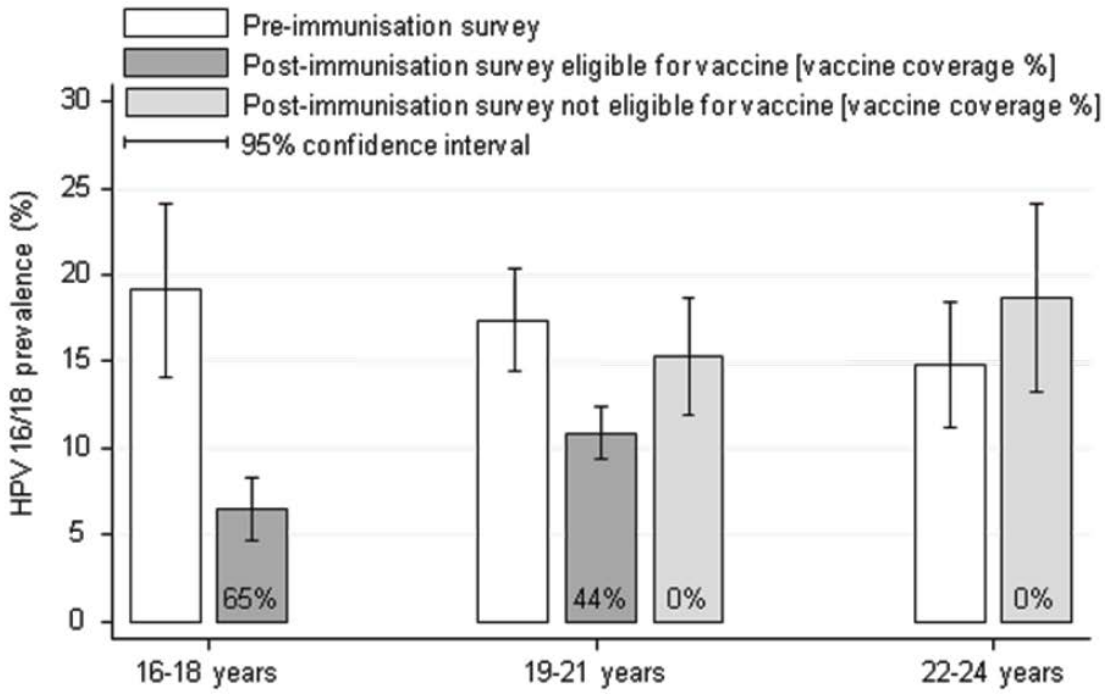
In September 2008, Cervarix was introduced into the routine immunisation schedule in England (and throughout the UK) and offered to girls aged 12-13 years. A catch-up programme also started in 2008 with girls aged 17 years (born Sept 90-Aug 91) and was extended to all girls born since Sept 1991 in subsequent years. Opportunistic sources of residual vulvo-vaginal specimens are used to monitor the seroprevalence for vaccine induced antibodies and the prevalence of type-specific genital HPV infections among young women in England.

Currently, the Phase 1 Report 1 is available, summarising the results on HPV type specific DNA prevalence in young women in the UK since HPV immunisation with Cervarix was introduced, based on data that were available up to the end of September 2012, i.e., after a follow-up period of 4 years. Phase 1 of the HPA surveillance study included 4 birth cohorts (born Sept 1995 to Aug 1999) from the routine immunisation and 5 birth cohorts (born Sept 1990 to Aug 1995) from the catch-up program. Coverage was around 80% in routine immunisation (86.8% in the 2011/2012 school year) and averaged 67% (40%-75%) for 1 or more dose across the catch-up cohorts. Note that HPA previously conducted surveillance for HPV type-specific DNA prevalence prior to introduction of HPV immunisation in 2008, which results are included in the HPA Phase 1 Report as reference. The results of this pre-immunisation surveillance have previously been published (Howell-Jones et al. Vaccine 2012; 30: 3867-3875).

The mean age of the subjects included in the post-immunisation surveillance was 19.3±2.1 years compared to 19.2±2.4 years in the pre-immunisation survey. Reported data on sexual behaviour were similar between the two surveys with around a half of respondents to these questions reporting 2 or more sexual partners in the previous 12 months and at least one new sexual partner in the previous 3 months.

The prevalence for HPV-16/18 infection in the pre-immunisation and post-immunisation surveillances by age (16-18 years, i.e., those with highest vaccination coverage [~65%] and youngest age at vaccination, 19-21 years and 22-24 years) is presented in Figure 3.

Figure 3 Prevalence of vaccine HPV types (HPV-16/18) by age group and survey period



2.2.3. Discussion

Pivotal study HPV-070

The primary objective of non-inferiority in the pivotal study HPV-070 was met at Month 7 in the ATP cohort for immunogenicity, since at one month post the last vaccination (Month 7), all initially

seronegative subjects in both Group (0,6) and Group (0,1,6) had seroconverted for anti-HPV-16 and anti-HPV-18 antibodies when measured by ELISA and PBNA (neutralizing antibodies).

Similar immune responses in terms of GMTs for anti-HPV-16 and anti-HPV-18 antibodies when measured by ELISA were observed in the [150-164], [165-194] and [195-210] days interval groups (overlapping 95% CIs). Therefore, if flexibility in the vaccination schedule is necessary, the second dose can be administered between 5 and 7 months after the first dose.

Additionally, one month post the last vaccination (at Month 7), all initially seronegative subjects in Group (0,6) had seroconverted for both anti-HPV-31 and anti-HPV-45 antibodies when measured by ELISA. In Group (0,1,6), all except one initially seronegative subject (98.9%) had seroconverted for anti-HPV-31 antibodies and all initially seronegative subjects had seroconverted for anti-HPV-45 antibodies. At the same time point, a substantial increase in HPV-16/18/31/45-specific CD4+ T-cell responses and HPV-16/18/31/45-specific B-cell responses (in terms of median frequencies of HPV-16/18/31/45-specific B-cells per 106 B-cells) was observed in both Group (0,6) and Group (0,1,6).

It was noted that in study HPV-070, Month 7, the subsample for detecting neutralizing antibodies against HPV-16/18 and ELISA antibodies against HPV-31/45 as well as for describing the cell-mediated immunity was not randomly selected, therefore during the procedure the MAH was requested to demonstrate that the subsample can be considered representative of the study population. The MAH investigated the difference in terms of immune response to the vaccine between subjects included in the subset and subjects not included in the subset. Based on descriptive statistics generated and reverse cumulative curves (RCCs) submitted, there was no evidence of a difference in the ELISA response following vaccination between the subset of subjects identified for further immune response evaluations and the rest of the studied population regardless of the group and the age strata. The CHMP considered that the titres of neutralizing antibodies against HPV-16 or HPV-18 in the subsample tested (not randomly selected) can be regarded as representative of the study population.

Supportive study HPV-048

One month after the last dose, the standard 3-dose schedule for subjects aged 15-25 years was not immunologically superior to the 2-dose schedule (2D) groups (20/20 M 0,6 group) for both HPV-16 and HPV-18 (lower limit of 95% CI GMR [2D/3D] >0.5). For both HPV-16 and HPV-18, the 2-dose schedules in girls aged 9-14 years were immunologically non-inferior to the 3-dose schedule in women aged 15-25 years, i.e., the age group in which efficacy has been demonstrated one month after the last dose (upper limit of 95% CI for GMR [3D/2D] <2).

These results indicate that the HPV-16/18 vaccine on a 2-dose M0,6 schedule is likely adequate for younger females aged 9-14 years.

Supportive study HPV-008

The efficacy against virological endpoints in initially HPV-naïve subjects who received 2 doses of vaccine in study HPV-008 as observed at Month 48 (end-of-study analysis) indicates that the HPV-16/18 vaccine also prevents HPV-16/18 infection in subjects who did not receive a complete 3-dose vaccination course.

Supportive study HPV-009

These results confirmed the data obtained with the other studies. However, the 2-dose regimen failed to demonstrate clinical cross-protection against persistent infection due to HPV-31/33/45 pooled in the post-hoc analysis.

Supportive data from the Health Protection Agency in the United Kingdom (HPA HPV Report Phase 1, report 1)

The findings of the HPV surveillance in the UK demonstrate that Cervarix prevents successfully the transmission of HPV-16 and HPV-18.

Concerning high risk types HPV-31, 33, 45 among girls 16-18 years of age (vaccine coverage, 65%), the prevalence was barely lower during the post-immunisation than during the pre-immunisation period (6.4% versus 8.6% respectively, HPA HPV Report Phase 1, report 1). The CHMP noted that in the post-hoc analysis of the Costa-Rica study (study HPV-009) (Kreimer A et al J Natl Cancer Inst 2011; 103: 1444-51), no evidence of cross-protection against persistent infection (12 month definition) with HPV-31/33/45 (combined) among women who received two vaccine doses (VE - 25.9% [95% CI -334%; + 61.1%]) was demonstrated, in contrast to women who received the standard three doses (VE 41.3% [95% CI 18.9%; 57.9%]. In addition, in the HPA HPV surveillance report from the UK (Phase 1, report 1 dated 30 January 2013), the reduction of HPV-31/33/45 in the post-immunisation period (after the standard 3-dose schedule) was very poor or even not existent, in contrast to the strong effect against HPV-16 and HPV-18. The lack of clinical protection in the post-hoc analysis of the Costa Rica study may be due to the fact that the diagnostic tests used in the pre-immunisation period (2008) had a lower sensitivity than the tests used in the post-immunisation period (2012). The prevalence of grouped types (individual types other than HPV-16/18 were not assessed in the validation exercise) may be subject to measurement error. Another potential explanation is the phenomenon of unmasking (=diagnostic artefact making an assay unable to detect some types in lower concentrations when multiple types are present in the sample). Indeed, considering that Cervarix protects against HPV-16/18 infection, mixed infections in the post-vaccination period will be less frequent in vaccinated subjects in comparison with unvaccinated subjects. Unmasking will more frequently occur in the former group and lead to a higher detection of concomitant infections, resulting in decreased protection.

Cervarix reduced the prevalence of non-vaccine types HPV-31, 33 and 45 in Scotland[1]; however detailed information is currently not available. These data seem to disagree with the data included in the HPA Report Phase 1 (dated 30 January 2013), where no cross-protection was observed. The CHMP considered that it is too early to draw conclusions from the first HPA report as additional data are expected from the 2nd HPA surveillance report due in March 2015.

In order to provide a more complete view on the protection against these high risk HPV types after 2 vaccine doses the MAH was requested to submit the cross-protection results for HPV-31/33/45 in study HPV-008 among subjects who received only two vaccine doses.

The limited number of cases accrued with non-vaccine types HPV-31, HPV-33 and HPV-45 in subjects aged 15-25 years who received only 2 doses of the vaccine (with the less favourable 0,1 month schedule) did not allow drawing firm conclusions. Data from incident infection showed a vaccine efficacy of 83.0% (95% CI [23.8-98.2]) against HPV-31/33/45 and 100.0% (95% CI [13.5-100]) against HPV31, and a trend for a higher accrual of cases in the control groups for HPV-33 and HPV-45 in subjects who had received only two doses at the vaccine (0,1 month schedule).

The clinical relevance of the statistical modelling in predicting antibody titres up to 20 years or beyond from the first vaccine dose remains unknown. However it was further substantiated with the plot of real life 9.4 years GMTs from study HPV-023 (Brazilian cohort of the HPV-001/007 study where subjects were followed up with a mean of 8.9 years and a maximum of 9.4 years). On the basis of the model there is no reason to believe that the simulation presented in the dossier under or over-estimates the immune responses elicited by 2 vaccine doses in 9-14 years old girls. The MAH committed to perform a new evaluation once the Month 60 data from study HPV-048 will be available. Additional modelling will be performed with data from study HPV-048 at Month 60 (5 years) and from study HPV-081 (up to 6.5 years

[1] Pollock et al: Introduction and sustained high coverage of the HPV bivalent vaccine in Scotland leads to a reduction in prevalence of HPV 16/18 and closely related HPV types:EP-721; 28th International papillomavirus Conference, Puerto Rico, November 2012.

after initial vaccination, if sufficient data are available). These additional data will further document the value of the model with the 2-dose schedule. In addition, according to the robustness and validity of the modelling approach, the MAH was requested to propose feasibility options of an observational study to investigate waning of protection with the 2 dose schedule vs. the 3 dose schedule in girls aged 9 to 14 years by June 2014.

Furthermore, the MAH will extend study HPV-048 by another year for some study arms (HPV-081) to provide follow-up data up to 6.5 years after initial vaccination.

The MAH submitted the ELISA results for HPV-33 obtained in study HPV-048. The HPV-33 ELISA was not routinely used in past studies. GMTs in the 2-dose schedule among subjects 9-14 years old and the 3 dose schedule among subjects 15-25 years old are very similar, although GMTs in the latter age group are slightly higher.

The CHMP requested clarification for not studying the 0-6 month schedule in women 15 to 25 years old. The MAH provided data observed in early clinical trials in which the immunogenicity in young girls aged less than 15 years was twice as high as in women 15-25 years. GMTs for HPV-16 in subjects of the older age group who received the 2-dose schedule appeared to be lower than those observed in the younger age group with non-overlapping confidence intervals, while GMTs for HPV-18 appear to be similar between both groups. From these data, the feasibility of demonstrating non-inferiority of the immune response after 2-dose (0,6 month) vs. 3-dose (0,1,6 month) in subjects aged 15 -25 years appears unlikely. Therefore studies in this age group were not pursued.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

The safety analysis in studies HPV-070 and HPV-048 was performed on the TVC (primary analysis). The primary analysis was complemented by an analysis based on the ATP cohort for safety.

2.3.1.1. Study HPV-070

In Study HPV-070, the following safety parameters were assessed:

- Solicited local and general symptoms within 7 days after each vaccination
- Unsolicited adverse events (AEs) within 30 days after each vaccination
- Serious adverse events (SAEs) during the entire primary active epoch (up to Month 7)
- Medically significant conditions (MSCs) during the entire primary active epoch (up to Month 7)
- Potential immune-mediated diseases (pIMDs) during the entire primary active epoch (up to Month 7)
- Pregnancies and pregnancy outcomes during the entire primary active epoch (up to Month 7)

Safety will be evaluated in Study HPV-070 up to Month 36.

2.3.1.2. Study HPV-048

In Study HPV-048, long-term safety data are available up to Month 48. In summary, the following safety parameters were assessed:

- Solicited local and general symptoms within 7 days after each vaccination (co-primary endpoint)
- Unsolicited AEs within 30 days after each vaccination
- SAEs during the entire study period up to Month 48
- MSCs during the entire study period up to Month 48
- New onset of chronic diseases (NOCDs) and new onset of autoimmune diseases (NOADs) during the entire study period up to Month 48 (NOCDs/NOADs are the previous assessment of pIMDs)
- Pregnancies and pregnancy outcomes during the entire study period up to Month 48
- Changes in haematological and biochemical parameters in blood samples taken from all subjects at Month 0 and Month 7.

Safety will be evaluated in Study HPV-048 up to Month 60.

2.3.2. Results

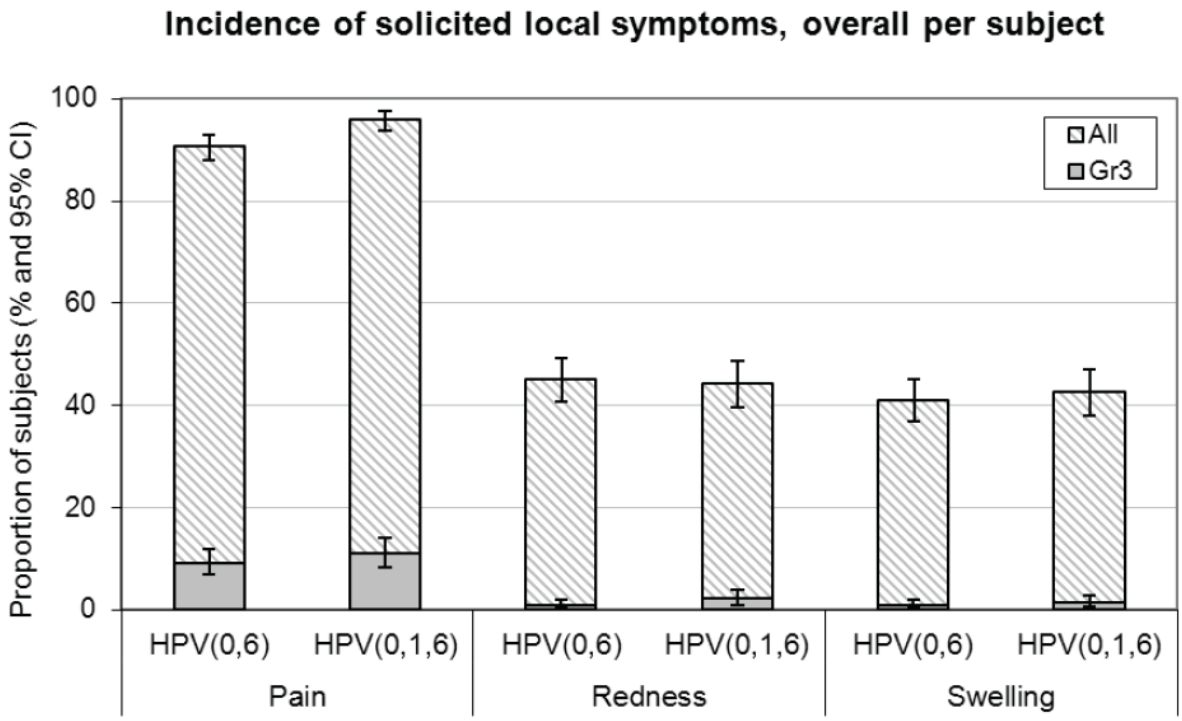
2.3.2.1. Study HPV-070[2]

Solicited symptoms

Solicited local symptoms

The percentage of subjects reporting individual solicited local symptoms during the 7-day (Days 0-6) post-vaccination period after any vaccination is graphically presented in Figure 4.

Figure 4 Study HPV-070: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following any dose by subject (Total vaccinated cohort)



[2] Note that Group (0,12) is not included in the safety analysis at Month 7.

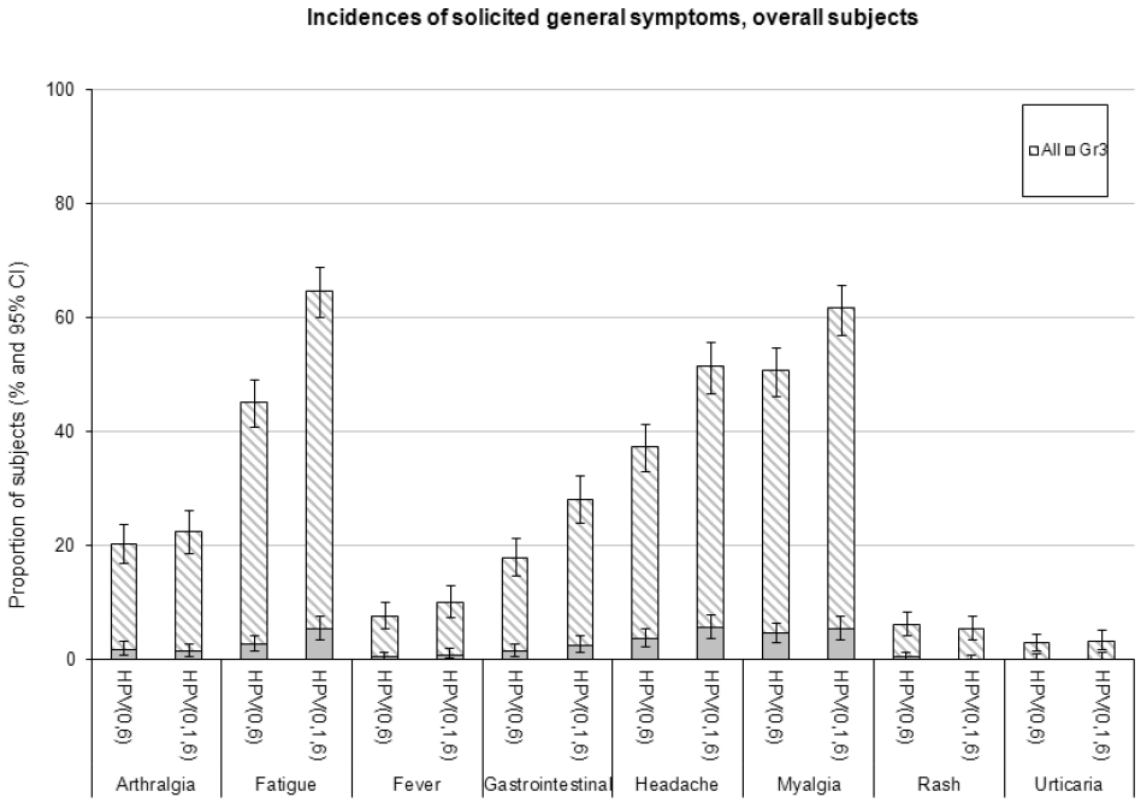
HPV(0,6) = Group (0,6) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 6
HPV(0,1,6) = Group (0,1,6) = Females aged 15-25 years who received 3 doses of Cervarix at Day 0, Month 1 and Month 6

During the 7-day post-vaccination period, solicited local symptoms were reported with similar incidence rates in both groups. Pain at the injection site was the most frequently reported solicited local symptom in both groups and was reported for 90.7% and 96.0% of subjects in Group (0,6) and Group (0,1,6), respectively, after 83.0% of doses in both groups. The incidence of Grade 3 solicited local symptom was low in both groups, i.e., in at most 9.1% of subjects after at most 5.2% of doses in Group (0,6) and in at most 11.0% of subjects after at most 4.7% of doses in Group (0,1,6).

Solicited general symptoms

The percentage of subjects reporting individual solicited general symptoms during the 7-day (Days 0-6) post-vaccination period after any vaccination is graphically presented in Figure 5.

Figure 5 Study HPV-070: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following any dose by subject (Total vaccinated cohort)



HPV(0,6) = Group (0,6) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 6
HPV(0,1,6) = Group (0,1,6) = Females aged 15-25 years who received 3 doses of Cervarix at Day 0, Month 1 andMonth 6

During the 7-day post-vaccination period, the most common solicited general symptom was myalgia in Group (0, 6) and fatigue in Group (0,1,6). The most frequently reported solicited general symptoms (≥ 20% of subjects in any group, i.e., fatigue, myalgia, headache, gastro-intestinal disorders and arthralgia) were reported with a higher incidence rate (non-overlapping 95% CI, except for arthralgia) in Group (0,1,6) than in Group (0,6). Note that subjects in Group (0,1,6) are older and received one more dose of Cervarix.

The majority of the solicited general symptoms were considered potentially related to vaccination. The incidence Grade 3 solicited general symptoms was low in both groups, i.e., reported in at most 4.4% of subjects after at most 2.7% of doses in Group (0,6) and in at most 5.4% of subjects after at most 2.3% of doses in Group (0,1,6).

Unsolicited adverse events

During the 30 day post-vaccination follow-up period, the overall incidence of unsolicited AEs was higher (non-overlapping 95% CIs) in Group (0,1,6) than in Group (0,6), i.e., 34.2% of subjects after 14.6% of doses vs. 18.0% of subjects after 9.7% of doses, respectively. By Preferred Term, the most frequently reported unsolicited AEs (≥ 2.0% of subjects in any group) were nasopharyngitis in Group (0,6) and nasopharyngitis, upper respiratory tract infection, dysmenorrhoea, oropharyngeal pain and headache in Group (0,1,6).

The incidence of Grade 3 unsolicited AEs was low in both groups, however, lower (non-overlapping 95% CIs) in Group (0,6) i.e., reported in 0.4% of subjects after 0.2% of doses than in Group (0,1,6), i.e., reported in 3.5% of subjects after 1.3% of doses. The incidence of unsolicited AEs considered by the investigator to have a possible causal relationship to vaccination was low, i.e., reported in 2.0% and 5.0% of subjects (overlapping 95% CIs) after 1.1% and 1.9% of doses in Group (0,6) and Group (0,1,6), respectively.

Serious adverse events and deaths

No fatal SAEs were reported during the primary active epoch (Day 0 to Month 7) of Study HPV-070. During this period, 7 non-fatal SAEs were reported in 6 (1.1%) subjects in Group (0,6) and 12 non-fatal SAEs were reported for 11 (2.3%) subjects in Group (0,1,6). None of these SAEs were considered by the investigator to have a possible causal relationship to vaccination.

Other significant adverse events

Medically significant conditions (MSCs)

During the primary active epoch (Day 0 to Month 7) of Study HPV-070, 107 MSCs were reported for 75 (13.6%) subjects in Group (0,6) and 129 MSCs were reported for 96 (19.9%) subjects in Group (0,1,6). Except for bronchitis and cystitis, which were each reported in 5 (1.0%) subjects in Group (0,1,6), no MSCs occurred in more than 4 (<1%) subjects in any group.

Potential immune-mediated diseases (pIMDs)

During the primary active epoch (Day 0 to Month 7) of Study HPV-070, 3 pIMDs (autoimmune thyroiditis, type 1 diabetes mellitus and Raynaud's phenomenon) were reported for 2 (0.4%) subjects in Group (0,6) and 1 pIMD (VIIth nerve paralysis) was reported for 1 (0.2%) subject in Group (0,1,6). Autoimmune thyroiditis and type 1 diabetes mellitus reported in one subject of Group (0,6) were also reported as SAEs. VIIth nerve paralysis reported in one subject in Group (0,1,6) was considered by the investigator to have a possible causal relationship to vaccination.

Pregnancies and pregnancy outcomes

A total of 9 pregnancies were reported in Group (0,1,6) during the primary active epoch (Day 0 to Month 7). Seven (77.8%) of these pregnancies were ongoing at the time of the Month 7 data lock point. One (11.1%) subject underwent an elective termination of the pregnancy and one (11.1%) subject had an ectopic pregnancy.

2.3.2.2. Study HPV-048

Solicited symptoms

The incidence of individual solicited local and general symptoms (any and grade 3) in the 20/20 M0,6 group and the HPV group receiving the vaccine according to the standard 0, 1, 6 month schedule was comparable and was similar to that observed in Group (0,6) and Group (0,1,6) in Study HPV-070.

Unsolicited adverse events

During the 30 day post-vaccination follow-up period, the overall incidence of unsolicited AEs was higher (non-overlapping 95% CIs in terms of proportion of subjects) in the group that received Cervarix according to the 0, 1, 6 schedule than in the 20/20 M0,6 group, i.e., 44.8% of subjects after 20.6% of doses vs. 31.7% of subjects after 19.3% of doses, respectively. By Preferred Term, the most frequently reported unsolicited AEs (≥ 2.0% of subjects in any group) were nasopharyngitis, influenza like illness, urinary tract infection and headache in the 20/20 M0,6 group and nasopharyngitis, headache, pharyngolaryngeal pain, upper respiratory tract infection, injection site bruising and influenza like illness in the HPV group.

The incidence of Grade 3 unsolicited AEs was similarly low in both groups, i.e., reported in 2.5% and 5.9% of subjects, after 1.3% and 2.1% of doses in the 20/20 M0,6 group and HPV group, respectively. Also the incidence of unsolicited AEs considered by the investigator to have a possible causal relationship to vaccination was similarly low, i.e., reported in 6.7% and 11.3% of subjects after 3.6% and 4.9% of doses in the 20/20 M0,6 group and the HPV group, respectively.

Serious adverse events and deaths

During the entire follow-up period from Month 0 to Month 48, no fatal SAEs were reported. Subject no. 258 in the 20/20 M0,6 group, underwent an elective pregnancy termination because of a congenital anomaly (spina bifida for the offspring resulting in a fatal outcome), which was considered by the investigator as not potentially related to vaccination.

During the entire follow-up period from Month 0 to Month 48, 21 non-fatal SAEs were reported in 19 (7.9%) subjects in the 20/20 M0,6 group and 19 non-fatal SAEs were reported for 13 (5.4%) subjects in the HPV group. In addition, one non-fatal SAE (foetal distress syndrome) was reported in a newborn infant of a study participant (Subject no. 99 in the 20/20 M0,6 group). None of these SAEs were considered as potentially related to vaccination according to the investigator.

With the exception of appendicitis, which was reported in 4 (1.7%) subjects in the 20/20 M0,6 group (and 1 [0.4%] subject in the HPV group), all individual SAEs by preferred term occurred in at most 2 subjects in either of both vaccine groups.

Other significant adverse events

Medically significant conditions (MSCs)

During the entire follow-up period from Month 0 to Month 48, 152 MSCs were reported for 88 (36.7%) subjects in the 20/20 M0,6 group and 135 MSCs were reported for 82 (34.3%) subjects in the HPV group. Except for depression and abdominal pain, all individual MSCs by preferred term were reported for at most 5 subjects in either of both vaccine groups. Depression was reported in 8 (3.3%) and 5 (2.1%)

subjects in the 20/20 M0,6 and HPV groups, respectively. Abdominal pain was reported in 2 (0.8%) and 6 (2.5%) subjects in the 20/20 M0,6 and HPV groups, respectively

New onset of chronic diseases (NOCDs)

During the entire follow-up period from Month 0 to Month 48, 15 NOCDs were reported for 13 (5.4%) subjects in the 20/20 M0,6 group and 7 NOCDs were reported for 6 (2.5%) subjects in the HPV group. Except for hypothyroidism and dermatitis contact reported in 4 (1.7%) and 2 (0.8%) subjects in the 20/20 M0,6 group, all individual NOCDs preferred terms were reported in at most one subject in either of both vaccine groups.

New onset auto-immune diseases (NOADs)

During the entire follow-up period from Month 0 to Month 48, 6 NOADs were reported for 5 (2.1%) subjects in the 20/20 M0,6 group and 4 NOADs were reported for 4 (1.7%) subjects in the HPV group. Except for hypothyroidism reported in 2 (0.8%) subjects in the 20/20 M0,6 group, all individual NOADs preferred terms were reported in at most one subject in either of both vaccine groups.

Pregnancies and pregnancy outcomes

24 pregnancies were reported in the 20/20 M0,6 group and 20 pregnancies in the HPV group. Most of the pregnancy outcomes in both groups were live infant with no apparent congenital anomaly, i.e., 15 (62.5%) and 12 (60.0%) subjects in the 20/20 M0,6 group and HPV group, respectively. In addition, the following pregnancy outcomes were reported in the 20/20 M0,6 group and HPV group: 3 (12.5%) and 5 (25.0%) cases of elective termination with no apparent congenital anomaly and 3 (12.5%) and 1 (5.0%) cases of spontaneous abortion with no apparent congenital anomaly, respectively. Finally, one subject in the 20/20 M0,6 group underwent an elective termination with congenital anomaly (spina bifida as child fatality). In each group, 2 pregnancies were still ongoing at the time of the Month 48 data lock point.

Clinical laboratory evaluations

The number and percentages of subjects outside the normal ranges for haematology and biochemistry at Month 7 were low and similar in both 20/20 M0,6 and the standard schedule group. There were no medically relevant alterations, especially no value corresponding to a grade 3 in toxicity according to the Center for Biologics Evaluation and Research (CBER) toxicity scale.

2.3.3. Conclusion on the safety aspects

No new safety information was collected in studies HPV-070 and HPV-048, the occurrence of adverse reactions is in line with the current information in the SmPC.

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the Committee agreed.

The new text is presented underlined while the deleted text marked as strikethrough.

4.2 Posology and method of administration

Posology

The vaccination schedule depends on the age of the subject.

Age at the time of the first injection	Immunization and schedule	Flexibility for immunization if required
9 to and including 14 years	Two doses each of 0.5 ml at 0, 6 months	Second dose between 5 and 7 months after the 1st dose
From 15 years and above	Three doses each of 0.5 ml at 0, 1, 6 months	Second dose between 1 and 2.5 months after 1st dose Third dose between 5 and 12 months after the 1st dose

~~The recommended vaccination consists of 3 separate 0.5 ml doses administered according to the schedule: 0, 1, 6 months.~~

~~If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.~~

If at any age the second vaccine dose is administered before the 5th month after the first dose, the third dose should always be administered.

5.1 Pharmacodynamic properties

Bridging the efficacy of Cervarix from young adult women to adolescents

In a pooled analysis (HPV-029,-30 & -48), 99.7% and 100% of females aged 9 years seroconverted to HPV types 16 and 18, respectively after the third dose (at month 7) with GMTs at least 1.4-fold and 2.4-fold higher as compared to females aged 10-14 years and 15 to 25 years, respectively.

In two clinical trials (HPV-012 & -013) performed in girls ~~and adolescents~~ aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years.~~On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.~~

In ongoing clinical trials (HPV-070 and HPV-048) performed in girls aged 9 to 14 years receiving a 2-dose schedule (0, 6 months) and young women aged 15-25 years receiving Cervarix according to the standard 0, 1,6 months schedule, all subjects seroconverted to both HPV types 16 and 18 after the second dose (at month 7). The immune response after 2 doses in females aged 9 to 14 years was non-inferior to the response after 3 doses in women aged 15 to 25 years.

On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Package leaflet

3. How Cervarix is given

How ~~much~~ the vaccine is given
The doctor or nurse will give Cervarix as an injection into the muscle of the upper arm.

How much is given
Cervarix is intended for females from 9 years of age onwards. ~~A total of three injections will be administered by your doctor or nurse according to the following schedule:~~

~~First injection: at chosen date~~
~~Second injection: 1 month after first injection~~
~~Third injection: 6 months after first injection~~
The total number of injections you will receive depends on your age at the time of the first injection:

If you are between 9 and 14 years old, Cervarix can be administered by your doctor according to the following 2-dose schedule:

First injection: at chosen date
Second injection: 6 months after first injection

If you are 15 years old or above, Cervarix can only be administered by your doctor according to the following 3-dose schedule:

First injection: at chosen date
Second injection: 1 month after first injection
Third injection: 6 months after first injection

If necessary, the vaccination schedule can be more flexible. Please speak to your doctor for more information.

When Cervarix is given for the first dose, it is recommended that Cervarix (and not another vaccine against HPV) be given for the complete ~~3-dose~~ vaccination course.

Cervarix is not recommended for use in girls below 9 years of age.

The vaccine should never be given into a vein.

If you miss a dose
It is important that you follow the instructions of your doctor or nurse regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

If you do not finish the complete vaccination course (two or three injections depending on your age at vaccination)~~of three injections~~, you may not get the best response and protection from the vaccination.

3. Overall conclusion and impact on the benefit / risk balance

The purpose of this variation is to update of the Summary of Product Characteristics (SmPC) for Cervarix with a reduced 2-dose schedule (0, 6 months) in females aged 9-14 years old.

The acceptability of a 2-dose schedule for Cervarix was evaluated in the proof-of-concept study HPV-048. Immunogenicity results have shown that a 2-dose schedule of Cervarix administered at 0, 6 months in 9-14 years old females was non-inferior to the standard 3-dose schedule in females aged 15-25 years at all time points tested up to Month 48.

As new efficacy studies are not feasible in 9-14 years old girls for ethical and practical reasons, the MAH conducted study HPV-070, a phase III confirmatory immunobridging study.

In addition, immunogenicity data from the pivotal phase III study were complemented by efficacy data in subjects receiving 2-doses of Cervarix in two large phase III studies (studies HPV-008 and HPV-009).

Furthermore, effectiveness results for a follow-up period of 4 years on Cervarix obtained from the surveillance of HPV-specific infection after introduction of the National HPV Immunisation Program in the UK in girls aged 12-13 years were submitted as supportive evidence.

The conclusions regarding similarity of the vaccine's immunogenicity and safety when administered as a 0, 6 months schedule to 9-14 years old girls in studies HPV-070 and HPV-48 vs. current 3-dose schedule were considered acceptable by the CHMP. The two-dose schedule using an interval of 5 to 7 months provides a suitable alternative to the three-dose schedule as it may improve the vaccine's coverage.

In addition to the data from studies HPV-070 and HPV-048, exploratory or post-hoc analyses of vaccine efficacy at Month 48 after the first vaccine dose among women aged 18-25 years who received only two doses in studies HPV-008 and HPV-009 demonstrate that two doses effectively protect against persistent infection due to HPV-16/18 combined (VE: 100 % [33.1%; 100] in study HPV-008 and 84.1% [50.2%; 96.3%] in study HPV-009).

Although there is no immunological correlate of protection, it is recognised (as demonstrated in animal models) that protection against oncogenic HPV infection in humans is mainly based on the presence of neutralizing antibodies as well as on cell-mediated immunity. Therefore as the immune responses are comparable between the reduced-dose schedule in the target population (9-14 years old girls) and the standard schedule in the population where clinical protection was demonstrated in previous clinical studies or in epidemiological surveillance, it is reasonable to conclude that Cervarix is expected to confer a clinical protection that is comparable with the standard schedule.

Based on the available data, the CHMP endorsed the introduction of a 2-dose schedule (0, 6 months) in females aged 9-14 years old. The Risk/Benefit profile for Cervarix remains unchanged and favourable.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) for Cervarix to include a reduced 2-dose schedule (0, 6 months) in females aged 9-14 years old. The MAH took the opportunity to add Croatia to the list of representatives. The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) for Cervarix to include a reduced 2-dose schedule (0, 6 months) in females aged 9-14 years old. The MAH took the opportunity to add Croatia to the list of representatives. The Package Leaflet is updated accordingly.

Summary

Following the immunogenicity results in the proof-of-concept study HPV-048 showing that a 2-dose schedule of Cervarix administered at 0, 6 months in 9-14 years old females was non-inferior to the standard 3-dose schedule in females aged 15-25 years, the MAH conducted study HPV-070 as a phase III confirmatory immunobridging study. Efficacy data in subjects receiving 2-doses of Cervarix in 2 large phase III studies (studies HPV-008 and HPV-009) was provided as supportive evidence, along with data

obtained from the surveillance of HPV-specific infection after introduction of the National HPV Immunisation Program in the UK in girls aged 12-13 years.

The overall immunogenicity and safety data provided demonstrate the non-inferiority of a 0, 6 months schedule in 9-14 years old girls vs. the standard 3-dose schedule. The 2-dose schedule using an interval of 5 to 7 months provides a suitable alternative to the 3-dose schedule as it may improve the vaccine's coverage.