21 July 2016
EMA/624001/2016
Procedure Management and Committees Support Division

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

Cervarix

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

Procedure no: EMEA/H/C/000721/P46/087

Note

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

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1. Introduction

On 28 January 2016, the MAH submitted the final clinical study report for paediatric study HPV-070 PRI Month 24 and Month 36 for Cervarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

HPV-070 is a paediatric study documenting immunogenicity and safety of Cervarix in healthy females aged 9-14 years in alternative 2-dose schedules vs. the standard 3-dose schedule in healthy females aged 15-25 years. Interim study results up at Month 7 and Month 13 were submitted previously as part of the variation II/48 and II/58, resp.

2.2. Information on the pharmaceutical formulation used in the study

Cervarix was developed and manufactured by GSK Biologicals.

Table 1 Study vaccine.

Treatment name	Vaccine name	Formulation	Presentation	Volume (mL)	Number of doses	Lot numbers
HPV-16/18	HPV-16/18 L1 VLP AS04	Each 0.5 mL dose contained: - 20 µg HPV-16 L1 VLP - 20 µg HPV-18 L1 VLP - 50 µg MPL - 500 µg aluminium as $Al(OH)_3$ - 8 mM sodium dihydrogen phosphate dehydrate - 150 mM sodium choloride - water for injection	Liquid in pre-filled syringes or vials	0.6*	2 or 3**	**Canada** AHPVA144C AHPVA155A **Germany** AHPVA133A AHPVA133E **Italy** AHPVA133A **Taiwan** AHPVA125B AHPVA155A **Thailand** AHPVA150A

* Volume to be injected = 0.5 mL.
** The total number of doses was 2 or 3 depending on the study group.

2.3. Clinical aspects

2.3.1. Introduction

Table 2 Overview of clinical study HPV-070 PRI

Study ID	**Study counties**	Study Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects	
					ATP (immune) cohort	TVC cohort
114700 (HPV-070 PRI)	Canada, Germany, Italy, Taiwan, Thailand	To assess the immunogenicity, reactogenicity and safety of the vaccine when administered intramuscularly according to alternative 2-dose schedules in 9-14 year old healthy females compared to the standard 3-dose schedule for GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine in 15 - 25 year old healthy females	- 9-14 years old girls (0,6 months or 0, 12 months schedules) - 15-25 years old women (0,1,6 months schedule)	**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 aged 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.	534 subjects in Group (0,6) 402 subjects in Group (0,12) 458 subjects in Group (0,1,6)	550 subjects in Group (0,6) 415 subjects in Group (0,12) 482 subjects in Group (0,1,6)

2.4. Clinical efficacy

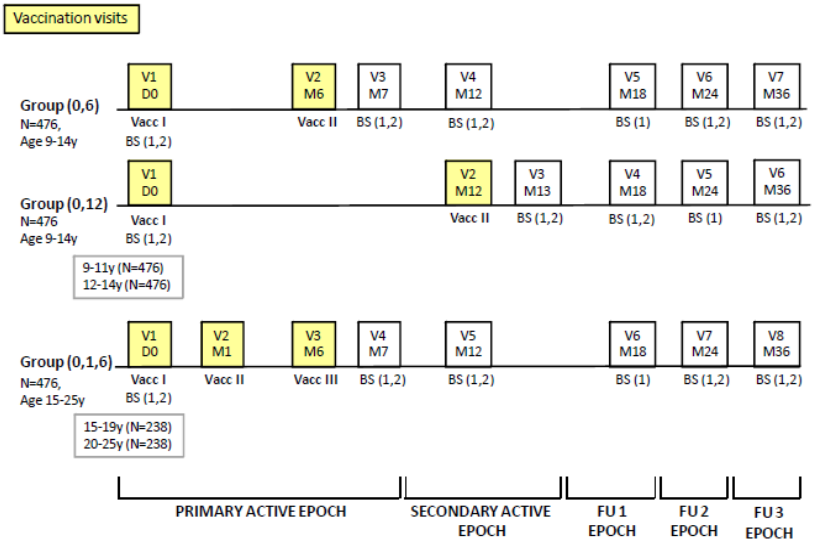
2.4.1. Methods

<u>Study design, laboratory evaluations, endpoints, study cohorts, statistical methods of Pivotal study HPV-070</u>

- Phase IIIb, open-label, randomized, age-stratified, multi-centre trial (Canada, Germany, Italy, Taiwan and Thailand)

- Study design in Figure 1. The study is terminated and lasted 36 months. Immunogenicity (humoral and cell mediated) and safety results obtained up to Month 24 and Month 36 time points are presented in chapter 2.5.2. Results.

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 schedules

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 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 summarized below.

Study	Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
All subjects							
HPV-070	Quantitative	Anti-HPV-16	ELISA†	GSK Biologicals	EL.U/mL	8♯	CEVAC GSK Biologicals
HPV-070	Quantitative	Anti-HPV-18	ELISA†	GSK Biologicals	EL.U/mL	7♯	CEVAC GSK Biologicals
HPV-070	Quantitative	Anti-HPV-16	ELISA†	GSK Biologicals	EL.U/mL	19$^{\Delta}$	CEVAC GSK Biologicals
HPV-070	Quantitative	Anti-HPV-18	ELISA†	GSK Biologicals	EL.U/mL	18$^{\Delta}$	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	Quantitative	Anti-HPV-31	ELISA†	GSK Biologicals	EL.U/mL	59	GSK Biologicals
HPV-070	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
ED_{50} = Estimated Dose: serum dilution giving a 50% reduction of the signal compared to a control without serum; ND = Not Defined
† ELISA testing based on methodology developed by MedImmune Inc, Gaithersburg, MD, USA and modified by GSK Biologicals.

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 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.

CHMP's note: please refer to the Study report p. 91 for the definition of the TVC cohort and p.92 for the definition of the TVC cohort.

Statistical evaluation

1.Within groups assessment

PBNA (pseudovirion-based neutralization 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.

Cellular-mediated immunity

1.CD4+/CD8+ T-cell response by ICS (IntraCellular Cytokine Staining)

Frequency of cytokines-positive (d-CD40L, d-IL2, d-TNFα, d-IFNγ or all doubles) CD4+ or CD8+ T cells, for each stimulant (HPV-16 and HPV-18 & HPV-31 and HPV-45) at each time point (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]) were summarised 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).

Threshold was determined on the basis of 95th percentile of frequency of CD4+ or CD8+ all doubles stimulated by HPV-16 or HPV-18 antigen at Month 0 for HPV seronegative subjects.

	Thresholds used		
	Group (0,6)	Group (0,12)	Group (0,1,6)
HPV-16			
CD4-ALL DOUBLES	247 HPV-16 specific CD4+ T-cells per million CD4+ T-cells	270 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	103 HPV-16 specific CD4+ 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	228 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	122 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	Not determined*	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	Not determined*	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	Not determined*	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	Not determined*	77 HPV-45 specific CD8+ T-cells per million CD8+ T-cells

Data Source: HPV-070 Report (Month 13)
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
HPV-31/45 thresholds could not be generated in this report as serology data were not available yet.

2. B-cell response

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

2.Inferential analysis : between-group assessment

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

- For each HPV antigen, the upper limit (UL) of the 2-sided standardised asymptotic 95% CI of the difference between the percentage of seroconverted subjects in the 3-dose schedule (15-25 year old group) minus the percentage of seroconverted subjects in the 2-dose schedule (9-14 year old group) was computed.

  Non-inferiority of HPV (0,6) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 was demonstrated if the upper limits of these 95% CIs was below the pre-defined clinical limit of 5%.
- If non-inferiority of HPV (0,6) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 seroconversion rates was reached, the 2-sided 95% CIs of GMT ratios was computed using an analysis of variance (ANOVA) model on the log10 transformation of the titres at each timepoint. The ANOVA model included the vaccine group as fixed effect.

  Non-inferiority of HPV (0,6) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 was demonstrated if the upper limits of these 95% CIs wass below the pre-defined clinical limit of 2.

Those 2 sequential steps was/ will be performed 1 month after the last dose of study vaccine (primary objective) and 6 months, 12 months, 18 months and 30 months after the last dose of study vaccine.

Similarly, non-inferiority testing would be performed between HPV (0, 12) schedule *vs.* HPV (0, 1, 6) schedule and between HPV (0, 12) schedule *vs*. HPV (0, 6) schedule 1 month, 6 months and 12 months after the last dose of study vaccine.

In the secondary active Epoch, the secondary objectives were to demonstrate non-inferiority in initially seronegative subjects in the ATP cohort for immunogenicity based on the following criteria:

- Between [Group (0,12)] vs [Group (0,1,6)], one month after the last dose of study vaccine

- For each HPV antigen, the upper limit of the 2-sided standardized asymptotic 95% CI of the difference between the percentage of seroconverted subjects in the 3-dose schedule (15-25 year old group) minus the percentage of seroconverted subjects in the 2-dose schedule (9-14 year old group) one month after the last dose was computed.

Non-inferiority of HPV (0,12) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 antibody seroconversion rates was demonstrated one month after the last dose if the upper limits of these 95% CIs was below the pre-defined clinical limit of 5%.

- If non-inferiority of HPV (0,12) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 seroconversion rates was reached (sequential analysis) one month after the last dose, the 2-sided 95% CIs of GMT ratios was computed using an analysis of variance (ANOVA) model on the log10 transformation of the GMTs at each time-point. The ANOVA model included the vaccine group as fixed effect.

Non-inferiority of HPV (0,12) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated one month after the last dose if the upper limits of these 95% CIs was below the pre-defined clinical limit of 2.

- Between [Group (0,12)] vs [Group (0,6)], one month after the last dose of study vaccine based on the following criteria:

- For each HPV antigen, the upper limit of the 2-sided standardized asymptotic 95% CI of the difference between the percentage of seroconverted subjects in the 2-dose schedule (9-14 year old group) (0,6) minus the percentage of seroconverted subjects in the 2-dose schedule (9-14 year old group) (0,12) one month after the last dose was computed.

Non-inferiority of HPV (0,12) schedule to HPV (0,6) schedule with respect to anti-HPV-16 and anti-HPV-18 antibody seroconversion rates was demonstrated one month after the last dose if the upper limits of these 95% CIs was below the pre-defined clinical limit of 5%.

- If non-inferiority of HPV (0,12) schedule to HPV (0,6) schedule with respect to anti-HPV-16 and anti-HPV-18 seroconversion rates was reached (sequential analysis) one month after the last dose, the 2-sided 95% CIs of GMT ratios was computed using an analysis of variance (ANOVA) model on the log10 transformation of the GMTs at each time-point. The ANOVA model included the vaccine group as fixed effect.

Non-inferiority of HPV (0,12) schedule to HPV (0,6) schedule with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated one month after the last dose if the upper limits of these 95% CIs was below the pre-defined clinical limit of 2.

- Between [Group (0,6)] vs [Group (0,1,6)], six months after the last dose of study vaccine:

- For each HPV antigen, the upper limit of the 2-sided standardized asymptotic 95% CI of the difference between the percentage of seroconverted subjects in the 3-dose schedule (15-25 year old

group) minus the percentage of seroconverted subjects in the 2-dose schedule (9-14 year old group), 6 months after the last dose was computed.

Non-inferiority of HPV (0,6) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 antibody seroconversion rates was demonstrated 6 months after the last dose if the upper limits of these 95% CIs was below the predefined clinical limit of 5%.

- If non-inferiority of HPV (0,6) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 seroconversion rates was reached (sequential analysis) 6 months after the last dose, the 2-sided 95% CIs of GMT ratios was computed using an analysis of variance (ANOVA) model on the log10 transformation of the GMTs at each time-point. The ANOVA model included the vaccine group as fixed effect.

Non-inferiority of HPV (0,6) schedule to HPV (0,1,6) schedule with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated 6 months after the last dose if the the upper limits of these 95% CIs was below the pre-defined clinical limit of 2.

Those 2 sequential steps were be performed 1 month after the last dose of study vaccine (primary objective) and 6 months, 12 months, 18 months and 30 months after the last dose of study vaccine.

2.4.2. Results

Study population results

The number of subjects planned and enrolled, subjects who completed the follow-up phase up to Month 24 and Month 36 and subjects included in the TVC and the ATP cohort are as follows:

	Group (0,6)	Group (0,12)	Group (0,1, 6)	Total
Number of subjects planned	476	476	476	1428
Number of subjects vaccinated (TVC)	550	415	482	1447
M24 Total vaccinated cohort	537	401	453	1391
M24 ATP cohort	519	385	407	1311
M36 Total vaccinated cohort	524	395	443	1362
M36 ATP cohort	506	378	401	1285

In the ATP cohorts at Month 24, the mean age in the 0, 6 month group was 13.5 years, 13.3 years in the 0,12 month group and 21.4 years in the the standard 3-dose schedule group.

In the ATP cohorts at Month 36, the mean age in the 0, 6 month group was 14.5 years, 14.3 years in the 0,12 month group and 22.4 years in the the standard 3-dose schedule group.

Most subjects (more than 97%) where from White Caucasian/European, East Asian or South- East Asian. Similar demographic characteristics were observed in the ATP cohort for immunogenicity.

Immunogenicity results

Non-inferiority assessments

The primary objective was met i.e. non-inferiority of the (M0,6) schedule in 9-14 years old females versus (M0,1,6) schedule in 15-25 years old females was demonstrated at Month 7 (one month after the last dose).

The secondary objectives of non-inferiority at Month 12 and Month 13 time points were also met.

1. Non-inferiority analysis between Group (0,6) and Group (0,1,6) at 18 months after the last vaccine dose in initially seronegative subjects (M24)

Non-inferiority of the seroconversion rates was demonstrated as the upper limit of the 95% CI for the for the differences in seroconversion rates (HPV [0,1,6] schedule minus HPV [0,6] schedule), 18 months after the last dose, for both anti- HPV-16 and anti-HPV-18, was below 5% (**Table 3**).

Table 3 Non-inferiority assessment of anti HPV-16 and HPV-18 seroconversion rates (HPV [0, 1, 6] schedule vs HPV [0, 6] schedule) 18 months after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M24)

							Difference in seroconversion rate (Group 2 minus Group 1)			
									95 % CI	
Antibody	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
HPV-16	Group(0,6)	468	100	Group(0,1,6)	334	100	Group(0,1,6) - Group(0,6)	0.00	-1.14	0.82
HPV-18	Group(0,6)	472	99.8	Group(0,1,6)	362	100	Group(0,1,6) - Group(0,6)	0.21	-0.84	1.19

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 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 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6

Non-inferiority of the antibody titers was demonstrated as the upper limit of the 95% CI for the GMT ratio (HPV [0,1,6] schedule divided by HPV [0,6] schedule), 18 months after the last dose, for both anti-HPV-16 and anti-HPV-18 was below 2 (**Table 4**).

Table 4 Non-inferiority assessment of HPV-16 and HPV-18 immune response for (HPV [0, 1, 6] schedule vs HPV [0, 6] schedule) 18 months after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M24)

							GMT ratio			
									95% CI	
Antibody	Group description	N	GMT	Group description	N	GMT	Ratio order	Value	LL	UL
HPV-16	Group(0,1,6)	334	1594.9	Group(0,6)	468	1488.4	Group(0,1,6)/Group(0,6)	1.07	0.95	1.21
HPV-18	Group(0,1,6)	362	664.0	Group(0,6)	472	715.8	Group(0,1,6)/Group(0,6)	0.93	0.81	1.06

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 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 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6
GMT = geometric mean antibody titre
N = Number of subjects with results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

2. Non-inferiority analysis between Group (0,12) and Group (0,1,6) at 12 months after the last dose in initially seronegative subjects (M24)

Non-inferiority of the seroconversion rates was demonstrated as the upper limit of the 95% CI for the for the differences in seroconversion rates (HPV [0,1,6] schedule minus HPV [0,12] schedule), 12 months after last dose at Month 24, for both anti-HPV-16 and anti-HPV-18, was below 5% (**Table 5**).

Table 5 Non-Inferiority assessment of anti HPV-16 and HPV-18 seroconversion rates (HPV [0, 1, 6] schedule vs HPV [0, 12] schedule) 12 months after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M24)

							Difference in seroconversion rate (Group 2 minus Group 1)			
									95 % CI	
Antibody	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
HPV-16	Group(0,12)	346	100	Group(0,1,6)	332	100	Group(0,1,6) - Group(0,12)	0.00	-1.15	1.10
HPV-18	Group(0,12)	360	100	Group(0,1,6)	361	100	Group(0,1,6) - Group(0,12)	0.00	-1.05	1.06

Group(0,12) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 12
Group(0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6

Non-inferiority of the antibody titers was demonstrated as the upper limit of the 95% CI for the GMT ratio (HPV [0,1,6] schedule divided by HPV [0,12] schedule), 12 months after last dose at Month 24, for both anti-HPV-16 and anti-HPV-18 was below 2 (

Table 6).

Table 6 Non-inferiority assessment HPV-16 and HPV-18 immune response for (HPV [0, 1, 6] schedule vs HPV [0, 12] schedule) one month after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M24)

							GMT ratio			
									95% CI	
Antibody	Group description	N	GMT	Group description	N	GMT	Ratio order	Value	LL	UL
HPV-16	Group(0,1,6)	332	1956.6	Group(0,12)	346	2183.6	Group(0,1,6)/Group(0,12)	0.90	0.78	1.03
HPV-18	Group(0,1,6)	361	837.1	Group(0,12)	360	1188.0	Group(0,1,6)/Group(0,12)	0.70	0.61	0.82

Group(0,12) = Females aged 9-14 years who received 2 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 12
Group(0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6
GMT = geometric mean antibody titre
N = Number of subjects with results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

3. Non-inferiority analysis between Group (0,12) and Group (0,6) at 12 months after the last dose in initially seronegative subjects (M24)

Non-inferiority of the antibody titers was demonstrated as the upper limit of the 95% CI for the differences in seroconversion rates (HPV [0,6] schedule minus HPV [0,12] schedule), 12 months after last dose at Month 24, for both anti-HPV-16 and anti-HPV-18, was below 5% (**Table 7**).

Table 7 Non-inferiority assessment of anti HPV-16 and HPV-18 seroconversion rates (HPV [0, 12] schedule vs HPV [0, 6] schedule) 12 months after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M24)

							Difference in seroconversion rate (Group 2 minus Group 1)			
									95 % CI	
Antibody	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
HPV-16	Group(0,12)	346	100	Group(0,6)	466	100	Group(0,6) - Group(0,12)	0.00	-0.82	1.10
HPV-18	Group(0,12)	360	100	Group(0,6)	470	99.8	Group(0,6) - Group(0,12)	-0.21	-1.20	0.85

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
Group(0,12) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 12

Non-inferiority of the antibody titers was demonstrated as the upper limit of the 95% CI for the GMT ratio (HPV [0,6] schedule divided by HPV [0,12] schedule), 12 months after last dose at Month 24, for both anti-HPV-16 and anti-HPV-18 was below 2 (**Table 8**).

Table 8 Non-inferiority assessment HPV-16 and HPV-18 immune response for (HPV [0, 12] schedule vs HPV [0, 6] schedule) 12 months after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M24)

							GMT ratio			
									95% CI	
Antibody	Group description	N	GMT	Group description	N	GMT	Ratio order	Value	LL	UL
HPV-16	Group(0,6)	466	1743.1	Group(0,12)	346	2183.6	Group(0,6)/Group(0,12)	0.80	0.71	0.89
HPV-18	Group(0,6)	470	870.9	Group(0,12)	360	1188.0	Group(0,6)/Group(0,12)	0.73	0.65	0.83

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
Group(0,12) = Females aged 9-14 years who received 2 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 12
GMT = geometric mean antibody titre
N = Number of subjects with results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

4. Non-inferiority analysis between Group (0,6) and Group (0,1,6) at 30 months after the last vaccine dose in initially seronegative subjects (M36)

Non-inferiority of the seroconversion rates was demonstrated as the upper limit of the 95% CI for the for the differences in seroconversion rates (HPV [0,1,6] schedule minus HPV [0,6] schedule), 30 months after the last dose in initially seronegative subjects, for both anti- HPV-16 and anti-HPV-18, was below 5% (**Table 9**).

Table 9 Non-inferiority assessment of anti HPV-16 and HPV-18 seroconversion rates (HPV [0, 1, 6] schedule vs HPV [0, 6] schedule) 30 months after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M36)

							Difference in seroconversion rate (Group 2 minus Group 1)			
									95 % CI	
Antibody	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
HPV-16	Group(0,6)	455	100	Group(0,1,6)	330	100	Group(0,1,6) - Group(0,6)	0.00	-1.15	0.84
HPV-18	Group(0,6)	462	99.8	Group(0,1,6)	356	99.7	Group(0,1,6) - Group(0,6)	-0.06	-1.37	0.96

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 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 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6

Non-inferiority of the antibody titers was demonstrated as the upper limit of the 95% CI for the GMT ratio (HPV [0,1,6] schedule divided by HPV [0,6] schedule), 30 months after the last dose, for both anti-HPV-16 and anti-HPV-18 was below 2 (**Table 10**).

Table 10 Non-inferiority assessment of HPV-16 and HPV-18 immune response for (HPV [0, 1, 6] schedule vs HPV [0, 6] schedule) 30 months after the last dose in initially seronegative subjects (ATP cohort for immunogenicity)(M36)

							GMT ratio			
									95% CI	
Anti body	Group description	N	GMT	Group description	N	GMT	Ratio order	Value	LL	UL
HPV-16	Group(0,1,6)	330	1326.4	Group(0,6)	455	1210.2	Group(0,1,6) /Group(0,6)	1.10	0.97	1.24
HPV-18	Group(0,1,6)	356	552.6	Group(0,6)	462	562.8	Group(0,1,6) /Group(0,6)	0.98	0.85	1.13

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 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 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6

Additional non-inferiority testing was performed at Month 36 [group (0,12) versus groups (0,6) and (0,1,6)]. Non-inferiority was demonstrated (data not shown here).

CHMP's comment

Non-inferiority of immune responses to HPV-16/-18 antigens in initially seronegative subjects was

demonstrated at M24 and M36 when Cervarix was administered according to

- a 2-dose schedule (0,6) in 9-14 year old females compared to a 3-dose schedule (0,1,6) in 15-25 year old females;
- a 2-dose schedule (0,12) in 9-14 year old females compared to a 3-dose schedule (0,1,6) in 15-25 year old females;
- a 2-dose schedule (0,12) compared to a 2-dose schedule (0,6) in 9-14 year old females.

Anti-HPV-16 and anti-HPV-18 antibody response

1.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 11**.

The proportion of subjects initially seropositive for both HPV-16 and HPV-18 was 1.7% and 1.3% in the youngest age group (9-14 years) receiving 2 doses of HPV-16/18 vaccine (Groups (0,6) and (0,12), respectively) and 5.2% in the older age group (15-25 years) receiving 3 doses of HPV-16/18 vaccine (Group (0,1,6)).

The majority of subjects was initially seronegative for both HPV-16 and HPV-18, i.e., 83.8% in Group (0,6), 85.9% in Group (0,12) and 75.4% in (Group (0,1,6). In Group (0,6), 8% and 6.5% of subjects were seropositive for only HPV-16 and only HPV-18, respectively. In Group (0,12), 8.7% and 4.1% of subjects were seropositive for only HPV-16 and only HPV-18, respectively. In Group (0,1,6), 13.2% and 6.1% of subjects were seropositive for only HPV-16 and only HPV-18, respectively.

No trend for a difference in initial serostatus by country was observed across the different age strata.

Table 11 **Study HPV-070: Seropositivity status at baseline (ATP cohort for immunogenicity)**

		Group(0,6) (N = 534)		Group(0,12) (N = 394)		Group(0,1,6) (N = 427)		Total (N = 1355)	
HPV 16.VLP Ab.IgG	HPV 18.VLP Ab.IgG	n	%	n	%	n	%	n	%
P	P	9	1.7	5	1.3	22	5.2	36	2.7
P	N	42	8	34	8.7	56	13.2	132	9.9
P	MISSING	1	-	0	-	0	-	1	-
N	P	34	6.5	16	4.1	26	6.1	76	5.7
N	N	441	83.8	335	85.9	319	75.4	1095	81.8
N	MISSING	5	-	4	-	2	-	11	-
MISSING	P	0	-	0	-	1	-	1	-
MISSING	N	2	-	0	-	1	-	3	-

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
Group(0,12) = Females aged 9-14 years who received 2 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 12
Group(0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals HPV-16/18 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6
P: Positive
N: Negative

2. Anti-HPV-16 and anti-HPV-18 antibody response as measured by ELISA

After a peak response at Month 7, GMTs for both antibodies gradually declined until Month 18, and reached a plateau phase between Month 18 and Month 36, see also **Figure 1** and **Figure 2**.

At Month24

All initially seronegative subjects in the (0,6), (0,1,6) and (0,12) groups remained seroconverted for antibodies against HPV-16 and all initially seronegative subjects, except one subject in group (0,6), remained seroconverted for antibodies against HPV-18 as measured by ELISA (**Table 12, Table 13**).

- For group (0,6) in initially seronegative subjects, GMTs observed at Month 24 were 1488.4 EL.U/mL [95% CI: 1388.9 - 1595.1] for anti-HPV-16 antibodies and 715.8 EL.U/mL [95% CI: 659.2 - 777.1] for anti-HPV-18 antibodies.
- For group (0,12), in initially seronegative subjects, GMTs observed at Month 24 were 2183.6 EL.U/mL [95% CI: 1998.9 - 2385.5] for anti-HPV-16 antibodies and 1188.0 EL.U/mL [95% CI: 1080.2 - 1306.6] for anti-HPV-18 antibodies.
- For group (0,1,6) in initially seronegative subjects, GMTs observed at Month 24 were 1594.9 EL.U/mL [95% CI: 1433.0 - 1775.1] for anti-HPV-16 antibodies and 664.0 EL.U/mL [95% CI: 592.2 - 744.5] for anti-HPV-18 antibodies.

At Month36

All initially seronegative subjects in the (0,6), (0,1,6) and (0,12) groups remained seroconverted for antibodies against HPV-16 and all initially seronegative subjects, except one subject each in groups (0,6) and (0,1,6), remained seroconverted for antibodies against HPV-18 as measured by ELISA (**Table 12, Table 13**).

- For group (0,6) in initially seronegative subjects, GMTs observed at Month 36 were 1210.2 EL.U/mL [95% CI: 1124.8 - 1302.1] for anti-HPV-16 antibodies and 562.8 EL.U/mL [95% CI: 516.4 - 613.4] for anti-HPV-18 antibodies.
- For group (0,12), in initially seronegative subjects, GMTs observed at Month 36 were 1559.3 EL.U/mL [95% CI: 1431.2 - 1699.0] for anti-HPV-16 antibodies and 804.0 EL.U/mL [95% CI: 731.8 - 883.4] for anti-HPV-18 antibodies.
- For group (0,1,6) in initially seronegative subjects, GMTs observed at Month 36 were 1326.4 EL.U/mL [95% CI: 1193.9 - 1473.5] for anti-HPV-16 antibodies and 552.6 EL.U/mL [95% CI: 494.1 - 618.0] for anti-HPV-18 antibodies.

Table 12 Number and percentage of subjects with an anti-HPV-16 antibody titre equal to or above 8 EU/ml and GMTs (ATP cohort for immunogenicity).

					≥ cut-off				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-HPV-16 antibody	Group(0,6)	S-	PRE D0	455	0	0.0	0.0	0.8	4.0	4.0	4.0	<8.0	<8.0
			POS 2 M7	455	455	100	99.2	100	9402.9	8792.4	10055.8	266.0	58139.0
			POS 2 M12	455	455	100	99.2	100	2653.5	2473.5	2846.6	60.0	21630.0
			POS 2 M18	453	453	100	99.2	100	1730.7	1608.6	1862.0	25.0	12254.0
			POS 2 M24	454	454	100	99.2	100	1483.8	1382.1	1592.9	25.0	10598.0
			POS 2 M36	455	455	100	99.2	100	1210.2	1124.8	1302.1	23.0	7322.0
		S+	PRE D0	49	49	100	92.7	100	23.1	16.4	32.4	8.0	2437.0
			POS 2 M7	49	49	100	92.7	100	9344.1	7447.4	11723.8	1824.0	60090.0
			POS 2 M12	49	49	100	92.7	100	2754.7	2128.1	3565.6	356.0	23984.0
			POS 2 M18	48	48	100	92.6	100	1843.9	1431.3	2375.5	195.0	16321.0
			POS 2 M24	48	48	100	92.6	100	1572.9	1213.1	2039.5	187.0	11138.0
			POS 2 M36	49	49	100	92.7	100	1297.4	997.5	1687.6	167.0	8085.0
		Total	PRE D0	504	49	9.7	7.3	12.6	4.7	4.5	5.0	<8.0	2437.0
			POS 2 M7	504	504	100	99.3	100	9397.2	8812.5	10020.6	266.0	60090.0
			POS 2 M12	504	504	100	99.3	100	2663.2	2488.4	2850.2	60.0	23984.0
			POS 2 M18	501	501	100	99.3	100	1741.2	1623.2	1867.8	25.0	16321.0
			POS 2 M24	502	502	100	99.3	100	1492.1	1393.2	1597.9	25.0	11138.0
			POS 2 M36	504	504	100	99.3	100	1218.4	1135.4	1307.5	23.0	8085.0
	Group(0,12)	S-	PRE D0	339	0	0.0	0.0	1.1	4.0	4.0	4.0	<8.0	<8.0
			POS 2 M13	339	339	100	98.9	100	11329.4	10509.3	12213.5	1850.0	104272.0
			POS 2 M18	339	339	100	98.9	100	3248.2	2974.2	3547.4	308.0	61624.0
			POS 2 M24	337	337	100	98.9	100	2191.0	2003.9	2395.5	88.0	37888.0
			POS 2 M36	339	339	100	98.9	100	1559.3	1431.2	1699.0	101.0	30625.0
		S+	PRE D0	39	39	100	91.0	100	17.6	13.8	22.4	8.0	189.0
			POS 2 M13	39	39	100	91.0	100	9934.7	7770.9	12701.1	1439.0	66505.0
			POS 2 M18	39	39	100	91.0	100	2896.5	2231.7	3759.2	482.0	15169.0
			POS 2 M24	39	39	100	91.0	100	2056.7	1572.5	2690.0	293.0	9941.0
			POS 2 M36	39	39	100	91.0	100	1423.4	1112.0	1821.8	205.0	5397.0
		Total	PRE D0	378	39	10.3	7.4	13.8	4.7	4.4	4.9	<8.0	189.0
			POS 2 M13	378	378	100	99.0	100	11176.9	10403.3	12008.0	1439.0	104272.0
			POS 2 M18	378	378	100	99.0	100	3210.0	2953.8	3488.4	308.0	61624.0
			POS 2 M24	376	376	100	99.0	100	2176.7	2000.7	2368.1	88.0	37888.0
			POS 2 M36	378	378	100	99.0	100	1544.7	1424.9	1674.6	101.0	30625.0
	Group(0,1,6)	S-	PRE D0	330	0	0.0	0.0	1.1	4.0	4.0	4.0	<8.0	<8.0
			POS 3 M7	330	330	100	98.9	100	10120.2	9162.7	11177.9	389.0	120538.0
			POS 3 M12	330	330	100	98.9	100	3290.4	2956.5	3662.0	100.0	69619.0
			POS 3 M18	329	329	100	98.9	100	1931.2	1735.4	2149.1	72.0	43534.0
			POS 3 M24	326	326	100	98.9	100	1575.9	1418.2	1751.2	55.0	39098.0
			POS 3 M36	330	330	100	98.9	100	1326.4	1193.9	1473.5	42.0	31401.0
		S+	PRE D0	69	69	100	94.8	100	36.5	26.9	49.5	8.0	1174.0
			POS 3 M7	69	69	100	94.8	100	9042.5	7405.6	11041.3	908.0	77851.0
			POS 3 M12	69	69	100	94.8	100	3690.6	3000.2	4540.0	702.0	72195.0
			POS 3 M18	69	69	100	94.8	100	2148.6	1700.3	2715.1	68.0	37980.0
			POS 3 M24	68	68	100	94.7	100	1840.6	1467.2	2309.0	127.0	30545.0
			POS 3 M36	69	69	100	94.8	100	1547.2	1252.2	1911.8	267.0	21416.0
		Total	PRE D0	399	69	17.3	13.7	21.4	5.9	5.3	6.5	<8.0	1174.0
			POS 3 M7	399	399	100	99.1	100	9925.1	9080.6	10848.1	389.0	120538.0
			POS 3 M12	399	399	100	99.1	100	3356.3	3051.5	3691.6	100.0	72195.0
			POS 3 M18	398	398	100	99.1	100	1967.3	1785.6	2167.5	68.0	43534.0
			POS 3 M24	394	394	100	99.1	100	1618.7	1471.4	1780.8	55.0	39098.0
			POS 3 M36	399	399	100	99.1	100	1362.2	1239.7	1496.7	42.0	31401.0

Group(0,6) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 6
Group(0,12) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 12
Group(0,1,6) = Females aged 15-25 years who received 3 doses of Cervarix at Day 0, Month 1 and Month 6
S- = seronegative subjects (antibody titre < 8 EU/ml) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 8 EU/ml) 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 titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE D0 =Pre-vaccination at Day 0 - POS 2 M7 = Post Dose 2 Month 7 - POS 3 M7 =Post Dose 3 Month 7 - POS 2 M13 = Post Dose 2 Month 13 - POS 3 M13 =Post Dose 3 Month 13 - POS 2 M18 = Post Dose 2 Month 18 - POS 3 M18 = Post Dose 3 Month 18 - POS 2 M24 = Post Dose 2 Month 24 - POS 3 M24 = Post Dose 3 Month 24 - POS 2 M36 = Post Dose 2 Month 36 - POS 3 M36 = Post Dose 3 Month 36

Table 13 Number and percentage of subjects with an anti-HPV-18 antibody titre equal to or above 7 EU/ml and GMTs (ATP cohort for immunogenicity).

					≥ cut-off				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-HPV-18 antibody	Group(0,6)	S-	PRE D0	462	0	0.0	0.0	0.8	3.5	3.5	3.5	<7.0	<7.0
			POS 2 M7	462	462	100	99.2	100	5935.6	5519.4	6383.3	162.0	63598.0
			POS 2 M12	462	462	100	99.2	100	1523.6	1403.7	1653.7	18.0	13849.0
			POS 2 M18	459	458	99.8	98.8	100	864.6	793.1	942.7	<18.0	8817.0
			POS 2 M24	460	459	99.8	98.8	100	715.5	658.1	777.9	<18.0	6691.0
			POS 2 M36	462	461	99.8	98.8	100	562.8	516.4	613.4	<18.0	5011.0
		S+	PRE D0	38	38	100	90.7	100	15.8	11.2	22.4	7.0	822.0
			POS 2 M7	38	38	100	90.7	100	6872.8	5257.9	8983.6	1248.0	30102.0
			POS 2 M12	38	38	100	90.7	100	2040.4	1603.3	2596.7	547.0	7828.0
			POS 2 M18	38	38	100	90.7	100	1263.7	1004.4	1589.8	416.0	4556.0
			POS 2 M24	38	38	100	90.7	100	967.8	776.6	1206.2	360.0	3781.0
			POS 2 M36	38	38	100	90.7	100	813.3	649.0	1019.2	324.0	3187.0
		Total	PRE D0	500	38	7.6	5.4	10.3	3.9	3.8	4.1	<7.0	822.0
			POS 2 M7	500	500	100	99.3	100	6002.1	5596.2	6437.4	162.0	63598.0
			POS 2 M12	500	500	100	99.3	100	1557.8	1440.9	1684.2	18.0	13849.0
			POS 2 M18	497	496	99.8	98.9	100	890.1	820.0	966.2	<18.0	8817.0
			POS 2 M24	498	497	99.8	98.9	100	732.2	676.4	792.6	<18.0	6691.0
			POS 2 M36	500	499	99.8	98.9	100	578.8	533.4	628.0	<18.0	5011.0
	Group(0,12)	S-	PRE D0	355	0	0.0	0.0	1.0	3.5	3.5	3.5	<7.0	<7.0
			POS 2 M13	355	355	100	99.0	100	6580.0	6075.8	7126.0	743.0	120278.0
			POS 2 M18	355	355	100	99.0	100	1860.3	1699.4	2036.4	111.0	47030.0
			POS 2 M24	353	353	100	99.0	100	1174.7	1067.1	1293.2	42.0	28974.0
			POS 2 M36	355	355	100	99.0	100	804.0	731.8	883.4	36.0	21391.0
		S+	PRE D0	20	20	100	83.2	100	15.9	11.0	23.1	7.0	119.0
			POS 2 M13	20	20	100	83.2	100	6131.8	4447.7	8453.4	2036.0	26461.0
			POS 2 M18	20	20	100	83.2	100	1694.6	1168.3	2458.0	533.0	7582.0
			POS 2 M24	20	20	100	83.2	100	1113.8	778.8	1592.8	334.0	4195.0
			POS 2 M36	20	20	100	83.2	100	769.6	541.0	1094.8	188.0	2419.0
		Total	PRE D0	375	20	5.3	3.3	8.1	3.8	3.6	3.9	<7.0	119.0
			POS 2 M13	375	375	100	99.0	100	6555.3	6068.9	7080.6	743.0	120278.0
			POS 2 M18	375	375	100	99.0	100	1851.0	1695.9	2020.4	111.0	47030.0
			POS 2 M24	373	373	100	99.0	100	1171.4	1067.7	1285.0	42.0	28974.0
			POS 2 M36	375	375	100	99.0	100	802.1	732.6	878.3	36.0	21391.0
	Group(0,1,6)	S-	PRE D0	356	0	0.0	0.0	1.0	3.5	3.5	3.5	<7.0	<7.0
			POS 3 M7	356	356	100	99.0	100	4984.2	4543.9	5467.1	310.0	127709.0
			POS 3 M12	356	356	100	99.0	100	1491.5	1339.0	1661.4	50.0	87515.0
			POS 3 M18	355	355	100	99.0	100	830.6	742.9	928.5	24.0	45815.0
			POS 3 M24	352	352	100	99.0	100	654.3	582.9	734.5	19.0	41839.0
			POS 3 M36	356	355	99.7	98.4	100	552.6	494.1	618.0	<18.0	32273.0
		S+	PRE D0	43	43	100	91.8	100	27.8	18.8	41.0	7.0	566.0
			POS 3 M7	43	43	100	91.8	100	3961.7	3015.2	5205.2	954.0	68716.0
			POS 3 M12	43	43	100	91.8	100	1440.3	1071.4	1936.1	202.0	9267.0
			POS 3 M18	43	43	100	91.8	100	940.0	691.1	1278.6	123.0	6610.0
			POS 3 M24	42	42	100	91.6	100	827.4	619.4	1105.2	116.0	4983.0
			POS 3 M36	43	43	100	91.8	100	598.9	451.9	793.7	67.0	3728.0
		Total	PRE D0	399	43	10.8	7.9	14.2	4.4	4.1	4.7	<7.0	566.0
			POS 3 M7	399	399	100	99.1	100	4862.4	4455.0	5306.9	310.0	127709.0
			POS 3 M12	399	399	100	99.1	100	1485.9	1343.2	1643.8	50.0	87515.0
			POS 3 M18	398	398	100	99.1	100	841.8	758.2	934.5	24.0	45815.0
			POS 3 M24	394	394	100	99.1	100	670.9	602.5	747.2	19.0	41839.0
			POS 3 M36	399	398	99.7	98.6	100	557.4	502.3	618.5	<18.0	32273.0

Group(0,6) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 6
Group(0,12) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 12
Group(0,1,6) = Females aged 15-25 years who received 3 doses of Cervarix at Day 0, Month 1 and Month 6
S- = seronegative subjects (antibody titre < 8 EU/ml) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 8 EU/ml) 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 titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE D0 =Pre-vaccination at Day 0 - POS 2 M7 = Post Dose 2 Month 7 - POS 3 M7 =Post Dose 3 Month 7 - POS 2 M13 = Post Dose 2 Month 13 - POS 3 M13 =Post Dose 3 Month 13 - POS 2 M18 = Post Dose 2 Month 18 - POS 3 M18 = Post Dose 3 Month 18 - POS 2 M24 = Post Dose 2 Month 24 - POS 3 M24 = Post Dose 3 Month 24 - POS 2 M36 = Post Dose 2 Month 36 - POS 3 M36 = Post Dose 3 Month 36

Antibody persistence up to Month36

In Study HPV-070, up to Month 36, the kinetics of the antibody response to HPV-16 and HPV-18 in the 9-14 year old girls who received 2 doses of Cervarix at 0,6 months and in the 15-25 year old who received the standard 3-dose schedule at 0,1,6 months followed a similar pattern, i.e. after an initial peak response, a decline in antibody titers is observed that reached a plateau phase between Month 18 and Month 36.

Figure 1 **Persistence of HPV-16 antibody titres (ELISA) in subjects seronegative at baseline (M36 ATP cohort for immunogenicity)**

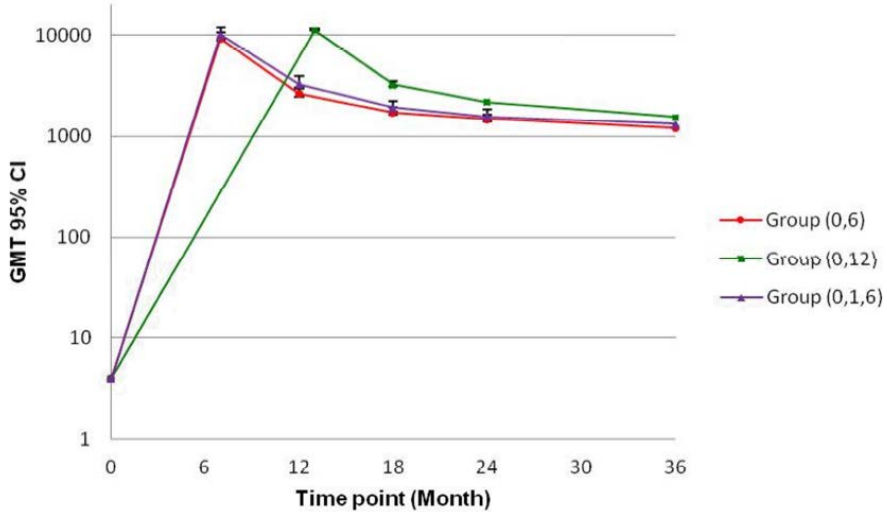
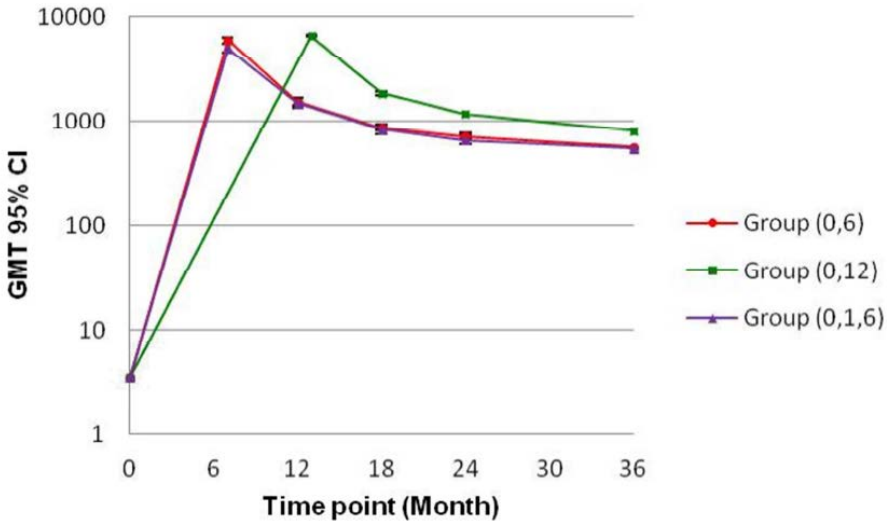


Figure 2 **Persistence of HPV-18 antibody titres (ELISA) in subjects seronegative at baseline (M36 ATP cohort for immunogenicity)**



CHMP's comment

Higher antibody titers are reached for HPV-16 than for HPV-18.

All initially seronegative subjects remained seroconverted for antibodies against HPV-16 (ELISA).

All initially seronegative subjects remained seroconverted for antibodies against HPV-18 (ELISA) except for one subject each in group (0,6) and (0,1,6).

GMT's were broadly comparable between initially seronegative and seropositive subjects, with overlapping 95%CI. In the (0,6) group, HPV-18 titers were higher in the S+ subjects compared to the S- subjects.

At all time points, a wide range was observed between the minimum and maximum GMT's.

The antibody kinetics are similar for the three schedules, with a slightly better antibody persistence in the (0,12) schedule.

3. 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 CMI testing.

At Month24

At Month 24, all (100%) of the initially seronegative subjects in all three groups [group (0,6), group (0,12) and group (0,1,6)] had seroconverted for anti-HPV-16 neutralising antibodies, and at least 97.8% of the initially seronegative subjects had seroconverted for anti-HPV-18 neutralising antibodies when measured by PBNA (**Table 14**, **Table 15**).

- For group (0,6), in initially seronegative subjects, GMTs observed at Month 24 were 6082.8 ED50 [95% CI: 5026.9 - 7360.5] for anti-HPV-16 neutralising antibodies and 2732.2 ED50 [95% CI: 2188.7 - 3410.7] for anti-HPV-18 neutralising antibodies.
- For group (0,12), in initially seronegative subjects, GMTs observed at Month 24 were 9964.3 ED50 [95% CI: 8169.7 - 12153.0] for anti-HPV-16 neutralising antibodies and 5373.2 ED50 [95% CI: 4340.4 - 6651.8] for anti-HPV-18 neutralising antibodies.
- For group (0,1,6), in initially seronegative subjects, GMTs observed at Month 24 were 7167.6 ED50 [95% CI: 5323.1 - 9651.3] for anti-HPV-16 neutralising antibodies and 2524.6 ED50 [95% CI: 1845.8 - 3453.2] for anti-HPV-18 neutralising antibodies.

Table 14 Number and percentage of subjects with an anti-HPV-16 Pseudovirion Ab titre equal to or above 40 ED50 and GMTs (M36 ATP cohort for immunogenicity)

					>= 40 ED50				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-HPV-16 neutra antibody	Group(0,6)	S-	PRE D0	95	0	0.0	0.0	3.8	20.0	20.0	20.0	<40.0	<40.0
			POS 2 M7	95	95	100	96.2	100	83050.3	67288.0	102505.0	5399.0	655360.0
			POS 2 M12	95	95	100	96.2	100	14721.3	11888.1	18229.7	1660.0	149857.0
			POS 2 M18	94	94	100	96.2	100	7351.0	5940.5	9096.5	520.0	152406.0
			POS 2 M24	95	95	100	96.2	100	6114.5	5030.7	7431.9	495.0	56200.0
			POS 2 M36	95	95	100	96.2	100	7660.2	6131.7	9569.7	626.0	77479.0
		S+	PRE D0	1	1	100	2.5	100	9582.0	-	-	9582.0	9582.0
			POS 2 M7	1	1	100	2.5	100	76203.0	-	-	76203.0	76203.0
			POS 2 M12	1	1	100	2.5	100	39159.0	-	-	39159.0	39159.0
			POS 2 M18	1	1	100	2.5	100	12718.0	-	-	12718.0	12718.0
			POS 2 M24	1	1	100	2.5	100	29891.0	-	-	29891.0	29891.0
			POS 2 M36	1	1	100	2.5	100	27441.0	-	-	27441.0	27441.0
		Total	PRE D0	96	1	1.0	0.0	5.7	21.3	18.8	24.2	<40.0	9582.0
			POS 2 M7	96	96	100	96.2	100	82975.9	67377.4	102185.6	5399.0	655360.0
			POS 2 M12	96	96	100	96.2	100	14872.1	12025.5	18392.4	1660.0	149857.0
			POS 2 M18	95	95	100	96.2	100	7393.6	5986.6	9131.1	520.0	152406.0
			POS 2 M24	96	96	100	96.2	100	6216.5	5111.0	7561.1	495.0	56200.0
			POS 2 M36	96	96	100	96.2	100	7762.7	6218.6	9690.1	626.0	77479.0
	Group(0,12)	S-	PRE D0	88	0	0.0	0.0	4.1	20.0	20.0	20.0	<40.0	<40.0
			POS 2 M13	88	88	100	95.9	100	74848.0	60521.9	92565.1	3240.0	655360.0
			POS 2 M18	88	88	100	95.9	100	16576.6	13127.4	20932.0	1027.0	174798.0
			POS 2 M24	87	87	100	95.8	100	10003.7	8114.1	12333.4	639.0	85250.0
			POS 2 M36	88	88	100	95.9	100	9214.3	7112.3	11937.5	343.0	99886.0
		Total	PRE D0	88	0	0.0	0.0	4.1	20.0	20.0	20.0	<40.0	<40.0
			POS 2 M13	88	88	100	95.9	100	74848.0	60521.9	92565.1	3240.0	655360.0
			POS 2 M18	88	88	100	95.9	100	16576.6	13127.4	20932.0	1027.0	174798.0
			POS 2 M24	87	87	100	95.8	100	10003.7	8114.1	12333.4	639.0	85250.0
			POS 2 M36	88	88	100	95.9	100	9214.3	7112.3	11937.5	343.0	99886.0
	Group(0,1,6)	S-	PRE D0	85	0	0.0	0.0	4.2	20.0	20.0	20.0	<40.0	<40.0
			POS 3 M7	85	85	100	95.8	100	32578.5	24651.7	43054.1	330.0	655360.0
			POS 3 M12	85	85	100	95.8	100	16197.1	12186.6	21527.5	823.0	502234.0
			POS 3 M18	85	85	100	95.8	100	8037.1	5976.7	10807.9	128.0	192531.0
			POS 3 M24	85	85	100	95.8	100	7136.9	5232.0	9735.4	91.0	196507.0
			POS 3 M36	85	85	100	95.8	100	5035.0	3726.9	6802.0	149.0	130444.0
		S+	PRE D0	7	7	100	59.0	100	165.2	75.5	361.5	45.0	543.0
			POS 3 M7	7	7	100	59.0	100	20137.3	10240.3	39599.8	8947.0	58828.0
			POS 3 M12	7	7	100	59.0	100	11706.0	4251.7	32229.2	2800.0	79779.0
			POS 3 M18	7	7	100	59.0	100	11267.9	3694.4	34367.4	3243.0	117679.0
			POS 3 M24	7	7	100	59.0	100	9056.9	3255.6	25195.5	1640.0	73141.0
			POS 3 M36	7	7	100	59.0	100	5425.6	1521.2	19352.1	1508.0	92180.0
		Total	PRE D0	92	7	7.6	3.1	15.1	23.5	20.7	26.6	<40.0	543.0
			POS 3 M7	92	92	100	96.1	100	31407.6	24181.5	40793.0	330.0	655360.0
			POS 3 M12	92	92	100	96.1	100	15801.8	12069.8	20687.8	823.0	502234.0
			POS 3 M18	92	92	100	96.1	100	8246.4	6224.6	10925.0	128.0	192531.0
			POS 3 M24	92	92	100	96.1	100	7267.5	5423.4	9738.6	91.0	196507.0
			POS 3 M36	92	92	100	96.1	100	5063.7	3800.4	6746.9	149.0	130444.0

Table 15 Number and percentage of subjects with an anti-HPV-18 Pseudovirion Ab titre equal to or above 40 ED50 and GMTs (M36 ATP cohort for immunogenicity)

					>= 40 ED50				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-HPV-18 neutra antibody	Group(0,6)	S-	PRE D0	95	0	0.0	0.0	3.8	20.0	20.0	20.0	<40.0	<40.0
			POS 2 M7	95	95	100	96.2	100	24539.8	20524.9	29340.2	1772.0	302537.0
			POS 2 M12	95	95	100	96.2	100	5828.3	4684.9	7250.7	337.0	67096.0
			POS 2 M18	94	94	100	96.2	100	3878.4	3092.4	4864.1	207.0	44518.0
			POS 2 M24	95	95	100	96.2	100	2790.2	2232.1	3487.7	252.0	32106.0
			POS 2 M36	94	94	100	96.2	100	2365.5	1868.2	2995.2	141.0	30300.0
		S+	PRE D0	1	1	100	2.5	100	3795.0	-	-	3795.0	3795.0
			POS 2 M7	1	1	100	2.5	100	76762.0	-	-	76762.0	76762.0
			POS 2 M12	1	1	100	2.5	100	23892.0	-	-	23892.0	23892.0
			POS 2 M18	1	1	100	2.5	100	28906.0	-	-	28906.0	28906.0
			POS 2 M24	1	1	100	2.5	100	20933.0	-	-	20933.0	20933.0
			POS 2 M36	1	1	100	2.5	100	17856.0	-	-	17856.0	17856.0
		Total	PRE D0	96	1	1.0	0.0	5.7	21.1	19.0	23.5	<40.0	3795.0
			POS 2 M7	96	96	100	96.2	100	24833.1	20777.0	29681.1	1772.0	302537.0
			POS 2 M12	96	96	100	96.2	100	5914.5	4756.0	7355.4	337.0	67096.0
			POS 2 M18	95	95	100	96.2	100	3961.2	3153.8	4975.4	207.0	44518.0
			POS 2 M24	96	96	100	96.2	100	2849.4	2276.0	3567.2	252.0	32106.0
			POS 2 M36	95	95	100	96.2	100	2416.4	1905.9	3063.5	141.0	30300.0
	Group(0,12)	S-	PRE D0	88	0	0.0	0.0	4.1	20.0	20.0	20.0	<40.0	<40.0
			POS 2 M13	88	88	100	95.9	100	39994.7	33327.2	47996.1	6932.0	552059.0
			POS 2 M18	88	88	100	95.9	100	9495.4	7744.4	11642.2	1067.0	127675.0
			POS 2 M24	87	87	100	95.8	100	5464.1	4377.8	6819.8	402.0	140195.0
			POS 2 M36	88	88	100	95.9	100	4046.4	3278.0	4994.8	609.0	82372.0
		Total	PRE D0	88	0	0.0	0.0	4.1	20.0	20.0	20.0	<40.0	<40.0
			POS 2 M13	88	88	100	95.9	100	39994.7	33327.2	47996.1	6932.0	552059.0
			POS 2 M18	88	88	100	95.9	100	9495.4	7744.4	11642.2	1067.0	127675.0
			POS 2 M24	87	87	100	95.8	100	5464.1	4377.8	6819.8	402.0	140195.0
			POS 2 M36	88	88	100	95.9	100	4046.4	3278.0	4994.8	609.0	82372.0
	Group(0,1,6)	S-	PRE D0	86	0	0.0	0.0	4.2	20.0	20.0	20.0	<40.0	<40.0
			POS 3 M7	86	86	100	95.8	100	14225.5	11058.3	18299.8	291.0	277779.0
			POS 3 M12	86	86	100	95.8	100	4866.2	3626.4	6530.0	103.0	49445.0
			POS 3 M18	86	86	100	95.8	100	2954.5	2183.7	3997.5	56.0	84558.0
			POS 3 M24	86	84	97.7	91.9	99.7	2485.0	1799.4	3431.8	<40.0	62886.0
			POS 3 M36	86	86	100	95.8	100	1881.4	1417.7	2496.7	56.0	62025.0
		S+	PRE D0	6	6	100	54.1	100	110.2	59.8	203.1	55.0	248.0
			POS 3 M7	6	6	100	54.1	100	10373.6	5623.6	19135.6	5368.0	20526.0
			POS 3 M12	6	6	100	54.1	100	9031.6	2499.0	32641.0	1085.0	31538.0
			POS 3 M18	6	6	100	54.1	100	3010.5	725.2	12497.0	441.0	14964.0
			POS 3 M24	6	6	100	54.1	100	3160.4	1152.9	8663.7	1105.0	10339.0
			POS 3 M36	6	6	100	54.1	100	3420.1	884.6	13223.3	1124.0	28157.0
		Total	PRE D0	92	6	6.5	2.4	13.7	22.4	20.4	24.5	<40.0	248.0
			POS 3 M7	92	92	100	96.1	100	13935.6	10991.0	17669.0	291.0	277779.0
			POS 3 M12	92	92	100	96.1	100	5066.5	3818.9	6721.7	103.0	49445.0
			POS 3 M18	92	92	100	96.1	100	2958.2	2213.9	3952.6	56.0	84558.0
			POS 3 M24	92	90	97.8	92.4	99.7	2524.3	1860.4	3425.2	<40.0	62886.0
			POS 3 M36	92	92	100	96.1	100	1956.2	1488.5	2570.7	56.0	62025.0

CHMP's comment

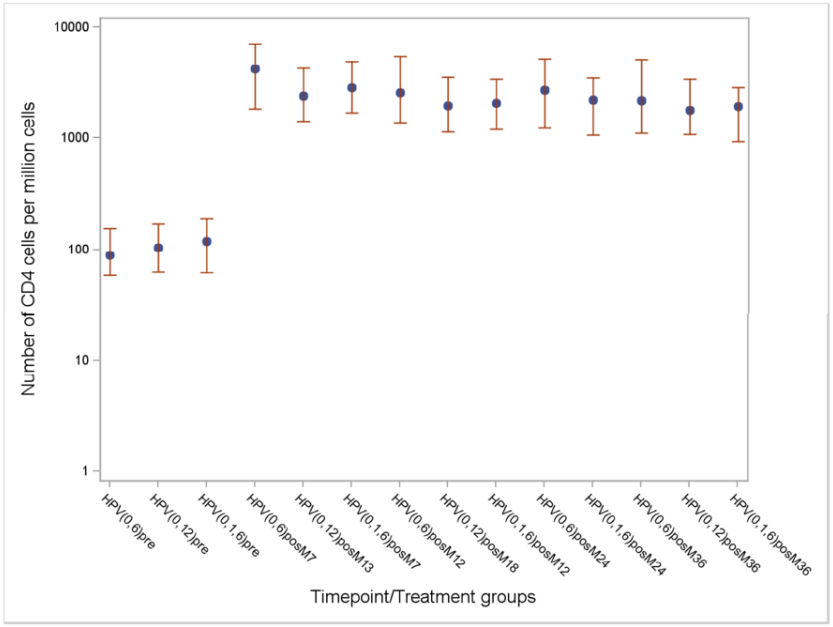
All initially S- subjects in all groups had seroconverted for both HPV-types at M36.

4. Cell-mediated immunity

T-cell response

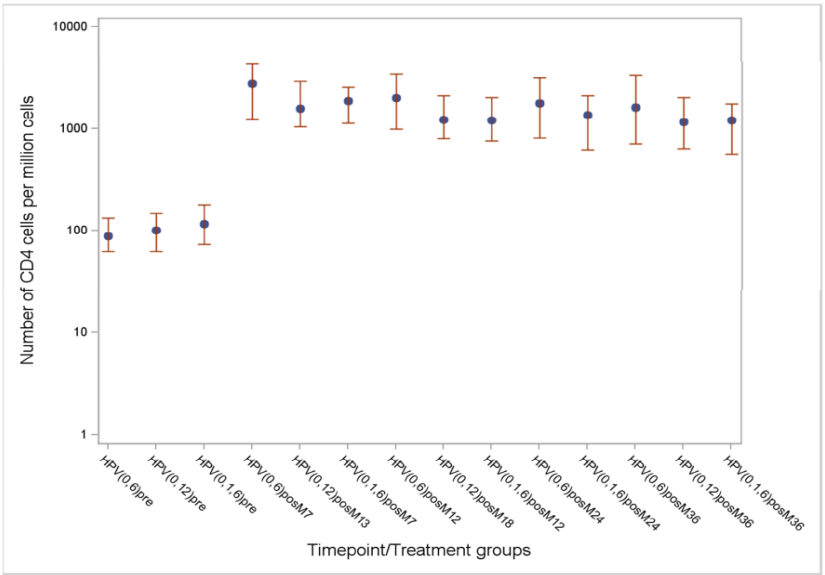
CD4+ and CD8+ T cells specific to HPV-16/18/31/45 were evaluated using Intracellular Cytokine Staining (ICS) assay at M24 and M36 in a subcohort of subjects (cfr PBNA). No substantial HPV-16/18/31/45 specific CD8+ T cell responses were detected at M24 and M36. The HPV-16/18/31/45 specific CD4+ T cell responses (median frequency of specific CD4+ cells expressing at least two different cytokines [all doubles]) are graphically presented in **Figure 3** to **Figure 6**, respectively.

Figure 3 CD4+ all doubles response by Intracellular cytokine staining to HPV-16 (M36 ATP cohort for immunogenicity)



HPV(0,6) = Group (0,6) = Females aged 9-14 years who received 2 doses of *Cervarix* at Day 0 and Month 6
HPV(0,12) = Group (0,12) = Females aged 9-14 years who received 2 doses of *Cervarix* at Day 0 and Month 12
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
pre = pre-vaccination at day 0; POS M7 = Post Dose 2/3 Month 7; POS M12 = Post Dose 2/3 Month 12; POS M13 = Post Dose 2 Month 13; POS M18 = Post Dose 2 Month 18; POS M24 = Post Dose 2/3 Month 24; POS M36 = Post Dose 2/3 Month 36

Figure 4 CD4+ all doubles response by Intracellular cytokine staining to HPV-18 (M36 ATP cohort for immunogenicity)



HPV(0,6) = Group (0,6) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 6
HPV(0,12) = Group (0,12) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 12
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
pre = pre-vaccination at day 0; pos = post-vaccination at Month 7 for Group (0,6) and Group (0,1,6), at Month 13 for Group (0,12) and at Month 12 for Group (0,6) and Group (0,1,6)

Figure 5 CD4+ all doubles response by Intracellular cytokine staining to HPV-31 (M36 ATP cohort for immunogenicity)

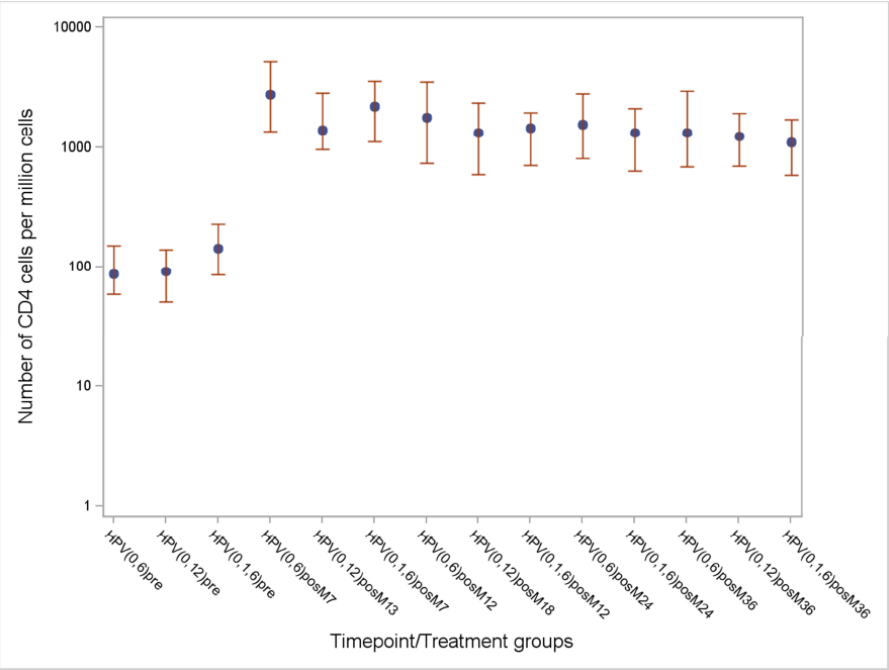
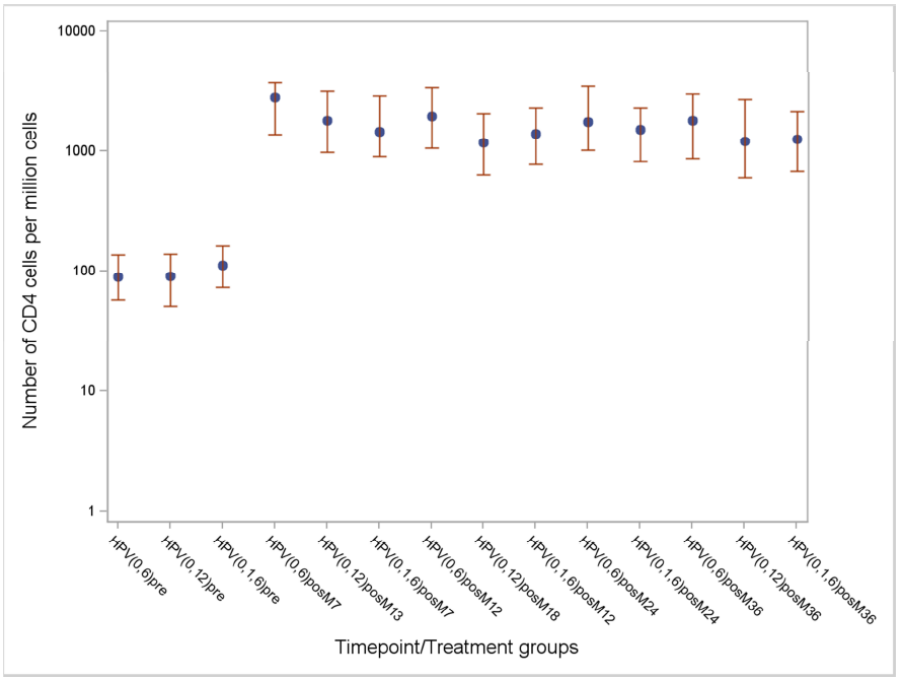


Figure 6 **CD4+ all doubles response by Intracellular cytokine staining to HPV-45 (M36 ATP cohort for immunogenicity)**



CD4+ T cell response above threshold by pre-vaccination status

In the M36 ATP cohort for immunogenicity,

- in group (**0,6**), the percentage of initially seronegative subjects with a specific CD4+ T-cell response (all doubles) above the threshold was at least 94% for HPV-16/18/31/45. The percentage of initially seropositive subjects with a specific CD4+ T-cell response (all doubles) above the threshold was 85.7% for HPV-16, 90% for HPV-18, 75% for HPV-31 and 100% for HPV-45.

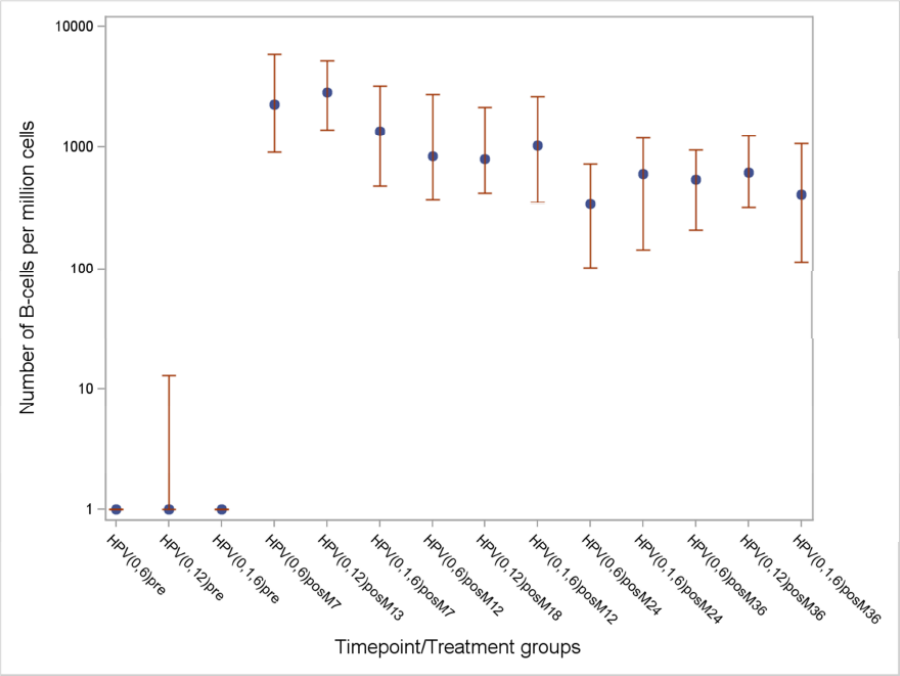
- in group (0,12), the percentage of initially seronegative subjects with a specific CD4+ T-cell response (all doubles) above the threshold was at least 94% for HPV-16/18. The percentage of initially seropositive subjects with a specific CD4+ T-cell response (all doubles) above the threshold was 85.7%for HPV-16 and 100% for HPV-18.
- in group (0,1,6), the percentage of initially seronegative subjects with a specific CD4+ T-cell response (all doubles) above the threshold was about 93% for HPV-16/18 and at least 85% for HPV-31/45. The percentage of initially seropositive subjects with a specific CD4+ T-cell response (all doubles) above the threshold was 100% for HPV-16, 84.6% for HPV-18, 71.4% for HPV-31 and 83.3% for HPV-45.

Memory B-cell response

- B cell responses to HPV-16/18/31/45 were evaluated using the B cell Elispot assay at M24 and M36 in a subcohort of subjects (cfr PBNA), see Figure 7 to

Figure 10.

Figure 7 Memory B-cell response to HPV-16 by B-cell ELISPOT (M36 ATP cohort for immunogenicity)



HPV(0,6) = Group (0,6) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 6
HPV(0,12) = Group (0,12) = Females aged 9-14 years who received 2 doses of Cervarix at Day 0 and Month 12
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
pre = pre-vaccination at day 0; pos = post-vaccination at Month 7 for Group (0,6) and Group (0,1,6), at Month 13 for Group (0,12) and at Month 12 for Group (0,6) and Group (0,1,6)

Figure 8 **Memory B-cell response to HPV-18 by B-cell ELISPOT (M36 ATP cohort for immunogenicity)**

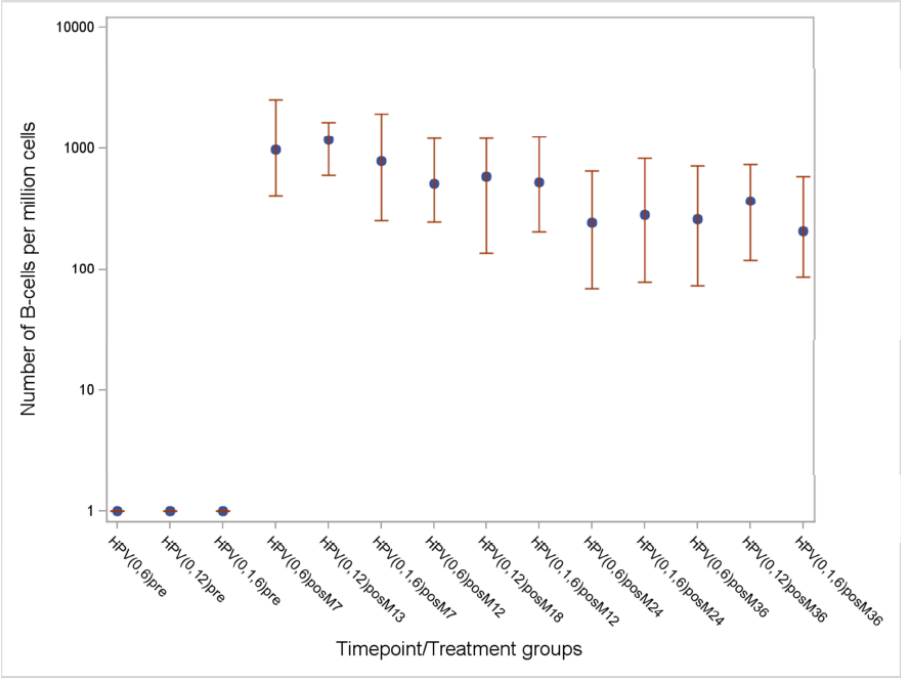


Figure 9 **Memory B-cell response to HPV-31 by B-cell ELISPOT (M36 ATP cohort for immunogenicity)**

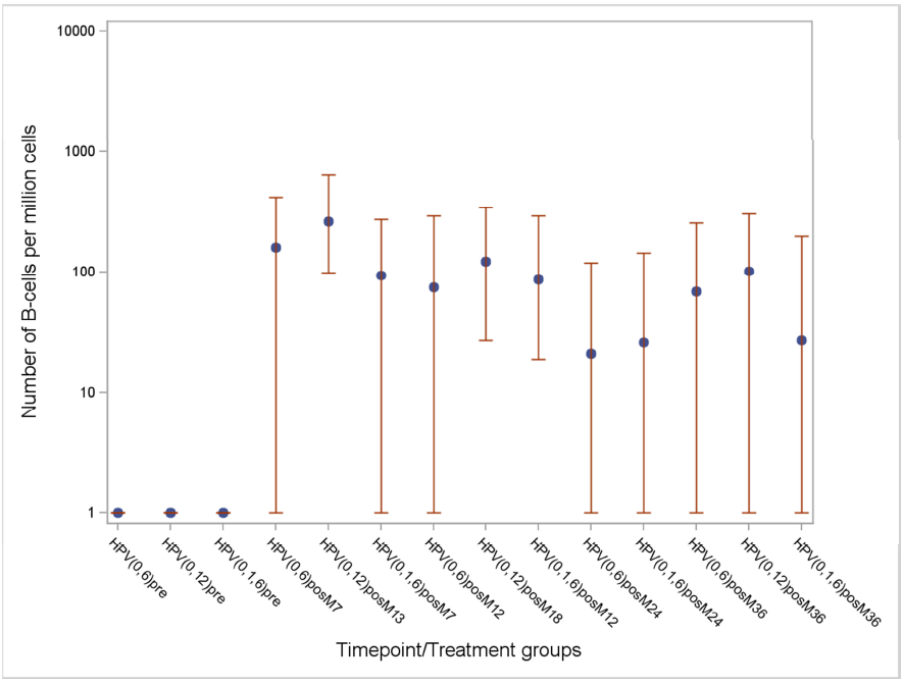
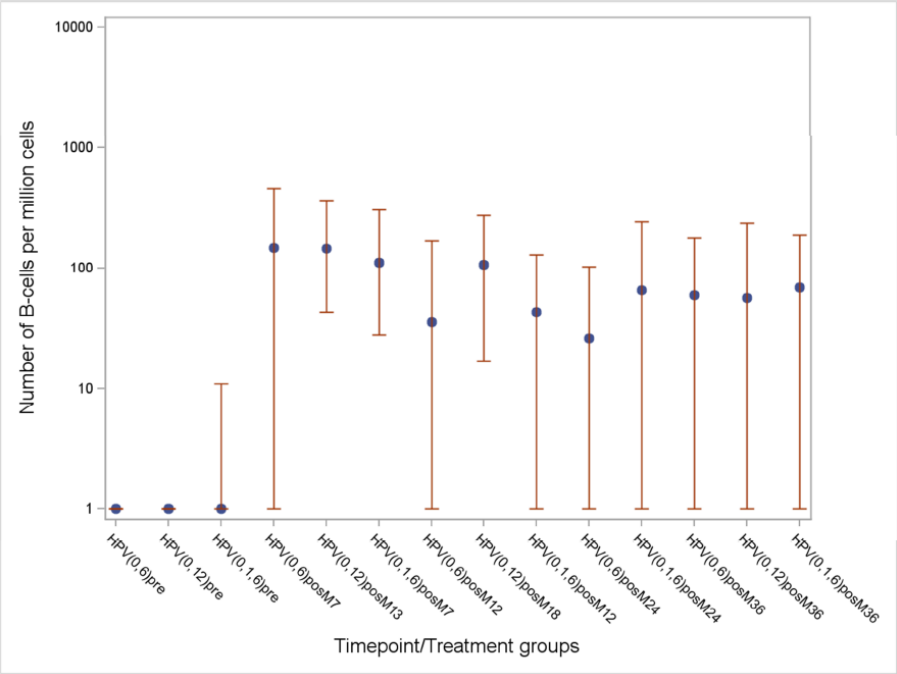


Figure 10 **Memory B-cell response to HPV-45 by B-cell ELISPOT (M36 ATP cohort for immunogenicity)**



Memory B cell response above threshold by pre-vaccination status

In the M36 ATP cohort for immunogenicity,

- in group (**0,6**), the percentage of initially seronegative subjects with a specific memory B-cell response (all doubles) above the threshold of 0 cells per million cells was about 80% for HPV-16/18 and about 60% for HPV-31/45. The percentage of initially seropositive subjects with a specific CD4+ T-cell response (all doubles) above the threshold above the threshold was 100% for HPV-16, 88.9% for HPV-18, 50% for HPV-31 and 66.7% for HPV-45.
- in group (0,12), the percentage of initially seronegative subjects with a specific CD4+ T-cell response (all doubles) above the threshold of 0 cells per million cells was at least 95.5% for HPV-16 and 84.7% for HPV-18. The percentage of initially seropositive subjects with a specific CD4+ T-cell response (all doubles) above the threshold was 83.3%for HPV-16 and 100% for HPV-18.
- in group (0,1,6), the percentage of initially seronegative subjects with a specific CD4+ T-cell response (all doubles) above the threshold of 0 cells per million cells was about 90% for HPV-16/18, 53.3% for HPV-31 and 65.6% for HPV-45. The percentage of initially seropositive subjects with a specific CD4+ T-cell response (all doubles) above the threshold was 61.5% for HPV-16, 75% for HPV-18, 71.4% for HPV-31 and 66.7% for HPV-45.

2.5. Clinical safety

2.5.1. Methods

Previously in AR721/II/0048 ((Day 0 to Month 6/7) and AR721/II/0058 ((Day 0 to Month 18), no new safety information were collected in studies HPV-070 and HPV-048, the occurrence of adverse reactions was in line with the current information in the SmPC.

Safety data from study HPV-008 have extensively been discussed in previously approved variations II-11 (event-driven final analysis) and II-22 (Month 48 analysis, end of the study) and are not the object of the current variation application.

Safety is evaluated in this final Study report HPV-070 up to Month 36.

Safety results from Study HPV-070 23 month after the last vaccination in the 2-dose [Group (0,12)] and up to Month 36 (30 months after the last vaccination) in the 2-dose [Group (0,6)] and the 3-dose [Group (0,1,6)] were presented and discussed by the MAH.

The analysis of safety presented was performed on the Total Vaccinated Cohort TVC (primary analysis). The primary analysis was complemented by an analysis based on the According-To-Protocol ATP cohort for safety which is presented in the HPV-070 (Month 36) Clinical Study Report CSR.

In Study HPV-070, the following safety parameters were assessed at months 24 and 36 :

- Serious adverse events (SAEs) (up to Month 36)
- Medically significant conditions (up to Month 36)
- Potential immune-mediated diseases (up to Mo 36)
- Pregnancies and pregnancy outcomes (up to Mo 36)

2.5.2. Results

1.Serious adverse events and deaths

No fatal SAEs were reported up to the Follow-up 2 & 3 Epoch (Day 0 to Month 24/36) of Study HPV-070.

Up to mo 13, 47 non-fatal SAEs were reported for 38 subjects (12 (2.2%) subjects in [Group (0,6)], 11 (2.7%) subjects in [Group (0,12)] and 15 (3.1%) subjects (3.1%) in [Group (0,1,6)].None of these SAEs were considered by the investigator to have a possible causal relationship to vaccination. All SAEs resolved without sequelae except for 2 events (1 event of autoimmune thyroiditis and type 1 diabetes mellitus), reported for one same subject in [Group (0,6)] during the primary epoch, which were not recovered/resolved.

During the follow-up period up to Month 24 (TVC), 53 subjects reported at least one SAE (none were fatal), and 326 subjects reported at least one medically significant conditions (MSCs). During the follow-up period up from Month 18 to Month 24 (Month 24 TVC), 16 subjects reported at least one SAE (none were fatal), and 81 subjects reported at least one MSC.

One SAE [systemic lupus erythematosus] reported by one subject (last visit final diagnosis was SLE, the sponsor adjusted pIMD) in group[0,12] was considered by the investigator as causally related to vaccination. The SAE was not recovered/resolved at the Month 36 time point. None of the other SAEs were considered to be causally related to vaccination by the investigator.

Severe - grade 3 systemic lupus erythematosus

Narrative: This 10-year-old female subject was enrolled in an open label study titled A Phase IIIb openlabel,randomised, multi-centre primary immunization study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine when administered intramuscularly according to alternative 2-dose schedules in 9 - 14 year old healthy females compared to the standard 3-dose schedule for GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine in 15 - 25 year old healthy females.The subject received the 1st dose of Human papilloma type 16 + 18 vaccine
(intramuscular) for prophylaxis.
Two hundreds and sixty four days after receiving Human papilloma type 16 + 18 vaccine the subject developed
severe - grade 3 systemic lupus erythematosus. Serious criteria included GSK medically significant and clinically significant/intervention required. The subject was treated with methotrexate and folic acid. Human papilloma type 16 + 18 vaccine was interrupted. The outcome of systemic lupus erythematosus was not recovered/not resolved.
The investigator considered that there was a reasonable possibility that the systemic lupus erythematosus may have been caused by Human papilloma type 16 + 18 vaccine.
Relevant Tests:

Blood ana profile : profile, blood anti centreomere protein B : Negative, blood anti DSDNA : less than 100 IU/mL (less than 100), blood anti histones : negative, blood anti Jo-1 : negative, blood anti nucleosomes : negative, blood anti RNP/SM : weakly positive, blood anti ro-52 recombinant : negative, blood anti sm : weakly positive, blood anti ss-aantive (60kda) ; negative, blood antinuclear ab : 160 (less than 80).

PLT smear : adequate, RBC morpho : normochromia, urine SP.GR : 1.009 (1.003-1.030), urine transparency : clear, blood urea/ratio : 9.5, urine color (chromaturia) : yellow.

Blood ovalocyte : few, PLT smear : adequate, blood sqamous epithelial cell : 0-1/hpf, urea/ration : 13.3, blood microcyte : 1+, urine SP.GR : 1.008 (1.003-1.030), urine transparency : clear, bllod Anisocytosis : +1, urine color (chromaturia) : pale yellow.

Investigator comments :
The subject followed up last visit and had SLE diagnosis.
Subject received first dose of vaccine project.
Height months after the first dosethe subject had pain at right knee and consult orthopidic and then work up Lab.
Diagnosis was suspected Fronsient synovitis.
Nine months after the first dose: the subject followed up other hospital and started medicines for disease.
Ten months after the first dose: the subject followed up per protocol for examination and postponed vaccination.
Sixteen months after the first dose: followed up by phone.Her mother sent summery lab and treament to site.
Thirty five months after the 1st dose last visit final diagnosis was SLE, The sponsor adjusted PIMD.
Subject still has got symptom .
Additional information received:
No additional symptoms and laboratory tests are available to confirm the diagnosis. The event is ongoing and not resolved.
This case contains an event assessed by the investigator as a serious possible immune mediated disorder (pIMD).
SLE with TTO of 10 months, no medical details were provided, TFUQ was requested, but no relevant infor could be obtained

During the follow-up period up to Month 36 (TVC), 69 subjects reported at least one SAE (none were fatal), and 374 subjects reported at least one MSC. During the follow-up period up from Month 24 to Month 36 (Month 36 TVC), 21 subjects reported at least one SAE (none were fatal), and 114 subjects reported at least one MSC.

2. Other significant adverse events

2.1. 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.
Up to the secondary active epoch, 489 MSCs were reported for 284 subjects: 99 (18.0%) subjects in [Group (0,6)], 61 (11.4%) subjects in [Group (0,12)] and 124 (25.7%) subjects in [Group (0,1,6)].

2.2. 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.

Up to the secondary active epoch, 8 pIMDS were reported for 6 subjects (2 subjects in each group). Except for one (VIIth nerve paralysis), none of the pIMDS had resolved by the Month 13 data lock point. None of the 8 pIMDS, except one, were considered by the investigator to have a possible causal relationship to vaccination. VIIth nerve paralysis, a non-serious pIMD reported for 1 subject (0.2%) in [Group (0,1,6)], was considered by the investigator to have a possible causal relationship to vaccination and had resolved without sequelae. Note that autoimmune thyroiditis and type I diabetes mellitus reported for one subject in [Group (0,6)] were also reported as SAEs.

Reports of the pIMDs are presented below except the SLE case.

- **Type 1 diabetes mellitus and Autoimmune thyroiditis**

Serious Events: Type 1 diabetes mellitus and Autoimmune thyroiditis
Narrative: This female subject was enrolled in the prophylactic open study 114700 (HPV-070).
She received the 1st dose of Human papillomavirus type 16 and 18 vaccine (HPV).
Two months after the 1st dose of HPV 16-18,
this 14-year-old subject developed insulin-dependent diabetes mellitus and Hashimoto thyreoiditis. The subject was hospitalised. The subject was treated with dextrose + electrolytes + insulin, human insulin and insulin. The events were unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the insulin-dependent diabetes mellitus and Hashimoto thyreoiditis may have been caused by HPV 16-18.
Investigator Comments:
Three months after the 1st dose blood exams were performed due to polyuria, polydipsia, polyphagia and weight
loss. Symptoms started about one month before. The exams showed hyperglycemia (glucose: 289 mg/dL) and ketonuria. The subject was hospitalized, and discharged
with diagnosis of Diabetes Mellitus Insulin-Dependent and Hashimoto Thyroiditis. The subject was discharged in therapy with Insulin in glycemic control. During hospitalization a goiter and positivity of Antibody anti-TPO were observed, so a thyroid echography was performed that showed inhomogeneity echostructural and pseudonodular lesion. No end date of SAEs are expected since they are chronic diseases; there is no family history of autoimmune disease; subject did not have any medical history or medical condition that could have contributed to the SAEs
This case contains two events assessed by the investigator as serious possible immune mediated disorders (pIMD).

- **Autoimmune thyroiditis**

Non-Serious Events: Autoimmune thyroiditis
Narrative: This female subject was enrolled in the prophylactic open study 114700 (HPV-070).
She received the 1st and 2nd dose of Human papillomavirus type 16 and 18 vaccine (HPV).
Seven months after the 1st dose of HPV 16-18, this 15-year-old subject developed
hashimoto thyreoiditis. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the hashimoto thyreoiditis may have been caused by HPV 16-18.
Investigator Comments:
Two months after the second dose subject performed TSH (2.3) AbTG (16) TPO:274, she was diagnosed with Hashimoto
Thyroiditis with preserced thyroid functions. No other symptoms, no familiar history, no concomitant medications/diseases that could have concurred to the pathology. No therapy given for the moment.
Additional information received:
thyroid tests were performed since subject had dysmenorrea, hence the request to perform tests.
Additional information received:
the start date (1st signs and symptoms) was 6 months after the 1st dose.
This case contains an event assessed by the investigator as a non-serious possible immune mediated disorder (pIMD).

- **VIIth nerve paralysis**

Non-Serious Events: **VIIth nerve paralysis**
Narrative: This female subject was enrolled in the prophylactic open study 114700 (HPV-070).
She received the 1st dose of Human papillomavirus type 16 and 18 vaccine (HPV).
Eighteen days after the 1st dose of HPV 16-18, this 21-year-old subject developed Bell's paralysis. The subject was treated with betamethasone, pantoprazole, Amoxicillin + clavulanate potassium, thioctic acid and ketoprofen. The event resolved the same month. The investigator considered that there was a reasonable possibility that the bell's paralysis may have been caused by HPV 16-18.
Investigator Comments:
The month she received the 1st dose the patient started to feel otalgia at the left ear and weakness in correspondance of the
left side of the forehead, of the eyelid and of the mouth. The day after this weakness became worse. She wasn t able to move the left side of the mouth and of the forehead and to close the left eye. She was visited by her physician that prescribed her one injection of betametasone (4mg), and an oral therapy of betametasone for two days (5mg/day). She didn t start the oral therapy but she continued with betametasone injection for other 5 days, she also started amoxicillin-clavulanate and alpha lipoic acid. To treat the otalgia the physician prescribed her oral ketoprofene 25mg. The same month of the 1st dose resolution of the otalgia. The next days improvement of the palsy.
The month of the 1st dose she had a neurologic visit that confirmed the diagnosis and prescribed to stop the therapies. The month of the 1st dose resolution of the palsy. She didn t do blood exam, CSF analysis or instrumental
investigations (MRI, EMG,CT). I visited the patient the month after the 1st dose and the paralisis was completely resolved. We consider the AE only temporarily linked to the vaccine administration. No history of demyelinating diseases, immunomediated diseases, autoimmune diseases; no similar symptoms in the past; no history of head trauma or cranial tumors; she doesn' t live in a region with endemic lyme disease; no documentated recent viral infection but the patient refers otalgy as symptom preceding the palsy. No family history of similar or other immunomediated/autoimmune disorder.
Additional information received:
The event didn't occur after next doses.
This case contains an event assessed by the investigator as a non-serious possible immune mediated disorder (pIMD).
Unlikely as event did not reoccur after next doses (confirmation needed).

Withdrawals due to adverse events /serious adverse events:
There was one withdrawal due to a non-serious adverse event in the group (0,12) at Month 12 (this subject was diagnosed with coeliac disease). There were no additional withdrawals due to SAEs during the course of the study.

5. Pregnancies and pregnancy outcomes
During the primary active epoch (Day 0 to Month 7), a total of 9 pregnancies were reported in Group (0,1,6). 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.

A total of 25 pregnancies were reported (1 in [Group (0,12)] and 24 in [Group (0,1,6)]) during the secondary active epoch (Day 0 to Month 13). Four (16.7%) of these pregnancies were ongoing at the time of the Month 13 data lock point. Eighteen (1 in [Group (0,12)] and 17 in [Group (0,1,6)] pregnancies resulted in a live infant with no apparent congenital anomaly. One (4.2%) subject had an ectopic pregnancy, one (4.2%) subject underwent an elective termination with no apparent congenital anomaly and one (4.2%) subject had a still birth with no apparent congenital anomaly, all in [Group (0,1,6)].

A total of 36 pregnancies were reported (TVC), [one pregnancy each in groups (0,6) and (0,12), and 34 in group (0,1,6)] up to Month 36. Of these, 32 pregnancies resulted in a live infant with no apparent congenital anomaly. There was one ectopic pregnancy, two elective terminations and one

stillbirth [all reported in group (0,1,6)], none of which were considered to be causally related to the vaccination by the investigator.

Table 20 Number of pregnancies and outcomes reported up to Month 36 (Total vaccinated cohort)

	Group(0,6) N = 1		Group(0,12) N = 1		Group(0,1,6) N = 34	
Categories	**n**	**%**	**n**	**%**	**n**	**%**
Ectopic pregnancy	0	0.0	0	0.0	1	2.9
Elective termination No apparent CA	0	0.0	0	0.0	2	5.9
Live Infant No apparent CA	1	100	1	100	30	88.2
Stillbirth No apparent CA (>22 wks)	0	0.0	0	0.0	1	2.9

Group(0,6) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 6
Group(0,12) = Females aged 9-14 years who received 2 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine at Day 0 and Month 12
Group(0,1,6) = Females aged 15-25 years who received 3 doses of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine at Day 0, Month 1 and Month 6
N = number of pregnancies
n = number of pregnancies in a given category
% = n / Number of pregnancies with available results x 100

2.5.3. Discussion on clinical aspects

Efficacy

The purpose of this study HPV-070 was to provide phase III confirmatory immunobridging data to support reduced 2-doses schedules (0, 5-13 months) in females aged 9-14 years.

In the follow-up epochs up to 30 months post-vaccination, non-inferiority of immune responses to both HPV-16 and HPV-18 antigens was demonstrated at Month 24 and Month 36 when Cervarix was administered according to a 2-dose schedule at 0,12 months in 9-14 year old females, compared to the administration according to a 2-dose schedule at 0,6 months in 9-14 year old females and according to the standard 3-dose schedule at 0,1,6 months in 15-25 year old females.

The clinical relevance of some observed immunological differences between the three investigated schedules, such as the slightly higher plateau in terms of antibody titers for the (0,12) schedule, remains unknown.

Although there is no immunological correlate of protection, it is believed (and 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. If the 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 will confer a clinical protection that is comparable with the standard schedule.

All initially seronegative subjects in group (0,6), group (0,1,6) and group (0,12) had seroconverted for anti-HPV-16 neutralising antibodies and at least 97.8% of the initially seronegative subjects had seroconverted for anti-HPV-18 neutralising antibodies when measured by PBNA at Month 24. All initially seronegative subjects in the three groups had seroconverted for anti-HPV-16 and anti-HPV-18 neutralising antibodies at Month 36. Although antibody levels are slowly declining, they remain well above the threshold conferred by natural infection and reach a plateau, conform earlier data.

The cell-mediated immunity was demonstrated by measurable CD4+ T cell responses which were maintained up to Month 36 for HPV-16/18/31/45. Memory B cell responses were maintained up to Month 36 for the vaccine HPV-types HPV-16/18.

Safety

In general, Cervarix administered at different schedules (0,6- months or 0,12-months in 9-14 year old healthy females or 0,1,6-months in 15-25 year old healthy females) had an acceptable safety profile in all groups in the follow-up period up to Month 36. No new safety information was collected in study HPV-070 during the follow up period of 36 months, the occurrence of adverse reactions is in line with the current information in the SmPC. One SAE [systemic lupus erythematosus (SLE)] reported by one subject in group[0,12] was considered by the investigator as causally related to vaccination. The SAE was not recovered/resolved at the Month 36 time point. None of the other SAEs were considered to be causally related to vaccination by the investigator.

Although recent results from pre-licensure clinical trials and current Post Marketing Surveillance data suggest that Cervarix has a clinically acceptable safety profile and is generally well tolerated, there remains a potential (theoretical) concern that Cervarix, and adjuvanted vaccines in general, might be associated with an excess risk of new onset of autoimmune diseases such as SLE. Autoimmune Diseases are reported in ongoing clinical trials with Cervarix. They are reported in ongoing clinical trials when they meet the criteria for SUSARS (Suspected, Unexpected, Serious Adverse Reactions) and are systematically included for review in the context of Cervarix Periodic Safety Update Reports (PSURs).

According to the latest PSUR, the cumulative data evaluated so far remains inconclusive to determine any potential pathogenic link between the vaccine and autoimmune diseases. The low reporting rates of autoimmune diseases combined with a background incidence in the population complicate causality assessment of such events to vaccination. From the cases reported in spontaneous reporting (passive surveillance), VIIth nerve paralysis, Systemic Lupus Erythematosus (SLE) and Guillain Barré Syndrome (GBS) were the most frequently reported pIMDs.

This SLE case which was assessed as causally related to vaccination should be further discussed by the MAH. Careful assessment of the medical and family history to identify potential risk factors is important in determining possible causes or triggers of the illness. In many of the cases reported as reviewed, confirmatory diagnostic information and/or relevant family and medical histories were not available. Hence, assessment of potential causality with vaccination could not be performed. The MAH is requested to further discuss the clinical history and the rationale of the diagnosis of this event assessed as causally related to vaccination. In this context, the MAH is invited to bring together information concerning SLE from individual case reviews, aggregate assessments of case reports from clinical trials and from the post-marketing settings, post-marketing observational safety studies.

It is important to note that women with SLE present higher risk of development HPV diseases. SLE predominantly affects women of reproductive age, that is the same group where the occurrence of HPV infection is increased. As the immune system of SLE patients is abnormal, the clearance of the virus is impaired. The result is the persistence of HPV virus in the cervix of SLE patients more often than in healthy women, what leads to higher prevalence of cervical dysplasia and cancer in SLE female population.Non-live HPV vaccines are safe and able to produce a protective response even in patients with autoimmune diseases (Grein et al. HPV infection and vaccination in Systemic Lupus Erythematosus patients: what we really should know Pediatric Rheumatology (2016) 14:12. DOI 10.1186/s12969-016-0072-x).

Recently, the results of the EPI-HPV-040 observational cohort study done in the UK became available (Procedure No. EMEA/H/C/000721/II/69). No evidence of increased risk was observed for the co-

primary objectives, including neuroinflammatory/ophthalmic autoimmune diseases (multiple sclerosis, transverse myelitis, optic neuritis, GBS and its variants, ADEM and its specific variants, autoimmune peripheral neuropathies and plexopathies and autoimmune uveitis). Higher risk was observed in exposed female vs non-exposed female cohort, [Relative risk (RR) 3.75; 95%CI: 3.25-11.3] for autoimmune thyroiditis (secondary objective). The risk became non-significant when all cases (Confirmed+Non-Confirmed, according to the study definition) are considered for calculation (RR 1.45; 95%CI: 0.79-2.64) (Procedure No. EMEA/H/C/000721/II/69).This finding is currently under investigation.

In France, a recent study based on a cohort of more than 2 million girls covered by the national health insurance general scheme, aged between 13 and 16 years, followed from 2008 to 2013, did not demonstrate any global increase of the risk of autoimmune disease among girls who had received at least one dose of HPV vaccine compared to unvaccinated girls. This overall result is in line with the data of the literature concerning the association between HPV vaccination and the risk of autoimmune diseases. A significant association with HPV vaccination was found for 2 of the 14 events studied, IBD and GBS.This association was particularly strong for Guillain Barré Syndrome GBS. As this is the first pharmaco-epidemiological study to suggest an association between HPV vaccination and these two autoimmune diseases, these results therefore need to be confirmed. HPV vaccines and risk of autoimmune disease: pharmaco-epidemiological study, Final report, September 2015, ANSM, France (in French) accessed on 4 april 2016 : file:///C:/Users/drh/Downloads/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf

Concerning Cervarix exposure during pregnancy risks, the RMP also proposes to generate further data based upon the results of a subgroup analysis of pre-licensure clinical trial data suggesting a numerical imbalance in spontaneous abortions among Cervarix recipients whose pregnancies occurred around the time of vaccination (defined as the last menstrual period [LMP] occurring 30 days before until 45 days after vaccination), compared to control subjects. Cervarix is not recommended for use in pregnancy, because safety has not been established in pregnant women; however, unintended exposure prior to the onset of pregnancy or during pregnancy is possible in the population recommended for vaccination. Pregnancies and their outcomes are being closely monitored in ongoing clinical trials and post-marketing setting (i.e. through spontaneous reporting and post marketing surveillance study including Pregnancy Exposure Registry established in the US and in the UK). Results from the EPI-HPV-018 PASS study have become available in 2015.

Apart from the above, GSK has not identified any new important risks that could be associated with the use of Cervarix in ongoing clinical trials and in post-marketing surveillance. Important safety concerns for Cervarix, which are included in the RMP are listed in Table 3.

Table 16 Important Safety Concerns at the Start of the Reporting Period 2015

Important Identified Risks	None
Important Potential Risks	Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination
Missing Information	Use of HPV-16/18 vaccine in HIV-infected women or subjects with known immune deficiencies Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine (As an outcome of assessment presented in Section 2.4.3.1. Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine, continous surveillance of pregnancy outcomes will be maintained through routine

	pharmacovigilance)

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The Article 46 paediatric submission is considered not fulfilled, and further regulatory action is needed. The provided data do not cause major concern regarding efficacy or safety of Cervarix but there needs to be additional clarifications concerning safety concern related to the Severe - grade 3 systemic lupus erythematosus reported case.

Meanwhile, the benefit/risk balance of Cervarix remains positive.

Recommendation

☒ **Not fulfilled:**

Additional clarifications requested

The systemic lupus erythematosus reported case which was assessed as causally related to HPV vaccination should be further discussed by the MAH. Careful assessment of the medical and family history to identify potential risk factors is important in determining possible causes or triggers of the illness. In many of the cases reported as reviewed, confirmatory diagnostic information and/or relevant family and medical histories were not available. Hence, assessment of potential causality with vaccination could not be performed. The MAH is requested to further discuss the clinical history and the rationale of the diagnosis of this event assessed as causally related to vaccination. In this context, the MAH is invited to bring together information concerning SLE from individual case reviews, aggregate assessments of case reports from clinical trials and from the post-marketing settings, post-marketing observational safety studies.

4. Rapporteur assessment report of the MAH responses to the Additional clarifications requested

Question 1

The systemic lupus erythematosus reported case which was assessed as causally related to HPV vaccination should be further discussed by the MAH. Careful assessment of the medical and family history to identify potential risk factors is important in determining possible causes or triggers of the illness. In many of the cases reported as reviewed, confirmatory diagnostic information and/or relevant family and medical histories were not available. Hence, assessment of potential causality with vaccination could not be performed. The MAH is requested to further discuss the clinical history and the rationale of the diagnosis of this event assessed as causally related to vaccination. In this context, the MAH is invited to bring together information concerning SLE from individual case reviews, aggregate assessments of case reports from clinical trials and from the post-marketing settings, post-marketing observational safety studies

Summary of MAH answer

The case of SLE in question concerns a 10-year-old female patient. No relevant medical history was reported and no risk factors for SLE were identified. The patient's familial medical history was not reported.

The patient received the first dose of Cervarix. Seven months after the 1st dose the patient was diagnosed with suspected transient synovitis. The patient had been experiencing right knee pain for an unreported length of time. Treatment with methotrexate and folic acid was initiated. Thirty five months after the 1st dose, the patient was diagnosed with SLE. Outcome is stated as unresolved. No other physical symptoms were reported by the Investigator. The following laboratory results were provided:

Test result
Blood anti centromere protein B: Negative, Blood anti dsDNA: less than 100 IU/mL (less than 100) Blood anti histones: negative Blood anti Jo-1: negative Blood anti nucleosomes: negative Blood anti RNP/SM: weakly positive Blood anti anti-Ro52 recombinant (TRIM21): negative Blood anti Sm: weakly positive Blood anti anti-Ro(SS-A) antibody (60kda); negative Blood antinuclear antibody (ANA): 160 (less than 80).
PLT smear: adequate RBC morpho: normochromia Urine SP.GR: 1.009 (1.003-1.030) Urine transparency: clear Blood urea/ratio: 9.5 Urine colour (chromaturia): yellow
Blood ovalocyte: few PLT smear: adequate Blood squamous epithelial cell: 0-1/hpf
Urea/ration: 13.3 Blood microcyte: 1+ Urine SP.GR: 1.008 (1.003-1.030) Urine transparency: clear Blood Anisocytosis: +1 Urine colour (chromaturia): pale yellow.

This case was assessed as related by the Investigator and no rationale for this assessment was provided. The Investigator stated there was 'a reasonable possibility the SLE may have been caused by Human papilloma type 16 + 18 vaccine'.

The diagnosis of SLE could not be confirmed based on the information provided. In this patient, SLE diagnostic criteria were not accomplished; there were unspecific weakly positive immunology results (low titres of positive ANA with weakly positive Sm antibodies) added to the described clinical features that were also unspecific starting about ten months after vaccination with a transient synovitis and right knee pain of unknown duration. No response to requests for further information from the Investigator was received. Insufficient clinical information is available for adequate assessment of this case.

A safety evaluation of all cases of SLE associated with Cervarix was performed and is attached in Appendix 1 of this response.

MAH conclusion on SLE (Appendix 1)

The currently available data do not indicate an increased risk of SLE following vaccination with Cervarix. The data seen in this review reflect what is seen in the general population:

- The majority of the cases were reported from Asian and Hispanic territories where it is known that SLE is more prevalent [Danchenko N, 2006].

- Available post-marketing information does not support a higher-than-expected rate of SLE in patients receiving vaccination with Cervarix.
- The age at which the onset of SLE was reported was between 14-58 years, with a mean age of 24 years. The onset of SLE in females is highest at child-bearing age [Danchenko N, 2006].
- The time-to-onset for confirmed Cervarix cases ranged from 10 days to 2.5 years and was on average 2.5 months. The literature review describes the onset of SLE symptoms as occurring between 8 days and 4 months after HPV vaccination.

Reports of SLE will continue to be monitored through normal proactive pharmacovigilance.

Rapporteur assessment of Question 1

Of the 13 confirmed cases, 11 were assessed as having a plausible causal association with Cervarix.

Table 17 Characteristics of the 13 confirmed cases.

Subject Age (n)	Range	14-58 years
	Median	24 years
Subject Gender (n, %)	Male	0 (0%)[2]
	Female	13 (100%)[2]
Report Type	Spontaneous Reports	44 (80%)
	Serious Clinical Trial Reports	10 (18%)
	Post Marketing Surveillance Reports	1 (2%)
Report Source	Health Care Professional	13 (100%)
	Consumer	0 (%)
Time to Onset of Event (n, %)[1]	Range	10 days - 2.5 years
	Median	2.5 months
Outcome (n, %)[1]	Fatal (due to event)	3 (23%)[2]
	Unresolved	7 (54%)[2]
	Resolved	3 (23 %)[2]

1. Number and percentage of reports with available data
2. Number of reports with available data was used as the denominator

Of the 13 confirmed cases, 11 were assessed as having a plausible causal association with Cervarix. In these cases, the time-to-onset (TTO) ranged from 10 days to 7 months and a possible association with vaccination cannot be excluded. For two of these 11 cases, alternative etiologies such as viral infection and pre-existing inflammatory disease were reported.

The remaining 2 out of the 13 confirmed cases were assessed as unlikely related to Cervarix. For one of these cases the time-to-onset was 2.5 years. For the final case, the patient had experienced joint pain for 4 years prior to administration of Cervarix, suggesting SLE was pre-existing.

For the three fatal cases, the cause of death in each case was due to SLE disease activity and related complications.

Section 4.8 of the SmPC should include "*all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC*."

Because vaccines stimulate the body's immune system it has been suggested that vaccines could increase the risk of developing an autoimmune disease. An autoimmune disease is a type of disease

that causes the body to attack its own tissues and organs. There are lots of different types of these diseases and they cause many different effects. Examples of these diseases are rheumatoid arthritis, diabetes, multiple sclerosis, Alzheimer's disease, Crohn's disease, lupus and asthma. About 5 – 8 % of the population have these conditions. In clinical trials, the risk of developing an autoimmune disease was not higher in the group of people who received Cervarix compared to the group of people who received a control (a fake vaccine or another vaccine).

Conclusion

The Applicant concludes that there is no increased risk of SLE following vaccination with Cervarix. It is acknowledged that the number of cases are too low to distinguish their incidence from the background incidence. On the other hand, the Applicant acknowledges both a temporal and causal relationship between SLE and Cervarix. In view of the potential theoretical risk of autoimmune diseases following vaccination and the temporal association of the SLE cases following vaccination with Cervarix, a causal relationship cannot be excluded and is indeed plausible.

At present, the level of evidence is too low to determine an increased risk of SLE following vaccination, despite the temporal relationship. The data are therefore inconclusive as to the risk of SLE following vaccination with Cervarix.

More data are being gathered as SLE is included as an important potential risk of Cervarix in the RMP (under the header "Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination") and a close monitoring is already ongoing, meaning that SLE cases are described in the PSUR/PBRER and a discussion on the cumulative cases is provided.

Since an increased risk of SLE cannot be distinguished from the background incidence of SLE, and for the sake of trust in the overall safety and benefit of Cervarix, the Rapporteur agrees with the MAH and considers that no further regulatory action is required.

The MAH is nevertheless requested to continue the close monitoring of SLE and to provide, in the next PSUR/PBRER, a detailed discussion of this safety issue together with an updated Observed versus Expected Analysis. Moreover, the MAH should describe which additional information regarding SLE diagnosis, case confirmation and causality assessment is requested from the SLE case reporter.

5. Rapporteur's overall conclusion and recommendation

Overall conclusion

The Article 46 paediatric submission is considered fulfilled. The provided data do not cause major concern regarding efficacy or safety of Cervarix. The benefit/risk balance of Cervarix remains positive.

The MAH is nevertheless requested to continue the close monitoring of SLE and to provide, in the next PSUR/PBRER, a detailed discussion of this safety issue together with an updated Observed versus Expected Analysis. Moreover, the MAH should describe which additional information regarding SLE diagnosis, case confirmation and causality assessment is requested from the SLE case reporter.

Recommendation

☒ Fulfilled:

Further regulatory action required **in the next PBRER**:

- The MAH is requested to continue the close monitoring of SLE and to provide a detailed discussion of this safety issue together with an updated Observed versus Expected Analysis.
- The MAH should describe which additional information regarding SLE diagnosis, case confirmation and causality assessment is requested from the SLE case reporter.