



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

Cervarix

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

Procedure No.: EMEA/H/C/000721/II/0021

Note

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



20 October 2011
EMA/891492/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/000721/II/0021

Invented name/name:	Cervarix
International non-proprietary name/common name:	human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)
Indication summary (as last approved):	prevention of cervical cancer
Marketing authorisation holder:	GlaxoSmithKline Biologicals S.A.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics and Package Leaflet Update of the Summary of Product Characteristics (SmPC) for Cervarix with data obtained in subjects of 9 years of age and to extend the current indication as from 9 years. The Package leaflet was updated accordingly. Update of local representatives.
Rapporteur:	Pieter Neels
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1, 2 and 5
Product Information affected:	SmPC and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	29 June 2011
Start of procedure:	24 July 2011
Rapporteur's preliminary assessment report circulated on:	12 September 2011
Rapporteur's updated assessment report circulated on:	12 October 2011
CHMP opinion:	20 October 2011

3. Scientific discussion

3.1. Introduction

Cervarix (HPV-16/18 L1 AS04 vaccine) is a prophylactic vaccine which contains 20µg per 0.5 mL dose of HPV-16 L1 protein and 20µg per 0.5ml dose of HPV-18 L1 protein assembled as virus-like particles (VLPs) as active ingredients. The L1 proteins are formulated with AS04 adjuvant system, which is composed of 50µg of 3-O-desacyl-4'-mono-phosphoryl-lipid A (MPL) and 500µg of aluminium hydroxide salt. The vaccine is preservative-free.

Cervarix was first registered in 2007 and the vaccine is currently licensed for use in more than 110 countries. In Europe, Cervarix is indicated for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. The indication is based on the demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years. The vaccination course consists of three doses administered according to a 0, 1, 6 month schedule via intramuscular injection.

The Marketing Authorisation Holder (MAH) has conducted a pooled analysis on the three studies HPV-029, HPV-030 and HPV-048 to evaluate the immunogenicity, safety and reactogenicity in 9 year old subjects as compared to 10-14 and 15-25 year old subjects.

The purpose of this variation is to update the summary of Product Characteristics (SmPC) for Cervarix with data obtained in subjects of 9 years of age and to extend the current indication as from 9 years.

The data from the pooled analysis demonstrate that 9 year old subjects are non-inferior to 10-14 and 15-25 year old subjects in terms of immune response and that the 9 year old subjects have a good safety and reactogenicity profile, therefore allowing for a change in the indication for the use of Cervarix as of the age of 9 years.

Type II

Variation(s) requested		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of the Summary of Product Characteristics (SmPC) for Cervarix with data obtained in subjects of 9 years of age and to extend the current indication as from 9 years. The Package leaflet was updated accordingly. Update of local representatives.

Information on Paediatric requirements

- Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended, the application included an EMA decision (Decision P/11/2009 on the granting of a product-specific waiver).

3.2. Clinical aspects

3.2.1. Background

The age at which HPV vaccination is recommended depends on National guidelines and Government vaccination schedules. Universal mass vaccination (UMV) is recommended at 12 years of age in Italy (

European Cervical Cancer Association, 2009; Dorleans F, 2010, Bonanni P, 2011), while in Spain UMC is recommended for girls from 11-14 years of age (European Cervical Cancer Association, 2009; Dorleans F, 2010, Bonanni P, 2011; Bermudez, 2011). In Austria UMC is recommended for girls from 9-15 years of age (European Cervical Cancer Association, 2009; Bonanni P, 2011; Impfplan, 2011).

Outside Europe, UMC is recommended from 9 years of age in some countries. In Canada UMC is recommended for girls from 9-14 years of age who have not yet become sexually active (Dube E, 2007). In the USA, vaccination can be started beginning at 9 years of age but routine vaccination is recommended for females aged 11 or 12 years (MMWR, 2010; Recommended Immunizations, 2011).

The WHO states that the primary target population is likely to be girls within the age range of 9 or 10 years through to 13 years (WHO, 2009).

In order to meet recommendations worldwide to vaccinate girls from the age of 9 years, the Company conducted a pooled analysis on three studies that enrolled female subjects from the age of 9 years. This pooling demonstrates non-inferiority in terms of GMT ratio to the age groups 10-14 and 15-25 years of age, the latter being the age range for which efficacy of Cervarix has been demonstrated before.

The data support an update of the following Sections 4.1, 4.2, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC).

3.2.2. Design and analysis of the pooled analysis

The pooled analysis included 1792 subjects aged 9 to 25 years of age in the TVC and 1663 in the ATP cohort for immunogenicity.

Subjects included were stratified by age (9 years, 10-14 years and 15-25 years) and pooled into three different vaccine groups:

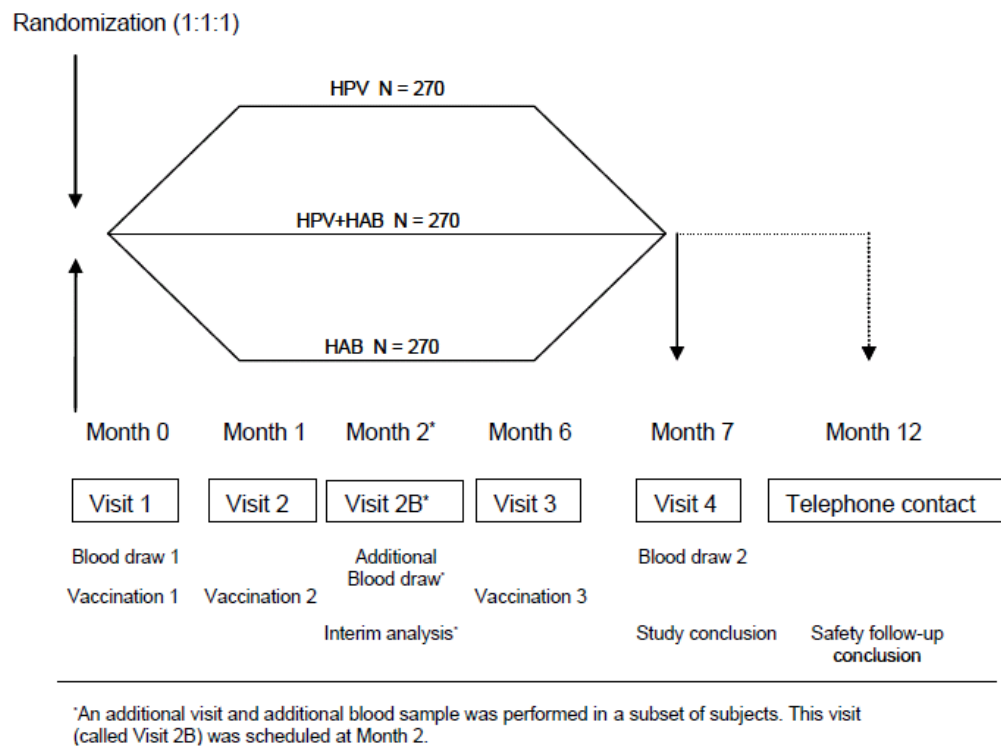
1. The **HPV only** group had received three doses of Cervarix at Month 0, Month 1 and Month 6;
2. The **HPV+co_ad** group had received Cervarix and HepB or HAB vaccines co-administered at Month 0, Month 1 and Month 6;
3. The **Co_ad only** group had received HepB or HAB vaccine at Month 0, Month 1 and Month 6.

From study HPV-048 only subjects who received the standard 3-dose-schedule were included in the pooled analysis.

An overview of each individual study is provided below.

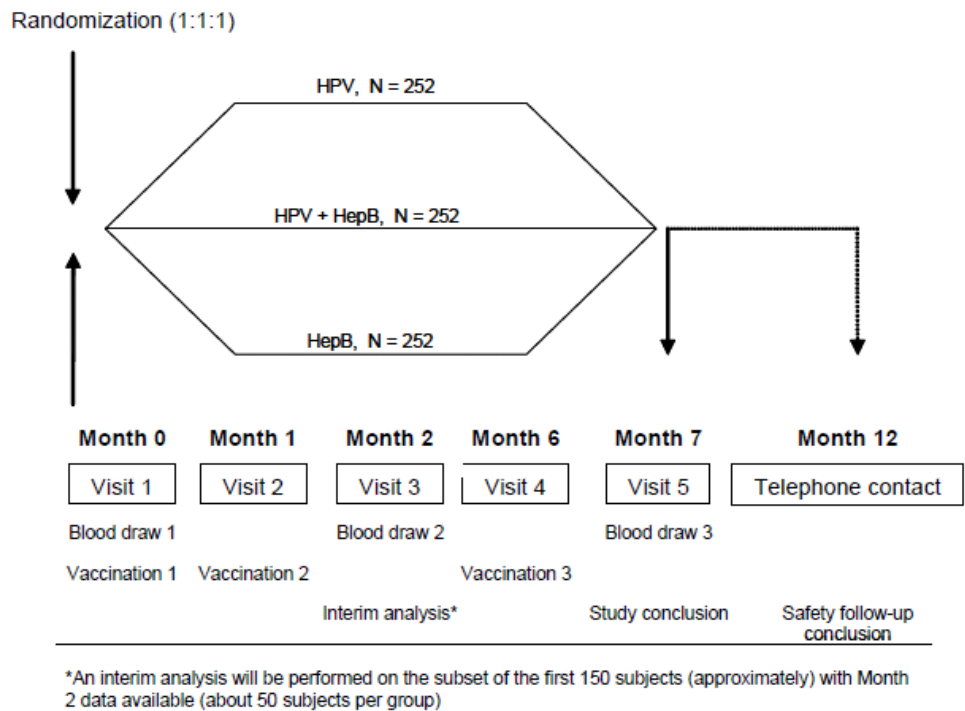
HPV-029 study title: A phase IIb, randomized, open, multicentre study to evaluate the immunogenicity and safety of HPV-16/18 L1 VLP AS04 vaccine co-administered with inactivated hepatitis A and hepatitis B vaccine adsorbed (Twinrix Paediatric) in healthy female subjects aged 9 – 15

HPV-029 study design



HPV-030 study title: A phase IIIb, randomized, open, multicentre study to evaluate the immunogenicity and safety of HPV-16/18 L1 VLP AS04 vaccine (Cervarix) co-administrated with Hepatitis B vaccine (Engerix-B) in healthy female subjects aged 9 - 15 years.

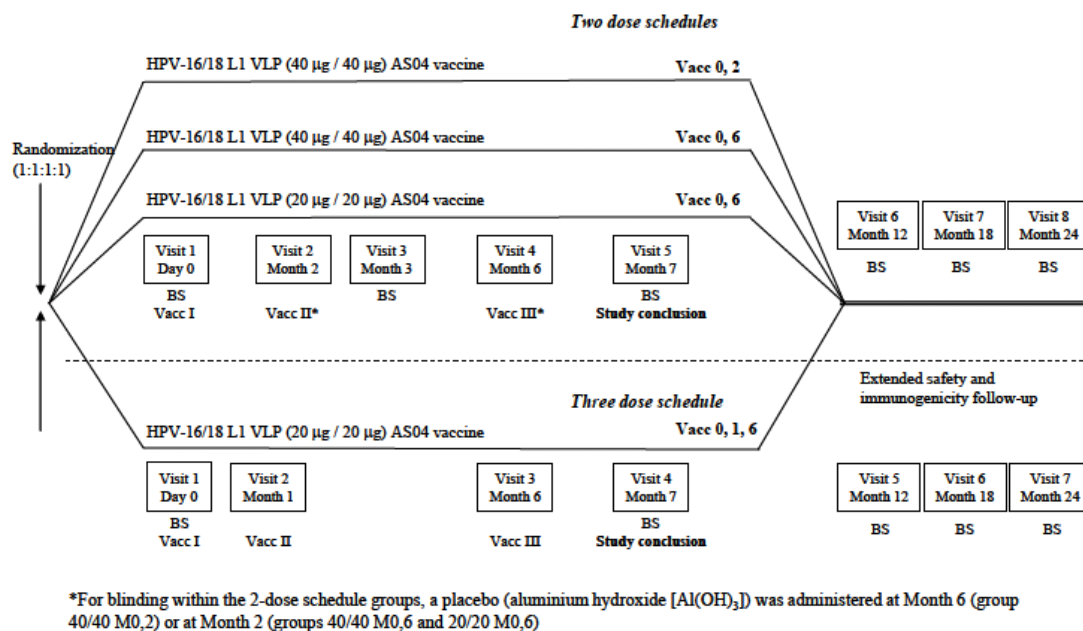
HPV-030 study design



Study HPV-049 title: A phase I/II, partially blind, randomized, multicenter, age-stratified, dose-range study in healthy females aged 9 - 25 years to assess the safety and immunogenicity of HPV-16/18 L1

VLP AS04 vaccine administered intramuscularly according to a 2-dose schedule (0,2-month or 0,6-month) when compared to a standard 3- dose schedule of HPV-16/18 L1 VLP AS04 vaccine.

HPV-049 study design



In order to increase the number of evaluable 9 year old subjects for the analysis of the immunogenicity objective, an analysis was conducted to demonstrate non-inferiority of the HPV-16 and HPV-18 immune response in the pooled 9 year old subjects who received Cervarix (HPV only) compared to the group of pooled 9 year old females who received Cervarix concomitantly with Engerix or Twinrix (HPV+co_ad) in terms of GMT ratio one month after completion of the three-dose vaccination schedule (Month 7).

If non-inferiority was to be shown then the two vaccine groups HPV only and HPV+co_ad for the 9 year old subjects were to be pooled to form the group HPV_pool/9y to be used for the two non-inferiority analyses as described below.

The pooled analysis had two objectives:

- **Immunogenicity (assessed sequentially)**
 - 1) To demonstrate non-inferiority of the HPV-16 and HPV-18 immune response between the pooled groups HPV only and HPV+co_ad for the 9 year old subjects (HPV_pool/9y) compared to the pooled groups HPV only and HPV+co_ad for the 10-14 year old subjects (HPV_pool/10-14y) in terms of GMT ratio one month after completion of three-dose vaccination (Month 7).
 - 2) To demonstrate non-inferiority of the HPV-16 and HPV-18 immune response between the pooled groups HPV only and HPV+co_ad for the 9 year old subjects (HPV_pool/9y) compared to the

pooled groups HPV only and HPV+co_ad for the 15-25 year old subjects (HPV_pool/15-25y) in terms of GMT ratio one month after completion of three-dose vaccination (Month 7).

- **Safety/Reactogenicity**

To evaluate the occurrence, intensity and causal relationship to vaccination of solicited local and general symptoms during the 7-day period (day 0 to 6) following each and any vaccination in the groups HPV only, HPV+co_ad and Co_ad only for 9 year old subjects; the occurrence, intensity and relationship to vaccination of unsolicited symptoms during the 30-day period (days 0 to 29) following each and any vaccination in the groups HPV only, HPV+co_ad and Co_ad only for 9 year old subjects; and the occurrence, intensity and relationship to vaccination of new onset chronic diseases (NOCs), new onset autoimmune diseases (NOADs), medically significant adverse events (AEs) and serious adverse events (SAEs) in the groups HPV only, HPV+co_ad and Co_ad only for 9 year old subjects up to Month 7.

Study power

The pooled analysis had no power and is purely descriptive. The three individual studies enrolled sufficient subjects per group in order to assure an acceptable global power to reach their primary objectives

Subjects evaluated

In the three individual studies HPV-029, HPV-030 and HPV-048, healthy females were enrolled after checking eligibility criteria at study entry. Exclusion criteria aimed to prevent administration of the study vaccines to individuals with medical conditions that might have interfered with the immune response; to those individuals at risk of possible adverse reactions to the vaccine; those in whom previous exposure to the vaccine antigens through vaccination, disease or known exposure would prevent interpretation of the results; and those who were breastfeeding, pregnant or at risk of becoming pregnant during the study.

All subjects included in the pooled analysis were females between 9 and 25 years. The subjects were stratified by age (9 years, 10-14 years and 15-25 years) and pooled into three different vaccine groups: HPV only group in which all subjects received Cervarix according to a three dose schedule at Months 0, 1 and 6; HPV+co_ad group in which the subjects received Cervarix and Engerix or Twinrix co-administered; and Co_ad only group in which the subjects received Engerix or Twinrix alone. The pooled analysis included 1792 subjects aged 9-25 years in the TVC (516 were 9 years old) and 1663 in the ATP cohort (473 were 9 years old).

The demographic characteristics for the TVC were similar to the ATP cohort for immunogenicity with no major differences.

Methodology

The primary cohort for the analysis of the immunogenicity of the pooled analysis was the According to protocol (ATP) cohort. The ATP immunogenicity cohort included all subjects who met all eligibility criteria, who complied with protocol-defined procedures, who had no elimination criteria during the study, and for whom data concerning immunogenicity endpoint measures were available.

For the purpose of this pooled analysis geometric mean antibody concentration/titre (GMT), with 95% CI, was calculated using standard methods.

In order to increase the evaluable number of 9 year old subjects, non-inferiority between the HPV only group and the HPV+co_ad group had to be demonstrated first to allow pooling of these two vaccine groups.

- To demonstrate non-inferiority for the 9 year old between the HPV only group and the HPV+co_ad group, the pre-required margin on the GMT ratios (HPV only / HPV+co_ad) was set at 2.

The immunogenicity endpoints were the following:

- To demonstrate non-inferiority between the pooled groups HPV only and HPV+co_ad for the 9 year old subjects compared to the pooled groups HPV only and HPV+co_ad for the 10-14 year old subjects. The pre-required margin on the GMT ratios (HPV_pool/10-14y / HPV_pool/9y) was set at 2;
- To demonstrate non-inferiority between the pooled groups HPV only and HPV+co_ad for the 9 year old subjects compared to the pooled groups HPV only and HPV+co_ad for the 15-25 year old subjects. The pre-required margin on the GMT ratios (HPV_pool/15-25y / HPV_pool/9y) was set at 2.

The safety endpoints are described below:

- The occurrence, intensity and causal relationship to vaccination of solicited local and general symptoms during the 7-day period (day 0 to 6) following each and any vaccination in the groups HPV only, HPV+co_ad and Co_ad only for 9 year old subjects.
- The occurrence, intensity and relationship to vaccination of unsolicited symptoms during the 30-day period (days 0 to 29) following each and any vaccination in the groups HPV only, HPV+co_ad and Co_ad only for 9 year old subjects.
- The occurrence, intensity and relationship to vaccination of NOCDs, NOADs, medically significant AEs and SAEs in the groups HPV only, HPV+co_ad and Co_ad only for 9 year old subjects up to Month 7.

Study cohorts

In addition to the ATP cohort, a complementary analysis was conducted on the total vaccinated cohort (TVC) which included all vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The TVC included all vaccinated subjects for whom data were available. The TVC for analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The TVC analysis was performed per treatment actually administered.

Derived and transformed data

A seronegative subject was a subject whose antibody titres were below the cut-off value. A seropositive subject was a subject whose antibody titre was greater than or equal to the cut-off value.

Seroconversion was defined as the appearance of anti-HPV-16 and anti-HPV-18 antibodies (i.e. titre greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.

The GMT calculations were performed by taking the anti-log of the mean of the log antibody titers transformations. Antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.

3.2.3. Efficacy Study Results

Immunogenicity

Pooled study population

For the pooled analysis, a total of 1663 subjects aged 9-25 years were included in the ATP cohort for immunogenicity. An overview about the numbers of subjects that were part of the different groups and age strata is provided in Table 1:

Table 1. Number of subjects per group and age strata (ATP cohort for immunogenicity)

Age at baseline	Vaccine groups						TOTAL
	HPV only		HPV+co_ad		Co_ad only		
9 y	162	HPV-029	152	HPV-029	159	HPV-029	473
		HPV-030		HPV-030		HPV-030	
		HPV-048					
10-14 y	353	HPV-029	288	HPV-029	299	HPV-029	940
		HPV-030		HPV-030		HPV-030	
		HPV-048					
15-25 y	174	HPV-029	42	HPV-029	34	HPV-029	250
		HPV-030		HPV-030		HPV-030	
		HPV-048					
TOTAL	689		482		492		1663

Y = year; HPV+co_ad = HPV with co-administration; Co_ad only = coadministration only

The mean age of all pooled 10-14 year old subjects at study entry in the ATP cohort for immunogenicity was 12.1 years with a SD of 1.41 years. The majority (92.6%) of the subjects was of White-Caucasian/European heritage. The mean age, race, height and weight were comparable between the 10-14 year old subjects in the different vaccine groups.

The mean age of all pooled 15-25 year old subjects at study entry in the ATP cohort for immunogenicity was 17.4 years with a SD of 3.20 years. The majority (97.2%) of the subjects was of White-Caucasian/European heritage. The mean age is slightly different between the three groups as the pooled 15-25 age strata in the HPV+co_ad and the Co_ad only groups only contain 15 year old subjects of studies HPV-029 and HPV-030 which enrolled subjects 9-15 years. The pooled 15-25 age strata of the HPV only group has a mean age of 18.5 years with a SD of 3.30 years as it included subjects from study HPV-048. The race, height and weight were comparable between the 15-25 year old subjects in the different vaccine groups.

The percentage of initially seronegative 9 year old subjects in the HPV only and HPV+co_ad groups with anti-HPV-16 titres ≥ 8 EL.U/mL and anti-HPV-16 GMTs are presented in Table 2. The percentage of initially seronegative subjects in the HPV only and the HPV+co_ad groups with anti-HPV-18 antibody titres ≥ 7 EL.U/mL and anti-HPV-18 GMTs are presented in Table 3.

Table 2. Seropositivity rates and GMTs for HPV-16 antibodies by pre-vaccination status for 9y subjects at baseline (ATP cohort for immunogenicity)

					≥ 8 ELU/ML				GMT					
							95% CI				95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max	
HPV-16	HPV only	S-	PRE	153	0	0.0	0.0	2.4	4.0	4.0	4.0	<8.0	<8.0	
			PIII(M7)	153	153	100	97.6	100	29931.5	26126.0	34291.2	1704.0	308377.0	
		S+	PRE	8	8	100	63.1	100	14.5	10.8	19.6	9.0	27.0	
			PIII(M7)	8	8	100	63.1	100	22852.3	12596.3	41458.9	10976.0	76961.0	
		Total	PRE	161	8	5.0	2.2	9.6	4.3	4.1	4.5	<8.0	27.0	
			PIII(M7)	161	161	100	97.7	100	29532.8	25892.9	33684.4	1704.0	308377.0	
	HPV+ co_ad	S-	PRE	137	0	0.0	0.0	2.7	4.0	4.0	4.0	<8.0	<8.0	
			PIII(M7)	137	136	99.3	96.0	100	29098.2	24080.1	35162.0	<8.0	468515.0	
		S+	PRE	13	13	100	75.3	100	15.7	10.5	23.5	8.0	65.0	
			PIII(M7)	13	13	100	75.3	100	25472.3	16166.9	40133.7	7406.0	95024.0	
		Total	PRE	150	13	8.7	4.7	14.4	4.5	4.2	4.8	<8.0	65.0	
			PIII(M7)	150	149	99.3	96.3	100	28764.5	24117.6	34306.8	<8.0	468515.0	

HPV+co_ad = HPV with co-administration

S- = seronegative subjects (antibody concentration < 8 ELU/ML) prior to vaccination

S+ = seropositive subjects (antibody concentration >= 8 ELU/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 concentration within the specified range

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

MIN/MAX = Minimum/Maximum; PIII(M7) = Post Dose 3, Month 7; PRE = Pre-vaccination

Table 3. Seropositivity rates and GMTs for HPV-18 antibodies by pre-vaccination status for 9y subjects at baseline (ATP cohort for immunogenicity)

					≥ 7 ELU/ML				GMT					
							95% CI				95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max	
HPV-18	HPV only	S-	PRE	150	0	0.0	0.0	2.4	3.5	3.5	3.5	<7.0	<7.0	
			PIII(M7)	150	150	100	97.6	100	11559.1	9998.1	13363.7	1031.0	185040.0	
		S+	PRE	9	9	100	66.4	100	18.2	9.9	33.5	9.0	110.0	
			PIII(M7)	9	9	100	66.4	100	9105.2	5453.5	15202.2	3725.0	21012.0	
		Total	PRE	159	9	5.7	2.6	10.5	3.8	3.6	4.1	<7.0	110.0	
			PIII(M7)	159	159	100	97.7	100	11404.0	9923.6	13105.2	1031.0	185040.0	
	HPV+ co_ad	S-	PRE	138	0	0.0	0.0	2.6	3.5	3.5	3.5	<7.0	<7.0	
			PIII(M7)	138	138	100	97.4	100	12149.4	10633.4	13881.5	1398.0	102722.0	
		S+	PRE	13	13	100	75.3	100	11.8	9.3	15.1	8.0	33.0	
			PIII(M7)	13	13	100	75.3	100	11273.7	7395.5	17185.6	3113.0	32362.0	
		Total	PRE	151	13	8.6	4.7	14.3	3.9	3.7	4.1	<7.0	33.0	
			PIII(M7)	151	151	100	97.6	100	12071.4	10644.5	13689.5	1398.0	102722.0	

HPV+co_ad = HPV with co-administration

S- = seronegative subjects (antibody concentration < 7 ELU/ML) prior to vaccination

S+ = seropositive subjects (antibody concentration >= 7 ELU/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 concentration within the specified range

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

MIN/MAX = Minimum/Maximum; PIII(M7) = Post Dose 3, Month 7; PRE = Pre-vaccination

Non-inferiority assessment between HPV only and HPV with coadministration for HPV-16 and HPV-18 antigens for 9 year old subjects

Non-inferiority of the pooled HPV only group to the pooled HPV+co_ad group with respect to the GMT ratio for 9 year old subjects was demonstrated for HPV-16 and HPV-18 since the UL of the 95% CIs on the GMT ratio was below the pre-defined limit of 2 (Table 4).

As non-inferiority of the pooled HPV only group to the pooled HPV+co_ad group with respect to the GMT ratio for 9 year old subjects was demonstrated for HPV-16 and HPV- 18, the two groups were pooled (HPV_pool/9y) for the assessment of the immunogenicity objective of this pooled analysis.

Table 4. Non-inferiority assessment in terms of GMT ratios between HPV and HPV with co-administration groups for HPV-16 and HPV-18 antigens, Post Dose 3, Month 7 for seronegative subjects at baseline, for 9 year old subjects at baseline (ATP cohort for immunogenicity)

					GMT ratio (HPV only / HPV+co_ad)		
	HPV only		HPV+co_ad		95% CI		
Anti body	N	GMT	N	GMT	Value	LL	UL
HPV-16 (ELU/ML)	153	29931.5	137	29098.2	1.03	0.82	1.29
HPV-18 (ELU/ML)	150	11559.1	138	12149.4	0.95	0.78	1.16

HPV+co_ad = HPV with co-administration

GMT = geometric mean antibody titre

N = Number of subjects with pre-vaccination results available

95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance)

LL = lower limit; UL = upper limit

HPV-16 and HPV-18 immune response for subjects receiving Cervarix (pooled group) in the different age strata (9 years, 10-14 years and 15-25 years)

The percentage of initially seronegative 9 year old, 10-14 year old and 15-25 year old subjects in the pooled groups HPV_pool/9y, HPV_pool/10-14y and the HPV_pool/15-25y with anti-HPV-16 titres ≥ 8 EL.U/mL and anti-HPV-16 GMTs are presented in Table 5. The percentage of initially seronegative 9 year old, 10-14 year old and 15-25 year old subjects in the pooled groups HPV_pool/9y, HPV_pool/10-14y and the HPV_pool/15-25y with anti-HPV-18 titres ≥ 7 EL.U/mL and anti-HPV-18 GMTs are presented in Table 6.

Table 5. Seropositivity rates and GMTs for HPV-16 antibodies by pre-vaccination status for subjects who received HPV vaccine (with co-administration or not), by age strata (ATP cohort for immunogenicity)

						≥ 8 ELU/ML				GMT				
						95% CI				95% CI				
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16	HPV_pool	9y	S-	PRE	290	0	0.0	0.0	1.3	4.0	4.0	4.0	<8.0	<8.0
				PIII(M7)	290	289	99.7	98.1	100	29534.9	26354.0	33099.7	<8.0	468515.0
			S+	PRE	21	21	100	83.9	100	15.3	11.8	19.7	8.0	65.0
				PIII(M7)	21	21	100	83.9	100	24440.5	17600.7	33938.4	7406.0	95024.0
			Total	PRE	311	21	6.8	4.2	10.1	4.4	4.2	4.6	<8.0	65.0
				PIII(M7)	311	310	99.7	98.2	100	29159.7	26166.9	32494.8	<8.0	468515.0
		10-14y	S-	PRE	573	0	0.0	0.0	0.6	4.0	4.0	4.0	<8.0	<8.0
				PIII(M7)	573	571	99.7	98.7	100	21152.2	19514.7	22927.2	<8.0	440516.0
			S+	PRE	64	64	100	94.4	100	16.6	14.2	19.5	8.0	102.0
				PIII(M7)	64	64	100	94.4	100	19839.9	16156.5	24363.1	2452.0	154583.0
			Total	PRE	637	64	10.0	7.8	12.6	4.6	4.4	4.8	<8.0	102.0
				PIII(M7)	637	635	99.7	98.9	100	21016.5	19493.7	22658.4	<8.0	440516.0
		15-25y	S-	PRE	184	0	0.0	0.0	2.0	4.0	4.0	4.0	<8.0	<8.0
				PIII(M7)	184	184	100	98.0	100	11926.2	10247.6	13879.8	154.0	148276.0
			S+	PRE	31	31	100	88.8	100	41.7	23.9	72.8	8.0	745.0
				PIII(M7)	31	31	100	88.8	100	8377.0	5800.5	12097.9	2019.0	99665.0
			Total	PRE	215	31	14.4	10.0	19.8	5.6	4.9	6.4	<8.0	745.0
				PIII(M7)	215	215	100	98.3	100	11334.0	9852.2	13038.7	154.0	148276.0

HPV_pool = Pooling of HPV only and HPV with co-administration

9y = 9 years at baseline; 10-14y = 10-14 years at baseline; 15-25y = 15-25 years at baseline

S- = seronegative subjects (antibody concentration < 8 ELU/ML) prior to vaccination

S+ = seropositive subjects (antibody concentration >= 8 ELU/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 concentration within the specified range

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

MIN/MAX = Minimum/Maximum: PIII(M7) = Post Dose 3. Month 7: PRE = Pre-vaccination

Table 6. Seropositivity rates and GMTs for HPV-18 antibodies by pre-vaccination status for subjects who received HPV vaccine (with co-administration or not), by age strata (ATP cohort for immunogenicity)

						≥ 7 ELU/ML					GMT				
								95% CI				95% CI			
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max	
HPV-18	HPV_pool	9y	S-	PRE	288	0	0.0	0.0	1.3	3.5	3.5	3.5	<7.0	<7.0	
				PIII(M7)	288	288	100	98.7	100	11838.2	10729.0	13062.2	1031.0	185040.0	
			S+	PRE	22	22	100	84.6	100	14.1	10.7	18.6	8.0	110.0	
				PIII(M7)	22	22	100	84.6	100	10330.3	7649.7	13950.3	3113.0	32362.0	
			Total	PRE	310	22	7.1	4.5	10.5	3.9	3.7	4.0	<7.0	110.0	
				PIII(M7)	310	310	100	98.8	100	11724.3	10677.2	12874.2	1031.0	185040.0	
		10-14y	S-	PRE	586	0	0.0	0.0	0.6	3.5	3.5	3.5	<7.0	<7.0	
				PIII(M7)	586	584	99.7	98.8	100	8608.0	7971.8	9295.0	<7.0	143884.0	
			S+	PRE	50	50	100	92.9	100	13.3	11.3	15.6	7.0	104.0	
				PIII(M7)	50	50	100	92.9	100	7164.5	5638.7	9103.2	1025.0	72119.0	
			Total	PRE	636	50	7.9	5.9	10.2	3.9	3.8	4.0	<7.0	104.0	
				PIII(M7)	636	634	99.7	98.9	100	8484.7	7886.3	9128.5	<7.0	143884.0	
		15-25y	S-	PRE	190	0	0.0	0.0	1.9	3.5	3.5	3.5	<7.0	<7.0	
				PIII(M7)	190	190	100	98.1	100	4905.3	4263.2	5644.1	391.0	135130.0	
			S+	PRE	26	26	100	86.8	100	18.2	12.3	27.0	7.0	161.0	
				PIII(M7)	26	26	100	86.8	100	4509.5	2896.7	7020.2	709.0	81284.0	
			Total	PRE	216	26	12.0	8.0	17.1	4.3	3.9	4.6	<7.0	161.0	
				PIII(M7)	216	216	100	98.3	100	4855.9	4250.6	5547.3	391.0	135130.0	

HPV_pool = Pooling of HPV only and HPV with co-administration

9y = 9 years at baseline; 10-14y = 10-14 years at baseline; 15-25y = 15-25 years at baseline

S- = seronegative subjects (antibody concentration < 7 ELU/ML) prior to vaccination

S+ = seropositive subjects (antibody concentration >= 7 ELU/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 concentration within the specified range

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

MIN/MAX = Minimum/Maximum; PIII(M7) = Post Dose 3, Month 7; PRE = Pre-vaccination

Non-inferiority assessment between 9 year old subjects and 10-14 and 15-25 year old subjects having received the HPV vaccine (with or without co-administration) for HPV-16 and HPV-18 antigens

Non-inferiority was demonstrated for HPV-16 and HPV-18 since the UL of the 95% CIs on the GMT ratio was below the pre-defined limit of 2 (Table 7).

Table 7. Non-inferiority assessment in terms of GMT ratios in the 9 years at baseline and in 10-14 years at baseline when administered HPV vaccine (with co-administration or not) for HPV-16 and HPV-18 antigens, Post Dose 3, Month 7 for seronegative subjects at baseline (ATP cohort for immunogenicity)

Anti body	HPV_pool/10-14y		HPV_pool/9y		GMT ratio (HPV_pool/10-14y / HPV_pool/9y)		
					Value	95% CI	
	N	GMT	N	GMT		LL	UL
HPV-16 (ELU/ML)	573	21152.2	290	29534.9	0.72	0.62	0.82
HPV-18 (ELU/ML)	586	8608.0	288	11838.2	0.73	0.64	0.83

HPV_pool = Pooling of HPV only and HPV with co-administration

9y = 9 years at baseline

GMT = geometric mean antibody titre

N = Number of subjects with pre-vaccination results available

95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance)

LL = lower limit; UL = upper limit

Non-inferiority for the pooled 9 year old subjects (vaccinated with Cervarix alone or co-administered) against the pooled 15-25 year old subjects (vaccinated with Cervarix alone or co-administered) with

respect to the GMT ratio was demonstrated for HPV-16 and HPV-18 since the UL of the 95% CIs on the GMT ratio was below the pre-defined limit of 2 (Table 8).

Table 8. Non-inferiority assessment in terms of GMT ratios in the 9 years at baseline and in 15-25 years at baseline when administered HPV vaccine (with co-administration or not) for HPV-16 and HPV-18 antigens, Post Dose 3, Month 7 for seronegative subjects at baseline (ATP cohort for immunogenicity)

	HPV_pool/15-25y		HPV_pool/9y		GMT ratio (HPV_pool/15-25y / HPV_pool/9y)		
					Value	95% CI	
Anti body	N	GMT	N	GMT		LL	UL
HPV-16 (ELU/ML)	184	11926.2	290	29534.9	0.40	0.34	0.49
HPV-18 (ELU/ML)	190	4905.3	288	11838.2	0.41	0.35	0.49

HPV_pool = Pooling of HPV only and HPV with co-administration

9y = 9 years at baseline

GMT = geometric mean antibody titre

N = Number of subjects with pre-vaccination results available

95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance)

LL = lower limit; UL = upper limit

3.2.4. Efficacy Conclusions

Non-inferiority of the HPV-16/18 immune response, with respect to GMT ratio at Month 7, was demonstrated for the 9 year old subjects when Cervarix was administered alone at Month 0, 1 and 6, compared to when Cervarix was co-administered with Engerix or Twinrix at Month 0, 1 and 6.

The pooling of these two groups of subjects increased the number of evaluable subjects for further analyses.

For the pooled 9 year old subjects who received Cervarix with or without co-administration with Engerix or Twinrix, GMTs for anti-HPV-16 and anti-HPV-18 antibodies at Month 7 were the following:

GMTs results for anti-HPV-16 antibodies at Month 7 were 29534.9 EL.U/mL in the HPV_pool/9y group, 21152.2 EL.U/mL in the HPV_pool/10-14y group and 11926.2 EL.U/mL in the HPV_pool/15-25y group.

GMTs for anti-HPV-16 antibodies at Month 7 in the HPV_pool/9y group were 1.4- fold higher than in the HPV_pool/10-14y group and 2.5-fold higher than in the HPV_pool/15-25y group.

GMTs results for anti-HPV-18 antibodies at Month 7 were 11838.2 EL.U/mL in the HPV_pool/9y group, 8608.0 EL.U/mL in the HPV_pool/10-14y group and 4905.3 EL.U/mL in the HPV_pool/15-25y group.

GMTs for anti-HPV-18 antibodies at Month 7 in the HPV_pool/9y group were 1.4- fold higher than in the HPV_pool/10-14y group and 2.4-fold higher than in the HPV_pool/15-25y group.

The immunogenicity objectives of this pooled analysis were met:

Non-inferiority of the HPV-16/18 immune response, with respect to GMT ratio at Month 7, was demonstrated for the pooled 9 year old subjects (when Cervarix was administered alone or co-administered with Engerix or Twinrix), compared to the pooled 10-14 year old subjects (when Cervarix was administered alone or co-administered with Engerix or Twinrix).

Non-inferiority of the HPV-16/18 immune response, with respect to GMT ratio at Month 7, was demonstrated for the pooled 9 year old subjects (when Cervarix was administered alone or co-administered with Engerix or Twinrix), compared to the pooled 15-25 year old subjects (when Cervarix was administered alone or co-administered with Engerix or Twinrix).

In conclusion, these data show that the 9 year old subjects are comparable to subjects aged 10-14 and 15-25 years of age in terms of seroconversion rates and that the immunological response (GMTs) in 9 year old subjects is non-inferior to the immune response in those older age groups.

3.2.5. Clinical safety

In the pooled analysis, a total of 516 subjects aged 9 years were included in the Total Vaccinated Cohort. Of these, 175 subjects received 3 doses of Cervarix only, 171 received 3 doses of Cervarix co-administered with HAB or HepB vaccines, and 170 received three doses of HAB or HepB only.

Common Adverse Events

The incidence and nature of symptoms (solicited only) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall is presented in Table 9.

Table 9. Incidence and nature of symptoms (solicited only) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall for 9 year old subjects (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	HPV only	173	162	93.6	88.9	96.8	173	84	48.6	40.9	56.3	173	155	89.6	84.1	93.7
	HPV+co_ad	169	156	92.3	87.2	95.8	169	90	53.3	45.4	61.0	169	154	91.1	85.8	94.9
	Co_ad only	170	112	65.9	58.2	73.0	170	77	45.3	37.7	53.1	170	93	54.7	46.9	62.3
Dose 2	HPV only	172	137	79.7	72.9	85.4	172	68	39.5	32.2	47.3	172	133	77.3	70.3	83.4
	HPV+co_ad	167	150	89.8	84.2	94.0	167	71	42.5	34.9	50.4	167	146	87.4	81.4	92.0
	Co_ad only	169	103	60.9	53.2	68.3	169	62	36.7	29.4	44.4	169	91	53.8	46.0	61.5
Dose 3	HPV only	169	141	83.4	77.0	88.7	169	79	46.7	39.0	54.6	169	136	80.5	73.7	86.2
	HPV+co_ad	166	149	89.8	84.1	93.9	166	80	48.2	40.4	56.1	166	148	89.2	83.4	93.4
	Co_ad only	167	106	63.5	55.7	70.8	167	54	32.3	25.3	40.0	167	91	54.5	46.6	62.2
Overall/dose	HPV only	514	440	85.6	82.3	88.5	514	231	44.9	40.6	49.4	514	424	82.5	78.9	85.7
	HPV+co_ad	502	455	90.6	87.7	93.0	502	241	48.0	43.6	52.5	502	448	89.2	86.2	91.8
	Co_ad only	506	321	63.4	59.1	67.6	506	193	38.1	33.9	42.5	506	275	54.3	49.9	58.8
Overall/subject	HPV only	174	168	96.6	92.6	98.7	174	126	72.4	65.1	78.9	174	164	94.3	89.7	97.2
	HPV+co_ad	169	164	97.0	93.2	99.0	169	127	75.1	67.9	81.5	169	163	96.4	92.4	98.7
	Co_ad only	170	140	82.4	75.8	87.8	170	98	57.6	49.8	65.2	170	132	77.6	70.6	83.7

HPV+co_ad = HPV with co-administration

Co_ad only = co-administration only

For each dose and overall/subject:

N= number of subjects with at least one documented dose

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

For overall/dose:

N= number of documented doses

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

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

The overall percentage of doses followed by grade 3 solicited symptoms during the 7-day post-vaccination period was 9.9%, 15.9% and 4.0% for the HPV only group, the HPV+co_ad group and the Co_ad only group, respectively (Table 10).

Table 10. Incidence and nature of grade 3 symptoms (solicited only) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall for 9 year old subjects (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	HPV only	173	14	8.1	4.5	13.2	173	2	1.2	0.1	4.1	173	13	7.5	4.1	12.5
	HPV+co_ad	169	20	11.8	7.4	17.7	169	3	1.8	0.4	5.1	169	17	10.1	6.0	15.6
	Co_ad only	170	7	4.1	1.7	8.3	170	5	2.9	1.0	6.7	170	2	1.2	0.1	4.2
Dose 2	HPV only	172	13	7.6	4.1	12.6	172	3	1.7	0.4	5.0	172	10	5.8	2.8	10.4
	HPV+co_ad	167	20	12.0	7.5	17.9	167	4	2.4	0.7	6.0	167	17	10.2	6.0	15.8
	Co_ad only	169	6	3.6	1.3	7.6	169	6	3.6	1.3	7.6	169	0	0.0	0.0	2.2
Dose 3	HPV only	169	24	14.2	9.3	20.4	169	7	4.1	1.7	8.3	169	20	11.8	7.4	17.7
	HPV+co_ad	166	40	24.1	17.8	31.3	166	10	6.0	2.9	10.8	166	33	19.9	14.1	26.8
	Co_ad only	167	7	4.2	1.7	8.4	167	6	3.6	1.3	7.7	167	1	0.6	0.0	3.3
Overall/dose	HPV only	514	51	9.9	7.5	12.8	514	12	2.3	1.2	4.0	514	43	8.4	6.1	11.1
	HPV+co_ad	502	80	15.9	12.8	19.4	502	17	3.4	2.0	5.4	502	67	13.3	10.5	16.6
	Co_ad only	506	20	4.0	2.4	6.0	506	17	3.4	2.0	5.3	506	3	0.6	0.1	1.7
Overall/subject	HPV only	174	42	24.1	18.0	31.2	174	11	6.3	3.2	11.0	174	35	20.1	14.4	26.8
	HPV+co_ad	169	59	34.9	27.8	42.6	169	16	9.5	5.5	14.9	169	51	30.2	23.4	37.7
	Co_ad only	170	17	10.0	5.9	15.5	170	14	8.2	4.6	13.4	170	3	1.8	0.4	5.1

HPV+co_ad = HPV with co-administration

Co_ad only = co-administration only

For each dose and overall/subject:

N= number of subjects with at least one documented dose

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

For overall/dose:

N= number of documented doses

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

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

During the 30-day post-vaccination period, the overall percentage of doses followed by symptoms (solicited and unsolicited) was 87.2%, 91.8% and 66.0% for the HPV only group, HPV+co_ad group and the Co_ad only group, respectively (Table 11).

Table 11. Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period following each dose and overall for 9 year old subjects (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	HPV only	173	162	93.6	88.9	96.8	173	97	56.1	48.3	63.6	173	155	89.6	84.1	93.7
	HPV+co_ad	169	159	94.1	89.4	97.1	169	102	60.4	52.6	67.8	169	154	91.1	85.8	94.9
	Co_ad only	170	116	68.2	60.7	75.2	170	87	51.2	43.4	58.9	170	94	55.3	47.5	62.9
Dose 2	HPV only	172	144	83.7	77.3	88.9	172	81	47.1	39.5	54.8	172	133	77.3	70.3	83.4
	HPV+co_ad	167	151	90.4	84.9	94.4	167	79	47.3	39.5	55.2	167	146	87.4	81.4	92.0
	Co_ad only	169	104	61.5	53.8	68.9	169	70	41.4	33.9	49.2	169	91	53.8	46.0	61.5
Dose 3	HPV only	169	142	84.0	77.6	89.2	169	89	52.7	44.9	60.4	169	136	80.5	73.7	86.2
	HPV+co_ad	166	151	91.0	85.5	94.9	166	89	53.6	45.7	61.4	166	148	89.2	83.4	93.4
	Co_ad only	167	114	68.3	60.6	75.2	167	68	40.7	33.2	48.6	167	91	54.5	46.6	62.2
Overall/dose	HPV only	514	448	87.2	84.0	89.9	514	267	51.9	47.5	56.3	514	424	82.5	78.9	85.7
	HPV+co_ad	502	461	91.8	89.1	94.1	502	270	53.8	49.3	58.2	502	448	89.2	86.2	91.8
	Co_ad only	506	334	66.0	61.7	70.1	506	225	44.5	40.1	48.9	506	276	54.5	50.1	58.9
Overall/subject	HPV only	174	169	97.1	93.4	99.1	174	144	82.8	76.3	88.1	174	164	94.3	89.7	97.2
	HPV+co_ad	169	167	98.8	95.8	99.9	169	136	80.5	73.7	86.2	169	163	96.4	92.4	98.7
	Co_ad only	170	146	85.9	79.7	90.7	170	116	68.2	60.7	75.2	170	132	77.6	70.6	83.7

HPV+co_ad = HPV with co-administration

Co_ad only = co-administration only

For each dose and overall/subject:

N= number of subjects with at least one documented dose

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

For overall/dose:

N= number of documented doses

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

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

The overall percentage of doses followed by grade 3 symptoms (solicited and unsolicited) during the 30-day post-vaccination period was 11.5%, 16.7% and 5.3% for the HPV only group, the HPV+co_ad group and the Co_ad only group, respectively (Table 12).

Table 12. Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period following each dose and overall for 9 year old subjects (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	HPV only	173	17	9.8	5.8	15.3	173	5	2.9	0.9	6.6	173	13	7.5	4.1	12.5
	HPV+co_ad	169	21	12.4	7.9	18.4	169	4	2.4	0.6	5.9	169	17	10.1	6.0	15.6
	Co_ad only	170	9	5.3	2.4	9.8	170	7	4.1	1.7	8.3	170	2	1.2	0.1	4.2
Dose 2	HPV only	172	15	8.7	5.0	14.0	172	6	3.5	1.3	7.4	172	10	5.8	2.8	10.4
	HPV+co_ad	167	21	12.6	8.0	18.6	167	6	3.6	1.3	7.7	167	17	10.2	6.0	15.8
	Co_ad only	169	8	4.7	2.1	9.1	169	8	4.7	2.1	9.1	169	0	0.0	0.0	2.2
Dose 3	HPV only	169	27	16.0	10.8	22.4	169	12	7.1	3.7	12.1	169	20	11.8	7.4	17.7
	HPV+co_ad	166	42	25.3	18.9	32.6	166	13	7.8	4.2	13.0	166	33	19.9	14.1	26.8
	Co_ad only	167	10	6.0	2.9	10.7	167	9	5.4	2.5	10.0	167	1	0.6	0.0	3.3
Overall/dose	HPV only	514	59	11.5	8.9	14.6	514	23	4.5	2.9	6.6	514	43	8.4	6.1	11.1
	HPV+co_ad	502	84	16.7	13.6	20.3	502	23	4.6	2.9	6.8	502	67	13.3	10.5	16.6
	Co_ad only	506	27	5.3	3.5	7.7	506	24	4.7	3.1	7.0	506	3	0.6	0.1	1.7
Overall/subject	HPV only	174	50	28.7	22.1	36.1	174	22	12.6	8.1	18.5	174	35	20.1	14.4	26.8
	HPV+co_ad	169	63	37.3	30.0	45.0	169	21	12.4	7.9	18.4	169	51	30.2	23.4	37.7
	Co_ad only	170	24	14.1	9.3	20.3	170	21	12.4	7.8	18.3	170	3	1.8	0.4	5.1

HPV+co_ad = HPV with co-administration

Co_ad only = co-administration only

For each dose and overall/subject:

N= number of subjects with at least one documented dose

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

For overall/dose:

N= number of documented doses

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

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

Solicited Local symptoms

During the 7-day post-vaccination period, pain was the most frequently reported solicited local symptom in all groups overall per dose. Pain at the injection site was reported following 78.2%, 86.5% and 50.2% of doses in the HPV only, HPV+co_ad and Co_ad only group, respectively.

Redness and swelling were reported more often for the HPV only and HPV+co_ad group than for the Co_ad only group. Redness was reported after 40.3%, 48.6% and 15.4% of the doses at the injection site for groups HPV only, HPV+co_ad and Co_ad only, respectively.

Swelling was reported after 32.5%, 42.6% and 11.3% of the doses in the HPV only group, HPV+co_ad group and the Co_ad only group, respectively.

An increase in the incidence in the reporting of swelling was observed with subsequent doses for the groups HPV only and HPV+co_ad. For group HPV only the reported swelling increased from 26.6% following Dose 1 to 42.0% following Dose 3. For group HPV+co_ad the reported swelling increased from 34.3% following Dose 1 to 51.8% following Dose 3.

Grade 3 pain was reported after 4.3% of the doses at the injection site in the HPV only group versus 9.8% of doses in the HPV+co_ad group and only 0.4% of the doses in the Co_ad only group.

Grade 3 redness was reported after 2.1% of the doses in the HPV only group, 2.8% in the HPV+co_ad group and 0.2% in the Co_ad only group. Grade 3 swelling was reported more often for groups HPV only and HPV+co_ad than for the Co_ad only group with an overall incidence no more than 3.2%. The majority of solicited local symptoms resolved within two days and the majority of grade 3 local symptoms resolved within one day.

An increase in the incidence of swelling was observed with subsequent doses for the groups HPV only and HPV+co_ad. The majority of solicited local symptoms resolved within two days and the majority of grade 3 local symptoms resolved within one day.

Solicited General symptoms

The most commonly reported solicited general symptom in all groups was fatigue; with a frequency of 21.2% in the HPV only group and of 26.3% in the HPV+co_ad group. For the Co_ad only group fatigue was similar to the HPV only group (21.9%). For all other solicited general symptoms, the incidences were within the same range across groups except for myalgia which was less pronounced in the Co_ad only group. No increase in solicited general symptoms was observed with subsequent doses.

The rate of reported solicited grade 3 general symptoms was low and within the same range across groups. Solicited grade 3 symptoms were reported after no more than 1.8% of doses for any individual symptom. The majority of solicited grade 3 general symptoms were considered related to the vaccination by the investigator. Most solicited general symptoms resolved within two days. The majority of grade 3 general symptoms resolved within one day.

Unsolicited symptoms

There are no major differences between the groups in terms of the number of subjects reporting at least one unsolicited symptom within the 30-day post-vaccination period and the number of unsolicited symptoms reported.

Medically significant adverse events

During the entire study period, 60 subjects (17 in the HPV only group [9.7%], 16 in the HPV+co_ad group [9.4%] and 27 in the Co_ad only group [15.9%]) reported 71 medically significant adverse events classified by MedDRA Primary System Organ Class and Preferred Term.

New onset chronic diseases and new onset of autoimmune diseases

Six subjects reported the occurrence of a symptom classified as a new onset of chronic disease (NOCD) based on GSK assessment, as shown in Table 13. There were two subjects in each group with two cases of urticaria in the HPV group, one case of hypoaesthesia and one case of atopic dermatitis in the HPV+co_ad group and one case of allergic cough and one case of allergic rhinitis in the Co_ad only group. None of the NOCDs were classified as SAEs and none were assessed as possibly related to vaccination by the investigator (see individual CSR provided in Module 5 for investigator's assessment). The incidence of reported new onset of chronic disease was within the same range in each group. None of the reported AEs was identified as a potential new onset of autoimmune disease (NOAD) (Company assessment).

Table 13. Percentage of subjects reporting the occurrence of New Onset Chronic Diseases (Company assessment) classified by MedDRA Primary System Organ Class and Preferred Term during the entire study period for 9 year old subjects (Total vaccinated cohort)

		HPV only N = 175				HPV+co_ad N = 171				Co_ad only N = 170			
		95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		2	1.1	0.1	4.1	2	1.2	0.1	4.2	2	1.2	0.1	4.2
Nervous system disorders (10029205)	Hypoaesthesia (10020937)	0	0.0	0.0	2.1	1	0.6	0.0	3.2	0	0.0	0.0	2.1
Respiratory, thoracic and mediastinal disorders (10038738)	Allergic cough (10053779)	0	0.0	0.0	2.1	0	0.0	0.0	2.1	1	0.6	0.0	3.2
	Rhinitis allergic (10039085)	0	0.0	0.0	2.1	0	0.0	0.0	2.1	1	0.6	0.0	3.2
Skin and subcutaneous tissue disorders (10040785)	Dermatitis atopic (10012438)	0	0.0	0.0	2.1	1	0.6	0.0	3.2	0	0.0	0.0	2.1
	Urticaria (10046735)	2	1.1	0.1	4.1	0	0.0	0.0	2.1	0	0.0	0.0	2.1

HPV+co_ad = HPV with co-administration

Co_ad only = co-administration only

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of subjects with at least one administered dose

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

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

Serious Adverse Events

Fatal Events: none

Non-Fatal SAE

Two subjects reported two non-fatal SAE during the study in the 30-day post-vaccination period. One non-fatal event occurred in the HPV+co_ad group and one in the Co_ad only group. None of the non-fatal SAEs were considered by the investigator to be related to the study vaccination.

3.2.6. Safety Conclusions

The safety analysis of the 9 year old subjects from this pooled analysis of studies HPV- 029, HPV-030 and HPV-048 did not show any clinically relevant differences between the different pooled vaccine groups. The rates of solicited local symptoms in the groups HPV only and HPV+co_ad tend to be higher when compared to the Co_ad only group.

However, the symptoms were generally of short duration and compliance was high.

The study vaccine administered in all three groups (either *Cervarix* alone (HPV only), *Cervarix* concomitantly with *Engerix* or *Twinrix* (HPV+co_ad) or *Engerix* or *Twinrix* alone (Co_ad only) was generally well tolerated. There were no new or unexpected safety issues following vaccination in any vaccine group.

3.3. Changes to the product information

The detailed changes can be found in the final approved highlighted SmPC, Annex II and PL attached to this report.

Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested by the CHMP and implemented:

1) Section 4.1: The following revision was endorsed

*“Cervarix is a vaccine **for use from the age of 9 years** for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.”*

2) Section 4.2: The following revision was endorsed:

Paediatric population

*“Cervarix is not recommended for use in girls below **9** years of age due to lack of data on safety and immunogenicity in this age-group.”*

3) Section 5.1: Immunogenicity data were updated.

3.4. Overall conclusions and benefit-risk assessment

In conclusion, non-inferiority of the HPV-16/18 immune response, with respect to GMT ratio at Month 7, was demonstrated for the pooled 9 year old subjects compared to the pooled 10-14 year old subjects and to the pooled 15-25 year old subjects.

These data showed that 9 year old subjects are comparable to subjects 10-14 and 15-25 years of age in terms of seroconversion rates and that the immunological response (GMTs) in 9 year old subjects is non-inferior to the immune response in those older age groups. No clinically relevant differences in the safety profile of the 9 year old subjects who received Cervarix alone or in co-administration with Engerix or Twinrix were observed.

Based on the safety and immunogenicity data in this pooled analysis the CHMP concluded that the risk/benefit balance for Cervarix is favourable to extend the indication to 9 years and adopted the opinion of extending its use to subjects 9 years of age.

4. Conclusion

On 20 October 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.