EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/CHMP/668339/2015
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Cervarix

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

Procedure No. EMEA/H/C/000721/II/0067

Marketing authorisation holder (MAH): GlaxoSmithKline Biologicals

Note

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

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Table of contents

List of abbreviations

AE Adverse Event

AIN Anal Intraepithelial Neoplasia

ATP According to Protocol

CHMP Committee for Medicinal Products for Human Use

CI Confidence Interval

CIN Cervical Intraepithelial Neoplasia

CSR Clinical Study Report

CVT Costa Rica HPV Vaccine Trial

DLP Data Lock Point

DNA DeoxyriboNucleic Acid

ED_{50} Estimated Dose = serum dilution giving a 50% reduction of the signal compared to a control without serum

ELISA Enzyme-Linked Immunosorbent Assay

EMA European Medicines Agency

GCP Good Clinical Practice

GMT Geometric Mean Titre

GSK GlaxoSmithKline

HBs Ag Hepatitis B surface Antigen

HPV Human Papillomavirus

MPL 3-O-desacyl-4'-mono-phosphoryl-lipid

MSC Medically significant conditions

MSM Men having sex with men

NCI National Cancer Institute

NOAD New Onset Autoimmune Disease

NOCD New Onset Chronic Disease

PBNA Pseudovirion-Based Neutralisation Assay

PBRER Periodic Benefit Risk Evaluation Report

PCR Polymerase Chain Reaction

PI Product Information

PSUR Periodic Safety Update Report

qHPV quadrivalent human papillomavirus vaccine (Gardasil/Silgard)

SAE Serious Adverse Event

SmPC Summary of Product Characteristics

TVC Total Vaccinated Cohort

VCSP Vaccines Clinical Safety and Pharmacovigilance

VLP Virus-like Particle

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals submitted to the European Medicines Agency on 12 March 2015 an application for a variation.

The following variation was requested:

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

Extension of Indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the RMP (v.11.0) including the new indication.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0008/2015) on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CHMP Rapporteur: Daniel Brasseur CHMP Co-Rapporteur: N/A

PRAC Rapporteur: Jean-Michel Dogné

Timetable	Actual dates
Submission date	12 March 2015
Start of procedure	28 March 2015
CHMP Rapporteur's preliminary assessment report circulated on	26 May 2015
PRAC Rapporteur's preliminary assessment report circulated on	26 May 2015
PRAC Rapporteur's updated assessment report circulated on	5 June 2015
PRAC RMP advice and assessment overview adopted by PRAC	11 June 2015
CHMP Rapporteur's updated assessment report circulated on	18 June 2015
Request for supplementary information and extension of timetable adopted by the CHMP on	25 June 2015
MAH's responses submitted to the CHMP on	15 September 2015
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	29 October 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	29 October 2015
PRAC RMP advice and assessment overview adopted by PRAC	6 November 2015
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	16 November 2015
2nd request for supplementary information and extension of timetable adopted by the CHMP on	19 November 2015
MAH's responses submitted to the CHMP on	28 January 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	2 March 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	2 March 2016
PRAC RMP advice and assessment overview adopted by PRAC	17 March 2016
3rd request for supplementary information and extension of timetable adopted by the CHMP on	1 April 2016
MAH's responses submitted to the CHMP on	24 May 2016
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	30 May 2016
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	31 May 2016
PRAC RMP advice and assessment overview adopted by PRAC	9 June 2016
CHMP opinion	23 June 2016

2. Scientific discussion

2.1. Introduction

The product

Cervarix is a HPV vaccine that contains recombinant C-terminally truncated major capsid L1 proteins of HPV types 16 and 18 as active ingredients. The L1 proteins of HPV-16 and HPV-18 are separately produced using a recombinant Baculovirus expression system. After expression of the L1 proteins and further purification, the L1 proteins assembled separately as virus-like particles (VLP). The VLPs of each HPV type are formulated with the AS04 adjuvant system composed of aluminium hydroxide and 3-O-desacyl-4-monophosphoryl lipid A (MPL). The MPL immunostimulant is a detoxified derivative of the lipopolysaccharide of the gram negative bacterium Salmonella minnesota R595 strain. One dose of Cervarix contains 20µg of HPV-16 L1 and 20µg of HPV-18 L1 proteins adjuvanted with AS04 and is presented as a sterile turbid liquid suspension for injection, filled as a 0.5ml monodose in either syringes or vials.

Cervarix was first registered in 2007 in Australia and the vaccine is currently licensed for use in more than 130 countries worldwide. In the European Union, Cervarix is indicated from 9 years of age onwards for the prevention of premalignant genital (cervical, vulvar and vaginal) lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. The vaccination schedule depends on the age of the subject. From 9 to and including 14 years, the vaccine is given as two doses, the second dose given between 5 and 13 months after the first dose. From 15 years and above, the vaccine is given as three doses at 0, 1, 6 months.

No Paediatric Investigational Plan (PIP) has been agreed for Cervarix. In 2008 a full-waiver was granted for “Infection by Human Papillomavirus in females”. In 2014 a waiver was submitted for all subsets of the paediatric male population for Human Papillomavirus type 18 L1 protein / Human Papillomavirus type 16 L1 protein (Cervarix) for the “Prevention of infection by human papillomavirus in males”. The Paediatric Committee (PDCO) granted a waiver on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as the needs are already covered by other approved HPV vaccines.

Problem statement

Anal HPV types 16 and 18 infection and anal cancer

Efficacy of prevention against high grade cervical lesions has been clinically demonstrated for both Cervarix and qHPV. As for cervical cancers, anal cancers are also associated with oncogenic HPV type infection. The anal canal is covered with epithelium similar to that covering the cervix. Analogous to the cervical transformation zone, the anal canal has a transformation zone, where columnar cells of the rectum meet squamous cells of the anus. HPV infection and the pathogenic process of disease development occur in a similar way in the anal canal as in the cervical canal (Alani, 1998; Hernandez, 2005). In the same way as cervical cancer is preceded by cervical intraepithelial neoplasia (CIN), HPV-related anal cancer is preceded by anal intraepithelial neoplasia (AIN) lesions, classified in grades 1 to 3 (Watson, 2006, Abbasakoor, 2005). HPV-related anal cancer is predominantly associated with infection with HPV types 16 and 18 (Chaturvedi, 2010), that are included in Cervarix. It is estimated that up to 90% of all anal cancers are caused by HPV-16 and HPV-18 (WHO, 2014) and HPV-16 and HPV-18 are responsible for approximately 78% of HPV-related high-grade anal (AIN 2/3) intraepithelial neoplasia (De Vuyst, 2009). In a large population-based case-controlled study conducted in both men and women in the US, 88% of all anal tumours were HPV DNA positive, with HPV-16 the most frequent

type found in the tissues (73% of all tumours), followed by HPV-18 (6.9%), regardless of gender. In the case of men who were not exclusively heterosexual, the proportion of HPV DNA positive anal tumours raised to 97.7% (Daling, 2004). A study conducted in France showed HPV-16 and HPV-18 infection (alone or in association with other HPV types) in 78% of all anal cancer cases (Abramowitz, 2011). The strong association between HPV infection, in particular of HPV types 16 and 18 and anal cancer is confirmed through two meta-analyses, with HPV DNA detected in 71% of invasive anal cancers (of which 72% were associated with HPV-16/18) in the first analysis (Hoots, 2009) and HPV prevalence of 84.3% in anal carcinoma in the second analysis (De Vuyst, 2009) of which 73.4% related to HPV-16, followed by HPV- 18 (5.2%). In the analysis of the placebo arm of a multi country clinical trial with qHPV, anogenital acquisition of HPV-6/11/16/18 was common among heterosexual males, with 9.0 cases per 100 person/years at risk observed and HPV-16 was the type found with the highest incidence (Moreira, 2014). Among HIV-1-negative men having sex with men (MSM) attending a clinic in Italy, 74.8% were DNA positive for any HPV type and 56.2% were positive for any oncogenic HPV type. The most common oncogenic HPV type was HPV-16 (17.8% of HPV-positive subjects) (Donà, 2012). In healthy young females enrolled in the Costa Rica HPV Vaccine Trial (CVT), also referred to as study HPV-009 (conducted by NCI in collaboration with GSK), overall anal HPV infection prevalence was 31.6%, with higher prevalence in women with history of anal intercourse (43.4% vs. 28.4% for women without history) (Castro, 2012). These observations demonstrate that HPV infection is common among women and men (both heterosexual and MSM).

Mode of action of HPV vaccines

The prevention by vaccination against premalignant genital lesions and cervical cancer is mediated by the subjects immune system eliciting antibodies against the VLPs present in the vaccine. No serological correlate of protection has been established for HPV vaccines, however high levels of antibodies against HPV-16/18 are indicative of an effective protection against HPV infection (Stanley, 2012; Safaeian, 2010; Romanowski, 2009; Castellsagué, 2014). The neutralising antibodies will prevent the entry of the virus into the basal epithelial cells, thereby preventing initial infection of the individual with the pathogen (Schiller, 2010; Day, 2010). Likewise, vaccination may also protect against infection of the anal basal epithelial cells with HPV types 16 and 18, thereby preventing the first step in the pathogenic development of anal cancer. Vaccination with qHPV has indeed been shown to be efficacious in preventing the development of pre-cancerous anal lesions in a clinical trial (Palefsky, 2011).

Current application

The purpose of this variation was to propose an extension of the therapeutic indication of Cervarix to include prevention against premalignant anal lesions and anal cancer in males and females aged 9 years and older, based on immunogenicity and safety data obtained from 4 clinical studies that were either completed (HPV-010, HPV-011) or ongoing at the time of the initial submission with interim data submitted (HPV-040, HPV-071). No efficacy data were generated as part of these studies.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Study country (ies)	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects	
					ATP cohort	TV cohort
Studies showing non-inferiority and superiority of the immune response to *Cervarix* over *Gardasil* in females						
HPV-010-108933	USA	Phase IIIb, observer-blind, multicenter, randomized trial Primary Objective: To compare the immune responses to HPV-16 and -18 induced by the *Cervarix* and *Gardasil*, in terms of HPV-16 and -18 geometric mean titers measured by neutralization assay, at Month 7 in healthy adult females 18 to 26 years of age (data already described in a separate submission). Secondary objectives (persistence and safety up to Month 60): • To evaluate the immune responses (by PBNA) in sera to HPV-16 and -18 induced by *Cervarix* and *Gardasil* in terms of HPV-16 and -18 GMTs and seroconversion rates in all subjects at Months 6, 12, 18, 24, 36, 48 and 60 and seroconversion rates at Month 7. • To evaluate the immune responses (by ELISA) in sera to HPV-16 and -18 induced by *Cervarix* and *Gardasil* in terms of HPV-16 and -18 GMTs and seroconversion rates in all subjects at Months 6, 7, 12, 18, 24, 36, 48 and 60. • To evaluate the safety of *Cervarix* and *Gardasil*.	Healthy Adult females (18-45 years of age) 3 doses: *Cervarix* (0, 1, 6-months) and *Gardasil* (0, 2, 6-months). Placebo [$Al(OH)_3$] was administered at either Month 2 (*Cervarix* recipients) or Month 1(*Gardasil* recipients)	*Cervarix* *Gardasil*	M7: 370 M60: 159 M7: 364 M60: 156	M7: 553 M60: 213 M7: 553 M60: 208
HPV-071 PRI-115411	Sweden, Hong Kong, France, Singapore	Phase IIIb, observer-blind, randomised, age-stratified, multi-centre study Primary Objective: To evaluate sequentially if the immunogenicity (as determined by ELISA) of GSK Biologicals' *Cervarix* vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior/superior to that of Merck's *Gardasil* vaccine administered according to a 2-dose schedule at 0, 6 months in 9-14 years old females, one month after the last dose (Month 7). Secondary objectives: **Immunogenicity** • If the primary non-inferiority objective is reached, the next objective is to evaluate sequentially if the immunogenicity (as determined by ELISA) of GSK Biologicals' *Cervarix* vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior/superior to that of Merck's *Gardasil* vaccine administered according to a 2-dose schedule at 0, 6 months at Months 12, 18, 24 and 36. • If the primary non-inferiority objective is reached, the next objective is to evaluate sequentially if the immunogenicity (as determined by ELISA) of GSK Biologicals' *Cervarix* vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior/superior to that of Merck's *Gardasil* vaccine administered according to the standard 3-dose schedule at 0, 2, 6 months at Months 7, 12, 18, 24 and 36. • To assess the immune responses to HPV types 16 and 18 by ELISA at Day 0 and Months 7, 12, 18, 24 and 36 in all subjects. • To assess the immune responses to HPV types 16 and 18 by PBNA in a subset of subjects at Day 0 and Months 7, 12, 18, 24 and 36. • To assess CMI, i.e., T-cell-mediated and memory B-cell immune	Adolescent females (9-14 years of age) 2 doses: *Cervarix* (0, 6-months) or *Gardasil* (0, 6-months). 3 doses: *Gardasil* (0, 2, 6-months).	HPV_2D Gard_2D Gard_3D	M7: 337 M12: 331 M7: 334 M12: 325 M7: 334 M12: 327	M7: 359 M12: 356 M7: 358 M12: 348 M7: 358 M12: 350

		responses specific to HPV-16 and HPV-18 in a sub-cohort of subjects at Day 0, Months 7, 12, 24 and 36. **Safety** • To assess the reactogenicity of the administered vaccines in all groups after each dose. • To assess the safety of the administered vaccines in all groups. • To evaluate compliance with completion of vaccination in all groups.				

Study ID	Study country (ies)	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects	
					ATP cohort	TV cohort
Studies documenting immunogenicity and safety of vaccination with *Cervarix* in males						
HPV-011-580299/ 011	Finland	Phase I/II, observer-blind, controlled, randomized (2:1) multicentric trial Primary Objective: To evaluate 1 month after the third dose (i.e. at Month 7), the immune responses to the GSK Biologicals' *Cervarix* vaccine (as determined by anti-HPV-16/18 ELISA) in healthy male subjects aged 10-18 years old. Secondary objectives: • To evaluate 1 month after the second dose (i.e., at Month 2) the immune responses to the GSK Biologicals' *Cervarix* vaccine (as determined by anti-HPV-16/18 ELISA) in healthy male subjects aged 10-18 years old. • To evaluate the safety and the reactogenicity of the GSK Biologicals' *Cervarix* vaccine compared to the *Engerix-B* [Hepatitis B virus (HBV)] control vaccine. • To demonstrate the non-inferiority of the immune responses to the GSK Biologicals' *Cervarix* vaccine (as determined by anti-HPV-16/18 ELISA) in healthy male subjects aged 10–18 years in this study, compared to the responses measured in sera from a subset of 15-25 year old females from the HPV-012 study, one month after administration of the third vaccine dose (i.e. at Month 7). *Criteria for non-inferiority: (1) one month after the third dose, the upper limits of the 95% Confidence Interval (CI) on the difference of seroconversion rates for HPV-16 and HPV-18 between the 15-25 year old female Cervarix vaccine recipients in study HPV-012 and the 10-18 year old males in the Cervarix vaccine group of this study were below 10%, (2) one month after the third dose, the upper limits of the 95% CI on the GMT ratios for HPV-16 and HPV-18 between the 15-25 year old females group of study HPV-012 and the 10-18 year old males in the Cervarix vaccine vaccine group of this study were below 2.*	Adolescents/Adults (10-18 years of age) 3 doses: *Cervarix* / *Engerix-B* control vaccine administered intramuscularly according to a 0, 1, 6 month schedule	*Cervarix* *Engerix-B*	M7: 173 M7: 86	M7: 181 M12*: 175 M7: 89 M12*: 86 * Extended safety follow up
HPV-040 PRI-106636	Finland	Phase III/IV, partially blinded, community-randomized, controlled trial Primary Objectives: • To demonstrate the overall (direct and indirect) effectiveness of GSK Biologicals' *Cervarix* vaccine in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age following community-based vaccination of 12 - 15 year old females only (Arm B versus Arm C). • To demonstrate the overall (direct and indirect) effectiveness of GSK Biologicals' *Cervarix* vaccine in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age, following community-based vaccination of 12 - 15 year old females and males (Arm A versus Arm C). Secondary objectives: • To monitor the safety of *Cervarix* vaccination in males and females. • To assess the immunogenicity of the *Cervarix* vaccine in a subset of males and females (Arm A immunogenicity subset).	Adolescents (12-15 years of age) 3 doses: *Cervarix* / *Engerix-B* control administered intramuscularly according to a 0, 1, 6-month schedule	Arm A (90% of male and female subjects vaccinated with the *Cervarix* vaccine and 10% with *Engerix-B* vaccine) Arm B (90% of female subjects vaccinated with the *Cervarix* vaccine and 10% with *Engerix-B* vaccine; all male subjects vaccinated with *Engerix-B*) [*4 male subjects were accidentally vaccinated with *Cervarix* vaccine] Arm C (All male and female subjects vaccinated with *Engerix-B* vaccine; no *Cervarix* vaccine administered)	1829 (*Cervarix*) 225 (*Engerix-B*)	14838 (*Cervarix*) (Arm A=8239; Arm B=6567; Arm C=32) 17338 (*Engerix-B*) (Arm A=988; Arm B=5666; Arm C=10684) **Male study participants with active follow-up M0-M12 for SAEs** 2436 (*Cervarix*) 1267 (*Engerix-B*) **Male study participants in the Diary Card subset** 643 (*Cervarix*) 1047 (*Engerix-B*)

2.4. Clinical efficacy

No efficacy data were generated as part of the studies HPV 010, HPV-011, HPV-040 (month 7) and HPV-071.

The MAH proposes to justify the potential clinical efficacy of Cervarix against anal lesions and anal cancer in both males and females by:

- In females: Immunogenicity bridging to another HPV vaccine that currently has the "anal" indication based on efficacy data in males (qHPV);
- In males: Immunogenicity bridging to a population in which vaccine efficacy in the "cervical" indication has been demonstrated (females aged 15-25 years).

Table 1. Overview of immunobridging to support the anal indication application

Gender	Age (years)	Comparison	Data point	Cervarix		qHPV	
				3-dose	2-dose	3-dose	2-dose
M	10-18	Seroresponses rate, GMT	M7	•			
	12-15	GMT	M7	**o**			
F	9-14	Seroresponses rate, GMT	M12		**xx**	**xx**	**xx**
	12-15	GMT	M7	**o**			
	15-25	Seroresponses rate, GMT	M7	•			
	18-45	Seroresponses rate, GMT	M60	**x**		**x**	

Similar symbols indicate where comparative analyses were performed

The following immunological assays were used for immunogenicity evaluation:

- Pseudovirion-Based Neutralization Assay (PBNA) was used to assess non-inferiority versus qHPV 1 month after the last dose (Month 7) as the primary immunogenicity endpoint in study HPV-010. The assay was also used for assessment of secondary immunogenicity objectives (e.g. long-term antibody persistence) in the same study and in study HPV-071.
- Enzyme-linked Immunosorbent Assay (ELISA) was used for the assessment of non-inferiority and superiority versus qHPV at Month 7 in study HPV-071 (primary immunogenicity endpoint) and for the immunogenicity assessments in studies HPV-011 and HPV-040. The ELISA assay was also used for secondary immunogenicity endpoints in study HPV-010 (non-inferiority versus qHPV at different time points).

2.4.1. Main studies

Studies documenting immunogenicity and safety of Cervarix in females

- HPV-010 demonstrates superiority of immune response to Cervarix over qHPV in healthy females aged 18-45 years in a 3-dose schedule. Final study results up to Month 60 are submitted herein. Interim study results were previously submitted (Variation II-36, published).
- HPV-071 demonstrates superiority of immune response to Cervarix in healthy females aged 9-14 years in a 2-dose schedule over qHPV administered in a 2-dose and in a 3-dose schedule (ELISA). Interim study results up to Month 12 are submitted herein. PBNA was performed in a

subset and results are in line with ELISA. This study was ongoing at the time of the initial submission for this application (see further below).

Studies documenting immunogenicity and safety of Cervarix in males

- HPV-011 was a Phase I/II study that demonstrated immunogenicity and acceptable safety in healthy males aged 10-18 years in a 3-dose schedule. Immune responses elicited by Cervarix in males (10-18 years of age) are non-inferior (in terms of seroconversion rates and GMTs) to immune responses elicited by Cervarix in females 15-25 years of age (the age range in which vaccine efficacy was demonstrated) enrolled in study HPV-012. Final study results at Month 12 were previously submitted (FUM 28).
- HPV-040 is a Phase III/IV study that demonstrated immunogenicity and acceptable safety in healthy males aged 12-15 years in a 3-dose schedule. This study was ongoing when this application started. Interim results at Month 7 were previously submitted (FUM 34).

Study HPV-009

In addition, the MAH referred to post-hoc data originated from the clinical efficacy study HPV-009, conducted by the National Cancer Institute (NCI, US) in collaboration with GSK i.e. the Costa Rica Vaccine Trial (CVT), to support the current application with vaccine efficacy data against clinical endpoints such as anal and cervical infection.

Inclusion criteria for all studies

Healthy subjects (of ages 9 years - 45 years) were enrolled in all studies, for whom the investigator believed that they and/or their parents/ Legally acceptable representative(s) (LARs) could and would comply with the requirements of the protocol. Written informed consent was obtained from the subject prior to enrolment and any study procedure. For subjects below the legal age of consent, a written informed consent was obtained from the subject's parent/LAR, and a written informed assent was obtained from the subject. For study HPV-040, for subjects above legal age of consent, written informed consent was obtained from the subject and an information letter was provided to their parent/LAR(s).

Exclusion criteria for all studies

In general, the objective of the exclusion criteria was to prevent the administration of the study vaccine to individuals with medical conditions that could potentially interfere with the evaluation of the immune response, and to individuals at risk of possible adverse reaction to a vaccine. Subjects were to be free of obvious health problems as established by medical history and clinical examination. In case of female subjects, they had to be of non-childbearing potential or, if of childbearing potential, had a negative pregnancy test on the day of vaccination, had to be abstinent or had to be using adequate contraceptive precautions for 30 days prior to vaccination and had to agree to continue such precautions for two months after completion of the vaccination series. No previous vaccination against HPV or hepatitis B (studies with Engerix-B as control) was allowed.

2.4.1.1. HPV-010

This study was a phase IIIb, observer-blind, randomized (1:1), multicentre study with two parallel groups to compare the immunogenicity of Cervarix versus qHPV, when administered intramuscularly according to a 3-dose schedule in healthy adult females 18-45 years of age. This study was a multicentre study conducted in 40 centres located in the USA.

The clinical study report for study HPV-010 (from Month 7 till Month 48) was previously submitted and assessed in the frame of EMEA/H/C/00721/II/036 (CHMP assessment report published). For this reason, only a brief summary of the study design and statistical methods are given below. The submission of the final report at Month 60 is discussed herein.

Methods

Recruitment

Healthy females 18-45 years of age were arranged in two parallel groups:

- One group received the GSK HPV vaccine (N=553)
- One group received the qHPV vaccine (N=553)

Enrolment into each treatment group was age-stratified with a slightly greater number of subjects in the 18-26 year-old cohort (417 subjects) than in the 27-35 year-old cohort (356 subjects) or the 36-45 year-old cohort (333 subjects).

For inclusion and exclusion criteria see section 2.4.1.

Treatment and blinding

Three doses of vaccine were administered according to the recommended schedule for Cervarix (0, 1, 6-months) and qHPV (0, 2, 6-months). To maintain blinding, all subjects received injections at Months 0, 1, 2 and 6. Placebo [Al(OH)3] was administered at either Month 2 (Cervarix recipients) or Month 1 (qHPV recipients). The subjects, investigator, study personnel and MAH staff remained blinded until completion of study follow-up. The method of data collection occurred through Remote Data Entry (RDE). Five visits were scheduled per subject on Day 0, at Months 1, 2, 6 and 7 in the active phase. Additionally, there were 6 follow-up study visits scheduled at Months 12, 18, 24, 36, 48 and 60. A cervical sample was collected from all subjects for HPV deoxyribonucleic acid (DNA) testing on Day 0. Blood samples of 20 mL were collected from all subjects on Day 0, at Months 6, 7, 12, 18, 24, 36, 48 and 60 for evaluation of antibody response. An additional 50 mL blood sample on Day 0, at Months 7, 12, 18, 24, 36 and 48 was collected for evaluation of CMI response in a subset of subjects from pre-selected sites. Cervico-vaginal Secretion Sample (CVS) were collected for HPV-16/18 antibody testing on Day 0, at Months 7, 12, 18, 24, 36 and 48 in a subset of subjects from preselected sites.

Between-group comparisons

- Primary between-group comparisons to assess superiority were performed in the total vaccinated cohort (TVC). At Month 7, the inferential analyses were statistically powered.
- At subsequent time points, including Month 60, inferential statistics were exploratory.

Non-inferiority and superiority criteria

For each serology assay (PBNA and/or ELISA), for each treatment group (Cervarix and qHPV), for each age group (18-26, 27-35 and 36-45 years of age), at each time point that a blood sample result was available: i) Seropositivity rates for HPV-16, HPV-18, HPV-31 and HPV-45 antibodies (with exact 95% confidence interval [CI]) were calculated; ii) GMT with 95% CI and range of antibody titres were tabulated for antibodies against HPV-16, HPV-18, HPV-31 and HPV-45.

- If the lower limits of the two-sided 97.6% confidence interval (CI) for the GMT ratios (Cervarix divided by qHPV) for anti-HPV-16 and anti-HPV-18 antibodies were above 0.5, non-inferiority of Cervarix to qHPV was to be concluded.

- If the lower limit of the two-sided 97.6% CI for the ratio of GMTs of a given antigen was above 1, the p-value associated with a test of superiority was also to be calculated for that antigen.

Study cohorts

- The Month 7 ATP cohort for immunogenicity consisted of 370 subjects in the Cervarix group and 364 subjects in the qHPV group.
- The Month 7 TVC consisted of 553 subjects in the two groups.
- The Month 60 ATP cohort for immunogenicity consisted of 159 subjects in the Cervarix group and 156 subjects in the qHPV group and the TVC consisted of 213 subjects in the Cervarix group and 208 subjects in the qHPV group.

Demographic characteristics

- The demographic profile of subjects in the Month 60 ATP cohort for immunogenicity was comparable between the two vaccine groups with respect to age (mean age in years: 31.6±7.68 in Cervarix group vs. 31.5±8.06 in qHPV group) and ethnicity/racial distribution (predominantly Caucasian and European: 88.7% in Cervarix vs. 87.8% in qHPV group). A similar demographic profile was seen in the TVC.

Study endpoints for immunogenicity

- The primary endpoint was HPV-16/18 geometric mean antibody titre (GMT) assessment by PBNA at M7 in healthy adult females 18-26 years of age.
- The secondary endpoints included the immunogenicity assessment using PBNA of
  - HPV-16/18 antibody titres at M7 in healthy adult females 27-35 and 36-45 years of age.
  - HPV-16/18 seroconversion status at M7 in healthy adult females 18-26 years of age.
  - HPV-16/18 seroconversion status at M7 in healthy adult females 27-35 and 36-45 years.
  - HPV-16/18 antibody titres and seroconversion status at M6, 12, 18, 24, 36, 48 and 60.
- The secondary endpoints included the immunogenicity assessment using ELISA of
  - HPV-16/18 antibody titres and seroconversion status at M 6, 7, 12, 18, 24, 36, 48 and 60.

Other secondary endpoints were also assessed in this study, but they are not relevant for the purpose of this application (for details see assessment report of variation II-36).

Results for study HPV-010

Study results for HPV-010 for the time points 7 Months, 24 Months and 60 Months have been published (Einstein, 2009; Einstein, 2011; Einstein, 2014). The most relevant results for this application are reported as follows.

Immunogenicity analysis at Month 7

The primary endpoint was met. All initially seronegative and DNA negative subjects in the Cervarix group seroconverted as measured by neutralisation assay at Month 7 for both HPV-16 and HPV-18. In the qHPV group all but two subjects (in the 27-35 age group for HPV-18) who were initially seronegative and DNA negative for HPV-18 seroconverted at Month 7. The primary objective of the study, i.e. the comparison of the GMTs (PBNA) of HPV-16 and -18 serum antibodies at Month 7 after first vaccination with Cervarix or qHPV in women aged 18–26 years old, showed non-inferiority and superiority of the antibody response elicited by Cervarix vaccination over qHPV. The HPV-16 GMTs for

the Cervarix group were 3.66-fold (2.56; 5.23) higher than for the qHPV group. Similarly, the HPV-18 GMT was 7.30-fold higher (5.14; 10.37) for the Cervarix group than the qHPV group. As the lower limits of the confidence intervals were greater than 0.5, non-inferiority was demonstrated. Non-inferiority was also demonstrated for the 27-35 age group as well as the 36-45 age group for both HPV types. Compared with qHPV, anti-HPV-16 and -18 GMTs with Cervarix were respectively 4.8-fold (3.3; 7.1) and 9.1- fold (6.0; 13.8) higher in women aged 27–35 years and 2.3-fold (1.5; 3.4) and 6.8-fold (4.6; 10.2) higher in women aged 36–45 years.

The primary superiority assessment was performed in the TVC (regardless of serostatus and DNA status at baseline) and demonstrated superiority of the antibody titres in the Cervarix group versus qHPV for all age groups and for both HPV-16 and HPV-18 (p value< 0.0001). Superiority was concluded if the p-value was ≤ 0.024.

Persistence of immune response as measured by PBNA after vaccination (Month 60 analysis, secondary endpoint)

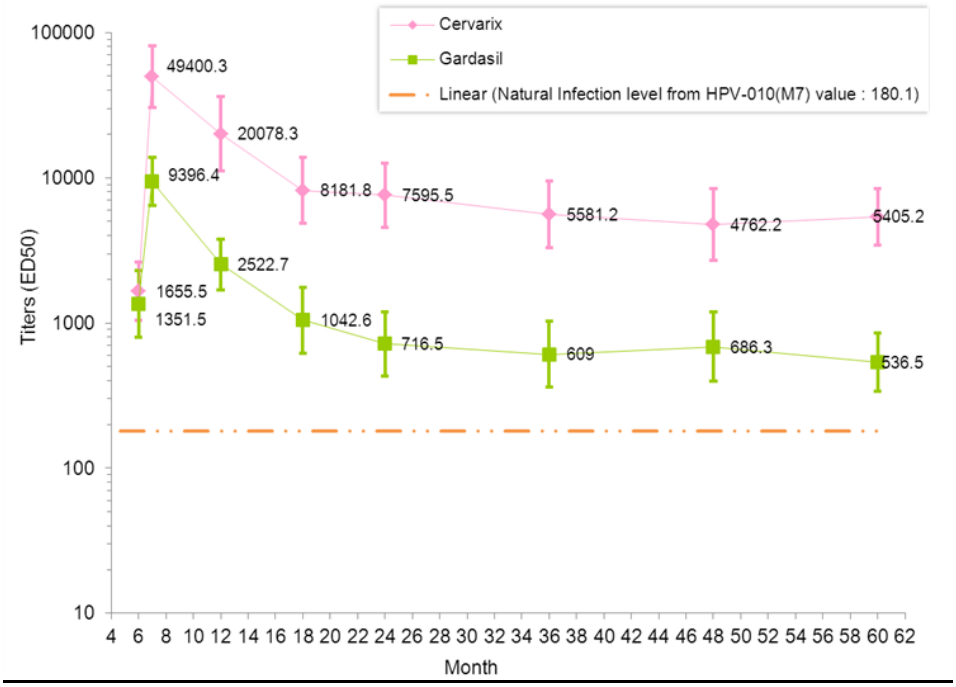
1. *Anti-HPV-16 immune response in seronegative and DNA negative subjects at baseline (Month 60 ATP cohort for immunogenicity)*

All initially seronegative and DNA negative subjects in the Cervarix group remain seropositive by PBNA for HPV-16 antibodies at Month 60, in all the age strata. In the qHPV group, depending on the age stratum, 95.7% to 97.5% of subjects remained seropositive for HPV-16 antibodies at Month 60.

HPV-16 antibody levels were higher in the Cervarix group when compared with the qHPV group for all age strata (7.77-fold (4.31; 14.02) in the 18-26 age group, 5.56-fold (3.03; 10.19) in the 27-35 age group and 2.23-fold (1.27; 4.29) in the 36-45 age group).

The kinetics of HPV-16 neutralising antibody levels (measured by PBNA) were analysed in the Month 60 kinetic cohort of subjects that were seronegative and DNA negative at baseline for the HPV type analysed and that had data available for all time points. For both vaccines, the GMTs for HPV-16 antibodies (PBNA) remain above the level obtained through natural HPV infection (ED_{50}: 180.1). The natural infection level has been defined as the mean antibody titre to a specific HPV-type in subjects seropositive and DNA negative for the same type prior to vaccination with Cervarix (i.e. subjects who have cleared a previous HPV infection) (Einstein, 2009). Figure 1 below shows the kinetics up to Month 60 in the 18-26 years stratum. The other 2 age strata showed similar trends.

Figure 1. GMTs with 95% CI for HPV-16 PBNA antibodies in female subjects seronegative (by PBNA) and DNA negative (by PCR) at baseline (kinetic cohort) - 18-26 years stratum



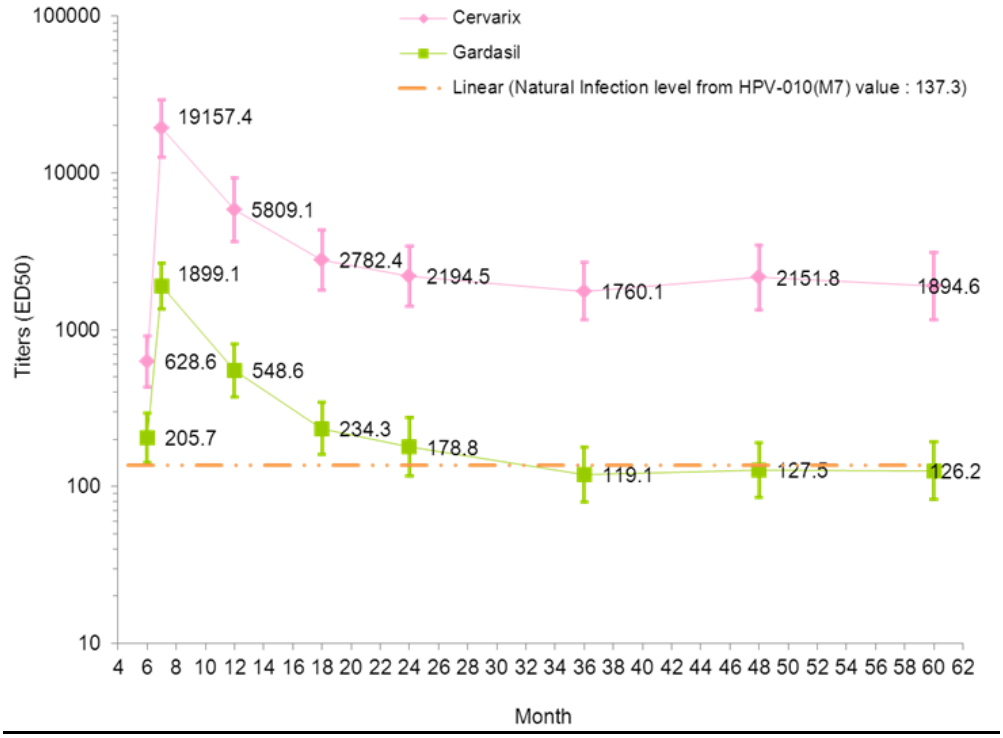
2. *Anti-HPV-18 immune response in seronegative and DNA negative subjects at baseline (Month 60 ATP cohort for immunogenicity)*

In the Cervarix group, 98.1% to 100% of initially seronegative and DNA negative subjects were still seropositive for HPV-18 antibodies at Month 60 (one subject in the 27-35 age group was tested seronegative at Month 60). In the qHPV group, 61.1% to 76.9% of subjects were still seropositive for HPV-18 antibodies at Month 60.

For seronegative and DNA negative subjects at baseline, HPV-18 antibody levels were higher in the Cervarix group when compared to the qHPV group for all age strata (12.07-fold (6.60; 22.08) in the 18-26 age group, 13.00-fold (7.59; 22.25) in the 27-35 age group and 7.76-fold (4.53; 13.29) in the 36-45 age group).

The kinetics of HPV-18 neutralising antibody levels (measured by PBNA) were analysed in the Month 60 kinetic cohort of subjects that were seronegative and DNA negative at baseline for the HPV type analysed and that had data available for all time points. The kinetics up to Month 60 are shown in Figure 2 for the 18-26 years stratum. In the other 2 age strata, whereas the GMTs within the Cervarix group remained sustainably above the level obtained through natural infection (ED_{50}: 137.3), the GMTs in the qHPV group dropped below that level from Month 18 in the 27 to 35 years stratum, and from Month 36 in the two other age strata (not shown).

Figure 2. GMTs with 95% CI for HPV-18 PBNA antibodies in female subjects seronegative (by PBNA) and DNA negative (by PCR) at baseline (kinetic cohort) - 18-26 years stratum



3. Exploratory inferential statistics at Month 60

Exploratory inferential analyses were performed with a type I error of 5%. Statistically significant differences (p-value [p] ≤ 0.05) should be interpreted with caution considering that there was no adjustment for multiplicity of comparisons and that the clinical relevance of the difference is unknown.

The analysis determined non-inferior GMTs in the Cervarix group as compared to the qHPV group in subjects seronegative and DNA negative at baseline (Month 60 ATP cohort for immunogenicity) (not shown).

The subsequent superiority test showed GMTs of HPV-16 and HPV-18 (PBNA) antibodies at Month 60 in the Cervarix group to be higher than those in the qHPV group in TVC regardless of baseline serostatus, across the three age strata (table 2).

Table 2. Superiority assessment in terms of antibody titres between Cervarix and qHPV for HPV16 and HPV18 PBNA antibodies at Month 60 (Total Vaccinated cohort)

		Cervarix		*Gardasil*			
Antibody	**Age**	**N**	**GMT**	**N**	**GMT**	**P_value ANOVA**	**P_value Kruskal Wallis**
HPV16.PsV AB	18-26 Y	62	4035.97	65	831.84	<.0001	<0.0001
	27-35 Y	76	2550.23	60	859.12	<.0001	<0.0001
	36-45 Y	75	2320.52	82	1109.69	0.0074	0.00496
HPV18.PsV AB	18-26 Y	62	1524.81	65	120.18	<.0001	<0.0001
	27-35 Y	76	1094.28	60	122.02	<.0001	<0.0001
	36-45 Y	75	870.21	82	189.51	<.0001	<0.0001

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
Exploratory analysis

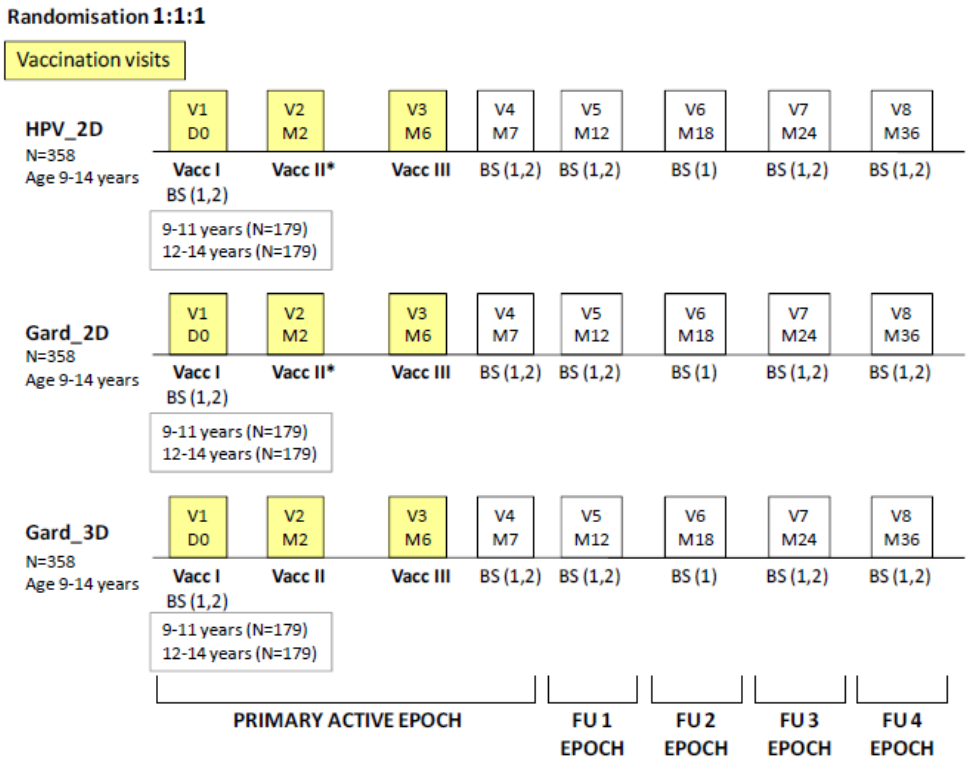
4. Immune response measured by ELISA

Overall, for HPV-16 and HPV-18, analyses by ELISA corroborated the results observed by PBNA.

As an overall conclusion for study HPV-010, in females 18-45 years of aged who received Cervarix according to a 3-dose schedule, final study results up to Month 60 show that GMTs for antibodies against both HPV-16 and HPV-18 reached a peak response at Month 7, showed a decline up to Month 12 in all three groups, and then remained relatively stable over time and always higher than qHPV.

2.4.1.2. Study HPV-071

HPV-071 is a Phase IIIb observer-blind, randomized, multi-centre trial (Sweden, Hong Kong, France and Singapore), which was ongoing at the time of the submission of this application (completed in December 2015). Interim results up to Month 12 were submitted for this application. The study design is shown below:



N = number of subjects; V = Visit; D = Day; M = Month; Vacc = Vaccination
BS (1) = blood sample for immunogenicity (assessment of ELISA in all subjects and PBNA in a subset of subjects)
BS (2) = blood sample for CMI in a sub-cohort of subjects
FU = follow-up
* Subjects in the 2-dose groups received placebo ($Al(OH)_3$ at Visit 2 (Vacc II) to maintain the study as observer-blind.
The results of the analyses conducted on data collected during the follow-up epochs are being/ will be reported in annex reports.

Methods – analysis of data submitted

Recruitment

- Females aged 9-14 years

For inclusion and exclusion criteria see section 2.4.1.

Treatment groups

- 3 parallel groups

  - Cervarix according to a 2-dose schedule (0, 6 months)
  - qHPV according to a 2-dose schedule (0, 6 months)
  - qHPV according to a 3-dose schedule (0, 2, 6 months)
- The two groups vaccinated according to the 2-dose schedule received one dose of placebo at Month 2 to maintain study blind (observer-blind).

Study objectives

- The primary objective of the trial was to evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix was non-inferior/superior to that of qHPV one month after the last dose (Month 7) according to a 2-dose schedule at 0, 6 months in 9-14 years old females.
- First secondary objective: if non-inferiority at Month 7 was shown, non-inferiority/superiority analysis by comparison of the immune response to both vaccine antigens between the Cervarix 2-dose group and the qHPV 2-dose group at Months 12, 18, 24 and 36 will be performed.
- Additional secondary objective: if the primary non-inferiority objective was reached, a secondary objective was to evaluate sequentially and at the different time points if the immunogenicity of Cervarix administered according to a 2-dose schedule at 0, 6 months was non-inferior/superior to that of qHPV administered according to the standard 3-dose schedule at 0, 2, 6 months. The immune responses to HPV types 16 and 18 by PBNA in a subset of subjects at the different time points up to Month 36 were additional secondary objectives as well. See also table below:

Table 3. Immunogenicity objectives for study HPV-071

Objective	Time point	Comparison	Sequential objectives (analysis)
Primary objectives (sequential)	Month 7	*Cervarix* 2-dose versus *Gardasil* 2-dose	Non-inferiority of seroconversion HPV-16 and HPV-18
			Non-inferiority of GMTs HPV-16 and HPV-18
			Superiority* of GMTs HPV-16 and HPV-18
First secondary objectives (sequential)	Months 12 and subsequent time points	*Cervarix* 2-dose versus *Gardasil* 2-dose	Non-inferiority of seroconversion HPV-16 and HPV-18
			Non-inferiority of GMTs HPV-16 and HPV-18
			Superiority* of GMTs HPV-16
			Superiority* of GMTs HPV-18
Additional secondary objectives (sequential)	Month 7 and subsequent time points	*Cervarix* 2-dose versus *Gardasil* 3-dose	Non-inferiority of seroconversion HPV-16 and HPV-18
			Non-inferiority of GMTs HPV-16 and HPV-18
			Superiority* of GMTs HPV-16 and HPV-18

*: Superiority assessment was performed if non-inferiority was reached, and if the lower limit of the two-sided 95% CI for the ratio of GMTs *Cervarix* divided by *Gardasil* of a given antigen was above 1 in the ATP cohort for immunogenicity

Numbers of subjects in the different cohorts are presented below:

Table 4. Number of subjects in HPV-071

Number of subjects	*Cervarix* 2-dose	*Gardasil* 2-dose	*Gardasil* 3-dose
Month 7 Total Vaccinated Cohort	359	358	358
Month 7 ATP cohort for immunogenicity	337	334	334
Month 12 Total Vaccinated Cohort	356	348	350
Month 12 ATP cohort for immunogenicity	331	325	327

Demographic characteristics

- In the ATP cohort, the age at vaccination was comparable between the different groups (11.5 ± 1.62 years in Cervarix group, 11.5 ± 1.55 years in qHPV 2-dose group and 11.6 ± 1.63 years in qHPV 3-dose group).
- The three groups had a comparable ethnical/racial distribution, with an approximate 50% of the subjects in each group of East Asian heritage and an approximate 25% of Caucasian heritage. Demographic characteristics in the TVC were similar.

Study endpoints

- Primary endpoints are the assessment of anti-HPV-16/18 seroconversion rates and antibody titres by ELISA, one month after the last dose of study vaccine (Month 7). For each HPV antigen (HPV-16 and HPV-18), the immune response in terms of seroconversion rates and GMTs at Month 7 was compared sequentially between the Cervarix group and the qHPV group by non-inferiority and superiority analyses.
- Secondary endpoints for immunogenicity:
  - If the primary non-inferiority objective is reached, the next objective is to evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix administered according to a 2-dose schedule at 0, 6 months is non-inferior/superior to that of qHPV administered according to a 2-dose schedule at 0, 6 months at Months 12, 18, 24 and 36.
  - If the primary non-inferiority objective is reached, the next objective is to evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix administered according to a 2-dose schedule at 0, 6 months is non-inferior/superior to that of qHPV administered according to the standard 3-dose schedule at 0, 2, 6 months at Months 7, 12, 18, 24 and 36.
  - To assess the immune responses to HPV types 16 and 18 by ELISA at Day 0 and Months 7, 12, 18, 24 and 36 in all subjects.
  - To assess the immune responses to HPV types 16 and 18 by PBNA in a subset of subjects at Day 0 and Months 7, 12, 18, 24 and 36.
  - To assess cell-mediated immunity (CMI), i.e., T-cell-mediated and memory B-cell immune responses specific to HPV-16 and HPV-18 in a sub-cohort of subjects at Day 0, Months 7, 12, 24 and 36.
- Secondary endpoints for safety:
  - To assess the reactogenicity of the administered vaccines in all groups after each dose.
  - To assess the safety of the administered vaccines in all groups.
  - To evaluate compliance with completion of vaccination in all groups.

Comparison between groups

- Primary between-group comparisons to assess the non-inferiority at Month 7 were performed in the ATP cohort for immunogenicity on subjects seronegative by ELISA at Day 0 for the antigen under analysis. Subjects seropositive for only one antigen were eliminated for the analysis of that antigen but were still evaluable for the analysis of the other antigen. In addition, non-inferiority assessment was also performed in the TVC on all subjects (regardless of serostatus at Day 0).
- Between-group comparisons to assess superiority were performed in the TVC on all subjects (regardless of serostatus at Day 0). In addition, superiority assessment was also performed in the ATP cohort for immunogenicity on subjects seronegative at Day 0 for the antigen under analysis.

Criteria for non-inferiority

- Non-inferiority with respect to seroconversion rates was shown if, one month after the last dose, for both anti-HPV-16 and anti-HPV-18 antibodies the upper limit of the 95% CI for the difference (qHPV minus Cervarix) was below 5%.
- Non-inferiority with respect to GMT for both anti-HPV-16 and anti-HPV-18 antibodies was shown if, one month after the last dose, the upper limit of the 95% CI for the GMT ratio (qHPV divided by Cervarix) was below 2.

Criteria for superiority

- If non-inferiority was reached, and if the lower limit of the two-sided 95% CI for the ratio of GMTs Cervarix divided by qHPV of a given antigen was above 1 in the ATP cohort for immunogenicity, the following criteria for superiority were to be assessed sequentially in the TVC:
  - First, superiority for HPV-18 was assessed. Superiority was shown if the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-18 antibodies (Cervarix divided by qHPV) was above 1 with the associated p-value.
  - Second, if superiority for HPV-18 is shown, superiority for HPV-16 was assessed. Superiority was shown if the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-16 antibodies (Cervarix divided by qHPV) was above 1 with the associated p-value.

Results and discussion for Study HPV-071

HPV-16/18 serostatus at baseline

The majority of subjects was initially seronegative for both HPV-16 and HPV-18, i.e. 96% in all groups (Table 5).

Table 5. Seropositivity status at Baseline (ATP cohort for immunogenicity)

		HPV_2D (N = 337)		Gard_2D (N = 334)		Gard_3D (N = 334)	
Anti-HPV-16	**Anti-HPV-18**	**n**	**%**	**n**	**%**	**n**	**%**
P	N	7	2.1	7	2.1	12	3.6
N	P	3	0.9	3	0.9	1	0.3
N	N	327	97	324	97	321	96.1

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
P=Positive
N=Negative

Non-inferiority analysis on primary objective (Cervarix 2-dose vs qHPV 2-dose, Month 7)

Non-inferiority assessment of seroconversion rates is presented in Table 6 at one month after the last dose (Month 7) in initially seronegative subjects (ATP cohort for immunogenicity). Non-inferiority assessment of anti-HPV-16 and anti-HPV-18 antibody GMTs as measured by ELISA is presented in Table 7.

Table 6. Non-Inferiority assessment of seroconversion rates one month after the last dose (Month 7) in initially seronegative subjects (ATP cohort for immunogenicity)

Antibody	*Cervarix* 2-dose		*qHPV* 2-dose		Difference in seroconversion rate (*qHPV* minus *Cervarix*)			
							95 % CI	
	N	%	N	%	Difference	%	LL	UL
HPV-16	330	100	327	100	*qHPV* minus *Cervarix*	0.00	-1.16	1.15
HPV-18	334	100	331	100	*qHPV* minus *Cervarix*	0.00	-1.15	1.14

N = number of subjects with available results
% = percentage of subjects with anti-HPV-16 antibody concentration ≥ 19 EU/ml; percentage of subjects with anti-HPV-18 antibody concentration ≥ 18 EU/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Non-inferiority criterion: the upper limit of the 95% CI for the difference in seroconversion rates (*qHPV* minus *Cervarix*) is below 5%

Table 7. Non-Inferiority assessment of anti-HPV-16 and anti-HPV-18 immune response one month after the last dose (Month 7) in initially seronegative subjects (ATP cohort for immunogenicity)

Antibody	*Cervarix 2-dose*		*qHPV 2-dose*		GMT ratio (*qHPV / Cervarix*)		
						95% CI	
	N	GMT	N	GMT	Value	LL	UL
HPV-16	330	8244.1	327	5056.0	0.61	0.54	0.69
HPV-18	334	5277.4	331	1207.2	0.23	0.20	0.26

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 criterion: the upper limit of the 95% CI for the GMT ratio (*qHPV* 2-dose schedule divided by *Cervarix* 2-dose schedule) is below 2

Superiority analysis on primary objective (Cervarix 2-dose vs qHPV 2-dose, Month 7)

Because non-inferiority was reached, and the lower limit of the two-sided 95% CI for the ratio of GMTs Cervarix divided by qHPV of a given antigen was above 1 in the ATP cohort for immunogenicity, a superiority analysis was performed (table 8).

Table 8. Superiority assessment of immune response one month after the last dose (Month 7, TVC)

Antibody	*Cervarix* 2-dose		*qHPV* 2-dose		GMT ratio (*Cervarix* / *qHPV*)		
						95% CI	
	N	GMT	N	GMT	Value	LL	UL
HPV-16	357	8256.4	353	4886.1	1.69	1.49	1.91
HPV-18	357	5267.8	353	1166.3	4.52	3.97	5.13

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit p-value= 0.0001
Superiority criterion: the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-16 and anti HPV-18 antibodies (*Cervarix* 2-dose schedule divided by *qHPV* 2-dose schedule) is above 1

Table 8 results show that the primary objective of the study was met.

In summary, after Cervarix vaccination as compared to qHPV vaccination, both administered according to a 2-dose schedule in females aged 9-14 years of age, study HPV-071 demonstrated at Month 7:

- Non-inferiority in terms of seroconversion rates
- Superiority in terms of GMT ratio in the Total Vaccinated Cohort.

Non-inferiority analysis on secondary objective (Cervarix 2-dose vs qHPV 3-dose, Month 7)

Secondary objectives included assessment of anti-HPV-16/18 seroconversion rates and antibody titres by ELISA at Day 0 and later time points.

The secondary objective to evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix administered according to a 2-dose schedule at 0, 6 months was non-inferior/superior to that of qHPV vaccine administered according to the standard 3-dose schedule (0, 2, 6 months) at Month 7, was met for this study (ATP cohort).

Table 9. Non-Inferiority assessment of seroconversion rates one month after the last dose (Month 7) in initially seronegative subjects (ATP cohort for immunogenicity)

Antibody	*Cervarix* 2-dose		*qHPV* 3-dose		Difference in seroconversion rate (*qHPV* minus *Cervarix*)			
							95 % CI	
	N	%	N	%	Difference	%	LL	UL
HPV-16	330	100	322	100	*qHPV* minus *Cervarix*	0.00	-1.18	1.15
HPV-18	334	100	333	100	*qHPV* minus *Cervarix*	0.00	-1.14	1.14

N = number of subjects with available results
% = percentage of subjects with anti-HPV-16 antibody concentration ≥ 19 EU/ml; percentage of subjects with anti-HPV-18 antibody concentration ≥ 18 EU/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
Non-inferiority criterion: the upper limit of the 95% CI for the difference in seroconversion rates (*qHPV* minus *Cervarix*) is below 5%

Table 10. Non-Inferiority assessment of anti-HPV-16 and anti-HPV-18 immune response one month after the last dose (Month 7) in initially seronegative subjects (ATP cohort for immunogenicity)

Antibody	*Cervarix* *2-dose*	*qHPV* *3-dose*	GMT ratio (*qHPV* / *Cervarix*)

						95% CI	
	N	GMT	N	GMT	Value	LL	UL
HPV-16	330	8244.1	322	4807.4	0.58	0.52	0.65
HPV-18	334	5277.4	333	1653.5	0.31	0.27	0.36

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 criterion: the upper limit of the 95% CI for the GMT ratio (*qHPV* 3-dose schedule divided by *Cervarix* 2-dose schedule) is below 2

Superiority analysis on secondary objective (Cervarix 2-dose vs qHPV 3-dose, Month 7, TVC)

In the TVC cohort, regardless of the HPV-16/18 serostatus at baseline, the GMT ratio (Cervarix 2-dose schedule divided by qHPV 3-dose schedule) for HPV-18 was 3.22 (2.82; 3.68), and for HPV-16 it was 1.72 (1.54; 1.93). As the statistical test was met for both anti-HPV 16 and anti-HPV18 antibodies at month 7, superiority was demonstrated (Table 11) (p-value=0.0001 for both antigens).

Table 11. Superiority assessment of anti HPV-16 and anti-HPV-18 immune response for (Cervarix 2-dose vs qHPV 3-dose) one month after the last dose (Month 7) (Total Vaccinated cohort)

Antibody	*Cervarix* 2-dose		*Gardasil* 3-dose		GMT ratio (*Cervarix* / *Gardasil*)		
						95% CI	
	N	GMT	N	GMT	Value	LL	UL
HPV-18	357	5267.8	351	1635.8	3.22	2.82	3.68
HPV-16	357	8256.4	351	4789.2	1.72	1.54	1.93

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit
p-value= 0.0001
Superiority criterion: the lower limit of the 95% CI for the ratio of GMTs (*Cervarix* 2-dose schedule divided by *Gardasil* 3-dose schedule) is above 1

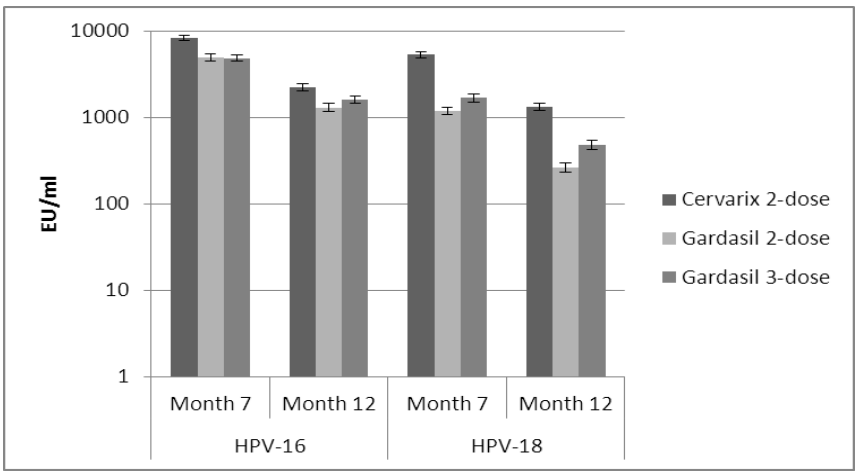
Non-inferiority analysis on secondary objective (Cervarix 2-dose vs qHPV 2-dose or 3-dose, Month 12)

As the primary non-inferiority/superiority objectives at Month 7 were reached, the protocol required that they be repeated at Month 12 as secondary objectives.

Of subjects who seroconverted one month after finalisation of the vaccination schedule (Month 7 analysis), all subjects in the qHPV 2-dose and qHPV 3-dose groups and all but one in the Cervarix 2-dose group were still seropositive for anti-HPV-16 antibodies when measured by ELISA. For HPV-18 antibodies, all subjects in the qHPV 3-dose group and all but one initially seronegative subject in the qHPV 2- dose and Cervarix 2-dose groups remained seropositive, when measured by ELISA.

GMTs for antibodies against both HPV-16 and HPV-18, which had reached a peak response at Month 7, showed a decline at Month 12 in all three groups, but remained higher in Cervarix group as compared to both qHPV groups. This is in line with the observations for study HPV-010.

Figure 3. Anti-HPV-16 and anti HPV-18 antibody titres (ELISA) in initially seronegative subjects (Month 12 ATP cohort for immunogenicity)



Sequential non-inferiority and superiority assessments at Month 12

At Month 12, non-inferiority of the immune response to 2 doses of Cervarix compared to 2 doses of qHPV at Month 12 in terms of seroconversion rates was demonstrated as the statistical criteria described before were met. The upper limit of the 95% CI for the GMT ratio (qHPV 2-dose group divided by Cervarix 2-dose group) for anti-HPV-16 and anti-HPV-18 antibodies was 0.67 and 0.23, respectively (i.e., below 2). Therefore, non-inferiority of GMTs after Cervarix vaccination as compared to qHPV vaccination, both in a 2-dose schedule, was demonstrated at Month 12 (ATP cohort).

Superiority of the immune response in terms of GMTs was also met at Month 12 in the TVC cohort, i.e., the lower limit of the 95% CI for the GMT ratio (Cervarix 2-dose divided by qHPV 2- dose) for anti-HPV-18 and anti-HPV-16 antibodies was above 1 (4.27 and 1.53, respectively, Month 12 TVC (p-value=0.0001 for both antigens).

For the comparison of Cervarix 2-dose group versus qHPV 3-dose group, non-inferiority of the immune response to 2 doses of Cervarix compared to 3 doses of qHPV at Month 12 in terms of seroconversion rates was demonstrated as the statistical criteria described before were met (ATP cohort). Non-inferiority at Month 12 in the ATP cohort for immunogenicity was also demonstrated when comparing the GMTs after Cervarix administration in a 2-dose schedule versus qHPV in a 3-dose schedule. The upper limit of the 95% CI for the ratio (qHPV 3-dose schedule divided by Cervarix 2-dose schedule) for anti-HPV-16 and anti-HPV-18 antibodies was 0.82 and 0.43, respectively (i.e., below 2).

Superiority of the immune response in terms of GMTs was demonstrated for the Cervarix 2-dose schedule over the qHPV 3-dose schedule as well, according to the statistical criteria described before (TVC cohort). The lower limit of the 95% CI for the ratio (Cervarix 2-dose schedule divided by qHPV 3-dose schedule) for anti-HPV-16 and anti-HPV-18 antibodies was 2.37 and 1.24, respectively (i.e. above 1) (p-value=0.0001 for both antigens).

Table 12. Superiority assessment of anti HPV-16 and anti HPV-18 immune response for (Cervarix 2-dose vs qHPV 3-dose) at Month 12 (Month 12 Total Vaccinated cohort)

Antibody	*Cervarix* 2-dose		*Gardasil* 3-dose		GMT ratio (*Cervarix* / *Gardasil*)		
					Value	95% CI	
	N	GMT	N	GMT		LL	UL
HPV-16	355	2217.5	348	1567.4	1.41	1.24	1.61
HPV-18	355	1296.1	348	469.2	2.76	2.37	3.22

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit
p-value= 0.0001
Superiority criterion: the lower limit of the 95% CI for the ratio of GMTs (*Cervarix* 2-dose schedule divided by *Gardasil* 3-dose schedule) is above 1

These persistence data demonstrate that the observed non-inferiority and superiority of the immune response to Cervarix administered in a 2-dose schedule as compared to qHPV vaccination and irrespective of the vaccination schedule, in terms of seroconversion rates as well as GMTs for both anti-HPV-16 and anti-HPV-18 antibodies at Month 7, is maintained at least up to Month 12.

Anti-HPV-16/18 neutralising antibodies measured by PBNA at Month 12

The data generated at Month 12 with PBNA, specifically measuring neutralising antibodies, complement the data and conclusions drawn from the ELISA measurements.

Of all subjects that had seroconverted one month after the last vaccination (Month 7), all remained seropositive for anti-HPV-16 neutralising antibodies when measured by PBNA. For HPV-18, all subjects in the Cervarix 2-dose and qHPV 3-dose groups remained seropositive as well. In the qHPV 2-dose group, the antibody titre at Month 12 was below the cut-off value for seropositivity for the assay (40 ED_{50}) for two subjects out of 93.

GMTs for neutralising antibodies against both HPV-16 and HPV-18 reached a peak response at Month 7 then declined to Month 12 in all three groups, in line with the data from study HPV-010. No statistical inferential analysis was performed to compare GMTs as measured with PBNA. These descriptive data are however in line with those obtained using ELISA testing, and suggest higher neutralising antibody titres in the Cervarix 2-dose group as compared to the two qHPV groups (2-dose and 3-dose).

2.4.1.3. Study HPV-011

This study was a phase I/II, observer-blind, randomised, controlled study to assess the immunogenicity and safety of Cervarix administered intramuscularly according to a 0, 1, 6 month schedule in healthy male subjects 10-18 years of age. The study was conducted in multiple centres in Finland. A total of 270 subjects were enrolled.

The clinical study report from study HPV-011 (Month 7 and Month 12) was previously submitted and assessed within the post-authorisation measure 028 (please refer to Rapporteur's Assessment Report for this procedure for details). For a brief summary of the study design and statistical methods see the tabular overview of clinical studies (section 2.3).

Treatment and randomisation

For inclusion and exclusion criteria see section 2.4.1.

Subjects were randomly allocated (2:1) to receive either Cervarix or GSK Biologicals' Hepatitis B vaccine, Engerix B, as control. Randomisation was age-stratified (10-12 years, 13-15 years and 16-18 years). All subjects were vaccinated according to a 0, 1, 6-month schedule. The duration of the study (including safety follow-up) per subject was approximately 12 months, with the last study visit at Month 7 and a telephone contact at Month 12.

Objectives

The primary objective of the study was to evaluate one month after the third dose (i.e. at Month 7), the immune responses to Cervarix, as determined by anti-HPV-16/18 ELISA in healthy male subjects aged 10-18 years old.

Secondary objectives included the evaluation of non-inferiority of the immune responses to Cervarix (as determined by anti- HPV-16/18 ELISA) in healthy male subjects aged 10–18 years in this study as compared to the responses measured in sera from a subset of 15-25 years old females from the HPV-012 study (the age range in which vaccine efficacy was demonstrated), one month after administration of the third vaccine dose (i.e. at Month 7). The evaluation of the immune response (ELISA) to Cervarix one month after the second dose (i.e. at Month 2) was a secondary objective of the study.

Immunogenicity analysis

The primary analysis of the immunogenicity (seropositivity and GMTs) was performed in the ATP cohort for immunogenicity. Non-inferiority evaluation for GMTs versus subjects from study HPV-012 was also performed based on the ATP cohort for immunogenicity.

For the Cervarix group, the ATP cohort for immunogenicity consisted of 173 subjects. The non-inferiority assessment for GMTs in the ATP cohort was based on a comparison with data from 359 and 364 female subjects from study HPV-012 for HPV-16 and HPV- 18 respectively.

Baseline data

The mean age in the Cervarix group of HPV-011 was 14.4 ± 2.14 years and the population was predominantly of Caucasian heritage (97.8%). In comparison, the demographic profile of the comparative HPV-012 female population had a mean age of 20.2 ± 2.9 years with 96.3% white/Caucasian heritage.

Statistical methods and analyses

The primary endpoint of the study was the assessment of HPV-16 and HPV-18 seroconversion rates and geometric mean titres (GMTs) at Month 7. The secondary endpoint was assessment of HPV-16 and HPV-18 seroconversion rates and GMTs at Month 2.

Comparison between groups

The secondary study objectives included non-inferiority analysis of the immune responses to Cervarix in healthy male subjects aged 10–18 years in this study, compared to the responses measured in sera from a subset of 15-25 years old females from the HPV-012 study, one month after administration of the third vaccine dose (i.e. at Month 7).

The following criteria for non-inferiority applied:

- Seroconversion: one month after the third dose, the upper limits of the 95% CI on the difference of seroconversion rates for HPV-16 and HPV-18 between the 15-25 years old female subjects of the Cervarix group in study HPV-012 and the 10-18 years old males in the Cervarix group of study HPV-011 were below 10%.

- GMT ratios: one month after the third dose, the upper limit of the 95% CI on the GMT ratios for HPV-16 and HPV-18 between the 15-25 years old females group of study HPV-012 and the 10-18 years old males in the Cervarix group of study HPV-011 was below 2.

Results for study HPV-011

Descriptive immunogenicity analysis in males as primary objective

Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and the TVC (secondary analysis).

After vaccination, all subjects (seropositive and seronegative at baseline) in the Cervarix group were seropositive at one month post dose 2 (Month 2) and remained seropositive up to one month post dose 3 (Month 7) for both HPV-16 and HPV-18.

High GMTs were observed in the Cervarix group at Month 2 (5,221.1 (4,660.8; 5,848.7) for HPV-16 and 3,663.8 (3,217.9; 4,171.6) and HPV-18), with approximately a four-fold increase for HPV-16 and a two-fold increase for HPV-18 between Month 2 and Month 7 (22,639 (19,825.5; 25,853.4) for HPV-16 and 8,416.1 (7,215.0; 9,817.1) HPV-18 at Month 7).

By age category (10-14 years and 15-18 years), higher GMTs were observed in the younger age group than in the older age group at Month 7. The Month 7 results of study HPV-011 have been published (Petäjä, 2009).

Non-inferiority assessment between males in study HPV-011 and females in study HPV-012

As secondary objective, the immunogenicity results in the 10 to 18 years old males in study HPV-011 were compared to the results in the 15 to 25 years old females from study HPV-012 (inter-study inferential analysis). Of note, the HPV-012 study results have been presented in the initial Marketing Authorisation Application (MAA) and have been published (Pedersen, 2007; Petäjä, 2011). HPV-012 was a pivotal study for the Cervarix MAA because it showed higher immunogenicity in the 10-14 year-olds population vs. the 15-25 year-olds population in which clinical efficacy was demonstrated (clinical efficacy trials HPV-001 and 008 of the MAA).

The comparison concerned demonstration of non-inferiority in males 10-18 years versus females 15-25 years for HPV-16/18 seroconversion rates and HPV-16/18 antibody GMTs, one month after administration of the third vaccine dose (i.e. at Month 7).

As shown in tables 13 and 14, the secondary immunogenicity objective of the study was met, as non-inferiority of the immune response in males versus females was demonstrated both for seroconversion rates and GMTs for HPV-16/18 antibodies. Concerning the seroconversion rate, one month after the third dose, the upper limits of the 95% CI on the difference in seroconversion rates between the female and the male subjects were below the pre-defined non-inferiority criterion of 10% for both HPV types. With regards to the GMTs, the upper limit of the 95% CI on the GMT ratios between females and males were below the pre-defined non-inferiority limit of 2 for both HPV types. Therefore, this inter-study inferential analysis between males and females demonstrates comparability of immune responses to Cervarix between genders, but more importantly non-inferiority of the immune response of 3 doses of Cervarix in males 10-18 years as compared to 3 doses of Cervarix in females 15-25 years (the population in which efficacy against cervical lesions and cancer was demonstrated).

A sub-analysis of antibody titres was performed for the age groups 10–14 and 15-18 years of age separately. In both age groups 100% seroconversion was observed at Month 7 for both antigens and overall higher GMTs were observed in the younger age group than in the older age group.

Table 13. Non-inferiority assessment in terms of seroconversion rates between males (10-18 years old) in study HPV-011 and females (15-25 years old) in study HPV-012, Post Dose III, Month 7 (ATP cohort for immunogenicity)

Antibody	Females 15-25 years (HPV-012)		Males 10-18 years (HPV-011)		Difference in seroconversion rates (females minus males)			
					Difference	%	95 % CI	
	N	%	N	%			LL	UL
HPV-16	359	100	163	100	Females - Males	0	-1.06	2.30
HPV-18	364	100	150	100	Females - Males	0	-1.04	2.50

N = number of subjects with available results
% = percentage of subjects with HPV-16 VLP IgG titres ≥ 8 EL.U/ml or HPV-18 VLP IgG titres ≥ 7 EL.U/ml
95% CI = 95% Standardised asymptotic confidence interval; LL = lower limit, UL = upper limit
Calculation performed on subjects seronegative prior to dose 1
Non-inferiority criterion: upper limit of the 95% CI around the difference in seroconversion rates below 10%

Table 14. Non-inferiority assessment in terms of GMT ratios between males (10-18 years old) in study HPV-011 and females (15-25 years old) in study HPV-012, Post Dose III, Month 7 (ATP cohort for immunogenicity)

Antibody	Females 15-25 years (HPV-012)		Males 10-18 years (HPV-011)		GMT ratio (Females / Males)		
					Value	95% CI	
	N	GMT	N	GMT		LL	UL
HPV-16	359	7292.9	163	22639.7	0.32	0.27	0.38
HPV-18	364	3318.8	150	8416.1	0.39	0.33	0.47

GMT = geometric mean antibody titres
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance);
Calculation performed on subjects seronegative prior to dose 1
Non-inferiority criterion: upper limit of the 95% CI around the GMT ratio below 2

2.4.1.4. Study HPV-040

This study is a phase III/IV, community-randomised, partially-blinded controlled study in 12–15 year-old male and female subjects, which was ongoing at the time of the submission of this application (global end of trial date: 14 December 2015). HPV-040 is a multi-centre study conducted in Finland.

The objective of this study is to evaluate the effectiveness of vaccination with Cervarix in reducing the prevalence of HPV-16/18 genital infection in females in communities where vaccination has been introduced in girls only, compared with communities where vaccination has been introduced in girls and boys. In the scope of the current submission however, study HPV-040 is presented to describe immunogenicity and safety results of Cervarix in males.

Immunogenicity data (ELISA) of Cervarix in a subset of males and females, 7 months after first vaccination, have been analysed whilst the study was ongoing and submitted in the current application as an interim report (see further below). A brief summary of results at month 7 was already submitted and assessed within the post-authorisation measure 034. The study was initiated on 04 October 2007 and the study completion date for last-subject/last-Month-12 contact for this interim analysis was 20 April 2011. The data lock point for immunogenicity analysis was 07 May 2012.

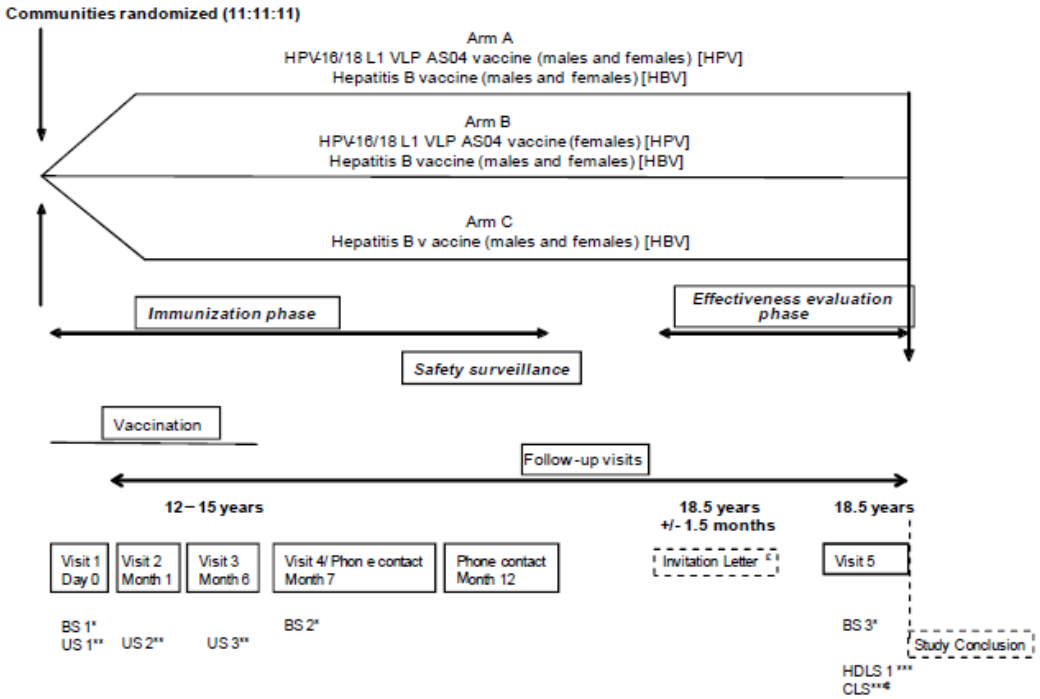
Methods

For a brief summary of the study design and statistical methods see the tabular overview of clinical studies (section 2.3).

The study includes two treatment groups: study participants who received Cervarix and study participants who received GSK Biologicals' hepatitis B vaccine Engerix B (HBV group).

The study design includes three arms (see also figure below):

- Arm A includes communities (N = 11) where 90% of male and female adolescents were to be vaccinated with Cervarix (vaccination strategy #1).
- Arm B includes communities (N = 11) where 90% of the female adolescents were to be vaccinated with Cervarix (vaccination strategy #2).
- Arm C includes communities (N = 11) where the adolescents were not vaccinated against HPV-16/18 (negative control). These male and female adolescents received Engerix B as negative control.



BS: Blood Sample; US: Urine Sample HDLS: HPV DNA LBC Sample; CLS: Cytology LBC Sample; OS: Oropharyngeal Sample
* Only a subset of selected study participants had/will have blood drawn at these time points (study participants in the immunogenicity subset)
** Urine sample for pregnancy test collected in female study participants for pregnancy testing if deemed appropriate according to the investigator's clinical judgement
*** Study procedure only applicable to female study participants
£ All community residents born between 1992 and 1995 will receive an invitation letter, an informed consent form and a behavioural questionnaire. All female community adolescents born in 1992, 1993, 1994, and 1995 will be invited to attend Visit 5 including female community adolescents not enrolled in the immunization phase. Male study participants included in the immunogenicity subset will also be invited to attend Visit 5, for collection of a blood sample for Hepatitis B or HPV antibody testing. All study participants that will participate in the effectiveness evaluation phase will join after informed consent has been obtained.
Oropharyngeal samples for HPV DNA testing will be collected at Visit 5 from female subjects born in 1993, 1994 and 1995, who join the effectiveness evaluation phase of the study.

Subjects in the Cervarix treatment groups received three doses of the vaccine according to a 0, 1, 6-month schedule. Arm A of the study includes male subjects vaccinated with Cervarix. An interim analysis was performed with the objectives to monitor the safety of Cervarix in males and females (all

arms) and to assess the immunogenicity of the vaccine in a subset of males and females (Arm A immunogenicity subset) at Month 7.

The primary analysis was based on the ATP cohort for analysis of immunogenicity (seropositivity rates and GMTs), which included 556 males and 1,273 females vaccinated with Cervarix. A second analysis based on the TVC for immunogenicity was performed to complement the ATP analysis. The TVC for immunogenicity included 643 males and 1,472 females for the Cervarix group.

In the ATP cohort for immunogenicity, the mean age at the time of first vaccination in the Cervarix group was 14.1 ± 0.75 years, 69.5% of subjects were female and the population was predominantly of Caucasian / European origin (98.5%).

Statistical analysis

Anti-HPV-16/18 antibody levels were assessed at Month 0 and Month 7 as a secondary endpoint at interim analysis (study participants in the immunogenicity subset).

No statistically powered inferential analyses were performed.

Results

The primary analysis of seropositivity rates and GMTs was based on the ATP cohorts for immunogenicity and included 556 subjects in the male cohort and 1,273 subjects in the female cohort, vaccinated with Cervarix.

For both sexes and for both vaccine HPV-types, seroconversion rates of 100% were observed 1 month after administration of the 3rd vaccine dose, in subjects that were seronegative at baseline (i.e. before first vaccination). The data are presented in table 15. Seropositivity was defined as antibody titres ≥ 8 ELISA Units (EL.U) per mL for HPV-16 and ≥ 7 EL.U/mL for HPV-18.

Furthermore, in a descriptive analysis, GMTs for antibodies to the vaccine HPV-types are high in both genders and comparable between the male and the female cohorts. Comparative data of the GMTs (with 95% confidence intervals) in the two cohorts are also presented in Table 15.

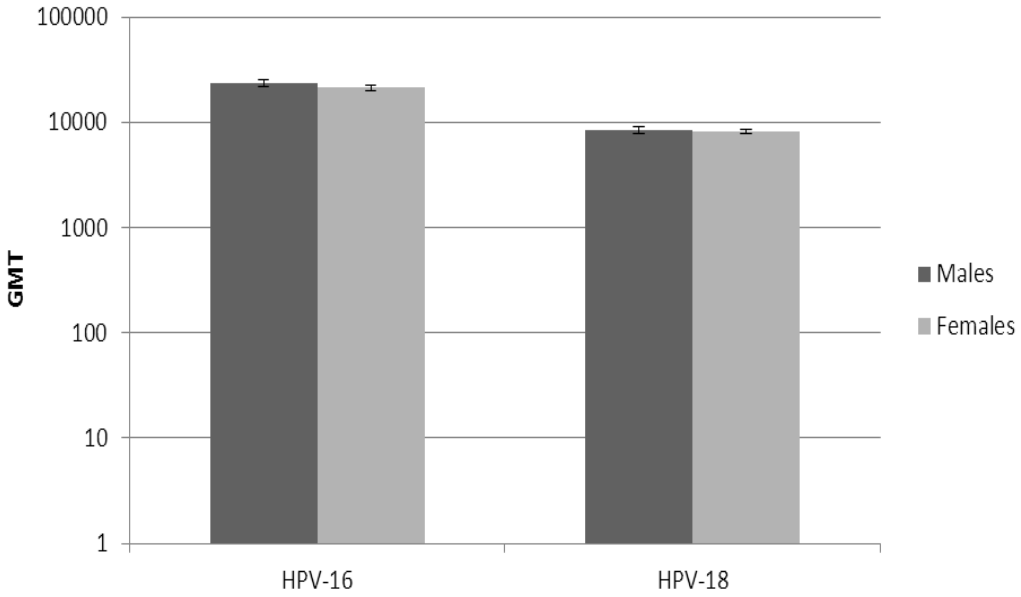
Table 15. HPV-040 – Seropositivity rates and GMTs for anti-HPV-16/18 antibodies by gender in subjects seronegative at baseline (ATP cohort for immunogenicity)

Antibody	threshold for seropositivity	pre-vaccination status	Timing	Sub-group	N	Seropositivity rate				GMT		
						n	%	95% CI		value	95% CI	
								LL	UL		LL	UL
HPV 16 IgG	≥ 8 EL.U/mL	S-	PIII (M7)	Males	496	496	100	99.3	100	23813	22110	25648
				Females	1077	1077	100	99.7	100	21247	20228	22317
HPV 18 IgG	≥ 7 EL.U/mL	S-	PIII (M7)	Males	504	504	100	99.3	100	8484	7879	9136
				Females	1076	1076	100	99.7	100	8150	7759	8561

EL.U/mL: ELISA Units per millilitre
S- = seronegative subjects 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 seropositivity threshold
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M7) = Post Dose 3, study Month 7 (1 month post dose 3)

GMTs for anti-HPV-16 and HPV-18 antibodies by gender for subjects seronegative at baseline (ATP cohort for immunogenicity) are presented in Figure 4.

Figure 4. Month 7 GMTs with 95% CI for anti-HPV-16 and anti-HPV-18 antibodies by ELISA by gender for subjects seronegative at baseline (ATP cohort for immunogenicity)



Results in the TVC were comparable to those seen in the ATP cohort for immunogenicity (not shown).

Irrespective of the pre-vaccination status of the subjects, the data indicate comparable immunogenicity in males and females elicited by Cervarix, when administered according to a 0, 1, 6-month schedule (not shown). Even though the comparison of immunogenicity between genders is descriptive (statistically-powered inferential analyses was not planned per protocol), a large number of subjects were included in this analysis, providing strong evidence of comparable immune responses to the vaccine by both sexes. The data from study HPV-040 confirm the previous findings from study HPV-011.

2.4.1.5. Supportive study

Study HPV-009 (post-hoc analysis)

HPV-009 is a randomised controlled (control: Hepatitis A vaccine) clinical efficacy Phase III trial in women 15-25 years of age, including those with current or prior infection with oncogenic HPV. HPV-009 was conducted in Costa Rica from 2004 to December 2010. See the table below for further details on study design.

HPV-009‡ (48 months)	III	Costa Rica	Females 18 - 25 yrs	**Primary objective:** Efficacy against CIN 2+ associated with HPV-16/18 post dose 3 in subjects HPV DNA negative (by PCR) at Months 0 and 6 for the corresponding HPV type. **Secondary objectives:** Efficacy against CIN2+ associated with other high-risk HPV types post dose 3 in subjects HPV DNA negative (by PCR) at Month 0 and 6 for the corresponding HPV type; Efficacy against 12-month persistent infections or CIN2+ with HPV-16/18 post dose 3 in subjects HPV DNA negative (by PCR) at Months 0 and 6 and seronegative (by ELISA) at Month 0 for the corresponding HPV type; Duration of protection against cervical infection with HPV-16/18; Safety; Immunogenicity (subset of subjects).	Double-blind, randomized, controlled, multicenter study with two parallel groups: - HPV-16/18 (20 µg/20 µg) L1 AS04 (Hi-5/Sf-9) - Hepatitis A vaccine (720 EI.U HAV / 500 µg $Al(OH)_3$) This study is supervised by an independent Data Safety Monitoring Committee (DSMB).	**3727** 3739

The final study results at 48 months were submitted as FUM 027 in June 2012 to provide clinical efficacy data of Cervarix in the 3-dose schedule in the prevention of cervical lesions and cervical cancer (advanced cervical intraepithelial neoplasia [CIN2, CIN3], adenocarcinoma in situ [AIS] and invasive cervical cancer) associated with HPV-16 or HPV-18 cervical infection in healthy young adult women in

Costa Rica. The FUM 027 submission enclosed a Clinical Overview and the Clinical Study Report at completion of the study (from Month 6 to Month 48).

In addition, HPV-009 data investigating the potential benefit of vaccination in women with prevalent infection with HPV-16 or HPV-18 were submitted within FUM 036 in June 2012. The CHMP concluded that women with a prevalent HPV 16 and/or 18 infection do not benefit from protection from disease caused by HPV types for which the subjects were HPV DNA positive at the time of the first vaccine dose administration. Therefore the outcome of FUM036 had no impact on the Cervarix SmPC.

At the final blinded study visit 4 years after vaccination, a number of women were selected to provide anal samples for assessment of vaccine efficacy against anal HPV-16/18 infection (Kreimer et al., Lancet Oncology 2011[1]). The efficacy of vaccination against anal infection with HPV-16/18 was estimated in two cohorts:

- The full cohort included all vaccinated women who had given an anal sample and had HPV results available. Thus, in this cohort, no exclusions were based on HPV-16/18 DNA positivity or HPV-16/18 serostatus. The cohort included 193 subjects that were HPV-16/18 DNA positive (at the cervix) before vaccination and 665 subjects that were HPV-16/18 seropositive before vaccination (please refer to figure 1 in the publication reflecting an erratum published online by The Lancet Oncology on October 28, 2011). Overall, at enrolment, 10% of subjects in the HPV group were HPV-16/18 DNA positive and 39% were HPV-16/18 sero-positive.
- The restricted cohort excluded women with evidence of prevalent cervical HPV-16/18 infection (DNA) or HPV-16/18 antibodies before vaccination.

The following efficacies against anal HPV-16/18 infection were estimated in the two cohorts: 62.0% (95% CI: 47.1, 73.1) in the full cohort and 83.6% (95% CI: 66.7, 92.8) in the restricted cohort. Similar data of lower estimated efficacy in the full cohort versus the restricted cohort were observed in the same study for cervical HPV-16/18 infection and for anal and cervical infection with the non-vaccine types HPV-31, HPV-33 and HPV-45 (exclusion of HPV-31, HPV-33 and HPV-45 DNA positive individuals at time of vaccination from the restricted cohort). However, subjects seropositive for HPV-31/33/45 were not excluded from the analysis as the serology was not performed at enrolment for these types. The data are published in the same article (Kreimer, 2011). The data described by Kreimer are in line with previous observations on the efficacy against cervical infection (Hildesheim, 2007; Szarewski, 2012), showing that vaccination did not impact the outcome of HPV infections present at the time of vaccination. The latter study however shows that individuals with prevalent infection with one HPV vaccine type at the time of vaccination, still benefit from the protection against infection with the other vaccine HPV-type and cross reacting HPV-types. Of note, in the same trial at baseline, less than 1% of the subjects were DNA positive for both HPV-16 and HPV-18, the main HPV types associated with cervical cancer (Paavonen, 2009).

Inclusion of HPV-009 post-hoc data in the SmPC

The MAH proposed to include the Kreimer data in SmPC section 5.1 as HPV-009 data providing evidence of vaccine efficacy against anal and cervical prevalent infection associated with HPV-16/18 and HPV-31/33/45. Further clarification and full data submission were requested to the MAH during the current variation procedure. The MAH confirmed that the efficacy of Cervarix against anal HPV infection associated with HPV-16/18 and HPV-31/33/45 has been evaluated by the National Cancer Institute (NCI, US) as a HPV-009 post-hoc study. The NCI was the study Sponsor and the MAH was not involved

[1] Kreimer AR, González P, Katki HA, Porras C, Schiffman M, Rodriguez AC, Solomon D, Jiménez S, Schiller JT, Lowy DR, van Doorn LJ, Struijk L, Quint W, Chen S, Wacholder S, Hildesheim A, Herrero R; CVT Vaccine Group. Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol. 2011;12(9):862-70.

in the conduct of the study. Consequently, the MAH does not have rights on the study data and materials and cannot develop a clinical study report. Nevertheless, in the view of the MAH, the data published by Kreimer et al. are highly relevant to the prescriber, as they represent key evidence of the vaccine efficacy against anal lesions.

The CHMP considered that an independent regulatory assessment of the study methodology including the selection of subjects and the full statistical analysis plan is not possible. Moreover, Kreimer et al. provides data on prevalent anal HPV infection at one time point i.e. 4 years post vaccination, but not on persistent anal infection that lasts for at least 6 months. For the cervical indication, persistent cervical infection that lasts for at least 6 months has been shown to be a relevant surrogate marker for cervical cancer. Data on persistent infection are therefore considered to be a measure for vaccine efficacy, and consequently are relevant for inclusion in the SmPC. Data on anal infection can be included in the SmPC provided that they reflect persistent anal infection that lasts for at least 6 months. Since Kreimer et al. do not provide these data, the CHMP concluded that these data, although encouraging, do not add important information in the SmPC.

Importantly, the MAH clarified that the NCI recently published the study design of the long term follow-up study of the Costa Rica Vaccine Trial (CVT or HPV-009, NCT00128661). The study started after completion of the CVT in 2010 and will provide 6 additional years of follow-up for a total of 10 years. One of the objectives is to assess the global impact of HPV vaccination in young adult women. Persistent anal infection data are an expected outcome of the study (Gonzalez, 2015[2]). The long-term follow-up study is registered under clinicaltrial.gov as NCT00867464 (https://clinicaltrials.gov/ct2/show/study/NCT00867464). The Sponsor is the US NCI.

2.4.1.6. Additional analyses

Estimation of absolute benefit of preventing anal cancer and study on vaccine effectiveness

During the procedure, the MAH was requested to estimate the absolute benefit of Cervarix preventing anal cancer in the general population by calculating the Number Needed to Vaccinate. As known, the incidence of anal cancers is quite low and varies between 0.55 and 2.4/100,000 person-years in women (Stier, 2015) and was estimated at 0.77/100,000 person-years in men (Faivre, 2012). The incidence rate of High-grade Anal Intraepithelial Neoplasia (HGAIN) was estimated at 1.19/100,000 and 9.24/100,000 respectively for women and men (Simard, 2013). Consequently, the number needed to vaccinate to prevent one anal cancer case, as calculated by the MAH, is relatively high (varying between 2762 and 1105 in 12 year-old boys and between 2066 and 826 12 year-old boys and girls depending on the vaccine effectiveness assumptions and the increase of the anal cancer incidence over the remaining life span).

The MAH has also modelled the maximum plausible benefit in terms of number of any HPV-related cancer cases avoided (including cervical, vulvar, vaginal, anal, penile and oropharyngeal cancers) in the United Kingdom (UK). Several hypotheses were made such as a vaccine coverage of 86.8% was applied (based on uptake figures for the HPV programme in England); the vaccine efficacy was assumed to be the same for all HPV cancers as observed for cervical cancers; the vaccine effectiveness was approximated by combining the vaccine efficacy with the Population Attributable Fraction for each cancer. As a result of vaccinating boys and girls, 3,748 cancer cases due to HPV in women compared with 1,043 cancer cases due to HPV in men could theoretically be prevented annually in the UK. These estimates include 541 avoidable anal cancer cases in women compared with 294 avoided anal cancer cases in men (ESPID Congress, 2014).

[2] Gonzalez et al. Rationale and design of a long term follow-up study of women who did and did not receive HPV 16/18 vaccination in Guanacaste, Costa Rica. Vaccine 2015 Apr 27;33(18):2141-51.

High risk populations like HIV infected, transplant recipients or MSM are more vulnerable to anal infections and thus represent a more realistic potential population than the general population to assess the vaccine effectiveness against anal cancers/lesions. The incidence rates of HGAIN vary between 8.5 and 15.5/100 person-years in HIV-positive MSM and between 3.3 to 6.0/100 person/years in HIV-negative MSM (Machalek, 2012). In a high risk population of HIV-uninfected adolescents, the rates of anal dysplasia were estimated at 2.7 and 13/100 person-years for girls and boys aged between 12 to 18 years (Mullins, 2013). In terms of persistence of anal HPV infection, one study has demonstrated that the 12-month persistence rate varies between 28% and 46% in HIV infected (Beachler, 2013).

During the procedure, the MAH was requested to thoroughly assess the feasibility of conducting a post-authorisation vaccine effectiveness study to estimate the prevention of persistent infection, anal lesions and anal cancer. The challenges as to the feasibility and bias of such study are acknowledged (e.g. a large sample size of approximately 300,000 individuals; no routine screening programmes for anal lesions are available which increases the difficulties of identifying cases or implementing a surveillance programme). The assessment of the available registries and databases suggests that the use of a large database like CPRD does not seem to be an adequate source of data for identifying anal cancer or lesion cases (due to e.g. lack of detail coding for case identification and no information on HPV type PCR testing, under-reporting of vaccination status, rarity of cases).

A prospective field data collection and a large sample size with a close (regular anal cytology and HPV screening) and long-term follow-up of the disease would be required. The Cancer Registry in Sweden, which collects AIN grade 3, would allow generating effectiveness data over time. However, the Cervarix uptake in this country is quite low. This registry would allow generating effectiveness data over time with qHPV. Therefore, it was considered highly relevant that the long-term impact of Cervarix on anal HPV persistence is being monitored in the Cervarix-vaccinated Costa Rican cohort by the US NCI, and this data should be submitted for review as they become available.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

CSRs for studies HPV-10 and HPV-011 were already submitted in previous applications and assessed. Design and conduct of the clinical studies presented in this submission are found acceptable by the CHMP.

Immunogenicity data

In the present application, data in support of the indication of prevention of anal lesions and anal cancer in males and females for Cervarix are submitted, based on a strategy of multiple immunogenicity bridging i.e. between the two HPV-vaccines in the female population, and between the male and female populations that received Cervarix.

The MAH demonstrated the potential clinical efficacy of Cervarix against anal lesions and anal cancer in both males and females by:

- In females: Immunogenicity bridging to another HPV vaccine that currently has the same indication (anal lesions and anal cancer) based on efficacy data in males (qHPV);
- In males: Immunogenicity bridging to a population in which vaccine efficacy in the indication against cervical cancer and lesions has been demonstrated (females aged 15-25 years).

Immunogenicity bridging between qHPV and Cervarix in the male population was not performed.

Table 16 provides an overview of the immunogenicity results and comparisons performed.

Table 16. Overview of immunobridging to support the anal indication application

Gender	Age (years)	Comparison	Data point	Cervarix		qHPV	
				3-dose	2-dose	3-dose	2-dose
M	10-18	Seroresponses rate, GMT	M7	●			
	12-15	GMT	M7	**o**			
F	9-14	Seroresponses rate, GMT	M12		**xx**	**xx**	**xx**
	12-15	GMT	M7	**o**			
	15-25	Seroresponses rate, GMT	M7	●			
	18-45	Seroresponses rate, GMT	M60	**x**		**x**	

(**x**): Superior GMTs of Cervarix compared to qHPV in females aged 18-45 years in a 3-dose schedule up to Month 60 (HPV-010) and (**xx**): Non-inferior seroconversion rate of Cervarix compared to qHPV in females aged 9-14 in a 2-dose schedule up to Month 12 (HPV-071)
(●): Non-inferior immune response in males aged 10-18 years and females aged 15-25 years in a 3-dose schedule of Cervarix at Month 7 (HPV-011).
(**o**): Similar GMTs in males and females aged 12-15 years in a 3-dose schedule of Cervarix at Month 7 (HPV-040).

Data in females

In study HPV-010 the primary superiority assessment was performed in the TVC (regardless of serostatus and DNA status at baseline) and demonstrated superiority of the antibody titres in the Cervarix group versus qHPV for all age groups (18-26 years; 27-35 years and 36-45 years) and for both HPV-16 and HPV-18 at month 7 post-vaccination.

Final results up to Month 60 in females 18-45 years old who received 3-dose Cervarix showed that antibody titres reached a peak response at Month 7, showed a decline up to Month 12 in all three groups, and then remain relatively stable over time (kinetic cohort) and superior to 3-dose qHPV regardless of baseline serostatus (TVC cohort), across the three age strata (table 2). Superiority testing at subsequent time points after month 7 was done by exploratory inferential statistics.

HPV-071 compared Cervarix 2-dose vaccination vs. qHPV 2-dose vaccination in females aged 9-14 years of age, demonstrating at Month 7: i) non-inferiority in terms of seroconversion rates and GMTs (ATP cohort); ii) superiority in terms of GMT ratio in the Total Vaccinated Cohort .

Subsequently this study showed that the immunogenicity (seroconversion and GMTs) of Cervarix administered according to a 2-dose schedule at 0, 6 months was non-inferior/superior to that of qHPV vaccine administered according to the standard 3-dose schedule (0, 2, 6 months) at Month 7 in the ATP cohort. Superiority was also demonstrated on secondary objective for Cervarix 2-dose vs qHPV 3-dose at Month 7 in the TVC cohort.

The same analyses were repeated as secondary objectives at Month 12, demonstrating non-inferiority of Cervarix 2-dose immune response vs qHPV 2-dose or 3-dose in the ATP cohort. Superiority of the immune response in terms of GMTs was also met at Month 12 in the TVC cohort for Cervarix 2-dose vs. qHPV 2-dose and 3-dose.

Overall studies conducted in girls aged 9 to 14 years (study HPV-071) and in women aged 18 to 45 years (study HPV-010) have consistently shown a higher immune response with Cervarix (either non-inferior or superior) than with the comparator for which efficacy data against anal premalignant lesions are conclusive and have shown protection. Results shown by ELISA were confirmed by PBNA.

Data in males

Study HPV-011 compared immunogenicity data from 3-dose Cervarix vaccination in males aged 10-18 years to immunogenicity data from 3-dose Cervarix vaccination in females aged 15-25 years from study HPV-012 (the age range in which Cervarix clinical efficacy against cervical lesions and cancer was demonstrated – studies HPV-001 and 008). At Month 7 in the ATP cohort, this inter-study inferential analysis demonstrated non-inferiority in terms of seroconversion rates (100%) and GMT ratios in males vs. females (22,600 vs. 7.300 for HPV16; 8,400 vs. 3,300 for HPV18). No post Month 7 immunogenicity data is available, which is a limitation to the presented comparison between males and females.

Interim results from Study HPV-040 showed that comparable seroconversion rates (100%) and GMTs at Month 7 (24,000 vs. 21,000 for HPV16 and 8,500 vs. 8,100 for HPV18) are achieved in the ATP cohort after a 3-dose Cervarix vaccination in males aged 12-15 years compared to females aged 12-15 years, for both HPV 16 and 18 types.

The 2 studies in males compared immune response to the vaccine between genders overall demonstrating similar immunogenicity of Cervarix in males versus females. The data indicate comparable immunogenicity in males and females elicited by Cervarix, when administered according to a 0, 1, 6-month schedule, even irrespective of the pre-vaccination status of the subjects (not shown). Even though the comparison of immunogenicity between genders is descriptive (statistically-powered inferential analyses was not planned per protocol), a large number of subjects were included in this analysis, providing strong evidence of comparable immune responses to the vaccine by both sexes.

In summary, the basis of this application for an indication including anal cancers and premalignant lesions for Cervarix is immunogenicity and safety data. Immune responses to Cervarix given either according to a 2- or 3-dose schedule, as appropriate for each age group, were shown to be superior to those of qHPV (HPV-011 and 071).

Efficacy data and additional analyses

No clinical efficacy data have been provided on the prevention of anal lesions or anal cancer by Cervarix.

The MAH clarified that, due to the widespread and/or recommended use and global licensure of qHPV for the prevention of anal lesions and anal cancer (without gender restriction), the conduct of a placebo controlled efficacy trial for Cervarix might potentially raise ethical concerns since a potentially efficacious vaccine would be withheld from the placebo group (*Reflection Paper on ethical and GCP aspects of clinical trials of human medicinal products conducted outside the EU/EEA and submitted in MAA to the EU regulatory authorities* (EMA/121340/2011)). On the other hand, the conduct of an active-controlled efficacy trial would not be feasible due to the high efficacy demonstrated by qHPV against AIN (78.6% [95% CI: -0.4-97.7] against HPV-16/18 in the per-protocol cohort) and persistent anal infection (95.8% [95% CI: 74.1-99.9] against HPV-16/18 in the per-protocol cohort] in the MSM study (Palefsky, 2011). In addition, HPV-related anal lesions and cancers are rare diseases (approximately 27,000 new cases per year globally, of which about 24,000 are HPV-related (de Martel, 2012) or approximately 0.1 to 2.8 cases per 100,000 among men and 0.0 to 2.2 per 100,000 among women (Hoots, 2009)). A clinical trial to assess the efficacy of Cervarix against anal lesions and cancer development would therefore require a very large sample size and would take many years to complete. This rationale is in line with the CHMP guideline on the clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/05), which recommends estimating the relative protective efficacy of a candidate vaccine by comparing it with a licensed vaccine that protects against the same infection, recognising that, in such a context, estimating protective efficacy may indeed not be feasible.

The CHMP agreed to the immunobridging strategy and considered that sufficient evidence based on immunological comparison has been provided to reasonably estimate Cervarix efficacy against anal lesions an anal cancer.

The post-hoc data on Cervarix efficacy against anal HPV infection published by Kreimer et al., which uses incident infection measured at one time point only as opposed to persistent infection, is not in itself supporting an indication of prevention of anal lesions, although the results of incident infection are encouraging 62.0% (95% CI: 47.1, 73.1) in the full non-naïve cohort and 83.6% (95% CI: 66.7, 92.8) in the restricted naïve cohort). The data described by Kreimer et al. are in line with previous observations on the efficacy against cervical infection showing that vaccination did not impact the outcome of cervical HPV infections present at the time of vaccination. Hence Cervarix is preferably administered to individuals as of 9 years of age, before sexual debut, to get full benefit of HPV vaccination. Data on anal HPV infections were not collected at baseline, but anal infection at baseline is anticipated to be in line with cervical infection at baseline. The data on protection against anal infection should not be included in the SmPC, as this is not an agreed surrogate marker for anal cancer or precancerous lesions. The data on persistent anal infection are an expected outcome of the Kremer follow up study, and are considered highly relevant and should be submitted for review a soon as available. However they are not considered necessary to approve the current application, based on the evidence available.

The absolute benefit of Cervarix preventing anal cancer in the general population was estimated by calculating the Number Needed to Vaccinate. These assumptions are not intended nor required in order to corroborate the evidence provided in support of the anal cancer indication for Cervarix; they show however that a substantial number of anal cancer cases could be avoided in the general population and, more specifically, in the male population by vaccinating individuals with Cervarix.

2.4.3. Conclusions on the clinical efficacy

A large proportion of anal lesions and cancer cases are associated with HPV, predominantly types 16 and 18. Prophylactic vaccination against these oncogenic HPV types and as such prevention of the disease represents a cornerstone among available medical approaches.

The basis of this application for an indication including anal cancers and premalignant lesions for Cervarix is immunogenicity and safety data. Immune responses to Cervarix given according to a 2- or 3-dose schedule based on age were shown to be superior to those of qHPV, which is approved for the prevention of anal cancers and premalignant lesions, based on efficacy against AIN 2/3 related to HPV 16/18 in MSM and based on immunological bridging to younger age groups of boys. Immunogenicity bridging has been indeed found acceptable before as the basis of inferring clinical efficacy of HPV vaccines in younger age groups based on demonstrated vaccine efficacy in older age groups. It is therefore considered reasonable to accept immunobridging data in support of an indication against anal lesions for Cervarix. Considering that the immune responses to Cervarix, generally are higher compared to qHPV in the comparative studies available, the expected benefit from Cervarix vaccination against anal lesions and cancers in a male and female population is considered similar to qHPV and acceptable for licensure.

For this application, it was considered that further investigations of Cervarix efficacy against clinical efficacy endpoints (persistent infection, high grade anal lesions and anal cancer) were not considered feasible. This rationale, in line with current guidelines, was found acceptable by the CHMP.

Efficacy of Cervarix against anal infection with HPV types 16 and 18, which is the first necessary step of the pathogenic process for HPV-16/18 related anal lesion and cancer, was shown in a post-hoc study

by Kreimer et al. following the HPV-009 Costa Rica vaccine trial. Analyses on persistent anal infection are ongoing.

The CHMP considers that it would be relevant to follow-up on such analyses, and thus recommends the following measure, to which the MAH agreed:

Submit as soon as available the efficacy results on persistent anal infection in women 15-25 years of age, which are an expected outcome of the Kremer follow up post-hoc study to study HPV-009 (Kreimer et al., Lancet Oncology 2011).

2.5. Clinical safety

Introduction

In the total Cervarix clinical development studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of enrolment), Cervarix was administered to 16,142 females whilst 13,811 females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix 8,130 vs. control 5,786), adverse events were followed for 30 days after each injection. Safety data in male was not required for inclusion in the SmPC prior to this application.

The most common adverse reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting.

Studies HPV-010 and HPV-071 were designed to compare the immunogenicity of Cervarix versus qHPV in healthy adult females. In both studies, safety and reactogenicity were assessed as secondary objectives. The results of study HPV-010 are already reflected in the SmPC. The safety of Cervarix for administration in females is well documented through clinical trials and its commercial use. The following sections will therefore focus on the safety and reactogenicity assessment of the administration of Cervarix in male subjects, documented as secondary objectives in studies HPV-011 and HPV-040 (HPV-011: 10-18 years of age; HPV-040: 12-15 years of age). In both studies, GSK Biologicals hepatitis B vaccine Engerix B1 was used as control.

Patient exposure

The safety and reactogenicity assessment of the administration of Cervarix in male subjects, documented as secondary objectives in studies HPV-011 and HPV-040 (HPV-011: 10-18 years of age; HPV-040: 12-15 years of age) are presented below. In both studies, GSK Biologicals hepatitis B vaccine Engerix B was used as control.

The total number of male subjects that received at least one Cervarix vaccination in the two trials concerned is 2,621 (181 subjects in study HPV-011 and 2,440 subjects in study HPV-040, see table 17).

For study HPV-040, passive surveillance will be performed in all study participants, up to the moment they reach the age of 18.5 years. Active surveillance using diary cards was performed in a subset of 1,690 male subjects (out of 32,176 subjects representing the TVC), from Arm A and Arm C communities, of which 643 in the Cervarix group. This subset of 1690 male subjects is referred to as the “Diary Card subset” in the ensuing sections of the current document. The number of male subjects in the Cervarix group with active safety follow-up for SAE up to Month 12 was 2,436.

Table 17. Number of subjects who received at least one dose of Cervarix vaccine or control and total number of doses administered in all studies

Studies	*Cervarix*		HBV	
	Number of subjects who received at least one dose of *Cervarix*	Number of doses administered	Number of subjects who received at least one dose of HBV	Number of doses administered
HPV-011	181 (males)	535	89 (males)	262
HPV-040	14,838 2,440 males 12,398 females	44,331*	17,338 9,221 males 8,117 females	51,789*

HBV: Hepatitis B vaccine (*Engerix B*), control
*Compliance to the 3-dose schedule was 99.2% for both treatment groups

Study HPV-011

Endpoints

The safety endpoints analysed in study HPV-011 were:

- Occurrence, intensity and causal relationship to vaccination of solicited general symptoms and solicited local symptoms within 7 days (Days 0 - 6) after each and any vaccination.
- Occurrence, intensity and causal relationship to vaccination of unsolicited symptoms within 30 days (Days 0-29) after any vaccination.
- Occurrence of New Onset Chronic Diseases (NOCDs) and other medically significant conditions throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity.
- Occurrence of clinically relevant abnormalities in biochemical and haematological parameters assessed at Day 0, Month 2 and Month 7.
- Occurrence of severe adverse events (SAEs) throughout the entire study period (up to Month 7).
- Occurrence of SAEs, NOCDs and other medically significant conditions from Month 7 through to the Month 12 telephone contact.

Solicited local adverse events

During the 7-day (Days 0-6) post-vaccination period following each dose, in the TVC, pain was the most frequently reported local solicited symptom. Pain was reported following 72.3% (68.2; 76.1) of doses in the Cervarix group and following 22% (17.1; 27.6) of doses in the HBV group. Grade 3 pain was reported after 1.9% (0.9, 3.5) of the doses in the Cervarix group and 0% (0.0; 1.4) in the HBV group. Swelling at the injection site was reported in the Cervarix group following 10.7% (8.2; 13.7) of doses compared to 3.1% (1.3; 6.0) of doses in the HBV group. Redness at the injection site was reported in the Cervarix group following 16.6% (13.5; 20.1) of doses compared to 11.2% (7.6; 15.7) of doses in the HBV group. The rate of reporting for redness and swelling was much lower than for pain.

Solicited general adverse events

During the 7-day (Days 0-6) post-vaccination period following each dose (TVC), the most frequently reported solicited general symptom was myalgia in the Cervarix group following 27% (23.2; 31.0) of doses, and following 12.4% (8.6; 17.0) of doses in the HBV group. Grade 3 myalgia was reported following 0.6% (0.1; 1.7) of doses in Cervarix group and following 0% (0.0; 1.4) of doses in HBV

group. Myalgia possibly related to vaccination was reported following 20.5% (17.1; 24.2) of the doses in Cervarix group and 7.7% (4.8; 11.7) in HBV group.

For the other solicited general adverse events, reporting frequency was lower. Arthralgia possibly related to vaccination was reported following 4.8% (3.1; 7.0) of the doses in Cervarix group and 2.3% (0.9; 5.0) in HBV group. Fatigue possibly related to vaccination was reported following 14.7% (11.8; 18.1) of the doses in Cervarix group and 14.7 % (10.6; 19.6) in HBV group. Fever possibly related to vaccination was reported following 0.6 % (0.1; 1.7) of the doses in Cervarix group and 0.4% (0.0; 2.0) in HBV group. Gastrointestinal possibly related to vaccination was reported following 5.7% (3.9; 8.1) of the doses in Cervarix group and 3.5% (1.6; 6.5) in HBV group. Headache possibly related to vaccination was reported following 10.5% (8.0; 13.5) of the doses in Cervarix group and 8.5% (5.4; 12.6) in HBV group. Rash possibly related to vaccination was reported following 1.1% (0.4; 2.5) of the doses in Cervarix group and 0.4% (0.0; 2.1) in HBV group. Urticaria possibly related to vaccination was reported following 0.2% (0.0; 1.1) of the doses in Cervarix group and 0.0% (0.0; 1.4) in HBV group.

Unsolicited adverse events

The number of doses followed by at least one unsolicited symptom reported within the 30-day (Days 0-29) post-vaccination period was 15.7% (12.7; 19.1) in the Cervarix group and 15.6% (11.5; 20.6) of doses in the HBV group. At least one unsolicited symptom was reported by 37.6% (30.5; 45.1) of subjects in the Cervarix group and by 34.8% (25.0; 45.7) of subjects in the HBV group.

The most frequently reported symptoms were headache (following 3.2% (1.9; 5.0) and 3.8% (1.8; 6.9) of doses in Cervarix and HBV group, respectively), nasopharyngitis (following 2.4% (1.3; 4.1) and 1.1% (0.2; 3.3) of doses in Cervarix and HBV group, respectively) and pharyngolaryngeal pain (following 1.7% (0.8; 3.2) and 1.1% (0.2; 3.3) of the doses in Cervarix and HBV group, respectively). With respect to these two latter events, the company considers that they are covered by the term “upper respiratory tract infections” that is reported as an uncommon side effect in the label information.

Grade 3 unsolicited symptoms were reported following 0.9% (0.3; 2.2) of doses in the Cervarix group and 0.8% (0.1; 2.7) of doses in the HBV group. Unsolicited signs and symptoms with causal relationship to vaccination were reported after 1.1% (0.4; 2.4) and 0.4% (0.0; 2.1) of the doses in the Cervarix and the HBV group, respectively.

Serious adverse events

There were no fatal SAEs reported.

Two serious adverse events (Crohn’s disease and epilepsy) were reported during the active phase of the study (i.e. up to Month 7), both in the Cervarix group (representing 1.1% (0.1; 3.9) of subjects), but neither of them was assessed by the investigator as related to vaccination.

During the Month 7 to Month 12 safety follow-up, two serious adverse events were reported (appendicitis in the Cervarix group (0.6% (0.0; 3.1) of subjects), osteochondrosis in the HBV group (0.6% (0.0; 3.1) of subjects)). None of them were considered by the investigator as possibly related to the vaccination.

New onset chronic diseases (NOCD)

During the active phase of the study (i.e. up to Month 7), three events were reported and determined by a GSK physician (GSK assessment) as NOCDs, two in the Cervarix group (Crohn’s disease and atopic dermatitis) and one in the HBV group (asthma). Crohn’s disease was also considered a NOAD.

None of these events were assessed as possibly related to vaccination in the opinion of the investigator. According to the investigators' assessment, none of the events reported during the active phase of the study were considered to be NOCDs.

No NOCDs were reported during the Month 7 to Month 12 extended safety follow-up period.

Medically significant conditions

Medically significant conditions were recorded during the active phase of the study (i.e. up to Month 7) in the two groups (12.2% (7.8; 17.8) in the Cervarix group and 11.2% (5.5; 19.7) in the HBV group).

Three subjects experienced a medically significant condition during the extended safety follow-up period: one subject in the Cervarix group (depression) and two subjects in the HBV group (herpes zoster and osteochondrosis). None of them were considered to be related to study vaccination.

One subject (in the Cervarix group) was withdrawn from the study due to an adverse event (panic reaction) following the first dose of vaccine and subsequent doses were not administered.

Haematological and biochemical assessment

No clinically relevant differences were observed in haematological and biochemical analyses at Month 2 or Month 7 as compared to the control.

Study HPV-040

Endpoints

Passive safety surveillance was performed in all communities based on a national health registry.

The following secondary safety endpoints were evaluated at the time of the submitted interim analysis:

1. Active safety surveillance was performed in all males from Arm A and Arm C communities (Diary Card subset) until Month 12 as follows:

- Males included in the Diary Card subset:
    - Solicited (local and general) signs and symptoms within 7 days (Days 0 - 6) after each vaccination;
    - Unsolicited adverse events (AEs) within 30 days (Days 0- 29) after each vaccination;
    - Occurrence of rash and urticaria within 30 minutes following each vaccination;
    - Occurrence of medically significant conditions between Month 0 and Month 12;
    - Occurrence of SAEs between Month 0 and Month 12.
- Male study participants from Arm A communities who were not included in the Diary Card subset:
    - Occurrence of SAEs between Month 0 and Month 12.

2. Passive safety surveillance was performed in all study participants from all communities (Arms A, B, C) starting from Dose 1.

3. Spontaneous reporting:

- Any SAEs reported to the investigator and considered by the investigator as possibly related to vaccination were reported to GSK Biologicals.

Solicited local adverse events

During the 7-day post-vaccination period, pain at the injection site was the most frequent solicited local symptom in both groups (reported after 70.4% (68.1; 72.7) and 14.0% (12.7; 15.4) of doses in the Cervarix and HBV groups, respectively). Pain assessed as grade 3 in intensity was reported following 2.0% (1.4; 2.8) and 0.1% (0.0; 0.3) of doses in the respective groups.

Solicited general adverse events

Of the solicited general symptoms during the 7-day post-vaccination period, fatigue (following 31.1% (28.8; 33.4) and 21.5% (20.0; 23.1) of doses in Cervarix and HBV groups, respectively), headache (following 23.9% (21.8; 26.0) and 18.8% (17.4; 20.3) of doses in Cervarix and HBV groups, respectively) and myalgia (following 33.8% (31.5; 36.2) and 12.5% (11.3; 13.8) of doses in Cervarix and HBV groups, respectively) were the most frequent in both groups. Solicited general symptoms assessed as grade 3 in intensity were reported following at most 1.1% of doses in the Cervarix group and 0.8% of doses in the HBV group. Solicited general symptoms with causal relationship to vaccination were reported after 45.2% (42.7; 47.7) and 30.1% (28.4; 31.9) of the doses in Cervarix and HBV groups, respectively.

Unsolicited adverse events

At least one unsolicited symptom was reported after 10.1% (8.8; 11.6) of doses in the Cervarix and 7.6% (6.7; 8.6) of doses in the HBV group during the 30-day post-vaccination period. Grade 3 unsolicited symptoms were reported following 1.6% and 1.5% of doses in the Cervarix and HBV groups, respectively.

Unsolicited AEs considered by the investigator to be possibly related to vaccination were reported after 0.7% (0.4; 1.2) and 0.6% (0.4; 1.0) of doses in the respective groups.

Medically significant conditions (MSCs)

Medically significant conditions were reported for 7.3% (5.4; 9.6) and 7.3% (5.8; 9.0) of subjects in Cervarix and HBV group, respectively, from dose 1 to Month 12 in the Diary Card subset. Three subjects in the Cervarix group (0.5%) and one subject in HBV group (0.1%) reported each one medically significant condition considered as possibly related to vaccination by the investigator (including concussion, type 1 diabetes mellitus, juvenile arthritis and oropharyngeal pain; blinded to treatment allocation). Type 1 diabetes mellitus and juvenile arthritis were reported and considered as possibly related to the treatment by the investigator (blinded to treatment group). Both were also reported as a NOAD. Overall events reporting rate was similar between test and comparator. Incidence rates for the specific events were lower than the comparator.

Serious adverse events (SAE)

Within the full male population with active safety surveillance, SAEs were reported for 2.4% (1.8; 3.1) of subjects in the Cervarix group and 2.0% (1.3; 2.9) of subjects in the HBV group. For four subjects in the Cervarix group (0.2%) and one subject in the HBV group (0.1%), the SAEs were considered as possibly related to vaccination according to the investigator (i.e., abdominal pain, colitis ulcerative, type 1 diabetes mellitus and juvenile arthritis; blinded to treatment allocation). No fatal SAEs were reported. For the administration of the vaccine in males, there seemed to be no difference between groups and the reported rate of SAE after Cervarix vaccination within the male population is comparable to that within the female population (Descamps, 2009).

New onset autoimmune disease (NOAD) (passive safety surveillance)

Within the 12-month post-vaccination period (i.e. from Dose 1 up to 12 months after the last vaccine dose), the most common NOADs in female study participants were juvenile arthritis, colitis ulcerative, coeliac disease, autoimmune thyroiditis, type 1 diabetes mellitus and idiopathic thrombocytopenic

purpura, in addition to uveitis (three cases blinded to treatment allocation). In male study participants, the most common NOADs were juvenile arthritis, colitis ulcerative and type 1 diabetes mellitus, in addition to Crohn's disease and coeliac disease (blinded to treatment allocation). No differences in the nature of the NOADs were observed between males and females.

Post-marketing experience

Cervarix was first registered in 2007 and the vaccine is currently licensed for use in more than 130 countries worldwide. 44,176,610 doses have been distributed since registration (data lock point 31 October 2013). As Cervarix was a 3-dose vaccine until end of 2013, post-marketing exposure to Cervarix since launch until 31 October 2013 is estimated as being between 14,725,537 and 44,176,610 subjects.

2.5.1. Discussion on clinical safety

Studies HPV-010 and HPV-071 submitted for this application were designed to compare the immunogenicity of Cervarix versus qHPV in healthy adult females. In both studies, safety and reactogenicity were assessed as secondary objectives. The results of study HPV-010 are already reflected in the SmPC. The safety of Cervarix for administration in females is well documented through clinical trials and its commercial use. The safety and reactogenicity assessment has therefore focused on the administration of Cervarix in male subjects, documented as secondary objectives in studies HPV-011 and HPV-040 (HPV-011: 10-18 years of age; HPV-040: 12-15 years of age). In both studies, GSK Biologicals hepatitis B vaccine Engerix B1 was used as control.

Safety data for Cervarix vaccination in males originate from a population of 2,617 subjects (181 subjects in HPV-011 and 2,436 subjects with active safety follow-up in HPV-040) within the 10 to 18 years age range, immunised with at least one dose of the product. Of note, no statistically significant comparative analysis has been performed between treatment groups. Therefore, any difference in the data between treatment groups or genders needs to be interpreted with caution.

Within the 10 to 18 years of age group (study HPV-011) and in line with previous observations in other studies conducted in females, the safety and reactogenicity profile of Cervarix seemed comparable to that of the control vaccine, with the exception of local solicited symptoms and myalgia. Local symptoms and myalgia seemed to be more frequent in the Cervarix group. The apparently higher rate of solicited symptoms did not negatively impact the acceptance of the vaccination, as 97% of both study groups in study HPV-011 completed the 3 dose vaccination schedule. Together with the overall low percentage of grade 3 symptoms (solicited and unsolicited) during the 30-day post-vaccination, which seemed comparable between the two treatment groups, these data indicate that the Cervarix vaccine is generally well tolerated in the male population.

In the larger set of subjects within the 12 to 15 years of age range (2,440 male subjects; HPV-040), the same conclusion can be drawn. Whereas the results suggested a higher frequency of local solicited symptoms (e.g. pain) in the Cervarix group as compared to the control group, reported as part of the active surveillance, the frequency of solicited general symptoms was lower as compared to the local symptoms and the potential difference between the treatment groups was less pronounced. The most frequently reported general symptoms are fatigue, headache and myalgia, which are already mentioned in the current label of the vaccine as very common symptoms. The percentage of these symptoms considered by the investigator as possibly related to vaccination seemed comparable between the groups.

For the administration of the vaccine in males, SAE rate was within the rate observed for female population, which is already approved. Also, no differences in the nature of the NOADs were observed

between males and females. In addition, overall SAEs reporting rate was similar between Cervarix and comparator. The incidence rates for the specific events were lower than the comparator. In any case, concerning NOADs, since the 'Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination' is part of the safety concerns in the RMP and is categorised as an important potential risk, auto-immune mediated diseases (AIDs) incidence in vaccinees and link to vaccination are closely monitored and reported in the PBRER/PSUR.

There are no data of Cervarix use in populations with high risk for HPV infection such as immunosuppressed patients.

Cervarix safety profile has been further evaluated in another Type II variation (EMEA/H/C/000721/II/0069) relating to risk for auto-immune diseases with Cervarix, which was ongoing in parallel to this procedure. Variation II/69 considered the following evidence:

1. a Post-Authorization Safety Study, EPI-HPV-040, investigating a potential risk of immune disorder linked to Cervarix vaccination in an adolescent and young adult population (results of observed versus expected analysis in post-marketing surveillance). Based on the results, the PRAC agreed that the data generated did not require an update of the current SmPC, since the results are either negative for the auto-immune disorders studied (e.g. for GBS) or inconclusive, particularly concerning auto-immune thyroiditis.

2. Best quality evidence from randomized controlled trials, in which the pooled analysis and the meta-analysis do not show an increased risk of autoimmune thyroiditis; data from other pharmacoepidemiological studies, which were powered to detect a risk of combined autoimmune diseases, show conflicting results but the observed incidence rates of autoimmune thyroiditis seems in line with background rates reported in the literature.

3. the results of a large pharmaco-epidemiological study performed by the ANSM in France were published online: http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information. The study investigated the incidence of auto-immune diseases in 2,256,716 girls (mean age at inclusion: 13.5 years), of whom 842,120 (33%) had been delivered at least one dose of anti-HPV vaccine during follow-up (qHPV: 93%; Cervarix: 7%). No overall increase in the risk of onset of auto-immune disease was observed in subjects after exposure to at least one dose of anti-HPV vaccine compared to those not exposed. However, the authors reported a significant association with HPV vaccination for inflammatory bowel disease (IBD) and Guillain-Barre syndrome (GBS). Due to the limitations of this study and the small numbers of events, these results should be interpreted with caution.

Overall based on the data shown in variation II-69 an update of the SmPC was not deemed necessary. The PRAC requested the MAH to provide updates on autoimmune thyroiditis diseases and GBS in the following PSURs.

Concerning this application, although discrepant reports are available in the literature, a slightly higher background incidence of GBS has been reported in males compared to females, at all age categories, in a systematic review and meta-analysis of published studies reporting GBS incidence to obtain estimates of population based age-specific incidence of GBS in North America and Europe[3] (with age-specific incidence rates estimated at 0.97/100,000 p-y in 10-19 year-old and 1.18/100,000 p-y in 20-

[3] Shui IM, Rett MD, Weintraub E, Marcy M, Amato AA, Sheikh SI et al. Guillain-Barré Syndrome incidence in a large United States cohort (2000-2009). Neuroepidemiology 2012;39:109-115.
Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-133.

29 year old for males versus 0.55 and 0.66/100,000 p-y in 10-19 year-old and in 20-29 year-old females, respectively). Based on these data, a gender-specific higher risk of developing GBS cannot be ruled out. However nothing is known about the risk following male immunization. Considering that Cervarix up until now does not have an indication in males, the available safety data from large epidemiological studies would include women only. Until such studies are available including males too, there is no evidence to suggest that the risk of autoimmune diseases following vaccination would differ substantially between genders.

The MAH proposed a meta-analysis (Study EPI-HPV-069) that will focus primarily on data obtained in females, and will therefore be of limited interest for the male population. Nevertheless, its value in terms of risk assessment is acknowledged. Such meta-analysis is intended to investigate the potential association of Cervarix vaccination and the risk of developing autoimmune thyroiditis, GBS and inflammatory bowel diseases.

All the evidences available to GSK arising from clinical trials, literature and epidemiological studies will be included in this assessment.

Further investigation on the data published by the French authorities is also planned. The RMP has been updated according to this information during the course of this procedure and in the PBRER/PSUR assessment procedure that was ongoing in parallel (versions 16.1 and 16.2).

2.5.2. Conclusions on clinical safety

The data from studies HPV-011 and HPV-040 demonstrate that Cervarix vaccination is well tolerated in the male population and that the vaccination of boys/men elicits similar antibody titres in the boys/men as compared to girls/women. No safety signals or adverse events differing from the safety profile of Cervarix observed in vaccinated females have so far been reported in males.

Taken together, the safety results from the two studies HPV-011 and HPV-040 indicate that administration of Cervarix is generally well tolerated in males within the range of 10 to 18 years of age. Overall, the safety profile in men is similar to that in women and is in line with the currently approved label. Therefore, the CHMP agrees to include vaccination of males as of 9 years of age in the Cervarix SmPC, in line with the currently indicated age range for women.

The theoretical risk of acquiring an autoimmune disease following vaccination is raised by the immunological action mechanism of vaccines. This important potential risk is identified for both males and females, although most autoimmune diseases disproportionally affect females. The RMP was updated to reflect the risk in males.

Multiple studies have been performed to assess the risk of autoimmune thyroiditis disease and GBS following HPV vaccination resulting, in some cases, to contrasting results (e.g. EPI-HPV-011[4], EPI-HPV-040, pharmacoepidemiological French study, pooling of clinical data). To address these findings, the MAH will further investigate the potential association of Cervarix vaccination and the risk of developing autoimmune thyroiditis diseases, GBS and inflammatory bowel diseases by conducting a meta-analysis of all available data from company's studies as well as any published studies performed by third parties (Study EPI-HPV-069). Potential immune-mediated diseases (pIMDs) are also followed up in PSURs.

[4] EPI-HPV-011 is a long-term safety surveillance of Cervarix in France assessing incidence of autoimmune diseases following Cervarix in young adult women. The objective of the study started in 2008 was to assess whether the use of Cervarix was associated with a modified risk of demyelination, type 1 diabetes, cutaneous lupus, inflammatory arthritis, idiopathic thrombocytopenic purpura, lupus erythematosus, myositis and dermatomyositis, Guillain-Barre syndrome, and autoimmune thyroiditis and Graves' disease.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 17 November 2016.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The PRAC considered that the risk management plan version 16.0 could be acceptable if the MAH implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The MAH implemented the changes in the RMP as requested by PRAC, and has also included the changes in RMP version 15, as agreed during the parallel PSUSA assessment.

The CHMP endorsed the Risk Management Plan version 17 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	None identified
Important potential risks	Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination
Missing information	Use of HPV-16/18 vaccine in HIV-infected subjects or subjects with known immune deficiencies Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine HPV type replacement Impact and effectiveness against anal lesions and cancer

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Study HPV-019 A phase I/II, partially-blind, randomized, controlled study to assess the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV-16/18 vaccine administered intramuscularly according to a three-dose schedule (0, 1, 6-month) in human immunodeficiency virus (HIV)-infected female subjects aged 18-25 years. (Category 3)	Safety and immunogenicity in HIV-positive women	Missing information: use in HIV-positive subjects	Study started	Month 24 study results were anticipated to be available by June 2014, but as the enrolment took longer than anticipated, results will be available at a later date (estimated March 2018).
Study HPV-039 A phase II/III, double-blind, randomized, controlled study to evaluate the efficacy, immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine,	Safety, immunogenicity and efficacy in Chinese female subjects	Potential risk of autoimmune diseases, Missing information: (Pregnancy	Study started	End of study report December 2016

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
administered intramuscularly according to a 0, 1, 6-month schedule in healthy Chinese female subjects aged 18-25 years. (Category 3)		and pregnancy outcome)		
Study HPV-040 A phase III/IV, community-randomized, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female and male study participants aged 12 – 15 years. (Category 3)	Effectiveness of two vaccination strategies in reducing the prevalence of HPV-16/18 infection in healthy female and male subjects.	Potential risk of autoimmune diseases, Missing information: (Pregnancy and pregnancy outcome),	Study started	Final study report June 2016
EPI-HPV-048 (Category 3) Surveillance study (follow-up of the EPI-HPV-033) of type-specific HPV infections among women in England to 2016. In addition, surveillance of type-specific HPV in cervical cancers in women under 30 years old.	Type-specific surveillance among sexually active females who have been offered HPV vaccination, to demonstrate vaccine effectiveness against vaccine and non-vaccine types (i.e. type replacement)	HPV type replacement	Planned	2nd quarter 2019
EPI-HPV-069 (Category 3) A meta-analysis using all available data from company's studies as well as published studies performed outside.	To assessing the potential association of Cervarix vaccination and the risk of developing autoimmune thyroiditis by providing an overall estimate of the relative risk of autoimmune thyroiditis following Cervarix vaccination.	Potential risk of autoimmune thyroiditis	Study started	September2016
Post-Marketing Surveillance Activity (Category 3): Monitoring of annual reporting of anal cancer and other HPV-related cancer by consulting 5 national cancer registries (Finland, The Netherlands, UK, Norway and Denmark)	To collect data for the quinquennial trend analysis of the occurrence of anal cancer and other HPV-related cancers	Missing information: Impact and effectiveness against anal lesions and cancer	Planned	December 2016
Post-Marketing Surveillance Activity (Category 3): Trend analysis of anal cancer and other HPV-related cancer every 5 years	To describe the potential changes over time in the occurrence of anal cancer and other HPV-related cancers in countries where Cervarix is used.	Missing information: Impact and effectiveness against anal lesions and cancer	Planned	December 2021 (submitted with next cyclical PBRER).
Post-Marketing Surveillance Activity (Category 3): Feasibility assessment to perform a case-control study to assess the	Re-assess the feasibility of an effectiveness/impact study of Cervarix	Missing information: Impact and effectiveness	Planned	December 2021 (submitted with next cyclical PBRER).

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
effectiveness and /or impact of HPV vaccination programmes using Cervarix. This feasibility assessment will be performed every 5 years.	vaccination against anal lesions and cancer.	against anal lesions and cancer		

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination	None	None
Use of HPV-16/18 vaccine in HIV infected women or subjects with known immune deficiencies	**Wording in SmPC (Warning and precautions)** *"Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited data are available (see "Pharmacodynamic Effects"); there are no data on the use of Cervarix in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals."*	None
Impact of HPV-16/18 vaccine in women who are inadvertently exposed to the vaccine around pregnancy onset or during pregnancy	**Wording in SmPC (Pregnancy section)** *"Specific studies of the vaccine in pregnant women were not conducted. Data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials are insufficient to conclude whether or not vaccination with Cervarix affects the risk of adverse pregnancy outcomes including spontaneous abortion. However, during the clinical development program, a total of 10,476 pregnancies were reported including 5,387 in women who had received Cervarix. Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar between treatment groups.* *Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.* *As a precautionary measure, it is preferable to avoid the use of Cervarix during pregnancy. Women who are pregnant or trying to become pregnant are advised to postpone or interrupt vaccination until completion of pregnancy."*	None
HPV Type replacement	None	None
Impact and effectiveness against anal lesions and cancer	None	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Section 4.1 Therapeutic indications

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, ~~and~~ vaginal and anal) ~~lesions~~ and cervical and anal cancers 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. The use of Cervarix should be in accordance with official recommendations.

Section 4.8 Undesirable effects

Summary of safety profile

In clinical studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of enrolment), Cervarix was administered to 16,142 ~~subjects~~ females whilst 13,811 ~~subjects~~ females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection. In two clinical studies that enrolled males aged 10 to 18 years, 2,617 males received Cervarix and were followed-up with active safety surveillance.

(For the updated table of adverse reactions, please see attached PI)

Section 5.1 Pharmacodynamic properties (main changes)

Clinical studies

Immunogenicity in males aged 10 to 18 years

Immunogenicity in males was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012.

Bridging of clinical efficacy against anal lesions and cancers

No efficacy study against anal premalignant lesions has been conducted with Cervarix. However, studies conducted in girls aged 9 to 14 years (study HPV-071) and in women aged 18 to 45 years (study HPV-010) have consistently shown a higher immune response with Cervarix than with the comparator for which efficacy data against anal premalignant lesions are conclusive and have shown protection.

Changes were also made to the PI to bring it in line with the current Agency/QRD template and SmPC guideline, which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

The Package Leaflet of Cervarix suspension for injection was subject to user testing at the time of the Marketing authorisation Application (MAA), consistent with the obligations under Articles 59(3) and 61(1) of Directive 2001/83/EC (as amended by Directive 2004/27/EC). The Package Leaflet was tested on clear comprehensibility (content) and clear legibility (format: font size, layout). The results of the

user testing were submitted to the EMA during the review process of the MAA. The conclusion of the report after the two rounds of testing was that the Package Leaflet was clear and legible.

According to Article 61(3) of Directive 2001/83/EC for changes to existing marketing authorisations, a justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: this variation does not contain major editorial changes to the package leaflet, and therefore it is agreed with the MAH that the package leaflet is still legible, clear and easy to use. The CHMP agreed that no new user testing should be provided.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Cervarix has demonstrated clinical efficacy against cervical lesions and cancer associated with HPV types 16 and 18 in females aged 15 years and older, and through immunogenicity bridging, vaccine efficacy is inferred in the 9-14 year old female group.

Cervarix vaccination consistently shows sustained immunogenicity across age groups and according to both licensed schedules. Immunogenicity of Cervarix has been compared to qHPV in studies HPV-010 and HPV-071 conducted in females 18-45 years of age and 9-14 years of age respectively. Non-inferiority to qHPV was demonstrated for both study groups. Final results from study HPV-010 up to Month 60 in females 18-45 years old who received 3-dose Cervarix showed that antibody titres remain relatively stable over time after month 12 and superior to 3-dose qHPV regardless of baseline serostatus (TVC cohort), across the three age strata. Superiority of the immune response elicited by Cervarix administered according to the 2-dose schedule 0, 6 months compared to that of qHPV administered according to the 2-dose 0, 6 months and the standard 3-dose 0, 2, 6 months schedules was demonstrated for both HPV-16 and HPV-18 by ELISA up to Month 12 regardless of baseline serostatus (TVC cohort) in HPV-071 study.

The data from studies HPV-011 and 040 in males subjects aged 10-18 and 12-15 years respectively indicate comparable immunogenicity between males and females, when administered Cervarix according to a 0, 1, 6-month schedule, irrespective of the pre-vaccination status of the subjects. Study HPV-040 showed that comparable seroconversion rates (100%) and GMTs at Month 7 (24,000 vs. 21,000 for HPV16 and 8,500 vs. 8,100 for HPV18) are achieved in the ATP cohort after a 3-dose Cervarix vaccination in males aged 12-15 years compared to females aged 12-15 years, for both HPV 16 and 18 types.

Another HPV vaccine (qHPV) was approved based on efficacy data against AIN 2/3 in the Men who have sex with men (MSM, 16-26 years of age) and against intra-anal persistent infection related to HPV16 and HPV18. Moreover, based on this clinical trial data, there is no evidence that efficacy of the vaccine is gender specific and the estimates obtained in MSM would be applicable to women and heterosexual men.

The issue whether or not AIN 2/3 lesions can be considered a surrogate marker for anal cancer is resolved on the basis of the literature data available and also based on the striking similarities between CIN and AIN as regards natural history, pathogenesis, histological appearance, spectrum of lesions and high-risk HPV types. Overall these elements provide strong evidence that AIN 2/3 lesions are a precursor of invasive HPV-related anal cancer and could be considered as a surrogate marker of invasive anal cancer, in the same way as CIN 2/3 lesions are a surrogate marker for cervical cancer.

In conclusion considering that the immune responses to Cervarix are consistently higher compared to the approved comparator in the comparative studies available, the expected benefit from Cervarix vaccination against anal lesions and cancers in a male and female population is considered acceptable for licensure.

Uncertainty in the knowledge about the beneficial effects

No efficacy data were generated with Cervarix in the prevention of persistent anal infection, anal lesions or anal cancer.

Published data following on from study HPV-009 data provide evidence of vaccine efficacy against anal and cervical prevalent infection associated with HPV-16/18 and HPV-31/33/45 (Kreimer et al., Lancet Oncology, 2011). The Kreimer data are obtained through a post-hoc study following the HPV-009 Costa Rica vaccine trial, of which the full data package is not available for assessment as it is conducted by NCI. Kreimer et al. data showed efficacy of Cervarix against anal infection with HPV types 16 and 18, which is the first necessary step of the pathogenic process for HPV-16/18 related anal lesion and cancer, but the most relevant analyses on persistent anal infection are ongoing. Such data should be submitted for review when available.

Further investigations of Cervarix efficacy against clinical efficacy endpoints (persistent infection, high grade anal lesions and anal cancer) are not considered feasible.

The duration of protection against premalignant anal lesions and anal cancer is currently unknown. It is considered to be the same as the duration of protection against cervical lesions, but the incidence of anal cancer most likely peaks at a higher age. However, the cause of anal cancer, i.e. HPV infection, is likely to occur within 5-20 years of vaccination in most cases and there is no reason to believe that the acquisition pattern of HPV differs substantially between men and women. Considering that the immune responses appear to decline slowly once a plateau value has been reached, the uncertainties regarding duration of protection are now considered reduced compared to what was known previously.

The absolute benefit of protection against anal cancer may be limited at the population level, because the incidence of anal cancer is low in the general population. However a substantial number of anal cancer cases could be avoided in the general population and, more specifically, in the male population by vaccinating individuals with Cervarix. There are uncertainties as to the magnitude of the increase of incidence of anal cancer.

Risks

Unfavourable effects

The safety of Cervarix for administration in females is well documented through clinical trials and its commercial use. The safety and reactogenicity assessment has therefore focused on the administration of Cervarix in male subjects.

The safety results from the two studies HPV-011 and HPV-040 indicate that administration of Cervarix is generally well tolerated in males 10 to 18 years of age. Overall, the safety profile in men is similar to that in women and is in line with the currently approved SmPC.

The most common adverse reactions observed after vaccine administration was injection site pain. These reactions were of mild to moderate severity and not long lasting.

Uncertainty in the knowledge about the unfavourable effects

The exposure of Cervarix in males (2.617 males exposed to at least one dose) is limited at present. Overall differences in the safety data between treatment groups or genders are not significant based on descriptive comparative analysis.

The theoretical risk of acquiring an autoimmune disease following vaccination is raised by the immunological action mechanism of vaccines. This important potential risk is identified for both males and females although most autoimmune diseases disproportionally affect females. The RMP has been updated to include this risk in males.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

A large proportion of anal lesions and cancer cases are associated with HPV, predominantly types 16 and 18. Prophylactic vaccination against these oncogenic HPV types and as such prevention of the disease represents a cornerstone among available medical approaches.

Cervarix consistently elicits sustained immunogenicity across age groups and according to both licensed schedules. A multiple immunobridging strategy demonstrates non-inferior and superior immune responses to the comparator in females of different age groups (from 9 to 45 years of age), including those for which clinical efficacy against anal lesions was previously demonstrated with the comparator. Comparative studies between genders show that Cervarix (3 dose schedule) elicits similar immunogenicity in male vs female.

There is strong evidence that AIN 2/3 lesions are a precursor of invasive HPV-related anal cancer and could be considered as a surrogate marker of invasive anal cancer, in the same way as CIN 2/3 lesions are universally considered a surrogate marker for cervical cancer.

The safety profile of Cervarix is well characterised in females. Overall and based on clinical trial data in men, the safety profile in men is similar to that in women and is in line with the currently approved label.

Benefit-risk balance

Considering the inferred potential of Cervarix to prevent anal lesions and anal cancer in both males and females, and the favourable safety profile, the benefit-risk balance is considered positive.

Discussion on the Benefit-Risk Balance

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. Since the immune responses are comparable between the two HPV vaccines Cervarix and qHPV, a vaccine approved for anal cancer prevention, it is reasonable to conclude that Cervarix will confer an acceptable clinical protection against premalignant anal lesions and cancer that is comparable with that of the approved vaccine. The safety profile is similar in males vs. females and is considered favourable.

As a consequence, the Risk/Benefit profile for Cervarix remains favourable in the new indication for the prevention of premalignant anal lesions and anal cancers causally related to certain oncogenic HPV types.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by majority of 29 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1 and 6.3 of the SmPC are updated. The Package Leaflet and the RMP (final version 17.0) are updated in accordance. In addition the MAH took the opportunity to implement QRD version 9.1 in the product information.

The variation leads to amendments to the Summary of Product Characteristics, annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

The divergent position to the majority recommendation is appended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include prevention against premalignant anal lesions and anal cancer as of 9 years of age for Cervarix; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 5.1 and 6.3 of the SmPC are updated. The Package Leaflet and the RMP (final version 17.0) are updated in accordance. In addition the MAH took the opportunity to implement QRD version 9.1 in the product information

Summary

Please refer to the published Assessment Report Cervarix H-C-721-II-67-AR.

APPENDIX

DIVERGENT POSITION

Divergent position expressed by CHMP members:

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the variation to the terms of the marketing authorisation for the following reason(s):

An extension of the indication with premalignant anal lesions and anal cancer is not endorsed. Anal cancer is a very uncommon cancer. Women have a higher incidence rate in age groups greater than 50 years but men dominate in the age ranges between 20 and 50 years old. In men and women, common risk factors are e.g. receptive anal sex, lifetime number of sexual partners and genital warts.

Taking into consideration that the incidence of anal cancer in the overall population is very low, the number of boys/adolescents prior to sexual debut to be vaccinated to prevent one case of anal (pre)malignancy is considered too high, making the yield of population based vaccination most likely extremely limited.

The benefit-risk balance of the proposed variation is considered negative.

London, 23 June 2016

…….
Pieter de Graeff

…….
Agnes Gyurasics