London, 18 October 2018
EMA/711964/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Cervarix

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

Procedure no.: EMEA/H/C/000721/P46/095

Marketing authorisation holder (MAH): GlaxoSmithkline Biologicals SA

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the Rapporteur	**Bart Van der Schueren**

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1. Introduction

On 26 July 2018, the MAH submitted a paediatric study report for study HPV-019 PRI (109823), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended:

A phase IV, observer-blind, randomized, controlled, multicentric study to assess the safety and immunogenicity of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix) administered intramuscularly according to a three-dose schedule (Day 0, Week 6, Month 6) in human immunodeficiency virus-infected (HIV+) female subjects aged 15 - 25 years, as compared to Merck's HPV-6/11/16/18 vaccine (Gardasil).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study HPV-019 PRI is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine containing HPV-16 and HPV-18 L1 VLP proteins and AS04 adjuvant was used in this study.

2.3. Clinical aspects

2.3.1. Introduction

Cervarix is currently indicated from the age of 9 years for the prevention of persistent infection, premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical, vulvar, vaginal and anal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV).

Human immunodeficiency virus-infected (HIV+) females are known to be predisposed to a higher risk of HPV infection and subsequent cervical intraepithelial neoplasia (CIN) lesions.

At the time of the HPV-019 study design, limited data were available on the use of the two HPV vaccines (Merck's Gardasil and GSK Biologicals' Cervarix) in HIV+ subjects. It is known that HIV+ women can mount a humoral response to HPV antigen. During the study conduct, data became available from a study conducted in South Africa, in which all HIV-positive and HIV-negative women aged 18-25 years who received Cervarix were seropositive for both HPV-16 and HPV-18 after the second vaccine dose and one year after the first dose, irrespective of baseline HPV status.

A study with Gardasil in HIV-infected women aged 13-45 years showed that the vaccine was generally safe and immunogenic. However, lower seroconversion rates for HPV types 6,11, 16 and 18 were observed in HIV+ women with a viral load of >10000 copies/mL and/or CD4 count <200 cells/µL.

Results from a large-scale comparative trial between the two licensed HPV vaccines show that immune responses were significantly higher with Cervarix compared to Gardasil, as indicated by HPV-16 and

HPV-18 neutralizing antibody levels in serum, positivity rates in cervicovaginal secretions (CVS) and HPV-16 and HPV-18 specific B cell frequencies, one month after the last dose.

Five years after vaccination, serum neutralizing antibody levels were still 7.8-fold higher in 18-26 year old subjects receiving Cervarix compared to those who received Gardasil.

These properties may prove important for HIV+ individuals to mount a good immunogenic response to HPV vaccination. Although inactivated vaccines can be administered safely to persons with altered immunocompetence, the safety and efficacy may differ depending on the type and severity of immunodeficiency. The fact that Cervarix and Gardasil do not contain live infectious agents greatly reduces concerns about potential harmful effects.

The current study was designed to assess the safety and immunogenicity of a 3-dose schedule of Cervarix in HIV+ subjects aged 15 - 25 years, as compared to Gardasil. For comparative purposes, a group of HIV- subjects was also evaluated.

2.3.2. Clinical study

HPV-019 PRI (109823): A phase IV, observer-blind, randomized, controlled, multicentric study to assess the safety and immunogenicity of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix) administered intramuscularly according to a three-dose schedule (Day 0, Week 6, Month 6) in human immunodeficiency virus-infected (HIV+) female subjects aged 15 - 25 years, as compared to Merck's HPV-6/11/16/18 vaccine (Gardasil).

Description

This study was conducted by 15 principal investigators in four countries (Brazil, Estonia, India, and Thailand).

Methods

Objective(s)

Co-primary:

Safety:

- To evaluate the safety and reactogenicity of both vaccines in HIV+ subjects for up to one month after the third dose of vaccine.

Immunogenicity:

The following objectives were assessed sequentially:

- To demonstrate non-inferiority of Cervarix versus (vs.) Gardasil in terms of geometric mean titres (GMTs) against HPV-16 and HPV-18 measured by Pseudovirion-based neutralization assay (PBNA) one month after administration of the third dose of vaccine in HIV+ subjects.

  Criterion: Non-inferiority was to be demonstrated if the lower limit of the 95% confidence interval (CI) for the ratio of GMTs (Cervarix over Gardasil) was above 0.5 for both HPV types.

- If the first primary objective for immunogenicity was demonstrated, superiority of Cervarix over Gardasil in terms of GMTs against HPV-16 and HPV-18 measured by PBNA in HIV+

subjects was to be assessed following a sequential approach. First, superiority for HPV-18 type was to be assessed.

Criterion: Superiority was to be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) was above 1 for HPV-18 type with a statistically significant p-value. Second, if superiority for HPV-18 was shown, superiority for HPV-16 was to be assessed. Criterion: Superiority was to be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) was above 1 for HPV-16 type with a statistically significant p-value.

Secondary:

Immunogenicity:

- To demonstrate superiority of Cervarix vs. Gardasil in terms of GMTs against HPV-16 or HPV-18 measured by PBNA one month after the administration of the third dose of vaccine in HIV- subjects.

  Criterion: Superiority of Cervarix vs. Gardasil was to be demonstrated if the lower limit of the 97.5% CI for the ratio of GMTs (Cervarix over Gardasil) was above 1 for the antigen considered with a statistically significant p-value.

- To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 antibody levels by Enzyme-Linked Immunosorbent Assay (ELISA) at Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 in all (HIV+ and HIV-) subjects.

- To evaluate the antibody response, by ELISA, against HPV-16 and HPV-18 in cervico-vaginal secretions (CVS) at Day 0, Week 6, Week 10, Months 7, 12 and 24 in post-menarcheal subjects who volunteer for this procedure.

- To evaluate the memory B and T cell-mediated immune (CMI) response against HPV-16 and HPV-18 at Day 0, Week 6, Week 10, Months 7 and 12 in a subset of approximately 100 subjects (50 HIV+ and 50 HIV-).

Safety:

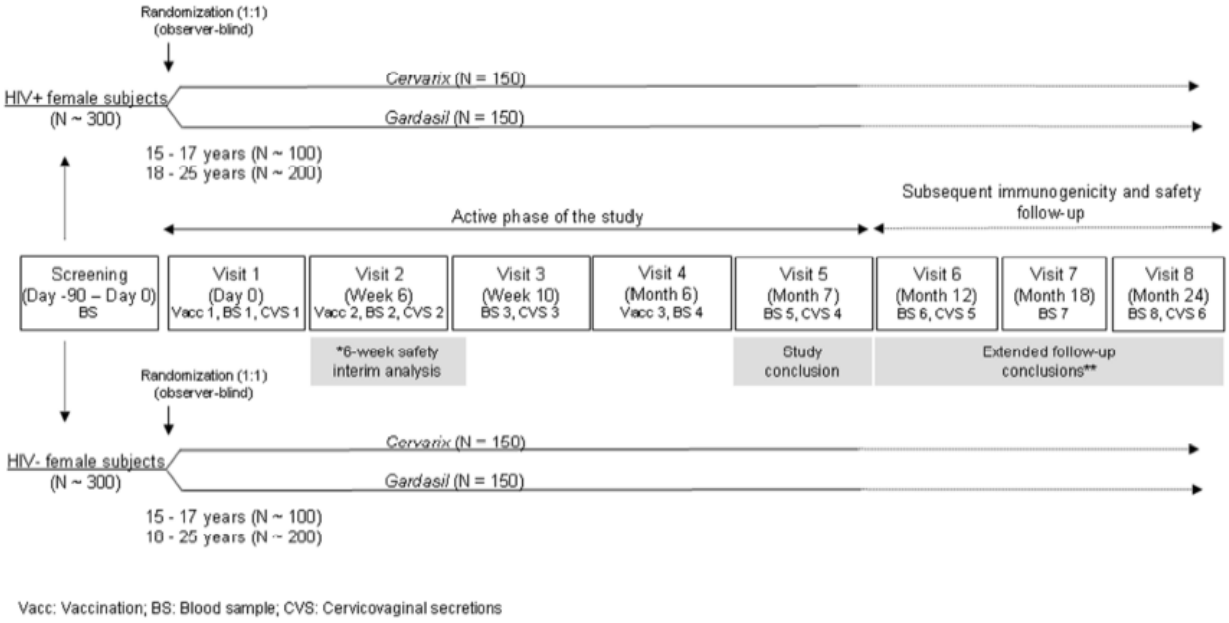
- To evaluate the safety and reactogenicity of both vaccines in HIV- subjects for up to one month after the third dose of vaccine.

- To evaluate the safety and reactogenicity of both vaccines in all subjects for up to 24 months after the first vaccine dose.

Study design

This was a multi-centre, observer-blind, controlled trial with two vaccine groups (Cervarix and Gardasil) and a staggered enrollment (Part A and Part B).as presented in the Figures below.

Figure 1 Study design



Vacc: Vaccination; BS: Blood sample; CVS: Cervicovaginal secretions

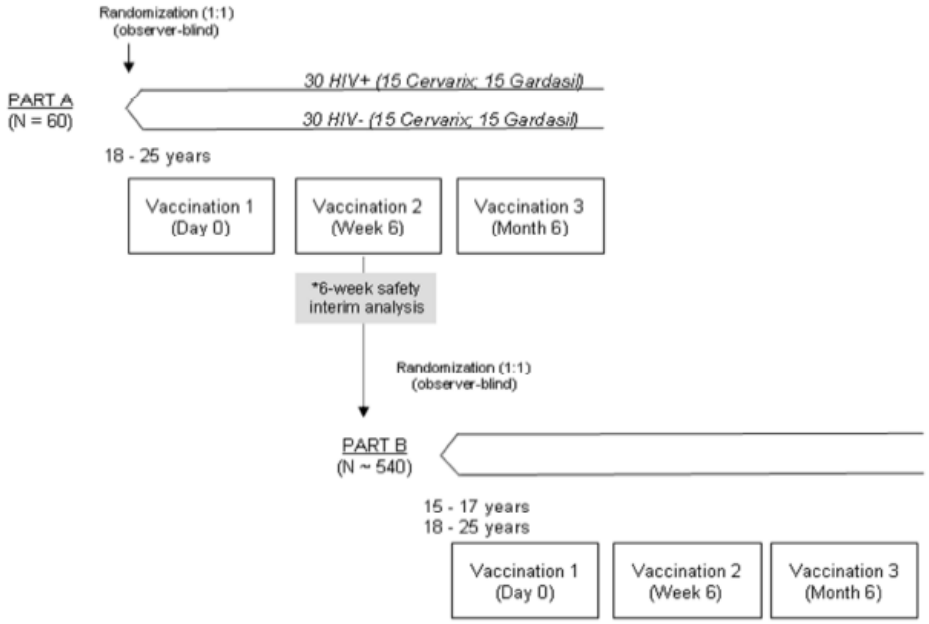
* The 6-week safety evaluation was to be assessed in a subset of approximately 60 subjects aged 18 – 25 years (30 HIV+ and 30 HIV- subjects) [Part A].

** The results of the analyses conducted on the data collected up to Months 12, 18, and 24 were to be written in annex reports.

The study was supervised by an Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician that oversaw safety and ethical aspects of the trial. Subjects were enrolled in a staggered manner (Part A and Part B). In Part A, a subset of 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) were to be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrolment and vaccination of the remaining subjects (Part B).

The results of this safety interim analysis were reviewed by the GSK Safety Review Team and the IDMC. The IDMC provided recommendation to the sponsor via the GSK Safety Review Team prior to proceeding with the enrolment of the remaining study subjects in Part B of the study.

Figure 2 Overview of staggered vaccination progress and safety evaluation



* if the safety evaluation did not indicate any safety concern, the remainder of the subjects were to be enrolled.

Study population /Sample size

The study included females between, and including, 15 and 25 years of age. For HIV seropositive subjects, subjects had to be HIV seropositive according to WHO case definition, i.e., positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay, confirmed by a second HIV antibody test relying on different antigens or of different operating characteristics and/or positive virological test for HIV or its components such as HIV-RNA, HIV-DNA or ultrasensitive HIV P24 antigen).

Subjects had to be asymptomatic regardless of their prior clinical stage. If they were currently taking antiretrovirals (ARVs), subjects were to be on Highly Active AntiRetroviral Therapy (HAART) for at least one year, have undetectable viral load (i.e., viral load < 400 copies/mm3) for at least six months, and have a CD4 cell count > 350 cells/mm3 at study entry. HIV+ subjects diagnosed with active tuberculosis (TB), or subjects on TB therapy were not enrolled. No previous vaccination against HPV or previous administration of monophosphoryl lipid (MPL) or AS04 adjuvant was allowed.

Treatments

This was a multi-centre, observer-blind, controlled trial with two vaccine groups:

- Cervarix group: approximately 300 subjects who received 3 doses of GSK Biologicals' HPV-16/18 vaccine at Day 0, Week 6, and Month 6
- Gardasil group: approximately 300 subjects who received 3 doses of Merck's HPV-6/11/16/18 vaccine at Day 0, Week 6, and Month 6.

Subjects were randomized 1:1 with central randomization call-in system on internet (SBIR), stratified by HIV infection status and by age (15-17 years and 18-25 years).

Outcomes/endpoints

Co-Primary endpoints:

Safety in HIV+ subjects up to Month 7:

- Occurrence and intensity of solicited local symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV+ subjects.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV+ subjects.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (Days 0 - 29) after any vaccination in HIV+ subjects.
- Occurrence of serious adverse events (SAEs) up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence of medically significant conditions (including potentially immune-mediated diseases [pIMDs]) up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence and outcome of pregnancies up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence of clinically relevant abnormalities in haematological and biochemical parameters up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- CD4 cell count up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- HIV viral load up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- HIV clinical staging up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.

Immunogenicity:

- HPV-16 and HPV-18 antibody titres by PBNA 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.

Secondary endpoints:

Safety:

- Occurrence and intensity of solicited local symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV- subjects.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV- subjects.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (Days 0 - 29) after any vaccination in HIV- subjects.
- Occurrence of SAEs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.

- Occurrence and outcome of pregnancies throughout the study (i.e., up to Month 24) in all subjects.
- Occurrence of clinically relevant abnormalities in haematological and biochemical parameters assessed at all study visits in all subjects.
- Occurrence of SAEs during the entire study period (i.e., up to Month 24) in all subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 12 months after the last dose of vaccine (i.e., Month 18) in all subjects.
- CD4 cell count, HIV viral load and HIV clinical staging at Months 12, 18 and 24 in HIV+ subjects.

Immunogenicity:

- HPV-16 and HPV-18 antibody titres by PBNA one month after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- HPV-16 and HPV-18 antibody titres and total IgG titres by ELISA in serum at Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 in all (HIV+ and HIV-) subjects.
- HPV-16 and HPV-18 antibody titres and total IgG titres by ELISA in CVS at Day 0, Week 6, Week 10, Months 7, 12 and 24 in post-menarcheal subjects who volunteer for this procedure.
- Frequencies of HPV-16 and HPV-18 specific B cells and T cells at Day 0, Week 6, Week 10, Months 7 and 12 in a subset of 100 subjects (50 HIV+ and 50 HIV-).

Statistical Methods

Analyses were performed as planned in the protocol amendment 8 (dated 26 April 2016) and the Statistical Analysis Plan Amendment (dated 23 November 2015), except for the following changes:

- Correlation between ELISA and PBNA was performed in HIV+ subjects.
- HPV-31 and HPV-45 antibodies were tested at Day 0, Month 7 and Month 24 for all subjects with remaining sample quantity ≥650 µl at all the three timepoints.
- Table for number and percentage of subjects with HPV-31 and HPV-45 above the cut-off and Geometric mean concentration was generated.
- Graphs for persistence of antibodies against HPV-31 and HPV-45 were generated.
- Reverse cumulative curves for HPV-31 and HPV-45 antibodies were generated.
- Because of GCP non-compliance issues at center 72321, all 172 subjects from this center were excluded from statistical analysis. Despite the fact that 6 of the enrolled subjects from this center should not have been excluded, it did not impact study conclusions, as shown by sensitivity analysis. Safety listings were separately generated for all 172 subjects.
- Sub-group immunogenicity analysis was performed by baseline CD4 category, instead of the Nadir CD4 as planned in the SAP.
- As the number of subjects in the subset considered for CMI analysis was very low, the CMI analysis performed by stratification is not presented in the study report.

Analysis of demographics/baseline characteristics:

Demographic characteristics (age, race, height and weight) of each study cohort were tabulated. Cohorts for analysis and withdrawal status were summarized per treatment group. The HIV mode of transmission, WHO clinical staging, HIV viral load, CD4 cell count and ARV use of the subjects at baseline were presented as a whole and by treatment group.

Analysis of safety:

The primary analysis was performed on the Total Vaccinated cohort (TVC). A second analysis based on the according-to-protocol (ATP) cohort for safety was performed to complement the TVC analysis. Analyses were done on HIV+ subjects (primary objectives) and on HIV- subjects (secondary objectives) according to the pre-specified objectives.

Analysis of immunogenicity:

Between group assessment:

Primary and secondary between-group comparisons to assess non-inferiority were done on the ATP cohort for immunogenicity (by PBNA, regardless of HPV serostatus at baseline) for the antigen under analysis. A second analysis on TVC was performed to support the primary analysis. Primary and secondary between-group comparisons to assess superiority were performed on the TVC (by PBNA; regardless of HPV serostatus at baseline). A second analysis on ATP cohort for immunogenicity was performed to support the primary analysis.

Two-sided 95% CIs of anti-HPV-16 and anti-HPV-18 GMT ratios (Cervarix over Gardasil), at Month 7, were computed using an analysis of variance (ANOVA) model on the log10 transformation of the titres for HIV+ subjects (primary objective) and for HIV- subjects (secondary objectives). The ANOVA model included the vaccine group as fixed effect.

Within group assessment:

The within-group comparisons were performed on the ATP cohort for analysis of immunogenicity. A second analysis based on the TVC was performed to complement the ATP analysis.

Results

Recruitment/ Number analysed

Of the 546 subjects in the TVC vaccinated in this study, a total of 448 subjects completed the study (117, 117, 103 and 111 subjects in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively). The main reasons for withdrawal from the study were withdrawal of consent not due to an AE, and loss to follow-up.

Table 1 Study population (Total vaccinated cohort)

Study population (Total vaccinated cohort)					
Number of subjects	**HIV+/HPV**	**HIV+/GAR**	**HIV-/HPV**	**HIV-/GAR**	**Total**
Planned, N	175	175	175	175	700
Randomised, N (Total Vaccinated Cohort)*	129	128	144	145	546
Completed, n (%)	117 (90.7)	117 (91.4)	103 (71.5)	111 (76.6)	448 (82.1)
Demographics	**HIV+/HPV**	**HIV+/GAR**	**HIV-/HPV**	**HIV-/GAR**	**Total**
N (Total Vaccinated Cohort)	129	128	144	145	546
Females:Males	129:0	128:0	144:0	145:0	546:0
Mean Age, years (SD)	20.4 (3.4)	20.1 (3.5)	19.3 (3.0)	19.6 (3.0)	19.8 (3.2)
Median Age, years (minimum, maximum)	21 (15, 25)	20 (15, 25)	19 (15, 25)	20 (15, 25)	20 (15, 25)
Asian - Central/South Asian Heritage, n (%)	20 (15.5)	18 (14.1)	67 (46.5)	68 (46.9)	173 (31.7)
Asian - South East Asian Heritage, n (%)	40 (31.0)	44 (34.4)	39 (27.1)	42 (29.0)	165 (30.2)
White - Caucasian / European Heritage, n (%)	33 (25.6)	37 (28.9)	24 (16.7)	19 (13.1)	113 (20.7)
White - Arabic / North African Heritage, n (%)	17 (13.2)	12 (9.4)	7 (4.9)	6 (4.1)	42 (7.7)
African Heritage / African American, n (%)	10 (7.8)	6 (4.7)	4 (2.8)	4 (2.8)	24 (4.4)
Asian - East Asian Heritage, n (%)	3 (2.3)	2 (1.6)	1 (0.7)	0	6 (1.1)
Asian - Japanese Heritage, n (%)	0	0	1 (0.7)	2 (1.4)	3 (0.5)
Other, n (%)	6 (4.7)	9 (7.0)	1 (0.7)	4 (2.8)	20 (3.7)

HIV+/HPV = HIV+ subjects receiving HPV-16/18 L1 VLP AS04 vaccine
HIV+/GAR = HIV+ subjects receiving Gardasil vaccine
HIV-/HPV = HIV- subjects receiving HPV-16/18 L1 VLP AS04 vaccine
HIV-/GAR = HIV- subjects receiving Gardasil vaccine
*Because of GCP non-compliance issues at center [redacted], all 172 subjects from this center were excluded from statistical analysis. Despite the fact that 6 of the enrolled subjects from this center should not have been excluded, it did not impact study conclusions, as shown by sensitivity analysis. Safety listings were separately generated for all 172 subjects.

The study lasted approximately 24 months for each subject, including an active phase from Day 0 to Month 7 and a subsequent extended safety and immunogenicity follow-up phase from Month 7 to Month 24. The first subject was enrolled in the study on 26 October 2010 and the last study visit was on 19 April 2017.

Baseline data

The demographic characteristics for the ATP cohort of immunogenicity are presented in the table below.

Table 2 Summary of demographic characteristics (ATP cohort for immunogenicity)

		HIV+/HPV N = 82		HIV+/GAR N = 84		HIV-/HPV N = 77		HIV-/GAR N = 80		Total N = 323	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years) at vaccination dose: 1	Mean	20.9	-	20.4	-	19.2	-	20.0	-	20.1	-
	SD	3.3	-	3.4	-	3.0	-	2.9	-	3.2	-
	Median	21.0	-	20.0	-	19.0	-	20.0	-	20.0	-
	Minimum	15	-	15	-	15	-	15	-	15	-
	Maximum	25	-	25	-	25	-	25	-	25	-
Gender	Female	82	100	84	100	77	100	80	100	323	100
	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Geographic Ancestry	African Heritage / African American	6	7.3	4	4.8	2	2.6	2	2.5	14	4.3
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	10	12.2	8	9.5	28	36.4	27	33.8	73	22.6
	Asian - East Asian Heritage	3	3.7	1	1.2	0	0.0	0	0.0	4	1.2
	Asian - Japanese Heritage	0	0.0	0	0.0	1	1.3	1	1.3	2	0.6
	Asian - South East Asian Heritage	24	29.3	28	33.3	19	24.7	24	30.0	95	29.4
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / North African Heritage	14	17.1	10	11.9	6	7.8	5	6.3	35	10.8
	White - Caucasian / European Heritage	22	26.8	30	35.7	20	26.0	18	22.5	90	27.9
	Other	3	3.7	3	3.6	1	1.3	3	3.8	10	3.1

HIV+/HPV = HIV+ subjects receiving HPV-16/18 L1 VLP AS04 vaccine
HIV+/GAR = HIV+ subjects receiving Gardasil vaccine
HIV-/HPV = HIV- subjects receiving HPV-16/18 L1 VLP AS04 vaccine
HIV-/GAR = HIV- subjects receiving Gardasil vaccine
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

The demographic profile of the TVC cohort for analysis of immunogenicity was comparable to the ATP cohort for analysis of immunogenicity.

The summary of vital signs characteristics and HIV disease characteristics at baseline for HIV+ subjects are presented in the Table below.

Table 3 Summary of HIV disease characteristics at baseline for HIV+ subjects by group (Total vaccinated cohort)

		HIV+/HPV N = 129		HIV+/GAR N = 128		Total N = 257	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Mode of transmission	Sexual	66	51.2	58	45.3	124	48.2
	Blood transfusion	0	0.0	2	1.6	2	0.8
	Drug_user by needles	4	3.1	1	0.8	5	1.9
	Transmission from your mother	50	38.8	60	46.9	110	42.8
	Other	7	5.4	5	3.9	12	4.7
	Unknown	2	1.6	1	0.8	3	1.2
	Mutliple mode	0	0.0	1	0.8	1	0.4
Clinical stage WHO	Clinical stage 1	120	93.0	120	93.8	240	93.4
	Clinical stage 2	7	5.4	3	2.3	10	3.9
	Clinical stage 3	1	0.8	1	0.8	2	0.8
	Clinical stage 4	1	0.8	4	3.1	5	1.9
Antiretroviral use	Yes	80	62.0	78	60.9	158	61.5
	No	49	38.0	50	39.1	99	38.5
Subject on Highly Active Antiretroviral Therapy	On HAART	80	62.0	78	60.9	158	61.5
	Not on HAART	49	38.0	50	39.1	99	38.5
	Missing	0	0.0	0	0.0	0	0.0
CD4 cell count	N	124	-	122	-	246	-
	Missing	5	-	6	-	11	-
	Mean	655.7	-	667.2	-	661.4	-
	Minimum	196.0	-	123.0	-	123.0	-
	Q1	444.0	-	488.0	-	448.0	-
	Median	569.1	-	609.0	-	586.5	-
	Q3	780.0	-	783.0	-	782.2	-
	Maximum	2703.0	-	1598.0	-	2703.0	-
HIV viral load	N	129	-	128	-	257	-
	Missing	0	-	0	-	0	-
	Mean	11002.1	-	10417.9	-	10711.2	-
	Minimum	0.0	-	0.0	-	0.0	-
	Q1	9.0	-	9.0	-	9.0	-
	Median	40.0	-	40.0	-	40.0	-
	Q3	2531.0	-	3343.0	-	2900.0	-
	Maximum	293840.0	-	600000.0	-	600000.0	-

HIV+/HPV = HIV+ subjects receiving HPV-16/18 L1 VLP AS04 vaccine
HIV+/GAR = HIV+ subjects receiving Gardasil vaccine
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100

Efficacy results

Immunogenicity results:

Co-Primary objectives

- Non-inferiority of Cervarix compared to Gardasil in terms of GMT ratio assessed by PBNA was demonstrated in HIV+ subjects, since the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) was above 0.5 for both HPV types.
- Superiority of Cervarix compared to Gardasil in terms of HPV-18 and HPV-16 GMT ratio assessed by PBNA was demonstrated in HIV+ subjects, since the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) was above 1 for both HPV types with a statistically significant p-value.

Secondary objectives

- Superiority of Cervarix compared to Gardasil in terms of HPV-18 and HPV-16 GMT ratios assessed by PBNA was demonstrated in HIV- subjects, since the lower limit of the 97.5% CI for the ratio of GMTs (Cervarix over Gardasil) was above 1 for both HPV types with a statistically significant p-value.
- At Month 7, by ELISA, all initially seronegative subjects had seroconverted for HPV-16 antibodies, and all except 3 subjects in the HIV+/GAR group had seroconverted for HPV-18 antibodies.
- GMCs for HPV-16 antibodies were 5110.1 EL.U/mL [95% CI: 4014.5, 6504.6], 2065.0 EL.U/mL [95% CI: 1538.1, 2772.3], 15748.1 EL.U/mL [95% CI: 12649.7, 19605.4], and 5947.8 EL.U/mL [95% CI: 5012.5, 7057.6] for the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively.
- GMCs for HPV-18 antibodies were 2892.6 EL.U/mL [95% CI: 2309.5, 3622.8], 458.6 EL.U/mL [95% CI: 324.5, 648.0], 6935.1 EL.U/mL [95% CI: 5484.6, 8769.1], and 1498.5 EL.U/mL [95% CI: 1216.7, 1845.6] for the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively.
- At Month 24, by ELISA, all initially seronegative subjects (100%) in the HIV+/HPV, HIV-/HPV and HIV-/GAR groups, and 94.7% of subjects in the HIV+/GAR group remained seroconverted for HPV-16, while seropositivity rates for HPV-18 antibodies were 96.3%, 67.6%, 100% and 98.5% in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively.

Figure 3 Persistence of HPV-16 antibody titres (ELISA) in subjects seronegative at baseline (Adapted ATP cohort for immunogenicity)

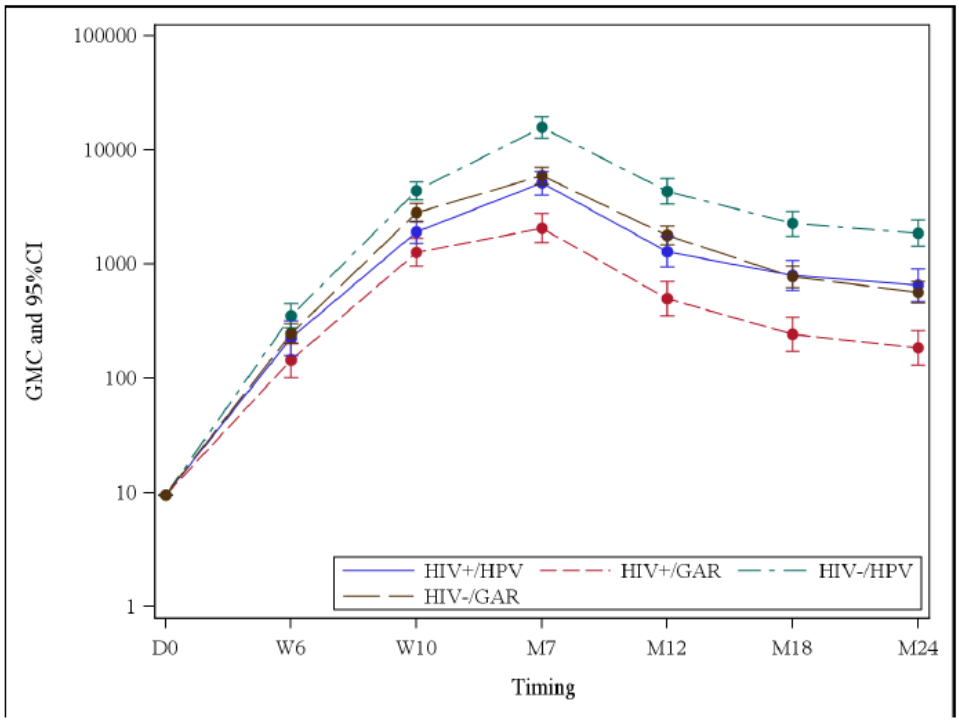
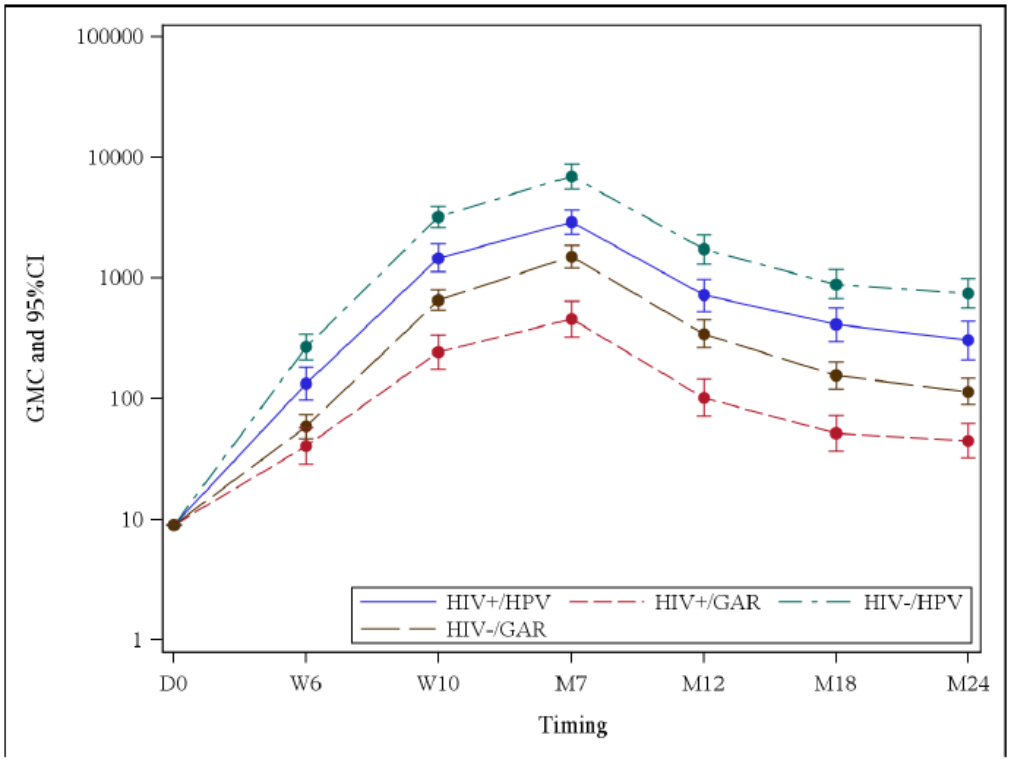


Figure 4 Persistence of HPV-18 antibody titres (ELISA) in subjects seronegative at baseline (Adapted ATP cohort for immunogenicity)



- GMCs for HPV-16 antibodies were 652.8 EL.U/mL [95% CI: 464.0, 918.6], 180.3 EL.U/mL [95% CI: 125.3, 259.4], 1869.3 EL.U/mL [95% CI: 1416.6, 2466.8], and 579.1 EL.U/mL [95% CI: 463.4, 723.8] for the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively.
- GMCs for HPV-18 antibodies were 292.3 EL.U/mL [95% CI: 199.4, 428.2], 44.9 EL.U/mL [95% CI: 31.9, 63.2], 763.3 EL.U/mL [95% CI: 572.5, 1017.8], and 114.1 EL.U/mL [95% CI: 87.1, 149.5] for the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively.
- A limited number of CVS samples were available for analysis. Antibodies against HPV-16 and HPV-18 were detected in most CVS samples tested.
- Overall, CD4+ T cell responses (in terms of median frequency of HPV-16/18 antigen-specific CD4+ T cells per million CD4+ T cells expressing at least two different immune markers [all doubles]) were detected in all groups and similar in HIV- and HIV+ and for both antigens. There was a trend for a higher response in the HPV groups compared to GAR groups.
- No substantial HPV-16 and HPV-18 specific CD8+ T cell responses were detected.
- A trend for lower B cell responses in HIV+ subjects versus HIV- was observed for HPV-16 and HPV-18, in both HPV and GAR groups.

Assessor's comment

The immunogenicity elicited by Cervarix in HIV+ individuals was superior to those elicited by Gardasil, which is expected in view of the presence of the AS04 adjuvant and is in line with earlier data.

Safety results

Safety results:

- Any symptom: During the 30-day post-vaccination period, any symptom (solicited and/or unsolicited) was reported by 96.1%, 86.6%, 96.5% and 88.2% of subjects after 87.4%, 69.8%, 86.3% and 73.5% of doses, in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups.
- Solicited local symptoms: During the 7-day post-vaccination period, pain at the injection site was the most frequently reported solicited local symptom in all groups, and was reported by 93.8%, 66.9%, 94.3% and 82.6% of subjects, after 80.6%, 47.4%, 81.8% and 64.3% of doses, in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. Grade 3 pain was the most frequently reported grade 3 symptom, reported by 8.6%, 4.7%, 15.6% and 5.6% of subjects after 3.8%, 2.2%, 6.5% and 2.2% of doses, in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively.
- Solicited general symptoms: During the 7-day post-vaccination period, headache was the most frequently reported solicited general symptom in all 4 groups, reported by 68.8%, 49.6%, 48.9% and 46.5% of subjects after 42.2%, 30.5%, 28.1% and 24.5% of doses, in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. Each individual Grade 3 solicited general symptom was reported for not more than 8.6%, 3.1%, 5.0% and 3.5% of subjects in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively.

The following table presents an overview of adverse events (any, local, and general) reported in the month following administration of each dose and overall.

Table 4 Incidence and nature of symptoms (solicited and unsolicited) reported during the 30-day (Days 0-29) post-vaccination period following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	HIV+/HPV	128	120	93.8	88.1	97.3	128	95	74.2	65.7	81.5	128	116	90.6	84.2	95.1
	HIV+/GAR	125	99	79.2	71.0	85.9	125	85	68.0	59.1	76.1	125	66	52.8	43.7	61.8
	HIV-/HPV	141	132	93.6	88.2	97.0	141	91	64.5	56.0	72.4	141	127	90.1	83.9	94.5
	HIV-/GAR	144	109	75.7	67.9	82.4	144	77	53.5	45.0	61.8	144	93	64.6	56.2	72.4
Dose 2	HIV+/HPV	127	107	84.3	76.7	90.1	127	81	63.8	54.8	72.1	127	98	77.2	68.9	84.1
	HIV+/GAR	125	83	66.4	57.4	74.6	125	63	50.4	41.3	59.5	125	60	48.0	39.0	57.1
	HIV-/HPV	136	116	85.3	78.2	90.8	136	72	52.9	44.2	61.6	136	109	80.1	72.4	86.5
	HIV-/GAR	139	101	72.7	64.5	79.9	139	64	46.0	37.6	54.7	139	94	67.6	59.2	75.3
Dose 3	HIV+/HPV	117	98	83.8	75.8	89.9	117	78	66.7	57.4	75.1	117	87	74.4	65.5	82.0
	HIV+/GAR	117	74	63.2	53.8	72.0	117	57	48.7	39.4	58.1	117	60	51.3	41.9	60.6
	HIV-/HPV	125	99	79.2	71.0	85.9	125	61	48.8	39.8	57.9	125	94	75.2	66.7	82.5
	HIV-/GAR	129	93	72.1	63.5	79.6	129	56	43.4	34.7	52.4	129	82	63.6	54.6	71.9
Overall/dose	HIV+/HPV	372	325	87.4	83.6	90.6	372	254	68.3	63.3	73.0	372	301	80.9	76.5	84.8
	HIV+/GAR	367	256	69.8	64.8	74.4	367	205	55.9	50.6	61.0	367	186	50.7	45.4	55.9
	HIV-/HPV	402	347	86.3	82.6	89.5	402	224	55.7	50.7	60.6	402	330	82.1	78.0	85.7
	HIV-/GAR	412	303	73.5	69.0	77.7	412	197	47.8	42.9	52.8	412	269	65.3	60.5	69.9
Overall/subject	HIV+/HPV	128	123	96.1	91.1	98.7	128	113	88.3	81.4	93.3	128	120	93.8	88.1	97.3
	HIV+/GAR	127	110	86.6	79.4	92.0	127	99	78.0	69.7	84.8	127	88	69.3	60.5	77.2
	HIV-/HPV	141	136	96.5	91.9	98.8	141	111	78.7	71.0	85.2	141	133	94.3	89.1	97.5
	HIV-/GAR	144	127	88.2	81.8	93.0	144	106	73.6	65.6	80.6	144	120	83.3	76.2	89.0

HIV+/HPV = HIV+ subjects receiving HPV-16/18 L1 VLP AS04 vaccine
HIV+/GAR = HIV+ subjects receiving Gardasil vaccine
HIV-/HPV = HIV- subjects receiving HPV-16/18 L1 VLP AS04 vaccine
HIV-/GAR = HIV- subjects receiving Gardasil vaccine
For each dose and overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

- Unsolicited symptoms: Within the 30-day post-vaccination follow-up period:
    - The most frequently reported unsolicited symptom in the HIV+/HPV group was headache, reported by 2.1% of subjects. In the HIV+/GAR and HIV-/GAR groups, nasopharyngitis was the most frequently reported unsolicited symptom, reported by 3.1% and 4.1% of subjects, respectively. In the HIV-/HPV group, the most frequently reported unsolicited symptom was dysmenorrhea, reported by 2.8% of subjects.
    - At least one grade 3 unsolicited symptom was reported by 5.4%, 3.1%, 0.7% and 2.1% of subjects after 1.9%, 1.1%, 0.2% and 0.7% of doses, in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. None of the grade 3 unsolicited symptoms were reported by more than 1 subject in any group.
    - At least one unsolicited symptom considered by the investigator to have a possible causal relationship to vaccination was reported by 7.0%, 6.3%, 2.8% and 1.4% subjects after 2.9%, 2.1%, 1.0% and 0.5% of doses in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. The most frequently reported unsolicited symptoms considered by the investigator to have a possible causal relationship to

vaccination in the HIV+/HPV group were headache and dizziness, reported by 2 subjects (1.6%).

- One subject (0.8%) in the HIV+/HPV group reported a grade 3 unsolicited symptom considered by the investigator to have a possible causal relationship to vaccination (immune thrombocytopenic purpura). The event was also a SAE and a pIMD.

- Fatal SAEs: Two fatal SAEs (bacterial pneumonia, pulmonary tuberculosis) were reported for 1 subject in the HIV+/GAR group. The investigator did not consider the SAEs to be possibly causally related to vaccination.

- Non-fatal SAEs: Within the 30-day period after last dose of vaccination in HIV+ subjects, 6 subjects in the HIV+/HPV and HIV+/GAR groups reported at least one SAE. During the entire study period, a total of 23 subjects (9 each in the HIV+/HPV and HIV+/GAR groups, 4 in the HIV-/HPV group and 1 in the HIV-/GAR group) reported a total of 29 SAEs (11, 12, 5 and 1 in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively). One SAE, which was also a pIMD (immune thrombocytopenic purpura), was considered by the investigator to have been due to underlying HIV infection which may have been aggravated by the study vaccine. All nonfatal SAEs resolved without sequelae.

- Withdrawals due to adverse events /serious adverse events: Apart from one subject in the HIV+/GAR group with fatal SAEs, no subjects were withdrawn from the study due to an AE/SAE.

- Medically significant conditions (MSC): Within the 30-day period after the last dose of vaccination (up to Month 7), in HIV+ subjects, a total of 44 subjects (17 in the HIV+/HPV group and 27 in the HIV+/GAR group) reported at least one MSC. In HIV- subjects, a total of 21 subjects (7 in the HIV-/HPV group and 14 in the HIV-/GAR group) reported at least one MSC. Up to Month 18 (12 months after the last dose of vaccination), at least one MSC was reported by 25 (19.4%), 37 (28.9%), 10 (6.9%) and 17 (11.7%) subjects in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. The most frequently reported MSCs (based on an incidence of ≥2 subjects [≥ 1.6%]) were herpes zoster, pain, anaemia and vulvovaginal pruritus in the HIV+/HPV group, reported by 2 subjects (1.6%) each, and diarrhea, reported by 5 subjects (3.9%) in the HIV+/GAR group. None of the MSCs were reported by more than 1 subject in the HIV- /HPV and HIV-/GAR groups.

- pIMDs: Up to Month 18,one subject (0.3%) in the HIV+/HPV group reported one pIMD (immune thrombocytopenic purpura).

- Pregnancies: A total of 9 pregnancies were reported up to Month 7. Seven pregnancies (3 in the HIV+/HPV group, 1 each in the HIV+/GAR and HIV-/HPV groups, and 2 in the HIV-/GAR group) resulted in live infants with no apparent congenital anomaly. Two pregnancies (one each in the HIV+/HPV and HIV+/GAR groups) resulted in spontaneous abortion with no apparent congenital anomaly. During the entire study period, a total of 28 pregnancies were reported. The majority of pregnancies (89.3%) resulted in live infants with no apparent congenital anomalies. One subject (10.0%) in the HIV+/HPV group underwent an elective termination, and two subjects (7.1%; 1 subject each in the HIV+/HPV and HIV+/GAR groups) had spontaneous abortions with no apparent congenital anomalies.

Assessor's comment

Cervarix is more reactogenic than Gardasil, which is expected in view of the presence of the AS04

adjuvant and is in line with earlier data.

2.3.3. Discussion on clinical aspects

Summary

The immunological co-primary objective of the study was met since:

- Non-inferiority of Cervarix compared to Gardasil in terms of GMT ratio assessed by PBNA was demonstrated, since the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) was above 0.5 for both HPV types.
- Superiority of Cervarix compared to Gardasil in terms of HPV-18 and HPV-16 GMT ratio assessed by PBNA was demonstrated, since the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) was above 1 for both HPV types with a statistically significant p-value.
- Superiority of Cervarix compared to Gardasil in terms of HPV-18 and HPV-16 GMT ratios assessed by PBNA was demonstrated in HIV- subjects, with the lower limit of the 97.5% CI for the ratio of GMTs (Cervarix over Gardasil) above 1 for both HPV types with a statistically significant p-value.
- At Month 7, all subjects seroconverted for HPV-16 and all except two in the HIV+/GAR had seroconverted for HPV-18.
- At Month 24, by ELISA, all initially seronegative subjects (100%) in the HIV+/HPV, HIV-/HPV and HIV-/GAR groups, and 94.7% of subjects in the HIV+/GAR group remained seroconverted for HPV-16, while seropositivity rates for HPV-18 antibodies were 96.3%, 67.6%, 100% and 98.5% in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively
- By ELISA, antibodies against HPV-16 and HPV-18 showed a peak in concentration one month after vaccination and a decline until Month 24.
- Antibodies against HPV-16 and HPV-18 were detected in most CVS samples tested.
- The co-primary objective of safety of the study was met as the safety and reactogenicity profile of both HPV vaccines in HIV+ subjects was acceptable.

Both HPV vaccines were generally well tolerated when administered to HIV+ and HIV- subjects. Cervarix is more reactogenic than Gardasil which is expected in view of the presence of the AS04 adjuvant and is in line with earlier data.

3. CHMP overall conclusion and recommendation

Study HPV-019 is a phase IV, observer-blind, randomized, controlled, multicentric study to assess the safety and immunogenicity of Cervarix three-dose schedule (Day 0, Week 6, Month 6) in HIV+ female subjects aged 15 - 25 years, as compared to Gardasil.

The study demonstrates superiority of immune responses to both HPV-16 and HPV-18 antigens 1 month after the last vaccination (Month 7) in HIV+ subjects when Cervarix was administered as compared to Gardasil. Both HPV vaccines were generally well tolerated when administered to HIV+ and HIV- subjects. Cervarix is more reactogenic than Gardasil which is expected in view of the presence of the AS04 adjuvant and is in line with earlier data.

The current SmPC presents the following information regarding HIV infected individuals:

> *Section 4.4*
>
> *Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited immunogenicity data are available (see section 5.1), 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.*
>
> *…*
>
> *Section 5.1*
>
> *Immunogenicity in HIV infected women*
>
> *In study HPV-020, conducted in South Africa, 22 HIV uninfected and 42 HIV infected subjects (WHO clinical stage 1; ATP cohort for immunogenicity) received Cervarix. All subjects were seropositive in the ELISA assay to both HPV 16 and 18 one month after the third dose (at Month 7) and the seropositivity for HPV 16 and 18 was maintained up to Month 12. The GMTs appeared to be lower in the HIV infected group (non overlapping 95% confidence interval). The clinical relevance of this observation is unknown. Functional antibodies were not determined. No information exists about protection against persistent infection or precancerous lesions among HIV infected women. No correlate of protection has been demonstrated so far for the HPV-16 and HPV-18 antigens used as part of Cervarix. Also, no information exists about protection against persistent infection or precancerous lesions among HIV infected women.*

The MAH concludes that the safety and immunogenicity data are in line with the approved SmPC. Meanwhile, an update of the SmPC is planned in 2019 as the data are more robust and informative on the HIV population studied.

As conclusion, the CHMP agrees with the conclusion of the MAH. Meanwhile, information about protection against persistent infection or precancerous lesions among HIV infected women is still missing. Also of note, no minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines.

☒ Fulfilled:

No further action required, however further data are expected in the context of the final study report of study HPV-019 prior any conclusion on product information amendments is made. The MAH is committed to submit a variation by 31 December 2019.