14 May 2020
EMA/267086/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cervarix

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

Procedure No. EMEA/H/C/000721/II/0106

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	14 Jan 2020	14 Jan 2020	☐
☐	CHMP Rapporteur Assessment Report	17 Feb 2020	18 Feb 2020	☐
☐	PRAC Rapporteur Assessment Report	24 Feb 2020	18 Feb 2020	☐
☐	PRAC members comments	28 Feb 2020	28 Feb 2020	☐
☐	CHMP members comments	02 Mar 2020	02 Mar 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	03 Mar 2020	05 Mar 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Mar 2020	05 Mar 2020	☐
☐	Start of written procedure	10 Mar 2020	10 Mar 2020	☐
☐	PRAC endorsed relevant sections of the assessment report	10 Mar 2020	10 Mar 2020	☐
☐	Request For supplementary information	12 Mar 2020	12 Mar 2020	☐
☐	Start of procedure	16 April 2020	16 April 2020	☐
☐	CHMP Rapporteur Assessment Report	29 April 2020	29 April 2020	☐
☐	PRAC Rapporteur Assessment Report	30 April 2020	29 April 2020	☐
☐	PRAC members comments	04 May 2020	n/a	☐
☐	CHMP members comments	04 May 2020	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	05 May 2020	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07 May 2020	06 May 2020	☐
☐	Start of written procedure	12 May 2020	12 May 2020	☐
☐	PRAC endorsed relevant sections of the assessment report	12 May 2020	12 May 2020	☐
☒	Opinion	14 May 2020	14 May 2020	☐

Procedure resources	
Rapporteur:	Christophe Focke
PRAC Rapporteur:	Jean-Michel Dogné

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithkline Biologicals SA submitted to the European Medicines Agency on 20 December 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II, IIIA and IIIB

Update of sections 4.4 and 5.1 of the SmPC based on final results from study HPV-019 listed as a category 3 study in the RMP; this is a safety and immunogenicity study of Cervarix in HIV-positive female subjects aged 15-25 years as compared to HPV-4, which was already submitted in P46.

In addition, the Marketing authorisation holder (MAH) took the opportunity to reflect an update in section 4.2 of the SmPC to indicate that limited clinical data is now available in 4-6 years old children based on study HPV-073 following assessment in P46/090; this is a safety and immunogenicity study of Cervarix in girls aged 4-6 years, as an alternative to the current adolescent HPV vaccination schedule.

The RMP version 21.0 has also been submitted to reflect the availability of the final results of the HPV-019 and HPV-073 studies, and the use of Cervarix in HIV-infected subjects or subjects with known immune deficiencies has been removed as missing information.

In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1.

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

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

Within this type II variation, the MAH is providing the results from study HPV-019 and HPV-073, already assessed within the context of Article P46 procedures, and the consequential amendments to the product information.

- HPV-019: phase IV, multi-centre, observer-blind, controlled, randomised (1:1) study, with 2 groups, stratified by HIV infection status (positive or negative) and by age (15-17 years and 18-25 years) in Brazil, Estonia, India and Thailand.
- HPV-073: phase III, single-blinded, randomised, controlled, multicentre study with 2 parallel groups in healthy girls 4 to 6 years of age at the time of vaccination in Colombia, Mexico and Panama.

There is evidence for multiple biological interactions between human immunodeficiency virus (HIV) and

human papilloma virus (HPV)[1]. These interactions have several important clinical, epidemiological and public health implications. In particular, the excess burden of HPV in Person Living with HIV (PLHIV) has implications for the clinical management of PLHIV requiring more frequent screening, follow-up and management of precancerous lesions due to HPV. HPV vaccination, which has been proven to be safe and immunogenic among PLHIV[2], may confer particular benefit to this group, and help to control HPV infections and related cancer more efficiently at population-level. Recent modelling studies suggest that as PLHIV are disproportionately infected with HPV they are more likely to transmit it making them an important group for focused HPV prevention. Interventions such as HPV vaccination could in theory have additional indirect benefits on HIV/AIDS, even if the relative risk of HIV acquisition due to HPV is modest. Given the burden of HPV and HIV and abundance of co-infections, HPV vaccination could prevent a non-negligible number of AIDS deaths particularly in Sub-Saharan Africa.

Immunocompromised patients, particularly HIV-infected patients with CD4 cell counts <200 cells/microL, are at especially high risk for HPV-related disease[3]. HPV vaccination with a three-dose schedule (at 0, 1 to 2, and 6 months) is recommended for all immunocompromised patients through 26 years of age if they have not already been vaccinated.

Direct efficacy data on HPV vaccination in immunocompromised hosts are lacking. Efficacy data are emerging in patients with HIV, but they are not conclusive. In a study of females older than nine years with HIV who received quadrivalent vaccination, the incidence of new persistent vaccine-type HPV infection was 1.1 per 100 person-years; this rate was higher than that reported in cohorts of women without HIV[4]. No cases of cervical intraepithelial neoplasia or worse were detected in women with normal baseline cytology.

Studies of the HPV quadrivalent vaccine in adult men with HIV, women aged 16 to 23 years with HIV, and boys and girls aged 7 to 12 years with HIV suggest that it is both immunogenic and safe in these populations[5]. However, in one study, seroconversion rates and titers were lower among perinatally infected HIV-positive youth compared with perinatally exposed but HIV-negative youth[6]. Some studies suggest a less robust and shorter-lived immune response in the setting of HIV infection[7].

The risk of HPV infection and subsequent cervical intraepithelial neoplasia lesions is higher in HIV+ females [WHO, 2017], but a humoral response to HPV antigens can still be mounted in this immunocompromised population. Thus, vaccination against HPV is likely to be beneficial for the high-risk group of HIV+ females.

In clinical trials, Cervarix has demonstrated clinical efficacy against cervical lesions and cancer associated with HPV 16/18 in females aged >15 years, and its efficacy was inferred in the 9 – 14-year old age group through immunogenicity bridging. In the **HPV-019** study, Cervarix was proven to be superior to quadrivalent HPV comparator vaccine, in terms of HPV-16/18 neutralising antibodies, in asymptomatic HIV+ woman aged 15 – 25 years. The vaccine was immunogenic and seroconversion

[1] Williamson AL. The interaction between human immunodeficiency virus and Human Papillomaviruses in heterosexuals in Africa. J Clin Med. 2015;4(4): 579–92.
[2] Kojic EM, Kang M, Cespedes MS, Umbleja T, Godfrey C, Allen RT, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis. 2014;59(1):127–35.
[3] Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014; 58:309.
[4] McClymont E, Lee M, Raboud J, et al. The Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living With Human Immunodeficiency Virus. Clin Infect Dis 2019; 68:788
[5] Bergman H, Buckley BS, Villanueva G, et al. Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males. Cochrane Database Syst Rev 2019; 2019.
[6] Moscicki AB, Karalius B, Tassiopoulos K, et al. Human Papillomavirus Antibody Levels and Quadrivalent Vaccine Clinical Effectiveness in Perinatally Human Immunodeficiency Virus-infected and Exposed, Uninfected Youth. Clin Infect Dis 2019; 69:1183.
[7] Brophy J, Bitnun A, Alimenti A, et al. Immunogenicity and Safety of the Quadrivalent Human Papillomavirus Vaccine in Girls Living With HIV. Pediatr Infect Dis J 2018; 37:595.

rates and antibody levels remained sustained until study conclusion, at Month 24. In subjects who received Cervarix, the cell mediated immune (CMI) response in HIV+ subjects was similar to that observed in HIV- subjects, up to one month post-dose 3. No safety concern for use of Cervarix in HIV+ women was identified in the HPV-019 study. Overall, the results of the HPV-019 study indicate that Cervarix is immunogenic and well tolerated in asymptomatic HIV+ females 15 – 25 years of age.

Of note, in a head-to-head comparison of the immunogenicity of quadrivalent and bivalent HPV vaccines in females aged 18 to 45 years, immunization with the bivalent vaccine induced geometric mean titers (GMT) of serum neutralizing antibodies 2.3- to 4.8-fold higher for HPV 16 and 6.8- to 9.1-fold higher for HPV 18 across all age strata compared with the quadrivalent vaccine[8]. However, whether the induction of higher serum titers against HPV 16 and 18 has any impact on the degree and duration of protection is unknown.

As a result of these data, sections 4.4 and 5.1 of the SmPC are updated to indicate the availability, no longer limited, of immunogenicity data for asymptomatic HIV infected subjects and to indicate the superiority of immune responses (neutralizing antibodies GMT ratios) to both HPV-16 and HPV-18 antigens with Cervarix compared to quadrivalent HPV vaccine, at month 7 in HIV infected subjects.

In the **HPV-073** study, 2 doses of Cervarix administered to girls aged 4 – 6 years induced a high and sustained immune response, with seropositivity rates that were similar to those observed in young adolescent girls. Seroconversion was 100% after 2 vaccine doses, and seropositivity was maintained up to 36 months. No data concerning vaccine efficacy in this age group are available and the Company is not seeking to recommend vaccination of 4 – 6-year old girls. A clinically-acceptable safety profile is well-established for Cervarix in all indicated ages (9 years and above) and has not changed after 12 years of post-marketing surveillance in the large population exposed to Cervarix vaccination. In the HPV-073 study, the frequencies of adverse events (AEs) after administration of Cervarix were comparable with those in controls who received any of the comparator non HPV-vaccine. The data provided are acceptable though some limitations of the study HPV-073 are to be considered, such as a lack of an immunogenicity control group and the data collected were from pre-school population from Latin American countries only with no assessment of vaccine efficacy. Of note, vaccine efficacy results in this pre-school population are not available.

As a result of this study, section 4.2 of the SmPC is updated to indicate that the use of Cervarix is not recommended in children below 9 years of age "due to limited data on safety and immunogenicity in this age-group", while before referred to "…due to lack of data on safety and immunogenicity in this age-group".

Regarding the RMP, as a result of the assessment version 22.0 is to be approved. The changes warranted as a result of this procedure are:

1. To reflect the availability of the final results of the HPV-019 and HPV-073 studies
2. Update of the safety concern to remove as missing information, the "Use of HPV-16/18 vaccine in HIV-infected subjects or subjects with known immune deficiencies" and the "Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine", and to remove as important potential risk the "Theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination";
3. Submission date for final results of supported study EPI-HPV-048 has been updated from Q2 2020 to Q3 2020;
4. Module SII - Non-clinical part of the safety specification has been revised;
5. Table 10 in Part V.3, has been aligned with the additional pharmacovigilance activities of 'HPV type

[8] Einstein MH, Baron M, Levin MJ, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccin 2009; 5:705.

replacement' and 'Impact and effectiveness against anal lesions and cancer' presented in tables 7 and 8.

The post-marketing surveillance addressing the "Impact and effectiveness of Cervarix against anal lesions and cancer" can be discussed in the next cyclical PSUR following the first analysis in 2021, providing that this will not lead to a delay in the provision of the data. Otherwise, the MAH is asked to provide the data via another adequate procedure.

Following the review of the overall available data from the HPV-019 and HPV-073 studies, the CHMP concludes that the benefit-risk balance of Cervarix remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II, IIIA and IIIB

Update of sections 4.4 and 5.1 of the SmPC based on final results from study HPV-019 listed as a category 3 study in the RMP; this is a safety and immunogenicity study of Cervarix in HIV-positive female subjects aged 15-25 years as compared to quadrivalent HPV, which was assessed in P46/095; and to update section 4.2 of the SmPC to indicate that limited clinical data is now available in 4-6 years old children based on final results from study HPV-073; a phase III, randomised, controlled, single-blind study to evaluate the safety and immunogenicity of Cervarix administered according to an alternative 2-dose schedule (0, 6 month) in 4-6 years old healthy female children, which was assessed in P46/090.

The RMP version 22.0 is to be approved including changes to the safety specifications in line with GVP module V revision 2.

In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Cervarix EMEA/H/C/000721/II/0106'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The final results of 2 studies are discussed below :

- Study HPV-019 : Phase IV, multi-centre, observer-blind, controlled, randomised (1:1) study, with 2 groups, stratified by HIV infection status (positive or negative) and by age (15-17 years and 18-25 years) in Brazil, Estonia, India and Thailand.
- HPV-073 : Phase III, single-blinded, randomised, controlled, multicentre study with 2 parallel groups in healthy girls 4 to 6 years of age at the time of vaccination in Colombia, Mexico and Panama. Of note, the results of HPV-073 were discussed in the assessment report EMA/658750/2018 dated 18th October 2018.

6. Clinical Efficacy aspects

6.1. HPV-019

Methods – analysis of data submitted

Overview of the clinical study supporting the application

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects		Publica-tions
					ATP cohort for immunogenicity	TVC	
HPV-019 (109823)	Brazil Estonia India Thailand	Phase IV, multi-centre, observer-blind, controlled, randomised (1:1) study, with 2 groups, stratified by HIV infection status (positive or negative) and by age (15-17 years and 18-25 years). Co-primary objectives: *Safety (descriptive)* • To evaluate the safety and reactogenicity of both vaccines in HIV+ subjects *Immunogenicity (confirmatory)* • To demonstrate non-inferiority of *Cervarix* vs. *Gardasil* in terms of GMTs against HPV-16 and HPV-18 measured by PBNA one month after administration of the third dose of the vaccine in HIV+ subjects • 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: o First, superiority of HPV-18 type o If superiority of HPV-18 was shown, superiority of HPV-16 was to be assessed Secondary objectives: *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. • To evaluate the antibody response of both vaccines to HPV-16 and HPV-18 antibody levels by ELISA, in all subjects. • To evaluate the antibody response against HPV-16 and HPV-18 by ELISA in CVS in post-menarcheal subjects who volunteer for this procedure. • To evaluate the memory B and T CMI response against HPV-16 and HPV-18 in a subset of subjects *Safety* • To evaluate the safety and reactogenicity of both vaccines in all subjects during the entire study period. Exploratory objectives: *Immunogenicity* • To demonstrate non-inferiority of *Cervarix* in HIV+ subjects vs. *Gardasil* in HIV- subjects in terms of GMTs against HPV-16 or HPV-18 measured by PBNA one month after the administration of the third dose of vaccine • To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA, in HIV+ subjects stratified by HIV mode of transmission and by nadir CD4 cell count category.	HIV seronegative or seropositive (asymptomatic) females aged 15-25 years at first vaccination. Vaccination with *Cervarix* or *Gardasil* according to a 3-dose schedule (Day 0, Week 6 and Month 6)	HIV+/HPV group: HIV+ subjects receiving *Cervarix* HIV+/GAR group: HIV+ subjects receiving *Gardasil* HIV-/HPV group: HIV- subjects receiving *Cervarix* HIV-/GAR group: HIV- subjects receiving *Gardasil*	Month 7 HIV+/HPV = 82 HIV+/GAR = 84 HIV-/HPV = 77 HIV-/GAR = 80 **Total = 323** Month 24 HIV+/HPV = 72 HIV+/GAR = 74 HIV-/HPV = 64 HIV-/GAR = 69 **Total = 279**	Month 7 and Month 24 HIV+/HPV = 129 HIV+/GAR = 128 HIV-/HPV = 144 HIV-/GAR = 145 **Total = 546**	

Study populations

Inclusion and Exclusion Criteria

The HPV-019 study enrolled HIV seropositive or seronegative female subjects aged 15 to 25 years (at the time of first vaccination), for which written consent/assent was obtained either form the subjects and/or the subject's parent or LAR.

HIV seropositive subjects were judged to be seropositive according to World Health Organization (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-ribonucleic acid [RNA], HIV-DNA or ultrasensitive HIV P24 antigen) [WHO, 2006].

The objective of the exclusion criteria was to prevent the administration of the candidate vaccine to individuals with any medical condition or who had/has planned administration of a product, that could potentially interfere with the evaluation of the immune response (such as previous vaccination against

HPV, previous administration of MPL or AS04 adjuvants, subjects with autoimmune diseases), and to individuals at risk of possible adverse reaction to the vaccine.

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.

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 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.

Demographic Characteristics (brazil, Estonia, India and Thailand)

In the HPV-019 study, the mean age (± SD) at the time of first vaccination was 20.1 (± 3.2) years, in the ATP cohort for immunogenicity. Most of the study participants were Asian/of South-east Asian heritage (29.4%), Caucasian/of European heritage (27.9%) and Asian/of Central/South Asian heritage (22.6%). The study groups included only female subjects and were balanced in terms of age and ethnicity.

Study Completion

In the HPV-19 study, the Total cohort consisted of 873 subjects. Of these subjects enrolled in the study, 173 were excluded from all statistical analysis (subjects from the Brazilian centre excluded due to GCP non-compliance) and a further 154 subjects received an allocated subject number but did not receive a vaccine dose.

Of the 546 subjects that were vaccinated, 448 completed the study. A total of 98 subjects were withdrawn from the study, the main reason being consent withdrawal (not due to an AE) for 41 subjects, and lost to follow-up for 37 subjects with complete vaccination course; one subject (in the HIV+/GAR group) was withdrawn due to an SAE.

Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

	HIV+/HPV	HIV+/GAR	HIV-/HPV	HIV-/GAR	Total
Number of subjects vaccinated	129	128	144	145	546
Number of subjects completed	117	117	103	111	448
Number of subjects withdrawn	12	11	41	34	98
Reasons for withdrawal :					
Subject died	0	0	0	0	0
Serious Adverse Event	0	1	0	0	1
Non-Serious Adverse Event	0	0	0	0	0
Eligibility criteria not fulfilled (inclusion and exclusion criteria)	0	0	0	0	0
Protocol violation	0	0	0	0	0
Consent withdrawal (not due to an adverse event)	2	3	18	18	41
Migrated/moved from study area	1	2	1	1	5
Lost to follow-up (subjects with incomplete vaccination course)	2	2	6	3	13
Lost to follow-up (subjects with complete vaccination course)	7	3	15	12	37
Sponsor study termination	0	0	0	0	0
Others	0	0	1	0	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
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit

Number of subjects enrolled in the study and number of subjects excluded from ATP analyses with reasons for exclusion at Month 7

	Total			HIV+/HPV		HIV+/GAR		HIV-/HPV		HIV-/GAR		NOGRP	
Title	n	s	%	n	s	n	s	n	s	n	s	n	s
Total cohort	873			178		173		166		168		188	
Subjects excluded from all stat analysis (code 900)	173	173		43	43	41	41	22	22	20	20	47	47
Total effective cohort	700			135		132		144		148		141	
Study vaccine dose not administrated but subject number allocated (code 1030)	154	154		6	6	4	4	0	0	3	3	141	141
Total vaccinated cohort	546		100	129		128		144		145		0	
Administration of vaccine(s) forbidden in the protocol (code 1040)	10	10		5	5	4	4	0	0	1	1	0	0
Randomisation failure (code 1050)	10	10		1	1	1	1	5	5	3	3	0	0
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0	0	0	0	0	0	0
Study vaccine dose not administered according to protocol (code 1070)	9	11		4	5	2	3	2	2	1	1	0	0
Vaccine temperature deviation (code 1080)	3	3		0	0	0	0	1	1	2	2	0	0
ATP cohort for safety	513		94.0	118		121		136		138		0	
Protocol violation (inclusion/exclusion criteria) (code 2010)	30	33		14	15	16	18	0	0	0	0	0	0
Administration of any medication forbidden by the protocol (code 2040)	1	2		0	1	1	1	0	0	0	0	0	0
Underlying medical condition forbidden by the protocol (code 2050)	2	2		1	1	0	0	1	1	0	0	0	0
Noncompliance with vaccination schedule (including wrong and unknown dates) (code 2080)	38	44		3	5	6	7	16	18	13	14	0	0
Noncompliance with blood sampling schedule (including wrong and unknown dates (code 2090)	55	76		8	13	8	13	15	21	24	29	0	0
Essential serological data missing (code 2100)	64	107		10	18	6	17	27	39	21	33	0	0
ATP cohort for immunogenicity	323		59.2	82		84		77		80		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
NOGRP = No assigned group
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Number of subjects enrolled in the study and number of subjects excluded from ATP analyses with reasons for exclusion at Month 24

	Total			HIV+/HPV		HIV+/GAR		HIV-/HPV		HIV-/GAR		NOGRP	
Title	n	s	%	n	s	n	s	n	s	n	s	n	s
Total cohort	873			178		173		166		168		188	
Subjects excluded from all stat analysis (code 900)	173	173		43	43	41	41	22	22	20	20	47	47
Total effective cohort	700			135		132		144		148		141	
Study vaccine dose not administrated but subject number allocated (code 1030)	154	154		6	6	4	4	0	0	3	3	141	141
Total vaccinated cohort	546		100	129		128		144		145		0	
Administration of vaccine(s) forbidden in the protocol (code 1040)	10	10		5	5	4	4	0	0	1	1	0	0
Randomisation failure (code 1050)	10	10		1	1	1	1	5	5	3	3	0	0
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0	0	0	0	0	0	0
Study vaccine dose not administered according to protocol (code 1070)	9	11		4	5	2	3	2	2	1	1	0	0
Vaccine temperature deviation (code 1080)	3	3		0	0	0	0	1	1	2	2	0	0
Protocol violation (inclusion/exclusion criteria) (code 2010)	30	33		14	15	16	18	0	0	0	0	0	0
Administration of any medication forbidden by the protocol (code 2040)	1	2		0	1	1	1	0	0	0	0	0	0
Underlying medical condition forbidden by the protocol (code 2050)	2	2		1	1	0	0	1	1	0	0	0	0
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	38	44		3	5	6	7	16	18	13	14	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	55	76		8	13	8	13	15	21	24	29	0	0
Essential serological data missing (code 2100)	64	107		10	18	6	17	27	39	21	33	0	0
Subject who missed the month 24 time point (code 5000)	25	106		5	12	3	11	10	41	7	35	0	7
Blood sample taken but non compliance with blood sampling schedules (code 5090)	19	26		5	7	7	8	3	5	4	6	0	0
Serological results not available for antigens post vaccination (code 5100)	0	40		0	10	0	10	0	10	0	10	0	0
Month 24 ATP cohort for analysis for immunogenicity	279		51.1	72		74		64		69		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
NOGRP = No assigned group
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Results

Demographic characteristics

In the ATP cohort for immunogenicity, the mean age (± SD) at the time of first vaccination was 20.1 (± 3.2) years. Study participants were Asian/of South-east Asian heritage (29.4%), Caucasian/of European heritage (27.9%) and Asian/of Central Asian heritage (22.6%). The study groups were balanced in terms of age and ethnicity.

Confirmatory primary and secondary objectives

Non-inferiority of *Cervarix* as compared to *Gardasil* immunogenicity in HIV+ subjects, in terms of HPV-16 and HPV-18 antibody GMT ratio was demonstrated as the LL of the 95% CI for the ratio of GMTs (*Cervarix* over *Gardasil*) as assessed by Pseudovirion-Based Neutralization Assay (PBNA) one month post-dose 3 was above 0.5 for both HPV-16 and HPV-18 types (Table below).

As the first co-primary confirmatory was met, the second co-primary objective could be assessed: the superiority of *Cervarix* over *Gardasil* in HIV+ subjects in terms of HPV-18 and HPV-16 antibody GMT ratios was demonstrated as the LL of the 95% CI for the ratio of GMTs (*Cervarix* over *Gardasil*) as assessed by PBNA one month post-dose 3 was above 1 for both antigens with a statistically significant p-value (Table below).

The secondary confirmatory objective of superiority of *Cervarix* compared to *Gardasil* immunogenicity in HIV- subjects in terms of HPV-16 and HPV-18 antibody GMT ratio assessed by PBNA was demonstrated was met, as the LL of the 97.5% CI for the ratio of GMTs (*Cervarix* over *Gardasil*) was above 1 for both the HPV-16 and HPV-18 types with a statistically significant p-value (TVC) (Table below).

Summary of confirmatory primary and secondary objective results in study HPV-019

	Variable measured	Cohort	N	Value	
Primary confirmatory objective					
				Adjusted GMT ratio (*Cervarix*/*Gardasil*) (95% CI)	**P-value**
Non-inferiority of *Cervarix* vs. *Gardasil* in HIV+ subjects in terms of HPV-16/18 antibody GMT, one month after administration of the last dose *	anti-HPV-16 neutra antibody (ED50)	ATP cohort for immunogenicity	*Cervarix* = 80 *Gardasil* = 83	2.95 (1.92; 4.52)	-
	anti-HPV-18 neutra antibody (ED50)		*Cervarix* = 80 *Gardasil* = 83	7.83 (4.84; 12.66)	-
Superiority of *Cervarix* over *Gardasil* in HIV+ subjects in terms HPV-16/18 antibody GMT, one month after administration of the last dose **	anti-HPV-18 neutra antibody (ED50)	TVC	*Cervarix* = 109 *Gardasil* = 110	7.44 (4.79; 11.54)	<0.0001
	anti-HPV-16 neutra antibody (ED50)		*Cervarix* = 109 *Gardasil* = 110	2.74 (1.83; 4.11)	<0.0001
Secondary confirmatory objective					
				Adjusted GMT ratio (*Cervarix*/*Gardasil*) (97.5% CI)	**P-value**
Superiority of *Cervarix* vs. *Gardasil* in HIV- subjects in terms of HPV-16/18 antibody GMT, one month after the administration of the third dose of vaccine ***	anti-HPV-18 neutra antibody (ED50)	TVC	*Cervarix* = 105 *Gardasil* = 112	5.38 (3.20; 9.06)	<0.0001
	anti-HPV-16 neutra antibody (ED50)		*Cervarix* = 105 *Gardasil* = 112	3.05 (1.84; 5.06)	<0.0001

* criterion: LL of the 95% CI for the ratio of GMTs >0.5 for both HPV types.
** criterion: LL of the 95% CI for the ratio of GMTs >1 for both HPV types, with a statistically significant p-value
***criterion: LL of the 97.5% CI for the ratio of GMTs >1 for the antigen considered with a statistically significant p-value
ATP, according to protocol; **TVC**, total vaccinated cohort; **N**, number of subjects with post-vaccination results available; **adjusted GMT**, geometric mean antibody titre adjusted for country; **95% CI**, 95% confidence interval for the adjusted GMT ratio; **97.5% CI**, 97.5% confidence interval for the adjusted GMT ratio.
Data source: HPV-019 PRI (109823) Report Main (25-Jun-2018), Table 20, Table 21, Table 37.

Secondary objectives

Baseline seropositivity

By PBNA, 67.9% and 79.5% of HIV+ subjects in the HIV+/HPV and HIV+/GAR groups, respectively, were seronegative for antibodies against both HPV types; 96.1% and 94.9% of the HIV- subjects in the HIV-/HPV and HIV-/GAR groups, respectively, were seronegative for both types of antibodies at baseline.

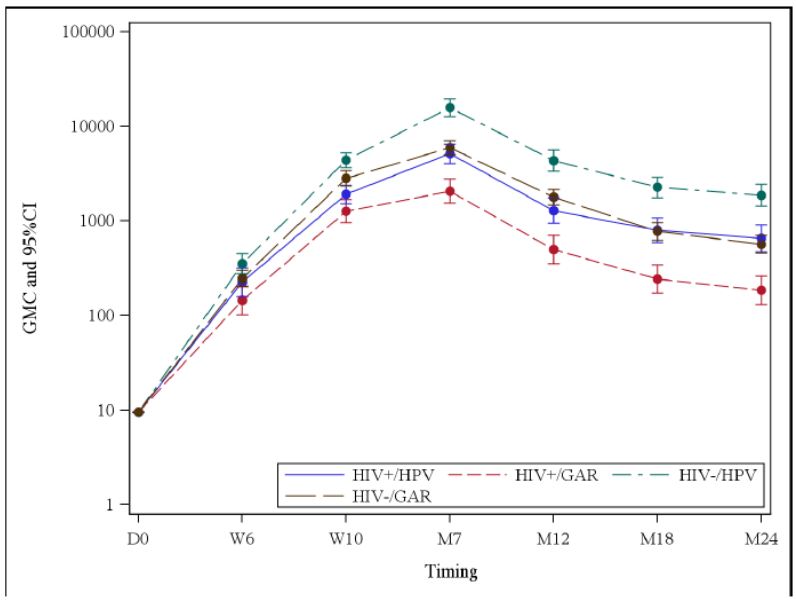
At baseline, by ELISA, 60.5% and 75.0% of HIV+ subjects in the HIV+/HPV and HIV+/GAR groups, respectively, were seronegative for both HPV 16 and 18 antibodies; 94.8% and 93.8% of the HIV- subjects, in the HIV-/HPV and HIV-/GAR groups, respectively, were seronegative for both HPV types.

Anti-HPV-16/18 antibodies measured by ELISA

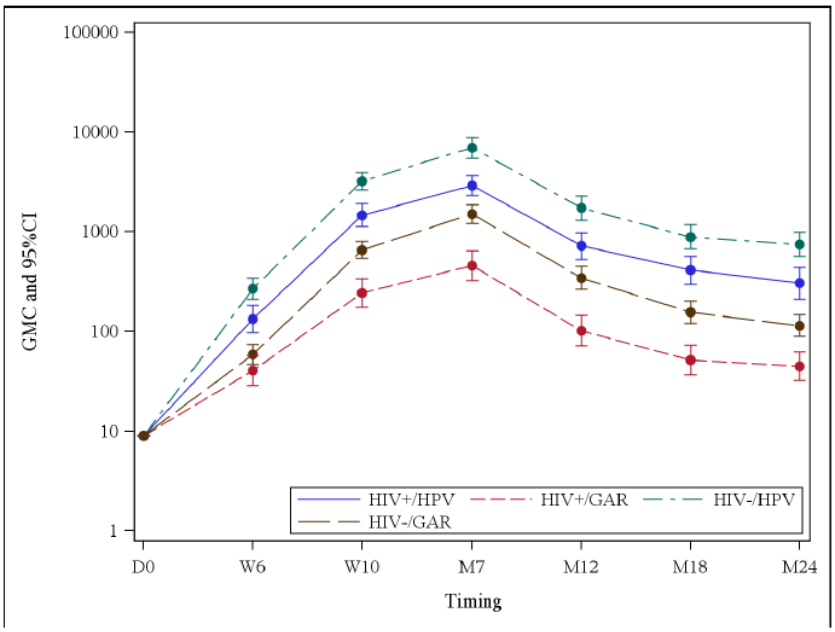
At Month 7, all initially seronegative subjects had seroconverted for anti-HPV-16 antibodies, in all groups, and remained positive up to Month 24, except for group HIV+/GAR, where the 94.7% of subjects had seroconverted for anti-HPV-16 antibodies. The antibody GMC values were 5 110.1 EL.U/mL, 2 065.0 EL.U/mL, 15 748.1 EL.U/mL and 5 947.8 EL.U/mL at Month 7, and 652.8 EL.U/mL, 180.3 EL.U/mL, 1 869.3 EL.U/mL and 579.1 EL.U/mL at Month 24, in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. Overall, the HPV-16 antibody GMCs appeared higher in the HPV groups.

At Month 7, all initially seronegative subjects had seroconverted for anti-HPV-18 antibodies, except for the HIV+/GAR group (96.1%). At Month 24, the percentage of subjects that seroconverted for anti-HPV-18 antibodies was 96.3%, 67.6%, 100% and 98.5% in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. The antibody GMC values were 2 892.6 EL.U/mL, 458.6 EL.U/mL, 6 935.1 EL.U/mL and 1 498.5 EL.U/mL, at Month 7, and 292.3 EL.U/mL, 44.9 EL.U/mL, 763.3 EL.U/mL and 114.1 EL.U/mL at Month 24, in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. As observed for HPV-16, the HPV-18 antibody GMC values appeared to be higher in the HPV groups.

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



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



Cell-mediated immune responses

CD4+ and CD8+ T-cell responses against HPV-16/18

Overall, CD4+ T-cell (in terms of median frequency of HPV-16/18 antigen-specific CD4+ T-cells per million CD4+ T-cells expressing at least 2 different immune markers [all doubles]) responses were detected in all groups, and appeared 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.

B-cell responses to HPV-16/18

B-cell responses were expressed in terms of median frequency of HPV-16 and HPV-18 antigen-specific memory B-cells per million memory B-cells in a limited subset of subjects (maximum of 20 subjects/group) with detectable B-cells.

Overall, a trend for lower B-cell responses was observed for HPV-16 and HPV-18 in HIV+ subjects compared to HIV- subjects, in both HPV and GAR groups.

Exploratory objectives

Non-inferiority assessment of Cervarix in HIV-positive subjects vs Gardasil in HIV negative subjects by PBNA

Non-inferiority of Cervarix in HIV+ subjects compared to Gardasil in HIV- subjects in terms of GMT ratio assessed by PBNA was shown, since the LL of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) was above 0.5 for both HPV types.

Non-inferiority assessment of HPV-16.PsV Ab and HPV-18.PsV Ab immune response (Cervarix in HIV+ subjects vs Gardasil in HIV subjects) one month after the last dose regardless of initial serostatus (Month 7 ATP cohort for immunogenicity)

					Adjusted GMT ratio (Cervarix / Gardasil)		
	Cervarix		Gardasil			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
anti-HPV-16 neutra antibody (ED50)	80	22 515.2	80	27 234.7	0.83	0.57	1.20
anti-HPV-18 neutra antibody (ED50)	80	12 397.4	80	7 002.5	1.77	1.20	2.61

Cervarix, HIV+ subjects receiving *Cervarix* vaccine; **Gardasil**, HIV- subjects receiving *Gardasil* vaccine; **adjusted GMT**, geometric mean antibody titre adjusted for country; **N**, number of subjects with post-vaccination results available; **95% CI**, 95% confidence interval for the adjusted GMT ratio; **LL**, lower limit, **UL**, upper limit.
Data source: HPV-019 PRI (109823) Report Main (25-Jun-2018), Table 36.

The results of the second analysis carried out on the TVC were in line with those in the ATP cohort for immunogenicity.

6.2. Discussion

Persons with HIV are at increased risk of HPV infection, HPV disease, and HPV-related cancers compared to HIV negative persons. In persons with HIV, immune responses to vaccination are often sub-optimal, and while these improve with Anti-Retroviral Treatment, they often remain lower and decline more rapidly than in HIV-negative individuals. Although the evidence base to support the immunogenicity of HPV vaccines in HIV+ persons is reasonable, the evidence base to support the efficacy of HPV vaccines in HIV+ individuals is inconsistent.

Cervarix has previously been shown to be immunogenic in 61 asymptomatic HIV+ women aged 18 – 25 years from South-Africa (study HPV-020) [Denny, 2013]. Humoral and cell-mediated immunity are both likely to be responsible for vaccine-induced protection. The AS04 adjuvant (a combination of aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A (MPL)) included in the vaccine is thought to play a key role in the difference of immunogenicity and efficacy profiles between Cervarix and Gardasil [Herrin, 2014; Ryser, 2019[9]].

Therefore, the current study investigated the immunogenicity of Cervarix and Gardasil, the latter only containing aluminium hydroxyphosphate sulphate as adjuvant, in a population of asymptomatic HIV+ women, aged 15 – 25 of years and from 4 countries in South America, Europe, and Asia.

The subjects were aged 15 – 25 years and were either HIV seropositive (asymptomatic and with an undetectable viral load for at least 6 months) or HIV seronegative females. The main exclusion criteria were: previous vaccination against HPV or with vaccines containing MPL or AS04 adjuvants, and active tuberculosis (TB). HIV+ subjects were judged to be asymptomatic and HIV seropositive according to the World Health Organization (WHO) case definition, i.e. meeting WHO criteria [WHO, 2006]. The randomisation was stratified according to the country, HIV infection status at baseline and age. In addition, HIV+ subjects were randomized according to baseline CD4 cell count and to their highly active anti-retroviral therapy HAART status. Subjects had to be asymptomatic regardless of their prior clinical stage. If they were currently taking antiretrovirals (ARVs), subjects were to be on 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 TB or subjects on TB therapy were not enrolled.

At Month 7, all initially seronegative subjects had seroconverted for HPV-16 antibodies, and all except 3 HIV+ subjects receiving Gardasil had seroconverted for HPV-18 antibodies. The immune response in terms of HPV-16/18 neutralising antibody titres was demonstrated to be superior following vaccination with Cervarix as compared to Gardasil, at Month 7. By ELISA, seroconversion rates and antibody

concentrations in the groups receiving Cervarix remained higher than those in the corresponding Gardasil groups for both antigens at Month 24. In the Gardasil group, seropositivity rates for HPV-18 decreased to 67.5% by Month 24. Antibody responses were overall lower in HIV+ versus HIV- subjects. Immunogenicity levels achieved in HIV+ subjects vaccinated with Cervarix were comparable to those achieved in HIV- subjects vaccinated with Gardasil.

In HPV-019, superiority of Cervarix over Gardasil in terms of HPV-16 and HPV-18 GMT ratio assessed by PBNA was also demonstrated in HIV- females. Both findings (in HIV+ and HIV- subjects) are in line with what was previously observed in a head to head study comparing the 2 vaccines in healthy women aged 18-45 years [Einstein, 2009; Einstein, 2014]. In both studies, the difference between the 2 vaccines was more pronounced for the HPV-18 type than for HPV-16.

Of interest, in all Cervarix recipients, the ELISA antibody GMCs for both HPV types at Month 24 remained higher than or similar to the plateau level associated with sustained protection against HPV-16/18 infection (397.8 EL.U/mL for HPV-16 and 297.3 EL.U/mL for HPV-18) [De Carvalho, 2010; GlaxoSmithKline Vaccine HPV-007 Study Group, 2009]. Moreover, antibody GMCs recorded in both groups at Month 24 in the HPV-019 study were more than 12 times higher (62.7 and 21.9-fold higher in HIV and HIV+ women, respectively, for HPV-16, and 33.8 and 12.9-fold higher in HIV- and HIV+ women, respectively, for HPV-18) than those recorded in women who have cleared previous natural HPV infection (29.8 EL.U/mL for HPV-16 and 22.6 EL.U/mL for HPV-18 [Paavonen, 2007]). A similar observation was reported in the HPV-007 study [GlaxoSmithKline Vaccine HPV-007 Study Group, 2009].

CD4 T-cell responses (i.e., median frequency of HPV-16 and HPV-18 specific CD4 T-cells per million CD4 T-cells expressing at least 2 different immune markers) were detected in all groups, and were comparable in HIV+ and HIV- subjects for both antigens; the responses remained substantial up to 6 months post-vaccination, similarly with previous reports from the HPV-020 study [Denny, 2013]. There was a trend for higher responses in Cervarix versus Gardasil groups from the second dose. Overall there was a trend for better memory B-cell responses with Cervarix versus Gardasil. In this study, anti-HPV-16/18 antibodies evaluated by ELISA in HIV+ subjects by CD4 cell count category showed a trend for a better response to the vaccines in subjects with a CD4 cell count >500 cells/mm3 at baseline compared to the subjects with baseline CD4 cell counts between >350 and □500 cells/mm3. This trend was not observed in the study HPV-020 (an opposite trend was observed, although the study sample size was limited) [Denny, 2013]. However, unlike in the HPV-019 study, women with CD4+T-cell count of <350 cells/mm3 were enrolled in the HPV-020 study: 2/61 and 35/61 of Cervarix recipients had a pre-vaccination CD4 cell count of <200 cells/mm3 and 200-500 cells/mm3, respectively.

When antibody GMCs and seroconversion rates for HPV-16/18 in HIV+ women were analysed by viral load, a tendency for decreased immune responses in subjects with increasing viral loads was observed, for Cervarix and Gardasil recipients. This observation is in line with data from a study conducted in the United States, Brazil, and South Africa, in which HIV+ women aged 13 – 45 years received 3 doses of Gardasil (at weeks 0, 8 and 24): lower seroconversion rates for HPV-16 and 18 were observed in HIV+ women with a viral load of >10 000 copies/mL compared to <10 000 copies/mL [Kojic, 2014].

Interestingly, non-inferiority of immune response in HIV+ Cervarix recipients versus in HIV- Gardasil recipients, in terms of HPV-16 and HPV-18 GMT ratio assessed by PBNA, was demonstrated at Month 7, thus providing clinically-relevant information, as the efficacy of Gardasil against HPV-caused cancers and intraepithelial neoplasias has already been established in HIV- women.

The results of this 4–arm vaccine RCT in 257 HIV+ (CD4>350, women with both vertical and sexually transmission) & 289 HIV- women aged 15–25yrs were discussed. Both HIV+ and HIV– women were

randomised 1:1 to Cervarix or Gardasil, and serology was measured using a pseudovirion-based neutralizing antibody PBNA assay. At 7 months Cervarix was superior to Gardasil in the HIV positive females, for HPV16 by 2.74 fold (CIs 1.83–4.11) and for HPV 18 b y 7.44 (4.79–11.54) in GMTs. Both CD4 cell and B memory cells were assayed out to 12 months. In general, in HIV negative women, the cellular responses are similar to those of Einstein et al[10], and in general, the responses in HIV+ women are similar to those in HIV- women in this study. However, the exception was memory B cell responses against HPV 18 in HIV+ women receiving Gardasil, which were poor with median responses of 0 across the whole 12 month period. Interestingly these poor anti-HPV18 responses appears to be in keeping with the data of McClymont et al[11]. Memory B cell priming induced by Gardasil to HPV 16 was also poor after the 1st dose with a medians of 0 spots. This data showing better immunogenicity in HIV with an additionally TLR agonist-adjuvanted vaccine compared to a classical alum-adjuvanted vaccine is in keeping with data obtained using different Hepatitis B virus (HBV) vaccines in HIV[12].

In conclusion, immune response to Cervarix was superior to Gardasil in terms of HPV- 16/18 neutralising antibodies measured by PBNA, in asymptomatic HIV+ female subjects aged 15 – 25 years, at Month 7. Humoral response was maintained until study conclusion at Month 24 in terms of high seroconversion rates and antibody levels. CMI response (up to Month 7) in HIV+ and HIV- subjects was similar and a trend for a better response was observed with Cervarix as compared to Gardasil. The clinical relevance of this observation is unknown. Meanwhile, evidence base to support the efficacy of HPV vaccines against the relevant clinical endpoints in HIV+ individuals is unavailable. No clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women. Also the limited HIV+ population was limited by an important list of exclusion criteria which is relayed in the SmPC section 5.1. The study HPV-019 generated robust and informative data on the use of Cervarix in HIV+ subjects, which complement the existing information in the current PI and need to be described with the comment that the clinical relevance of these differences e.g. superiority is unknown. No clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women.

[10] Einstein et al., Comparative humoral and cellular immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18–45 years: follow-up through month 48 in a phase III randomized study, Hum. Vaccines Immunother. 10 (12) (2014) 3455–3465.
[11] McClymont et al., The efficacy of the quadrivalent human papillomavirus vaccine in girls and women living with HIV, Clin. Infect. Dis. 68 (2019) 788–794.
[12] C.L. Cooper, J.B. Angel, I. Seguin, H.L. Davis, D.W. Cameron, CPG 7909 adjuvant plus hepatitis B virus vaccination in HIV-infected adults achieves long-term seroprotection for up to 5 years, Clin. Infect. Dis. 46 (2008) 1310–1314.

6.3. HPV-073

Overview of the clinical study supporting the application

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects		Publica-tions
					ATP cohort for immunogenicity	TVC	
HPV-073 (115887)	Mexico Colombia Panama	Phase III, single-blind, randomised, controlled, multi-centre study with 2 parallel groups Co-primary objectives: *Safety* • To assess the safety, reactogenicity and occurrence of clinically relevant abnormalities in biochemistry and haematology parameters after administration of *Cervarix*, up to one month after the last dose (Month 7) *Immunogenicity* • To evaluate the immunogenicity (by ELISA) of *Cervarix*, one month after the last dose (Month 7) Secondary objectives: *Immunogenicity* • To assess the immune responses to *Cervarix*, on Day 0 and at Months 7, 12, 18, 24 and 36 • To assess the immunogenicity of *Priorix* and *Infanrix* *Safety* • To assess the safety of *Cervarix* throughout the study period • To evaluate compliance with completion of vaccination	Healthy female children aged 4–6 years at the time of first vaccination Vaccination with *Cervarix* according to a 2-dose schedule at Day 0 and Month 6 Vaccination with *Priorix* at Day 0 and *Infanrix* at Month 6	HPV_2D: Subjects receiving 2 doses of *Cervarix* MMR_DTPa Subjects receiving *Priorix* and *Infanrix*	Month 7 HPV_2D = 65 MMR_DTPa = 47 **Total = 112**	Month 7 HPV_2D = 74 MMR_DTPa = 74 **Total = 148**	Lin, 2018 Lin, 2019

ATP, according-to-protocol; **TVC**, total vaccinated cohort; **HIV**, human immunodeficiency virus; **GMT**, geometric mean titres; **HPV**, human papillomavirus; **PBNA**, pseudovirion-based neutralization assay; **ELISA**, enzyme-linked immunosorbent assay; **CVS**, cervico-vaginal secretion; **CMI**, cell-mediated immunity; **MMR**, measles, mumps, and rubella vaccine; **DTPa**, diphtheria, tetanus, acellular pertussis vaccine.
Data source: HPV-019 PRI (109823) Report Main (25-Jun-2018) and HPV-073 (115887) Report (31-May-2018).

Results

Study population

Study population (Total vaccinated cohort)			
Number of subjects	**HPV_2D**	**MMR_DTPa**	**Total**
Planned, N	75	75	150
Randomised, N (Total Vaccinated Cohort)	74	74	148
Completed, n (%)	73 (98.6)	71 (95.9)	144 (97.3)
Demographics	**HPV_2D**	**MMR_DTPa**	**Total**
N (Total Vaccinated Cohort)	74	74	148
Females: Males	74:.0	74:.0	148:.0
Mean Age, years (SD)	4.3 (0.5)	4.4 (0.5)	4.3 (0.5)
Median Age, years (minimum, maximum)	4 (4, 6)	4 (4, 6)	4 (4, 6)
African Heritage / African American, n (%)	4 (5.4)	2 (2.7)	6 (4.1)
White - Caucasian / European Heritage, n (%)	2 (2.7)	4 (5.4)	6 (4.1)
Other, n (%)	68 (91.9)	68 (91.9)	136 (91.9)
HPV_2D = Females aged 4-6 years who received two doses of HPV-16/18 vaccine at Day 0 and Month 6 MMR_DTPa = Females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6 Other includes mixed race, Mestizo, Hispanic/Mexican and Indigenous N = total number of subjects; n (%) = number (percentage of subjects in a given category) SD = standard deviation; Mean Age = Age calculated from date of birth to first study vaccination			

Healthy female subjects between, and including, 4-6 years of age at the time of the first vaccination, who received four doses of DTP containing vaccine (i.e., three doses in the first year of life and a fourth dose in the second year of life) as well as first dose of MMR vaccine according to the local schedule applicable in the participating countries. The primary analysis was based on the according-to-protocol (ATP) cohort for analysis of immunogenicity. A second analysis based on the total vaccinated cohort (TVC) was performed to complement the ATP analysis.

In summary, the results in the population studied of girls aged 4 to 6 years support a correct antibody response that is comparable to the results seen in the 9 to 14 years of age. Of importance, the kinetics of serum antibody responses in the preteen/adolescent population receiving 2 doses of the HPV-16/18 vaccine within a 6-month period are similar to those observed in young adult women who receive the standard 3-dose schedule within 6 months, suggesting that long lasting protection can be expected.

The vaccine administered according to a 2-dose schedule at 0, 6 months in children of pre-school age induced a similarly high and sustained immune response seen in young adolescent girls. High seroconversion rates and GMTs reached for the 2 HPV types, which (although declining over time) were sufficiently maintained up to 36 months.

The results were extensively discussed in the assessment report EMA/658750/2018 dated 18th October 2018.

6.4. Discussion

Two doses of Cervarix administered to healthy females aged 4–6 years induced high levels of antibodies that persisted until at least Month 36 (30 months post-dose 2). All subjects seroconverted to HPV-16 and HPV-18 after dose 2 and remained seropositive until Month 36. Few reports describing the use of HPV vaccines in young children were identified in the literature [Mészner, 2015; Katsuta, 2016; Papaioannou] and data on immune responses to vaccination are scarce. Thus, in the HPV-073 study, seropositivity rates of 100% observed up to Month 36 after 2 Cervarix doses in 4–6-year old girls who were seronegative prior to vaccination are consistent with rates reported after 2 doses administered to 9–14-year old girls in the currently approved *Cervarix* PI.

Some limitations of the study HPV-073 are to be considered such as a lack of an immunogenicity control group, data were collected from Latin American children only, no assessment of vaccine efficacy was performed in this population. Of note, vaccine efficacy results in this pre-school population are not available.

When the clinical study report of HPV-073 was submitted to the EMA in accordance with Art.46 of regulation (EC) N°1901/2006, the MAH's position was that no update of the PI was needed. However in this assessment report (EMA/658750/2018), the Rapporteur considered that an update of the SmPC was warranted to reflect that clinical data are available in this new paediatric age group (very limited data, and outside the indication). The following wording was proposed in Section 4.2, with a cross-reference to a brief description of the available data to be included in section 5.1.

> *The safety, immunogenicity and efficacy of Cervarix in children below 9 years of age has not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.*

Meanwhile, the MAH proposes to update section 4.2 of the PI to indicate that limited data are available for use of Cervarix in 4–6-year old children. The Company proposes not to add clinical data to Section 5.1 as the Company perceives a potential risk that inclusion of data about vaccine use in 4–6-year old girls could lead to confusion amongst prescribers and potential off-label use of the vaccine. As there is no medical need to vaccinate girls aged 4–6 years with Cervarix and the Company is not aware of any existing public health recommendations to vaccinate this population, at this time, it is the Company's position not to include the 4–6 years old age range in the vaccine indication. Although not included in the proposed PI, clinical data have been published and are available for the medical community [Lin, 2018; Lin, 2019] .

The Rapporteur agrees with the MAH's discussion and proposal not to add clinical data to Section 5.1.

The proposed wording by the MAH for the section 4.2 is deemed acceptable, i.e.

> '*Cervarix is not recommended for use in children below 9 years of age due to limited data on safety and immunogenicity in this age-group.*'

7. Clinical Safety aspects

7.1. HPV-019

Methods – analysis of data submitted

In the HPV-019 study, solicited local (pain, redness and swelling) and general (fatigue, fever, gastrointestinal symptoms, headache, arthralgia, myalgia, rash, urticaria) adverse events (AEs), and unsolicited AEs occurring within 7 and 30 days after each vaccination, respectively, were collected. SAEs were recorded from the first receipt of the study vaccine up to study end; MSCs and Potential Immune-Mediated Disease (pIMDs) were recorded up to 12 months post-last vaccination and followed up until study end.

Primary endpoints

- Occurrence and intensity of solicited local symptoms within 7 days (Days 0–6) after each and any vaccination in HIV+ subjects.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within 7 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 up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.

Secondary endpoints

- Occurrence and intensity of solicited local and general symptoms (and relationship to vaccination) within 7 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 and MSCs (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 MSCs (including pIMDs) up to 12 months after the last dose of vaccine (i.e., Month 18) and SAEs during the entire study period (i.e., up to Month 24) in all subjects.

Results

Overall, during the entire study, 273 subjects in each group received at least one dose of the study vaccines, and a total of 785 doses of *Cervarix* and 795 doses of *Gardasil* were administered.

Solicited local AEs

During the 7-day (Days 0–6) post-vaccination period, the most frequently reported solicited local AE in all groups was pain, reported 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 reported 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 AEs

During the 7-day (Days 0–6) post-vaccination period, the most frequently reported solicited general AE was headache (reported 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) followed by fatigue (reported after 34.4%, 32.2%, 27.6% and 21.4% of doses) and myalgia (reported after 30.9%, 22.1%, 26.4% and 21.8% of doses). A maximum of 29.0%, 20.7%, 19.4% and 14.8% of doses in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups were followed by at least one solicited general AE assessed by the investigator as causally related to vaccination. In all 4 study groups, a maximum of 3% of doses were followed by at least one grade 3 solicited general AE, among which no more than 2.0% were followed by at least one grade 3 related solicited general AE assessed by the investigator as causally related to vaccination.

Unsolicited AEs

Within the 30-day (Days 0–29) post-vaccination period, at least one unsolicited AE was reported after 14.4%, 14.4%, 7.3% and 10.5% of doses in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups, respectively. No more than 2.9%, 2.1%, 1.0% and 0.5% of doses in the HIV+/HPV, HIV+/GAR, HIV-/HPV and HIV-/GAR groups were followed by unsolicited AEs assessed by the investigator as causally related to vaccination.

The most frequently reported unsolicited symptoms considered by the investigator to have a causal relationship to vaccination in the HIV+/HPV group were headache and dizziness, reported by 2 subjects (1.6%).

Within the 30-day (Days 0–29) post-vaccination period, at least one grade 3 unsolicited AE was reported 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. Only one grade 3 unsolicited AE considered by the investigator to have a causal relationship to vaccination was reported for one subject (0.8%) in the HIV+/HPV group (immune thrombocytopenic purpura); this was reported as a SAE and a pIMD.

SAEs

During the entire study period, a total of 23 subjects (9 in the HIV+/HPV group, 9 in the HIV+/GAR group, 4 in the HIV-/HPV group and one in the HIV-/GAR group) reported a total of 29 SAEs (11 in the HIV+/HPV group, 12 in the HIV+/GAR group, 5 in the HIV- /HPV group and one in the HIV-/GAR group). One SAE, which was also reported as a pIMD (immune thrombocytopenic purpura), was reported in the HIV+/HPV group, and was considered by the investigator to have been due to underlying HIV infection which may have been aggravated by the study vaccine. The other SAEs reported throughout the study were not considered as causally related to vaccination and resolved without sequelae.

Fatal SAEs

One fatal outcome case was reported one month after dose 3, in the HIV+/GAR group (with the preferred term pneumonia bacterial, pulmonary tuberculosis). The subject died 6 days later due to acute respiratory failure, complications of pneumonia and septicaemia. The SAE was not considered to be causally related to vaccination by the investigator.

Other significant AEs

MSCs

Up to 12 months after the last dose (Month 18), 89 subjects reported at least one MSC: 25 (19.4%) subjects in the HIV+/HPV group, 37 (28.9%) subjects in the HIV+/GAR, 10 (6.9%) subjects in the HIV-/HPV group, and 17 (11.7%) subjects in the HIV-/GAR group.

pIMDs

Up to Month 18, one subject (0.3%) in the HIV+/HPV group reported one pIMD (with the preferred term immune thrombocytopenic purpura), which was also reported as a SAE. This event was reported within 30 days after the third vaccine dose and was considered by the investigator to be caused by the underlying HIV infection, which may have been aggravated by the study vaccine. None of the HIV- subjects reported any pIMDs during the entire study (up to Month 18).

Listing of SAEs reported during the entire study period, in the HPV-019 study (total vaccinated cohort)

Group	Sex	Country	Race	Age at onset (Year)	Verbatim	Preferred term	Primary System Organ Class	MED type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
HIV+/HPV	F	India	Asian - Central/South Asian Heritage	23	Viral fever	Viral infection	Infections and infestations	HO	2	9	15	3	N	Recovered/resolved
	F	India	Asian - Central/South Asian Heritage	24	Tubercular meningitis.	Meningitis tuberculous	Infections and infestations	HO	3	16	242	3	N	Recovered/resolved
				25	Allergic reaction	Hypersensitivity	Immune system disorders	HO	3	304	14	3	N	Recovered/resolved
	F	Thailand	Asian - South East Asian Heritage	18	Injuries from traffic accident	Road traffic accident	Injury, poisoning and procedural complications	HO	2	18	21	3	N	Recovered/resolved
	F	Thailand	Asian - South East Asian Heritage	17	Renal insufficiency	Renal failure	Renal and urinary disorders	HO	3	182	12	2	N	Recovered/resolved
				17	Acute tonsillitis	Tonsillitis	Infections and infestations	HO	3	180	10	3	N	Recovered/resolved
	F	Thailand	Asian - South East Asian Heritage	22	Immune thrombocytopenia	Immune thrombocytopenic purpura	Blood and lymphatic system disorders	MD	2	0	524	3	Y	Recovered/resolved
	F	Thailand	Asian - South East Asian Heritage	22	Collapse t- spine from car accident	Spinal compression fracture	Injury, poisoning and procedural complications	HO	3	506	188	2	N	Recovered/resolved
	F	Brazil	African Heritage / African American	17	Pneumonia	Pneumonia	Infections and infestations	HO	3	202	10	3	N	Recovered/resolved
	F	Estonia	White - Caucasian / European Heritage	22	pneumonia (mycoplasma pn.)	Pneumonia mycoplasmal	Infections and infestations	HO	1	13	20	2	N	Recovered/resolved
	F	Estonia	White - Caucasian / European Heritage	18	Spontaneous abortion	Abortion spontaneous	Pregnancy, puerperium and perinatal conditions	ER	2	89	1	1	N	Recovered/resolved

Pregnancy and pregnancy outcome

A total of 9 pregnancies were reported up to Month 7. Seven pregnancies (3 in the HIV+/HPV group, one 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 anomaly. One subject (10.0%) in the HIV+/HPV group underwent an elective termination, and 2 subjects (7.1%; one subject each in the HIV+/HPV and HIV+/GAR groups) had spontaneous abortions with no apparent congenital anomaly.

Discussion

Cervarix, when administered in a 3-dose schedule in HIV+ female subjects, was well tolerated in the HPV-019 study. The incidence of solicited AEs in the HPV groups receiving *Cervarix* was in line with previous reports, with the most frequently reported local AE being pain, while the most frequently reported solicited general AEs were headache, fatigue and myalgia. The frequency of the solicited AEs was similar to that observed in 2 large pooled analyses of overall safety data from the clinical development program of *Cervarix* [Angelo, 2014; Descamps, 2009], and in the 15–25 years age group [Descamps, 2009]. Unsolicited AEs were also reported with comparable frequencies between *Cervarix* groups and were consistent with the safety profile described for women in this age category, and for HIV+ women 18–25 years in the HPV-020 study [Denny, 2013]. As expected, more MSCs were reported in HIV+ than HIV- subjects, but their incidence remained within that previously reported from clinical trials in the 15–25 years age group [Descamps, 2009].

Of the 39 SAEs reported by 23 subjects, only one event (with the onset on the day of the second dose) was considered related to vaccination: a case of immune thrombocytopenic purpura (also reported as a pIMD) in the HIV+/HPV group. The event was considered by the investigator to have been due to underlying HIV infection which may have been aggravated by the study vaccine. Of note, immune thrombocytopenic purpura occurs in 5–10% of HIV+ individuals [Oksenhendler, 1990]. All non-fatal SAEs recovered/resolved by study end. One fatal outcome (pneumonia bacterial, pulmonary tuberculosis) occurred in the HIV+/GAR group and was not considered related to vaccination.

Pregnancies occurring during the study were reported in the HIV+ groups and resulted in life infants with no apparent congenital anomaly. One elective termination (in the HIV+/HPV group) and 2 spontaneous abortions (one in each of the HIV+/HPV and HIV+/GAR groups) were reported.

In conclusion, in the HPV-019 study, *Cervarix* had shown an acceptable clinical safety profile, consistent with the current PI. This is endorsed by the Rapporteur.

7.2. HPV-073

Study population

Healthy female subjects between, and including, 4-6 years of age at the time of the first vaccination, who received four doses of DTP containing vaccine (i.e., three doses in the first year of life and a fourth dose in the second year of life) as well as first dose of MMR vaccine according to the local schedule applicable in the participating countries.

Study population (Total vaccinated cohort)			
Number of subjects	**HPV_2D**	**MMR_DTPa**	**Total**
Planned, N	75	75	150
Randomised, N (Total Vaccinated Cohort)	74	74	148
Completed, n (%)	73 (98.6)	71 (95.9)	144 (97.3)
Demographics	**HPV_2D**	**MMR_DTPa**	**Total**
N (Total Vaccinated Cohort)	74	74	148
Females: Males	74:.0	74:.0	148:.0
Mean Age, years (SD)	4.3 (0.5)	4.4 (0.5)	4.3 (0.5)
Median Age, years (minimum, maximum)	4 (4, 6)	4 (4, 6)	4 (4, 6)
African Heritage / African American, n (%)	4 (5.4)	2 (2.7)	6 (4.1)
White - Caucasian / European Heritage, n (%)	2 (2.7)	4 (5.4)	6 (4.1)
Other, n (%)	68 (91.9)	68 (91.9)	136 (91.9)
HPV_2D = Females aged 4-6 years who received two doses of HPV-16/18 vaccine at Day 0 and Month 6 MMR_DTPa = Females aged 4-6 years who received MMR vaccine at Day 0 and DTPa vaccine at Month 6 Other includes mixed race, Mestizo, Hispanic/Mexican and Indigenous N = total number of subjects; n (%) = number (percentage of subjects in a given category) SD = standard deviation; Mean Age = Age calculated from date of birth to first study vaccination			

Solicited adverse events: During the 7-day post-vaccination period, overall/dose incidence of at least one solicited symptom was 73.3% in the HPV_2D group and 60.7% in the control (MMR_DTPa) group.

- The overall incidence of solicited local symptoms was 63.7% in HPV_2D group and 40.0% in MMR_DTPa group. The most frequently reported local solicited symptom was pain at injection site, with an incidence of 60.3% of HPV doses in 73.0% of subjects, 20.3% after MMR vaccination and 50.7% after DTPa vaccination. Grade 3 solicited local symptoms after HPV-16/18 vaccination included injection site pain (2.7% of HPV doses in 5.4% of subjects), swelling (2.7% of HPV doses in 5.4% of subjects) and redness (0.7% of HPV doses in 1.4% of subjects). Grade 3 solicited local symptoms after DTPa vaccination included injection site swelling (9.9%), redness (5.6%) and pain (1.4%). No Grade 3 solicited local symptoms reported after MMR vaccination.
- The overall incidence of solicited general symptoms was 47.3% in HPV_2D group and 46.2% in MMR_DTPa group. The most frequent solicited general symptom after HPV-16/18 vaccination was irritability/fussiness (21.2% of HPV doses in 29.7% of subjects). The most frequently reported solicited general symptom was headache (25.7%) after MMR vaccination and irritability/fussiness (23.9%) after DTPa vaccination. Grade 3 solicited general symptoms reported after HPV-16/18 vaccination included drowsiness (2.1% of HPV doses in 4.1% of subjects), fever (0.7% of HPV doses in 1.4% of subjects), irritability/fussiness (0.7% of HPV doses in 1.4% of subjects) and loss of appetite (0.7% of HPV doses in 1.4% of subjects). Grade 3 solicited general symptoms reported after DTPa vaccination included loss of appetite (1.4%). No Grade 3 solicited general symptoms reported after MMR vaccination.

Unsolicited adverse events: Overall 64.9% of subjects in the HPV_2D group reported at least one unsolicited AE. In the control (MMR_DTPa) group, 54.1% of subjects reported at least one unsolicited AE after the MMR vaccination and 18.3% of girls reported at least one unsolicited AE after the DTPa vaccination. In both groups, the most frequently reported unsolicited AE was nasopharyngitis (in 32.4% vs. 36.5% of girls in the HPV_2D and the control (MMR_DTPa) group, respectively).

Serious adverse events (SAEs): A total of 3 SAEs were reported by 2 subjects (in the MMR_DTPa group) till Month 7, and 4 SAEs were reported by 3 subjects till Month 12 (3 SAEs were reported by 2 subjects in the MMR_DTPa group and one SAE was reported by one subject in the HPV_2D group). The SAEs were not considered to be causally related to vaccination. No fatal SAE was reported.

Withdrawal due to adverse events (AEs)/serious adverse events (SAEs): None of the subjects were withdrawn due to AEs/SAEs. Medically significant conditions (MSCs): MSCs were reported by 38 (51.4%) subjects in the HPV_2D group and 29 (39.2%) subjects in the MMR_DTPa group till Month 12.

Potential Immune-Mediated Diseases (pIMDs): None was reported till Month 12.

Clinical laboratory evaluations: In both groups, most of the subjects with haematological and biochemical parameters within the normal ranges at study entry remained as such after each vaccine dose.

Discussion

Healthy female subjects between, and including, 4-6 years of age at the time of the first vaccination, who received four doses of DTP containing vaccine (i.e., three doses in the first year of life and a fourth dose in the second year of life) as well as first dose of MMR vaccine according to the local schedule applicable in the participating countries.

The reactogenicity and safety profile of *Cervarix* administered to 4 – 6-year old girls was found to be acceptable, and there was no evidence of medically significant haematological or biochemical anomalies after vaccination. It should be noted that some of the general symptoms solicited in this study may have differed compared to other studies of *Cervarix* conducted in older populations due to the younger age of the subjects. However, overall the results can be considered consistent with the safety profile reported in the currently approved *Cervarix* PI. The nature and incidence of unsolicited AEs, SAEs and MSCs was comparable in the 2 study groups and reflected medical conditions common to this age group.

Some limitations of the study HPV-073 are to be considered such as a lack of an immunogenicity control group, data were collected from Latin American children only, no assessment of vaccine efficacy was performed in this population, the sample size too small to detect serious or clinically relevant AEs and thus cannot address long-term risk.

In conclusion, *Cervarix* was well tolerated in 4 – 6-year old girls and no safety concerns were identified during the HPV-073 study. Meanwhile, the Company proposes to update section 4.2 of the PI to indicate that limited data are available using *Cervarix* in 4 – 6-year old children which is endorsed.

8. Risk management plan

The MAH submitted an updated RMP version with this application. The proposed RMP changes were the following:

- The RMP has been updated to reflect the availability of the final results of the HPV-019 and HPV-073 studies
- The results of the re-analysis of meta-analysis EPI-HPV-069 following the complementary analysis performed by ANSM to estimate the absolute and relative risks of thyroiditis (autoimmune or not) in young girls exposed to a HPV vaccine compared to those not exposed have been included.
- Use of HPV-16/18 vaccine in HIV-infected subjects or subjects with known immune deficiencies has been removed as missing information
- Impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine has been removed as missing information

- Submission date for final results of supported study EPI-HPV-048 has been updated from Q2 2020 to Q3 2020
- Module SII - Non-clinical part of the safety specification has been revised

8.1. Safety Specification

Non-clinical part of the Safety Specifications

Key safety findings from non-clinical studies have been revised: overall, the non-clinical safety results indicated that *Cervarix* was well tolerated without key safety findings.

Clinical trial exposure

Clinical trial exposure data have been updated. In total, 56,755 subjects were recruited in completed clinical trials (formally 55,968) and 1,791 subjects were recruited in on-going clinical trials (formally 946).

Populations not studied in clinical trials

The number of HIV infected women recruited has been corrected and is now estimated at 233 women from 15 to 25 years (formally 210 women).

Post-authorisation experience

Post-authorization exposure data and data lock point have been updated. A total of 83,127,716 doses were sold.

Additional EU requirements for the safety specification

Specific paediatric issues

Section on paediatric safety issues that are of particular concern in the paediatric population has been updated to reflect the availability of final data of the HPV-073 study (4-6-year old girls):

> *"Clinical evaluation of HPV vaccination with a 2-dose schedule in preschool girls (4-6 years old) was conducted in Latin American countries (Study HPV-073). The rationale for the two-dose schedule came from data in clinical studies indicating that two doses of Cervarix administered in pre-teen/adolescent girls was non-inferior to the 3-dose standard schedule in females 15-25 years of age."*

Identified and potential risks

Details on important potential risks (RMP Part II, SVII 3.1)

The description of the potential mechanisms of the theoretical risk of acquiring autoimmune disease following vaccination has been revised.

The results of the re-analysis of meta-analysis EPI-HPV-069 following the complementary analysis performed by ANSM to estimate the absolute and relative risks of thyroiditis (autoimmune or not) in young girls exposed to a HPV vaccine compared to those not exposed have been included. The section has been revised. The conclusion of the company is that:

> *"Having reviewed the totality of available data, the company does not believe that a modification of the Reference Safety Information (RSI) with respect to above AEs for Cervarix is warranted at this point in time. Autoimmune thyroiditis will remain as a potential risk in the RMP as part of the theoretical risk of acquiring vaccine-induced autoimmune diseases. A Targeted Follow-Up Questionnaire will be implemented for autoimmune thyroiditis to allow for enhanced monitoring of this event to help obtain from the reporters supplementary detailed information significant for the scientific evaluation of the reported cases and its diagnostic certainty. GBS and IBD, as well as all other potential immune-mediated diseases will continue to be monitored through routine pharmacovigilance."*

Missing information

1. **Missing information 1 on the use of HPV-16/18 vaccine in HIV-infected subjects** or subjects with known immune deficiencies has been removed (RMP Part II section VII.1.2, VII.2, VII.3.2, VIII).

   Rationale: The results of study HPV-019 became available in July 2018 and showed that the safety profile of the HPV-16/18 vaccine administered to 15- to 25-year-old asymptomatic HIV-infected women is in line with the known safety profile of the HPV-16/18 vaccine.

   The results of this study confirmed the results of the HPV-020 study which evaluated the safety and immunogenicity of the HPV-16/18 vaccine in HIV-infected subjects and expands the findings up to month 24.

   No additional pharmacovigilance activities are planned.

   Routine risk minimization measures are implemented in SmPC section 4.4

2. **Missing information 2 on the impact of H-16/18 vaccine in pregnant women** who are inadvertently exposed to the vaccine has been removed (RMP Part II section VII.1.2, VII.2, VII.3.2, VIII).

   Rationale: The impact of Cervarix on pregnancy related outcomes has been evaluated in a pregnancy registry (EPI-HPV-067), observational cohort studies (EPI-HPV-018 and EPI-HPV-020) and clinical trials (HPV-039 and HPV-040). The results of these studies have been submitted in previous variations and indicate that there is no evidence that vaccination with HPV-16/18 vaccine alters the risk of abnormal pregnancy outcomes including birth defects. However, the data are not sufficient to recommend vaccination during pregnancy.

   No additional pharmacovigilance activities are planned to investigate this safety concern.

   The product information contains specific risk minimization measures to minimize the risk (SmPC section 4.6) reflecting that the available data are not sufficient to recommend vaccination during pregnancy.

3. **Risk-benefit impact of missing information on type replacement** has been updated in view of recent literature (RMP section VII.1.2). The following chapter has been added:

"Similarly, in the UK and other countries where the HPV-16/18 vaccine was used as part of universal mass vaccination, no evidence of type replacement was observed. Furthermore, a cross protective effect was observed [Donken, 2018; Kavanagh, 2017; Mesher, 2018; Woestengerg, 2018]"

8.2. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• **Theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination**
Missing information	• ~~Use of HPV-16/18 vaccine in HIV infected 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**

Missing information in breakthrough are proposed for deletion.

The following issue should be addressed:

- "Theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination" should not be a safety concern. The pharmacovigilance plan does not include or plan any additional pharmacovigilance activity to address this concern. Follow-up questionnaire for investigating reported thyroiditis is part of routine pharmacovigilance. No routine or additional risk minimisation measure is proposed. In consequence, and in accordance with the GVP guideline module V (rev 2), this concern is proposed for removal from the safety specification. However, auto-immune diseases occurring after HPV 16/18 vaccination should continue to be discussed through the PSURs.
- Other concerns listed above are appropriate.

8.3. Pharmacovigilance plan

Information on study HPV-019 has been removed from the on-going and planned additional pharmacovigilance activities.

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3: Required additional pharmacovigilance activities				
EPI-HPV-048 Ongoing	HPV infection type-specific surveillance among sexually active females who have been offered HPV vaccination.	HPV Type replacement	Interim report	Submitted on 18 May 2018
			Final report	Q3 2020
Post-Marketing Surveillance Activity Ongoing	Monitoring of annual reporting of anal 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	Impact and effectiveness against anal lesions and cancer	N/A	Data collection through consultation of the registries will start in 2016 and will be conducted yearly to prepare the quinquennial trend analysis described below.
Post-Marketing Surveillance Activity Planned	Trend analysis of HPV-related cancer every 5 years To describe the potential changes over time in the occurrence of anal cancer in countries where Cervarix is used.	Impact and effectiveness against anal lesions and cancer	Quinquennial report	The first analysis will be performed in 2021 (submitted with next cyclical PBRER).
Post-Marketing Surveillance Activity Planned	Feasibility assessment to perform a case-control study to assess the effectiveness and /or impact of HPV vaccination programmes using Cervarix. This feasibility assessment will be performed every 5 years	Impact and effectiveness against anal lesions and cancer	Quinquennial report	The first analysis will be performed in 2021 (submitted with next cyclical PBRER).

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product. However, the PRAC Rapporteur has two remarks for discussion:

1. No additional activities are proposed for "Theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination" which is proposed for removal.
2. In Table Part III.3.1, the company plans to submit the reports of post-marketing surveillance activity addressing missing information on "Impact and effectiveness against anal lesions and cancer" (a category 3 study) with the next cyclical PBRER. An adequate procedure should be used as PBRER is not appropriate for primary evaluation of study results. The RMP should be updated accordingly.

8.4. Risk minimisation measures

Routine risk minimisation measures

Use of HPV-16/18 vaccine in HIV-infected subjects or subjects with known immune deficiencies and impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine has been removed from the risk minimization measures.

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Theoretical risk of acquiring vaccine-induced autoimmune disease after vaccination	None proposed
HPV type replacement	None
Impact and effectiveness against anal lesions and cancer	None

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

In the RMP Part V.3, Summary of risk minimisation measures, table 10 reports no additional pharmacovigilance activities of '*HPV type replacement"* and *"Impact and effectiveness against anal lesions and cancer".* This table should be in line with additional pharmacovigilance activities presented in tables 7 and 8.

8.5. Elements for a public summary of the RMP

The following sections were updated:

Part VI, section VI.1.3: Use of HPV-16/18 vaccine in HIV-infected subjects or subjects with known immune deficiencies and impact of HPV-16/18 vaccine in pregnant women who are inadvertently exposed to the vaccine has been removed from list of important risks and missing information and summary of important risks

Part VI, section II.C.2 : Information on study HPV-019 has been removed from post-authorisation development plan

Overall conclusions on the public summary of the RMP

The elements for a public summary of the RMP require revision following the conclusion of the procedure:

- "Theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination" should be removed from the safety specifications.

8.6. Annexes

The annexes have been updated appropriately <and the following further changes are recommended:

8.7. Overall conclusion on the RMP

☒ The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

9. Changes to the Product Information

As a result of this variation, sections 4.2, 4.4 and 5.1 of the SmPC are being updated by the MAH

SECTION 4.2

Paediatric population (children < 9 years of age)

Cervarix is not recommended for use in children below 9 years of age due to ~~lack of~~limited data on safety and immunogenicity in this age-group.

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.

There are no safety, immunogenicity or efficacy data to support interchangeability of Cervarix with other HPV vaccines.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

SECTION 5.1

This section was updated following RSI.

Two clinical studies assessed safety and immunogenicity of Cervarix:

1. 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.
2. Study HPV-019, a comparative study of Cervarix and quadrivalent HPV vaccine was conducted in 289 (ATP cohort = 157) HIV uninfected and 257 (ATP cohort = 166) HIV infected female subjects aged 15-25 years in Brazil, Estonia, India and Thailand.

At study entry, HIV infected subjects in both studies had to: be asymptomatic regardless of their prior clinical stage; have undetectable viral load (i.e., viral load < 400 copies/mm^3) for at least six months if on antiretroviral therapy (ART) (HPV-020) or highly active antiretroviral therapy (HAART) for at least one year (HPV-019); not be diagnosed with active tuberculosis (TB) or on TB therapy; in HPV-019 only - have a CD4 cell count > 350 cells/mm^3.
In both studies, seroconversion at month 7 in HIV infected subjects receiving Cervarix was 100% for both antigens in the ATP cohort. In HPV-019, seropositivity at month 24 after Cervarix vaccination was 100% for HPV-16 antibodies and >96% for HPV-18 antibodies with a Geometric Mean Concentration (GMC) level more than 12 times higher than the response to natural HPV infection.
In both studies, the antibody GMCs in HIV infected subjects appeared lower than in the HIV negative Subjects (non-overlapping 95% confidence interval). In HPV-019, superiority of immune responses (neutralizing antibodies GMT ratios) to both HPV-16 and HPV-18 antigens was demonstrated with

Cervarix compared to quadrivalent HPV vaccine, at month 7 in HIV infected subjects. The clinical relevance of ~~thisese~~ observations ~~is~~ are unknown. No clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women.

The observed reactogenicity and safety profile of Cervarix in HIV infected women was in line with the known safety profile in healthy subjects (see section 4.8).

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

1. The proposed wording by the MAH for the section 4.2 are acceptable provided the following changes are made : *Cervarix is not recommended for use in children below 9 years of age due to lack of data on efficacy and limited data on safety and immunogenicity in this age-group.*

2. The clinical relevance of the immunogenicity data observed in HPV-019 is unknown and no clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women.

   The paragraph that is proposed to mention the superiority in immunogenicity data when comparison between Cervarix and Gardasil is not justified as the clinical relevance of this observation is unknown.

   Also this special HIV+ population enrolled was limited by an important list of exclusion criteria which needs to be relayed in the SmPC section 5.1 as this vulnerable population was limited to subjects that were asymptomatic stable under HAART and with no comorbidities.

   The proposed wording by the MAH for the section 5.1 are acceptable provided the following changes are made :

   Immunogenicity in HIV infected women

   Two clinical studies assessed safety and immunogenicity of Cervarix:

   1. 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.

   2. Study HPV-019, a comparative study of Cervarix and quadrivalent HPV vaccine was conducted in 289 (ATP cohort = 157) HIV uninfected and 257 (ATP cohort = 166) HIV infected female subjects aged 15-25 years in Brazil, Estonia, India and Thailand.

   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.

   In both studies, seroconversion at month 7 in HIV infected subjects receiving Cervarix was 100% for both antigens in the ATP cohort. In HPV-019, seropositivity at month 24 after Cervarix vaccination was 100% for HPV-16 antibodies and >96% for HPV-18 antibodies with a Geometric Mean Concentration (GMC) level more than 12 times higher than the response to natural HPV infection. In both studies, the antibody GMCs in HIV infected subjects appeared lower than in the HIV negative Subjects *(non-overlapping 95% confidence interval).* The clinical relevance of this observation is unknown. No clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women.

~~In HPV-019, superiority of immune responses (neutralizing antibodies) to both HPV-16 (GMT ratio = 2.74 [95% CI 1.83; 4.11]) and HPV-18 (GMT ratio = 7.44 [95% CI 4.79; 11.54]) antigens was demonstrated with Cervarix compared to quadrivalent HPV vaccine, at month 7 in HIV infected subjects.~~

The observed reactogenicity and safety profile of Cervarix in HIV infected women was in line with the known safety profile in healthy subjects (see section 4.8).

RMP aspects

3. "Theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination" should not be a safety concern. The pharmacovigilance plan does not include or plan any additional pharmacovigilance activity to address this concern. Follow-up questionnaire for investigating reported thyroiditis part of routine pharmacovigilance. No routine or additional risk minimisation measure is proposed. In consequence, and in accordance with the GVP guideline module V (rev 2), this concern is proposed for removal from the safety specification. However, auto-immune diseases occurring after HPV 16/18 vaccination should continue to be discussed through the PSURs.

4. In the RMP Part V.3, Summary of risk minimisation measures, table 10 reports no additional pharmacovigilance activities of '*HPV type replacement"* and *"Impact and effectiveness against anal lesions and cancer".* This table should be in line with additional pharmacovigilance activities presented in tables 7 and 8.

5. In Table Part III.3.1, the company plans to submit the reports of post-marketing surveillance activity addressing missing information on "Impact and effectiveness against anal lesions and cancer" (a category 3 study) with the next cyclical PBRER. An adequate procedure should be used as PBRER is not appropriate for primary evaluation of study results. The RMP should be updated accordingly.

11. Assessment of the responses to the request for supplementary information

11.1. Other concerns

Clinical aspects

Question 1 - The proposed wording by the MAH for the section 4.2 are acceptable provided the following changes are made : Cervarix is not recommended for use in children below 9 years of age due to lack of data on efficacy and limited data on safety and immunogenicity in this age-group.

Summary of the MAH's response

As mentioned in the Clinical Overview Addendum submitted with the variation, there is no efficacy data in children below 9 years of age.

The Company would like to emphasize that clinical efficacy data shall not be generated in this age group due to the same ethical and practical reasons as for the 9 to15-year old age range: cervical examination shouldn't be performed prior to puberty and sexual debut.

As described in the SmPC, section 5.1, the indication in the 9-15year-old age group is based on the bridging of immunogenicity data with the 15-25 year-old age range in which efficacy was demonstrated. In the 9-15-year-old age group no efficacy data were generated and SmPC does not explicitly mention it. The Company is of the opinion that, for consistency within the SmPC, the section 4.2 on paediatric populations should not refer to a lack of data on efficacy data below 9 years of age.

Therefore, the Company proposes to remove the part of the sentence referring to the lack of data on efficacy, and to keep the wording as proposed in the original submission:

Cervarix is not recommended for use in children below 9 years of age due to limited data on safety and immunogenicity in this age-group.

Assessment of the MAH's response

The arguments of the MAH are acknowledged and deemed acceptable. The wording proposed by the MAH is endorsed.

Issue resolved

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 2 - The clinical relevance of the immunogenicity data observed in HPV-019 is unknown and no clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women.

The paragraph that is proposed to mention the superiority in immunogenicity data when comparison between Cervarix and Gardasil is not justified as the clinical relevance of this observation is unknown.

Also this special HIV+ population enrolled was limited by an important list of exclusion criteria which needs to be relayed in the SmPC section 5.1 as this vulnerable population was limited to subjects that were asymptomatic stable under HAART and with no comorbidities.

The proposed wording by the MAH for the section 5.1 are acceptable provided the following changes are made :

<u>Immunogenicity in HIV infected women</u>

Two clinical studies assessed safety and immunogenicity of Cervarix:

1. 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.

2. Study HPV-019, a comparative study of Cervarix and quadrivalent HPV vaccine was conducted in 289 (ATP cohort = 157) HIV uninfected and 257 (ATP cohort = 166) HIV infected female subjects aged 15-25 years in Brazil, Estonia, India and Thailand.

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.

In both studies, seroconversion at month 7 in HIV infected subjects receiving Cervarix was 100% for both antigens in the ATP cohort. In HPV-019, seropositivity at month 24 after Cervarix vaccination was 100% for HPV-16 antibodies and >96% for HPV-18 antibodies with a Geometric Mean Concentration (GMC) level more than 12 times higher than the response to natural HPV infection. In both studies, the antibody GMCs in HIV infected subjects appeared lower than in the HIV negative Subjects *(non-overlapping 95% confidence interval).* The clinical relevance of this observation is unknown. No clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women.

~~**In HPV-019, superiority of immune responses (neutralizing antibodies) to both HPV-16 (GMT ratio = 2.74 [95% CI 1.83; 4.11]) and HPV-18 (GMT ratio = 7.44 [95% CI 4.79; 11.54]) antigens was demonstrated with Cervarix compared to quadrivalent HPV vaccine, at month 7 in HIV infected subjects.**~~

The observed reactogenicity and safety profile of Cervarix in HIV infected women was in line with the known safety profile in healthy subjects (see section 4.8).

Summary of the MAH's response

The Company agrees with the addition of a paragraph on the inclusion criteria of the study, however since the proposal provided in the RSI only relates to the HPV-019 study, the Company proposes modifications to reflect the inclusion criteria of each study i.e. HPV-019 and HPV-020. See the proposed SmPC included in Module 1.

Concerning superiority, the Company believes that the data generated in the study HPV-019 support the inclusion of the information on the superiority of immune response demonstrated with Cervarix compared to Gardasil and that this is relevant information for the prescribers, for reasons explained below.

The HPV-019 study was designed with statistical power to show non-inferiority and superiority of immune response to Cervarix compared to Gardasil in HIV-infected subjects. In parallel, healthy females also received Gardasil or Cervarix. Lower immune response to vaccines in HIV infected population versus healthy subjects is expected.

This study has first demonstrated the non-inferiority of the immune response to Cervarix compared to Gardasil in HIV infected subjects. As a sequential primary objective, the study also demonstrated the superiority of the immune response to Cervarix compared to Gardasil in HIV infected females, that is proposed in the current label update.

Although a correlate of protection following HPV vaccination has not been established, it is well known that the mechanism of action for HPV vaccine and vaccine-induced protection is based on the immune response involving both humoral and cell mediated immunity.

Nearly all HIV infected subjects seroconverted after vaccination with either vaccine.

However, in terms of persistence of antibodies, at Month 24, seropositivity rate for HPV18 had dropped to 68·4% for Gardasil vaccinees, while Cervarix group maintained a high seroconversion rate (96·3%). Antibody GMCs in the Cervarix group also remained above those in the Gardasil vaccinees.

Decline in seropositivity rates for HPV18 have been observed in a previous Gardasil trial in 7 to 12-year old HIV infected children, 4 to 5 years after vaccination [Levin, 2017]. To date, no efficacy data or evidence of protection offered by the immune response developed by Gardasil in HIV infected population have been published [Lacey, 2019; Moscicki, 2019; Wilkin, 2018] except one efficacy study with Gardasil in HIV infected subjects in Canada [McClymont, 2019]. This was a one-arm study assessing HPV infection and disease endpoints data in women aged 13-66-year-old living with HIV compared to historical controls. The results of this study suggested that a rate of persistent qHPV infection among vaccinated HIV-infected women was lower than among unvaccinated HIV-infected

women (2.3 vs 6.0/100 person-years). However, four breakthrough infections were observed, all with HPV18, that was unexpected considering the low HPV18 prevalence in that study. The authors concluded that vaccinated HIV-infected women may be at a higher risk for vaccine failure compared to vaccinated women without HIV [McClymont, 2019].

Despite the absence of an immune correlate of protection, the differences in immune responses elicited by the vaccines, especially for HPV-18, may relate to the duration of protection rendered by the vaccines. Moreover, in this immunocompromised population an immune response to HPV vaccination may be impaired due to underlying disease and that may further compromise vaccine efficacy and protection. Therefore, we believe that immunogenicity levels significantly higher than the ones shown for another approved vaccine is relevant to the prescriber.

The AS04 adjuvant system in Cervarix (3-O-desacyl-4'-monophosphoryl lipid A (MPL) and aluminium hydroxide) is likely to play a key role in the high humoral and cellular responses to the vaccine [Giannini, 2006]. MPL mimics a toll-like receptor 4 (TLR) agonist and serves as a potent immune-stimulant providing higher antibody responses compared to Gardasil, as seen in healthy and HIV infected women.

Furthermore, as described in the clinical overview submitted with the variation, an exploratory analysis in the study demonstrated that the antibody levels achieved in HIV infected subjects vaccinated with Cervarix were comparable and non-inferior to those achieved in HIV uninfected subjects vaccinated with Gardasil, a population in which Gardasil has demonstrated high efficacy. Based on the immunobridging principle, antibody concentration obtained with Cervarix in HIV infected women that are similar to those reported with Gardasil HIV uninfected (as in the efficacy trials) is reassuring.

Based on this rationale, the Company believes that the information on the superiority of immune response of Cervarix versus Gardasil in HIV infected subjects is relevant to the prescriber and should be included in the product information.

Assessment of the MAH's response

The proposed modifications to reflect the inclusion criteria of each study i.e. HPV-019 and HPV-020 are endorsed.

The Rapporteur acknowledged the arguments regarding the superiority of the immune responses induced by Cervarix versus Gardasil in HIV infected subjects that were presented by the MAH. Additionally, the section 5.1, subheading *Bridging of clinical efficacy against anal lesions and cancers* also includes a statement on the superiority of the immunogenicity of Cervarix over Gardasil (for which efficacy against anal premalignant lesions has shown protection).
The Rapporteur therefore agrees with the MAH to include the information on the superiority of immune response of Cervarix versus Gardasil in HIV infected subjects.
However to be consistent with the presentation of the immunogenicity results throughout the SmPC, the Rapporteur recommends not to include the values of the GMT ratios. It is proposed to modify the text as followed: *In HPV-019, superiority of immune responses (neutralizing antibodies GMT ratios) to both HPV-16 ~~(GMT ratio = 2.74 [95% CI 1.83; 4.11])~~ and HPV-18 ~~(GMT ratio = 7.44 [95% CI 4.79; 11.54])~~ antigens was demonstrated with Cervarix compared to quadrivalent HPV vaccine, at month 7 in HIV infected subjects.*
It is also recommended to have this paragraph appear earlier in the text, i.e. '*In both studies, seroconversion at month 7 in HIV infected subjects receiving Cervarix was 100% for both antigens in the ATP cohort. In HPV-019, seropositivity at month 24 after Cervarix vaccination was 100% for HPV-16 antibodies and >96% for HPV-18 antibodies with a Geometric Mean Concentration (GMC) level more than 12 times higher than the response to natural HPV infection. In both studies, the antibody GMCs in HIV infected subjects appeared lower than in the HIV negative Subjects (non-overlapping 95% confidence interval). In HPV-019, superiority of immune responses (neutralizing antibodies GMT ratios) to both HPV-16 ~~(GMT ratio = 2.74 [95% CI 1.83; 4.11])~~ and HPV-18 ~~(GMT ratio = 7.44 [95% CI 4.79; 11.54])~~ antigens was demonstrated with Cervarix compared to quadrivalent HPV vaccine, at month 7 in HIV infected subjects. The clinical relevance of th~~is~~ese observation~~s is~~ are unknown. No clinical efficacy*

data exist about protection against persistent infection or precancerous lesions among HIV infected women.'

On 06/05/2020, the MAH agrees with the new proposed wording by the rapporteur for section 5.1 of the Cervarix SmPC.

Issue resolved

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

Question 3 - "Theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination" should not be a safety concern. The pharmacovigilance plan does not include or plan any additional pharmacovigilance activity to address this concern. Follow-up questionnaire for investigating reported thyroiditis part of routine pharmacovigilance. No routine or additional risk minimisation measure is proposed. In consequence, and in accordance with the GVP guideline module V (rev 2), this concern is proposed for removal from the safety specification. However, auto-immune diseases occurring after HPV 16/18 vaccination should continue to be discussed through the PSURs.

Summary of the MAH's response

As requested, the company has removed the theoretical risk of acquiring vaccine-induced auto-immune disease after vaccination as a safety concern from the RMP.

Assessment of the MAH's response

The RMP has been updated appropriately.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 4 - In the RMP Part V.3, Summary of risk minimisation measures, table 10 reports no additional pharmacovigilance activities of 'HPV type replacement" and "Impact and effectiveness against anal lesions and cancer". This table should be in line with additional pharmacovigilance activities presented in tables 7 and 8.

Summary of the MAH's response

As requested, the Company has updated the table 10 in Part V.3, Summary of risk minimisation measures, to align with the additional pharmacovigilance activities of "HPV replacement" and "Impact and effectiveness against anal lesions and cancer" presented in tables 7 and 8.

Assessment of the MAH's response

The RMP has been updated appropriately.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 5 - In Table Part III.3.1, the company plans to submit the reports of post-marketing surveillance activity addressing missing information on "Impact and effectiveness against anal lesions and cancer" (a category 3 study) with the next cyclical PBRER. An adequate procedure should be used as PBRER is not appropriate for primary evaluation of study results. The RMP should be updated accordingly.

Summary of the MAH's response

During the third round of supplementary information on the variation to extend the Cervarix indication with males and anal cancer (procedure EMEA/H/C/000721/II/0067), the Company committed to perform the following pharmacovigilance activities to address the impact and effectiveness of Cervarix against anal lesions and cancer:

- to perform a trend analysis of anal and other HPV-related cancer every 5 years, and
- to perform a feasibility assessment to perform a case control study to assess the effectiveness and/or impact of HPV vaccination programmes using Cervarix every 5 years.

The proposal was to submit the results of the trend analysis and the feasibility assessment with the next cyclical PBRER. The plan was included in the EU-RMP version 17, and was endorsed by the CHMP and the PRAC, as mentioned in the CHMP extension of indication variation assessment report (EMA/CHMP/668339/2015).

The trend analysis, which will be based on the monitoring of annual reporting of anal cancer and other HPV-related cancers by consulting 5 national cancer registries, will be performed in 2021. A critical analysis of the information obtained through the monitoring of the national cancer registries as well as an analysis of the benefits of the vaccine in the approved indication for males and anal cancer will be performed. The Company believes that the discussion of the results of such monitoring activities falls under the scope of the PBRER and therefore proposes to not update the RMP and to submit the report of the trend analysis with the next cyclical PBRER as previously agreed by CHMP and PRAC The same strategy will be used for submission of the feasibility assessment to perform a case control study to assess the effectiveness and/or impact of HPV vaccination programmes using Cervarix.

Assessment of the MAH's response

It is acknowledged that the submission of the post-marketing surveillance in PBRER was previously agreed by CHMP and PRAC. However, the Assessor wants to point out that the PSUR cycle is currently under discussion in PSUSA procedure EMEA/H/C/PSUSA/00009175/201911 and has been proposed to be updated to 3 years by the PRAC Rapporteur. In conclusion, **the post-marketing surveillance can be discussed in the next cyclical PBRER following the first analysis in 2021, providing that this will not lead to a delay in the provision of the data. Otherwise, the MAH is asked to provide the data via another adequate procedure**.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance