EUROPEAN MEDICINES AGENCY
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Procedure Management and Committees Support Division

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

Cervarix

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

Procedure no: EMEA/H/C/000721/P46/084.1

Note

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

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Extension study of the primary vaccination study, study HPV-013 and subsequent follow-up study Ext HPV-013 designed to evaluate the long-term immunogenicity and safety of the HPV-16/18 VLP L1 AS04 vaccine in pre-teen and adolescent females aged 10 to 14 years at the time of first vaccination, for a period of approximately 10 years after first HPV vaccination in the primary study (study HPV-013). *The current report presents the results of the interim analysis up to Month 96 (Year 8).*

1.1. Steps taken for the assessment

Submission date:	24/11/2014
Start of procedure:	28/05/2014
CHMP Rapporteur's preliminary assessment report circulated on:	23/12/2014
CHMP Rapporteur's updated assessment report circulated on:	12/01/2015
CHMP opinion with request for supplementary information:	22/01/2015
Submission date of the responses:	11/02/2015
Start of procedure:	22/02/2015
CHMP Rapporteur's preliminary assessment report circulated on:	24/03/2015
CHMP Comments :	08/04/2015
CHMP opinion:	23/04/2015

2. Assessment of the post-authorisation measure PAM

This extension study of the primary vaccination study, study HPV-013 and subsequent follow-up study Ext HPV-013 was designed to evaluate the long-term immunogenicity and safety of the HPV-16/18 VLP L1 AS04 vaccine in pre-teen and adolescent females aged 10 to 14 years at the time of first vaccination, for a period of approximately 10 years (120 months) after first HPV vaccination in the primary study (study HPV- 013). The current report presents the results of the interim analysis up to Month 96 (Year 8). No confirmatory analyses were performed on the primary or secondary objectives.

At Month 96, all subjects were still seropositive for both HPV-16 and HPV-18 antibodies. In the ATP cohort, in subjects who were initially seronegative, GMTs at Month 96 were 1653.1 EL.U/mL [95% CI: 1528.2– 1788.2] for HPV-16 and 667.2 EL.U/mL [95% CI: 612.0 – 727.5] for HPV-18.

With respect to the Month 84 interim report 7 years after administration of the HPV-16/18 vaccine (i.e. at Month 84), in initially seronegative subjects, GMTs at Month 84 were 1747.9 EL.U/mL [95% CI: 1610.1 – 1897.5] for HPV-16 and 597.0 EL.U/mL [95% CI: 547.0 – 651.5] for HPV-18. The MAH

should discuss this latter result as the GMTs at Month 84 is higher than the ones at Month 96 for HPV 18.

The HPV-16 and HPV-18 antibody titers in ATP baseline seronegative subjects were 3.8 and 2.7 fold higher, respectively, than the titers observed at an equivalent timepoint (i.e. Month 95 – Month 100 time interval) in female subjects aged 15-25 years at the time of enrolment in the HPV-001/007/023 study.

The HPV-16 and HPV-18 antibody titers in ATP baseline seronegative subjects were 55.47 and 29.39 fold higher, respectively, than those associated with natural infection found in subjects aged 15-25 years at the time of vaccination in study HPV-008.

At month 84 in the HPV-025 EXT-013 long-term follow-up study, the primary analysis of safety was based on Month 84 Total Vaccinated Cohort (TVC) for data collected during the follow-up period Month 72 to Month 84 (N=523). In addition, an analysis on the same Month 84 TVC was performed on data collected during the entire HPV-013-Ext HPV-013 and HPV-025 study period (Month 0 to Month 84). A further analysis was performed on the whole HPV-013-Ext HPV-013-HPV-025 TVC (N=1035).

As requested by the Rapporteur in the AR of the EMEA-H-C-721-P46 065.1 PAM, a safety analysis in subjects who were selected for HPV-025 was performed. Total Vaccinated Cohort (TVC) for HPV-025 was defined as subjects who were invited for HPV-025 study with the following criteria:

- Subjects who received three doses of HPV vaccine in primary study HPV-013
- Subjects who were included in the immunogenicity subset of study HPV-013
- Subjects who were part of one of the extensions of HPV-013, i.e. Ext HPV-013 (Month 12 to Month 48)

The number of subjects included in TVC of HPV-025 is 611 (included for Month 0- Month 96). The Company will perform a similar analysis in subsequent reports for HPV-025 EXT-013 (Months 108 and 120). During the study period Month 0 to Month 96, a total of 81 subjects (13.3%) reported 120 SAEs in the TVC of HPV-025. None of the events were considered by the investigator to be related to vaccination. The most commonly reported SAEs classified by MedDRA Preferred Term were appendicitis (nine subjects [1.5%]), incomplete spontaneous abortion (8 subjects [1.3%]) and abdominal pain (four subjects [0.7%]) (Table 1).

No fatal SAEs were reported during the follow-up period from Month 84 to Month 96. Fatal SAEs were reported for two subjects for the whole period; none of them were considered to be related to vaccination.

During the follow-up period from Month 84 to Month 96, 8 subjects reported 11 SAEs, none of which were considered by the investigator to be causally related to vaccination. For comparison, during the follow-up period from Month 72 to Month 84, 20 subjects reported 24 SAEs, none of which were considered by the investigator to be causally related to vaccination. There were no withdrawals from this study due to AEs or SAEs this far.

In conclusion, the results from this interim analysis confirm the sustained immunogenicity of the HPV-16/18 L1 VLP AS04 vaccine up to 96 months after administration of the first dose in subjects aged 10 - 14 years at the time of first vaccination both in terms of anti-HPV-16/18 GMTs and seropositivity and with an acceptable safety profile.

Table 1 **Percentage of subjects reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, during the entire study period (Month 0-Month 96) (HPV -025 TVC).**

		HPV N = 611			
				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL
At least one symptom		81	13.3	10.7	16.2
Blood and lymphatic system disorders (10005329)	Splenomegaly (10041660)	1	0.2	0.0	0.9
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	4	0.7	0.2	1.7
	Constipation (10010774)	2	0.3	0.0	1.2
	Crohn's disease (10011401)	1	0.2	0.0	0.9
	Diverticulum intestinal (10013559)	1	0.2	0.0	0.9
	Duodenal ulcer (10013836)	2	0.3	0.0	1.2
	Gastritis (10017853)	1	0.2	0.0	0.9
	Malocclusion (10061274)	1	0.2	0.0	0.9
	Umbilical hernia (10045458)	1	0.2	0.0	0.9
General disorders and administration site conditions (10018065)	Pain (10033371)	1	0.2	0.0	0.9
	Pyrexia (10037660)	1	0.2	0.0	0.9
Infections and infestations (10021881)	Abscess (10000269)	1	0.2	0.0	0.9
	Acute tonsillitis (10001093)	1	0.2	0.0	0.9
	Appendicitis (10003011)	9	1.5	0.7	2.8
	Breast abscess (10006171)	1	0.2	0.0	0.9
	Campylobacter gastroenteritis (10007048)	1	0.2	0.0	0.9
	Cellulitis (10007882)	1	0.2	0.0	0.9
	Chronic sinusitis (10009137)	1	0.2	0.0	0.9
	Cystitis (10011781)	1	0.2	0.0	0.9
	Dengue fever (10012310)	3	0.5	0.1	1.4
	Endometritis (10014791)	1	0.2	0.0	0.9
	Endometritis decidual (10014792)	1	0.2	0.0	0.9
	Epstein-barr virus infection (10015108)	1	0.2	0.0	0.9
	Gastroenteritis (10017888)	3	0.5	0.1	1.4
	Gastroenteritis viral (10017918)	1	0.2	0.0	0.9
	Helicobacter gastritis (10054272)	1	0.2	0.0	0.9
	Herpangina (10019936)	1	0.2	0.0	0.9
	Meningitis viral (10027260)	1	0.2	0.0	0.9
	Peritonitis (10034674)	1	0.2	0.0	0.9
	Peritonsillar abscess (10034686)	1	0.2	0.0	0.9
	Pharyngeal abscess (10067781)	2	0.3	0.0	1.2
	Pneumonia bacterial (10060946)	1	0.2	0.0	0.9
	Pyelonephritis (10037596)	1	0.2	0.0	0.9
	Pyelonephritis acute (10037597)	1	0.2	0.0	0.9
	Subcutaneous abscess (10042343)	1	0.2	0.0	0.9
	Upper respiratory tract infection (10046306)	2	0.3	0.0	1.2
	Urinary tract infection (10046571)	2	0.3	0.0	1.2
Injury, poisoning and procedural complications (10022117)	Abdominal injury (10060924)	1	0.2	0.0	0.9
	Alcohol poisoning (10001605)	2	0.3	0.0	1.2
	Burns third degree (10006803)	1	0.2	0.0	0.9
	Concussion (10010254)	1	0.2	0.0	0.9
	Craniocerebral injury (10070976)	1	0.2	0.0	0.9
	Gun shot wound (10018794)	1	0.2	0.0	0.9
	Injury (10022116)	1	0.2	0.0	0.9
	Joint dislocation (10023204)	1	0.2	0.0	0.9
	Ligament rupture (10065433)	2	0.3	0.0	1.2
	Lower limb fracture (10061599)	1	0.2	0.0	0.9
	Multiple injuries (10028224)	3	0.5	0.1	1.4
	Skull fractured base (10040960)	1	0.2	0.0	0.9
	Stab wound (10041899)	1	0.2	0.0	0.9
Investigations (10022891)	Investigation (10062026)	1	0.2	0.0	0.9
Metabolism and nutrition disorders (10027433)	Dehydration (10012174)	2	0.3	0.0	1.2
Musculoskeletal and connective tissue disorders	Arthralgia (10003239)	1	0.2	0.0	0.9

	Myalgia (10028411)	1	0.2	0.0	0.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Fibroadenoma of breast (10016613)	1	0.2	0.0	0.9
	Ovarian germ cell teratoma benign (10033236)	1	0.2	0.0	0.9
	Uterine leiomyoma (10046798)	1	0.2	0.0	0.9
Nervous system disorders (10029205)	Cerebral cyst (10061445)	1	0.2	0.0	0.9
	Syncope (10042772)	1	0.2	0.0	0.9
Pregnancy, puerperium and perinatal conditions (10036585)	Abortion spontaneous complete (10061616)	1	0.2	0.0	0.9
	Abortion spontaneous incomplete (10061617)	8	1.3	0.6	2.6
	Cervical incompetence (10008267)	1	0.2	0.0	0.9
	Foetal death (10055690)	1	0.2	0.0	0.9
	Gestational diabetes (10018209)	1	0.2	0.0	0.9
	Oligohydramnios (10030289)	2	0.3	0.0	1.2
	Pre-eclampsia (10036485)	2	0.3	0.0	1.2
	Premature labour (10036600)	1	0.2	0.0	0.9
	Threatened labour (10043508)	2	0.3	0.0	1.2
Psychiatric disorders (10037175)	Depressed mood (10012374)	1	0.2	0.0	0.9
	Drug abuse (10013654)	1	0.2	0.0	0.9
	Postpartum depression (10056393)	1	0.2	0.0	0.9
	Schizophreniform disorder (10039647)	1	0.2	0.0	0.9
	Suicide attempt (10042464)	3	0.5	0.1	1.4
Reproductive system and breast disorders (10038604)	Ovarian cyst (10033132)	3	0.5	0.1	1.4
	Ovarian cyst ruptured (10033136)	1	0.2	0.0	0.9
	Ovarian cyst torsion (10049670)	1	0.2	0.0	0.9
Respiratory, thoracic and mediastinal disorders (10038738)	Asthmatic crisis (10064823)	1	0.2	0.0	0.9
Surgical and medical procedures (10042613)	Abortion induced (10000220)	1	0.2	0.0	0.9
Vascular disorders (10047065)	Aortic rupture (10060874)	1	0.2	0.0	0.9
	Hypertension (10020772)	1	0.2	0.0	0.9

HPV = HPV-16/18 VLP/AS04 Hi5 10-14
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

3. Request for Supplementary Information

At Month 96, all subjects were still seropositive for both HPV-16 and HPV-18 antibodies. In the ATP cohort, in subjects who were initially seronegative, GMTs at Month 96 were 1653.1 EL.U/mL [95% CI: 1528.2– 1788.2] for HPV-16 and 667.2 EL.U/mL [95% CI: 612.0 – 727.5] for HPV-18.

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Applicant Response:

The Company reviewed QC chart and QC panel data for HPV-18 ELISA. The QC chart did not show any drift during the testing period. The QC panel data showed a small increase of around 10% from July 2011 till October 2013 (M84 serum samples were tested in 2011-2012 and M96 serum samples were tested in 2013). This increase was within the acceptable range of variability for the HPV-18 ELISA, i.e. <20% (The acceptance criteria for the GMT ratio on a QC panel tested every 6 months is [0.8-1.25]). No stability alert was observed based on the review of the QC chart and QC panel data from the period of HPV-18 ELISA testing of both time points.

The HPV-18 GMT at M96 from the M96 ATP cohort (667.2 EL.U/mL, 95% CI: 612.0 – 727.5) seemed to be slightly higher than the GMT at M84 from the M84 ATP cohort (597.0 EL.U/mL, 95% CI: 547.0 –

651.5). However, the Company noticed the overlapping of the 95% CIs of the two time-points. The observed difference in HPV-18 GMTs between M96 and M84, calculated as GMT ratio 1.11 (95% CI: 0.98, 1.26, P=0.09) was within the acceptable variability for the HPV-18 ELISA.

Discussion

The Issue is resolved. The MAH's overall conclusions are endorsed and no further actions are required. Please note that the Article 46 for the study HPV-025 Ext-013 Month 108 for Cervarix has been submitted on 29 January 2015 (eCTD sequence 0189).

4. Rapporteur's overall conclusion

The MAH Discussion is generally endorsed. The results of this annual update report were in agreement with previous annual reports. The results are in line with expectations. The MAH's overall conclusions are endorsed and no further actions are required for this PAM at Month 96. No further regulatory action is considered necessary based on these results. The final results of this study are expected at month 120. A complete safety profile of this long term follow up is expected at the end of the study including all subjects from the TVC that were originally selected for inclusion in HPV025 EXT-13.

☒ Fulfilled