Amsterdam, 14 October 2021
EMA/620385/2021
Human Medicines 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/P46/098

Note

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

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1. Introduction

On 14/05/2021, the MAH submitted a completed paediatric study Cervarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and 45 years, when administered according to the Prescribing Information (PI) as per routine practice" is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study<ies>

N/A.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and 45 years, when administered according to the Prescribing Information (PI) as per routine practice

2.3.2. Clinical study

Study EPI-HPV-070:

A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and 45 years, when administered according to the Prescribing Information (PI) as per routine practice.

Description

Methods

Objectives

Primary

- To assess the safety of Cervarix in terms of medically attended adverse event following immunisation (AEFIs) occurring within 30 days (Day 1-30) following each immunisation, in all enrolled subjects.

Secondary

- To assess the safety of Cervarix in terms of serious AEFIs occurring during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with Cervarix (whichever occurred first), in all enrolled subjects.
- To assess the safety of Cervarix in terms of pIMDs (potential immune-mediated disease) detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with Cervarix (whichever occurred first), in all enrolled subjects.
- To assess the safety of Cervarix in terms of PO when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- To assess the safety of Cervarix in terms of congenital anomalies when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

Study design

- Type of design: A prospective, descriptive, self-contained, multi-centre cohort study.
- This was a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).
- Study population: The study planned to involve approximately 3000 female Chinese subjects aged between 9 and 45 years, vaccinated voluntarily as per standard practice.
- Data collection: electronic Case Report form (eCRF) was used to collect data.
- Study duration: The follow-up was to be performed from enrolment until either 12 months following the third immunisation or 24 months following the first immunisation with Cervarix (whichever occurred first). This represented an individual subject's total follow-up time between 18 and 24 months for subjects completing the immunisation course (3 doses) as per Cervarix PI schedule. Subjects who reported exposure to Cervarix during pregnancy or pregnancy onset up to 60 days following the last immunisation were to be followed-up till the end of pregnancy, to observe the PO and for any possible congenital anomalies diagnosed during the first 12 months of the child's life. Thus, in such cases, an extended follow-up beyond 24 months may have occurred.
- Epoch 001: Prospective data collection starting at Visit 1 (Day 1) and ending at Call 3 (either 12 months following the third immunisation or 24 months following the first immunisation, whichever occurred first).

Study population /Sample size

The study involved female Chinese subjects aged between 9 and 45 years, vaccinated voluntarily as per standard practice. The planned sample size of the study was approximately 3000 subjects.

Outcomes/endpoints

Primary

- Occurrence, intensity and causal relationship to vaccination, of medically attended AEFIs reported during the 30-day period (Day 1-30) following each immunisation with Cervarix.

Secondary

- Occurrence, intensity and causal relationship to vaccination of serious AEFI reported during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with Cervarix (whichever occurred first), in all enrolled subjects.
- Occurrence, intensity and causal relationship of pIMDs detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with Cervarix (whichever occurred first), in all enrolled subjects.
- Occurrence of PO when Cervarix was administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- Occurrence of any congenital anomalies when Cervarix was administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

Statistical Methods

Data sources:

This prospective study collected data using active and enhanced passive surveillance methods:

- Subject interview and observation at immunisation visits (events that have occurred since the previous visits or that occurred during or just after the visit).
- Structured telephone follow-up.
- Direct reporting by the subjects/subjects parent(s)/legally acceptable representative(s) (LAR[s]).
- Reporting by physician not part of this study: A physician could report a suspected AEFI by contacting the study investigator or his/her delegate.

Results

Recruitment/ Number analysed

A total of 3016 subjects were enrolled in this study, of which 3013 subjects were vaccinated and part of the exposed set (ES).

Table 1 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal - Exposed Set

	HPV N=3013	
	n	%
Number of subjects vaccinated	3013	100
Number of subjects completed	2895	96.1
Number of subjects withdrawn	118	3.9
Reasons for withdrawal :		
Serious Adverse Event And/ Or pIMD And/Or Non-Serious Related Adverse Event	1	0.03
Non-Serious Adverse Event	0	0
Protocol Deviation	0	0
Consent Withdrawal, Not Due To An Adverse Event	47	1.6
Migrated / Moved From The Study Area	0	0
Lost To Follow-Up (subjects with incomplete vaccination course)	48	1.6
Lost To Follow-Up (subjects with complete vaccination course)	19	0.6
Not Willing To Participate This Visit	0	0
Not Willing / Not Able To Be Contacted	3	0.1
Study Sponsor Termination	0	0
Other	0	0

Vaccinated = number of subjects vaccinated with *Cervarix* (outside the study, as per routine practice)
Completed = number of subjects who completed last study visit.
Withdrawn = number of subjects who did not come for the last visit

Table 2 Number and percentage of subjects who received Cervarix - Exposed Set

	HPV N=3013	
Total number of doses received	**n**	%
1	57	1.9
2	86	2.9
3	2870	95.3
Any	3013	100

N = Number of subjects vaccinated with at least one dose of *Cervarix*
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Safety results

- A total of 8839 doses of Cervarix were administered to 3013 subjects by the end of the study and were included in the analysis. Of these 3013 subjects, 147 subjects (4.9%) reported medically attended AEFIs within 30 days of vaccination, after 160 doses (1.8%). The medically attended AEFIs were mainly "Infections and infestations" (118 events in 96 subjects [3.2%] after 104 doses [1.2%]). The most frequently reported medically attended AEFIs were upper respiratory tract infection (32 events, reported by 30 subjects [1.0%]), bronchitis (27 events, reported by 25 subjects [0.8%]) and tonsillitis (12 events reported by 12 subjects [0.4%]).
- During the 30-day follow-up period after vaccination, a total of 55 medically attended AEFIs were reported by 49 subjects (1.6%) post dose 1. The most frequently reported medically

attended AEFI post dose 1 was upper respiratory tract infection (9 events, reported by 9 subjects [0.3%]). A total of 71 medically attended AEFIs were reported by 55 subjects (1.8%) post dose 2. The most frequently reported medically attended AEFI post dose 2 was bronchitis (14 events, reported by 13 subjects [0.4%]). A total of 85 medically attended AEFIs were reported by 56 subjects (1.9%) post dose 3. The most frequently reported medically attended AEFI post dose 3 was upper respiratory tract infection (13 events, reported by 13 subjects [0.4%])

- During the 30-day follow-up period after vaccination, a total of 3 medically attended AEFIs of grade 3 intensity was reported by 1 subject. The medically attended grade 3 AEFIs were pyrexia, bronchitis and rhinitis allergic. None of them were considered by the investigator to be causally related to vaccination.
- Among the medically attended AEFIs reported within 30 days following vaccination, 195 medically attended AEFIs reported by 143 subjects (4.7%) were non-serious. Of these, 2 cases of pyrexia were considered by the investigator to be related to vaccination (reported by 2 subjects [0.1%], after 2nd dose).
- A total of 40 serious AEFIs were reported by 22 subjects (0.7%), after 22 doses (0.2%). The most frequently reported serious AEFIs were pneumonia (4 events, reported by 4 subjects [0.1%]) and ectopic pregnancy (4 events, reported by 4 subjects [0.1%]). None of these serious AEFIs were considered by the investigator to be related to vaccination and most were of moderate (50%) or mild (37.5%) severity. Two events (5.0%) were severe. All serious AEFIs were recovered/resolved (95%) or recovering/resolving (5%) at the end of study.
- By the end of the follow-up period, 1 subject reported a pIMD (neuritis, (mild, grade 1) that was considered by the investigator not to be causally related to the vaccination, and the subject had recovered following treatment.
- Furthermore, 65 subjects reported pregnancies during the entire follow-up period. Of these, 34 subjects (52.3%) had a live infant with no apparent congenital anomaly, 20 subjects (30.8%) had an elective termination with no apparent congenital anomaly, 4 subjects (6.2%) had an ectopic pregnancy, 1 subject (1.5%) had a live infant with congenital anomaly, and 1 subject (1.5%) had a spontaneous abortion with no apparent congenital anomaly. Five subjects (7.7%) were lost to follow-up.

Table 3 Incidence and nature of reported AEFIs following each dose and overall - Exposed Set

	Any AEFI in the entire study period			Medically attended AEFI within 30 days			Serious AEFI in the entire study period		
	N	n	%	N	n	%	N	n	%
Dose 1	3013	57	1.9	3013	49	1.6	3013	5	0.2
Dose 2	2956	64	2.2	2956	55	1.9	2956	9	0.3
Dose 3	2870	59	2.1	2870	56	2.0	2870	8	0.3
Overall/dose	8839	180	2.0	8839	160	1.8	8839	22	0.2
Overall/subject	3013	167	5.5	3013	147	4.9	3013	22	0.7

For each dose and overall/subject:
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects presenting at least one type of symptom
For overall/dose
N = number of administered doses
n/% = number/percentage of doses followed by at least one type of symptom
AEFI = Adverse Event Following Immunisation
All AEFIs reported excludes the AEFIs reported for offspring

Table 4 Summary of occurrences and subjects with at least one medically attended AEFI with onset within 30 days of vaccination classified by MedDRA Primary System Organ Class and Preferred Term - Exposed Set

	HPV N=3013				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	events	n	%	LL	UL
Any	211	147	4.9	4.1	5.7
Blood and lymphatic system disorders (10005329)	2	2	0.1	0.0	0.2
Anaemia (10002034)	1	1	0.03	0.0	0.2
Lymphadenopathy (10025197)	1	1	0.03	0.0	0.2
Cardiac disorders (10007541)	2	2	0.1	0.0	0.2
Sinus node dysfunction (10075889)	1	1	0.03	0.0	0.2
Tachycardia (10043071)	1	1	0.03	0.0	0.2
Congenital, familial and genetic disorders (10010331)	1	1	0.03	0.0	0.2
Type V hyperlipidaemia (10060755)	1	1	0.03	0.0	0.2
Ear and labyrinth disorders (10013993)	2	2	0.1	0.0	0.2
Ear pruritus (10052138)	1	1	0.03	0.0	0.2
Tinnitus (10043882)	1	1	0.03	0.0	0.2
Endocrine disorders (10014698)	1	1	0.03	0.0	0.2
Hyperthyroidism (10020850)	1	1	0.03	0.0	0.2
Eye disorders (10015919)	3	3	0.1	0.0	0.3
Chalazion (10008388)	1	1	0.03	0.0	0.2
Conjunctival oedema (10010726)	1	1	0.03	0.0	0.2
Dry eye (10013774)	1	1	0.03	0.0	0.2
Gastrointestinal disorders (10017947)	15	15	0.5	0.3	0.8
Abdominal pain (10000081)	2	2	0.1	0.0	0.2
Chronic gastritis (10008882)	2	2	0.1	0.0	0.2
Enteritis (10014866)	2	2	0.1	0.0	0.2
Gastritis (10017853)	5	5	0.2	0.1	0.4
Gastritis erosive (10017865)	1	1	0.03	0.0	0.2
Mouth ulceration (10028034)	1	1	0.03	0.0	0.2
Stomatitis (10042128)	1	1	0.03	0.0	0.2
Tooth impacted (10044042)	1	1	0.03	0.0	0.2
General disorders and administration site conditions (10018065)	15	14	0.5	0.3	0.8
Influenza like illness (10022004)	5	4	0.1	0.0	0.3
Pyrexia (10037660)	10	10	0.3	0.2	0.6
Hepatobiliary disorders (10019805)	3	2	0.1	0.0	0.2
Hepatic function abnormal (10019670)	1	1	0.03	0.0	0.2
Hepatic steatosis (10019708)	1	1	0.03	0.0	0.2
Hyperbilirubinaemia (10020578)	1	1	0.03	0.0	0.2

	HPV N=3013				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	**events**	**n**	**%**	**LL**	**UL**
Immune system disorders (10021428)	1	1	0.03	0.0	0.2
Hypersensitivity (10020751)	1	1	0.03	0.0	0.2
Infections and infestations (10021881)	118	96	3.2	2.6	3.9
Acute sinusitis (10001076)	3	3	0.1	0.0	0.3
Bronchitis (10006451)	27	25	0.8	0.5	1.2
Conjunctivitis (10010741)	1	1	0.03	0.0	0.2
Gastroenteritis (10017888)	5	5	0.2	0.1	0.4
Gingivitis (10018292)	1	1	0.03	0.0	0.2
Helicobacter infection (10054263)	2	2	0.1	0.0	0.2
Herpangina (10019936)	1	1	0.03	0.0	0.2
Influenza (10022000)	1	1	0.03	0.0	0.2
Nasopharyngitis (10028810)	4	4	0.1	0.0	0.3
Otitis media chronic (10033081)	1	1	0.03	0.0	0.2
Paronychia (10034016)	1	1	0.03	0.0	0.2
Pelvic inflammatory disease (10034254)	3	3	0.1	0.0	0.3
Periodontitis (10034539)	1	1	0.03	0.0	0.2
Pharyngitis (10034835)	9	9	0.3	0.1	0.6
Pneumonia (10035664)	5	5	0.2	0.1	0.4
Tonsillitis (10044008)	12	12	0.4	0.2	0.7
Upper respiratory tract infection (10046306)	32	30	1.0	0.7	1.4
Urethritis (10046480)	1	1	0.03	0.0	0.2
Urinary tract infection (10046571)	5	5	0.2	0.1	0.4
Vaginal infection (10046914)	2	2	0.1	0.0	0.2
Vulvovaginal mycotic infection (10064899)	1	1	0.03	0.0	0.2
Injury, poisoning and procedural complications (10022117)	2	2	0.1	0.0	0.2
Animal scratch (10002519)	1	1	0.03	0.0	0.2
Ligament rupture (10065433)	1	1	0.03	0.0	0.2
Metabolism and nutrition disorders (10027433)	2	2	0.1	0.0	0.2
Hyperuricaemia (10020903)	2	2	0.1	0.0	0.2
Musculoskeletal and connective tissue disorders (10028395)	5	5	0.2	0.1	0.4
Arthritis (10003246)	1	1	0.03	0.0	0.2
Back pain (10003988)	1	1	0.03	0.0	0.2
Costochondritis (10011219)	1	1	0.03	0.0	0.2
Intervertebral disc protrusion (10050296)	1	1	0.03	0.0	0.2
Spinal osteoarthritis (10041591)	1	1	0.03	0.0	0.2
Nervous system disorders (10029205)	5	5	0.2	0.1	0.4
Diabetic neuropathy (10012680)	1	1	0.03	0.0	0.2
Dizziness (10013573)	1	1	0.03	0.0	0.2

	HPV N=3013				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	**events**	**n**	**%**	**LL**	**UL**
Headache (10019211)	1	1	0.03	0.0	0.2
Migraine (10027599)	1	1	0.03	0.0	0.2
Neuritis (10029240)	1	1	0.03	0.0	0.2
Pregnancy, puerperium and perinatal conditions (10036585)	1	1	0.03	0.0	0.2
Ectopic pregnancy (10014166)	1	1	0.03	0.0	0.2
Psychiatric disorders (10037175)	5	5	0.2	0.1	0.4
Anxiety (10002855)	1	1	0.03	0.0	0.2
Insomnia (10022437)	2	2	0.1	0.0	0.2
Sleep disorder (10040984)	2	2	0.1	0.0	0.2
Renal and urinary disorders (10038359)	4	4	0.1	0.0	0.3
Calculus urinary (10007027)	1	1	0.03	0.0	0.2
Diabetic nephropathy (10061835)	1	1	0.03	0.0	0.2
Nephrolithiasis (10029148)	1	1	0.03	0.0	0.2
Stress urinary incontinence (10066218)	1	1	0.03	0.0	0.2
Reproductive system and breast disorders (10038604)	7	7	0.2	0.1	0.5
Adenomyosis (10056268)	1	1	0.03	0.0	0.2
Breast hyperplasia (10006256)	1	1	0.03	0.0	0.2
Menstruation irregular (10027339)	3	3	0.1	0.0	0.3
Polymenorrhoea (10036086)	1	1	0.03	0.0	0.2
Vaginal haemorrhage (10046910)	1	1	0.03	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	7	7	0.2	0.1	0.5
Asthma (10003553)	1	1	0.03	0.0	0.2
Cough (10011224)	2	2	0.1	0.0	0.2
Respiratory disorder (10038683)	1	1	0.03	0.0	0.2
Rhinitis allergic (10039085)	3	3	0.1	0.0	0.3
Skin and subcutaneous tissue disorders (10040785)	10	10	0.3	0.2	0.6
Acne (10000496)	1	1	0.03	0.0	0.2
Dermatitis allergic (10012434)	2	2	0.1	0.0	0.2
Dermatitis contact (10012442)	1	1	0.03	0.0	0.2
Eczema (10014184)	3	3	0.1	0.0	0.3
Urticaria (10046735)	3	3	0.1	0.0	0.3

events: number of occurrences = number of medically attended AEFIs with onset within 30 days
N = Number of subjects vaccinated with at least one dose of *Cervarix*
n = number of subjects who reported the medically attended AEFI with onset within 30 days in a given category
% = n / N x 100
AEFI = Adverse Event Following Immunisation
All AEFIs reported excludes the AEFIs reported for offspring

Table 5 Summary of occurrences and subjects with at least one medically attended AEFI causally related to vaccination with onset within 30 days of vaccination classified by MedDRA Primary System Organ Class and Preferred Term - Exposed Set

	HPV N=3013				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	events	n	%	LL	UL
Any	2	2	0.1	0.0	0.2
General disorders and administration site conditions (10018065)	2	2	0.1	0.0	0.2
Pyrexia (10037660)	2	2	0.1	0.0	0.2

Events: number of occurrences = number of medically attended AEFIs causally related to vaccination with onset within 30 days
N = Number of subjects vaccinated with at least one dose of *Cervarix*
n = number of subjects reporting the medically attended AEFIs causally related to vaccination with onset within 30 days of vaccination in a given category
% = n / N x 100
AEFI = Adverse Event Following Immunisation
All AEFIs reported excludes the AEFIs reported for offspring

Table 6 Summary of occurrences and subjects with at least one medically attended grade 3 AEFI with onset within 30 days of vaccination classified by MedDRA Primary System Organ Class and Preferred Term - Exposed Set

	HPV N=3013				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	events	n	%	LL	UL
Any	3	1	0.03	0.0	0.2
General disorders and administration site conditions (10018065)	1	1	0.03	0.0	0.2
Pyrexia (10037660)	1	1	0.03	0.0	0.2
Infections and infestations (10021881)	1	1	0.03	0.0	0.2
Bronchitis (10006451)	1	1	0.03	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	1	1	0.03	0.0	0.2
Rhinitis allergic (10039085)	1	1	0.03	0.0	0.2

events: number of occurrences = number of medically attended grade 3 AEFIs with onset within 30 days
N = Number of subjects vaccinated with at least one dose of *Cervarix*
n = number of subjects reporting the medically attended grade 3 AEFIs with onset within 30 days in a given category
% = n / N x 100
AEFI = Adverse Event Following Immunisation
All AEFIs reported excludes the AEFIs reported for offspring

Table 7 Summary of occurrences and vaccine doses followed by at least one medically attended AEFI with onset within 30 days of vaccination classified by MedDRA Primary System Organ Class and Preferred Term - Exposed Set

	HPV N=8839				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	events	n	%	LL	UL
Any	211	160	1.8	1.5	2.1
Blood and lymphatic system disorders (10005329)	2	2	0.02	0.0	0.1
Anaemia (10002034)	1	1	0.01	0.0	0.1
Lymphadenopathy (10025197)	1	1	0.01	0.0	0.1
Cardiac disorders (10007541)	2	2	0.02	0.0	0.1
Sinus node dysfunction (10075889)	1	1	0.01	0.0	0.1
Tachycardia (10043071)	1	1	0.01	0.0	0.1
Congenital, familial and genetic disorders (10010331)	1	1	0.01	0.0	0.1
Type V hyperlipidaemia (10060755)	1	1	0.01	0.0	0.1
Ear and labyrinth disorders (10013993)	2	2	0.02	0.0	0.1
Ear pruritus (10052138)	1	1	0.01	0.0	0.1
Tinnitus (10043882)	1	1	0.01	0.0	0.1
Endocrine disorders (10014698)	1	1	0.01	0.0	0.1
Hyperthyroidism (10020850)	1	1	0.01	0.0	0.1
Eye disorders (10015919)	3	3	0.03	0.0	0.1
Chalazion (10008388)	1	1	0.01	0.0	0.1
Conjunctival oedema (10010726)	1	1	0.01	0.0	0.1
Dry eye (10013774)	1	1	0.01	0.0	0.1
Gastrointestinal disorders (10017947)	15	15	0.2	0.1	0.3
Abdominal pain (10000081)	2	2	0.02	0.0	0.1
Chronic gastritis (10008882)	2	2	0.02	0.0	0.1
Enteritis (10014866)	2	2	0.02	0.0	0.1
Gastritis (10017853)	5	5	0.1	0.0	0.1
Gastritis erosive (10017865)	1	1	0.01	0.0	0.1
Mouth ulceration (10028034)	1	1	0.01	0.0	0.1
Stomatitis (10042128)	1	1	0.01	0.0	0.1
Tooth impacted (10044042)	1	1	0.01	0.0	0.1
General disorders and administration site conditions (10018065)	15	15	0.2	0.1	0.3
Influenza like illness (10022004)	5	5	0.1	0.0	0.1
Pyrexia (10037660)	10	10	0.1	0.1	0.2
Hepatobiliary disorders (10019805)	3	2	0.02	0.0	0.1
Hepatic function abnormal (10019670)	1	1	0.01	0.0	0.1
Hepatic steatosis (10019708)	1	1	0.01	0.0	0.1
Hyperbilirubinaemia (10020578)	1	1	0.01	0.0	0.1

	HPV N=8839				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	**events**	**n**	**%**	**LL**	**UL**
Immune system disorders (10021428)	1	1	0.01	0.0	0.1
Hypersensitivity (10020751)	1	1	0.01	0.0	0.1
Infections and infestations (10021881)	118	104	1.2	1.0	1.4
Acute sinusitis (10001076)	3	3	0.03	0.0	0.1
Bronchitis (10006451)	27	26	0.3	0.2	0.4
Conjunctivitis (10010741)	1	1	0.01	0.0	0.1
Gastroenteritis (10017888)	5	5	0.1	0.0	0.1
Gingivitis (10018292)	1	1	0.01	0.0	0.1
Helicobacter infection (10054263)	2	2	0.02	0.0	0.1
Herpangina (10019936)	1	1	0.01	0.0	0.1
Influenza (10022000)	1	1	0.01	0.0	0.1
Nasopharyngitis (10028810)	4	4	0.05	0.0	0.1
Otitis media chronic (10033081)	1	1	0.01	0.0	0.1
Paronychia (10034016)	1	1	0.01	0.0	0.1
Pelvic inflammatory disease (10034254)	3	3	0.03	0.0	0.1
Periodontitis (10034539)	1	1	0.01	0.0	0.1
Pharyngitis (10034835)	9	9	0.1	0.0	0.2
Pneumonia (10035664)	5	5	0.1	0.0	0.1
Tonsillitis (10044008)	12	12	0.1	0.1	0.2
Upper respiratory tract infection (10046306)	32	32	0.4	0.2	0.5
Urethritis (10046480)	1	1	0.01	0.0	0.1
Urinary tract infection (10046571)	5	5	0.1	0.0	0.1
Vaginal infection (10046914)	2	2	0.02	0.0	0.1
Vulvovaginal mycotic infection (10064899)	1	1	0.01	0.0	0.1
Injury, poisoning and procedural complications (10022117)	2	2	0.02	0.0	0.1
Animal scratch (10002519)	1	1	0.01	0.0	0.1
Ligament rupture (10065433)	1	1	0.01	0.0	0.1
Metabolism and nutrition disorders (10027433)	2	2	0.02	0.0	0.1
Hyperuricaemia (10020903)	2	2	0.02	0.0	0.1
Musculoskeletal and connective tissue disorders (10028395)	5	5	0.1	0.0	0.1
Arthritis (10003246)	1	1	0.01	0.0	0.1
Back pain (10003988)	1	1	0.01	0.0	0.1
Costochondritis (10011219)	1	1	0.01	0.0	0.1
Intervertebral disc protrusion (10050296)	1	1	0.01	0.0	0.1
Spinal osteoarthritis (10041591)	1	1	0.01	0.0	0.1
Nervous system disorders (10029205)	5	5	0.1	0.0	0.1
Diabetic neuropathy (10012680)	1	1	0.01	0.0	0.1
Dizziness (10013573)	1	1	0.01	0.0	0.1

	HPV N=8839				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	**events**	**n**	**%**	**LL**	**UL**
Headache (10019211)	1	1	0.01	0.0	0.1
Migraine (10027599)	1	1	0.01	0.0	0.1
Neuritis (10029240)	1	1	0.01	0.0	0.1
Pregnancy, puerperium and perinatal conditions (10036585)	1	1	0.01	0.0	0.1
Ectopic pregnancy (10014166)	1	1	0.01	0.0	0.1
Psychiatric disorders (10037175)	5	5	0.1	0.0	0.1
Anxiety (10002855)	1	1	0.01	0.0	0.1
Insomnia (10022437)	2	2	0.02	0.0	0.1
Sleep disorder (10040984)	2	2	0.02	0.0	0.1
Renal and urinary disorders (10038359)	4	4	0.05	0.0	0.1
Calculus urinary (10007027)	1	1	0.01	0.0	0.1
Diabetic nephropathy (10061835)	1	1	0.01	0.0	0.1
Nephrolithiasis (10029148)	1	1	0.01	0.0	0.1
Stress urinary incontinence (10066218)	1	1	0.01	0.0	0.1
Reproductive system and breast disorders (10038604)	7	7	0.1	0.0	0.2
Adenomyosis (10056268)	1	1	0.01	0.0	0.1
Breast hyperplasia (10006256)	1	1	0.01	0.0	0.1
Menstruation irregular (10027339)	3	3	0.03	0.0	0.1
Polymenorrhoea (10036086)	1	1	0.01	0.0	0.1
Vaginal haemorrhage (10046910)	1	1	0.01	0.0	0.1
Respiratory, thoracic and mediastinal disorders (10038738)	7	7	0.1	0.0	0.2
Asthma (10003553)	1	1	0.01	0.0	0.1
Cough (10011224)	2	2	0.02	0.0	0.1
Respiratory disorder (10038683)	1	1	0.01	0.0	0.1
Rhinitis allergic (10039085)	3	3	0.03	0.0	0.1
Skin and subcutaneous tissue disorders (10040785)	10	10	0.1	0.1	0.2
Acne (10000496)	1	1	0.01	0.0	0.1
Dermatitis allergic (10012434)	2	2	0.02	0.0	0.1
Dermatitis contact (10012442)	1	1	0.01	0.0	0.1
Eczema (10014184)	3	3	0.03	0.0	0.1
Urticaria (10046735)	3	3	0.03	0.0	0.1

Events: number of occurrences = number of medically attended AEFIs with onset within 30 days
N = Total number of doses
n = number of doses followed by medically attended AEFIs with onset within 30 days of vaccination in a given category
% = n / N x 100
AEFI = Adverse Event Following Immunisation
All AEFIs reported excludes the AEFIs reported for offspring

Table 8 Summary of occurrences and subjects with at least one Serious AEFI* in the entire study period classified by MedDRA Primary System Organ Class and Preferred Term - Exposed Set

	HPV N=3013				
				95% CI	
Primary System Organ Class (CODE) Preferred Term (CODE)	**events**	**n**	**%**	**LL**	**UL**
Any	40	22	0.7	0.5	1.1
Blood and lymphatic system disorders (10005329)	2	2	0.1	0.0	0.2
Anaemia (10002034)	1	1	0.03	0.0	0.2
Thrombocytopenia (10043554)	1	1	0.03	0.0	0.2
Congenital, familial and genetic disorders (10010331)	2	2	0.1	0.0	0.2
Glycogen storage disease type I (10018464)	1	1	0.03	0.0	0.2
Type V hyperlipidaemia (10060755)	1	1	0.03	0.0	0.2
Gastrointestinal disorders (10017947)	1	1	0.03	0.0	0.2
Gastritis (10017853)	1	1	0.03	0.0	0.2
Hepatobiliary disorders (10019805)	3	2	0.1	0.0	0.2
Hepatic function abnormal (10019670)	1	1	0.03	0.0	0.2
Hepatic steatosis (10019708)	1	1	0.03	0.0	0.2
Hyperbilirubinaemia (10020578)	1	1	0.03	0.0	0.2
Infections and infestations (10021881)	9	8	0.3	0.1	0.5
Bronchitis (10006451)	2	2	0.1	0.0	0.2
Mastitis (10026883)	1	1	0.03	0.0	0.2
Pelvic inflammatory disease (10034254)	1	1	0.03	0.0	0.2
Pneumonia (10035664)	4	4	0.1	0.0	0.3
Viral hepatitis carrier (10047458)	1	1	0.03	0.0	0.2
Metabolism and nutrition disorders (10027433)	3	3	0.1	0.0	0.3
Electrolyte imbalance (10014418)	1	1	0.03	0.0	0.2
Hyperuricaemia (10020903)	1	1	0.03	0.0	0.2
Hypoproteinaemia (10021083)	1	1	0.03	0.0	0.2

Musculoskeletal and connective tissue disorders (10028395)	1	1	0.03	0.0	0.2
Intervertebral disc protrusion (10050296)	1	1	0.03	0.0	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	2	2	0.1	0.0	0.2
B-cell lymphoma (10003899)	1	1	0.03	0.0	0.2
Colon cancer (10009944)	1	1	0.03	0.0	0.2
Nervous system disorders (10029205)	1	1	0.03	0.0	0.2
Diabetic neuropathy (10012680)	1	1	0.03	0.0	0.2
Pregnancy, puerperium and perinatal conditions (10036585)	8	7	0.2	0.1	0.5
Abortion missed (10000230)	1	1	0.03	0.0	0.2
Ectopic pregnancy (10014166)	4	4	0.1	0.0	0.3
Gestational diabetes (10018209)	1	1	0.03	0.0	0.2
High risk pregnancy (10052744)	1	1	0.03	0.0	0.2
Premature delivery (10036595)	1	1	0.03	0.0	0.2
Psychiatric disorders (10037175)	1	1	0.03	0.0	0.2
Sleep disorder (10040984)	1	1	0.03	0.0	0.2
Renal and urinary disorders (10038359)	2	2	0.1	0.0	0.2
Diabetic nephropathy (10061835)	1	1	0.03	0.0	0.2
Stress urinary incontinence (10066218)	1	1	0.03	0.0	0.2
Reproductive system and breast disorders (10038604)	2	2	0.1	0.0	0.2
Cervical dysplasia (10008263)	1	1	0.03	0.0	0.2
Uterine scar (10074527)	1	1	0.03	0.0	0.2
Surgical and medical procedures (10042613)	2	2	0.1	0.0	0.2
Abortion induced (10000220)	2	2	0.1	0.0	0.2
Vascular disorders (10047065)	1	1	0.03	0.0	0.2
Venous thrombosis (10047249)	1	1	0.03	0.0	0.2

Events: number of occurrences = number of serious AEFIs* reported by a subject
N = Number of subjects vaccinated with at least one dose of *Cervarix*
n = number of subjects who reported serious AEFIs* in a given category
% = n / N x 100
AEFI = Adverse Event Following Immunisation
All AEFIs reported excludes the AEFIs reported for offspring
* Serious AEFIs occurring within 12 months following the third immunisation or 24 months following the first immunisation (whichever occurs first)
Source: Table 16.2.6 (15APR2021 8:43 GMT)

2.3.3. **Discussion on clinical aspects**

• A total of 8839 doses of Cervarix were administered to 3013 subjects by the end of the study and were included in the analysis. Of these 3013 subjects, 147 subjects (4.9%) reported medically attended AEFIs within 30 days of vaccination, after 160 doses (1.8%). The medically attended AEFIs were mainly "Infections and infestations" (118 events in 96 subjects [3.2%] after 104 doses [1.2%]).

• Among the medically attended AEFIs reported within 30 days following vaccination, 195 medically attended AEFIs reported by 143 subjects [4.7%] were non-serious. Of these, 2 cases of pyrexia were considered by the investigator to be related to vaccination (reported by 2 subjects [0.1%], after 2nd dose).

• A total of 40 serious AEFIs were reported by 22 subjects (0.7%). None of these serious AEFIs were considered by the investigator to be related to vaccination and most were of moderate (50%) or mild (37.5%) severity. All serious AEFIs were recovered/resolved (95%) or recovering/resolving (5%) at the end of study.

• By the end of the follow-up period, 1 subject reported a pIMD (neuritis) that was considered by the investigator not to be causally related to the vaccination, and the subject had recovered following treatment.

• Furthermore, 65 subjects out of 3031 subjects reported pregnancies during the entire follow-up period. Of these, 34 subjects (52.3%) had a live infant with no apparent congenital anomaly, 20 subjects (30.8%) had an elective termination with no apparent congenital anomaly, 4 subjects (6.2%) had an ectopic pregnancy, 1 subject (1.5%) had a live infant with congenital anomaly, and 1 subject (1.5%) had a spontaneous abortion with no apparent congenital anomaly. Five subjects (7.7%) were lost to follow-up.

No worrying signals were detected in this prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and 45 years, when administered according to the Prescribing Information (PI) as per routine practice.

The most reported adverse events are in the system organ class "Infections and infestations".

The MAH has reviewed the safety results of study EPI-HPV-070 VS CN PMS and has concluded that they are in line with the approved product information for Cervarix in the EU. In general, this is agreed.

However, tree cases of « pelvic inflammatory disease » (medically attended AEFI) were observed out of 3013 subjects vaccinated with HPV (within 30 days of vaccination). In general, it is agreed, as proposed by the MAH, that Pelvic Inflammatory disease is a consequence of infectious pathology and that it is not clear by which mechanism a vaccine could be the cause of PID. Although this possibility cannot totally be excluded, the observed number of cases is not worrisome. Since there was no control arm in the EPI-HPV-070 study, it is not possible to make a direct comparison, so the Company has provided some data from 2 previous large efficacy studies HPV-008 and HPV-039 conducted in similar age groups (15-25 and 18-25 years). Based on these, it can be concluded that the observed number of cases is within the expected rate (0.1%-0.3%).

Overall, the number of reported pregnancies was too low to draw definitive conclusions, and, as stated in the SmPC, as a precautionary measure, it is preferable to avoid the use of Cervarix during pregnancy.

Therefore, no additional changes to the Summary of Product Characteristics (SmPC) for Cervarix are considered necessary for the time being.

The benefit/risk of Cervarix in the approved indications remains positive.

3. **Rapporteur's overall conclusion and recommendation**

No worrying signals were detected in this prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and 45 years, when administered according to the Prescribing Information (PI) as per routine practice.

Therefore, no additional changes to the Summary of Product Characteristics (SmPC) for Cervarix are considered necessary for the time being.

The benefit/risk of Cervarix in the approved indications remains positive.

Fulfilled:

No regulatory action required.

Based on the data submitted, the MAH should provide an answer to the question below as part of this procedure. (see section "Additional clarification requested")

4. Additional clarification requested

Based on the data submitted, the MAH should address the following question as part of this procedure:

- Three cases of « pelvic inflammatory disease » (medically attended AEFI) were observed out of 3013 subjects vaccinated with HPV (within 30 days of vaccination). This incidence should be discussed in the light of the observation made during previous clinical studies.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

The EPI-HPV-070 study was a prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine (Cervarix) in female Chinese subjects aged between 9 and 45 years, when administered according to the Prescribing Information (PI) as per routine practice. The primary objective of this study was to assess the safety of Cervarix in terms of medically attended adverse events following immunisation (AEFIs) occurring within 30 days (Day 1-30) following each immunisation, in all enrolled subjects.

During this study three cases of pelvic inflammatory disease (PID) were reported:

☐ **Case no. 1 (serious)**: A 23-year-old female experienced progressive pain in the lower abdomen; had fever for 3 days; and developed PID sixteen days after receiving the first dose of Cervarix. She was hospitalised for 6 days, her human chorionic gonadotropin result was less than 2.39 mIU/mL, white blood cell count was 12×10^9/L. Ultrasound scan showed fluid at the back of uterus. Physical examination showed that abdomen was soft, there was tenderness in lower abdomen, no rebound pain, liver, and spleen less that the costal. The examination also showed vulva, vagina (unobstructed), cervix smooth with lifting pain, uterus was tender, there was untouched abnormality and tenderness in the adnexa. She was treated with traditional Chinese medicine nos (Jin Ying Jiao Nang and Kang Fu Yan Jiao Nang), cefixime, ornidazole, and ceftriaxone sodium. The subject got recovered from PID. In the opinion of the investigator, the event was considered not related to the administration of Cervarix.

☐ **Case no. 2 (non-serious)**: A 32-year-old female experienced mild PID twenty-two days after receiving the first dose of Cervarix. The subject got recovered from PID and the event was considered by the investigator not related to Cervarix.

☐ **Case no. 3 (non-serious)**: A 35-year-old female experienced mild PID eleven days after receiving the second dose of Cervarix. The subject got recovered from PID and the event was considered by the investigator not related to Cervarix.

Background on pelvic inflammatory disease [CDC, 2021]:

PID is a clinical syndrome that results from the ascension of microorganisms from the cervix and vagina to the upper genital tract.

A number of different microorganisms can cause or contribute to PID. The sexually transmitted pathogens C. trachomatis and N. gonorrhoeae have been implicated in a third to half of PID cases. However, endogenous microorganisms, including gram positive and negative anaerobic organisms and aerobic/facultative gram positive and negative rods and cocci, found at high levels in women with bacterial vaginosis, also have been implicated in the pathogenesis of PID. Newer data suggest that

Mycoplasma genitalium may also play a role in PID and may be associated with milder symptoms although studies have failed to demonstrate a significant increase in PID following detection of M. genitalium in the lower genital tract. Because of the polymicrobial nature of PID, broad-spectrum regimens that provide adequate coverage of likely pathogens are recommended.

PID is a serious complication of chlamydia and gonorrhea, two of the most common reportable infectious diseases and sexually transmitted diseases (STDs) in the US.

Clinical signs and symptoms range from unnoticeable or subtle and mild to severe, and even when the symptoms are mild it might be unrecognized by women and their health care providers. Despite lack of symptoms, histologic evidence of endometritis has been demonstrated in women with subclinical PID.

Based on the above information, pelvic inflammatory disease is considered a consequence of infectious pathology and women who are sexually active or had a history of sexually transmitted diseases are at higher risk to develop PID in their lifetime.

Incidence of pelvic inflammatory disease in EPI-HPV-070 and other clinical studies:

In the EPI-HPV-070 study medically attended adverse events following immunisation (AEFI) were collected up to 30 days following vaccination. In this prospective postmarketing surveillance study, only subjects who had received Cervarix were enrolled, not allowing comparison of the incidence of PID with subjects that did not receive Cervarix in the study.

In the other clinical studies performed in the Cervarix program, medically attended AEFIs were collected throughout the entire study (including the 30 days post vaccination timepoint). Since medically attended AEFIs are also included in the unsolicited adverse events collected up to 30 days post vaccination, the tables presenting the percentage of subjects reporting unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0 to 29) post-vaccination from other studies were used to discuss the incidence of PID in the EPI-HPV-070 study. The data from the large efficacy studies HPV-008 and HPV-039 conducted in similar age groups (15-25 and 18-25 years) worldwide or in China are discussed below. Furthermore, the sample size of the analysis sets from these large efficacy studies was comparable with the analysis set of the EPI-HPV-070 study.

- HPV-008 study: A phase III, double-blind, randomized, controlled, multi-center study to evaluate the efficacy of GlaxoSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine compared to hepatitis A vaccine as control in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy females 15-25 years of age.
- HPV-039: A phase II/III, double-blind, randomised, controlled study to evaluate the efficacy, immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy Chinese female subjects aged 18-25 years.

A summary of the data from the different studies is presented in Table 1 (Data based on Table 2 (EPI-HPV-070), Table 3 (HPV-008) and Table 4 (HPV-039)).

Table 9 Summary table of percentage of subjects reporting the occurrence of pelvic inflammatory disease within the 30-days post-vaccination period

Study		HPV					Control[a]			
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
EPI-HPV-070[b]	3013	3	0.1	0.0	0.3	-	-	-	-	-
HPV-008[c]	3184	7[d]	0.2	0.1	0.5	3187	4[d]	0.1	0.0	0.3
HPV-039[c]	3026	10[d]	0.3	0.2	0.6	3025	9[e]	0.3	0.1	0.6

a. HPV-008: Hepatitis A vaccine (Havrix) was administered in the control group; HPV-039: Aluminium hydroxide [Al(OH)3] was administered in the control group
b. PID collected as medically attended AEFI within 30 days of vaccination
c. PID collected as unsolicited symptom (HPV-008 & HPV-039) within 30 days of vaccination
d. All PIDs were reported as medically significant (based on individual data of HPV-008 & HPV-039)
e. For 6 subjects out of 9 subjects, PIDs were reported as medically significant (based on individual data for HPV-039)

The observed percentage of subjects reporting PID in the EPI-HPV-070 study is in line with the percentage observed in the HPV and control groups of the HPV-008 and HPV039 studies.

Given the low number of reported PID cases in these studies and the above-mentioned differences in collection of data between the studies, data should be interpreted with caution. Based on the above data no indication for increased incidence of PID was observed in the EPI-HPV-070 study.

Of note, Goller et al. (2016) reported that 2.8% [95% CI 2.5% to 3.0%] of women 16–49 years attending an Australian sexual health clinic between 2006 and 2013, were diagnosed with PID [Goller, 2016], while analysis of data from the US National Health and Nutrition Examination Survey 2013-2014 cycle on self-reported lifetime PID in sexually experienced women of reproductive age (18-44 years) showed that the estimated prevalence of was 4.4% [Kreisel, 2017].

MAH's Conclusion

Pelvic inflammatory disease is considered a consequence of infectious pathology. Women who are sexually active or had a history of sexually transmitted diseases are at higher risk to develop PID in their lifetime. The EPI-HPV-070 study was conducted in a population who are also sexually active and the reports of PID occurring post HPV vaccination were coincidental with no causal association to Cervarix. Furthermore, the observed incidence of PID in this study is in line with the incidence observed in other clinical studies in similar population/ age group.

Based on the above information and evaluation, no concern is raised regarding incidence of PID reports in this EPI-HPV-070 post-marketing surveillance study.

Assessment of Applicant's response

In general, it is agreed, as proposed by the MAH, that Pelvic Inflammatory disease is a consequence of infectious pathology and that it is not clear by which mechanism a vaccine could be the cause of PID. Although this possibility cannot totally be excluded, the observed number of cases is not worrisome. Since there was no control arm in the EPI-HPV-070 study, it is not possible to make a direct comparison, so the Company has provided some data for 2 previous large efficacy studies HPV-008

and HPV-039 conducted in similar age groups (15-25 and 18-25 years). Based on these, it can be concluded that the observed number of cases is within the expected rate (0.1%-0.3%).

No further regulatory action is required.

Conclusion - Issue resolved.