9 November 2017
EMA/787348/2017
Human Medicines Evaluation 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/P46/092.1

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:

The Company submits the Abridged ***Annex clinical study report*** HPV-040 PRI in accordance with Art.46 of Regulation No11901/2006 of the European Parliament.

The ***Annex report*** includes additional analyses with one additional year of safety follow-up and effectiveness data on exploratory endpoints (abnormal cytology, CIN2/3+) and registry safety data with one additional follow-up year (New Onset Autoimmune Diseases [NOADs] from HILMO and pregnancy outcomes from the Medical Birth Registry) for the study entitled : "A phase III/IV, community-randomised, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLPAS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female and male study participants aged 12 - 15 years." The ***Annex report*** was submitted in February 2017.

The ***final study report*** for HPV-040 PRI was submitted in June 2016 as a type II variation EMEA/H/C/000721/0081.

Since it is pivotal to protect the majority of adolescent females prior to sexual activities beginning , the first target group for national implementation of HPV vaccine programs will be early adolescents. The HPV-040 PRI was designed as a Community RCT to enable the evaluation of the overall impact (direct & indirect effectiveness) of 2 vaccination strategies. This phase III/IV multi-centre study included 3 Arms:

- Arm A: vaccinating female and male adolescents (aged 12-15 years)
- Arm B: vaccinating female adolescents only
- Arm C: males and females adolescents were vaccinated with a control vaccine (HepB)

The study was coordinated by one principal investigator in Finland.

The MAH conclusions in the ***final study report*** on the results were:

1. HPV vaccine coverage among the female participants was 47.4% in Arm A, 45.3% in Arm B and 0% in Arm C. Among the male participants, HPV vaccine coverage was 19.5% in Arm A, and 0% in Arms B and C.
2. Effectiveness:

   The first confirmatory objective to demonstrate the overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against HPV-16/18 genital infection (Arm A versus ***Arm*** C) was not met. As a hierarchical procedure was applied to assess the confirmatory objectives and as the first confirmatory objective was not met, none of the confirmatory objectives were met.

   Indirect effectiveness (herd protection) against genital HPV-16/18 infection was not observed.

   High total effectiveness against genital HPV-16/18 infection was observed, consistent with findings in efficacy studies.

Evidence of high effectiveness against oropharyngeal infection with vaccine HPV types (HPV-16/18) and with non-vaccine HPV types (HPV-31/33/45) were observed.

In conclusion for the CHMP about the ***final report***, Study HPV-040 could not identify the best HPV vaccination strategy (gender-neutral versus girls only) in adolescents between the age of 12-15 years in Finland to protect against genital HPV-16/18 incident infections after 3.5 to 6.5 years post-dose 1. The herd effect proved to be not statistically significant in the gender-neutral HPV immunization scenario.

3. Safety:

The safety profile of Cervarix collected from active and spontaneous reporting and Finnish health registry surveillance was acceptable. The results of the present final analysis show that no significant differences in the rates of any specific outcome were observed between the treatment groups. The safety profile of the HPV vaccine group was generally similar to that of the control HepB vaccine and in line with what is presented in the current PI.

Safety outcomes were balanced between the treatment groups (except for local reactions). The safety profile in both males and females as collected from active reporting and health registry surveillance was acceptable. Overall, the results of active and passive safety surveillance up to study end confirm the results of the interim analysis and are supportive of an acceptable safety profile of Cervarix in adolescent girls as well as in adolescent boys 12-15 years of age.

Following the CHMP AR of the final clinical report, *the Study HPV-040 did not identify new safety concerns.*

In the 14,837 female and male adolescents who received Cervarix, there was no evidence suggesting a potential association with NOADs including autoimmune thyroiditis or GBS. During the entire follow-up period, 1252 pregnancies were reported without indicating abnormal frequencies of adverse pregnancy outcomes. Safety outcomes were balanced between the treatment groups (except for local reactions).

Safety profile of Cervarix based on the data submitted in this LTFU HPV040 final report was acceptable.

The *Annex report*, subject of this current submission, has been provided as part of a response to RSI in the context of the variation II - EMEA/H/C/000721/0081.

RSI : “The analysis of pregnancy outcome according to the study arm was based on the final study data and will be available in the annex report. The MAH is invited to clarify when the annex report will be submitted to allow for full assessment of the data. Issue not resolved.”

In this variation final assessment report, the CHMP requested the MAH to present the data from this *Annex report* in a separate, stand-alone submission, in the context of a P46 PAM, to allow sufficient time for assessment. A preliminary assessment of the annex data was been made in march 2017.

1.1. Steps taken for the assessment

Submission date:	10/10/2017
Start of procedure:	11/10/2017
CHMP Rapporteur's preliminary assessment report circulated on:	25/10/2017
CHMP Rapporteur's updated assessment report circulated on:	03/11/2017
CHMP opinion:	09/11/2017

2. Assessment of the post-authorisation measure PAM

The following study endpoints were analysed in the ***Annex*** report:

- ***Secondary endpoints (registry safety data with one additional follow-up year)***

Safety data from local health registries of the 1995 cohort in 2014 were not available at the time of the final analysis (end of study in 2014), due to the reason that there is always a one-year gap between event occurrence and data uploading into registries. These data were therefore retrieved in early 2016 and included in the additional analysis:

  - New Onset Autoimmune Diseases (NOAD) from HILMO registry
  - Pregnancy outcomes from the Medical Birth Registry.

- ***Tertiary endpoints***

  - Effectiveness of the vaccine in reducing cytological abnormalities associated with oncogenic HPV types
  - Occurrence of CIN2+ lesions (spontaneous reporting from study subjects)
  - Occurrence of CIN3+ lesions and invasive cervical cancer associated with oncogenic HPV types (from Cancer Registry)

According to the MAH, the safety and effectiveness results obtained from the annex analysis are in line with the previous results as presented in the final study report of HPV-040 (submitted in 2016):

- Overall effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing cytological abnormalities associated with HPV-16/18 types was aligned with overall effectiveness against HPV-16/18 genital infection.
- The incidence rates of NOADs and pregnancy outcomes were generally balanced between the treatment groups. The safety profile in both males and females was acceptable.

Effectiveness results:

They were based on the results of the cervical biopsies collected from the subjects after Visit 5 at the local hospitals.

The majority of the subjects had normal (negative) cervical cytology (85.4% in Arm A, 86.0% in Arm B, 84.8% in Arm C). Cytological abnormality was diagnosed in 13.5% and 18.1 %of subjects in the HPV and HepB groups, respectively, in Arm A; 13.7% and 14.5% of subjects in the HPV and HepB groups, respectively, in Arm B; and 15.1% of subjects in the HepB group in Arm C (Table 7).

- Overall effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing cytological abnormalities associated with HPV-16/18 types (VE Arm A versus C = 25% [95% CI: -26.1, 55.4] and VE Arm B versus C = 46.8% [95% CI: 8.4, 69.1]) was aligned with overall effectiveness against HPV-16/18 genital infection reported in the Clinical Study Report 106636 (HPV-040 PRI).
- Overall effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing all cytological abnormalities (regardless of HPV types) in Arm A versus Arm C and Arm B versus Arm C was not observed.
- Post-hoc analysis of overall effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing cytological abnormalities associated with HPV-16/18 types in Arm A versus Arm C and Arm B versus Arm C, using Mantel-Haenszel adjusted for clustering and stratified by the area type (urban, semi-urban) was also aligned with the post-hoc analysis of overall effectiveness against HPV-16/18 genital infection reported in the Clinical Study Report 106636 (HPV-040 PRI) (Table 7).
- Fifteen CIN2+ cases were reported (diagnosed in local hospitals): 6 cases in Arm A, 1 case in Arm B and 8 cases in Arm C. None of the CIN2+ cases associated with HPV-16/18 (8 cases) received HPV vaccine in the study (Table 5 and 6).
- Two cases of cervical carcinoma (one each in the HPV and HepB groups) were reported in the Cancer registry search during the study period

Table 7 Cervical cytological interpretation at Visit 5, by Arm and Vaccine group (Female study participants, Total enrolled cohort)

	Arm A								Arm B								Arm C					
	HPV N = 2803		HepB N = 348		Not vaccinated N = 502		Total N = 3653		HPV N = 3080		HepB N = 372		Not vaccinated N = 598		Total N = 4050		HepB N = 2735		Not vaccinated N = 463		Total N = 3198	
Categories	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Negative	2425	86.5	285	81.9	411	81.9	3121	85.4	2659	86.3	318	85.5	504	84.3	3481	86.0	2321	84.9	391	84.4	2712	84.8
AGC	1	0.0	0	0.0	0	0.0	1	0.0	0	0.0	1	0.3	0	0.0	1	0.0	3	0.1	0	0.0	3	0.1
ASC-H	3	0.1	0	0.0	2	0.4	5	0.1	5	0.2	0	0.0	1	0.2	6	0.1	7	0.3	1	0.2	8	0.3
ASCUS ONCOGENIC HPV NEGATIVE	65	2.3	5	1.4	12	2.4	82	2.2	83	2.7	6	1.6	7	1.2	96	2.4	66	2.4	7	1.5	73	2.3
ASCUS ONCOGENIC HPV POSITIVE	89	3.2	15	4.3	24	4.8	128	3.5	84	2.7	12	3.2	19	3.2	115	2.8	96	3.5	11	2.4	107	3.3
ASCUS ONCOGENIC HPV QNS	2	0.1	0	0.0	1	0.2	3	0.1	8	0.3	1	0.3	1	0.2	10	0.2	7	0.3	1	0.2	8	0.3
HSIL	4	0.1	4	1.1	3	0.6	11	0.3	6	0.2	0	0.0	5	0.8	11	0.3	13	0.5	1	0.2	14	0.4
LSIL	214	7.6	39	11.2	49	9.8	302	8.3	235	7.6	34	9.1	61	10.2	330	8.1	222	8.1	51	11.0	273	8.5
Invasive malignancy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Cytological abnormality	378	13.5	63	18.1	91	18.1	532	14.6	421	13.7	54	14.5	94	15.7	569	14.0	414	15.1	72	15.6	486	15.2

Table 5 **Local laboratory diagnosis CIN2+ lesions in specimens (cervical biopsy, ECC or treatment) collected post Visit 5 at local hospitals, by Arm and Vaccine group (Female study participants, Total enrolled cohort)**

	Arm A				Arm B				Arm C		
Parameters	HPV	HepB	Not vaccinated	Total	HPV	HepB	Not vaccinated	Total	HepB	Not vaccinated	Total
N	7	4	3	14	12	1	6	19	18	1	19
n	2	3	1	6	0	0	1	1	8	0	8
%	28.6	75.0	33.3	42.9	0.0	0.0	16.7	5.3	44.4	0.0	42.1

Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
N = number of subjects with result available for at least one specimen (cervical biopsy, ECC and or treatment) collected
n = number of subjects with CIN2+ lesions detected in at least one specimen
n/% = n/N x 100

Table 6 **Local laboratory diagnosis CIN2+ lesions associated with HPV-16/18 types in specimens (cervical biopsy, ECC or treatment) collected post Visit 5 at local hospitals, by Arm and Vaccine group (Female study participants, Total enrolled cohort)**

	Arm A				Arm B				Arm C		
Parameters	HPV	HepB	Not vaccinated	Total	HPV	HepB	Not vaccinated	Total	HepB	Not vaccinated	Total
N	7	4	3	14	12	1	6	19	18	1	19
n	0	2	1	3	0	0	0	0	5	0	5
%	0.0	50.0	33.3	21.4	0.0	0.0	0.0	0.0	27.8	0.0	26.3

Assessment comment

The study activities to characterize the female study participants were described in the study design[1]. The Applicant was asked to further investigate and describe this case as it could have been a breakthrough case. Unfortunately, no further data were available on this specific case.

Safety results:

NOADs reported during the entire study

All study participants

Table 23 Incidence rate (per 100,000 person-years) of subjects reporting the occurrence of NOADs, classified by MedDRA Primary System Organ Class and High Level Group Term, during the entire study period* and estimated relative risks (All study participants, Total Vaccinated cohort)

[1] **Evaluation of vaccine-induced HPV antibody responses**
Blood samples were to be collected at Visit 1 (Day 0), Visit 4 (Month 7) and Visit 5 (at 18.5 years of age) in a subset of study participants (immunogenicity subset) to evaluate antibody responses against HPV types or Hepatitis B.
☐ **Effectiveness evaluation at Visit 5 for female study participants only:**
All female community residents born between 1992 and 1995 joining the effectiveness evaluation phase of the trial were to undergo pelvic examination at Visit 5, during which cervical Liquid-Based Cytology (LBC) samples were to be collected for HPV DNA PCR testing and cytopathological examination. In case of a cytology reading of ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA or an abnormal cytology reading of ☐LSIL (low grade squamous intraepithelial lesion), female study participants were to be referred to the local health care system for diagnosis and treatment (repeated cytological examination/HPV DNA testing orcolposcopy/endocervical curettage [ECC] referral) according to local medical practice and standard of care).

		HPV T = 63932.7				HepB T = 75460.8				Relative Risk adjusted for gender (HPV / HepB)		
				95% CI				95% CI			95% CI	
Primary System Organ Class (CODE)	High Level Group Term (CODE)	n	n/T (Per 100,000)	LL	UL	n	n/T (Per 100,000)	LL	UL	RR	LL	UL
At least one symptom		149	233.1	197.1	273.6	180	238.5	205.0	276.0	0.92	0.72	1.17
Blood and lymphatic system disorders (10005329)	Platelet disorders (10035534)	3	4.7	1.0	13.7	4	5.3	1.4	13.6	0.75	0.10	5.10
Endocrine disorders (10014698)	Thyroid gland disorders (10043739)	14	21.9	12.0	36.7	4	5.3	1.4	13.6	2.61	0.80	11.26
Eye disorders (10015919)	Ocular infections, irritations and inflammations (10021877)	9	14.1	6.4	26.7	9	11.9	5.5	22.6	0.84	0.29	2.54
Gastrointestinal disorders (10017947)	Gastrointestinal inflammatory conditions (10017969)	31	48.5	32.9	68.8	44	58.3	42.4	78.3	0.92	0.54	1.57
	Malabsorption conditions (10025477)	10	15.6	7.5	28.8	16	21.2	12.1	34.4	0.53	0.21	1.29
Hepatobiliary disorders (10019805)	Bile duct disorders (10004606)	1	1.6	0.0	8.7	0	0.0	0.0	4.9	INF	0.02	INF
Immune system disorders (10021428)	Immune disorders nec (10027665)	1	1.6	0.0	8.7	0	0.0	0.0	4.9	INF	0.02	INF
Infections and infestations (10021881)	Ancillary infectious topics (10002252)	1	1.6	0.0	8.7	2	2.7	0.3	9.6	0.51	0.01	12.38
	Infections - pathogen unspecified (10021879)	0	0.0	0.0	5.8	1	1.3	0.0	7.4	0.00	0.00	149.07
Metabolism and nutrition disorders (10027433)	Glucose metabolism disorders (incl diabetes mellitus) (10018424)	14	21.9	12.0	36.7	28	37.1	24.7	53.6	0.72	0.33	1.52
Musculoskeletal and connective tissue disorders (10028395)	Connective tissue disorders (excl congenital) (10010761)	2	3.1	0.4	11.3	3	4.0	0.8	11.6	0.44	0.04	3.80
	Joint disorders (10023213)	18	28.2	16.7	44.5	25	33.1	21.4	48.9	0.71	0.35	1.41
Nervous system disorders (10029205)	Cranial nerve disorders (excl neoplasms) (10011305)	5	7.8	2.5	18.3	12	15.9	8.2	27.8	0.48	0.12	1.60
	Demyelinating disorders (10012303)	4	6.3	1.7	16.0	1	1.3	0.0	7.4	4.29	0.36	252.97
	Peripheral neuropathies (10034606)	1	1.6	0.0	8.7	1	1.3	0.0	7.4	1.58	0.01	175.12
	Sleep disturbances (incl subtypes) (10040998)	3	4.7	1.0	13.7	2	2.7	0.3	9.6	2.11	0.20	30.93
	Spinal cord and nerve root disorders (10041543)	1	1.6	0.0	8.7	1	1.3	0.0	7.4	1.58	0.01	175.12
Renal and urinary disorders (10038359)	Nephropathies (10029149)	1	1.6	0.0	8.7	1	1.3	0.0	7.4	1.58	0.01	175.12
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions (10014982)	17	26.6	15.5	42.6	18	23.9	14.1	37.7	1.08	0.50	2.38
	Pigmentation disorders (10035023)	2	3.1	0.4	11.3	1	1.3	0.0	7.4	2.59	0.10	201.11
	Skin and subcutaneous tissue disorders nec (10040790)	6	9.4	3.4	20.4	1	1.3	0.0	7.4	3.92	0.48	180.39
	Skin appendage conditions (10040798)	3	4.7	1.0	13.7	5	6.6	2.2	15.5	0.55	0.08	3.16
	Skin vascular abnormalities (10047043)	2	3.1	0.4	11.3	2	2.7	0.3	9.6	0.98	0.06	16.17
Vascular disorders (10047065)	Arteriosclerosis, stenosis, vascular insufficiency and necrosis (10003216)	2	3.1	0.4	11.3	0	0.0	0.0	4.9	INF	0.32	INF
	Vascular inflammations (10047116)	1	1.6	0.0	8.7	1	1.3	0.0	7.4	1.58	0.01	175.12

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
At least one symptom = at least one symptom experienced (regardless of the MedDRA High Level Group Term)
T(years) = sum of follow-up period expressed in years
n = number of subjects reporting at least once the symptom
n/T = incidence rate (per 100,000 person-years) of subjects reporting at least once the symptom
95% CI for n/T = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
95% CI for RR = 95% confidence interval for Relative Risk adjusted for gender (Exact Stratified Conditional to total number of cases)
*From Dose 1 up to Visit 5 for subjects who attended Visit 5; from Dose 1 up to the day before 19 years of age for subjects who did not attend Visit 5

Assessment comment

Increased RR is clearly confirmed for the Endocrine disorders ***[RR:2.61 (95%CI: 0.80;11.26)] and concerns the female cohort in the HPV group.***

All female participants

Six new cases (five in the HPV group and one in the HepB group) had been reported since the previous registry download.

Table 15 **Incidence rate (per 100,000 person-years) of subjects reporting the occurrence of NOADs, classified by MedDRA Primary System Organ Class and Preferred Term, during the entire study period* and estimated relative risks (All female study participants, Total Vaccinated cohort)**

		HPV T = 53305.4				HepB T = 34841.4				Relative Risk (HPV / HepB)		
				95% CI				95% CI			95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	n/T (Per 100,000)	LL	UL	n	n/T (Per 100,000)	LL	UL	RR	LL	UL
At least one symptom		132	247.6	207.2	293.7	86	246.8	197.4	304.8	1.00	0.76	1.33
Blood and lymphatic system disorders (10005329)	Immune thrombocytopenic purpura (10074667)	3	5.6	1.2	16.4	2	5.7	0.7	20.7	0.98	0.11	11.74
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	5	9.4	3.0	21.9	1	2.9	0.1	16.0	3.27	0.37	154.58
	Basedow's disease (10004161)	8	15.0	6.5	29.6	2	5.7	0.7	20.7	2.61	0.52	25.27
	Thyroiditis (10043778)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Eye disorders (10015919)	Iridocyclitis (10022941)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Iritis (10022955)	1	1.9	0.0	10.5	3	8.6	1.8	25.2	0.22	0.00	2.71
	Uveitis (10046851)	7	13.1	5.3	27.1	3	8.6	1.8	25.2	1.53	0.35	9.14
Gastrointestinal disorders (10017947)	Coeliac disease (10009839)	10	18.8	9.0	34.5	11	31.6	15.8	56.5	0.59	0.23	1.54
	Colitis ulcerative (10009900)	15	28.1	15.7	46.4	8	23.0	9.9	45.2	1.23	0.49	3.34
	Crohn's disease (10011401)	9	16.9	7.7	32.1	6	17.2	6.3	37.5	0.98	0.31	3.35
	Proctitis ulcerative (10036783)	3	5.6	1.2	16.4	1	2.9	0.1	16.0	1.96	0.16	102.94
Hepatobiliary disorders (10019805)	Cholangitis sclerosing (10008609)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Immune system disorders (10021428)	Sarcoidosis (10039486)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Infections and infestations (10021881)	Reiter's syndrome (10038294)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
Metabolism and nutrition disorders (10027433)	Type 1 diabetes mellitus (10067584)	10	18.8	9.0	34.5	10	28.7	13.8	52.8	0.65	0.24	1.75
Musculoskeletal and connective tissue disorders (10028395)	Ankylosing spondylitis (10002556)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Arthritis reactive (10003267)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Juvenile idiopathic arthritis (10059176)	7	13.1	5.3	27.1	8	23.0	9.9	45.2	0.57	0.18	1.80
	Psoriatic arthropathy (10037162)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
	Rheumatoid arthritis (10039073)	2	3.8	0.5	13.6	4	11.5	3.1	29.4	0.33	0.03	2.28
	Scleroderma (10039710)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Sjogren's syndrome (10040767)	0	0.0	0.0	6.9	2	5.7	0.7	20.7	0.00	0.00	3.48
	Spondyloarthropathy (10051265)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
	Systemic lupus erythematosus (10042945)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
Nervous system disorders (10029205)	Facial paralysis (10016062)	2	3.8	0.5	13.6	5	14.4	4.7	33.5	0.26	0.02	1.60
	Mononeuritis (10027910)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Multiple sclerosis (10028245)	3	5.6	1.2	16.4	0	0.0	0.0	10.6	INF	0.27	INF
	Multiple sclerosis relapse (10048393)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Narcolepsy (10028713)	3	5.6	1.2	16.4	0	0.0	0.0	10.6	INF	0.27	INF
	Optic neuritis (10030942)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Radiculopathy (10037779)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Renal and urinary disorders (10038359)	Tubulointerstitial nephritis and uveitis syndrome (10069034)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Skin and subcutaneous tissue disorders (10040785)	Alopecia areata (10001761)	2	3.8	0.5	13.6	4	11.5	3.1	29.4	0.33	0.03	2.28
	Dermatitis herpetiformis (10012468)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Dermatitis psoriasiform (10058675)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Erythema nodosum (10015226)	6	11.3	4.1	24.5	1	2.9	0.1	16.0	3.92	0.48	180.39
	Guttate psoriasis (10018797)	5	9.4	3.0	21.9	2	5.7	0.7	20.7	1.63	0.27	17.16
	Henoch-schonlein purpura (10019617)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Psoriasis (10037153)	7	13.1	5.3	27.1	7	20.1	8.1	41.4	0.65	0.20	2.18
	Vitiligo (10047642)	2	3.8	0.5	13.6	0	0.0	0.0	10.6	INF	0.12	INF
Vascular disorders (10047065)	Behcet's syndrome (10004213)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Raynaud's phenomenon (10037912)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
T(years) = sum of follow-up period expressed in years
n = number of subjects reporting at least once the symptom

Assessment comment

When comparing the first incidence rates discussed in the first analysis (refer to the summary of clinical safety of HPV-040 PRI with the current data addressed in the abridged annex report final, the NOADs cases in HPV group were 1 case each of Crohn, Sarcoidosis, Scleroderma, Erythema nodosum and psoriasis.

Meanwhile, n=132 in the HPV group is not consistent with n=128 of the previous analysis and the 5 NOADs cases in the HPV group detected by the MAH. The same remark is applied to the n=86 data in the HepB group which should count one more NOADs case compared to the previous data. The MAH is invited to comment on this inconsistency.

By MedDRA Preferred Term, the incidence rates of the most common NOADs in female study participants (>10 per 100 000 person-years in any group) were as follows:

- 15.0 and 5.7 cases per 100 000 person-years in the HPV and HepB groups, respectively, for **Basedow's disease [RR:2.61 (95%CI: 0.52;25.27)]**
- 13.1 and 8.6 cases per 100 000 person-years in the HPV and HepB groups, respectively, for Uveitis
- 18.8 and 31.6 cases per 100 000 person-years in the HPV and HepB groups, respectively, for coeliac disease
- 28.1 and 23.0 cases per 100 000 person-years in the HPV and HepB groups, respectively, for colitis ulcerative
- 16.9 and 17.2 cases per 100 000 person-years in the HPV and HepB groups, respectively, for Crohn's disease
- 18.8 and 28.7 cases per 100 000 person-years in the HPV and HepB groups, respectively, for Type 1 diabetes mellitus
- 13.1 and 23.0 cases per 100 000 person-years in the HPV and HepB groups, respectively, for juvenile idiopathic arthritis
- 13.1 and 20.1 cases per 100 000 person-years in the HPV and HepB groups, respectively, for psoriasis

All male participants

Five new cases (one in the HPV group and four in the HepB group) had been reported since the previous registry download. By MedDRA Preferred Term, the incidence rates of the most common NOADs in male study participants ([illegible]) were as follows:

- 28.2 and 41.9 cases per 100 000 person-years in the HPV and HepB groups, respectively, for colitis ulcerative
- 37.6 and 44.3 cases per 100 000 person-years in the HPV and HepB groups, respectively, for Type 1 diabetes mellitus
- 9.4 and 27.1 cases per 100 000 person-years in the HPV and HepB groups, respectively, for Crohn's disease
- 18.8 and 9.8 cases per 100 000 person-years in the HPV and HepB groups, respectively, for **juvenile idiopathic arthritis [RR=1.91 (0.17-13.33)]**
- 18.8 and 4.9 cases per 100 000 person-years in the HPV and HepB groups, respectively, for **Psoriasis [RR=3.82 (0.28-52.73)]**

Serious NOADs

All female participants

One new case in the HPV group had been reported since the previous registry download.

Table 24 Incidence rate (per 100,000 person-years) of subjects reporting the occurrence of serious NOADs, classified by MedDRA Primary System Organ Class and High Level Group Term, during the entire study period and estimated relative risks (All female study participants, Total Vaccinated cohort)

		HPV T = 53305.4				HepB T = 34841.4				Relative Risk (HPV / HepB)		
				95% CI				95% CI			95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	n/T (Per 100,000)	LL	UL	n	n/T (Per 100,000)	LL	UL	RR	LL	UL
At least one symptom		41	76.9	55.2	104.3	23	66.0	41.8	99.1	1.17	0.68	2.03
Blood and lymphatic system disorders (10005329)	Immune thrombocytopenic purpura (10074667)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
Endocrine disorders (10014698)	Thyroiditis (10043778)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Gastrointestinal disorders (10017947)	Colitis ulcerative (10009900)	11	20.6	10.3	36.9	4	11.5	3.1	29.4	1.80	0.53	7.74
	Crohn's disease (10011401)	6	11.3	4.1	24.5	5	14.4	4.7	33.5	0.78	0.20	3.25
	Proctitis ulcerative (10036783)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Immune system disorders (10021428)	Sarcoidosis (10039486)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Metabolism and nutrition disorders (10027433)	Type 1 diabetes mellitus (10067584)	9	16.9	7.7	32.1	8	23.0	9.9	45.2	0.74	0.25	2.19
Musculoskeletal and connective tissue disorders (10028395)	Juvenile idiopathic arthritis (10059176)	2	3.8	0.5	13.6	3	8.6	1.8	25.2	0.44	0.04	3.80
	Rheumatoid arthritis (10039073)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Sjogren's syndrome (10040767)	0	0.0	0.0	6.9	1	2.9	0.1	16.0	0.00	0.00	25.49
Nervous system disorders (10029205)	Multiple sclerosis (10028245)	2	3.8	0.5	13.6	0	0.0	0.0	10.6	INF	0.12	INF
	Narcolepsy (10028713)	2	3.8	0.5	13.6	0	0.0	0.0	10.6	INF	0.12	INF
	Optic neuritis (10030942)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Renal and urinary disorders (10038359)	Tubulointerstitial nephritis and uveitis syndrome (10069034)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Skin and subcutaneous tissue disorders (10040785)	Henoch-schonlein purpura (10019617)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31

The most common serious NOADs in female study participants (>10 per 100 000 person-years in any group) were as follows:

- 20.6 and 11.5 cases per 100 000 person-years in the HPV and HepB groups, respectively, for **serious Colitis Ulcerative [RR=1.80 (0.53-7.74)].** The IR for the serious and non-serious CU were 28.1 and 23.0 cases per 100 000 person-years in the HPV and HepB groups, respectively.
- 11.3 and 14.4 cases per 100 000 person-years in the HPV and HepB groups, respectively, for serious Crohn's disease
- 16.9 and 23.0 cases per 100 000 person-years in the HPV and HepB groups, respectively, for serious Type 1 diabetes mellitus

All male participants

One new case in the HPV group had been reported since the previous registry download. The most common serious NOADs in male study participants ([illegible] years in any group) were as follows:

- 9.4 and 24.6 cases per 100 000 person-years in the HPV and HepB groups, respectively, for serious colitis ulcerative and serious Crohn's disease
- 37.6 and 41.9 cases per 100 000 person-years in the HPV and HepB groups, respectively, for serious Type 1 diabetes mellitus

Assessment comment

With regards to the safety results, the NOADs observed are consistent with the recent safety signal for Autoimmune Thyroiditis in female subjects. Meanwhile, the observed increased RR for Basedow's disease and for Endocrine disorders in the vaccinated female subjects should be further discussed in the next PSUR. The results for females vaccinated for serious NOADs observed showed an increased RR in the HPV group for the Ulcerative colitis. In the context of the new indication of anal cancer, the males vaccinated showed an increased RR for juvenile idiopathic arthritis and for Psoriasis and this

should also be addressed in the next PSUR. ***These safety issues will be further commented in the assessment of Procedure No. EMEA/H/C/000721/II/0085.***

Pregnancy results in all female participants

- The results for pregnancies and pregnancy outcomes over the total number of pregnancies reported during the entire study period. The incidence of subjects with pregnancies according to pregnancy outcome is presented by Arm in Table 37.
- During the entire study, a total of 1344 pregnancies were reported (777 in the HPV group and 567 in the HepB group). Since the previous registry download, **92 new pregnancies had been reported.**
- The majority of pregnancies resulted in elective termination with no apparent congenital anomaly [786 (58.5%)] or birth of a live infant with no apparent congenital anomaly [437 (32.5%)]. The other pregnancy outcomes were spontaneous abortion with no apparent congenital anomaly [107 (8.0%)], ectopic pregnancy [10 (0.7%)], molar pregnancy [3 (0.2%)] and stillbirth with no apparent congenital anomaly [1 (0.1%)].

Table 37 Percentage of subjects with pregnancies according to pregnancy outcome (TVC)

		Arm A N = 6467					Arm B N = 7364					Arm C N = 6681				
					95% CI					95% CI					95% CI	
Pregnancy outcome	Preferred Term (CODE)	n*	n	Per 1000	LL	UL	n*	n	Per 1000	LL	UL	n*	n	Per 1000	LL	UL
Any outcome		461	385	59.5	53.9	65.6	411	358	48.6	43.8	53.8	472	391	58.5	53.0	64.4
spontaneous abortion	Spontaneous abortion no apparent congenital anomaly	39	38	5.9	4.2	8.1	30	30	4.1	2.8	5.8	38	35	5.2	3.7	7.3
elective termination	Elective termination no apparent congenital anomaly	247	225	34.8	30.5	39.6	268	249	33.8	29.8	38.2	271	242	36.2	31.9	41.0
other outcome	Ectopic pregnancy	5	5	0.8	0.3	1.8	1	1	0.1	0.0	0.8	4	4	0.6	0.2	1.5
	Live infant no apparent congenital anomaly	168	159	24.6	21.0	28.7	112	106	14.4	11.8	17.4	157	147	22.0	18.6	25.8
	Molar pregnancy	2	2	0.3	0.0	1.1	0	0	0.0	0.0	0.5	1	1	0.1	0.0	0.8
	Stillbirth no apparent congenital anomaly	0	0	0.0	0.0	0.6	0	0	0.0	0.0	0.5	1	1	0.1	0.0	0.8

Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N = number of subjects with at least one administered dose
n* = number of pregnancies with a specific outcome
n/Per 1000 = number/percentage of subjects reporting a specific pregnancy outcome
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Assessment comment

The Pregnancy results do not show a safety signal regarding the pregnancy outcome.

And results are in line with the final study report of HPV-040.

Assessment of the MAH's response

Assessment comment

With regards to the safety results, the NOADs observed are consistent with the recent safety signal for Autoimmune Thyroiditis in female subjects. Meanwhile, the observed increased RR for Basedow's disease and for Endocrine disorders in the vaccinated female subjects should be further discussed in the next PSUR. The results for females vaccinated for serious NOADs observed showed an increased RR in the HPV group for the Ulcerative colitis. In the context of the new indication of anal cancer, the males vaccinated showed an increased RR for juvenile idiopathic arthritis and for Psoriasis and this should also be addressed in the next PSUR. These safety issues will also be further commented in the Procedure No. EMEA/H/C/000721/II/0085. Issue resolved.

Overall effectiveness against all cytological abnormalities (regardless of HPV types) in Arm A versus Arm C and Arm B versus Arm C was not observed while the overall effectiveness on specifically HPV16/18 cytological abnormalities (VE Arm A versus C = 25% [95% CI: -26.1, 55.4] and VE Arm B versus C = 46.8% [95% CI: 8.4, 69.1]) did not bring evidence for a beneficial impact of a male & female immunization program on reducing the burden in females after 3.5 to 6.5 years post-dose 1.

With regards to the effectiveness data, the Applicant was asked to further investigate the case of adenocarcinoma after 5 years post-vaccination of a girl of 13 yoa, especially for the HPV specification of the lesions and the clinical outcome of the patient. ***This could have been a potential breakthrough case. Unfortunately, the MAH could not find more relevant clinical information on this case listed in the cancer registry.***

3. Rapporteur's overall conclusion

As part of their Responses to the 2nd Response to Supplementary Informations, the MAH submitted an 'Abridged Annex Clinical Study Report for Study 106636 HPV-040 PRI' containing additional analysis with one additional year of safety follow-up data and effectiveness data regarding abnormal cytology, CIN2+ and CIN3+. This study was a phase III/IV, community-randomised, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female and male study participants aged 12 - 15 years. It started in October 2007 and completed in December 2014.

A preliminary assessment of the annex data was been made in march 2017.These data were asked to be presented as a separate, stand-alone submission, in the context of this current P46 PAM, to allow sufficient time for assessment.

The Pregnancy results do not show a safety signal regarding the pregnancy outcomes.

The MAH was requested to take the following points into consideration when submitting the annex report as a separate P46 PAM:

1. With regards to the safety results, the NOADs observed are consistent with the recent safety signal for Autoimmune Thyroiditis in female subjects. Meanwhile, the observed increased RR for Basedow's disease and for Endocrine disorders in the vaccinated female subjects should be further discussed in the next PSUR. The results for females vaccinated for serious NOADs observed showed an increased RR in the HPV group for the Ulcerative colitis. In the context of the new indication of anal cancer, the

males vaccinated showed an increased RR for juvenile idiopathic arthritis and for Psoriasis and this should also be addressed in the next PSUR. ***These safety issues will also be further commented in the Procedure No. EMEA/H/C/000721/II/0085. Issue resolved.***

2. Overall effectiveness against all cytological abnormalities (regardless of HPV types) in Arm A versus Arm C and Arm B versus Arm C was not observed while the overall effectiveness on specifically HPV16/18 cytological abnormalities (VE Arm A versus C = 25% [95% CI: -26.1, 55.4] and VE Arm B versus C = 46.8% [95% CI: 8.4, 69.1]) did not bring evidence for a beneficial impact of a male & female immunization program on reducing the burden in females after 3.5 to 6.5 years post-dose 1.

With regards to the effectiveness data, the Applicant was asked to further investigate the case of adenocarcinoma after 5 years post-vaccination of a girl of 13 yoa, especially for the HPV specification of the lesions and the clinical outcome of the patient. This could have been a possible breakthrough case. Unfortunately, the MAH could not find more relevant clinical information on this case listed in the cancer registry. The common encountered lack of background-baseline clinical data on specific ('eventually breakthrough') cases is considered as problematic as the possibility to discover those cases increase with post-marketing time. The lack of evidence precludes any conclusions on those clinically relevant occurrence. As to address this uncertainty, the MAH is invited to discuss in the next PSUR on how it could better characterize breakthrough cases as part of post-marketing surveillance. ***This issue is considered as resolved.*** *No need to update overall conclusion and impact on benefit-risk balance.*

Meanwhile, minor questions relative to the data inconsistencies are still to be addressed by the MAH. ***Issue not resolved.***

☐ PAM fulfilled (all commitments fulfilled) - No further action required

☒ PAM not fulfilled (not all commitments fulfilled) and further action required

4. List of Outstanding Issues

Six new cases (five in the HPV group and one in the HepB group) in the female participants had been reported since the previous registry download.

When comparing the first incidence rates discussed in the first analysis (refer to the summary of clinical safety of HPV-040 PRI with the current data addressed in the abridged annex report final, the NOADs cases in HPV group were 1 case each of Crohn, Sarcoidosis, Scleroderma, Erythema nodosum and psoriasis.

Meanwhile, n=132 in the HPV group is not consistent with n=128 of the previous analysis and the 5 NOADs cases in the HPV group detected by the MAH (see Table 15). The same remark is applied to the n=86 data in the HepB group which should count one more NOADs case compared to the previous data. The MAH is invited to comment on this inconsistency. ***Issue not resolved.***

5. Assessment of company's response to the outstanding issue

Company's response:

The Company verified the number of subjects with NOADs (new onset of auto-immune diseases) reported in the Annex Study Report HPV-040 PRI (submitted in the P46 092 procedure) compared to the data reported in the main Study Report (previously submitted with the variation EMEA/H/C/000721/II/0081).

For all female study participants in the total vaccinated cohort:

• In the main Study Report (Table 34): 128 subjects in HPV group and 86 subjects in HepB group reported at least one NOAD

Table 34 **Incidence rate (per 100,000 person-years) of subjects reporting the occurrence of NOADs, classified by MedDRA Primary System Organ Class and Preferred Term, between Dose 1 and Visit 5 or 31DEC2013, whichever occurred first*, and estimated relative risks (All female study participants, Total vaccinated cohort)**

		HPV T = 52260.3				HepB T = 34110.8				Relative Risk (HPV / HepB)		
				95% CI				95% CI			95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	n/T (Per 100,000)	LL	UL	n	n/T (Per 100,000)	LL	UL	RR	LL	UL
At least one symptom		128	244.9	204.3	291.2	86	252.1	201.7	311.4	0.97	0.73	1.29
Blood and lymphatic system disorders (10005329)	Immune thrombocytopenic purpura (10074667)	3	5.7	1.2	16.8	2	5.9	0.7	21.2	0.98	0.11	11.72
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	5	9.6	3.1	22.3	1	2.9	0.1	16.3	3.26	0.37	154.35
	Basedow's disease (10004161)	8	15.3	6.6	30.2	2	5.9	0.7	21.2	2.61	0.52	25.24
	Thyroiditis (10043778)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
Eye disorders (10015919)	Iridocyclitis (10022941)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
	Iritis (10022955)	1	1.9	0.0	10.7	2	5.9	0.7	21.2	0.33	0.01	6.27
	Uveitis (10046851)	7	13.4	5.4	27.6	3	8.8	1.8	25.7	1.52	0.35	9.13
Gastrointestinal disorders (10017947)	Coeliac disease (10009839)	10	19.1	9.2	35.2	11	32.2	16.1	57.7	0.59	0.23	1.54
	Colitis ulcerative (10009900)	15	28.7	16.1	47.3	8	23.5	10.1	46.2	1.22	0.49	3.33
	Crohn's disease (10011401)	8	15.3	6.6	30.2	6	17.6	6.5	38.3	0.87	0.26	3.04
	Proctitis ulcerative (10036783)	3	5.7	1.2	16.8	1	2.9	0.1	16.3	1.96	0.16	102.80
Hepatobiliary disorders (10019805)	Cholangitis sclerosing (10008609)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
Infections and infestations (10021881)	Encephalitis (10014581)	0	0.0	0.0	7.1	1	2.9	0.1	16.3	0.00	0.00	25.46
	Reiter's syndrome (10038294)	1	1.9	0.0	10.7	1	2.9	0.1	16.3	0.65	0.01	51.24
Metabolism and nutrition disorders (10027433)	Type 1 diabetes mellitus (10067584)	10	19.1	9.2	35.2	10	29.3	14.1	53.9	0.65	0.24	1.75
Musculoskeletal and connective tissue disorders (10028395)	Ankylosing spondylitis (10002556)	2	3.8	0.5	13.8	1	2.9	0.1	16.3	1.31	0.07	77.01
	Arthritis reactive (10003267)	2	3.8	0.5	13.8	1	2.9	0.1	16.3	1.31	0.07	77.01
	Juvenile idiopathic arthritis (10059176)	7	13.4	5.4	27.6	8	23.5	10.1	46.2	0.57	0.18	1.80
	Psoriatic arthropathy (10037162)	1	1.9	0.0	10.7	1	2.9	0.1	16.3	0.65	0.01	51.24
	Rheumatoid arthritis (10039073)	2	3.8	0.5	13.8	4	11.7	3.2	30.0	0.33	0.03	2.28

	Sjogren's syndrome (10040767)	0	0.0	0.0	7.1	2	5.9	0.7	21.2	0.00	0.00	3.48
	Spondyloarthropathy (10051265)	1	1.9	0.0	10.7	1	2.9	0.1	16.3	0.65	0.01	51.24
	Systemic lupus erythematosus (10042945)	1	1.9	0.0	10.7	1	2.9	0.1	16.3	0.65	0.01	51.24
Nervous system disorders (10029205)	Mononeuritis (10027910)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
	Multiple sclerosis (10028245)	3	5.7	1.2	16.8	0	0.0	0.0	10.8	INF	0.27	INF
	Multiple sclerosis relapse (10048393)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
	Narcolepsy (10028713)	3	5.7	1.2	16.8	0	0.0	0.0	10.8	INF	0.27	INF
	Optic neuritis (10030942)	2	3.8	0.5	13.8	1	2.9	0.1	16.3	1.31	0.07	77.01
	Radiculopathy (10037779)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
	Viith nerve paralysis (10050040)	2	3.8	0.5	13.8	5	14.7	4.8	34.2	0.26	0.02	1.59
Renal and urinary disorders (10038359)	Tubulointerstitial nephritis and uveitis syndrome (10069034)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
Skin and subcutaneous tissue disorders (10040785)	Alopecia areata (10001761)	2	3.8	0.5	13.8	4	11.7	3.2	30.0	0.33	0.03	2.28
	Dermatitis herpetiformis (10012468)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
	Dermatitis psoriasiform (10058675)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
	Erythema nodosum (10015226)	5	9.6	3.1	22.3	1	2.9	0.1	16.3	3.26	0.37	154.35
	Guttate psoriasis (10018797)	5	9.6	3.1	22.3	2	5.9	0.7	21.2	1.63	0.27	17.14
	Henoch-schonlein purpura (10019617)	2	3.8	0.5	13.8	1	2.9	0.1	16.3	1.31	0.07	77.01
	Psoriasis (10037153)	6	11.5	4.2	25.0	7	20.5	8.3	42.3	0.56	0.16	1.94
	Vitiligo (10047642)	2	3.8	0.5	13.8	0	0.0	0.0	10.8	INF	0.12	INF
Vascular disorders (10047065)	Behcet's syndrome (10004213)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF
	Raynaud's phenomenon (10037912)	1	1.9	0.0	10.7	0	0.0	0.0	10.8	INF	0.02	INF

• In the Annex Report (Table 15): 132 subjects in HPV group and 86 subjects in HepB group reported at least one NOAD.

Table 15 **Incidence rate (per 100,000 person-years) of subjects reporting the occurrence of NOADs, classified by MedDRA Primary System Organ Class and Preferred Term, during the entire study period* and estimated relative risks (All female study participants, Total Vaccinated cohort)**

		HPV T = 53305.4				HepB T = 34841.4				Relative Risk (HPV / HepB)		
				95% CI				95% CI			95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	n/T (Per 100,000)	LL	UL	n	n/T (Per 100,000)	LL	UL	RR	LL	UL
At least one symptom		132	247.6	207.2	293.7	86	246.8	197.4	304.8	1.00	0.76	1.33
Blood and lymphatic system disorders (10005329)	Immune thrombocytopenic purpura (10074667)	3	5.6	1.2	16.4	2	5.7	0.7	20.7	0.98	0.11	11.74
Endocrine disorders (10014698)	Autoimmune thyroiditis (10049046)	5	9.4	3.0	21.9	1	2.9	0.1	16.0	3.27	0.37	154.58
	Basedow's disease (10004161)	8	15.0	6.5	29.6	2	5.7	0.7	20.7	2.61	0.52	25.27
	Thyroiditis (10043778)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Eye disorders (10015919)	Iridocyclitis (10022941)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Iritis (10022955)	1	1.9	0.0	10.5	3	8.6	1.8	25.2	0.22	0.00	2.71
	Uveitis (10046851)	7	13.1	5.3	27.1	3	8.6	1.8	25.2	1.53	0.35	9.14
Gastrointestinal disorders (10017947)	Coeliac disease (10009839)	10	18.8	9.0	34.5	11	31.6	15.8	56.5	0.59	0.23	1.54
	Colitis ulcerative (10009900)	15	28.1	15.7	46.4	8	23.0	9.9	45.2	1.23	0.49	3.34
	Crohn's disease (10011401)	9	16.9	7.7	32.1	6	17.2	6.3	37.5	0.98	0.31	3.35
	Proctitis ulcerative (10036783)	3	5.6	1.2	16.4	1	2.9	0.1	16.0	1.96	0.16	102.94
Hepatobiliary disorders (10019805)	Cholangitis sclerosing (10008609)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Immune system disorders (10021428)	Sarcoidosis (10039486)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Infections and infestations (10021881)	Reiter's syndrome (10038294)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
Metabolism and nutrition disorders (10027433)	Type 1 diabetes mellitus (10067584)	10	18.8	9.0	34.5	10	28.7	13.8	52.8	0.65	0.24	1.75
Musculoskeletal and connective tissue disorders (10028395)	Ankylosing spondylitis (10002556)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Arthritis reactive (10003267)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Juvenile idiopathic arthritis (10059176)	7	13.1	5.3	27.1	8	23.0	9.9	45.2	0.57	0.18	1.80
	Psoriatic arthropathy (10037162)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
	Rheumatoid arthritis (10039073)	2	3.8	0.5	13.6	4	11.5	3.1	29.4	0.33	0.03	2.28
	Scleroderma (10039710)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Sjogren's syndrome (10040767)	0	0.0	0.0	6.9	2	5.7	0.7	20.7	0.00	0.00	3.48
	Spondyloarthropathy (10051265)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
	Systemic lupus erythematosus (10042945)	1	1.9	0.0	10.5	1	2.9	0.1	16.0	0.65	0.01	51.31
Nervous system disorders (10029205)	Facial paralysis (10016062)	2	3.8	0.5	13.6	5	14.4	4.7	33.5	0.26	0.02	1.60
	Mononeuritis (10027910)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Multiple sclerosis (10028245)	3	5.6	1.2	16.4	0	0.0	0.0	10.6	INF	0.27	INF
	Multiple sclerosis relapse (10048393)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Narcolepsy (10028713)	3	5.6	1.2	16.4	0	0.0	0.0	10.6	INF	0.27	INF
	Optic neuritis (10030942)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Radiculopathy (10037779)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Renal and urinary disorders (10038359)	Tubulointerstitial nephritis and uveitis syndrome (10069034)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
Skin and subcutaneous tissue disorders (10040785)	Alopecia areata (10001761)	2	3.8	0.5	13.6	4	11.5	3.1	29.4	0.33	0.03	2.28
	Dermatitis herpetiformis (10012468)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Dermatitis psoriasiform (10058675)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Erythema nodosum (10015226)	6	11.3	4.1	24.5	1	2.9	0.1	16.0	3.92	0.48	180.39
	Guttate psoriasis (10018797)	5	9.4	3.0	21.9	2	5.7	0.7	20.7	1.63	0.27	17.16
	Henoch-schonlein purpura (10019617)	2	3.8	0.5	13.6	1	2.9	0.1	16.0	1.31	0.07	77.13
	Psoriasis (10037153)	7	13.1	5.3	27.1	7	20.1	8.1	41.4	0.65	0.20	2.18
	Vitiligo (10047642)	2	3.8	0.5	13.6	0	0.0	0.0	10.6	INF	0.12	INF
Vascular disorders (10047065)	Behcet's syndrome (10004213)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF
	Raynaud's phenomenon (10037912)	1	1.9	0.0	10.5	0	0.0	0.0	10.6	INF	0.02	INF

In the HPV vaccinated group:

• 4 subjects who did not report NOADs in the main analysis reported a NOAD in the one additional year of safety follow-up, captured in the annex analysis.

• 1 subject who reported a NOAD in the main analysis (Preferred Term (PT)=Raynaud's phenomenon) also reported an additional NOAD in the annex analysis (PT=Scleroderma)

This confirms there are 5 additional NOADs reported in the annex analysis compared to the main analysis. However, as a second NOAD is reported in the additional year of safety follow-up for a subject for which another NOAD was already reported in the main Study Report, there are only 4 additional subjects in the HPV vaccinated group reporting at least one NOAD (128 subjects in the main

report + 4 new subjects in the abridged annex report=132 subjects in HPV group that reported at least one NOAD).

In the HepB control group:

• One Subject, who did not report any NOADs in the main analysis, reported a NOAD in the annex analysis

• One other Subject reported an adverse event (PT= Encephalitis) which was classified as a NOAD in the main analysis. The list of terms considered as potential immune-mediated diseases (pIMD) are based on MedDRA PTs and as such is subject to change based on MedDRA version updates. There was an update to the MedDRA version (Nov 2015) between the main analysis and the annex analysis for study HPV-040 PRI, which led to the removal of the PT 'encephalitis' from the list of pIMDs. The targeted pIMD is now acute disseminated encephalomyelitis/demyelination (including site specific variants). Consequently, for any subsequent analyses following this MedDRA update, 'encephalitis' was no longer considered to be a pIMD.

This confirms one new case of NOAD as compared to the main analysis. However, the total number of subjects in the control group reporting at least one NOADs remained unchanged (86 +1 subject - 1 subject = 86 subjects).

We can thus confirm that six new cases of NOADs (five in the HPV group and one in the HepB group) had been reported since the previous registry download and that the number of subjects in table 15 of the Annex report are correct.

Rapporteur's Assessment of the Company's response:

The minor question relative to the data inconsistencies has been correctly addressed by the MAH.
Issue is considered resolved.

6. Final overall conclusion

☒ PAM fulfilled (all commitments fulfilled) - No further action required