24 September 2015
EMA/677871/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Cervarix

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

Procedure No. EMEA/H/C/000721/P46 019.7

Note

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

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

Table of contents

1. Introduction

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

the clinical study report for the following paediatric study: HPV-025 EXT013 Month 120 and the Post-Authorisation Measure P46 19.7 , a follow-up request from CHMP " a summary analysis of all pregnancy data from study HPV-025 Ext 013 up to Month 120 should be included in the final CSR of study HPV-025 Ext 013 "

The **primary study HPV-013** evaluated the safety and immunogenicity of the HPV-16/18 vaccine as compared to hepatitis A virus (HAV) vaccine in 2,067 healthy adolescent female subjects aged 10-14 years. The immunogenicity subset comprised of 1244 vaccinated subjects enrolled at pre-specified centres in Taiwan, Germany, Honduras, Panama and Colombia.

A four-year **follow-up study Ext HPV-013** was conducted in the same countries to assess the long-term persistence of HPV-16 and HPV-18 antibody responses 18, 24, 36 and 48 months after the first vaccine dose given in study HPV-013. In addition, this follow-up study also assessed long-term vaccine safety. To participate in the follow-up study until Month 48, subjects had to be part of the immunogenicity subset of study HPV-013, had to have completed the study and had to have received three doses of HPV-16/18 vaccine.

The primary indication of the HPV-16/18 vaccine is for use in young adolescent females. It is therefore important to establish the long-term persistence of the immune response and safety of the vaccine in this population. The current study **HPV-025 EXT 013** was designed to extend the long-term follow-up (LTFU) for an additional six years and to provide follow-up data up to approximately 10 years after administration of the first HPV-16/18 vaccine dose in study HPV-013. All subjects from the HPV-16/18 vaccine ngroup in study HPV-013, who had received three doses of the HPV-16/18 vaccine, were included in the immunogenicity subset and participated in the FU study Ext HPV-013, were invited to the present study HPV-025 EXT 013.

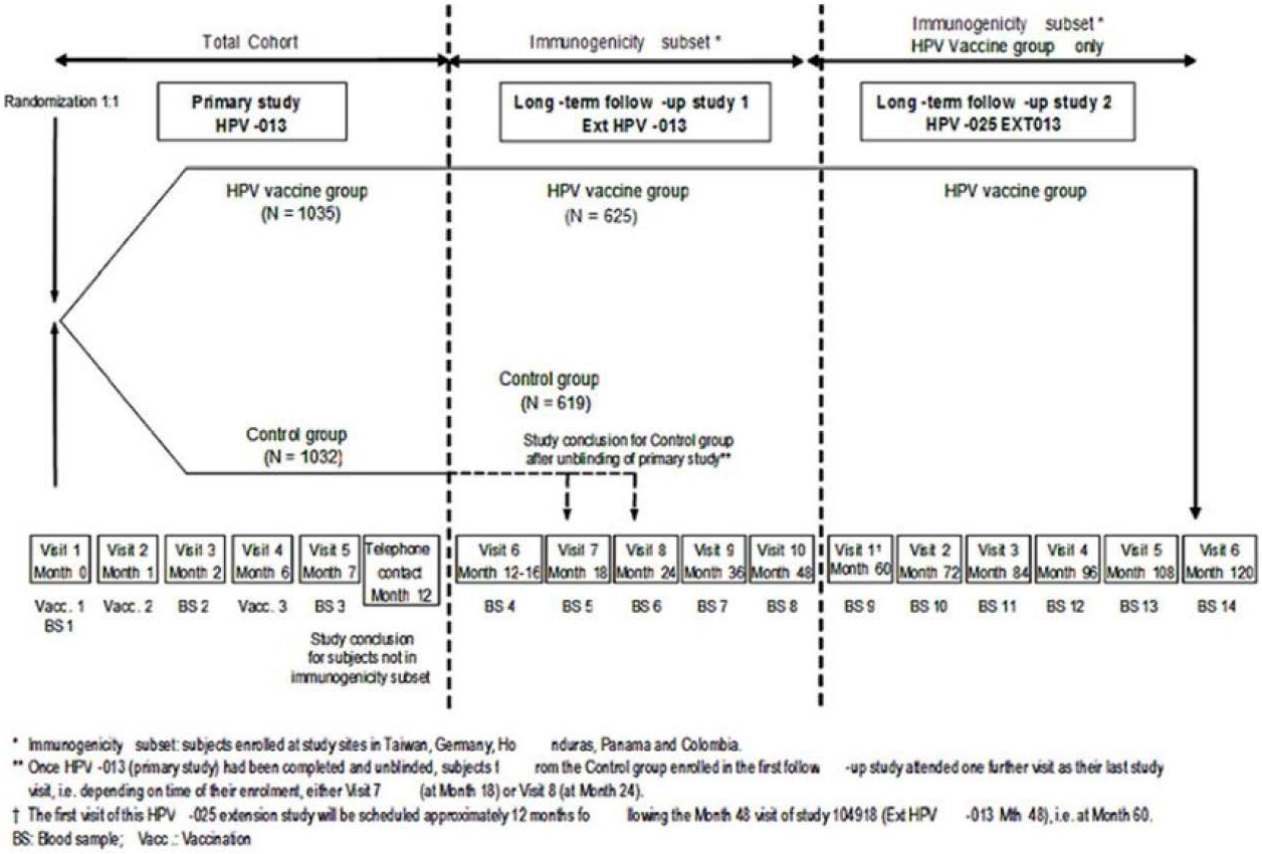
Previously, a long-term efficacy follow-up study in women aged 15-25 years at the time of first vaccination demonstrated high vaccine efficacy against incident and persistent HPV-16/18 infections and their associated cervical lesions up to 9.4 years of follow-up.

1.1. Steps taken for the assessment

Submission date:	15/06/2015
Start of procedure:	26/07/2015
CHMP Rapporteur's preliminary assessment report circulated on:	25/08/2015
CHMP Rapporteur's updated assessment report circulated on:	14/09/2015
CHMP opinion:	24/09/2015

2. Assessment of the PAM EMEA-H-C-721-P46

Overall study design - Description



* Immunogenicity subset: subjects enrolled at study sites in Taiwan, Germany, Ho nduras, Panama and Colombia.
** Once HPV -013 (primary study) had been completed and unblinded, subjects f rom the Control group enrolled in the first follow -up study attended one further visit as their last study visit, i.e. depending on time of their enrolment, either Visit 7 (at Month 18) or Visit 8 (at Month 24).
† The first visit of this HPV -025 extension study will be scheduled approximately 12 months fo llowing the Month 48 visit of study 104918 (Ext HPV -013 Mth 48), i.e. at Month 60.
BS: Blood sample; Vacc.: Vaccination

The primary study, **HPV-013**, was designed as follows:

- A total of 2067 healthy females were enrolled and randomised (1:1) in two parallel groups:
- HPV-16/18 L1 VLP (20 μg HPV-16 and 20 μg HPV-18) vaccine formulated with AS04 (N = 1035),
- HAV Control vaccine (360 ELISA Unit [EL.U]/0.5 millilitre [mL] dose) (N = 1032).
- Immunogenicity follow-up was for seven months, safety follow-up was for 12 months.
- Double-blinding was maintained up to Month 7. Thereafter up to Month 12, study investigators and subjects remained blinded to the study/control vaccine administered.

The first follow-up study, **Ext HPV-013**, was designed as follows:

- A total of 1244 subjects who had received three doses of HPV vaccine in study HPV-013 and who were included in the immunogenicity subset at study sites in Taiwan, Germany, Honduras, Panama and Colombia were enrolled such that:
    - Up to the unblinding of study HPV-013, there were two parallel groups HPV-16/18 vaccine group (N = 625) and control group (N = 619);
    - After completion and unblinding of study HPV-013, the study was open-label and subjects in the HPV-16/18 vaccine group continued their participation until Month 48. Subjects in the control group attended one further visit as study completion visit, i.e. Visit 7 (Month 18) or Visit 8 (Month 24), depending on the time of their enrolment.
- Immunogenicity and safety follow-up was for 36 months (i.e. up to Month 48 after administration of the first vaccine dose).

In the current study, **HPV-025 EXT-013**, all subjects from the HPV-16/18 vaccine group in study HPV-013 who had received three doses of the HPV-16/18 vaccine, who were included in the immunogenicity subset and participated in study Ext HPV-013, were invited for an additional six years of follow-up. Subjects who did not participate at a particular persistence time point in study HPV-025 EXT-013
were still eligible to be included/continue participation in the study at later time points.

- Blinding: Open-label.
- Type of study: Extension of study HPV-013 and subsequent follow-up study (i.e. protocol numbers 104896 [Ext HPV-013 M18], 104902 [M24], 104904 [M36] and 104918 [M48]).
- Data collection: electronic Case Report Form (eCRF).
- Blood sampling: At each yearly visit, i.e. at Months 60, 72, 84, 96, 108 and 120.
- Safety monitoring during the entire study period: Serious adverse events (SAEs) were reported.
- Duration of the study: Approximately six years.
- Total duration: Approximately 10 years from administration of the first HPV-16/18 vaccine dose in HPV-013 study.
- Analysis: Interim analyses were performed on a yearly basis (i.e. at Months 60, 72, 84, 96 and 108). The final analysis was carried out on all data up to Month 120, i.e. up to 10 years after administration of the first HPV-16/18 vaccine dose in study HPV-013.

Subjects could be invited to participate in a booster vaccination study and/or parallel research studies to evaluate the HPV vaccine response. Such studies will be described in detail in separate study protocols and separate consents will be obtained.

Criteria for evaluations

Primary endpoint:
Immunogenicity
☐ Anti-HPV-16/18 antibody titres and seroconversion rates (ELISA).

Secondary endpoints:
Safety
☐ Occurrence of serious adverse events (SAEs) throughout the entire study period.
Immunogenicity
☐ Anti-HPV-16/18 antibody titres and seroconversion rates (ELISA) from efficacy studies (HPV-001/HPV-007/HPV-023).
☐ Anti-HPV-16/18 antibody titres (ELISA) elicited after natural infection (study HPV-008).

Statistical methods:

This study was conducted according to protocol amendment 1 (dated 02 December 2013) and the analysis was conducted according to the Statistical Analysis Plan with the following exceptions:

- The demographic parameter ‘region’ was not tabulated for each study cohort.
- The mean age (plus range and standard deviation [SD]) was not calculated per pre-vaccination status
- The distribution of subjects enrolled among the study sites was not tabulated.
- The administration of concomitant medication was not tabulated.
- The assay used to measure anti-HPV-16/-18 antibody concentrations was improved to increase the assay precision by changing the assay cut-off value from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18. This change in the assay was implemented for the testing of samples from Year 8 (Month 96) onwards.
- The primary analysis of safety was based on the HPV-025 Total Vaccinated cohort (TVC) instead of the Month 120 TVC. Additional analyses were based on the Month 120 TVC for the follow-up period from Month 0 to Month 120 and from Month 108 to Month 120.
- The protocol defined interval between Dose 1 and Visit 6 (Month 120) (3569 Days - 3691 Days) was considered for the analysis instead of an adapted interval.
- Analysis of pregnancies/pregnancy outcomes for data collected during the ten-year follow-up period was performed on the HPV-025 TVC.

Immunogenicity:
The primary analysis of immunogenicity was based on the Month 120 according-to-protocol (ATP) cohort for immunogenicity. A second analysis based on the Month 120 TVC was performed to complement the ATP analysis.
For all subjects, at the time of this final analysis at Month 120:

- Seropositivity rates with exact 95% confidence interval (CI) were calculated for anti-HPV-16 and anti-HPV-18 antibodies.
- Geometric mean titres (GMTs) (with 95% CI and range) were tabulated for anti-HPV-16 and
  anti-HPV-18 antibodies.
- The distribution of anti-HPV-16 and anti-HPV-18 antibody titres was displayed using reverse
  cumulative distribution curves (RCCs).
- A descriptive comparison with anti-HPV-16 and anti-HPV-18 serology results from efficacy studies (HPV-001/007) and anti-HPV-16 and anti-HPV-18 antibody titres after natural infection (study HPV-008) was performed.
- A descriptive comparison with anti-HPV-16 and anti-HPV-18 serology results at the end of the approximately 9.4-year follow-up in study HPV-001/007/023 was performed.

Safety:
The primary analysis of SAEs was based on the HPV-025 TVC. In addition, analyses on the Month 120 TVC were performed on data collected during the entire ten-year follow-up period (Month 0 to Month 120) and for events reported between Month 108 and Month 120.

- The proportion of subjects with at least one report of a SAE classified by the Medical Dictionary of Regulatory Activities (MedDRA), whenever available, was tabulated with exact 95% CI throughout the study period.
- SAEs were described in detail and were further evaluated for their clinical relevance and relationship to vaccination.
- The analysis of pregnancies/pregnancy outcomes was based on the HPV-025 TVC for data collected during the ten-year follow-up period.
- Withdrawal(s) due to adverse event(s)/SAE(s) were described in detail.

Study population (Month 120 Total vaccinated cohort) -	
Number of subjects	**HPV Group**
Planned, N	NA
Randomised, N (Total Vaccinated Cohort)	NA
Completed, Visit 6 (Month120)	495
Demographics	**HPV Group**
N	495
Females	495
Mean Age, months (SD)	22.0 (1.4)
Hispanic, n (%)	228 (46.1)
White/Caucasian, n (%)	163 (32.9)
HPV = HPV-16/18 VLP/AS04 Hi5 10-14, N = total number of subjects, n/% = number / percentage of subjects in a given category, SD = standard deviation.	

The investigator, or his/her designee, was instructed to collect pregnancy information on any subject who became pregnant since the last visit in the previous study and until Month 120 of the current study HPV-025 EXT 013. The investigator, or his/her designee, was to record pregnancy information on the Pregnancy Report Form and submit it to GSK Biologicals within 24 hours of learning of a subject's pregnancy. The subject was followed up to determine the outcome of the pregnancy. At the end of the pregnancy, whether it was full-term or premature, information on the status of the mother and child was forwarded to GSK Biologicals. Generally, the follow-up was no longer than six to eight weeks following the estimated delivery date.

While pregnancy itself was not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons was recorded as an AE or a SAE. A spontaneous abortion was always considered to be a SAE and had to be reported as such.

Immunogenicity results

Ten years after the administration of three doses of the HPV-16/18 vaccine at the age of 10-14 years (i.e. at Month 120), among subjects in the ATP cohort who were initially seronegative for the HPV type analysed at baseline, all subjects (i.e. 100% [95% CI: 99.1 - 100.0]) were still seropositive for both HPV-16 and HPV-18 antibodies.

In initially seronegative subjects, the GMT values at Month 120 were 1589.9 EL.U/mL [95% CI: 1459.8 - 1731.6] and 597.2 EL.U/mL [95% CI: 541.7 - 658.5] for HPV-16 and HPV-18, respectively. These values were 53.35-fold [95% CI: 47.38 - 60.07] and 26.31-fold [95% CI: 23.58 - 29.35] higher, respectively, than those elicited after natural infection in 15-25 year old subjects in study HPV-008.

The GMT values for HPV-16 and HPV-18 antibodies were 3.80-fold [95% CI: 3.11 - 4.64] and 2.46-fold [95% CI: 1.97 - 3.08] higher, respectively, than those measured at the end of the approximately 9.4 year follow-up from subjects vaccinated at the age of 15-25 years in the study HPV-001/007/023, wherein the plateau level of vaccine-induced antibodies was associated with protection against HPV-16 and HPV-18 infection and/or associated cytological and histopathological lesions.

Number and percentage of subjects with an anti-HPV 16.VLP AB.IGG titre equal to or above the cut-off and GMTs (Month 120 ATP Cohort for Immunogenicity)

					≥ cut-off				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV 16.VLP IGG	HPV	S-	PRE	393	0	0.0	0.0	0.9	4.0	4.0	4.0	<8.0	<8.0
			PII(M2)	393	391	99.5	98.2	99.9	4562.6	4188.1	4970.7	<8.0	46001.0
			PIII(M7)	393	393	100	99.1	100	20557.4	18948.5	22302.8	706.0	244471.0
			[M12-M16]	336	334	99.4	97.9	99.9	4657.8	4148.3	5230.0	<8.0	162392.0
			PIII(M18)	393	393	100	99.1	100	4014.7	3681.8	4377.6	299.0	67894.0
			PIII(M24)	392	392	100	99.1	100	3312.4	3043.2	3605.4	333.0	44630.0
			PIII(M36)	389	389	100	99.1	100	2775.0	2550.5	3019.3	267.0	46642.0
			PIII(M48)	385	385	100	99.0	100	2427.7	2231.5	2641.2	234.0	28259.0
			PIII(M60)	266	266	100	98.6	100	2413.6	2181.5	2670.5	244.0	30868.0
			PIII(M72)	381	381	100	99.0	100	2053.8	1886.5	2235.9	242.0	25920.0
			PIII(M84)	385	385	100	99.0	100	1850.0	1696.4	2017.6	115.0	23959.0
			PIII(M96)	385	385	100	99.0	100	1752.5	1611.3	1906.1	112.0	17113.0
			PIII(M108)	335	335	100	98.9	100	2013.1	1845.8	2195.6	197.0	18377.0
			PIII(M120)	393	393	100	99.1	100	1589.9	1459.8	1731.6	114.0	17033.0
		S+	PRE	23	23	100	85.2	100	16.3	11.2	23.7	8.0	141.0
			PII(M2)	23	23	100	85.2	100	6606.4	4805.3	9082.6	2565.0	26626.0
			PIII(M7)	23	23	100	85.2	100	26220.6	20006.5	34364.9	6662.0	67566.0
			[M12-M16]	19	19	100	82.4	100	5718.8	4116.5	7944.8	1016.0	22603.0
			PIII(M18)	23	23	100	85.2	100	4534.7	3406.1	6037.3	898.0	15320.0
			PIII(M24)	23	23	100	85.2	100	3948.9	3058.4	5098.8	864.0	11861.0
			PIII(M36)	22	22	100	84.6	100	3066.3	2431.5	3867.0	655.0	7730.0
			PIII(M48)	22	22	100	84.6	100	2824.5	2187.6	3646.7	554.0	7799.0
			PIII(M60)	18	18	100	81.5	100	2699.4	2057.8	3541.2	673.0	7345.0
			PIII(M72)	23	23	100	85.2	100	2287.3	1819.4	2875.5	592.0	5795.0
			PIII(M84)	21	21	100	83.9	100	2044.1	1588.3	2630.7	726.0	5149.0
			PIII(M96)	22	22	100	84.6	100	2076.6	1582.8	2724.5	492.0	7291.0
			PIII(M108)	17	17	100	80.5	100	2141.7	1596.6	2872.8	987.0	7775.0
			PIII(M120)	23	23	100	85.2	100	1950.1	1416.9	2683.8	709.0	19439.0
		Total	PRE	416	23	5.5	3.5	8.2	4.3	4.2	4.5	<8.0	141.0
			PII(M2)	416	414	99.5	98.3	99.9	4657.0	4286.4	5059.6	<8.0	46001.0
			PIII(M7)	416	416	100	99.1	100	20835.8	19264.8	22534.9	706.0	244471.0
			[M12-M16]	355	353	99.4	98.0	99.9	4709.3	4214.9	5261.6	<8.0	162392.0
			PIII(M18)	416	416	100	99.1	100	4041.8	3719.5	4392.0	299.0	67894.0
			PIII(M24)	415	415	100	99.1	100	3344.8	3083.9	3627.8	333.0	44630.0
			PIII(M36)	411	411	100	99.1	100	2789.9	2573.7	3024.3	267.0	46642.0
			PIII(M48)	407	407	100	99.1	100	2447.7	2257.7	2653.6	234.0	28259.0
			PIII(M60)	284	284	100	98.7	100	2430.8	2208.3	2675.7	244.0	30868.0
			PIII(M72)	404	404	100	99.1	100	2066.4	1905.5	2240.9	242.0	25920.0
			PIII(M84)	406	406	100	99.1	100	1859.6	1711.3	2020.7	115.0	23959.0
			PIII(M96)	407	407	100	99.1	100	1768.6	1631.5	1917.3	112.0	17113.0
			PIII(M108)	352	352	100	99.0	100	2019.1	1857.3	2195.1	197.0	18377.0
			PIII(M120)	416	416	100	99.1	100	1607.9	1480.8	1746.1	114.0	19439.0

cut-off :

- 8 ELU/mL at PRE, PII(M2), PIII(M7), [M12-M16], PIII(M18), PIII(M24), PIII(M36), PIII(M48), PIII(M72) and PIII(M84)
- 19 ELU/mL at PIII(M96), PIII(M108) and PIII(M120)
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre equal to or above specified value
- n/% = number/percentage of subjects with titre equal to or above 8 ELU/mL at PRE, PII(M2), PIII(M7), [M12- M16], PIII(M18), PIII(M24), PIII(M36), PIII(M48), PIII(M60), PIII(M72), PIII(M84)
- n/% = number/percentage of subjects with titre equal to or above 19 ELU/mL at PIII(M96), PIII(M108), PIII(M120)
PRE = Prevaccination
PII (M2) = Post Dose II (Month 2) - PIII (M7) = Post Dose III (Month 7) - [M12-M16] = Post Dose III (Month 12- Month 16)
PIII (M18) = Post Dose III (Month 18) - PIII (M24) = Post Dose III (Month 24)
PIII (M36) = Post Dose III (Month 36) - PIII (M48) = Post Dose III (Month 48)
PIII (M60) = Post Dose III (Month 60) - PIII (M72) = Post Dose III (Month 72)
PIII (M84) = Post Dose III (Month 84) - PIII (M96) = Post Dose III (Month 96)
PIII (M108) = Post Dose III (Month 108)
PIII (M120) = Post Dose III (Month 120)

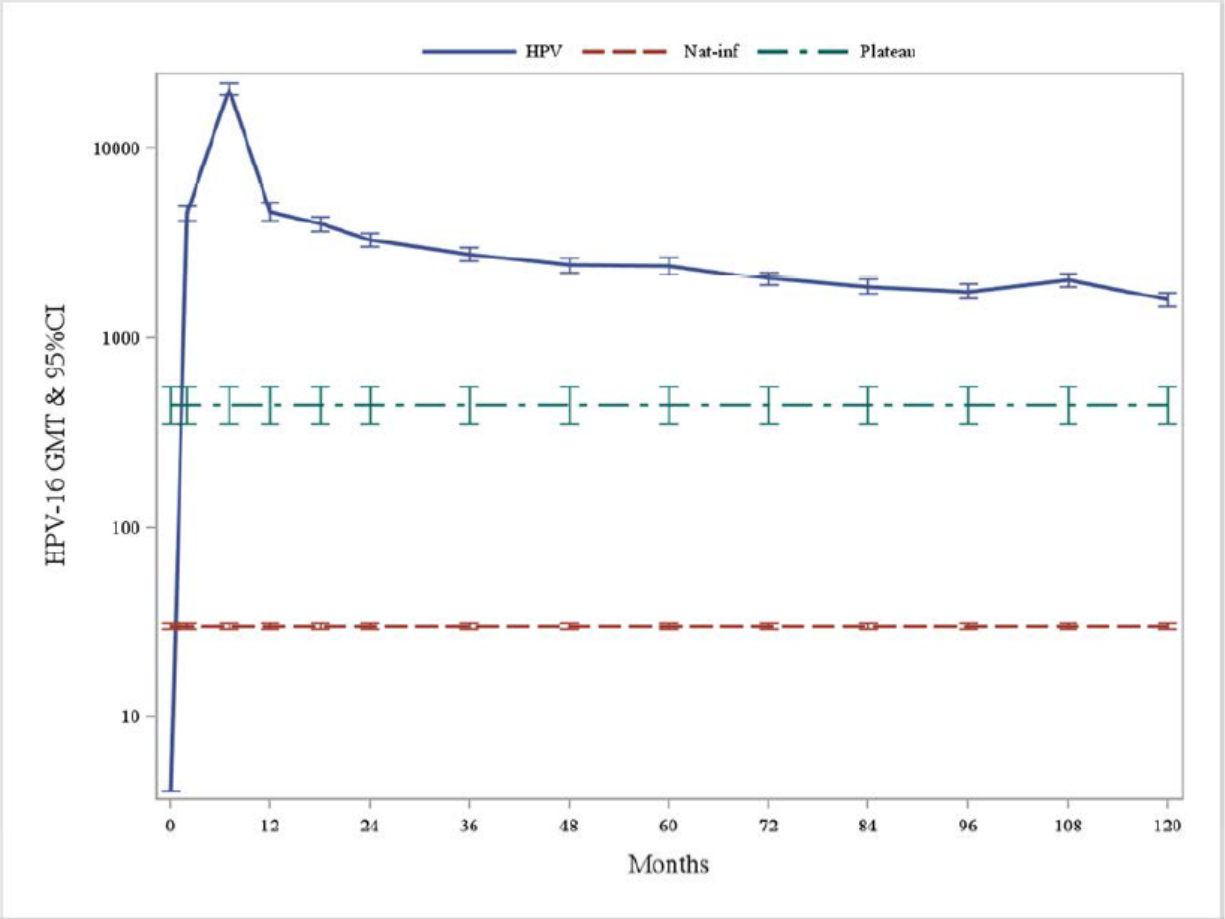
Number and percentage of subjects with an anti-HPV 18.VLP AB.IGG titre equal to or above the cut-off and GMTs (Month 120 ATP Cohort for Immunogenicity)

					≥ cut-off				GMT				
							95% CI			95% CI			
Antibody	Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV 18.VLP IGG	HPV	S-	PRE	395	0	0.0	0.0	0.9	3.5	3.5	3.5	<7.0	<7.0
			PII(M2)	395	394	99.7	98.6	100	3620.5	3338.4	3926.5	<7.0	47111.0
			PIII(M7)	395	395	100	99.1	100	8390.0	7693.0	9150.2	606.0	187560.0
			[M12-M16]	339	338	99.7	98.4	100	1811.6	1620.4	2025.4	<7.0	53993.0
			PIII(M18)	395	395	100	99.1	100	1554.1	1412.9	1709.5	38.0	57489.0
			PIII(M24)	394	394	100	99.1	100	1230.4	1121.3	1350.1	45.0	34318.0
			PIII(M36)	390	390	100	99.1	100	964.4	878.1	1059.2	57.0	27854.0
			PIII(M48)	387	387	100	99.1	100	858.4	781.5	942.8	53.0	27951.0
			PIII(M60)	269	269	100	98.6	100	791.4	705.5	887.8	38.0	18021.0
			PIII(M72)	383	383	100	99.0	100	768.5	700.3	843.4	40.0	15982.0
			PIII(M84)	387	387	100	99.1	100	624.4	567.7	686.6	18.0	12654.0
			PIII(M96)	387	387	100	99.1	100	690.7	628.4	759.2	24.0	11420.0
			PIII(M108)	333	333	100	98.9	100	762.2	692.0	839.4	43.0	10836.0
			PIII(M120)	395	395	100	99.1	100	597.2	541.7	658.5	22.0	10488.0
		S+	PRE	20	20	100	83.2	100	17.3	12.6	23.7	7.0	86.0
			PII(M2)	20	20	100	83.2	100	4132.3	2820.2	6054.9	1124.0	14514.0
			PIII(M7)	20	20	100	83.2	100	10082.1	6638.4	15312.3	2244.0	61522.0
			[M12-M16]	15	15	100	78.2	100	2591.8	1358.4	4945.0	362.0	19000.0
			PIII(M18)	20	20	100	83.2	100	1932.6	1168.5	3196.5	333.0	12858.0
			PIII(M24)	20	20	100	83.2	100	1608.2	990.7	2610.6	241.0	10257.0
			PIII(M36)	20	20	100	83.2	100	1295.4	795.0	2110.7	143.0	6202.0
			PIII(M48)	19	19	100	82.4	100	1154.6	685.9	1943.3	132.0	6750.0
			PIII(M60)	14	14	100	76.8	100	1012.8	511.1	2007.0	115.0	5009.0
			PIII(M72)	20	20	100	83.2	100	952.5	575.6	1576.4	114.0	4881.0
			PIII(M84)	18	18	100	81.5	100	833.6	463.0	1500.8	65.0	4845.0
			PIII(M96)	19	19	100	82.4	100	929.3	552.9	1561.8	83.0	3714.0
			PIII(M108)	18	18	100	81.5	100	988.0	637.3	1531.9	229.0	6108.0
			PIII(M120)	20	20	100	83.2	100	866.0	533.4	1406.1	103.0	3844.0
		Total	PRE	415	20	4.8	3.0	7.3	3.8	3.6	3.9	<7.0	86.0
			PII(M2)	415	414	99.8	98.7	100	3643.7	3366.7	3943.5	<7.0	47111.0
			PIII(M7)	415	415	100	99.1	100	8464.6	7777.6	9212.4	606.0	187560.0
			[M12-M16]	354	353	99.7	98.4	100	1839.3	1648.1	2052.8	<7.0	53993.0
			PIII(M18)	415	415	100	99.1	100	1570.5	1430.4	1724.4	38.0	57489.0
			PIII(M24)	414	414	100	99.1	100	1246.4	1137.9	1365.2	45.0	34318.0
			PIII(M36)	410	410	100	99.1	100	978.4	892.4	1072.7	57.0	27854.0
			PIII(M48)	406	406	100	99.1	100	870.4	793.6	954.5	53.0	27951.0
			PIII(M60)	283	283	100	98.7	100	801.1	715.3	897.3	38.0	18021.0
			PIII(M72)	403	403	100	99.1	100	776.8	709.0	851.1	40.0	15982.0
			PIII(M84)	405	405	100	99.1	100	632.4	575.7	694.8	18.0	12654.0
			PIII(M96)	406	406	100	99.1	100	700.4	638.2	768.6	24.0	11420.0
			PIII(M108)	351	351	100	99.0	100	772.4	703.1	848.5	43.0	10836.0
			PIII(M120)	415	415	100	99.1	100	608.0	552.5	669.1	22.0	10488.0

cut-off :
- 7 ELU/mL at PRE, PII(M2), PIII(M7), [M12-M16], PIII(M18), PIII(M24), PIII(M36), PIII(M48), PIII(M72) and PIII(M84)
- 18 ELU/mL at PIII(M96), PIII(M108) and PIII(M120)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre equal to or above specified value
- n/% = number/percentage of subjects with titre equal to or above 7 ELU/mL at PRE, PII(M2), PIII(M7), [M12-M16], PIII(M18), PIII(M24), PIII(M36), PIII(M48), PIII(M60), PIII(M72), PIII(M84)
- n/% = number/percentage of subjects with titre equal to or above 18 ELU/mL at PIII(M96), PIII(M108), PIII(M120)

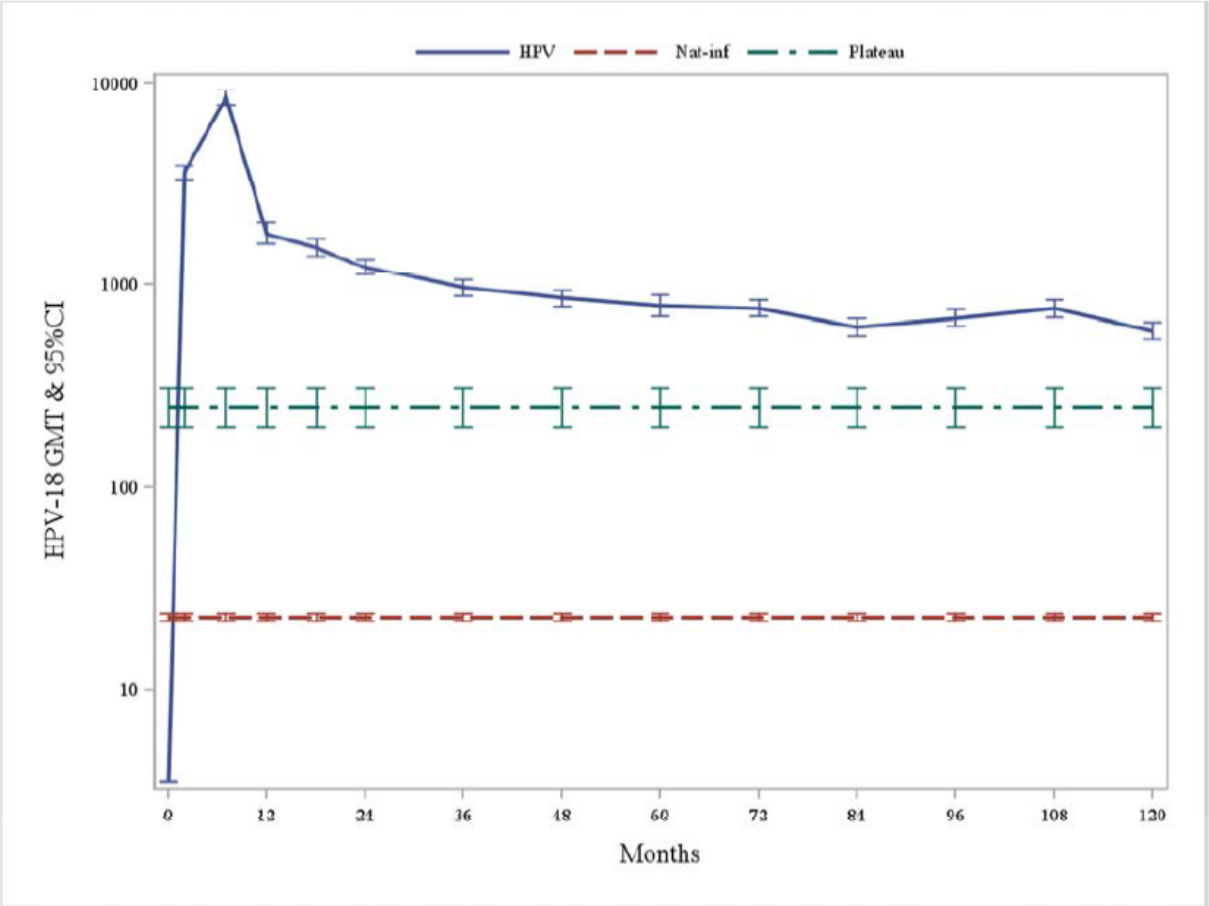
PRE = Prevaccination
PII (M2) = Post Dose II (Month 2)
PIII (M7) = Post Dose III (Month 7)
[M12-M16] = Post Dose III (Month 12- Month 16)
PIII (M18) = Post Dose III (Month 18)
PIII (M24) = Post Dose III (Month 24)
PIII (M36) = Post Dose III (Month 36)
PIII (M48) = Post Dose III (Month 48)
PIII (M60) = Post Dose III (Month 60)
PIII (M72) = Post Dose III (Month 72)
PIII (M84) = Post Dose III (Month 84)
PIII (M96) = Post Dose III (Month 96)
PIII (M108) = Post Dose III (Month 108)
PIII (M120) = Post Dose III (Month 120)

Kinetics of HPV-16 antibodies for subjects seronegative for HPV-16 at pre-vaccination (Month 120 ATP cohort for immunogenicity)



HPV = HPV-16/18 VLP/AS04 Hi5 10-14 (Study HPV-025)
Nat-inf = GMTs from subjects who were seropositive for anti-HPV-16 but negative for HPV-DNA at the baseline (study HPV-008)
Plateau (Month 107-113) = GMTs at time point Month 107-113 of the plateau phase in study HPV-001/007/023

Kinetics of HPV-18 antibodies for subjects seronegative for HPV-18 at pre-vaccination (Month 120 ATP cohort for immunogenicity)



HPV = HPV-16/18 VLP/AS04 Hi5 10-14 (Study HPV-025)
Nat-inf = GMTs from subjects who were seropositive for anti-HPV-18 but negative for HPV-DNA at the baseline (study HPV-008)
Plateau (Month 107-113) = GMTs at time point Month 107-113 of the plateau phase in study HPV-001/007/023

Safety results

During the ten-year follow-up period (i.e. Month 0 to Month 120), a total of 99 out of 557 subjects (17.8%) who received three doses of HPV-16/18 vaccine in the primary study HPV-013 (i.e. the HPV-025 TVC) reported 155 SAEs, none of which were considered by the investigator to be causally related to vaccination. None of the subjects experienced a fatal SAE.

Of the 161 pregnancies that occurred during the entire ten-year follow-up period, 134 pregnancies (83.2%) resulted in a live infant with no apparent congenital anomaly. Eleven pregnancies resulted in spontaneous abortion and five pregnancies were electively terminated. Five cases of congenital anomalies were reported. None of the spontaneous abortions and congenital anomalies were considered to be causally related to the study vaccine by the investigator.

☐ one live infant was born with developmental hip dysplasia and ventricular septal defect,
☐ one live infant was born with congenital mega-ureter, congenital hydronephrosis and talipes,
☐ one pregnancy was electively terminated due to suspected renal agenesis and fulminant intrauterine growth retardation of the foetus,
☐ one pregnancy underwent a spontaneous abortion due to skull malformation of the foetus,
☐ one pregnancy ended in a stillbirth due to congenital heart disease and pulmonary malformation of the foetus.

Number of subjects with pregnancies and their outcome during the entire study period (HPV-025 Total Vaccinated cohort)

		HPV N = 161	
Characteristics	**Categories**	**n**	**%**
Outcome	Live infant NO apparent congenital anomaly	134	83.2
	Live infant congenital anomaly	2	1.2
	Elective termination NO apparent congenital anomaly	4	2.5
	Elective termination congenital anomaly	1	0.6
	Spontaneous abortion NO apparent congenital anomaly	10	6.2
	Spontaneous abortion congenital anomaly	1	0.6
	Stillbirth congenital anomaly	1	0.6
	Ectopic pregnancy	2	1.2
	Lost to follow-up	3	1.9
	Pregnancy ongoing	3	1.9

HPV = HPV-16/18 VLP/AS04 Hi5 10-14
N = number of case id
n = number of case id in a given category
% = n / Number of case id with available results x 100

Conclusions

- The final report presents the results of the end of study analysis up to Month 120 (Year 10). No confirmatory analyses were performed on the primary or secondary objectives.
- Ten years after the administration of three doses of the HPV-16/18 vaccine at the age of 10-14 years, among subjects in the ATP cohort who were initially seronegative for the HPV type analysed at baseline, all of the subjects (100% [95% CI: 99.1 - 100.0]) were seropositive for HPV-16 and HPV-18 antibodies. The GMT values at Month 120 were 1589.9 EL.U/mL [95% CI: 1459.8 - 1731.6] for HPV-16 and 597.2 EL.U/mL [95% CI: 541.7 - 658.5] for HPV-18.
- The HPV-16 and HPV-18 antibody titres detected ten years after vaccination in young adolescents aged 10-14 years were 3.80-fold and 2.46-fold higher, respectively, than the titres observed at the end of the approximately 9.4-year follow-up during the plateau phase in female subjects vaccinated at the age of 15-25 years at the time of vaccination in the HPV-001/007/023 study, wherein the plateau level of vaccine-induced antibodies was associated with protection against HPV-16 and HPV-18 infection and/or associated cytological and histopathological lesions.
- The HPV-16 and HPV-18 antibody titres detected ten years after vaccination in young adolescents aged 10-14 years were 53.35-fold and 26.31-fold higher, respectively, than those elicited after natural infection in subjects aged 15-25 years who were seropositive but HPV-DNA negative for the HPV type analysed prior to the vaccination in study HPV-008.
- During the entire ten-year follow-up period, 99 subjects reported a total of 155 SAEs, none of which were considered by the investigator to be causally related to vaccination. None of the subjects experienced a fatal SAE.
- During the entire ten-year follow-up period, a total of 161 pregnancies were reported, 134 of which resulted in a live infant with no apparent congenital anomaly.

In conclusion, the results from this analysis suggest that the HPV-16/18 L1 VLP AS04 vaccine in female subjects aged 10-14 years induces sustained antibody responses several folds higher than those induced in subjects aged 15-25 years up to ten years after administration of the first dose, and
exhibits an acceptable safety profile.

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

3. CHMP overall conclusion

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

☐ PAM not fulfilled (not all commitments fulfilled) and further action required: