The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 111375 (HPV-025 EXT 013)

Title: Follow-up study to evaluate the long-term immunogenicity and safety of a HPV vaccine (580299) in healthy female subjects.

GSK580299 (HPV): GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine

Rationale: The aim of this extension study was to evaluate the long-term safety and immunogenicity of HPV vaccine up to 10 years after administration of the first dose in the primary study HPV-013.

This summary presents the results up to Month 72 time point. It will be updated when additional data become available. For results of the primary study, please refer to the CTRS of HPV-013 (580299/013).

Phase: III

Study Period: 07 May 2009 to:

- 19 Jan 2010 (Month 60)
- 27 Dec 2010 (Month 72)

Study Design: Multicentric, open study with 1 group.

Centers: The study was conducted in 25 centers, located in Taiwan, Germany and Honduras, until Month 60 and in 26 centers until Month 72 (2 centers entered the study and 1 center from Germany withdrew from the study after Month 60 time point).

Indication: Active immunization of females from the age of 10 years onwards for the prevention of persistent infection, premalignant cervical lesions and cervical cancer (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic human papillomaviruses.

Treatment: There was only one group in this study:

HPV Group: All subjects from the HPV Group in study HPV-013 who received 3 doses of HPV vaccine, who were
included in the immunogenicity subset and participated in the Ext HPV-013 study.

No vaccine was administered in this study.

Objectives:

To evaluate the long-term immunogenicity of HPV vaccine by enzyme-linked immunosorbent assay (ELISA).

Primary Outcome/Efficacy Variable:

Anti-HPV-16/18 antibody titers and seroconversion rates (SCR) (ELISA).*

Seroconversion was defined as the appearance of antibodies (i.e. titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.

*This summary presents results up to Month 72 only. It will be updated when additional data become available.

Secondary Outcome/Efficacy Variable(s):

- Anti-HPV-16/18 antibody titers and SCR (ELISA) from efficacy studies (HPV-001/HPV-007/HPV-023).*
- Anti-HPV-16/18 antibody titers (ELISA) elicited after natural infection (study HPV-008).*
- Occurrence of serious adverse events (SAEs) throughout the entire study period.*

*This summary presents results up to Month 72 only. It will be updated when additional data become available.

Statistical Methods:

Analyses were performed on the Total Vaccinated cohort and on the According-to-Protocol (ATP) cohort for immunogenicity.

- The Total Vaccinated cohort included all vaccinated subjects (i.e. subjects from the immunogenicity subset of HPV-013 who received three doses of HPV-16/18 vaccine in the primary HPV-013 study) for whom data were available at the considered time points.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e. subjects that were included in the ATP immunogenicity analysis in the primary study [HPV-013], meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom serology results were available at the considered sampling time points.

Analysis of Immunogenicity:

The analysis of immunogenicity was performed on the ATP cohort for immunogenicity.

For all subjects, at each time point that a blood sample was available, seropositivity rates (with exact 95% confidence interval [CI]), and geometric mean titers (GMTs) with 95% CI were calculated for anti-HPV-16 and anti-HPV-18. A descriptive comparison with anti-HPV-16 and anti-HPV-18 serology results from efficacy studies (HPV-001/007/023) and

HPV-16 and HPV-18 antibody titers after natural infection (study HPV-008) were performed. For GMT calculations,						
antibody titers below the assay cut-off were given an arbitrary value of	half the cut-off.					
Analysis of Safety:						
The analysis of safety was performed on the Total Vaccinated cohort.						
The proportion of subjects with at least one report of an SAE classified by the Medical Dictionary of Regulatory Activities						
(MedDRA) preferred term was tabulated throughout the extension study period up to Month 72.						
Study Population: Female subjects enrolled in the immunogenicity subset of study HPV-013, who had received 3 doses						
of the HPV 16/18 vaccine and participated in the long-term follow-up study Ext HPV-013. Written informed consent was						
obtained from the subject. For subjects below the legal age of consent,	written informed consent was obtained from a					
parent or legally acceptable representative and, in addition, the subject	signed a written informed assent form.					
Number of Subjects*	HPV Group					
Planned, N	625					
Entered, N (Month 60 Total Vaccinated cohort)	397					
Completed up to Month 60, n (%)	397 (100)					
Total Number Subjects Withdrawn, n (%)	0 (0.0)					
Withdrawn due to Adverse Events n (%)	0 (0.0)					
Withdrawn due to Lack of Efficacy n (%) Not applicable						
Withdrawn for other reasons n (%) 0 (0.0)						
Demographics HPV Group						
N (Month 60 Total Vaccinated cohort) 397						
Females: Males	397:0					
Mean Age, years (SD)	17.1 (1.40)					
White/Caucasian, n (%)	200 (50.4)					
Number of subjects	HPV Group					
Planned, N	625					
Entered, N (Month 72 Total Vaccinated cohort)	529					
Completed up to Month 72, n (%)	529 (100)					
Total Number Subjects Withdrawn, n (%)	0 (0.0)					
Withdrawn due to Adverse Events, n (%)	0 (0.0)					
Withdrawn due to Lack of Efficacy, n (%)	Not applicable					
Withdrawn for other reasons, n (%)	0 (0.0)					
Demographics	HPV Group					
N (Month 72 Total Vaccinated cohort)	529					
Females:Males	529:0					
Mean Age, years (SD)	18.0 (1.40)					
Hispanic, n (%)	224 (42.3)					
White/Caucasian 196 (37.1)						
*A subject who did not come for a specific visit was not withdrawn from the study and was still allowed to participate in the						

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subsequent follow-up phase(s) foreseen in the protocol. **Primary Efficacy Results:** Seropositivity rates and GMTs for anti-HPV-16 antibodies (ELISA) by pre-vaccination status (Month 60 ATP cohort for immunogenicity)

					≥ 8 E	L.U/mL		GMT		
						95% CI		95		6 CI
Antibody	Pre-vacc	Timing	N	n	%	LL	UL	value	LL	UL
	status									
Anti-HPV-	S-	PRE	353	0	0.0	0.0	1.0	4.0	4.0	4.0
16		PII(M2)	353	351	99.4	98.0	99.9	4611.3	4189.5	5075.5
		PIII(M7)	353	353	100	99.0	100	19309.7	17666.4	21105.9
		[M12-M16]	338	336	99.4	97.9	99.9	4561.4	4054.8	5131.3
		PIII(M18)	352	352	100	99.0	100	3993.0	3624.3	4399.1
		PIII(M24)	350	350	100	99.0	100	3239.8	2948.2	3560.2
		PIII(M36)	350	350	100	99.0	100	2689.4	2445.3	2957.9
		PIII(M48)	353	353	100	99.0	100	2348.6	2137.8	2580.3
		PIII(M60)	353	353	100	99.0	100	2242.2	2042.3	2461.7
	S+	PRE	23	23	100	85.2	100	15.5	11.3	21.3

		PII(M2)	23	23	100	85.2	100	6465.7	4703.9	8887.5
		PIII(M7)	23	23	100	85.2	100	27226.3	21118.0	35101.4
		[M12-M16]	23	23	100	85.2	100	5993.3	4273.8	8404.5
		PIII(M18)	23	23	100	85.2	100	5019.1	3512.1	7172.9
		PIII(M24)	23	23	100	85.2	100	4191.8	3050.1	5760.8
		PIII(M36)	23	23	100	85.2	100	3197.7	2346.8	4357.1
		PIII(M48)	23	23	100	85.2	100	2920.2	2077.5	4104.6
		PIII(M60)	23	23	100	85.2	100	2606.2	1898.3	3578.2
Total	PRE	376	23	6.1	3.9	9.0	4.3	4.2	4.5	
		PII(M2)	376	374	99.5	98.1	99.9	4707.6	4293.0	5162.3
		PIII(M7)	376	376	100	99.0	100	19719.8	18110.6	21472.1
		[M12-M16]	361	359	99.4	98.0	99.9	4641.4	4148.8	5192.6
		PIII(M18)	375	375	100	99.0	100	4049.4	3688.6	4445.4
		PIII(M24)	373	373	100	99.0	100	3291.6	3006.7	3603.6
		PIII(M36)	373	373	100	99.0	100	2718.3	2481.6	2977.5
		PIII(M48)	376	376	100	99.0	100	2380.1	2174.1	2605.7
		PIII(M60)	376	376	100	99.0	100	2262.9	2069.1	2475.0

S- = seronegative subjects (antibody titer < 8 EL.U/mL) prior to vaccination

S+ = seropositive subjects (antibody titer \ge 8 EL.U/mL) prior to vaccination

Seroconversion was defined as the appearance of antibodies (i.e. titer \ge 8 EL.U/mL) in the serum of subjects seronegative before vaccination.

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with pre-vaccination results available

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = Pre-vaccination

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)

Primary Efficacy Results: Seropositivity rates and GMTs for anti-HPV-16 antibodies (ELISA) by pre-vaccination status (Month 72 ATP cohort for immunogenicity)

					≥ 8	EL.U/mL		GMT		
						95% CI		95%		% CI
Antibody	Pre-vacc	Timing	N	n	%	LL	UL	value	LL	UL
	status									
Anti-HPV-	S-	PRE	475	0	0.0	0.0	0.8	4.0	4.0	4.0
16		PII(M2)	475	473	99.6	98.5	99.9	4640.6	4297.4	5011.2
		PIII(M7)	475	475	100	99.2	100	19776.7	18341.7	21324.0
		[M12-M16]	409	407	99.5	98.2	99.9	4460.2	4021.3	4947.1
		PIII(M18)	475	475	100	99.2	100	3823.7	3526.8	4145.6
		PIII(M24)	472	472	100	99.2	100	3148.5	2909.7	3406.9
		PIII(M36)	471	471	100	99.2	100	2602.6	2406.0	2815.2
		PIII(M48)	468	468	100	99.2	100	2284.9	2112.6	2471.2
		PIII(M60)	351	351	100	99.0	100	2244.1	2044.2	2463.6
		PIII(M72)	475	475	100	99.2	100	1962.0	1811.3	2125.3
	S+	PRE	27	27	100	87.2	100	15.7	11.4	21.5
		PII(M2)	27	27	100	87.2	100	6757.9	5116.9	8925.2
		PIII(M7)	27	27	100	87.2	100	24915.1	19405.4	31989.2
		[M12-M16]	23	23	100	85.2	100	5405.7	3894.5	7503.3
		PIII(M18)	27	27	100	87.2	100	4338.8	3217.2	5851.4

	PIII(M24)	27	27	100	87.2	100	3828.4	2904.9	5045.5
	PIII(M36)	25	25	100	86.3	100	2964.5	2248.4	3908.8
	PIII(M48)	25	25	100	86.3	100	2726.6	2015.0	3689.6
	PIII(M60)	21	21	100	83.9	100	2515.6	1785.0	3545.2
	PIII(M72)	27	27	100	87.2	100	2194.4	1674.8	2875.1
Total	PRE	502	27	5.4	3.6	7.7	4.3	4.2	4.4
	PII(M2)	502	500	99.6	98.6	100	4735.3	4395.8	5101.2
	PIII(M7)	502	502	100	99.3	100	20023.9	18623.3	21529.9
	[M12-M16]	432	430	99.5	98.3	99.9	4506.1	4079.4	4977.4
	PIII(M18)	502	502	100	99.3	100	3849.8	3561.0	4162.1
	PIII(M24)	499	499	100	99.3	100	3182.0	2949.1	3433.3
	PIII(M36)	496	496	100	99.3	100	2619.7	2428.7	2825.8
	PIII(M48)	493	493	100	99.3	100	2305.5	2137.1	2487.2
	PIII(M60)	372	372	100	99.0	100	2258.6	2064.6	2470.9
	PIII(M72)	502	502	100	99.3	100	1973.9	1827.9	2131.6

S- = seronegative subjects (antibody titer < 8 EL.U/mL) prior to vaccination

S+ = seropositive subjects (antibody titer ≥ 8 EL.U/mL) prior to vaccination

Seroconversion was defined as the appearance of antibodies (i.e. titer ≥ 8 EL.U/mL) in the serum of subjects seronegative before vaccination.

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with pre-vaccination results available

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = Pre-vaccination

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)

Primary Efficacy Results: Seropositivity rates and GMTs for anti-HPV-18 antibodies (ELISA) by pre-vaccination status (Month 60 ATP cohort for immunogenicity)

					≥7E	L.U/mL		GMT		
							95% CI		95% CI	
Antibody	Pre-vacc	Timing	N	n	%	LL	UL	value	LL	UL
	status									
Anti-HPV-	S-	PRE	358	0	0.0	0.0	1.0	3.5	3.5	3.5
18		PII(M2)	358	357	99.7	98.5	100	3838.9	3500.5	4210.0
		PIII(M7)	358	358	100	99.0	100	8128.3	7420.7	8903.5
		[M12-M16]	344	343	99.7	98.4	100	1811.5	1617.3	2029.1
		PIII(M18)	357	357	100	99.0	100	1569.1	1417.9	1736.4
		PIII(M24)	355	355	100	99.0	100	1263.7	1143.3	1396.6
		PIII(M36)	355	355	100	99.0	100	977.0	881.9	1082.3
		PIII(M48)	358	358	100	99.0	100	853.9	770.4	946.4
		PIII(M60)	358	358	100	99.0	100	761.9	687.1	844.9
	S+	PRE	18	18	100	81.5	100	20.8	15.0	28.9
		PII(M2)	18	18	100	81.5	100	4044.4	2717.6	6019.0
		PIII(M7)	18	18	100	81.5	100	10724.8	6996.0	16441.1
		[M12-M16]	17	17	100	80.5	100	2884.1	1555.2	5348.7
		PIII(M18)	18	18	100	81.5	100	2419.9	1364.1	4293.0
		PIII(M24)	18	18	100	81.5	100	1951.6	1107.8	3438.0
		PIII(M36)	18	18	100	81.5	100	1614.2	929.9	2801.9

	PIII(M48)	18	18	100	81.5	100	1352.6	759.4	2409.2
	PIII(M60)	18	18	100	81.5	100	1196.9	679.1	2109.4
Total	PRE	376	18	4.8	2.9	7.5	3.8	3.7	4.0
	PII(M2)	376	375	99.7	98.5	100	3848.5	3518.9	4208.9
	PIII(M7)	376	376	100	99.0	100	8236.9	7536.5	9002.4
	[M12-M16]	361	360	99.7	98.5	100	1851.6	1656.0	2070.4
	PIII(M18)	375	375	100	99.0	100	1602.1	1449.5	1770.7
	PIII(M24)	373	373	100	99.0	100	1290.4	1169.0	1424.5
	PIII(M36)	373	373	100	99.0	100	1001.0	904.8	1107.3
	PIII(M48)	376	376	100	99.0	100	872.9	788.6	966.2
	PIII(M60)	376	376	100	99.0	100	778.6	703.1	862.1

S- = seronegative subjects (antibody titer < 7 EL.U/mL) prior to vaccination

S+ = seropositive subjects (antibody titer \ge 7 EL.U/mL) prior to vaccination

Seroconversion was defined as the appearance of antibodies (i.e. titer \ge 7 EL.U/mL) in the serum of subjects seronegative before vaccination.

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with pre-vaccination results available

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = Pre-vaccination

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)

Primary Efficacy Results: Seropositivity rates and GMTs for anti-HPV-18 antibodies (ELISA) by pre-vaccination status (Month 72 ATP cohort for immunogenicity)

		v			≥7	EL.U/mL			GMT		
						95	95% CI		95% CI		
Antibody	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	
Anti-HPV-	S-	PRE	478	0	0.0	0.0	0.8	3.5	3.5	3.5	
18		PII(M2)	478	477	99.8	98.8	100	3731.5	3464.4	4019.1	
		PIII(M7)	478	478	100	99.2	100	8100.6	7489.5	8761.6	
		[M12-M16]	413	412	99.8	98.7	100	1744.3	1575.7	1930.8	
		PIII(M18)	478	478	100	99.2	100	1481.2	1357.1	1616.5	
		PIII(M24)	475	475	100	99.2	100	1184.3	1087.2	1290.1	
		PIII(M36)	472	472	100	99.2	100	929.3	852.7	1012.8	
		PIII(M48)	470	470	100	99.2	100	821.3	753.2	895.5	
		PIII(M60)	354	354	100	99.0	100	754.9	680.4	837.6	
		PIII(M72)	478	478	100	99.2	100	749.6	687.7	817.0	
	S+	PRE	24	24	100	85.8	100	18.3	13.8	24.3	
		PII(M2)	24	24	100	85.8	100	3873.1	2787.6	5381.3	
		PIII(M7)	24	24	100	85.8	100	10589.9	7227.1	15517.4	
		[M12-M16]	19	19	100	82.4	100	2885.8	1650.9	5044.3	
		PIII(M18)	24	24	100	85.8	100	2148.2	1360.7	3391.4	
		PIII(M24)	24	24	100	85.8	100	1782.6	1152.2	2757.9	
		PIII(M36)	24	24	100	85.8	100	1451.0	941.8	2235.4	
		PIII(M48)	23	23	100	85.2	100	1311.7	828.7	2076.3	
		PIII(M60)	18	18	100	81.5	100	1196.9	679.1	2109.4	
		PIII(M72)	24	24	100	85.8	100	1081.0	696.3	1678.3	
	Total	PRE	502	24	4.8	3.1	7.0	3.8	3.7	3.9	





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Nat-inf = GMTs from su	bjects who were seropositive for HPV-18 but cervical HPV-18 DNA neg	pative at the baseline (study
HPV-008)		
Plateau = GM Is at the p Safety results: Only da	plateau level in study HPV-001/007/023 (Month 45-50) ata on serious adverse events were collected during the study. See resi	Its below for serious
adverse events.		
Safety results: Numbe	r (%) of subjects with SAEs from Month 48 to Month 60 (Month 60 Tota	I Vaccinated cohort)
Serious adverse event	t, n (%) [n considered by the investigator to be related to study me	dication]
All SAES		HPV Group
All SAES		HPV Group N = 397
All SAEs Subjects with any SAE(s), n (%) [n assessed by investigator as related]	HPV Group N = 397 9 (2.3) [0]
Subjects with any SAE(Abortion spontaneous c	s), n (%) [n assessed by investigator as related] complete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous c Abortion spontaneous in	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous c Abortion spontaneous in Abscess	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous c Abortion spontaneous ir Abscess Appendicitis	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous c Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour	s), n (%) [n assessed by investigator as related] complete ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs	s), n (%) [n assessed by investigator as related] complete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs	s), n (%) [n assessed by investigator as related] complete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAE	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related]	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous c Abortion spontaneous ir Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAEI Skull malformation (in a	s), n (%) [n assessed by investigator as related] complete ncomplete (s), n (%) [n assessed by investigator as related] subject's offspring)	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous c Abortion spontaneous ir Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAE Skull malformation (in a Safety results: Numbe	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related] (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0] All Vaccinated cohort)
All SAEs Subjects with any SAE(Abortion spontaneous c Abortion spontaneous ir Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAEs Subjects with fatal SAEs Skull malformation (in a Safety results: Numbe Serious adverse event	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0] HV Group N = 397 1 (0.3) [0] 1 (0.3) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAE(Skull malformation (in a Safety results: Numbe Serious adverse event All SAEs	s), n (%) [n assessed by investigator as related] complete ncomplete (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0] HPV Group N = 520
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAE(Skull malformation (in a Safety results: Numbe Serious adverse event All SAEs	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related] (subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0] HPV Group N = 397 20 (3 8) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAEs Subjects with fatal SAEs Subjects with any SAE(Abortion spontaneous in	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me s), n (%) [n assessed by investigator as related] complete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0] HPV Group N = 529 20 (3.8) [0] 3 (0 6) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAE(Skull malformation (in a Safety results: Numbe Serious adverse event All SAEs Subjects with any SAE(Abortion spontaneous in Dengue fever	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me s), n (%) [n assessed by investigator as related] ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0] HPV Group N = 529 20 (3.8) [0] 3 (0.6) [0] 2 (0.4) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAEI Skull malformation (in a Safety results: Numbe Serious adverse event All SAEs Subjects with any SAE(Abortion spontaneous in Dengue fever Pharyngeal abscess	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me s), n (%) [n assessed by investigator as related] hcomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] HPV Group N = 397 1 (0.3) [0] 1 (0.3) [0] 1 (0.3) [0] HPV Group N = 529 20 (3.8) [0] 3 (0.6) [0] 2 (0.4) [0] 2 (0.4) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAEI Skull malformation (in a Safety results: Numbe Serious adverse event All SAEs Subjects with any SAE(Abortion spontaneous in Dengue fever Pharyngeal abscess Alcohol poisoning	s), n (%) [n assessed by investigator as related] complete (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me s), n (%) [n assessed by investigator as related] ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] 3 (0.6) [0] 2 (0.4) [0] 2 (0.4) [0] 1 (0.2) [0]
All SAEs Subjects with any SAE(Abortion spontaneous of Abortion spontaneous of Abortion spontaneous in Abscess Appendicitis Cystitis Duodenal ulcer Ovarian cyst Pyelonephritis Skull malformation Threatened labour Fatal SAEs Subjects with fatal SAE Skull malformation (in a Safety results: Numbe Serious adverse event All SAEs Subjects with any SAE(Abortion spontaneous in Dengue fever Pharyngeal abscess Alcohol poisoning Appendicitis	s), n (%) [n assessed by investigator as related] complete ncomplete (s), n (%) [n assessed by investigator as related] subject's offspring) r (%) of subjects with SAEs from Month 60 to Month 72 (Month 72 Tota t, n (%) [n considered by the investigator to be related to study me s), n (%) [n assessed by investigator as related] ncomplete	HPV Group N = 397 9 (2.3) [0] 1 (0.3) [0] 2 (0.3) [0] 3 (0.6) [0] 2 (0.4) [0] 2 (0.4) [0] 1 (0.2) [0] 1 (0.2) [0]

Breast abscess	1 (0.2) [0]
Burns third degree	1 (0.2) [0]
Chronic sinusitis	1 (0.2) [0]
Circulatory collapse	1 (0.2) [0]
Endometritis	1 (0.2) [0]
Multiple injuries	1 (0.2) [0]
Ovarian germ cell teratoma benign	1 (0.2) [0]
Pain	1 (0.2) [0]
Peritonitis	1 (0.2) [0]
Pre-eclampsia	1 (0.2) [0]
Suicide attempt	1 (0.2) [0]
Threatened labour	1 (0.2) [0]
Type 1 diabetes mellitus	1 (0.2) [0]
Fatal SAEs	HPV Group
	N = 529
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]

For SAEs reported during the primary study (up to Month 48) please refer to the CTRS of HPV-013 (580299/013) study. One subject death was reported between the Month 48 visit of the previous Ext HPV-013 study and the Month 60 visit of the current HPV-025 study (subject did not participate in study HPV-025). Four years after the third dose of HPV-16/18, a 15-year-old subject, with congenital heart anomaly, experienced aortic rupture during a heart operation. This SAE was assessed by the investigator as not related to the study vaccination.

Conclusion:

Five years after administration of the first dose of HPV vaccine (i.e. at Month 60), the GMT values for antibodies against HPV-16 and HPV-18 were 2262.9 and 778.6, respectively.

Six years after administration of the first dose of HPV vaccine (i.e. at Month 72), the GMT values for antibodies against HPV-16 and HPV-18 were 1973.9 and 762.8, respectively.

Between the last time point of HPV-013 study (Month 48) and Month 60, 9 (2.3%) subjects reported at least one SAE. One SAE was fatal (in a subject's offspring); all were assessed by the investigators as not related to study vaccination. Between the Month 60 and the Month 72, 20 (3.8%) subjects reported at least one SAE. None of the SAEs were fatal and none were assessed by the investigators as related to the study vaccination.

Publications:

Schwarz TF et al. Long-term immunogenicity and safety of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in adolescent girls: results from a 5 year follow-up. Abstract presented at the 29th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID). The Hague, The Netherlands, 7-11 June 2011.

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