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.: 109628 (HPV-024 BST 001)

Title: Safety and immunogenicity study of an additional dose of HPV vaccine (580299) in young, adult women in North America.

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

**Rationale:** The aim of the study was to assess the immunogenicity and safety of a 4<sup>th</sup> HPV dose in young adult women in North America who received 3 doses of HPV vaccine in study HPV-001 (580299/001) (approved schedule) and were followed-up during study HPV-007 (580299/007). The study was initiated after completion of study HPV-007.

Phase: II

Study Period: 29 November 2007 to 01 December 2009 (end of follow-up phase)

Study Design: Open, multicentric study with 2 treatment groups

Centers: 16 study centers in North America (3 in Canada and 13 in the USA)

**Indication:** Active immunization of girls and women from 10 years of age onwards for the prevention of persistent HPV infections and related clinical outcomes (cytological abnormalities and pre-cancerous lesions) caused by oncogenic HPV types 16 and 18.

**Treatment:** The study groups were as follows:

- HPV-4D Group received 1 dose (i.e. the 4<sup>th</sup> dose) of HPV vaccine on Day 0 (non-approved schedule). These
  subjects previously completed a 3-dose vaccination course (approved schedule) with the HPV vaccine in study
  HPV-001
- HPV-3D Group received 3 doses of the HPV vaccine according to a 0, 1, 6 month schedule (approved schedule). These subjects had received a placebo in study HPV-001.

HPV vaccine was injected intramuscularly in the non-dominant deltoid.

Visits 1, 2, 3, 4, 5, & 6 correspond to Day 0, 7, Month 1, 7, 12 & 18 in the schedule for the group receiving a 4th dose of HPV vaccine.

Visits 1, 2, 3, 4, 5, 6, & 7 correspond to Day 0, 7, Month 1, 6, 7, 12 & 18 in the schedule for the group receiving 3 dose of vaccine.

## **Objectives:**

 To compare the immunogenicity of a 4<sup>th</sup> dose of HPV vaccine versus the first administration of the HPV vaccine in terms of antibody response to the HPV-16 and HPV-18 antigens by enzyme-linked immunosorbent assay (ELISA) on Day 7 and at Month 1 (Day 30).

#### **Primary Outcome/Efficacy Variable:**

- Anti-HPV-16 and anti-HPV-18 seroconversion rates\* and antibody titers assessed by ELISA in all subjects at Day 7 and Month 1 (Day 30).
- \*. Seropositivity rates were calculated. A seropositive subject was a subject with antibody titers greater than or equal to the cut-off value.

# Secondary Outcome/Efficacy Variable(s):

Immunogenicity:

- Anti-HPV-16 and anti-HPV-18 seroconversion\* rates and antibody titers assessed by ELISA in all subjects at Month 7 and Month 18.
- Anti-HPV seroconversion\* rates and antibody titers assessed by ELISA to other oncogenic HPV types, including anti-HPV-31 and anti-HPV-45, in all subjects on Day 7, at Month 1 (Day 30), Month 7 and Month 18.
- T-cell-mediated immune responses specific to HPV types 16, 18 (frequency of cytokine-positive CD4 or CD8 T-lymphocytes) and other oncogenic HPV types including 31 and 45 (Day 0, Month 1 [Day 30], Month 7 and Month 18) in a subset of subjects.
- B-cell-mediated immune responses specific to HPV types 16, 18 (frequency of HPV-specific memory B-cells) and other oncogenic HPV types including 31 and 45 (Day 0, Month 1 [Day 30], Month 7 and Month 18) in a subset of subjects.
- Anti-HPV-16 and anti-HPV-18 conversion rates and antibody titers in cervico-vaginal secretion (CVS) samples\*\*
   on Day 0, at Month 1 (Day 30), Month 7 and Month 18 in a subset of subjects by ELISA or neutralization test.

## Safety:

- Occurrence and intensity of solicited local symptoms within 7 days (Days 0-6) of vaccination.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within 7 days (Days 0-6) of

- vaccination.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (Days 0-29) of vaccination.
- Occurrence of new onset chronic diseases (NOCDs, including new onset autoimmune diseases [NOADs]) and medically significant conditions during the entire study period (including follow-up).
- Occurrence of serious adverse events (SAEs) during the entire study period (including follow-up).
- Pregnancy and outcomes during the entire study period (including follow-up).
- \* Seropositivity rates were calculated...
- \*\*Conversion for CVS analyses was defined as the presence of antibodies (i.e. titer greater than or equal to the Limit of Quantification (LOQ)) in the CVS.

#### Statistical Methods:

The analyses were performed on the Total Vaccinated cohort and According-To-Protocol (ATP) cohort for immunogenicity.

- The Total Vaccinated cohort included all vaccinated subjects.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) with immunogenicity data available at the considered time points. The ATP cohort for immunogenicity included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

### Analysis of immunogenicity

The analysis was based on the ATP cohort for immunogenicity.

For each treatment group, at each time point with blood sample results available, seropositivity rates with exact 95% confidence interval (CI) and Geometric Mean Titers (GMTs) with 95% CI were calculated for antibodies against each antigen. The same parameters were calculated in a subset of subjects that provided CVS. These analyses were performed for CVS samples with < 200 erythrocytes/ $\mu$ L and also independently of quantity of erythrocytes/ $\mu$ L (except at Month 18). Also the cell-mediated immune (CMI) response (T-cell by intracellular cytokine staining [ICS]; B-cell by ELISPOT) was calculated in a subset of subjects.

## Analysis of safety

The analysis was based on the Total Vaccinated cohort.

The percentage of subjects with each individual solicited local and general symptom during the 7-Day (Day 0-6) solicited follow-up period was tabulated with exact 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The percentage of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and reported up to 30 days (days 0-29) after vaccination was tabulated. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. During the entire period (including follow-up), the percentage of subjects with at least one report of NOCD, NOAD and medically significant AE (MSAE) classified by MedDRA preferred terms was tabulated. Pregnancies and outcomes were described by group and the occurrence of SAEs was tabulated by MedDRA preferred terms during the entire period.

**Study Population:** Healthy young adult women from the North American cohort who participated in the primary study 580299/001 (HPV-001) and received all 3 doses of either vaccine or placebo, and completed the follow-up study 580299/007 (HPV-007). Subjects were to have a negative pregnancy urine test before vaccination and were to be of non-childbearing potential or, if of childbearing potential, abstinent or using adequate contraception for 30 days prior to vaccination and agreed to continue such precautions for 2 months after completion of the vaccination series. Written informed consent had to be obtained from each subject prior to study entry.

Number of subjects	HPV-4D Group	HPV-3D Group
Planned, N	75	75
Randomized, N (Total Vaccinated cohort)	65	50
Completed to Month 1 (Visit 3), n (%)	62 (95.4)	48 (96.0)
Completed to Month 7 (Visit 4), n (%)	61 (93.8)	Not applicable
Completed to Month 7 (Visit 5), n (%)	Not applicable	45 (90.0)
Completed to Month 18 (Visit 6), n (%)	61 (93.8)	Not applicable
Completed to Month 18 (Visit 7), n (%)	Not applicable	43 (86.0)
Total Number Subjects Withdrawn, n (%)	4 (6.2)	7 (14.0)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	4 (6.2)	7 (14.0)

Demographics	accinated cohort)				HPV-4	1D Group			HPV-3D Gr	oup		
	accinated cohort)					65			50	•		
Females:Males	,					65:0			50:0			
Mean Age, years	s (SD)				27.8	3 (2.82)		27.0 (2.89)				
White - Caucasi		ın heritage, n	(%)		46	(70.8)			36 (72.0)	)		
Primary Efficac	y Results: S	Seropositivity r	ates and G	MTs fo	or HPV-16	antibodie	s (ATP co	hort for imi	munogenicit	ty)		
Antibody: anti-l			≥8 E	L.U/mL	•		GMT	• /				
						95%	6 CI		95	% CI		
Study	Group	Timing	N	n	%	님	IJ	value	LL	UL		
HPV-024	HPV-4D	PRE-4D	59	59	100	93.9	100	720.7	523.8	991.7		
		PIV(D7)*	61	61	100	94.1	100	5894.9	4734.0	7340.7		
		PIV(M1)*	57	57	100	93.7	100	15410.7	12807.9	18542.4		
		PIV(M7)	55	55	100	93.5	100	5826.9	4742.4	7159.5		
		PIV (M18)	49	49	100	92.7	100	3936.6	3128.7	4953.1		
	HPV-3D	PRE	45	13	28.9	16.4	44.3	8.6	5.4	13.7		
		PI(D7)*	45	30	66.7	51.0	80.0	67.9	27.2	169.7		
		PI(M1)*	45	45	100	92.1	100	1231.1	709.6	2135.9		
		PIII(M7)	43	43	100	91.8	100	7166.5	5954.3	8625.5		
		PIII(M18)	40	40	100	91.2	100	1626.9	1252.4	2113.5		
HPV-001	HPV-001	PRE	46	4	8.7	2.4	20.8	4.4	4.0	4.9		
		PIII(M7)	45	45	100	92.1	100	6064.3	4444.0	8275.4		
		PIII(M12)	46	46	100	92.3	100	1932.0	1299.3	2873.0		
		PIII(M18)	44	44	100	92.0	100	1098.4	764.4	1578.3		
HPV-007		[M25-M32]	27	26	96.3	81.0	99.9	763.8	409.8	1423.9		
		[M33-M38]	17	17	100	80.5	100	464.1	239.8	898.2		
		[M39-M44]	25	25	100	86.3	100	683.5	420.1	1112.2		
		[M45-M50]	20	20	100	83.2	100	453.2	262.7	781.9		
		[M51-M56]	26	26	100	86.8	100	950.5	614.8	1469.5		
		[M57-M62]	21	21	100	83.9	100	461.0	255.9	830.5		
		[M63-M68]	25	25	100	86.3	100	732.3	448.1	1196.7		
		[M69-M74]	20	20	100	83.2	100	492.5	299.2	810.8		
		[M75-M76]	1	1	100	2.5	100	1313.0	-	-		

N = number of subjects with available results

n (%) = number (percentage) of subjects with concentration within the specified range

\*Primary results

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

PRE = Pre-vaccination in HPV-024 (HPV-3D group) or HPV-001 study

PRE-4D = Pre-fourth dose in HPV-024 study (HPV-4D group)

PI(D7) = Post Dose I (Day 7) in HPV-024 study (HPV-3D group)

PIV(D7) = Post Dose IV (Day 7) in HPV-024 study (HPV-4D group)

PI(M1) = Post Dose I (Month 1) in HPV-024 study (HPV-3D group)

PIV(M1) = Post Dose IV (Month 1) in HPV-024 study (HPV-4D group)

PIII(M7) = Post Dose III (Month 7) in HPV-024 study (HPV-3D group)

PIV(M7) = Post Dose IV (Month 7) in HPV-024 study (HPV-4D group)

PIII(M18) = Post Dose III (Month 18) in HPV-024 study (HPV-3D group)

PIV(M18) = Post Dose IV (Month 18) in HPV-024 study (HPV-4D group)

PIII(M7) = Post Dose III (Month 7) in HPV-001 study

PIII(M12) = Post Dose III (Month 12) in HPV-001 study

PIII(M18) = Post Dose III (Month 18) in HPV-001 study

[Mxx-Myy] = Post Dose III (xx<=Month<=yy) in HPV-007 study

Primary Efficacy Results: Seropositivity rates and GMTs for HPV-18 antibodies (ATP cohort for immunogenicity)

Antibody: anti-HPV-18					≥7 E	L.U/mL		GMT		
				95% CI				95% CI		
Study	Group	Timing	N	n	%	LL	UL	value	LL	UL
HPV-024	HPV-4D	PRE-4D	59	59	100	93.9	100	502.9	374.1	676.1

		PIV(D7)*	61	61	100	94.1	100	3916.2	3087.7	4967.0
		PIV(M1)*	57	57	100	93.7	100	8362.7	6930.4	10091.1
		PIV(M7)	55	55	100	93.5	100	2940.3	2385.0	3625.0
		PIV (M18)	49	49	100	92.7	100	1802.5	1407.9	2307.6
	HPV-3D	PRE	45	12	26.7	14.6	41.9	5.9	4.3	7.9
		PI(D7)*	45	26	57.8	42.2	72.3	20.7	10.2	42.2
		PI(M1)*	45	45	100	92.1	100	442.0	269.8	724.3
		PIII(M7)	43	43	100	91.8	100	3584.3	2913.9	4408.9
		PIII(M18)	40	40	100	91.2	100	520.1	382.9	706.4
HPV-001	HPV-001	PRE	45	2	4.4	0.5	15.1	3.6	3.5	3.8
		PIII(M7)	45	45	100	92.1	100	4923.8	3674.1	6598.7
		PIII(M12)	46	46	100	92.3	100	1583.7	1131.6	2216.3
		PIII(M18)	44	44	100	92.0	100	908.0	644.3	1279.7
HPV-007		[M25-M32]	27	26	96.3	81.0	99.9	660.4	353.7	1233.3
		[M33-M38]	17	17	100	80.5	100	492.3	280.8	863.1
		[M39-M44]	26	25	96.2	80.4	99.9	550.5	287.7	1053.5
		[M45-M50]	20	20	100	83.2	100	350.3	205.2	598.0
		[M51-M56]	26	26	100	86.8	100	648.2	417.2	1007.1
		[M57-M62]	21	21	100	83.9	100	430.0	259.4	712.8
		[M63-M68]	25	25	100	86.3	100	500.3	309.1	809.9
		[M69-M74]	20	20	100	83.2	100	413.9	254.3	673.9
		[M75-M76]	1	1	100	2.5	100	688.0	-	-

N = number of subjects with available results

n (%) = number (percentage) of subjects with concentration within the specified range

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

\* Primary results

PRE = Pre-vaccination in HPV-024 (HPV-3D group)/HPV-001 study

PRE-4D = Pre-fourth dose in HPV-024 study (HPV-4D group)

PI(D7) = Post Dose I (Day 7) in HPV-024 study (HPV-3D group)

PIV(D7) = Post Dose IV (Day 7) in HPV-024 study (HPV-4D group)

PI(M1) = Post Dose I (Month 1) in HPV-024 study (HPV-3D group)

PIV(M1) = Post Dose IV (Month 1) in HPV-024 study (HPV-4D group)

PIII(M7) = Post Dose III (Month 7) in HPV-024 study (HPV-3D group)

PIV(M7) = Post Dose IV (Month 7) in HPV-024 study (HPV-4D group)

PIII(M18) = Post Dose III (Month 18) in HPV-024 study (HPV-3D group)

Pili(M18) = Post Dose III (Month 18) III nPV-024 study (nPV-3D group)

PIV(M18) = Post Dose IV (Month 18) in HPV-024 study (HPV-4D group)

PIII(M7) = Post Dose III (Month 7) in HPV-001 study

PIII(M12) = Post Dose III (Month 12) in HPV-001 study

PIII(M18) = Post Dose III (Month 18) in HPV-001 study

[Mxx-Myy] = Post Dose III (xx<=Month<=yy) in HPV-007 study

Secondary Outcome Variables: Seropositivity rates and GMTs for HPV-31 and HPV-45 antibodies (ATP cohort for immunogenicity)

Antibody: and	ti-HPV-31				≥ 59	EL.U/mL			GMT	
				95% CI		95%		95% CI		
Study	Group	Timing	N	n	%	LL	UL	value	LL	UL
HPV-024	HPV-4D	PRE-4D	59	52	88.1	77.1	95.1	222.4	160.3	308.6
		PIV(D7)	61	61	100	94.1	100	2075.3	1635.4	2633.6
		PIV(M1)	58	58	100	93.8	100	3705.8	2902.4	4731.5
		PIV(M7)	55	55	100	93.5	100	1193.8	879.6	1620.2
		PIV (M18)	49	48	98.0	89.1	99.9	667.0	470.2	946.3
	HPV-3D	PRE	45	11	24.4	12.9	39.5	51.0	37.0	70.3
		PI(D7)	45	20	44.4	29.6	60.0	90.7	55.8	147.4
		PI(M1)	45	31	68.9	53.4	81.8	192.1	110.7	333.4
		PIII(M7)	43	43	100	91.8	100	878.3	641.2	1202.9
		PIII(M18)	40	35	87.5	73.2	95.8	225.4	147.9	343.6

HPV-001	HPV-001	PRE	22	2	9.1	1.1	29.2	33.5	27.6	40.8
		PIII(M7)	21	21	100	83.9	100	971.2	572.8	1646.6
		PIII(M12)	5	4	80.0	28.4	99.5	227.3	55.1	938.0
		PIII(M18)	21	17	81.0	58.1	94.6	158.5	95.1	264.2
HPV-007		[M25-M32]	14	10	71.4	41.9	91.6	147.1	68.7	315.2
		[M33-M38]	10	10	100	69.2	100	189.5	123.2	291.7
		[M39-M44]	14	9	64.3	35.1	87.2	175.7	77.9	396.5
		[M45-M50]	13	12	92.3	64.0	99.8	273.9	127.2	589.5
		[M51-M56]	14	11	78.6	49.2	95.3	164.9	82.8	328.3
		[M57-M62]	13	13	100	75.3	100	171.7	112.7	261.7
		[M63-M68]	13	8	61.5	31.6	86.1	117.6	54.7	252.6
		[M69-M74]	12	12	100	73.5	100	189.8	129.5	278.2
Antibody: an	iti-HPV-45				≥ 59	EL.U/mL			GMT	
						95%	√ CI	95% CI		
Study	Group	Timing	N	n	%	L	UL	value	LL	UL
HPV-024	HPV-4D	PRE	59	52	88.1	77.1	95.1	202.7	154.1	266.5
		PIV(D7)	61	61	100	94.1	100	2347.7	1896.9	2905.6
		PIV(M1)	58	58	100	93.8	100	4491.5	3655.6	5518.5
		PIV(M7)	55	55	100	93.5	100	1503.1	1149.7	1965.0
		PIV (M18)	49	49	100	92.7	100	890.2	663.6	1194.1
	HPV-3D	PRE	45	8	17.8	8.0	32.1	37.4	31.7	44.1
		PI(D7)	45	18	40.0	25.7	55.7	76.4	49.9	116.9
		PI(M1)	45	32	71.1	55.7	83.6	189.9	113.6	317.4
		PIII(M7)	43	43	100	91.8	100	981.0	778.6	1236.0
		PIII(M18)	40	35	87.5	73.2	95.8	185.1	129.5	264.5
HPV-001	HPV-001	PRE	22	1	4.5	0.1	22.8	30.7	28.2	33.5
		PIII(M7)	22	22	100	84.6	100	1295.3	843.7	1988.7
		PIII(M12)	6	6	100	54.1	100	232.5	109.2	495.4
		PIII(M18)	21	19	90.5	69.6	98.8	177.5	113.4	277.9
HPV-007		[M25-M32]	14	13	92.9	66.1	99.8	194.4	104.3	362.5
		[M33-M38]	10	10	100	69.2	100	225.9	122.9	415.3
		[M39-M44]	14	12	85.7	57.2	98.2	198.8	102.3	386.3
		[M45-M50]	13	13	100	75.3	100	345.0	153.8	774.0
		[M51-M56]	14	12	85.7	57.2	98.2	174.9	97.7	313.1
		[M57-M62]	13	12	92.3	64.0	99.8	173.7	101.2	298.2
		[M63-M68]	13	9	69.2	38.6	90.9	134.4	63.8	283.0
		[M69-M74]	12	11	91.7	61.5	99.8	204.7	104.7	400.2

N = number of subjects with available results

n (%) = number (percentage) of subjects with concentration within the specified range

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

PRE = Pre-vaccination in HPV-024 (HPV-3D group)/HPV-001 study

PRE-4D = Pre-fourth dose in HPV-024 study (HPV-4D group)

PI(D7) = Post Dose I (Day 7) in HPV-024 study (HPV-3D group)

PIV(D7) = Post Dose IV (Day 7) in HPV-024 study (HPV-4D group)

PI(M1) = Post Dose I (Month 1) in HPV-024 study (HPV-3D group)

PIV(M1) = Post Dose IV (Month 1) in HPV-024 study (HPV-4D group)

PIII(M7) = Post Dose III (Month 7) in HPV-024 study (HPV-3D group)

PIV(M7) = Post Dose IV (Month 7) in HPV-024 study (HPV-4D group)

PIII(M18) = Post Dose III (Month 18) in HPV-024 study (HPV-3D group)

PIV(M18) = Post Dose IV (Month 18) in HPV-024 study (HPV-4D group)

PIII(M7) = Post Dose III (Month 7) in HPV-001 study

PIII(M12) = Post Dose III (Month 12) in HPV-001 study

[Mxx-Myy] = Post Dose III (xx<=Month<=yy) in HPV-007 study

**Secondary Outcome Variables:** Proportion of subjects with HPV specific CD4 T-cells per million CD4 T-cells (Intracellular Cytokine staining) (ATP cohort for immunogenicity)

					Group = 34		D Group = 25
Test description	Stimulating Ag	Timing	Parameters or Categories	Value or n	%	Value or n	%
CD4.AII	HPV-16	PRE	N	33	-	25	-
Doubles			<500	3	11.1	23	100
			≥500	24	88.9	0	0.0
			Missing	6	-	2	-
		PIV/PI(M1)	N	34	-	24	-
		, ,	<500	0	0.0	18	78.3
			≥500	25	100	5	21.7
			Missing	9	-	1	-
		PIV/PIII(M7)	N	30	-	26	-
			<500	4	15.4	5	23.8
			≥500	22	84.6	16	76.2
			Missing	4	-	5	-
		PIV/PIII(M18)	N	27	-	21	-
			<500	1	4.2	7	35.0
			≥500	23	95.8	13	65.0
			Missing	3	-	1	-
	HPV-18	PRE	N	33	-	25	-
			<500	10	37.0	22	95.7
			≥500	17	63.0	1	4.3
			Missing	6	-	2	-
		PIV/PI(M1)	N	34	-	24	-
			<500	1	4.0	20	87.0
			≥500	24	96.0	3	13.0
			Missing	9	-	1	-
		PIV/PIII(M7)	N	30	-	26	-
			<500	5	19.2	8	38.1
			≥500	21	80.8	13	61.9
			Missing	4	-	5	-
		PIV/PIII(M18)	N	27	-	21	-
			<500	4	16.7	12	60.0
			≥500	20	83.3	8	40.0
			Missing	3	-	1	-
	HPV-31	PRE	N	33	-	25	-
			<500	7	25.9	22	95.7
			≥500	20	74.1	1	4.3
			Missing	6	-	2	-
		PIV/PI(M1)	N	34	-	24	-
			<500	1	4.0	20	87.0
			≥500	24	96.0	3	13.0
		DIV (DIV (2.4-)	Missing	9	-	1	-
		PIV/PIII(M7)	N	30	-	26	-
			<500	7	26.9	9	42.9
			≥500	19	73.1	12	57.1
		DIVIDIU(\$446)	Missing	4	-	5	-
		PIV/PIII(M18)	N	27	-	21	-
			<500	2	8.3	10	50.0
			≥500	22	91.7	10	50.0
	LIBY: :=		Missing	3	-	1	-
	HPV-45	PRE	N	33	-	25	-

	<500	11	42.3	22	95.7
	≥500	15	57.7	1	4.3
	Missing	7	-	2	-
PIV/PI(M1)	N	34	-	24	-
	<500	1	4.0	21	91.3
	≥500	24	96.0	2	8.7
	Missing	9	-	1	-
PIV/PIII(M7)	N	30	-	26	-
	<500	10	38.5	10	47.6
	≥500	16	61.5	11	52.4
	Missing	4	-	5	-
PIV/PIII(M18)	N	27	-	21	-
	<500	2	9.1	14	73.7
	≥500	20	90.9	5	26.3
	Missing	5	-	2	-

N = number of subjects

n = number of subject number in a given category

Value = value of the considered parameter

% = n / Number of subject number with available results x 100

All doubles = cells producing at least 2 different cytokines (CD40 Ligand, Interleukin-2, Tumour Necrosis Factor alpha, Interferon gamma)

PRE = pre-vaccination

PIV/PI(M1) = Post Dose IV (Month 1) for HPV-4D Group or Post Dose I (Month 1) for HPV-3D group PIV/PIII(M7) = Post Dose IV (Month 7) for HPV-4D Group or Post Dose III (Month 7) for HPV-3D Group PIV/PIII(M18) = Post Dose IV (Month 18) for HPV-4D Group or Post Dose III (Month 18) for HPV-3D Group

Secondary Outcome Variables: Proportion of subjects with HPV specific CD8 T-cells per million CD8 T-cells (Intracellular Cytokine staining) (ATP cohort for immunogenicity)

					Group 34	HPV-3D N =	Group : 25
Test description	Stimulating Ag	Timing	Parameters or Categories	Value or n	%	Value or n	%
CD8.All	HPV-16	PRE	N	33	_	25	_
Doubles	1 1.0		<200	27	100	23	100
			Missing	6	-	2	-
		PIV/PI(M1)	N	34	-	24	-
			<200	24	96.0	23	100
			≥200	1	4.0	0	0.0
			Missing	9	-	1	-
		PIV/PIII(M7)	N	30	-	26	-
		,	<200	26	100	19	90.5
			≥200	0	0.0	2	9.5
			Missing	4	-	5	-
		PIV/PIII(M18)	N	27	-	21	-
			<200	23	95.8	20	100
			≥200	1	4.2	0	0.0
			Missing	3	-	1	-
	HPV-18	PRE	N	33	-	25	-
			<200	27	100	23	100
			Missing	6	-	2	-
		PIV/PI(M1)	N	34	-	24	-
			<200	25	100	22	95.7
			≥200	0	0.0	1	4.3
			Missing	9	-	1	-
		PIV/PIII(M7)	N	30	-	26	-
			<200	26	100	19	95.0
			≥200	0	0.0	1	5.0

		Missing	4	_	6	_
	PIV/PIII(M18)	N	27	-	21	-
	,()	<200	23	95.8	20	100
		≥200	1	4.2	0	0.0
		Missing	3	•	1	-
HPV-31	PRE	N	33	-	25	-
		<200	27	100	23	100
		Missing	6	-	2	-
	PIV/PI(M1)	N	34	-	24	-
	, ,	<200	25	100	23	100
		Missing	9	-	1	-
	PIV/PIII(M7)	N	30	-	26	-
	, ,	<200	24	92.3	20	95.2
		≥200	2	7.7	1	4.8
		Missing	4	-	5	-
	PIV/PIII(M18)	N	27	-	21	-
	,	<200	23	95.8	20	100
		≥200	1	4.2	0	0.0
		Missing	3	•	1	
HPV-45	PRE	N	33	•	25	
		<200	26	100	23	100
		Missing	7	-	2	-
	PIV/PI(M1)	N	34	-	24	-
	, ,	<200	25	100	22	95.7
		≥200	0	0.0	1	4.3
		Missing	9	-	1	-
	PIV/PIII(M7)	N	30	-	26	-
	, ,	<200	24	92.3	21	100
		≥200	2	7.7	0	0.0
		Missing	4	-	5	-
	PIV/PIII(M18)	N	27	-	21	-
	, ,	<200	22	100	19	100
		Missing	5	-	2	-

N = number of subjects

n = number of subject number in a given category

Value = value of the considered parameter

% = n / Number of subject number with available results x 100

All doubles = cells producing at least 2 different cytokines (CD40 Ligand, Interleukin-2, Tumour Necrosis Factor alpha, Interferon gamma)

PRE = pre-vaccination

PIV/PI(M1) = Post Dose IV (Month 1) for HPV-4D Group or Post Dose I (Month 1) for HPV-3D group PIV/PIII(M7) = Post Dose IV (Month 7) for HPV-4D Group or Post Dose III (Month 7) for HPV-3D Group PIV/PIII(M18) = Post Dose IV (Month 18) for HPV-4D Group or Post Dose III (Month 18) for HPV-3D Group

**Secondary Outcome Variables**: Proportion of subjects with HPV specific B-cells per million cells by ELISPOT (ATP cohort for immunogenicity)

				O Group = 34	HPV-3D Group N = 25		
Stimulating Ag	Timing	Parameters or Categories	n	%	n	%	
HPV-16	PRE	N	33	-	25	-	
		= 0	7	25.9	23	95.8	
		>0	20	74.1	1	4.2	
		Missing	6	-	1	-	
	PIV/PI(M1)	N	34	-	24	-	
		= 0	0	0.0	1	4.5	
		>0	27	100	21	95.5	

		I see .		I	1 -	1
	B11 (1811) (2.5-)	Missing	7	-	2	-
	PIV/PIII(M7)	N	30	-	26	-
		= 0	4	13.3	1	4.8
		>0	26	86.7	20	95.2
		Missing	0	-	5	-
	PIV/PIII(M18)	N	27	-	21	-
		= 0	7	29.2	6	35.3
		>0	17	70.8	11	64.7
		Missing	3	-	4	-
HPV-18	PRE	N	33	-	25	-
		= 0	6	22.2	21	87.5
		>0	21	77.8	3	12.5
		Missing	6	-	1	-
	PIV/PI(M1)	N	34	-	24	-
		= 0	0	0.0	4	18.2
		>0	27	100	18	81.8
		Missing	7	-	2	-
	PIV/PIII(M7)	N	30	-	26	-
	, ,	= 0	4	13.3	1	4.8
		>0	26	86.7	20	95.2
		Missing	0	-	5	-
	PIV/PIII(M18)	N	27	-	21	-
	1 11/1()	= 0	6	25.0	2	11.8
		>0	18	75.0	15	88.2
		Missing	3	-	4	-
HPV-31	PRE	N	33	_	25	-
		= 0	14	51.9	22	91.7
		>0	13	48.1	2	8.3
		Missing	6	-	1	-
	PIV/PI(M1)	N	34	-	24	-
	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	= 0	1	3.7	15	68.2
		>0	26	96.3	7	31.8
		Missing	7		2	
	PIV/PIII(M7)	N	30	-	26	-
	FIV/FIII(WI/)	= 0	9	30.0	6	28.6
		>0 Missing	21	70.0	15	71.4
	DIV/DIII/M40	Missing	0	-	5	
	PIV/PIII(M18)	N	27	- 54.0	21	- 04.7
		= 0	13	54.2	11	64.7
		>0	11	45.8	6	35.3
110)/ 45	DDE	Missing	3	-	4	-
HPV-45	PRE	N	33	-	25	-
		= 0	14	51.9	24	100
		>0	13	48.1	0	0.0
	Bu (B)	Missing	6	-	1	-
	PIV/PI(M1)	N	34	-	24	-
		= 0	1	3.7	12	54.5
		>0	26	96.3	10	45.5
		Missing	7	-	2	-
	PIV/PIII(M7)	N	30	-	26	-
		= 0	12	40.0	10	47.6
		>0	18	60.0	11	52.4
		Missing	0	-	5	-
	PIV/PIII(M18)	N	27	-	21	-

	= 0	10	41.7	11	64.7
	>0	14	58.3	6	35.3
	Missing	3	-	4	-

N = number of subjects

n = number of subject number in a given category

% = n / Number of subject number with available results x 100

PRE = pre-vaccination

PIV/PI(M1) = Post Dose IV (Month 1) for HPV-4D Group or Post Dose I (Month 1) for HPV-3D group PIV/PIII(M7) = Post Dose IV (Month 7) for HPV-4D Group or Post Dose III (Month 7) for HPV-3D Group PIV/PIII(M18) = Post Dose IV (Month 18) for HPV-4D Group or Post Dose III (Month 18) for HPV-3D Group

**Secondary Outcome Variables**: Seropositivity rates and GMTs for HPV-16 & HPV-18 secretion antibodies (ATP cohort for immunogenicity)

				≥LOQ			GMT			
						95%	6 CI		95	5% CI
Antibody	Group	Timing	N	n	%	LL	UL	value	L	UL
< 200 eryt	hrocytes/μL									
HPV	HPV 4D	PRE-4D	12	8	66.7	34.9	90.1	323.8	84.0	1247.3
16.VLP		PIV(M1)	13	13	100	75.3	100	562.1	312.8	1010.3
IgG		PIV(M7)	12	12	100	73.5	100	220.5	104.7	464.1
		PIV(M18)	15	15	100	78.2	100	110.9	46.2	266.0
	HPV 3D	PRE	10	2	20.0	2.5	55.6	147.0	93.3	231.6
		PI(M1)	11	5	45.5	16.7	76.6	331.2	100.3	1093.6
		PIII(M7)	11	11	100	71.5	100	299.2	153.4	583.3
		PIII(M18)	17	14	82.4	56.6	96.2	52.8	34.3	81.4
HPV	HPV 4D	PRE-4D	12	9	75.0	42.8	94.5	177.1	43.6	719.0
18.VLP		PIV(M1)	13	13	100	75.3	100	375.1	257.8	545.8
IgG		PIV(M7)	12	12	100	73.5	100	111.5	57.1	217.7
		PIV(M18)	15	13	86.7	59.5	98.3	73.6	31.2	173.4
	HPV 3D	PRE	10	1	10.0	0.3	44.5	58.6	•	•
		PI(M1)	11	6	54.5	23.4	83.3	54.0	10.1	288.5
		PIII(M7)	11	11	100	71.5	100	178.0	88.0	359.9
		PIII(M18)	17	13	76.5	50.1	93.2	29.6	16.0	54.8
Regardles	s of quantity of	of erythrocytes	/μL*							
HPV	HPV 4D	PRE-4D	31	25	80.6	62.5	92.5	68.9	35.1	135.1
16.VLP		PIV(M1)	30	30	100	88.4	100	743.6	450.5	1227.3
IgG		PI(M7)	32	32	100	89.1	100	411.3	255.8	661.5
	HPV 3D	PRE	25	4	16.0	4.5	36.1	62.7	11.4	345.9
		PI(M1)	24	17	70.8	48.9	87.4	121.6	55.4	267.1
		PIII(M7)	22	22	100	84.6	100	274.5	165.9	454.1
HPV	HPV 4D	PRE-4D	31	24	77.4	58.9	90.4	57.5	29.8	110.8
18.VLP		PIV(M1)	30	29	96.7	82.8	99.9	507.2	359.3	716.0
lgG		PI(M7)	32	32	100	89.1	100	176.5	111.6	278.9
	HPV 3D	PRE	25	1	4.0	0.1	20.4	58.6	-	-
		PI(M1)	24	15	62.5	40.6	81.2	63.8	23.4	174.1
NI sassanala as		PIII(M7)	22	22	100	84.6	100	162.6	99.9	264.8

N = number of subjects with available results

n (%) = number (percentage) of subjects with titers within the specified range

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

LOQ= Limit of Quantification

PRE = Pre-vaccination in HPV-3D group

PRE-4D = Pre-fourth vaccination in HPV-4D group

PI(M1) = Post Dose I (Month 1) in HPV-3D group

PIV(M1) = Post Dose IV (Month 1) in HPV-4D group

PIII(M7) = Post Dose III (Month 7) in HPV-024 study (HPV-3D group)

PIV(M7) = Post Dose IV (Month 7) in HPV-024 study (HPV-4D group)

PIII(M18) = Post Dose III (Month 18) in HPV-024 study (HPV-3D group)

PIV(M18) = Post Dose IV (Month 18) in HPV-024 study (HPV-4D group)

\*This analysis was not performed for Month 18.

**Secondary Outcome Variables:** Occurrence and intensity of solicited local symptoms within 7 days (Days 0-6) of vaccination (Total Vaccinated cohort).

,	,		HPV-4D Group		HPV-3D Group						
					95	% CI				95	% CI
Symptom	Intensity	N	n	%	LL	UL	N	n	%	LL	UL
-			Dos	se 1							
Pain	Any	64	61	95.3	86.9	99.0	48	43	89.6	77.3	96.5
	Grade 3	64	13	20.3	11.3	32.2	48	10	20.8	10.5	35.0
Redness	Any	64	24	37.5	25.7	50.5	48	9	18.8	8.9	32.6
	>50 mm	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
Swelling	Any	64	22	34.4	22.9	47.3	48	8	16.7	7.5	30.2
	>50 mm	64	1	1.6	0.0	8.4	48	0	0.0	0.0	7.4
			Dos	se 2							
Pain	Any						43	29	67.4	51.5	80.9
	Grade 3						43	3	7.0	1.5	19.1
Redness (mm)	Any							7	16.3	6.8	30.7
	>50 mm						43	0	0.0	0.0	8.2
Swelling (mm)	Any						43	5	11.6	3.9	25.1
	>50 mm						43	0	0.0	0.0	8.2
			Dos	se 3							
Pain	Any						45	33	73.3	58.1	85.4
	Grade 3						45	4	8.9	2.5	21.2
Redness	Any						45	7	15.6	6.5	29.5
	>50 mm						45	0	0.0	0.0	7.9
Swelling	Any						45	7	15.6	6.5	29.5
	>50 mm						45	0	0.0	0.0	7.9
			Across	Doses							
Pain	Any	64	61	95.3	86.9	99.0	48	45	93.8	82.8	98.7
	Grade 3	64	13	20.3	11.3	32.2	48	15	31.3	18.7	46.3
Redness	Any	64	24	37.5	25.7	50.5	48	18	37.5	24.0	52.6
	>50 mm	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
Swelling	Any	64	22	34.4	22.9	47.3	48	16	33.3	20.4	48.4
	>50 mm	64	1	1.6	0.0	8.4	48	0	0.0	0.0	7.4

N= number of subjects with at least one documented dose

n (%)= number (percentage) of subjects reporting at least once the symptom

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Any= occurrence of any local symptom regardless of intensity grade

Grade 3 pain= pain that prevented normal activity

**Secondary Outcome Variables:** Occurrence, intensity and relationship to vaccination of solicited general symptoms within 7 days (Days 0-6) of vaccination (Total Vaccinated cohort).

			HPV-4D Group				HPV-3D Group				
					95 °	% CI				95 °	% CI
Symptom	Intensity/ Relationship	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Arthralgia	Any	64	10	15.6	7.8	26.9	48	4	8.3	2.3	20.0
	Grade 3	64	2	3.1	0.4	10.8	48	1	2.1	0.1	11.1
	Related	64	10	15.6	7.8	26.9	48	4	8.3	2.3	20.0
Fatigue	Any	64	33	51.6	38.7	64.2	48	26	54.2	39.2	68.6
	Grade 3	64	5	7.8	2.6	17.3	48	1	2.1	0.1	11.1
	Related	64	30	46.9	34.3	59.8	48	22	45.8	31.4	60.8

Fever/(Axillary)	≥ 37.5	64	4	6.3	1.7	15.2	48	1	2.1	0.1	11.1
(°C)	>39.0	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
( 0)	Related	64	3	4.7	1.0	13.1	48	0	0.0	0.0	7.4
Gastrointestinal	Any	64	16	25.0	15.0	37.4	48	14	29.2	17.0	44.1
symptoms	Grade 3	64	1	1.6	0.0	8.4	48	0	0.0	0.0	7.4
Symptomo	Related	64	11	17.2	8.9	28.7	48	12	25.0	13.6	39.6
Headache	Any	64	32	50.0	37.2	62.8	48	24	50.0	35.2	64.8
ricadacric	Grade 3	64	4	6.3	1.7	15.2	48	2	4.2	0.5	14.3
	Related	64	23	35.9	24.3	48.9	48	20	41.7	27.6	56.8
Myalgia	Any	64	30	46.9	34.3	59.8	48	19	39.6	25.8	54.7
wyaigia	Grade 3	64	3	4.7	1.0	13.1	48	0	0.0	0.0	7.4
	Related	64	27	42.2	29.9	55.2	48	17	35.4	22.2	50.5
Rash	Any	64	0	0.0	0.0	5.6	48	1	2.1	0.1	11.1
ridori	Grade 3	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
	Related	64	0	0.0	0.0	5.6	48	1	2.1	0.1	11.1
Urticaria	Any	64	2	3.1	0.4	10.8	48	2	4.2	0.5	14.3
Ortioana	Grade 3	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
	Related	64	1	1.6	0.0	8.4	48	2	4.2	0.5	14.3
	Tiolatou	04	Dos		0.0	0.4	70		7.2	0.0	17.0
Arthralgia	Any						44	1	2.3	0.1	12.0
	Grade 3						44	0	0.0	0.0	8.0
	Related						44	1	2.3	0.1	12.0
Fatigue	Any						44	12	27.3	15.0	42.8
· angue	Grade 3						44	0	0.0	0.0	8.0
	Related						44	12	27.3	15.0	42.8
Fever/(Axillary)	≥ 37.5						44	1	2.3	0.1	12.0
(°C)	>39.0						44	0	0.0	0.0	8.0
( - /	Related						44	1	2.3	0.1	12.0
Gastrointestinal	Any						44	6	13.6	5.2	27.4
symptoms	Grade 3						44	0	0.0	0.0	8.0
•	Related						44	5	11.4	3.8	24.6
Headache	Any						44	13	29.5	16.8	45.2
	Grade 3						44	0	0.0	0.0	8.0
	Related						44	12	27.3	15.0	42.8
Myalgia	Any						44	9	20.5	9.8	35.3
, 0	Grade 3						44	0	0.0	0.0	8.0
	Related						44	9	20.5	9.8	35.3
Rash	Any						44	1	2.3	0.1	12.0
	Grade 3						44	0	0.0	0.0	8.0
	Related						44	0	0.0	0.0	8.0
Urticaria	Any						44	1	2.3	0.1	12.0
	Grade 3						44	0	0.0	0.0	8.0
	Related						44	1	2.3	0.1	12.0
		l .	Dos	e 3				1	1		
Arthralgia	Any						44	2	4.5	0.6	15.5
	Grade 3						44	0	0.0	0.0	8.0
	Related						44	2	4.5	0.6	15.5
Fatigue	Any						44	14	31.8	18.6	47.6
	Grade 3						44	1	2.3	0.1	12.0
	Related						44	13	29.5	16.8	45.2
Fever/(Axillary)	≥ 37.5						44	3	6.8	1.4	18.7
	>39.0						44	0	0.0	0.0	8.0
(°C)	>39.0										
	Related						44	2	4.5	0.6	15.5

symptoms	Grade 3						44	0	0.0	0.0	8.0
, , , , ,	Related	Ī					44	3	6.8	1.4	18.7
Headache	Any	1					44	15	34.1	20.5	49.9
	Grade 3	1					44	2	4.5	0.6	15.5
	Related						44	14	31.8	18.6	47.6
Myalgia	Any						44	9	20.5	9.8	35.3
, 3	Grade 3	1					44	0	0.0	0.0	8.0
	Related	1					44	9	20.5	9.8	35.3
Rash	Any	1					44	0	0.0	0.0	8.0
	Grade 3						44	0	0.0	0.0	8.0
	Related	1					44	0	0.0	0.0	8.0
Urticaria	Any	1					44	0	0.0	0.0	8.0
	Grade 3	1					44	0	0.0	0.0	8.0
	Related	1					44	0	0.0	0.0	8.0
Across Doses											
Arthralgia	Any	64	10	15.6	7.8	26.9	48	4	8.3	2.3	20.0
	Grade 3	64	2	3.1	0.4	10.8	48	1	2.1	0.1	11.1
	Related	64	10	15.6	7.8	26.9	48	4	8.3	2.3	20.0
Fatigue	Any	64	33	51.6	38.7	64.2	48	33	68.8	53.7	81.3
	Grade 3	64	5	7.8	2.6	17.3	48	2	4.2	0.5	14.3
	Related	64	30	46.9	34.3	59.8	48	30	62.5	47.4	76.0
Fever/(Axillary)	≥ 37.5	64	4	6.3	1.7	15.2	48	5	10.4	3.5	22.7
(°C)	>39.0	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
	Related	64	3	4.7	1.0	13.1	48	3	6.3	1.3	17.2
Gastrointestinal	Any	64	16	25.0	15.0	37.4	48	16	33.3	20.4	48.4
symptoms	Grade 3	64	1	1.6	0.0	8.4	48	0	0.0	0.0	7.4
	Related	64	11	17.2	8.9	28.7	48	14	29.2	17.0	44.1
Headache	Any	64	32	50.0	37.2	62.8	48	31	64.6	49.5	77.8
	Grade 3	64	4	6.3	1.7	15.2	48	4	8.3	2.3	20.0
	Related	64	23	35.9	24.3	48.9	48	29	60.4	45.3	74.2
Myalgia	Any	64	30	46.9	34.3	59.8	48	21	43.8	29.5	58.8
, ,	Grade 3	64	3	4.7	1.0	13.1	48	0	0.0	0.0	7.4
	Related	64	27	42.2	29.9	55.2	48	19	39.6	25.8	54.7
Rash	Any	64	0	0.0	0.0	5.6	48	2	4.2	0.5	14.3
	Grade 3	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
	Related	64	0	0.0	0.0	5.6	48	1	2.1	0.1	11.1
Urticaria	Any	64	2	3.1	0.4	10.8	48	2	4.2	0.5	14.3
	Grade 3	64	0	0.0	0.0	5.6	48	0	0.0	0.0	7.4
	Related	64	1	1.6	0.0	8.4	48	2	4.2	0.5	14.3

N= number of subjects with one documented dose at least

n (%)= number (percentage) of subjects reporting the symptom at least once 95%Cl= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Any= occurrence of any general symptom regardless of intensity grade Grade 3 urticaria: urticaria distributed on at least 4 body areas

Grade 3 symptoms: symptoms that prevented normal activity

Related: general symptom assessed by the investigator as causally related to the study vaccination.

Secondary Outcome Variables: Percentage of subjects reporting the occurrence of NOCDs up to Month 18 (Total Vaccinated cohort)

Most frequent NOCDs reported up to Month 18 post-vaccination	HPV-4D Group N = 65	HPV-3D Group N = 50
Subjects with any NOCD(s), n (%)	2 (3.1)	4 (8.0)
Seasonal allergy	2 (3.1)	1 (2.0)
Goitre	-	1 (2.0)
Insulin resistance	-	1 (2.0)
Psoriasis	-	1 (2.0)

# -: AE absent in that group

Secondary Outcome Variables: Percentage of subjects reporting the occurrence of NOADs up to Month 18 (Total Vaccinated cohort)

Most frequent NOADs reported up to Month 18 post-vaccination	HPV-4D Group	HPV-3D Group
	N = 65	N = 50
Subjects with any NOAD(s), n (%)	0 (0.0)	2 (4.0)
Goitre	-	1 (2.0)
Psoriasis	-	1 (2.0)

# -: AE absent in that group

Secondary Outcome Variables: Percentage of subjects reporting the occurrence of medically significant AEs (MSAEs) up to Month 18 (Total Vaccinated cohort)

Most frequent MSAEs reported up to Month 18 post-vaccination	HPV-4D Group	HPV-3D Group
0.1: 1. :11. MOAT (.) (0/)	N = 65	N = 50
Subjects with any MSAE (s), n (%)	16 (24.6)	19 (38.0)
Chlamydial infection		4 (8.0)
Pharyngitis streptococcal	2 (3.1)	2 (4.0)
Seasonal allergy	2 (3.1)	1 (2.0)
Anxiety	1 (1.5)	1 (2.0)
Back pain	1 (1.5)	1 (2.0)
Nephrolithiasis	1 (1.5)	1 (2.0)
Abdominal pain	-	1 (2.0)
Abdominal pain upper	-	1 (2.0)
Anaemia	1 (1.5)	-
Body temperature increased	1 (1.5)	-
Breast discharge	1 (1.5)	-
Cellulitis	-	1 (2.0)
Cervical polyp	-	1 (2.0)
Cholecystitis	1 (1.5)	-
Concussion	1 (1.5)	-
Conjunctivitis	1 (1.5)	-
Costochondritis	-	1 (2.0)
Depression	-	1 (2.0)
Eczema	-	1 (2.0)
Eye irritation	-	1 (2.0)
Folliculitis	1 (1.5)	- (2.0)
Fungal infection	1 (1.5)	_
Genital herpes	-	1 (2.0)
Haemangioma	1 (1.5)	- (2.0)
Hepatic steatosis	- (1.5)	1 (2.0)
Hidradenitis	1 (1.5)	-
Hypertension	- (1.5)	1 (2.0)
Insulin resistance	<u> </u>	1 (2.0)
	•	
Labyrinthitis Limb initiative	- 1 /1 E\	1 (2.0)
Limb injury Management	1 (1.5)	
Menorrhagia Menorrhagia	1 (1.5)	- 4 (0.0)
Migraine Polymetic avarias	4 /4 5\	1 (2.0)
Polycystic ovaries	1 (1.5)	- 4 (0.0)
Psoriasis	-	1 (2.0)
Pulmonary embolism	-	1 (2.0)
Pyogenic granuloma	1 (1.5)	-
Rash	1 (1.5)	-
Rash generalised	1 (1.5)	-
Renal pain	1 (1.5)	-
Skin infection	-	1 (2.0)
Tinnitus	1 (1.5)	-
Toothache	-	1 (2.0)

Urticaria	-	1 (2.0)
- : AE absent in that group	1	
Secondary Outcome Variables: Pregnancies up to Month 18 and outcome	omes (Total Vaccinated col	nort).
Categories	HPV-4D Group	HPV-3D Group
ů	N = 10	N = 6
Total number of pregnancies	11*	6
Elective termination, no apparent congenital anomaly	0 (0.0)	2 (33.3)
Premature birth	2 (18.2)	0 (0.0)
Live infant, no apparent congenital anomaly	8 (72.7)	4 (66.7)
Pregnancy ongoing	1 (9.1)	0 (0.0)
N= Number of subjects reporting pregnancy		
n(%) = number(percentage) of pregnancies/outcomes.		
*One subject was pregnant twice during the study		
Safety results: Number (%) of subjects with unsolicited adverse events		
Most frequent adverse events -	HPV-4D Group	HPV-3D Group
On-Therapy (occurring within Day 0-29 following vaccination)	N = 65	N = 50
Subjects with any AE(s), n (%)	24 (36.9)	25 (50.0)
Subjects with grade 3 AE(s), n (%)	2 (3.1)	5 (10.0)
Subjects with related AE(s), n (%)	9 (13.8)	3 (6.0)
Upper respiratory tract infection	1 (1.5)	4 (8.0)
Dizziness	4 (6.2)	-
Pharyngitis streptococcal	2 (3.1)	2 (4.0)
Abdominal pain upper	1 (1.5)	2 (4.0)
Headache	2 (3.1)	1 (2.0)
Injection site haematoma	2 (3.1)	1 (2.0)
Abdominal pain	-	2 (4.0)
Back pain	-	2 (4.0)
Injection site warmth	2 (3.1)	-
Migraine	-	2 (4.0)
Musculoskeletal stiffness	1 (1.5)	1 (2.0)
Oropharyngeal pain	1 (1.5)	1 (2.0)
Seasonal allergy	1 (1.5)	1 (2.0)
Urinary tract infection	2 (3.1)	-
Anxiety	1 (1.5)	-
Arthralgia	-	1 (2.0)
Arthropod bite	-	1 (2.0)
Body temperature increased	1 (1.5)	-
Breast tenderness	1 (1.5)	-
Cellulitis	-	1 (2.0)
Cervical polyp	-	1 (2.0)
Cholecystitis	1 (1.5)	-
Confusional state	1 (1.5)	-
Conjunctivitis	1 (1.5)	- (2.2)
Cough	-	1 (2.0)
Cytology abnormal	-	1 (2.0)
Diarrhoea	1 (1.5)	-
Dysgeusia	1 (1.5)	-
Eczema	-	1 (2.0)
Eye irritation	-	1 (2.0)
Flatulence	-	1 (2.0)
Goitre	- 4 (4.5)	1 (2.0)
Haemangioma	1 (1.5)	- 1 (0.0)
Hepatic steatosis	-	1 (2.0)
Hypertension	-	1 (2.0)

Injection site nodule	-	1 (2.0)
Labyrinthitis	-	1 (2.0)
Local swelling	1 (1.5)	=
Localised infection	1 (1.5)	-
Nasal congestion	-	1 (2.0)
Nasopharyngitis	-	1 (2.0)
Nausea	1 (1.5)	=
Neck pain	1 (1.5)	-
Nephrolithiasis	1 (1.5)	-
Pharyngitis	1 (1.5)	=
Platelet count decreased	1 (1.5)	=
Pruritus	-	1 (2.0)
Pyogenic granuloma	1 (1.5)	=
Pyrexia	-	1 (2.0)
Rash	1 (1.5)	<u>=</u>
Rhinitis	1 (1.5)	-
Sinus congestion	-	1 (2.0)
Skin infection	-	1 (2.0)
Throat irritation	-	1 (2.0)
Toothache	-	1 (2.0)
Vaginitis bacterial	1 (1.5)	-
1	· · · · · · · · · · · · · · · · · · ·	

## -: AE absent in that group

Grade 3 = event that prevented normal activities

Related = event assessed by the investigator as causally related to the study vaccination

Safety results: Number (%) of subjects with serious adverse events up to Month 18 (Total Vaccinated cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

Solidas davoles stolin, in (70) [in solicitation by the introdugator to be related to study insulation]						
All SAEs	HPV-4D Group N = 65	HPV-3D Group N = 50				
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	1 (1.5) [0]	1 (2.0) [0]				
Cholecystitis	1 (1.5) [0]	0 (0.0) [0]				
Pulmonary embolism	0 (0.0) [0]	1 (2.0) [0]				
Fatal SAEs	HPV-4D Group	HPV-3D Group				
	N = 65	N = 50				
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]				

### Conclusion:

On average 6.8 years after the initial 3-dose vaccination course in study HPV 001, all subjects in the HPV-4D Group were seropositive at HPV 024 study start for both HPV-16 (GMT value = 720.7) and HPV-18 antibodies (GMT value = 502.9). In the HPV-3D Group, prior to the first vaccination, 28.9% and 26.7% of subjects were seropositive for antibodies against HPV 16 (GMT value = 8.6) and HPV-18 (GMT value = 5.9), respectively (natural infection).

Seven days after the fourth dose, all subjects in the HPV 4D Group (non-approved schedule) were seropositive for antibodies against HPV-16 (GMT value = 5894.9) and HPV-18 (GMT value = 3916.2). One month after receiving a 4th dose of the HPV vaccine, all subjects in the HPV-4D Group ) were seropositive for antibodies against HPV-16 (GMT value = 15410.7) and HPV-18 (GMT value = 8362.7).

Seven days after the first dose, 66.7% and 57.8% of subjects in the HPV 3D Group (approved schedule) were seropositive for antibodies against HPV-16 (GMT value = 67.9) and HPV-18 (GMT value = 20.7), respectively. One month after the first dose, all subjects in that group were seropositive for antibodies against both antigens (GMT value for HPV-16 = 1231.1 and for HPV-18 = 442.0).

During the post vaccination follow-up period, 24 (36.9%) subjects in HPV-4D Group and 25 (50.0%) subjects in HPV-3D Group reported unsolicited AEs. One subject in each group reported SAEs from Day 0 up to Month 18; none were assessed by the investigators as related to the study vaccination. No fatal SAEs were reported during the study. Please also refer to the publications below.

#### **Publications:**

Moscicki B et al. Anamnestic response elicited by a fourth dose of the HPV-16/18 AS04-adjuvanted vaccine in young

women. Abstract presented at European Research Organization on Genital Infection and Neoplasia 2010 (EUROGIN). Monte Carlo, Monaco, 17-20 February 2010.

Moscicki B et al. Anamnestic response to non-vaccine types elicited by a fourth dose of the HPV-16/18 ASO4-adjuvanted vaccine in young women. Abstract presented at European Research Organization on Genital Infection and Neoplasia 2010 (EUROGIN). Monte Carlo, Monaco, 17-20 February 2010.

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