he 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.: 104772 (HPV-016)

Title: A phase III, double-blind, randomized study to assess the consistency of the immunogenicity of three production lots of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects aged 18 – 25 years and to demonstrate non-inferiority of the candidate HPV vaccine manufactured at 600L scale compared with a lower (80L) manufacturing scale.
HPV: Human Papillomavirus

Rationale: The aim of this study was to compare the immunogenicity of 3 industrial production lots (600L scale) of the HPV-16/18 L1/AS04 vaccine in 18 to 25 years old women. In addition, the immunogenicity of these 3 lots was compared to the immunogenicity of an 80L scale lot.

Phase: III

Study Period: 28 October 2005 to 01 March 2007

Study Design: Double-blinded, multi-country, controlled, randomized (1:1:1:1) study with 4 parallel groups.

Centres: This study was conducted in 9 centres located in Denmark (1 centre), Lithuania (5 centres) and Poland (3 centres).

Indication: Active immunisation of females from 10 years of age onwards for the prevention of cervical cancer by protecting against incident and persistent infections, cytological abnormalities including Atypical Squamous Cells of Undetermined Significance (ASC-US), cervical intraepithelial neoplasia (CIN) and pre-cancerous lesions (CIN 2/3) caused by oncogenic HPV.

Treatment: The treatment groups were as follows:

- 600L L1 Group received HPV-16/18 L1/AS04 vaccine Lot 1 manufactured at 600L scale;
- 600L L2 Group received HPV-16/18 L1/AS04 vaccine Lot 2 manufactured at 600L scale;
- 600L L3 Group received HPV-16/18 L1/AS04 vaccine Lot 3 manufactured at 600L scale;
- 80L Group received HPV-16/18 L1/AS04 vaccine manufactured at lower (80L) scale.

All vaccines were administered by intramuscular injection into the deltoid region of the non-dominant arm according to a 0, 1, 6 month schedule. For data analysis, the 3 study groups receiving the 3 different lots of HPV vaccine manufactured at 600L scale were to be pooled (Pooled Group) if consistency was demonstrated.

Objectives:

- To demonstrate lot-to-lot consistency in terms of immunogenicity between three industrial production lots (600L scale) of the HPV-16/18 L1/AS04 vaccine one month after the third dose (Month 7).
  Criteria for consistency: one month after the third dose, the two-sided 95 % confidence intervals (CI) of the geometric mean titre (GMT) ratio between all pairs of lots were within [0.5, 2].
  If consistency was demonstrated, the three lots would be pooled and non-inferiority of the 600L scale lot vaccine versus the 80L scale lot vaccine would be evaluated as a second primary objective (If consistency was not demonstrated, non-inferiority could not be tested).
- To demonstrate that the HPV vaccine produced at 600L manufacturing scale was non-inferior in terms of immunogenicity to the HPV vaccine produced at 80L scale one month after the third dose (Month 7).
  Two criteria for non-inferiority were assessed sequentially (if the first one was not demonstrated, the second one could not be tested):
  - one month after the third dose, the upper limit of the 95% Confidence Interval (CI) for the difference between the percentage of subjects who seroconverted after administration of the 80L scale lot vaccine versus the pooled 600L scale vaccine lots was below 5%;
  - one month after the third dose, the upper limit of the 95% CI for the GMT ratio between the 80L scale vaccine and pooled 600L scale vaccine lots was below two.

Primary Outcome/Efficacy Variable:

- Anti-HPV-16/18 seroconversion* rates and seropositivity rates in subjects receiving the three 600L scale lots of the HPV-16/18 L1/AS04 vaccine assessed by ELISA at Month 7.
- Anti-HPV-16/18 seroconversion* rates and seropositivity rates in subjects receiving the 80L scale lot HPV vaccine assessed by ELISA at Month 7.

*Seroconversion was defined as the appearance of anti-HPV-16 and/or anti-HPV-18 antibodies (anti-HPV-16 titres $\geq$ 8 EL.U/mL and anti-HPV-18 titres $\geq$ 7 EL.U/mL) in the serum of subjects seronegative before vaccination.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

- Anti-HPV-16/18 seroconversion rates and seropositivity rates in subjects receiving the three 600L scale lots of the HPV-16/18 L1/AS04 vaccine assessed by ELISA at Month 2.
- Anti-HPV-16/18 seroconversion rates and seropositivity rates in subjects receiving the 80L scale lot HPV vaccine assessed by ELISA at Month 2.

Safety

- Occurrence, intensity and relationship to vaccination of solicited general symptoms, and occurrence and intensity of solicited local symptoms within 7 days (Day 0 – 6) after each and any vaccination.
- Occurrence, intensity and causal relationship to vaccination of unsolicited symptoms within 30 days (Day 0 – 29) after any vaccination.
- Occurrence and relationship to vaccination of serious adverse events (SAEs) throughout the study period (up to Month 7).
- Occurrence of New Onset Chronic Diseases (NOCDs) and other medically significant conditions* prompting emergency room visits or physician visits that are not related to common diseases throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity.
- Occurrence of SAEs, NOCDs and other medically significant conditions up to Month 12 (extended safety follow-up).

* This definition was changed to: AEs prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

Statistical Methods:

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

- The Total Vaccinated Cohort included all vaccinated subjects. The Total Vaccinated cohort for analysis of safety included all subjects with at least one vaccine administration documented.
- 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) for whom data concerning immunogenicity measures were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component at Month 7.

Analysis of immunogenicity

The analysis was performed on the ATP cohort for immunogenicity.

Inferential analysis:

The GMT ratios of anti-HPV-16 and anti-HPV-18 antibodies, one month post Dose 3, were computed with 95% CIs for each pair among the three 600L vaccine lots, using an ANOVA model. The ANOVA model included the vaccine group as fixed effect. The first primary objective was reached if the 95% CIs of the GMT ratios between each pair was within [0.5; 2] for both anti-HPV-16 and anti-HPV-18 antibodies.

If consistency was demonstrated, the three lots would be pooled and non-inferiority of the 600L scale lot vaccine versus the 80L scale lot vaccine would be evaluated as a second primary objective. (If consistency was not demonstrated, non-inferiority could not be tested).

Non-inferiority of the HPV vaccine produced at 600L manufacturing scale compared to the HPV vaccine produced at 80L scale in terms of the immunogenicity, one month after the third dose (Month 7) was demonstrated using two sequentially assessed criteria (if the first one was not demonstrated, the second one could not be tested):

- The standardized asymptotic 95% CIs for the difference in seroconversion rate to anti-HPV-16 and anti-HPV-18 (80L lot rate minus pooled 600L lot rate) one month post Dose 3 were computed. The second primary objective was reached if the upper limit of the 95% CIs of the difference in seroconversion rates for both anti-HPV-16 and anti-HPV-18 antibodies was below 5%.
- 95% CIs of anti-HPV-16 and anti-HPV-18 GMT ratios (80L lot GMT divided by pooled 600L lot GMT), one month post Dose 3, were computed using an ANOVA model. The ANOVA model included the vaccine group as fixed effect (pooled 600L lot versus 80L lot). The second primary objective was reached if the upper limit of the 95% CIs of the GMT ratios for both anti-HPV-16 and anti-HPV-18 antibodies were below 2.

Descriptive analysis:

At each time point that a blood sample result was available (Months 0, 2 and 7), seroconversion rates with exact 95% CIs and GMTs with 95% CIs for anti-HPV-16 and anti-HPV-18 were calculated for each treatment group per pre-vaccination status.

Analysis of safety

The analysis was performed on the Total Vaccinated Cohort.

For each group, the percentage of subjects with each individual solicited local and general symptom reported during the 7-day (Day 0-6) solicited follow-up period after each vaccination was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 solicited local and general symptoms and for solicited general symptoms with relationship to vaccination.
The occurrence, intensity and causal relationship to vaccination of unsolicited adverse events (AEs) within 30 days (Day 0-29) after any vaccination was tabulated per group according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. For each group, the occurrence of NOCDs and other medically significant conditions prompting emergency room visits or physician visits that were not related to common diseases or routine visits for physical examination or vaccination throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity, was tabulated with exact 95% CI, according to the MedDRA preferred terms. The occurrence of SAEs throughout the entire study period (up to Month 7) was tabulated per group according to the MedDRA preferred terms. Occurrence of SAEs, NOCDs and other medically significant conditions up to Month 12 (extended safety follow-up) was tabulated per group according to the MedDRA preferred terms.

Study Population: Healthy female subjects between, and including 18 and 25 years of age at the time of the first vaccination, free of obvious health problems as established by medical history and history-oriented physical examination and having had a negative urine pregnancy test. Subjects of childbearing potential had to be abstinent or using effective birth control methods for 30 days prior to vaccination and had to agree to continue such precautions for 2 months after completion of vaccination series. In addition, prior to the performance of any study procedures, written informed consent was obtained from the subject.

Number of subjects	**600L L1 Group**	**600L L2 Group**	**600L L3 Group**	**Pooled Group**	**80L Group**
Planned, N	195	195	195	585	195
Randomised, N (Total Vaccinated Cohort)	199	198	201	598	200
Completed, n (%)	182 (91.5)	177 (89.4)	182 (90.5)	541 (90.5)	181 (90.5)
Total Number Subjects Withdrawn, n (%)	17 (8.5)	21 (10.6)	19 (9.5)	57 (9.5)	19 (9.5)
Withdrawn due to Adverse Events, n (%)	2 (1.0)	0 (0.0)	1 (0.5)	3 (0.5)	2 (1.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	15 (7.5)	21 (10.6)	18 (9.0)	54 (9.0)	17 (8.5)
Demographics	**600L L1 Group**	**600L L2 Group**	**600L L3 Group**	**Pooled Group**	**80L Group**
N (Total Vaccinated Cohort)	199	198	201	598	200
Females:Males	199:0	198:0	201:0	598:0	200:0
Mean Age, years (SD)	21.8 (2.08)	21.8 (2.08)	21.9 (2.00)	21.8 (2.05)	22.0 (1.96)
White/Caucasian, n (%)	195 (98.0)	194 (98.0)	194 (96.5)	583 (97.5)	198 (99.0)

Primary Efficacy Results:
GMT ratios between the three 600L lots for anti-HPV-16/18 antibodies, Post Dose III at Month 7 (ATP cohort for immunogenicity)

Antibody	**Group**	**N**	**GMT† EL.U/ mL**	**Group**	**N**	**GMT† EL.U/m L**	**GMT ratio†**			
							Ratio order	**Value**	**95% CI**	
									LL	**UL**
HPV-16 IgG	600L L1	118	9073.6	600L L2	127	8687.9	600L L1 /600L L2	1.04	0.81*	1.34*
	600L L1	118	9073.6	600L L3	126	7176.6	600L L1 /600L L3	1.26	0.98*	1.63*
	600L L2	127	8687.9	600L L3	126	7176.6	600L L2 /600L L3	1.21	0.94*	1.55*
HPV-18 IgG	600L L1	129	4348.9	600L L2	143	3652.1	600L L1 /600L L2	1.19	0.95*	1.49*
	600L L1	129	4348.9	600L L3	135	2941.8	600L L1 /600L L3	1.48	1.18*	1.85*
	600L L2	143	3652.1	600L L3	135	2941.8	600L L2 /600L L3	1.24	1.00*	1.55*

†: Calculation performed on subjects seronegative prior to Dose 1.
N = number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance with more than 2 groups); LL = lower limit, UL = upper limit
*The first primary objective was reached as the 95% CIs of the GMT ratios between each pair were within [0.5; 2] for both anti-HPV-16 and anti-HPV-18 antibodies. As a result, the three 600L lots were pooled for evaluation of subsequent study objectives.

Primary Efficacy Results:
Non-inferiority assessment in terms of seroconversion rates between the 80L lot and the pooled 600L lots for anti-HPV-

16/18 antibodies, Post Dose III at Month 7 (ATP cohort for immunogenicity)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seroconversion rate (Group 2 - Group 1)			
							Difference†	%	95 % CI	
									LL	UL
HPV-16 IgG	Pooled	371	100	80L	102	100	80L - Pooled	0.00	-3.63	1.02*
HPV-18 IgG	Pooled	407	100	80L	117	100	80L - Pooled	0.00	-3.18	0.94*

†: Calculation performed on subjects seronegative prior to Dose 1.
N = number of subjects with available results
% = percentage of subjects with HPV-16 IgG titre ≥ 8 EL.U/mL or with HPV-18 IgG titre ≥ 7 EL.U/mL
95% CI = 95% standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
*The second primary objective was reached as the upper limits of the 95% CIs of the difference in seroconversion rates for both anti-HPV-16 and anti-HPV-18 antibodies were below 5%.

Primary Efficacy Results:
Non-inferiority assessment in terms of GMT ratios between the 80L lot and the pooled 600L lots for anti-HPV-16/18 antibodies, Post Dose III at Month 7 (ATP cohort for immunogenicity)

Antibody	80L Group		Pooled Group		GMT ratio (80L Group / Pooled Group)†		
	N	GMT(EL.U/mL)	N	GMT (EL.U/mL)	Value	95% CI	
						LL	UL
HPV-16 IgG	102	7190.8	371	8255.2	0.87	0.70	1.08*
HPV-18 IgG	117	2891.8	407	3592.7	0.80	0.66	0.97*

†: Calculation performed on subjects seronegative prior to Dose 1
N = number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance); LL = lower limit, UL = upper limit
*The second primary objective was reached as the upper limits of the 95% CIs of the GMT ratios for both anti-HPV-16 and anti-HPV-18 antibodies were below 2.

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

Group	Pre-vaccination status	Timing	N	≥ 8 EL.U/mL				GMT (EL.U/mL)		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
600L L1	S-	PRE	118	0	0.0	0.0	3.1	4.0	4.0	4.0
		PII(M2)	117	117	100	96.9	100	3134.1	2765.8	3551.4
		PIII(M7)*	118	118	100	96.9	100	9073.6	7545.8	10910.7
	S+	PRE	54	54	100	93.4	100	58.9	39.0	89.0
		PII(M2)	54	54	100	93.4	100	4905.7	3789.4	6350.7
		PIII(M7)	54	54	100	93.4	100	6736.7	5306.0	8553.0
	Total	PRE	172	54	31.4	24.5	38.9	9.3	7.4	11.7
		PII(M2)	171	171	100	97.9	100	3610.4	3199.5	4074.1
		PIII(M7)	172	172	100	97.9	100	8263.7	7132.8	9573.9
600L L2	S-	PRE	127	0	0.0	0.0	2.9	4.0	4.0	4.0
		PII(M2)	126	126	100	97.1	100	2971.5	2636.3	3349.3
		PIII(M7)*	127	127	100	97.1	100	8687.9	7256.0	10402.3
	S+	PRE	38	38	100	90.7	100	55.9	34.6	90.3
		PII(M2)	38	38	100	90.7	100	4101.7	3060.4	5497.4
		PIII(M7)	38	38	100	90.7	100	5967.3	4381.4	8127.3
	Total	PRE	165	38	23.0	16.8	30.2	7.3	6.0	9.0
		PII(M2)	164	164	100	97.8	100	3201.9	2855.3	3590.7
		PIII(M7)	165	165	100	97.8	100	7967.9	6815.6	9314.9
600L L3	S-	PRE	126	0	0.0	0.0	2.9	4.0	4.0	4.0
		PII(M2)	125	125	100	97.1	100	2818.9	2466.1	3222.3
		PIII(M7)*	126	126	100	97.1	100	7176.6	6038.5	8529.2
	S+	PRE	43	43	100	91.8	100	57.1	38.1	85.4
		PII(M2)	43	43	100	91.8	100	4502.4	3420.8	5926.2
		PIII(M7)	43	43	100	91.8	100	5178.4	3980.8	6736.1

	Total	PRE	169	43	25.4	19.1	32.7	7.9	6.4	9.6
		PII(M2)	168	168	100	97.8	100	3177.9	2806.3	3598.6
		PIII(M7)	169	169	100	97.8	100	6604.8	5711.1	7638.3
Pooled	S-	PRE	371	0	0.0	0.0	1.0	4.0	4.0	4.0
		PII(M2)	368	368	100	99.0	100	2968.6	2761.3	3191.5
		PIII(M7)*	371	371	100	99.0	100	8255.2	7447.9	9150.0
	S+	PRE	135	135	100	97.3	100	57.4	45.1	73.2
		PII(M2)	135	135	100	97.3	100	4538.9	3887.5	5299.5
		PIII(M7)	135	135	100	97.3	100	5987.3	5147.7	6963.7
	Total	PRE	506	135	26.7	22.9	30.8	8.1	7.2	9.2
		PII(M2)	503	503	100	99.3	100	3326.9	3105.0	3564.8
		PIII(M7)	506	506	100	99.3	100	7577.2	6951.5	8259.2
80L	S-	PRE	102	0	0.0	0.0	3.6	4.0	4.0	4.0
		PII(M2)	102	102	100	96.4	100	2660.1	2319.8	3050.3
		PIII(M7)*	102	102	100	96.4	100	7190.8	5992.8	8628.2
	S+	PRE	57	57	100	93.7	100	74.3	52.6	105.0
		PII(M2)	56	56	100	93.6	100	4078.6	3166.0	5254.3
		PIII(M7)	57	57	100	93.7	100	4137.2	3369.3	5080.2
	Total	PRE	159	57	35.8	28.4	43.8	11.4	8.9	14.7
		PII(M2)	158	158	100	97.7	100	3095.2	2722.2	3519.3
		PIII(M7)	159	159	100	97.7	100	5898.1	5112.4	6804.7

S- = seronegative subjects (antibody titre < 8 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 8 EL.U/mL) prior to vaccination
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with antibody titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M2) = post Dose II at Month 2
PIII(M7) = post Dose III at Month 7
*Primary efficacy results

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

Group	**Pre-vaccination status**	**Timing**	**N**	**≥ 7 EL.U/mL**				**GMT (EL.U/mL)**		
				n	**%**	**95% CI**		**Value**	**95% CI**	
						LL	**UL**		**LL**	**UL**
600L L1	S-	PRE	129	0	0.0	0.0	2.8	3.5	3.5	3.5
		PII(M2)	128	128	100	97.2	100	2537.6	2220.5	2900.1
		PIII(M7)*	129	129	100	97.2	100	4348.9	3695.9	5117.3
	S+	PRE	43	43	100	91.8	100	33.7	23.2	49.0
		PII(M2)	43	43	100	91.8	100	2608.2	2033.9	3344.6
		PIII(M7)	43	43	100	91.8	100	2830.5	2284.6	3506.9
	Total	PRE	172	43	25.0	18.7	32.2	6.2	5.2	7.3
		PII(M2)	171	171	100	97.9	100	2555.2	2273.9	2871.2
		PIII(M7)	172	172	100	97.9	100	3906.2	3412.3	4471.6
600L L2	S-	PRE	143	0	0.0	0.0	2.5	3.5	3.5	3.5
		PII(M2)	142	142	100	97.4	100	2403.1	2113.2	2732.9
		PIII(M7)*	143	143	100	97.5	100	3652.1	3105.1	4295.4
	S+	PRE	22	22	100	84.6	100	35.8	20.1	63.8
		PII(M2)	22	22	100	84.6	100	2139.7	1462.6	3130.4
		PIII(M7)	22	22	100	84.6	100	2777.3	1971.9	3911.7
	Total	PRE	165	22	13.3	8.5	19.5	4.8	4.1	5.5
		PII(M2)	164	164	100	97.8	100	2366.0	2096.3	2670.4
		PIII(M7)	165	165	100	97.8	100	3521.2	3038.7	4080.3
600L L3	S-	PRE	135	0	0.0	0.0	2.7	3.5	3.5	3.5

		PII(M2)	134	134	100	97.3	100	2215.6	1911.5	2568.1
		PIII(M7)*	135	135	100	97.3	100	2941.8	2527.0	3424.6
	S+	PRE	34	34	100	89.7	100	27.9	19.1	40.6
		PII(M2)	34	34	100	89.7	100	2778.7	1973.3	3912.8
		PIII(M7)	34	34	100	89.7	100	3901.4	2828.3	5381.7
	Total	PRE	169	34	20.1	14.4	27.0	5.3	4.6	6.1
		PII(M2)	168	168	100	97.8	100	2319.5	2025.3	2656.5
		PIII(M7)	169	169	100	97.8	100	3113.7	2714.7	3571.4
Pooled	S-	PRE	407	0	0.0	0.0	0.9	3.5	3.5	3.5
		PII(M2)	404	404	100	99.1	100	2380.0	2200.4	2574.2
		PIII(M7)*	407	407	100	99.1	100	3592.7	3275.5	3940.7
	S+	PRE	99	99	100	96.3	100	32.0	25.3	40.5
		PII(M2)	99	99	100	96.3	100	2550.8	2140.9	3039.1
		PIII(M7)	99	99	100	96.3	100	3147.0	2680.8	3694.3
	Total	PRE	506	99	19.6	16.2	23.3	5.4	4.9	5.9
		PII(M2)	503	503	100	99.3	100	2412.6	2246.0	2591.7
		PIII(M7)	506	506	100	99.3	100	3500.8	3229.7	3794.7
80L	S-	PRE	117	0	0.0	0.0	3.1	3.5	3.5	3.5
		PII(M2)	116	116	100	96.9	100	1891.9	1624.2	2203.7
		PIII(M7)*	117	117	100	96.9	100	2891.8	2470.2	3385.4
	S+	PRE	41	41	100	91.4	100	36.7	25.7	52.4
		PII(M2)	41	41	100	91.4	100	2762.8	2145.6	3557.6
		PIII(M7)	41	41	100	91.4	100	3197.4	2463.7	4149.5
	Total	PRE	158	41	25.9	19.3	33.5	6.4	5.4	7.8
		PII(M2)	157	157	100	97.7	100	2088.5	1830.5	2382.9
		PIII(M7)	158	158	100	97.7	100	2968.2	2596.9	3392.5

S- = seronegative subjects (antibody titre < 7 EL.U/mL) prior to vaccination
S+ = seropositive subjects (antibody titre ≥ 7 EL.U/mL) prior to vaccination
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with antibody titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M2) = post Dose II at Month 2
PIII(M7) = post Dose III at Month 7
*Primary efficacy results

Secondary Outcome Variable (s):
Incidence of solicited local symptoms reported during the 7-day (Day 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

Symptom	**Intensity**	**600L L1 Group**				**600L L2 Group**				**600L L3 Group**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
Dose 1													
		N=198				**N=197**				**N=199**			
Pain	Any	188	94.9	90.9	97.6	190	96.4	92.8	98.6	178	89.4	84.3	93.3
	Grade 3	20	10.1	6.3	15.2	16	8.1	4.7	12.9	17	8.5	5.1	13.3
Redness	Any	74	37.4	30.6	44.5	71	36.0	29.3	43.2	77	38.7	31.9	45.8
	> 50 mm	0	0.0	0.0	1.8	0	0.0	0.0	1.9	0	0.0	0.0	1.8
Swelling	Any	58	29.3	23.1	36.2	57	28.9	22.7	35.8	57	28.6	22.5	35.5
	> 50 mm	9	4.5	2.1	8.5	2	1.0	0.1	3.6	2	1.0	0.1	3.6
Dose 2													
		N=196				**N=195**				**N=198**			
Pain	Any	167	85.2	79.4	89.9	166	85.1	79.3	89.8	170	85.9	80.2	90.4
	Grade 3	17	8.7	5.1	13.5	10	5.1	2.5	9.2	19	9.6	5.9	14.6
Redness	Any	78	39.8	32.9	47.0	85	43.6	36.5	50.9	79	39.9	33.0	47.1

	> 50 mm	3	1.5	0.3	4.4	6	3.1	1.1	6.6	0	0.0	0.0	1.8
Swelling	Any	64	32.7	26.1	39.7	59	30.3	23.9	37.2	56	28.3	22.1	35.1
	> 50 mm	7	3.6	1.4	7.2	2	1.0	0.1	3.7	2	1.0	0.1	3.6
Dose 3													
		N=181				**N=178**				**N=184**			
Pain	Any	164	90.6	85.4	94.4	151	84.8	78.7	89.8	162	88.0	82.5	92.4
	Grade 3	21	11.6	7.3	17.2	14	7.9	4.4	12.8	11	6.0	3.0	10.4
Redness	Any	94	51.9	44.4	59.4	102	57.3	49.7	64.7	96	52.2	44.7	59.6
	> 50 mm	5	2.8	0.9	6.3	6	3.4	1.2	7.2	4	2.2	0.6	5.5
Swelling	Any	92	50.8	43.3	58.3	84	47.2	39.7	54.8	85	46.2	38.8	53.7
	> 50 mm	8	4.4	1.9	8.5	3	1.7	0.3	4.8	2	1.1	0.1	3.9
Across doses													
		N=198				**N=197**				**N=199**			
Pain	Any	194	98.0	94.9	99.4	192	97.5	94.2	99.2	190	95.5	91.6	97.9
	Grade 3	45	22.7	17.1	29.2	29	14.7	10.1	20.5	34	17.1	12.1	23.0
Redness	Any	118	59.6	52.4	66.5	128	65.0	57.9	71.6	127	63.8	56.7	70.5
	> 50 mm	8	4.0	1.8	7.8	9	4.6	2.1	8.5	4	2.0	0.6	5.1
Swelling	Any	116	58.6	51.4	65.5	112	56.9	49.6	63.9	113	56.8	49.6	63.8
	> 50 mm	15	7.6	4.3	12.2	6	3.0	1.1	6.5	6	3.0	1.1	6.4

		Pooled Group				**80L Group**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Dose 1									
		N=594				**N=196**			
Pain	Any	556	93.6	91.3	95.4	185	94.4	90.2	97.2
	Grade 3	53	8.9	6.8	11.5	12	6.1	3.2	10.5
Redness	Any	222	37.4	33.5	41.4	75	38.3	31.4	45.5
	> 50 mm	0	0.0	0.0	0.6	0	0.0	0.0	1.9
Swelling	Any	172	29.0	25.3	32.8	54	27.6	21.4	34.4
	> 50 mm	13	2.2	1.2	3.7	4	2.0	0.6	5.1
Dose 2									
		N=589				**N=194**			
Pain	Any	503	85.4	82.3	88.2	161	83.0	76.9	88.0
	Grade 3	46	7.8	5.8	10.3	12	6.2	3.2	10.6
Redness	Any	242	41.1	37.1	45.2	62	32.0	25.5	39.0
	> 50 mm	9	1.5	0.7	2.9	1	0.5	0.0	2.8
Swelling	Any	179	30.4	26.7	34.3	53	27.3	21.2	34.2
	> 50 mm	11	1.9	0.9	3.3	5	2.6	0.8	5.9
Dose 3									
		N=543				**N=181**			
Pain	Any	477	87.8	84.8	90.5	156	86.2	80.3	90.9
	Grade 3	46	8.5	6.3	11.1	15	8.3	4.7	13.3
Redness	Any	292	53.8	49.5	58.0	92	50.8	43.3	58.3
	> 50 mm	15	2.8	1.6	4.5	5	2.8	0.9	6.3
Swelling	Any	261	48.1	43.8	52.4	82	45.3	37.9	52.9
	> 50 mm	13	2.4	1.3	4.1	3	1.7	0.3	4.8
Across doses									
		N=594				**N=197**			
Pain	Any	576	97.0	95.3	98.2	192	97.5	94.2	99.2
	Grade 3	108	18.2	15.2	21.5	30	15.2	10.5	21.0
Redness	Any	373	62.8	58.8	66.7	126	64.0	56.8	70.7
	> 50 mm	21	3.5	2.2	5.4	6	3.0	1.1	6.5
Swelling	Any	341	57.4	53.3	61.4	107	54.3	47.1	61.4
	> 50 mm	27	4.5	3.0	6.5	10	5.1	2.5	9.1

N = number of subjects with a 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 = any solicited local symptom irrespective of intensity grade
Grade 3 pain = pain that prevented normal activity

Secondary Outcome Variable (s):
Incidence of solicited general symptoms reported during the 7-day (Day 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

Symptom	Intensity /relation-ship	600L L1 Group				600L L2 Group				600L L3 Group			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
Dose 1													
		N=198				N=197				N=199			
Arthralgia*	Any	19	9.6	5.9	14.6	19	9.6	5.9	14.7	13	6.5	3.5	10.9
	Grade 3	1	0.5	0.0	2.8	0	0.0	0.0	1.9	2	1.0	0.1	3.6
	Related	14	7.1	3.9	11.6	17	8.6	5.1	13.5	8	4.0	1.8	7.8
Fatigue	Any	81	40.9	34.0	48.1	84	42.6	35.6	49.9	73	36.7	30.0	43.8
	Grade 3	4	2.0	0.6	5.1	1	0.5	0.0	2.8	4	2.0	0.6	5.1
	Related	60	30.3	24.0	37.2	62	31.5	25.1	38.5	48	24.1	18.4	30.7
Fever (axillary)	≥ 37.5°C	4	2.0	0.6	5.1	7	3.6	1.4	7.2	4	2.0	0.6	5.1
	> 39.0°C	0	0.0	0.0	1.8	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	1	0.5	0.0	2.8	5	2.5	0.8	5.8	3	1.5	0.3	4.3
Gastro-intestinal	Any	32	16.2	11.3	22.0	39	19.8	14.5	26.1	34	17.1	12.1	23.0
	Grade 3	1	0.5	0.0	2.8	2	1.0	0.1	3.6	0	0.0	0.0	1.8
	Related	17	8.6	5.1	13.4	24	12.2	8.0	17.6	19	9.5	5.8	14.5
Headache	Any	69	34.8	28.2	41.9	70	35.5	28.9	42.6	60	30.2	23.9	37.0
	Grade 3	8	4.0	1.8	7.8	4	2.0	0.6	5.1	2	1.0	0.1	3.6
	Related	44	22.2	16.6	28.7	49	24.9	19.0	31.5	38	19.1	13.9	25.3
Myalgia	Any	45	22.7	17.1	29.2	55	27.9	21.8	34.7	50	25.1	19.3	31.7
	Grade 3	3	1.5	0.3	4.4	2	1.0	0.1	3.6	3	1.5	0.3	4.3
	Related	36	18.2	13.1	24.3	44	22.3	16.7	28.8	41	20.6	15.2	26.9
Rash	Any	4	2.0	0.6	5.1	4	2.0	0.6	5.1	6	3.0	1.1	6.4
	Grade 3	0	0.0	0.0	1.8	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	2	1.0	0.1	3.6	3	1.5	0.3	4.4	4	2.0	0.6	5.1
Urticaria	Any	5	2.5	0.8	5.8	3	1.5	0.3	4.4	3	1.5	0.3	4.3
	Grade 3	0	0.0	0.0	1.8	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	2	1.0	0.1	3.6	2	1.0	0.1	3.6	2	1.0	0.1	3.6
Dose 2													
		N=195				N=195				N=198			
Arthralgia	Any	14	7.2	4.0	11.8	14	7.2	4.0	11.8	14	7.1	3.9	11.6
	Grade 3	0	0.0	0.0	1.9	0	0.0	0.0	1.9	1	0.5	0.0	2.8
	Related	12	6.2	3.2	10.5	11	5.6	2.8	9.9	10	5.1	2.4	9.1
Fatigue	Any	63	32.3	25.8	39.4	73	37.4	30.6	44.6	69	34.8	28.2	41.9
	Grade 3	2	1.0	0.1	3.7	4	2.1	0.6	5.2	3	1.5	0.3	4.4
	Related	39	20.0	14.6	26.3	55	28.2	22.0	35.1	38	19.2	14.0	25.4
Fever (axillary)	≥ 37.5°C	7	3.6	1.5	7.3	5	2.6	0.8	5.9	7	3.5	1.4	7.1
	> 39.0°C	0	0.0	0.0	1.9	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	5	2.6	0.8	5.9	2	1.0	0.1	3.7	2	1.0	0.1	3.6
Gastro-intestinal	Any	22	11.3	7.2	16.6	21	10.8	6.8	16.0	28	14.1	9.6	19.8
	Grade 3	1	0.5	0.0	2.8	0	0.0	0.0	1.9	1	0.5	0.0	2.8
	Related	14	7.2	4.0	11.8	14	7.2	4.0	11.8	12	6.1	3.2	10.3
Headache	Any	47	24.1	18.3	30.7	51	26.2	20.1	32.9	46	23.2	17.5	29.7

	Grade 3	2	1.0	0.1	3.7	4	2.1	0.6	5.2	2	1.0	0.1	3.6
	Related	27	13.8	9.3	19.5	33	16.9	11.9	22.9	29	14.6	10.0	20.4
Myalgia	Any	30	15.4	10.6	21.2	37	19.0	13.7	25.2	39	19.7	14.4	25.9
	Grade 3	0	0.0	0.0	1.9	1	0.5	0.0	2.8	3	1.5	0.3	4.4
	Related	22	11.3	7.2	16.6	30	15.4	10.6	21.2	31	15.7	10.9	21.5
Rash	Any	1	0.5	0.0	2.8	3	1.5	0.3	4.4	8	4.0	1.8	7.8
	Grade 3	0	0.0	0.0	1.9	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	1	0.5	0.0	2.8	3	1.5	0.3	4.4	5	2.5	0.8	5.8
Urticaria	Any	2	1.0	0.1	3.7	2	1.0	0.1	3.7	2	1.0	0.1	3.6
	Grade 3	0	0.0	0.0	1.9	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	0	0.0	0.0	1.9	1	0.5	0.0	2.8	2	1.0	0.1	3.6
Dose 3													
		N=181				**N=178**				**N=184**			
Arthralgia	Any	18	9.9	6.0	15.3	19	10.7	6.6	16.2	18	9.8	5.9	15.0
	Grade 3	1	0.6	0.0	3.0	1	0.6	0.0	3.1	0	0.0	0.0	2.0
	Related	15	8.3	4.7	13.3	16	9.0	5.2	14.2	12	6.5	3.4	11.1
Fatigue	Any	76	42.0	34.7	49.5	67	37.6	30.5	45.2	64	34.8	27.9	42.1
	Grade 3	9	5.0	2.3	9.2	1	0.6	0.0	3.1	2	1.1	0.1	3.9
	Related	58	32.0	25.3	39.4	50	28.1	21.6	35.3	49	26.6	20.4	33.6
Fever (axillary)	≥ 37.5°C	7	3.9	1.6	7.8	6	3.4	1.2	7.2	4	2.2	0.6	5.5
	> 39.0°C	0	0.0	0.0	2.0	0	0.0	0.0	2.1	1	0.5	0.0	3.0
	Related	1	0.6	0.0	3.0	4	2.2	0.6	5.7	1	0.5	0.0	3.0
Gastro-intestinal	Any	17	9.4	5.6	14.6	19	10.7	6.6	16.2	25	13.6	9.0	19.4
	Grade 3	2	1.1	0.1	3.9	1	0.6	0.0	3.1	1	0.5	0.0	3.0
	Related	8	4.4	1.9	8.5	9	5.1	2.3	9.4	14	7.6	4.2	12.4
Headache	Any	53	29.3	22.8	36.5	44	24.7	18.6	31.7	49	26.6	20.4	33.6
	Grade 3	5	2.8	0.9	6.3	2	1.1	0.1	4.0	4	2.2	0.6	5.5
	Related	34	18.8	13.4	25.2	31	17.4	12.2	23.8	29	15.8	10.8	21.8
Myalgia	Any	44	24.3	18.3	31.2	38	21.3	15.6	28.1	39	21.2	15.5	27.8
	Grade 3	3	1.7	0.3	4.8	2	1.1	0.1	4.0	1	0.5	0.0	3.0
	Related	35	19.3	13.9	25.9	35	19.7	14.1	26.3	32	17.4	12.2	23.7
Rash	Any	7	3.9	1.6	7.8	4	2.2	0.6	5.7	9	4.9	2.3	9.1
	Grade 3	0	0.0	0.0	2.0	0	0.0	0.0	2.1	0	0.0	0.0	2.0
	Related	5	2.8	0.9	6.3	2	1.1	0.1	4.0	6	3.3	1.2	7.0
Urticaria	Any	3	1.7	0.3	4.8	0	0.0	0.0	2.1	5	2.7	0.9	6.2
	Grade 3	0	0.0	0.0	2.0	0	0.0	0.0	2.1	0	0.0	0.0	2.0
	Related	1	0.6	0.0	3.0	0	0.0	0.0	2.1	2	1.1	0.1	3.9
Across doses													
		N=198				**N=197**				**N=199**			
Arthralgia	Any	38	19.2	14.0	25.4	40	20.3	14.9	26.6	32	16.1	11.3	21.9
	Grade 3	2	1.0	0.1	3.6	1	0.5	0.0	2.8	2	1.0	0.1	3.6
	Related	31	15.7	10.9	21.5	32	16.2	11.4	22.2	22	11.1	7.1	16.3
Fatigue	Any	117	59.1	51.9	66.0	117	59.4	52.2	66.3	106	53.3	46.1	60.4
	Grade 3	13	6.6	3.5	11.0	6	3.0	1.1	6.5	8	4.0	1.8	7.8
	Related	90	45.5	38.4	52.7	95	48.2	41.1	55.4	78	39.2	32.4	46.3
Fever (axillary)	≥ 37.5°C	16	8.1	4.7	12.8	18	9.1	5.5	14.1	14	7.0	3.9	11.5
	> 39.0°C	0	0.0	0.0	1.8	0	0.0	0.0	1.9	1	0.5	0.0	2.8
	Related	6	3.0	1.1	6.5	11	5.6	2.8	9.8	5	2.5	0.8	5.8
Gastro-intestinal	Any	55	27.8	21.7	34.6	61	31.0	24.6	37.9	57	28.6	22.5	35.5
	Grade 3	4	2.0	0.6	5.1	3	1.5	0.3	4.4	2	1.0	0.1	3.6
	Related	32	16.2	11.3	22.0	38	19.3	14.0	25.5	33	16.6	11.7	22.5
Headache	Any	99	50.0	42.8	57.2	103	52.3	45.1	59.4	95	47.7	40.6	54.9
	Grade 3	14	7.1	3.9	11.6	9	4.6	2.1	8.5	8	4.0	1.8	7.8
	Related	68	34.3	27.8	41.4	77	39.1	32.2	46.3	57	28.6	22.5	35.5

Myalgia	Any	75	37.9	31.1	45.0	82	41.6	34.7	48.8	73	36.7	30.0	43.8
	Grade 3	6	3.0	1.1	6.5	5	2.5	0.8	5.8	6	3.0	1.1	6.4
	Related	62	31.3	24.9	38.3	70	35.5	28.9	42.6	62	31.2	24.8	38.1
Rash	Any	11	5.6	2.8	9.7	10	5.1	2.5	9.1	19	9.5	5.8	14.5
	Grade 3	0	0.0	0.0	1.8	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	7	3.5	1.4	7.1	7	3.6	1.4	7.2	13	6.5	3.5	10.9
Urticaria	Any	7	3.5	1.4	7.1	5	2.5	0.8	5.8	7	3.5	1.4	7.1
	Grade 3	0	0.0	0.0	1.8	0	0.0	0.0	1.9	0	0.0	0.0	1.8
	Related	3	1.5	0.3	4.4	3	1.5	0.3	4.4	4	2.0	0.6	5.1

Symptom	**Intensity / relation-ship**	**Pooled Group**				**80L Group**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Dose 1									
		N=594				**N=196**			
Arthralgia	Any	51	8.6	6.5	11.1	17	8.7	5.1	13.5
	Grade 3	3	0.5	0.1	1.5	0	0.0	0.0	1.9
	Related	39	6.6	4.7	8.9	14	7.1	4.0	11.7
Fatigue	Any	238	40.1	36.1	44.1	80	40.8	33.9	48.0
	Grade 3	9	1.5	0.7	2.9	5	2.6	0.8	5.9
	Related	170	28.6	25.0	32.4	61	31.1	24.7	38.1
Fever (axillary)	≥ 37.5°C	15	2.5	1.4	4.1	5	2.6	0.8	5.9
	> 39.0°C	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	9	1.5	0.7	2.9	3	1.5	0.3	4.4
Gastro-intestinal	Any	105	17.7	14.7	21.0	30	15.3	10.6	21.1
	Grade 3	3	0.5	0.1	1.5	1	0.5	0.0	2.8
	Related	60	10.1	7.8	12.8	19	9.7	5.9	14.7
Headache	Any	199	33.5	29.7	37.5	65	33.2	26.6	40.2
	Grade 3	14	2.4	1.3	3.9	4	2.0	0.6	5.1
	Related	131	22.1	18.8	25.6	46	23.5	17.7	30.0
Myalgia	Any	150	25.3	21.8	28.9	42	21.4	15.9	27.8
	Grade 3	8	1.3	0.6	2.6	0	0.0	0.0	1.9
	Related	121	20.4	17.2	23.8	30	15.3	10.6	21.1
Rash	Any	14	2.4	1.3	3.9	5	2.6	0.8	5.9
	Grade 3	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	9	1.5	0.7	2.9	4	2.0	0.6	5.1
Urticaria	Any	11	1.9	0.9	3.3	4	2.0	0.6	5.1
	Grade 3	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	6	1.0	0.4	2.2	4	2.0	0.6	5.1
Dose 2									
		N=588				**N=193**			
Arthralgia	Any	42	7.1	5.2	9.5	17	8.8	5.2	13.7
	Grade 3	1	0.2	0.0	0.9	0	0.0	0.0	1.9
	Related	33	5.6	3.9	7.8	14	7.3	4.0	11.9
Fatigue	Any	205	34.9	31.0	38.9	58	30.1	23.7	37.1
	Grade 3	9	1.5	0.7	2.9	5	2.6	0.8	5.9
	Related	132	22.4	19.1	26.0	40	20.7	15.2	27.1
Fever (axillary)	≥ 37.5°C	19	3.2	2.0	5.0	5	2.6	0.8	5.9
	> 39.0°C	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	9	1.5	0.7	2.9	3	1.6	0.3	4.5
Gastro-intestinal	Any	71	12.1	9.6	15.0	24	12.4	8.1	17.9
	Grade 3	2	0.3	0.0	1.2	1	0.5	0.0	2.9
	Related	40	6.8	4.9	9.1	9	4.7	2.2	8.7
Headache	Any	144	24.5	21.1	28.2	41	21.2	15.7	27.7

	Grade 3	8	1.4	0.6	2.7	1	0.5	0.0	2.9
	Related	89	15.1	12.3	18.3	24	12.4	8.1	17.9
Myalgia	Any	106	18.0	15.0	21.4	31	16.1	11.2	22.0
	Grade 3	4	0.7	0.2	1.7	1	0.5	0.0	2.9
	Related	83	14.1	11.4	17.2	21	10.9	6.9	16.2
Rash	Any	12	2.0	1.1	3.5	5	2.6	0.8	5.9
	Grade 3	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	9	1.5	0.7	2.9	3	1.6	0.3	4.5
Urticaria	Any	6	1.0	0.4	2.2	5	2.6	0.8	5.9
	Grade 3	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	3	0.5	0.1	1.5	3	1.6	0.3	4.5
Dose 3									
		N=543				**N=181**			
Arthralgia	Any	55	10.1	7.7	13.0	13	7.2	3.9	12.0
	Grade 3	2	0.4	0.0	1.3	0	0.0	0.0	2.0
	Related	43	7.9	5.8	10.5	11	6.1	3.1	10.6
Fatigue	Any	207	38.1	34.0	42.4	60	33.1	26.3	40.5
	Grade 3	12	2.2	1.1	3.8	6	3.3	1.2	7.1
	Related	157	28.9	25.1	32.9	49	27.1	20.7	34.2
Fever (axillary)	≥ 37.5°C	17	3.1	1.8	5.0	8	4.4	1.9	8.5
	> 39.0°C	1	0.2	0.0	1.0	0	0.0	0.0	2.0
	Related	6	1.1	0.4	2.4	4	2.2	0.6	5.6
Gastro-intestinal	Any	61	11.2	8.7	14.2	15	8.3	4.7	13.3
	Grade 3	4	0.7	0.2	1.9	3	1.7	0.3	4.8
	Related	31	5.7	3.9	8.0	7	3.9	1.6	7.8
Headache	Any	146	26.9	23.2	30.8	39	21.5	15.8	28.3
	Grade 3	11	2.0	1.0	3.6	1	0.6	0.0	3.0
	Related	94	17.3	14.2	20.8	30	16.6	11.5	22.8
Myalgia	Any	121	22.3	18.9	26.0	29	16.0	11.0	22.2
	Grade 3	6	1.1	0.4	2.4	1	0.6	0.0	3.0
	Related	102	18.8	15.6	22.3	24	13.3	8.7	19.1
Rash	Any	20	3.7	2.3	5.6	9	5.0	2.3	9.2
	Grade 3	0	0.0	0.0	0.7	0	0.0	0.0	2.0
	Related	13	2.4	1.3	4.1	6	3.3	1.2	7.1
Urticaria	Any	8	1.5	0.6	2.9	6	3.3	1.2	7.1
	Grade 3	0	0.0	0.0	0.7	0	0.0	0.0	2.0
	Related	3	0.6	0.1	1.6	4	2.2	0.6	5.6
Across doses									
		N=594				**N=197**			
Arthralgia	Any	110	18.5	15.5	21.9	35	17.8	12.7	23.8
	Grade 3	5	0.8	0.3	2.0	0	0.0	0.0	1.9
	Related	85	14.3	11.6	17.4	31	15.7	10.9	21.6
Fatigue	Any	340	57.2	53.1	61.3	105	53.3	46.1	60.4
	Grade 3	27	4.5	3.0	6.5	12	6.1	3.2	10.4
	Related	263	44.3	40.2	48.4	90	45.7	38.6	52.9
Fever (axillary)	≥ 37.5°C	48	8.1	6.0	10.6	15	7.6	4.3	12.2
	> 39.0°C	1	0.2	0.0	0.9	0	0.0	0.0	1.9
	Related	22	3.7	2.3	5.6	7	3.6	1.4	7.2
Gastro-intestinal	Any	173	29.1	25.5	33.0	49	24.9	19.0	31.5
	Grade 3	9	1.5	0.7	2.9	5	2.5	0.8	5.8
	Related	103	17.3	14.4	20.6	25	12.7	8.4	18.2
Headache	Any	297	50.0	45.9	54.1	93	47.2	40.1	54.4
	Grade 3	31	5.2	3.6	7.3	5	2.5	0.8	5.8
	Related	202	34.0	30.2	38.0	68	34.5	27.9	41.6

Myalgia	Any	230	38.7	34.8	42.8	66	33.5	27.0	40.6
	Grade 3	17	2.9	1.7	4.5	2	1.0	0.1	3.6
	Related	194	32.7	28.9	36.6	48	24.4	18.5	31.0
Rash	Any	40	6.7	4.9	9.1	15	7.6	4.3	12.2
	Grade 3	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	27	4.5	3.0	6.5	11	5.6	2.8	9.8
Urticaria	Any	19	3.2	1.9	5.0	10	5.1	2.5	9.1
	Grade 3	0	0.0	0.0	0.6	0	0.0	0.0	1.9
	Related	10	1.7	0.8	3.1	8	4.1	1.8	7.8

N = number of subjects with a 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 = any solicited general symptom irrespective of intensity grade or relationship to vaccination
Grade 3 = symptom that prevented normal activity
Related = symptom related to study vaccination according to the investigator
*Arthralgia (joint pain) was defined as pain occurring only in joints that were distal from the injection site

Secondary Outcome Variable (s):
Percentage of subjects reporting the occurrence of NOCDs during the active phase of the study (up to Month 7) (Total Vaccinated Cohort)

New Onset Chronic Diseases	**600L L1 Group N = 199**				**600L L2 Group N = 198**				**600L L3 Group N = 201**			
	n	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom	3	1.5	0.3	4.3	4	2.0	0.6	5.1	7	3.5	1.4	7.0
Hypersensitivity	0	0.0	0.0	1.8	2	1.0	0.1	3.6	3	1.5	0.3	4.3
Seasonal allergy	2	1.0	0.1	3.6	0	0.0	0.0	1.8	2	1.0	0.1	3.5
Arthritis reactive	1	0.5	0.0	2.8	0	0.0	0.0	1.8	0	0.0	0.0	1.8
Hyperthyroidism	0	0.0	0.0	1.8	1	0.5	0.0	2.8	0	0.0	0.0	1.8
Allergy to arthropod sting	0	0.0	0.0	1.8	1	0.5	0.0	2.8	0	0.0	0.0	1.8
Arthritis	0	0.0	0.0	1.8	0	0.0	0.0	1.8	1	0.5	0.0	2.7
Dermatitis allergic	0	0.0	0.0	1.8	0	0.0	0.0	1.8	1	0.5	0.0	2.7
Gastritis erosive	0	0.0	0.0	1.8	0	0.0	0.0	1.8	0	0.0	0.0	1.8
Urticaria	0	0.0	0.0	1.8	0	0.0	0.0	1.8	0	0.0	0.0	1.8

	Pooled Group N = 598				**80L Group N = 200**			
	n	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**
At least one symptom	14	2.3	1.3	3.9	3	1.5	0.3	4.3
Hypersensitivity	5	0.8	0.3	1.9	0	0.0	0.0	1.8
Seasonal allergy	4	0.7	0.2	1.7	0	0.0	0.0	1.8
Arthritis reactive	1	0.2	0.0	0.9	1	0.5	0.0	2.8
Hyperthyroidism	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Allergy to arthropod sting	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Arthritis	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Dermatitis allergic	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Gastritis erosive	0	0.0	0.0	0.6	1	0.5	0.0	2.8
Urticaria	0	0.0	0.0	0.6	1	0.5	0.0	2.8

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with an administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable (s):
During the active phase of the study (from Month 0 up to Month 7), medically significant AEs were reported by 71 (11.9%) subjects in the Pooled Group and by 23 (11.5%) in the 80L Group (Total Vaccinated Cohort).

Secondary Outcome Variable (s):

Percentage of subjects reporting the occurrence of NOCDs during the entire follow-up period (Month 0 to Month 12) (Total Vaccinated Cohort)

New Onset Chronic Diseases	600L L1 Group N = 199				600L L2 Group N = 198				600L L3 Group N = 201			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL			LL	UL
At least one symptom	4	2.0	0.6	5.1	4	2.0	0.6	5.1	7	3.5	1.4	7.0
Autoimmune thyroiditis	0	0.0	0.0	1.8	0	0.0	0.0	1.8	1	0.5	0.0	2.7
Hypersensitivity	0	0.0	0.0	1.8	2	1.0	0.1	3.6	3	1.5	0.3	4.3
Seasonal allergy	2	1.0	0.1	3.6	0	0.0	0.0	1.8	2	1.0	0.1	3.5
Arthritis reactive	1	0.5	0.0	2.8	0	0.0	0.0	1.8	0	0.0	0.0	1.8
Allergy to arthropod sting	0	0.0	0.0	1.8	1	0.5	0.0	2.8	0	0.0	0.0	1.8
Arthritis	0	0.0	0.0	1.8	0	0.0	0.0	1.8	1	0.5	0.0	2.7
Autoimmune thyroiditis	0	0.0	0.0	1.8	0	0.0	0.0	1.8	1	0.5	0.0	2.7
Basedow's disease	1	0.5	0.0	2.8	0	0.0	0.0	1.8	0	0.0	0.0	1.8
Dermatitis allergic	0	0.0	0.0	1.8	0	0.0	0.0	1.8	1	0.5	0.0	2.7
Gastritis erosive	0	0.0	0.0	1.8	0	0.0	0.0	1.8	0	0.0	0.0	1.8
Hyperthyroidism	0	0.0	0.0	1.8	1	0.5	0.0	2.8	0	0.0	0.0	1.8
Urticaria	0	0.0	0.0	1.8	0	0.0	0.0	1.8	0	0.0	0.0	1.8

	Pooled Group N = 598				80L Group N = 200			
	n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL
At least one symptom	15	2.5	1.4	4.1	3	1.5	0.3	4.3
Autoimmune thyroiditis	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Hypersensitivity	5	0.8	0.3	1.9	0	0.0	0.0	1.8
Seasonal allergy	4	0.7	0.2	1.7	0	0.0	0.0	1.8
Arthritis reactive	1	0.2	0.0	0.9	1	0.5	0.0	2.8
Allergy to arthropod sting	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Arthritis	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Autoimmune thyroiditis	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Basedow's disease	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Dermatitis allergic	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Gastritis erosive	0	0.0	0.0	0.6	1	0.5	0.0	2.8
Hyperthyroidism	1	0.2	0.0	0.9	0	0.0	0.0	1.8
Urticaria	0	0.0	0.0	0.6	1	0.5	0.0	2.8

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with an administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable (s):
During the entire study follow-up (from Month 0 up to Month 12), medically significant AEs were reported by 78 (13.0%) subjects in the Pooled Group and by 23 (11.5%) in the 80L Group (Total Vaccinated Cohort).

Safety Results: Number (%) of subjects with unsolicited AEs during the active phase (up to Month 7) (Total Vaccinated Cohort)

Most frequent adverse events* - On-Therapy (occurring within Day 0-29 following vaccination)	600L L1 Group N = 199	600L L2 Group N = 198	600L L3 Group N = 201	Pooled Group N = 598	80L Group N = 200
Subjects with any AE(s), n (%)	58 (29.1)	56 (28.3)	76 (37.8)	190 (31.8)	67 (33.5)
Subjects with Grade 3** AE(s), n (%)	5 (2.5)	6 (3.0)	14 (7.0)	25 (4.2)	7 (3.5)
Subjects with related*** AE(s), n (%)	22 (11.1)	23 (11.6)	30 (14.9)	75 (12.5)	32 (16.0)
Nasopharyngitis	8 (4.0)	8 (4.0)	10 (5.0)	26 (4.3)	7 (3.5)
Injection site pruritus	7 (3.5)	3 (1.5)	4 (2.0)	14 (2.3)	10 (5.0)
Cystitis	7 (3.5)	3 (1.5)	4 (2.0)	14 (2.3)	3 (1.5)
Injection site induration	4 (2.0)	3 (1.5)	3 (1.5)	10 (1.7)	2 (1.0)

Pharyngolaryngeal pain	4 (2.0)	3 (1.5)	2 (1.0)	9 (1.5)	3 (1.5)
Injection site reaction	1 (0.5)	5 (2.5)	3 (1.5)	9 (1.5)	2 (1.0)
Influenza	2 (1.0)	2 (1.0)	4 (2.0)	8 (1.3)	3 (1.5)
Dizziness	1 (0.5)	4 (2.0)	3 (1.5)	8 (1.3)	2 (1.0)
Vaginal infection	3 (1.5)	2 (1.0)	2 (1.0)	7 (1.2)	4 (2.0)
Headache	1 (0.5)	3 (1.5)	4 (2.0)	8 (1.3)	1 (0.5)
Pharyngitis	3 (1.5)	3 (1.5)	2 (1.0)	8 (1.3)	1 (0.5)
Sinusitis	3 (1.5)	0 (0.0)	4 (2.0)	7 (1.2)	3 (1.5)
Acne	0 (0.0)	2 (1.0)	2 (1.0)	4 (0.7)	3 (1.5)
Cough	1 (0.5)	0 (0.0)	3 (1.5)	4 (0.7)	3 (1.5)
Neck pain	0 (0.0)	3 (1.5)	2 (1.0)	5 (0.8)	0 (0.0)
Vaginal candidiasis	0 (0.0)	3 (1.5)	1 (0.5)	4 (0.7)	1 (0.5)

* More than 30 subjects/treatment group and > 3 groups: the most frequent 5 events in each treatment group are presented.
** Grade 3 AE: AE that prevented normal activity
*** Related AE: AE considered by the investigator to be causally related to the study vaccination

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) during the active phase of the study (up to Month 7) (Total Vaccinated Cohort)

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

All SAEs	**600L L1 Group N = 199**	**600L L2 Group N = 198**	**600L L3 Group N = 201**	**Pooled Group N = 598**	**80L Group N = 200**
Subjects with any SAE(s), n (%) [n related]	2 (1.0) [0]	0 (0.0) [0]	2 (1.0) [0]	4 (0.7) [0]	3 (1.5) [0]
Appendicitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (1.0) [0]
Femur fracture	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Intervertebral disc protrusion	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	1 (0.2) [0]	0 (0.0) [0]
Pelvic inflammatory disease	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Road traffic accident	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	1 (0.2) [0]	0 (0.0) [0]
Supraventricular tachycardia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Syncope	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Fatal SAEs	**600L L1 Group N = 199**	**600L L2 Group N = 198**	**600L L3 Group N = 201**	**Pooled Group N = 598**	**80L Group N = 200**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) during the during the entire follow-up period (Month 0 to Month 12) (Total Vaccinated Cohort)

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

All SAEs	**600L L1 Group N = 199**	**600L L2 Group N = 198**	**600L L3 Group N = 201**	**Pooled Group N = 598**	**80L Group N = 200**
Subjects with any SAE(s), n (%) [n related]	6 (3.0) [0]	1 (0.5) [0]	2 (1.0) [0]	9 (1.5) [0]	3 (1.5) [0]
Appendicitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (1.0) [0]
Abortion missed	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Abortion spontaneous	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Basedow's disease	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Cerebral malaria	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Femur fracture	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Intervertebral disc protrusion	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	1 (0.2) [0]	0 (0.0) [0]
Pelvic inflammatory disease	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Road traffic accident	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	1 (0.2) [0]	0 (0.0) [0]
Supraventricular tachycardia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Syncope	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Tuberculosis	1 (0.6) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]
Fatal SAEs	**600L L1 Group**	**600L L2 Group**	**600L L3 Group**	**Pooled Group**	**80L Group**

	N = 199	N = 198	N = 201	N = 598	N = 200
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: Lot to lot consistency for the 3 HPV lots manufactured at 600L scale and non inferiority to HPV vaccine produced at 80L scale were assessed. One month after Dose 3 (i.e. Month 7), all subjects from all study groups seropositive for anti-HPV-16 and anti-HPV-18 antibodies. During the active phase of the study (up to Month 7), unsolicited AEs were reported for 190 (31.8%) and 67 (33.5%) subjects from the Pooled group and the 80L Group, respectively; SAEs were reported for 4 and 3 subjects from the Pooled group and the 80L Group, respectively. During the extended safety follow-up period (from Month 7 to Month 12), SAEs were reported for 3 subjects from the Pooled group. None of the SAEs were considered by the investigator to be related to the study vaccination. No fatal SAEs were reported throughout the study.

Date of update: 21-July-2014