APPENDIX 1: Primary and secondary immunogenicity objectives in study HAV-048 and respective results which did not provide support for approval of supplement are included in Appendix 1.

Primary Immunogenicity Objective – Evaluate immunogenicity of HPV 16/18 L1 VLP AS04 vaccine one month after the last dose when administered at different dosages (20 or 40μg of each HPV antigen) and on different sche4dules (0, 2 or 0, 6 months) compared with the standard HPV 16/18 L1 VLP AS04 vaccine administered on a 3 dose schedule (0, 1 and 6 months).

Secondary Immunogenicity Objectives: – Includes three sequential secondary immunogenicity objectives. [See Appendix 1 for these objectives and results.]

- **First secondary immunogenicity objective:** Demonstrate non-inferiority of two different formulations (20 or 40μg of each HPV type) on different schedules (0, 2 or 0, 6 months) in 9-14 year old subjects with standard dose and regimen (20μg of each HPV antigen given at 0, 2 and 6 months) in 15-25 year old subjects. *Non-inferiority was demonstrated if the upper limit of the 95% confidence interval (CI) for the geometric mean titer (GMT) ratio between the standard 3-dose schedule of HPV-16/18 L1 VLP AS04 vaccine in subjects 15 - 25 years of age over the 2-dose schedules in the 9 - 14 year age stratum was below 2. If NI proven, proceed to next secondary immunoegenicity objective.*
- **Second secondary immunogenicity objective:** Demonstrate non-inferiority of two different formulations (20 or 40μg of each HPV type) on different schedules (0, 2 or 0, 6 months) in 15-19 year old subjects with standard dose and regimen (20μg of each HPV antigen given at 0, 2 and 6 months) in 15-25 year old subjects. *Non-inferiority was demonstrated if the upper limit of the 95% confidence interval (CI) for the geometric mean titer (GMT) ratio between the standard 3-dose schedule of HPV-16/18 L1 VLP AS04 vaccine in subjects 15 - 25 years of age over the 2-dose schedules in the 15 - 25 year age stratum was below 2. If NI demonstrated, proceed to the third secondary immunogenicity objective.*
- **Third secondary immunogenicity objective:** Demonstrate non-inferiority of two different formulations (20 or 40μg of each HPV type) on different schedules (0, 2 or 0, 6 months) in 20-25 year old subjects with standard dose and regimen (20μg of each HPV antigen given at 0, 2 and 6 months) in 15-25 year old subjects. *Non-inferiority was demonstrated if the upper limit of the 95% confidence interval (CI) for the geometric mean titer (GMT) ratio between the standard 3-dose schedule of HPV-16/18 L1 VLP AS04 vaccine in subjects 15 - 25 years of age over the 2-dose schedules in the 20-25 year age stratum was below 2.*

If any of the secondary immunogenicity objectives were not demonstrated, the Following objective was to be evaluated:

- Examine the pair-wise comparisons of the antibody response between the 2-dose schedule group and the 3-dose schedule group, one month after the last dose of vaccine within each age stratum.
- Evaluate the antibody response to all dose schedules and dosages of the HPV 16/18 L1 VLP AS04 vaccine in each age stratum during the extended follow-up period (at Month 12, Month 18, and Month 24).

Statistical considerations: The sample size of 960 enrolled subjects (768 evaluable subjects) was to allow detection of a 2-fold difference between the four groups in terms of GMTs (HPV-16 and -18 ELISA titers) one month after the last dose with at least 90% power (α=0.025 for both HPV-16 and HPV-18).

Interim Analysis: See Appendix 1. An unblinded interim immunogenicity analysis was planned after all subjects in all 2-dose schedule groups had completed Visit 3 (Month 3, Post vaccination II). This analysis was performed on the Total Vaccinated Cohort by an external statistician to safeguard the blinding in the remainder of the trial. No stopping rules were applied. Since the primary endpoint was immunogenicity at Month 7, no adjustment was made for the analysis at Month 3.

Immunogenicity Results:

The immune responses were noted to be generally similar for Groups 1 and 2 at 1 month after the last dose of active vaccine (dose 3 for Group 1 and dose 2 for Group 2). These are presented in Table A1 for HPV-16 VLP and in Table A2 for HPV-18 for subjects in the ATP cohort for immunogenicity.

Table A1: Study HPV-048 - Seropositivity rates and geometric mean titers (GMT) for anti-HPV-16 antibody titers by treatment group group at Month 7 (1 month after last dose of Cervarix (ATP cohort for immunogenicity) [Groups 1 and 2]

		≥ 8 ELUmL			GMT	
Group	Timing	n/N	%	95% CI	Value	95% CI
1: 20/20 @ M0, 1, 6	M7	208/208	100%	98.2, 100%	13045.3	11211.4, 15179.2
2: 20/20 @ M0, 6	M7	204/204	100%	98.2, 100%	7741.6	6868.2, 8726.1

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
Source: STN 125259/132.2, Module 5.3.5.1.3, CSR HPV-048, Table 22, p. 86

Table A2: Study HPV-048 - Seropositivity rates and geometric mean titers (GMT) for anti-HPV-18 antibody titers by treatment group at Month 7 (1 month after last dose of Cervarix (ATP cohort for immunogenicity) [Groups 1 and 2]

		≥ 7 ELUmL			GMT	
Group	Timing	n/N	%	95% CI	Value	95% CI
1: 20/20 @ M0, 1, 6	M7	208/208	100%	98.2, 100%	5087.1	4460.2, 5802.1
2: 20/20 @ M0, 6	M7	204/204	100%	98.2, 100%	4811.4	4282.7, 5405.3

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
Source: STN 125259/132.2, Module 5.3.5.1.3, CSR HPV-048, Table 24, p. 90

When the 20/20 mg formulation administered either at M0, 1, and 6 (group 1) as compared to M0 and 6 (group 2), the following were noted:

- **HPV-16 immune response:** All subjects in groups 1 and 2 in the ATP cohort for immunogenicity seroconverted for antibodies to HPV-16 by ELISA (i.e., had a higher GMT than the assay cutoff) at 1 month after the last dose of vaccine received (month 7), although the GMTs were lower in the group that received 2 doses of vaccine as compared to the group who received the vaccine at the approved dosing regimen and 95% CIs did not overlap for GMTs.
- **HPV-18 immune response:** All subjects in both groups 1 and 2 in the ATP cohort for immunogenicity seroconverted for antibodies to HPV-18 by ELISA (i.e., had a higher GMT than the assay cutoff) at 1 month after the last dose of vaccine received (month 7),and the GMTs were only slightly lower in the group that received 2 doses of active vaccine as compared to the group who received the vaccine at the approved dosing regimen (95% CIs overlapped for GMTs).

When the 40/40μg formulation at M0 and 6 (Group 3) as compared to Month 0 and 2 (Group 4), the following were noted:

- **HPV-16 immune responses:** At Month 7, both groups 3 and 4 had seropositivity rates of 100%. At Month 7, GMTs were higher in Group 3 (10500.9 [95% CI: 9356.9, 11784.8]) as compared to Group 4 (1483.0 [95% CI: 1311.0, 1677.5]). Although this supplement will not support change in dosage, the 95% CIs for immune responses in subjects who received the 40/40μg formulation at Months 0 and 6 were similar to those who received the licensed 20/20μg formulation according to the licensed regimen at Months 0, 1, and 6 with overlapping 95% CIs. Subjects who received the 40/40μg formulation at Months 0 and 2 had the lowest GMTs at Month 7 (as compared to the other 3 groups). For HPV-18 immune responses.
- **HPV-18 immune responses:** At Month 7, both groups 3 and 4 had seropositivity rates of 100%. At Month 7, GMTs were higher in Group 3 (5997.5 [95% CI: 5310.9, 6772.8]) as compared to Group 4 (817.3 [95% CI: 715.6, 933.4]). While emphasizing that this supplement will not support change in dosage or dosing regimen, it was noted that the 95% CIs for the 40/40μg formulation who received doses at Months 0 and 6 were similar to those who received the licensed 20/20μg formulation at the licensed regimen at Months 0, 1, and 6 with overlapping 95% CIs. Subjects who received the 40/40μg formulation at Months 0 and 2 had the lowest GMTs at Month 7 (as compared to the other 3 groups).

Comparison of immune responses by age group: Tables A3 and A4 below present seroconversion rates and GMTs for anti-HPV 16 and anti-HPV-18 for Groups 1 and 2 by age group, respectively.

Table A3: Study HPV-048 - Seropositivity rates and geometric mean titers (GMT) for anti-HPV-16 antibody titers by treatment group and age strata at Month 7 (1 month after last dose of Cervarix (ATP cohort for immunogenicity) [Groups 1 and 2]

			≥ 8 ELUmL			GMT	
Treatment Group	Age Group	Timing	n/N	%	95% CI	Value	95% CI
1: 20/20 @ M0, 1, 6	9-14 years	M7	75/75	100%	95.2, 100%	22066.3	18140.7, 26841.2
	15-19 years		66/66	100%	94.6, 100%	12817.4	9723.2, 16896.2
	20-25 years		67/67	100%	94.6, 100%	7370.0	5673.6, 9573.6
2: 20/20 @ M0, 6	9-14 years	M7	69/69	100%	94.8, 100%	11058.6	9273.8, 13186.7
	15-19 years		70/70	100%	94.9, 100%	7869.6	6488.9, 9543.9
	20-25 years		65/65	100%	94.5, 100%	5209.2	4166.5, 6512.7

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
Source: STN 125259/132.2, Module 5.3.5.1.3, CSR HPV-048, Table 23, p. 87-89

Table A4: Study HPV-048 - Seropositivity rates and geometric mean titers (GMT) for anti-HPV-18 antibody titers by treatment group and age strata at Month 7 (1 month after last dose of Cervarix (ATP cohort for immunogenicity) [Groups 1 and 2]

			≥ 7 ELUmL			GMT	
Treatment Group	Age Group	Timing	n/N	%	95% CI	Value	95% CI
1: 20/20 @ M0, 1, 6	9-14 years	M7	75/75	100%	95.2, 100%	7192.9	5952.6, 8691.6
	15-19 years		66/66	100%	94.6, 100%	4907.0	3780.8, 6368.7
	20-25 years		67/67	100%	94.6, 100%	3576.8	2886.5, 4432.2
2: 20/20 @ M0, 6	9-14 years	M7	69/69	100%	94.8, 100%	5630.7	4772.1, 6643.7
	15-19 years		69/69	100%	94.8, 100%	5039.3	4283.4, 5928.5
	20-25 years		66/66	100%	94.6, 100%	3889.2	2980.9, 5074.3

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
Source: STN 125259/132.2, Module 5.3.5.1.3, CSR HPV-048, Table 25, p. 91-93

Immune responses by Age Strata:

- **HPV-16 immune response:**
  - In Groups 1 and 2 (ATP cohort for immunogenicity), all subjects in different age strata seroconverted for anti-HPV 16 at Month 7 (1 month after last dose of active vaccine). GMTs were higher in subjects in Group 1 who received three doses of Cervarix as compared to subjects in Group 2 who received two doses of Cervarix. For the 9-14 year old and 15-19 year old age groups, GMTs were higher in the three dose group in both age strata and 95% CIs around those GMTs did not overlap. In the 20-25 year old age strata, although GMTs were higher in the three dose Cervarix group as compared to the two dose Cervarix group, 95% CIs around the GMTs of all age strata overlapped.
  - In Groups 3 and 4, subjects in the 9-14 year age group had the highest GMTs as compared to the 15-19 years and 20-25 years strata.
- **HPV-18 immune response:**
  - In Groups 1 and 2, all subjects in the different age strata seroconverted at 1 month after the last dose of Cervarix in both groups for anti-HPV 18, and all 95% CIs around GMTs overlapped for the three age groups when groups 1 and 2 are compared. For both antigens and in all study groups, there was a decrease in GMTs as a function of age, which was less pronounced for HPV-18 than for HPV-16.

- In Groups 3 and 4, subjects in the 9-14 year age group had the highest GMTs as compared to subjects 15-19 and 20-25 years of age.

Total Vaccinated Cohort: Seropositivity rates and GMTs in the Total Vaccinated Cohort were comparable to those presented for the ATP cohort for immunogenicity. (Source; STN 125259/132.2, Module 5.3.5.1.3, Supplements 16-19, pp. 156-163, not shown here).

Inferential analyses conducted: In pre-specified primary analyses, GSK conducted pair-wise comparisons between the two-dose group and the three-dose standard group using Dunnett's tests. The standard Cervarix dosing was to be considered superior to a 2-dose formulation/schedule if the lower limit of the 95%CI was inferior to 0.5 (2-fold difference). Using these criteria, the standard Cervarix dosing was not "superior" to the two-dose regimen for immune responses to both HPV-16 and HPV-18.

In the secondary analyses, immune responses to HPV-16 and HPV-18 were compared by age group and treatment group. Immune response for HPV 16 and HPV 18 in the 20µg/20µg M0, 6 group were non-inferior in 9-14 year old subjects compared to the standard dosing of Cervarix vaccine in subjects 15-25 years of age because for each comparison, the UL of the 95% CI around the GMT ratio (standard 3-dose/2-dose) was < 2.0. These comparisons are shown in Table A5 for anti-HPV 16 immune responses and in Table A6 for anti-HPV 18 immune responses.

Table A5: Study HPV-048 - Non-inferiority of the anti-HPV-16 titers response to the 2-dose schedule of Cervarix in subjects 9- 14 years of age stratum compared to the standard 3-dose schedule in subjects 15-25 years of age, one month after the last dose of active vaccine (ATP cohort for immunogenicity)

Standard 3-dose regimen		2-dose regimen		GMT ratio 3-dose/2-dose	
N	GMT	N	GMT	Value	95% CI
111	10322.0	65	11066.9	0.93	0.68, 1.28

GMT = geometric mean antibody titer
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance)
Source: STN 125259/132.2, Module 5.3.5.1.3, CSR HPV-048, Table 32, p. 100

Table A6: Study HPV-048 - Non-inferiority of the anti-HPV-18 titers response to the 2-dose schedule of Cervarix in subjects 9- 14 years of age stratum compared to the standard 3-dose schedule in subjects 15-25 years of age, one month after the last dose of active vaccine (ATP cohort for immunogenicity)

Standard 3-dose regimen		2-dose regimen		GMT ratio 3-dose/2-dose	
N	GMT	N	GMT	Value	95% CI
114	4261.5	64	5509.8	0.77	0.59, 1.01

GMT = geometric mean antibody titer
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance)
Source: STN 125259/132.2, Module 5.3.5.1.3, CSR HPV-048, Table 35, p. 103

Safety: Additional Safety Tables

Table A7: Listing of Subjects with Grade 3 Unsolicited Adverse Events - Treatment Group 1

PID	Age	Event by PT	Time to event	Duration of event	Serious or non-serious	Related or unrelated	Recovered or not recovered
Group 1							
722	12	Dysmenorrhea	3 days after dose 1	3 days	Not serious	Related	Recovered Received doses 2 & 3
163	13	Pharyngolaryngeal pain	Day of dose 1	4 days	Not serious	Unrelated	Recovered Received doses 2 & 3
719	14	Vomiting Abdominal pain Headache	21 days after dose 1	1 day	Not serious	Unrelated	Recovered Received doses 2 & 3
201	14	Joint sprain (right ankle)	28 days after dose 1	11 days	Not serious	Unrelated	Recovered Received doses 2 & 3
180	15	Arthralgia (right elbow)	25 days after dose 1	1 day	Not serious	Unrelated	Recovered Received doses 2 & 3
117	17	Pharyngolaryngeal pain Saliva altered	Day of dose 1	7 days	Not serious	Unrelated	Recovered Received doses 2 & 3
714	17	Nausea Dysmenorrhea	14 days after dose 3	1 day	Not serious	Unrelated	Recovered
169	18	Appendicitis	2 days after dose 1	5 days	Serious	Unrelated	Recovered Received doses 2 & 3
742	18	Back injury	6 days after dose 3	13 days	Not serious	Unrelated	Recovered
2262	22	Nasopharyngitis	5 days after dose 1	7 days	Not serious	Unrelated	Recovered Received doses 2 & 3
134	22	Drug toxicity	2 days after dose 2	3 days	Not serious	Unrelated	Recovered Received dose 3
83	22	Neck and back pain	13 days after dose 1	12 days	Not serious	Unrelated	Recovered Received doses 2 & 3
16	23	Rash Migraine	20 days after dose 3 27 days after dose 3	1 day 1 day	Not serious	Unrelated	Recovered

Source: STN 125259/132.1, Module 5.3.1.25.3.1, CSR HPV-048, wunsol.xpt dataset and pid.xpt and wdates.xpt.

Table A8: Listing of Subjects with Grade 3 Unsolicited Adverse Events - Treatment Group 2

PID	Age	Event by PT	Time to event	Duration of event	Serious or non-serious	Related or unrelated	Outcome
Group 2							
707	11	Gastroenteritis	20 days after dose 2 [ALUM]	5 days	Not serious	Related	Received dose 3
101	13	Left arm pain	Day of dose 1	3 days	Not serious	Unrelated	Received dose 3
1597	13	Induration left upper arm	1 day after dose 3	1 day	Not serious	Related	Recovered
56	14	Influenza like illness	25 days after dose 2 [ALUM]	3 days	Not serious	Unrelated	Received dose 3
766	14	Food allergy	57 & 76 days after dose 2 [ALUM]	1 day each event	Not serious	Unrelated	Received dose 3
148	15	Dizziness	1 day after dose 1	5 days	Not serious	Related	Received doses 2 and 3
17	16	Muscle strain (chest wall) Pain (wisdom tooth extraction)	29 days after dose 2 13 days after dose 2 [ALUM]	32 days 9 days	Not serious Not serious	Unrelated Unrelated	Recovered Received dose 3
708	16	Gastrointestinal disorder	29 days after dose 2 [ALUM]	8 days	Not serious	Related	Recovered Received dose 3
124	20	Mumps	21 days after dose 3	14 days	Not serious	Unrelated	Recovered
2223	20	Nasopharyngitis	2 days after dose 2 [ALUM]	5 days	Not serious	Unrelated	Received dose 3
12	21	Pharyngitis	11 days after dose 1	27 days	Not serious	Unrelated	Received doses 2 and 3
197	21	Influenza like illness	22 days after dose 2 [ALUM]	2 days	Not serious	Unrelated	Received dose 3
177	21	Back pain	22 days after dose 2 [ALUM]	5 days	Not serious	Unrelated	Received dose 3
258	23	Dysmenorrhea, exacerbation Infection (wisdom tooth)	16 days after dose 1 17 days after dose 2[ALUM]	93 days 7 days	Not serious Not serious	Unrelated Unrelated	Received dose 2 Received dose 3
265	23	Headache (worsening intermittent)	7 days after dose 2 [ALUM]	5 days	Not serious	Unrelated	Received dose 3
34	25	Pharyngitis streptococcal	7 days after dose 2 [ALUM]	17 days	Not serious	Unrelated	Received dose 3
619	25	Appendicitis	59 days after dose 2 [ALUM]	4 days	Serious	Unrelated	Received dose 3
2251	25	MVA	15 days after dose 3	29 days	Serious	Unrelated	Recovered

Source: STN 125259/132.1, Module 5.3.1.25.3.1, CSR HPV-048, wunsol.xpt dataset and pid.xpt and wdates.xpt

Table A9: Listing of Subjects with Grade 3 Unsolicited Adverse Events - Treatment Group 3

PID	Age	Event by PT	Time to event	Duration of event	Serious or non-serious	Related or unrelated	Outcome
Group 2							
262	13	First degree burns	12 days after dose 2 [ALUM]	15 days	Not serious	Unrelated	Received dose 3
272	13	Headache	28 days after dose 2 [ALUM]	84 days	Not serious	Unrelated	Received dose 3
706	13	Headache	23 days after dose 2 [ALUM]	8 days	Not serous	Related	Received dose 3
181	14	Hypoacusis Blurred vision Chest discomfort Asthenia Dizziness Hyperhidrosis	12 days after dose 2 [ALUM]	1 day	Not serious	Unrelated	Received dose 3
762	14	Tendonitis	22 days after dose 1	107 days	Not serious	Unrelated	Received doses 2 and 3
720	14	Uterine leiomyoma Vaginitis	1 day after dose 1 4 days after dose 1	21 days 8 days	Not serious Not serious	Unrelated Unrelated	Recovered Recovered Received doses 2 and 3
212	15	Concussion after MVA	19 days after dose 1	Ongoing	Not serious	Unrelated	Ongoing, Received doses 2 and 3
519	16	Psychotic disorder	28 days after dose 2 [ALUM]	Ongoing	Serious	Unrelated	Ongoing, did not receive dose 3
7	17	Renal colic, exacerbation	4 days after dose 2 [ALUM]	52 days	Not serious	Unrelated	Received dose 3
138	19	Sinusitis	25 days after dose 1	5 days	Not serious	Unrelated	Received doses 2 and 3
27	20	Influenza like illness	21 days after dose 3	8 days	Not serious	Unrelated	Recovered
130	21	Irritable bowel syndrome, exacerbation	28 days after dose 1	1 day	Not serious	Unrelated	Received doses 2 and 3
603	21	Diarrhea	12 days after dose 2 [ALUM]	6 days	Not serious	Unrelated	Received dose 3
2247	23	Ear pain	1 day after dose 1	3 days	Not serious	Unrelated	Received doses 2 and 3
39	23	Tooth infection	3 days after dose 1	13 days	Not serious	Unrelated	Received doses 2 and 3
264	23	Pharyngitis streptococcal	28 days after dose 2 [ALUM]	Ongoing	Not serious	Unrelated	Ongoing, did not receive dose 3
167	24	Fatigue Tooth infection	44 days after dose 1 3 days after dose 2 [ALUM]	122 days 22 days	Not serious Not serious	Unrelated Unrelated	Received dose 3

Source: STN 125259/132.1, Module 5.3.1.25.3.1, CSR HPV-048, wunsol.xpt dataset and pid.xpt and wdates.xpt

Table A10: Listing of Subjects with Grade 3 Unsolicited Adverse Events - Treatment Group 4

PID	Age	Event by PT	Time to event	Duration of event	Serious or non-serious	Related or unrelated	Outcome
Group 2							
110	9	Nasopharyngitis	20 days after dose 1	4 days	Not serious	Unrelated	Received doses 2 and 3
228	10	Dizziness	Day of dose 2	4 days	Not serious	Unrelated	Received dose 3
81	12	Irritable bowel syndrome	33 days after dose 2	Ongoing	Not serious	Unrelated	Ongoing, Received dose 3
1599	13	Skin injury	Day of dose 1	2 days	Not serious	Unrelated	Received doses 2 and 3
155	13	Musculoskeletal stiffness	5 days after dose 2	8 days	Not serious	Unrelated	Received dose 3
161	13	Cough Pharyngolaryngeal pain	1 day after dose 3 [ALUM]	5 days	Not serious	Unrelated	Recovered
777	14	Abdominal pain Musculoskeletal chest pain Dysmenorrhea	1 day after dose 1 1 day after dose 1 6 days after dose 3 [ALUM]	2 days 2 days 6 days	Not serious Not serious Not serious	Related Related Related	Recovered, Received dose 2 Recovered, Received dose 2 Recovered
182	14	Influenza like illness	24 days after dose 2	8 days	Not serious	Unrelated	Received dose 3
51	15	Peritonsillar abscess	19 days after dose 1	34 days	Not serious	Unrelated	Received doses 2 and 3
765	16	Joint sprain (ankle)	1 day after dose 1	3 days	Not serious	Unrelated	Received doses 2 and 3
154	17	Dyspepsia	45 days after dose 1	8 days	Not serious	Unrelated	Received doses 2 and 3
72	17	Pharyngolaryngeal pain	3 days after dose 3 [ALUM]	2 days	Not serious	Unrelated	Recovered
775	17	Pharyngolaryngeal pain	4 days after dose 2	7 days	Not serious	Related	Received dose 3
2253	19	Injection site pruritus	1 day after dose 2	2 days	Not serious	Related	Received dose 3
2268	19	Myometritis and adnexitis	6 days after dose 2	13 days	Not serious	Unrelated	Received dose 3
35	21	Influenza like illness	19 days after dose 3 [ALUM]	6 DAYS	Not serious	Unrelated	Recovered
2257	25	Vestibular neuronitis	107 days after dose 2	10 days	Serious	Unrelated	Received dose 3
165	25	Abdominal pain Coccydynia	163 days after dose 1 135 days after dose 1	14 days 27 days	Serious Serious	Unrelated Unrelated	Recovered, did not receive doses 2 and 3 (Pregnancy) Recovered
295	25	Drug toxicity unknown drug	16 days after dose 3 [ALUM]	3 days	Not serious	Unrelated	Recovered

Source: STN 125259/132.1, Module 5.3.1.25.3.1, CSR HPV-048, wunsol.xpt dataset and pid.xpt and wdates.xpt

Table A11: Study HPV-048 – Serious Adverse Events by Treatment Groups and Age Strata

Treatment Group #-formulation @ regimen	Age Group (years)	PID, age, race, country	SAE	Onset postdose X duration (days)	Grade	Related/Not Related Comments	Out
1-20/20 @ 0, 1, 6 M [OPEN]	9-17	2322, 14yo, white, GE	Erythema multiforme, polyarthritis	147 days postdose 3x4d	2	NR (IgM + mycoplasma)	Res
		102, 15yo, white, CA	Grave's disease	13 days postdose 2	1	NR (TSH ↓ and Thyroid Ab ↑ day of dose 1)	Ong
		224, 15yo, white, CA	Abnormal behavior	60 days postdose 3x4d	2	NR (alcohol and ecstasy ingestion, hx Wilson's disease)	Res
	18-25	169, 18yo, white, CA	Appendicitis	3 days postdose 1 x 5d	3	NR	Res
		1566, 21yo, white, GE	Depression	45 days postdose 3	3	NR	Ong
2-20/20 @ 0, 6 M $Al(OH)_3$ @ 2 months [Vaccinator blinded]	9-17	1663, 11yo, white, GE	Humerus fracture	78 days postdose 3x74d	3	NR	Res
		1546, 15yo, white, GE	Basilar artery thrombosis	168 days postdose 3	3	NR	Ong
		2006, 17yo, white, GE	Bulimia	96 days postdose 2[A]	2	NR	Ong, imp
	18-25	1627, 18yo, white, GE	Circulatory collapse [H – no abnls]	28 days postdose 2[A]x4d	2	NR	Res
		506, 23yo, wihte, CA	Depression [hx bipolar, on paxil]	29 days postdose 2[A]x90d	2	NR	Res
		619, 25yo, Native Am, CA	Appendicitis	59 days postdose 2[A]x4d	3	NR	Res
		2251, 25yo, white, GE	Motorcycle accident	15 days postdose 3x29d	3	NR	Res
3-40/40 @ 0, 6 M $Al(OH)_3$ @ 2 months [Vaccinator blinded]	9-17	1999, 10yo, white, GE	Tibial fracture	44 days postdose 2 [A]x4d	1	NR	Res
		2407, 10yo, white, GE	Appendicitis	163 days postdose 3x15d	2	NR	Res
		2411, 15yo, white, GE	Fibroma leg Fibrosarcoma	6 days postdose 2[A] x 107 days [1/20/08-5/508] 49 days postdose 3 [6/23/08-]	2	NR	Res Imp
		519, 16yo, white-North African, CA	Psychosis [taking unknown med]	28 days postdose 2 [A] x ongoing	3	NR	Ong
	18-25	2293, 23yo, white, GE	Vestibular neuronitis	33 days postdose 1 x 9d	2	NR	Res
4-40/40 @ 0, 2 M $Al(OH)_3$ @ 6 months [Vaccinator blinded]	9-17	1897, 12yo, white, GE	Hepatomegaly Hx of abd pain 2 months pre-vax	4 days postdose 2 x 4d	2	NR	Res
		1783, 13yo, white, GE	Concussion (ski accident)	20 days postdose 1x2d	2	NR	Res
	18-25	165, 25yo, white, CA	Coccydinia Abdominal pain UTI Pregnant 2 M after dose 1	135 days postdose 1x27d 162 days postdose 1x14d 180 days postdose 1x4 d	3 3 2	NR NR NR	Res Res Res