Merck & Co., Inc. Study Synopsis

1. Proprietary Drug Name:	**2. Generic Drug Name:**	**3. Therapeutic area and FDA-approved indications:**
GARDASIL®	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine	GARDASIL® is a vaccine indicated in girls and women 9 to 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18: • Cervical cancer • Genital warts (condyloma acuminata) and the following precancerous or dysplastic lesions: • Cervical adenocarcinoma *in situ* (AIS) • Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3 • Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3 • Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3 • Cervical intraepithelial neoplasia (CIN) grade 1
4. Name of Sponsor/Company:	Merck & Co., Inc.	
5. Title of Study:	A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents NCT00092547 (PN018)	
6. Study Investigators/Study Center(s):	Multicenter (47)	
7. Studied Period (years): *(Date of first enrollment) (date of last completed)* 08-Oct-2003 to 19-Jan-2005. Clean file was achieved on 31-Jan-2005. The database was unblinded on 2-Feb-2005.		**8. Phase of development:** III

9. Primary Hypotheses and Secondary Hypothesis:

Primary Safety Hypothesis

The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents.

Secondary Immunogenicity Hypotheses

1. The quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induces noninferior immune responses with respect to each of the vaccine components individually at Week 4 Postdose 3 in preadolescent and adolescent boys who are seronegative to the relevant HPV type at Day 1, relative to preadolescent and adolescent girls who are seronegative to the relevant HPV type at Day 1. *(The statistical criterion for noninferiority requires that the lower bounds of the 95% confidence intervals for the fold difference in GMTs (boys/girls) exclude a decrease of 2-fold or more. Each vaccine HPV type will be analyzed separately.)*
2. Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine induces similar immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, 18 by Week 4 Postdose 3, in preadolescent/adolescent boys and preadolescent/adolescent girls. *(Each vaccine component will be analyzed separately. The assumed response rate to each HPV type is ~99%. The statistical criterion for non-inferiority requires that the lower bound of the 95% confidence interval for the difference in proportions between the 2 groups (boys-girls) exclude a decrease of 5 percentage points or more for each HPV type.)*

10. Study Design/ Methodology:	This study was a randomized, double-blind (operating under third party blinding and in-house blinding procedures), placebo-controlled, multicenter study with a target enrollment of approximately 1650 preadolescent and adolescent subjects.

11. Number of Patients (planned and analyzed):

SUBJECT DISPOSITION:

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	Non-Alum Placebo	Total
SCREENING FAILURES:			20
RANDOMIZED:	1184	597	1781
Female (age range – years)	617 (9 to 15)	322 (9 to 15)	939
Male (age range – years)	567 (9 to 16)	275 (9 to 15)	842
VACCINATED AT:			
Dose 1	1179	596	1775
Dose 2	1149	573	1722
Dose 3	1123	562	1685
VACCINATION PERIOD (Day 1 Through Month 7)			
ENTERED	1179	596	1775
COMPLETED	1120	560	1680
CONTINUING†	1	0	1
DISCONTINUED	58	36	94
With Long-Term Follow-Up	7	4	11
Clinical Adverse Experience	2	0	2
Other	5	4	9
Without Long-Term Follow-Up	51	32	83
Clinical Adverse Experience	1	0	1
Lost to Follow-up	17	7	24
Moved	4	1	5
Other Reasons	1	2	3
Parent withdrew consent	9	8	17
Withdrew consent	19	14	33

† Subject did not complete Month 7 visit prior to the Month 7 visit date cutoff of 19-Jan-2005.

HPV = Human papillomavirus; VLP = Virus-like particles.

12. Diagnosis and main criteria for inclusion:	Healthy preadolescent or adolescent subjects between the ages of 9 years and 0 days and 15 years and 364 days; must not yet have had coitarche and did not plan on becoming sexually active through the course of the study; must have agreed to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes; no temperature ≥100°F or ≥37.8°C (oral) within 24 hours prior to the first injection; not pregnant at study start (as determined by a serum pregnancy test or urine pregnancy test sensitive to 25 IU Human Chorionic Gonadotropin [hCG]) or is a male.
13. Test product and reference therapy (if applicable); dose and mode of administration; batch number:	Subjects received one 0.5-mL intramuscular dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine or non-aluminum-containing placebo at Day 1, Month 2, and Month 6. Formulation numbers and dosage for the clinical material can be found in the table that follows:

Formulation Numbers, Dosage, and Package Information for Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine and Placebo

Clinical Material	Formulation Number	Dosage	Package and Storage
Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	V501 VAI025T004	40/80/80/40 mcg plus 225 mcg aluminum adjuvant /mL 0.5 mL	0.75-mL single dose vial
Placebo for Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	PV501 VAI036P001	Carrier Solution Only /0.5 mL	0.75-mL single dose vial
HPV = Human papillomavirus; VLP = Virus-like particles.			

14. Duration of treatment:	Vaccination at Day 1, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after administration of each dose. All subjects will be followed for persistence of antibody response and safety evaluation through Month 18.

15. Criteria for Evaluation:

Immunogenicity: This study included 2 secondary objectives relating to immunogenicity. The first was to demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 competitive Luminex immunoassay (cLIA) responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls. Two immunogenicity measurements were used to address this objective: (1) geometric mean

anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 serum cLIA levels at Month 7; and (2) among subjects who were baseline naïve to HPV 6, HPV 11, HPV 16, and/or HPV 18, the proportion who became seropositive to the relevant vaccine HPV type by Month 7. Serum samples were to be collected from all subjects at Day 1, Month 7, and Month 18. The second immunogenicity objective was to describe the persistence of immune response to a 3-dose regimen of the vaccine. This objective will be addressed in a separate report summarizing immune responses through Month 18. **Safety:** The primary objective of this study related to the safety of the vaccine. The primary hypothesis stated that a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine will be generally well tolerated in adolescents and preadolescents. In order to address this objective, the study called for a detailed tolerability analysis, with emphasis on the following prespecified adverse experiences: vaccine-related adverse experiences, vaccination report card (VRC)-prompted injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever.

16. Statistical methods:

Immunogenicity: The first immunogenicity hypothesis regarding noninferiority of boys to girls with respect to Geometric Mean Titers (GMTs) at Week 4 Postdose 3 was tested using an analysis of variance (ANOVA) model. The natural log of the individual titers of the subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group was modeled as a function of gender, age at enrollment, and geographic region, which were considered fixed effects. The analysis was performed using the Mean Squared Error (MSE) from the ANOVA model as an estimate of variance and a one-sided test for the similarity of two means was performed at the 0.025 level using a t-distribution. The anti-log of the estimated treatment difference in the ANOVA model and the confidence interval associated with this difference was computed.

In order to reject the null hypothesis for a given HPV type, the lower bound of the 95% confidence interval on the ratio of GMTs had to be greater than 0.5 (i.e., to rule out a 2-fold decrease). The null hypothesis for each HPV type had to be rejected in order for boys to be declared noninferior to girls with respect to GMTs. The second immunogenicity hypothesis regarding noninferiority between genders (boys minus girls) with respect to the percentage of subjects who seroconvert for each HPV type by Week 4 Postdose 3 was addressed by 4 one-sided tests of noninferiority (one corresponding to each HPV type) conducted at the 0.025 level. These tests above were conducted based on methods developed by Miettinen and Nurminen for testing the equivalence of 2 proportions, which allows for stratification by age and geographic region. In order to reject the null hypothesis for a given HPV type, the lower bound of the 95% confidence interval on the difference in percentages of seroconverters between boys and girls had to be greater than -0.05. The null hypothesis for each HPV type had to be rejected in order for boys to be declared noninferior to girls with respect to seroconversion rates. In order to declare the immune responses of boys to the quadrivalent HPV vaccine at Week 4 Postdose 3 noninferior to those of girls, the statistical criterion had to be met for each HPV type and for each endpoint (GMTs and seroconversion rates). The per-protocol population (PPI) was the population from which inference was made.

Safety: All subjects who received at least one injection and had follow-up data were included in the safety summaries. Adverse experiences were summarized descriptively as frequencies and percentages by vaccination group and type of adverse experience, by vaccination visit and across all vaccination visits. Elevated temperatures (≥100° F, ≥37.8° C, oral or oral equivalent) within 5 days following each vaccination were summarized in a similar manner. In addition, risk differences and associated 95% confidence intervals were computed comparing the vaccine and placebo groups across all vaccination visits with respect to adverse experiences with ≥1% incidence in either vaccination group and elevated temperatures. p-Values were computed only for those adverse experiences that were prompted for on the VRC (elevated temperatures, injection-site pain, injection-site swelling, injection-site redness, muscle/joint pain, headaches, hives, rashes, diarrhea). In order to provide a basis for bridging the large safety database acquired in previous HPV studies for female subjects to the safety profiles for male subjects, adverse experiences were also summarized separately for boys and girls (within each vaccination group) and by age group. No formal comparisons were made between boys and girls or age group with respect to adverse experiences. The placebo used in this study contained no aluminum. In order to eliminate the impact of aluminum-containing non-study vaccinations received during the course of this study on the assessment of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine and the non-aluminum-containing placebo groups in terms of the incidence of adverse experiences, summaries of incidence rates of overall adverse experiences, specific adverse experiences that occur in ≥1% of subjects in either vaccination group, and elevated temperatures were also provided, by vaccination group, excluding those subjects who received any aluminum-containing non-study vaccinations during this study. These summaries were provided across all vaccination visits. No formal comparisons were performed in this subset of subjects.

17. Summary:

Immunogenicity: The first secondary immunogenicity objective of this study was to demonstrate that the Week 4 Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are non-inferior to the responses observed in preadolescent and adolescent girls. To address this objective, estimated GMTs at Week 4 Postdose 3 and seroconversion rates by Week 4 Postdose 3 were compared between boys and girls in the PPI population. The tables that follow present the results of these analyses. For both endpoints, the statistical criterion for non-inferiority was met for each vaccine HPV type.

Safety: The primary safety objective of this study was to demonstrate that the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is well tolerated in preadolescents and adolescents. The table that follows displays a summary of clinical adverse experiences reported from Days 1 through 15 following any vaccination visit by vaccination group. The following observations can be made:

- Overall, a higher proportion of subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group reported one or more adverse experiences compared with subjects in the non-aluminum-containing placebo group.
- The difference between vaccination groups in the proportion of subjects who reported one or more adverse experiences Days 1 to 15 following any vaccination visit was

primarily due to a higher proportion of subjects reporting one or more injection-site adverse experiences in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group compared with the non-aluminum-containing placebo group.

- Very few subjects experienced a serious adverse experience. None of the serious adverse experiences reported in the study were judged by the study investigator to be vaccine-related.
- Very few subjects discontinued study participation due to an adverse experience.

Statistical Analysis of Non-Inferiority of Month 7 HPV cLIA Geometric Mean Titers
Comparing Boys With Girls Among Subjects Who Received Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine
(Per-Protocol Immunogenicity Population[†])

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine					
	Boys (Comparison Group A) (N=564)		Girls (Comparison Group B) (N=615)		Estimated Fold Difference	
Assay (cLIA)	n	Estimated GMT[‡] (mMU/mL)	n	Estimated GMT[‡] (mMU/mL)	Group A/Group B (95% CI)[‡]	p-Value for Non-Inferiority[‡,§]
Anti-HPV 6	471	1,003.7	501	807.7	1.24 (1.03, 1.49)	<0.001
Anti-HPV 11	471	1,333.8	501	1,184.7	1.13 (0.93, 1.36)	<0.001
Anti-HPV 16	471	6,345.1	502	4,513.0	1.41 (1.11, 1.78)	<0.001
Anti-HPV 18	474	1,577.5	503	1,073.8	1.47 (1.17, 1.85)	<0.001
Overall conclusion: Non-Inferior[‖].						

[†] The per-protocol immunogenicity population includes all subjects who were not general protocol violators; received all 3 vaccinations within acceptable day ranges; were seronegative at Day 1 for the relevant HPV type(s); and had a Month 7 serum sample collected within an acceptable day range.

[‡] Parameter estimates, confidence intervals, and p-values are based on a statistical model adjusting for region and age.

[§] For the null hypothesis that $GMT_{Boys}/GMT_{Girls} \leq 0.5$ (2-fold decrease), a p-value <0.025 supports a conclusion that the specific type anti-HPV response in Boys is non-inferior to the response in Girls.

[‖] The quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine induces similar immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3, in adolescent boys 9 to 15 years of age, as compared to adolescent girls 9 to 15 years of age.

N = Number of subjects in the respective demographic cohort who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; VLP = Virus-like particles..

Statistical Analysis of Non-Inferiority of Month 7 Anti-HPV Seroconversion Rates
Comparing Boys With Girls Among Subjects Who Received Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine
(Per-Protocol Immunogenicity Population[†])

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine				Estimated Percentage Point Difference	
	Boys (N=564)		Girls (N= 615)			
Anti-HPV Response	n	Estimated Response[‡] (%)	n	Estimated Response[‡] (%)	Boys minus Girls (95% CI)[‡]	p-Value for Non-Inferiority[‡§]
HPV 6 cLIA ≥20 mMU/mL	471	99.8	501	99.8	-0.0 (-1.1, 0.9)	<0.001
HPV 11 cLIA ≥16 mMU/mL	471	99.8	501	99.8	-0.0 (-1.1, 0.9)	<0.001
HPV 16 cLIA ≥20 mMU/mL	471	99.6	502	99.8	-0.2 (-1.4, 0.7)	<0.001
HPV 18 cLIA ≥24 mMU/mL	474	99.8	503	99.6	0.2 (-0.8, 1.2)	<0.001
Overall conclusion: Non-inferior[‖]						

[†] The per-protocol immunogenicity population includes all subjects who were not general protocol violators; received all 3 vaccinations within acceptable day ranges; were seronegative at Day 1 for the relevant HPV type(s); and had a Month 7 serum sample collected within an acceptable day range.

[‡] Parameter estimates, confidence intervals, and p-values are based on a statistical model adjusting for region and age.

[§] For the null hypothesis that p_{Boys}-$p_{Girls} \leq -0.05$, a p-value <0.025 supports a conclusion that the specific type anti-HPV seroconversion rate in Boys is non-inferior to the seroconversion rate in Girls.

[‖] The Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine induces similar immune responses, as measured by the percentages of subjects who seroconvert for each of HPV Types 6, 11, 16, and 18 by Week 4 Postdose 3, in adolescent boys 9 to 15 years of age, as compared to adolescent girls 9 to 15 years of age.

Seropositive is defined as anti-HPV serum cLIA levels ≥20, 16, 20, 24 mMU/mL for HPV types 6, 11, 16, and 18, respectively.

N = Number of subjects in the respective demographic cohort who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.

VLP = Virus-like particles.

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects without follow-up	14		10	
Subjects with follow-up	1165		584	
Number (%) of subjects:				
with no adverse experience	202	(17.3)	192	(32.9)
with one or more adverse experiences	963	(82.7)	392	(67.1)
injection-site adverse experiences	877	(75.3)	292	(50.0)
systemic adverse experiences	541	(46.4)	260	(44.5)
with vaccine-related[†] adverse experiences	913	(78.4)	339	(58.0)
injection-site adverse experiences	877	(75.3)	292	(50.0)
systemic adverse experiences	274	(23.5)	134	(22.9)
with serious adverse experiences	5	(0.4)	0	(0.0)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse experience	3	(0.3)	0	(0.0)
discontinued due to a vaccine-related adverse experience	2	(0.2)	0	(0.0)
discontinued due to a serious adverse experience	1	(0.1)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

[‡] Discontinued = Subject discontinued from therapy.

Percentages are calculated based on the number of subjects with follow-up.

N = Number of subjects who received only the clinical material in the given column.

HPV = Human papillomavirus; VLP = Virus-like particles.

18. Date of the report:	04-Jan-08
19. Contact:	Merck National Service Center 1.800.672.6372