Statistical Review and Evaluation

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Subject STN: BL 125126/1297 Supplement
GARDASIL: Human Papillomavirus [Types 6, 11, 16 and 18] Recombinant Vaccine – Expanded Efficacy indication in boys and men 9 through 26 years of age
Merck & Co, Inc.

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Executive Summary

On December 17, 2008, Merck & Co., Inc. submitted a supplemental Biologics License Application (sBLA) for human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine, (STN 125126, GARDASIL). GARDASIL is currently indicated in girls and women 9 through 26 years of age for prevention of cancer, precancerous or dysplastic lesions, genital warts caused by the Human Papillomavirus (HPV) types targeted by the vaccine. This submission intends to extend the indication for use of the vaccine to include boys and men 9 to 26 years of age.

The purpose of this sBLA is to provide efficacy, immunogenicity, and safety data acquired in the interim analysis from Protocol 020. Results of these analyses are reviewed and evaluated in this document.

Results of the primary efficacy analysis performed in the per-protocol efficacy cohort show that all of the cases in the qHPV vaccine group and 28 out of 31 cases in the placebo group who had positive PCR for HPV types 6 and/or 11 were from diagnoses of condyloma. Given that only three cases were due to diagnoses of PIN 1 or worse, and the confidence interval of the VE for the endpoint of PIN 1 or worse was very wide, it indicates that more data should be collected for assessing this endpoint. Therefore, we recommend that the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11 in boys and men 9 through 26 years of age be included in the label indication.

TABLE OF CONTENTS

LIST OF TABLES

I. BACKGROUND

GARDASIL is a non-infectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. It is indicated in girls and women 9 through 26 years of age. The original license application for GARDASIL was approved in 2006 on the basis that GARDASIL demonstrated high efficacy in preventing cervical cancer caused by vaccine HPV types in pre-specified interim analysis of pivotal efficacy studies.

This supplemental application (STN 125126/1267) is to extend the original indication to include boys and men 9 through 26 years of age for the prevention of external genital lesions caused by HPV types 6, 11, 16, and 18.

This statistical review focuses on the provided efficacy, immunogenicity, and safety data accrued in the interim analysis from Protocol 020 which is a Phase III study of the use of GARDASIL in young men (16-26 years of age).

II. CLINICAL STUDIES

II.1 Overview

The pivotal clinical efficacy study of GARDASIL (Protocol 020) provides data in the current supplemental application. Study design, efficacy endpoints, statistical methodology, and study results will be included in the following subsections.

II.2 Study Design

Phase III Efficacy Studies (Protocol 020)

Protocol 020, entitled "A Study to Evaluate the Efficacy of GARDASIL in Reducing the Incidence of HPV 6-, 11-, 16-, and 18-Related External Genital Warts, PIN, Penile, Perianal and Perineal Cancer, and the Incidence of HPV 6-, 11-, 16-, and 18-Related Genital Infection in Young Men," is a Phase III, randomized, double-blind, placebo-controlled, multicenter study. The study enrolled Heterosexual men (HM) aged 16 to 23 years and Men having sex with men (MSM) aged 16 to 26 years with limited lifetime number of sexual partners. A total of 4065 subjects were randomized into 2 treatment groups: group that received GARDASIL (referred to as qHPV in the study) (n=2032) and group that received placebo (n=2033). Subjects received vaccination with qHPV or placebo at Day 1, Month 2, and Month 6. Follow-up visits at Months 12, 18, 24, 30, and 36 were scheduled from Day 1.

II.3 Clinical Efficacy Endpoints

Primary Efficacy Objective: To demonstrate that qHPV when given in a 3-dose regimen reduces the incidence of HPV 6-, 11-, 16- or 18-related external genital warts,

penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal, or perineal cancer in young men who are naïve to the relevant HPV type, compared with placebo.

Men having Sex with Men (MSM) Substudy Efficacy Objective: To investigate the impact of administration of a 3-dose regimen of qHPV on the combined incidence of HPV 6-, 11-, 16-, or 18-related anal intraepithelial neoplasia (AIN) or Anal Cancer in MSM subjects who are naïve to the relevant HPV type.

Secondary Efficacy Objective: (1) To demonstrate that qHPV, when given in a 3-dose regimen, reduces the incidence of persistent HPV 6, 11, 16, or 18 infection in young men who are naïve to the relevant HPV type, compared with placebo; (2) To demonstrate that qHPV, when given in a 3-dose regimen, reduces the incidence of HPV 6, 11, 16, or 18 detection at one or more visits, in young men who are naïve to the relevant HPV type, compared with placebo.

II.4 Statistical Methods for Efficacy Analyses

Analysis Populations

All populations for the analysis of prophylactic efficacy are defined in Table 1. The per-protocol population (PPE) was the main analysis population. Analyses of efficacy in pre-defined populations for HPV-naïve to the relevant type (HNRT), and the Full Analysis Set (FAS) were also conducted.

In addition, in order to be included in the PPE analysis for HPV 6- and HPV 11-related endpoints, subjects must be seronegative to **both** HPV 6 and 11 at Day 1 and be PCR negative to both HPV 6 and 11 from Day 1 through Month 7.

The Generally HPV-Naïve (GHN) population was used for the exploratory population benefit analyses. This population includes only subjects who were seronegative and PCR negative at enrollment to HPV 6, 11, 16 and 18, who were PCR-negative at enrollment to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, who received at least one dose of study material, who had follow-up after Day 1, and, for MSM subjects, who had a Pap test result at enrollment that was negative for SIL.

Table 1. Definition of Analysis Populations

	PPE	HNRT	FAS
Definition	A vaccine HPV **type-specific** population: - Naïve by serology and PCR to the **relevant** HPV type at Day 1 - Free of infection with the relevant HPV type through Month 7 - Received all 3 doses	An HPV type-specific population: - Received at least 1 dose of study Vaccine -HPV-naïve (i.e., seronegative and PCR negative) at Day 1 to the vaccine HPV type	A single population: - Received at least 1 dose of study Vaccine - Regardless of initial serology and PCR status

	of study vaccine - No major protocol violations	being analyzed	
Case Counting	Starting after the Month 7 Visit	Starting after Day 1	Starting after Day 1

Statistical methods

The analyses of the study are case driven. At the time when 32 cases of HPV 6, 11, 16 or 18-related genital warts/PIN/penile/perineal/perianal cancer have been observed in the PPE population, the primary efficacy analysis was conducted, along with secondary and exploratory analyses.

The primary hypothesis to be tested is

$$H_0: \lambda \leq 0.2 \text{ vs. } H_1: \lambda \geq 0.2$$

where λ is vaccine efficacy (defined as [1 – Relative Risk]*100%). The corresponding 95% confidence intervals were estimated using an exact procedure which accounted for the amount of follow-up (i.e., person-time at risk) in the vaccine and placebo groups. Subjects were pooled across the studies by vaccination group (vaccine or placebo) for analysis.

Kaplan-Meier estimates of the time-to-event curves were generated for certain efficacy endpoints. Subjects who did not experience the endpoint were censored at the end of their follow-up time.

II.5 Efficacy Results

Table 2 (Table 11-1 in Reference P020V1) presents the results of analysis of efficacy performed in the PPE population to address the primary hypothesis. The vaccine efficacy against HPV 6/11/16/18-related EGL was 90.4% (95% CI: 69.2, 98.1). Success was achieved in the test of the primary efficacy hypothesis showing that vaccine efficacy against HPV 6/11/16/18-related EGL is above 20% with a p-value < 0.001.

Table 2. Analysis of Efficacy of qHPV Vaccine against HPV 6/11/16/18-Related EGL in the PPE Population

	qHPV Vaccine (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%) & 95% CI	P-value
HPV 6/11/16/18 -Related EGL	1,397	3	2,830.90	0.1	1,408	31	2,812.20	1.1	90.4 (69.2, 98.1)	< 0.001
By Lesion Type										
Condyloma	1,397	3	2,830.90	0.1	1,408	28	2,813.90	1	89.4 (65.5, 97.9)	< 0.001*
PIN 1 or worse	1,397	0	2,833.30	0	1,408	3	2,824.50	0.1	100 (-141.2, 100)	
PIN 1	1,397	0	2,833.30	0	1,408	2	2,826.00	0.1	100 (-431.1, 100)	
PIN 2/3 or Cancer	1,397	0	2,833.30	0	1,408	1	2,824.70	0	100 (-3788.2, 100)	
PIN 2/3	1,397	0	2,833.30	0	1,408	1	2,824.70	0	100 (-3788.2, 100)	
Penile/Perianal /Perineal Cancer	1,397	0	2,833.30	0	1,408	0	2,826.20	0	NA	
By Sexual Orientation										
HM Subjects	1,200	2	2,594.10	0.1	1,198	26	2,563.30	1	92.4 (69.6, 99.1)	
MSM Subjects	197	1	236.8	0.4	210	5	248.9	2	79 (-87.9, 99.6)	
By HPV Type										
HPV 6-Related EGL	1,245	3	2,562.30	0.1	1,244	19	2,553.80	0.7	84.3 (46.5, 97.0)	
HPV 11-Related EGL	1,245	1	2,563.70	0	1,244	11	2,552.60	0.4	90.9 (37.7, 99.8)	
HPV 16-Related EGL	1,295	0	2,644.00	0	1,271	2	2,586.20	0.1	100 (-420.8, 100)	
HPV 18-Related EGL	1,335	0	2,723.30	0	1,354	1	2,726.60	0	100 (-3804.6, 100)	

A p-value<0.025 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 20% and supports the conclusion that the vaccine is efficacious against the given endpoint.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.
* The post-hoc analysis was conduct by the statistical reviewer.

Reviewer's comments: *The primary efficacy endpoint is the incidence of HPV 6-, 11-, 16-, and 18-related external genital lesions including external genital warts, penile/perianal/perineal intraepithelial neoplasia, and/or penile, perianal, or perineal cancer. This composite endpoint was pre-specified in Protocol HPV-020. However, by investigating the confidence intervals of the VEs for the endpoints of PIN1, PIN2/3 or cancer, it appears that the vaccine effect may in fact be limited to the incidence of genital warts. Therefore, a post-hoc analysis was performed*

for testing the endpoint of condyloma only. The clinical relevance of this endpoint (incidence of HPV6-/11- related condyloma) should be determined by the clinical reviewer, Dr. Jeff Roberts.

Results of this efficacy endpoint in the supportive analyses in the HNRT (Table 3, Table 11-4 in Reference P020V1) and FAS (Table 4, Table 11-5 in Reference P020V1) populations were consistent with those in the PPE population.

Table 3 Analysis of Efficacy of qHPV Vaccine against HPV 6/11/16/18-Related EGL in the HNRT Population

	qHPV Vaccine (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
By Lesion Type										
Condyloma	1775	10	4268.6	0.2	1770	48	4187.9	1.1	79.6	(59.1, 90.8)
PIN 1 or worse	1775	4	4274.0	0.1	1770	4	4223.5	0.1	1.2	(-430.5, 81.6)
PIN 1	1775	2	4278.9	0	1770	3	4225.0	0.1	34.2	(-474.7, 94.5)
PIN 2/3 or Cancer	1775	2	4276.1	0	1770	1	4223.9	0	-97.6	(-11555.6, 89.7)
PIN 2/3	1775	2	4276.1	0	1770	1	4223.9	0	-97.6	(-11555.6, 89.7)
Penile/Perianal /Perineal Cancer	1775	0	4280.9	0	1770	0	4225.4	0	NA	NA

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer;
PIN = Penile/Perianal/Perineal intraepithelial neoplasia.

Table 4 Analysis of Efficacy of qHPV Vaccine against HPV 6/11/16/18-Related EGL in FAS Population

	qHPV Vaccine (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
By Lesion Type										
Condyloma	1943	24	4635.4	0.5	1937	72	4558.8	1.6	67.2	(47.3, 80.3)
PIN 1 or worse	1943	6	4658.7	0.1	1937	5	4628.2	0.1	-19.2	(-393.8, 69.7)
PIN 1	1943	3	4666.1	0.1	1937	4	4629.7	0.1	25.6	(-339.9, 89.1)
PIN 2/3 or Cancer	1943	3	4663.1	0.1	1937	2	4628.6	0	-48.9	(-1682.6, 82.9)
PIN 2/3	1943	3	4663.1	0.1	1937	2	4628.6	0	-48.9	(-1682.6, 82.9)
Penile/Perianal /Perineal Cancer	1943	0	4670.6	0	1943	0	4630.5	0	NA	NA

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects who have at least one follow-up visit after Month 7.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; PIN = Penile/Perianal/Perineal intraepithelial neoplasia.

The analysis of the MSM substudy endpoint will be conducted after 17 cases have been detected. Since the target was not met at the time of the primary analysis, the analysis of the MSM endpoint will be submitted in a separate report.

With respect to the secondary hypotheses, the vaccine efficacy against HPV 6/11/16/18-related persistent infection was 85.6% (97.5% CI: 73.4, 92.9) and against HPV 6/11/16/18-related DNA detection was 44.7% (95% CI: 31.5, 55.6). Success was achieved in the test of both secondary hypotheses showing that vaccine efficacy against HPV 6/11/16/18-related persistent infection and HPV 6/11/16/18-related DNA detection is above 20% with a p-value < 0.001.

II.6 Clinical Immunogenicity Endpoints

The immunogenicity endpoints included on 2 parameters: (1) anti-HPV levels (geometric mean titers [GMTs]), which is a standard summary measure of immunogenicity; and (2) the proportion of subjects who became seropositive to vaccine HPV types at 4 weeks Post-dose 3.

The immunogenicity time points of interest were:

- Month 7. The primary immunogenicity endpoint of the clinical studies was defined as the immunologic response at Month 7 because this time point reflected the time frame during which peak vaccine-induced immune responses were expected.
- Persistence time points. Depending on the protocol, subjects underwent serology testing at 6- to 24-month intervals following the Month 7 visit. The data collected at these time points were used to evaluate the durability of vaccine-induced anti-HPV responses.

II.7 Statistical Methods for Immunogenicity Analyses

Analysis Populations

Immunogenicity analyses were conducted in the per-protocol immunogenicity (**PPI**) population. The PPI population included subjects who: (1) received all 3 injections with the correct dose of the correct clinical material; (2) had a Day 1 serum sample and Day 1 PCR samples within acceptable day ranges of the first vaccination; (3) had a Month 7 visit within a day range considered acceptable for defining the subject's Month 7 PCR status; (4) had a Month 7 serum sample collected within an acceptable day range; (5) were seronegative to the appropriate vaccine HPV types before the first injection and PCR-negative to the appropriate vaccine HPV types through Month 7 (on swabs and biopsies); (6) did not receive any non-study inactivated or recombinant vaccine within 14 days before or after a dose of study vaccine or any non-study live vaccine within 21 days before or 14 days after a dose of study vaccine; (7) did not receive immune globulin or blood products at any time through the Month 7 time point of the study; (8) did not receive immuno-suppressive or have an immune disorder considered by the Clinical Monitor to potentially interfere with the subject's response to the vaccine; (9) were not enrolled in another study of an investigational agent considered by the Clinical Monitor to potentially interfere with the subject's response to the vaccine.

To be included in the immunogenicity analysis for the HPV 6- and HPV 11-related endpoints, subjects must have been seronegative to HPV Types 6 and 11 at Day 1 and PCR-negative to HPV Types 6 and 11 from Day 1 through Month 7 (on swabs and biopsies).

The supportive analyses of immunogenicity were conducted using the all naïve subjects with serology (ANSS) population. This population included subjects who: (1) received at least one dose of the study vaccine; (2) provided serology data; and (3) were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV types. Subjects who received incorrect clinical material were included in this population in the group to which they were randomized.

Statistical Methods

- GMTs were computed by fitting an analysis of variance (ANOVA) model on the natural logarithm (log) of HPV titers, computing log-HPV titer means and their corresponding 95% CIs, and then taking the anti-log of the means of log-HPV titers and their corresponding 95% CIs to obtain point and asymmetric 95% CI estimates of GMTs.
- Seroconversion to HPV types 6, 11, 16, and 18 was defined as follows:
  - Subjects who at Day 1 have HPV 6, 11, 16, and 18 titers less than the serostatus cutoffs of **20, 16, 20**, and **24** mMU/mL, respectively, and have HPV titers greater than or equal to aforementioned HPV type-specific serostatus cutoffs during follow-up, are defined to have seroconverted to HPV type 6, 11, 16, and 18, respectively.

II.8 Immunogenicity Results

Study HPV-020 is ongoing. All subjects were to take serology testing for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 levels at Day 1, and Months 7, 24, and 36. The current supplemental Application includes serology results from all visits through 29-Aug-2008.

Table 5 (Table 11-34 in Reference P020V1) and Table 6 (Table 11-35 in Reference P020V1) show the anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs and the percent seroconversion for the qHPV vaccine group and placebo group in the PPI population at Day 1, Month 7, and Month 24, respectively. For each of the vaccine HPV types, and at all the time points evaluated, the GMTs in the placebo group were below the lower limit of quantitation (LLOQ) of the assay. The percent seroconversion in each of the vaccine HPV types at all time points evaluated were at most 2.1%. For each vaccine HPV type, measurable immune responses well above the LLOQ were induced by a 3-dose vaccination of qHPV vaccine at 4 weeks Post-dose 3 (Month 7). The percent seroconversion at 4 weeks Post-dose 3 (Month 7) was at least 97.4% for each of the vaccine HPV types.

Table 5. Summary of Anti-HPV Geometric Mean Titers by Vaccination Group (Per-Protocol Immunogenicity Population)

Assay (cLIA v2.0) Study Time	qHPV Vaccine (N=2,025)			Placebo (N=2,030)			
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI	P-value
Anti-HPV 6							
Day 1	1093	< 7	(<7, <7)	1110	< 7	(<7, <7)	-
Month 7	1093	447	(422.1, 473.5)	1110	< 7	(<7, <7)	<0.001
Month 24	906	80.3	(76.2, 84.6)	904	< 7	(<7, <7)	-
Anti-HPV 11							
Day 1	1093	< 8	(<8, <8)	1109	< 8	(<8, <8)	-
Month 7	1093	624.2	(594.4, 655.6)	1109	< 8	(<8, <8)	<0.001
Month 24	906	94.5	(89.8, 99.5)	902	< 8	(<8, <8)	-
Anti-HPV 16							
Day 1	1136	< 11	(<11, <11)	1128	< 11	(<11, <11)	-
Month 7	1136	2402.5	(2,270.6, 2,542.0)	1128	< 11	(<11, <11)	<0.001
Month 24	937	347.8	(329.3, 367.4)	904	< 11	(<11, <11)	-
Anti-HPV 18							
Day 1	1175	< 10	(<10, <10)	1205	< 10	(<10, <10)	-
Month 7	1175	402.2	(380.2, 425.6)	1205	< 10	(<10, <10)	<0.001
Month 24	966	38.7	(36.2, 41.3)	952	< 10	(<10, <10)	-

The p-value provided is based on the Wilcoxon Rank Sum test. A p-value <0.025 (1-sided) supports the conclusion that the qHPV Vaccine group has a higher GMT than the Placebo group.
The estimated GMTs and associated CIs are calculated using an ANOVA model with a term for vaccination group.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
ANOVA = Analysis of variance; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 6. Summary of Anti-HPV Percent Seroconversion by Vaccination Group (Per-Protocol Immunogenicity Population)

Anti-HPV Response Study Time	qHPV Vaccine (N=2,025)				Placebo (N=2,030)				
	Seroconversion				Seroconversion				
	n	m	Percent	95% CI	n	m	Percent	95% CI	P-value
Anti-HPV 6									
Day 1	1093	0	0	(0.0%, 0.3%)	1110	0	0	(0.0%, 0.3%)	-
Month 7	1093	1081	98.9	(98.1%, 99.4%)	1110	18	1.6	(1.0%, 2.6%)	<0.001
Month 24	906	823	90.8	(88.8%, 92.6%)	904	19	2.1	(1.3%, 3.3%)	-
Anti-HPV 11									
Day 1	1093	0	0	(0.0%, 0.3%)	1109	0	0	(0.0%, 0.3%)	-
Month 7	1093	1084	99.2	(98.4%, 99.6%)	1109	23	2.1	(1.3%, 3.1%)	<0.001
Month 24	906	866	95.6	(94.0%, 96.8%)	902	11	1.2	(0.6%, 2.2%)	
Anti-HPV 16									
Day 1	1136	0	0	(0.0%, 0.3%)	1128	0	0	(0.0%, 0.3%)	-
Month 7	1136	1122	98.8	(97.9%, 99.3%)	1128	20	1.8	(1.1%, 2.7%)	<0.001
Month 24	937	930	99.3	(98.5%, 99.7%)	904	7	0.8	(0.3%, 1.6%)	-
Anti-HPV 18									
Day 1	1175	0	0	(0.0%, 0.3%)	1205	0	0	(0.0%, 0.3%)	-
Month 7	1175	1144	97.4	(96.3%, 98.2%)	1205	21	1.7	(1.1%, 2.7%)	<0.001
Month 24	966	602	62.3	(59.2%, 65.4%)	952	10	1.1	(0.5%, 1.9%)	-

The p-value provided is based on Fisher's Exact test. A p-value <0.025 (1-sided) supports the conclusion that the qHPV Vaccine group has a higher proportion of subjects who have
seroconverted than the Placebo group.
Percent is calculated as 100*(m/n).
The CIs are computed based on exact methods.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
m = Number of subjects with the indicated response.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; qHPV Vaccine = Quadrivalent Human Papillomavirus
(Types 6, 11, 16, 18) Recombinant Vaccine.

The GMTs in vaccinated subjects at Month 24 are lower than at Month 7 for all vaccine HPV types. For anti-HPV 6, 11, and 16 GMTs, levels at Month 24 remained above the estimated antibody levels induced by natural infection for each HPV type. The estimated antibody levels induced by natural infection are the Day 1 GMTs among subjects who were seropositive and PCR negative (previously HPV infected subjects who had cleared the infection). For anti-HPV 18, the GMT at Month 24 was not significantly different from the GMT among subjects with natural infection. In the placebo group, the GMTs were below the LLOQ of the assay for all vaccine HPV types at all time points evaluated.

At Month 24, the seroconversion percentages for vaccine recipients decreased for all vaccine HPV types with the exception of HPV type 16. The estimates of percent seroconversion dropped, 8.1, 3.6, and 35.1 percentage points for HPV types 6, 11, and 18, respectively. In the placebo group, seroconversion percentages were at most 2.1% for all vaccine HPV types at Month 24.

The results for GMTs and seroconversion in the ANSS population are very similar to the results presented for the PPI population for all vaccine HPV types and time points.

II.9 Bridging Studies

Immunobridging between adult and adolescent males was targeted by comparing anti-HPV levels and demonstrating that GMTs and seroconversion rates among adolescent males are not inferior to what is observed among men. Anti-HPV responses (Month 7 GMTs and seroconversion rates) among 9- to 15-year-old male subjects from previously conducted Protocols 016 and 018 were compared with responses from 16- to 26-year-old men in Protocol 020.

Table 7 (Table 2.7.3-exgenlesions: 17 in Summary of Clinical Efficacy) shows that GMTs in 9- to 15-year-old boys were non-inferior to GMTs in 16- to 26-year-old men. Thus, it can be concluded that qHPV vaccine is efficacious in preventing HPV 6-, 11-, 16-, and 18-related external genital lesions in boys and men 9 to 26 years of age.

Table 7. Statistical Analysis of Month 7 Anti-HPV Geometric Mean Titers among Male Subjects Vaccinated with qHPV Vaccine Comparing Boys to Adult Men (Per-Protocol Immunogenicity Population)

	9 to 15 Year-olds[1] (Comparison Group A) (N = 1,073)		16 to 26 Year-olds[2] (Comparison Group B) (N = 2,025)		Estimated Fold Difference Group A / Group B (95% CI)[3]	p-Value for Non-Inferiority[4]
Assay	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)		
Anti-HPV 6	885	1036.9	1093	447.0	2.32 (2.10, 2.56)	<0.001
Anti-HPV 11	886	1386.3	1093	624.2	2.22 (2.03, 2.43)	<0.001
Anti-HPV 16	883	6047.1	1136	2402.5	2.52 (2.27, 2.79)	<0.001
Anti-HPV 18	888	1356.9	1175	402.2	3.37 (3.02, 3.76)	<0.001

[1]9-15 year-old male subjects from Protocols 016 and 018.
[2]6-26 year-old male subjects from Protocol 020
[3]Parameter estimates, confidence intervals, and p-values are based on a statistical model with a term for age group.
[4]For the null hypothesis that $GMT_{Boys}/GMT_{Men} <= 0.5$ (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 Men.
N = Number of subjects randomized in the respective group who received at least 1 injection.
n = Number of subjects in the indicated immunogenicity population.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; HPV = Human papillomavirus.

Table 8 (Table 2.7.3-exgenlesions: 18 in Summary of Clinical Efficacy) shows that seroconversion rates in 9- to 15-year-old boys were non-inferior to seroconversion rates in 16- to 26-year-old men.

Table 8. Statistical Analysis of Month 7 Anti-HPV Seroconversion Rates among Male Subjects Vaccinated with qHPV Vaccine Comparing Boys to Adult Men (Per-Protocol Immunogenicity Population)

	9 to 15 Year-olds[1] (Comparison Group A) (N = 1,073)		16 to 26 Year-olds[2] (Comparison Group B) (N = 2,025)		Estimated Percent Point Difference Group A - Group B (95% CI)[3]	p-Value for Non-Inferiority[4]
Anti-HPV Response	n	Estimated Response (%)	n	Estimated Response (%)		
HPV 6 cLIA .20 mMU/mL	885	99.9	1093	98.9	1.0 (0.4, 1.8)	<0.001
HPV 11 cLIA .16 mMU/mL	886	99.9	1093	99.2	0.7 (0.1, 1.5)	<0.001

HPV 16 cLIA .20 mMU/mL	883	99.8	1136	98.8	1.0 (0.3, 1.9)	<0.001
HPV 18 cLIA .24 mMU/mL	888	99.8	1175	97.4	2.4 (1.5, 3.5)	<0.001

[1]9-15 year-old male subjects from Protocols 016 and 018.
[2]6-26 year-old male subjects from Protocol 020
[3]Parameter estimates, confidence intervals, and p-values are based on the methods developed by Miettinen and Nurminen.
[4] For the null hypothesis that $p_{Boys}-p_{Men} <= -0.05$, 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 Men.

II.10 Safety Assessments

All subjects were to be followed for adverse experiences for 15 days (day of vaccination plus 14 calendar days) after each injection.

The study's primary safety hypothesis stated that the qHPV vaccine will be generally well tolerated in 16-to-26-year-old young male subjects. All subjects who received at least one dose of qHPV vaccine or placebo were followed for safety. A total of 4049 subjects received at least one dose of qHPV vaccine or placebo.

The following observations can be made from clinical adverse experiences reported by subjects at any time during the study:

- The proportion of subjects who reported at least one clinical adverse experience was slightly higher in the qHPV vaccine group than in the placebo group;
- The proportion of subjects who reported at least one injection-site adverse experience was slightly higher in the qHPV vaccine group than in the placebo group;
- The proportion of subjects who reported at least one systemic adverse experience was generally comparable between the vaccine and placebo groups;
- Few subjects discontinued the study due to an adverse experience. The proportion of subjects who discontinued the study due to an adverse experience was slightly higher in the placebo group than in the qHPV vaccine group.
- There were no vaccine-related serious adverse experiences.
- A total of 13 subjects died during the study. The proportion of subjects who died was higher in the placebo group than in the qHPV vaccine group. A total of 3 subjects died in the qHPV vaccine group and a total of 10 subjects died in the placebo group. None of the deaths were considered to be vaccine related.

II.11 Gender, Age, and Other Subgroup Populations

Protocol 020 included only male subjects aged 16 to 23 years. Given that only 3 cases of HPV-6/11 related genital warts occurred in the HPV group, any subgroup analysis was not applicable.

III. STUDY CONCLUSIONS

Efficacy conclusion

Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is efficacious in preventing development of HPV 6/11-related genital warts.

Immunogenicity Conclusion

Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men generates robust anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses.

Safety Conclusion

Prophylactic administration of a 3-dose regimen of qHPV vaccine is generally well tolerated in men 16-26 years of age.

IV. RECOMMENDATION

Results of the primary efficacy analysis performed in the per-protocol efficacy cohort show that all of the cases in the qHPV vaccine group and 28 out of 31 cases in the placebo group who had positive PCR for HPV types 6 and/or 11 were from diagnoses of condyloma. Given that only three cases were due to diagnoses of PIN 1 or worse, and the confidence interval of the VE for the endpoint of PIN 1 or worse was very wide, it indicates that more data should be collected for assessing this endpoint. Therefore, we recommend that for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11 in boys and men 9 through 26 years of age to be included in the label indication.

V. COMMENTS AND QUESTIONS TO CBER REVIEW COMMITTEE

- The primary efficacy endpoint is the incidence of HPV 6-, 11-, 16-, and 18-related external genital lesions including external genital warts, penile/perianal/perineal intraepithelial neoplasia, and/or penile, perianal, or perineal cancer. This composite endpoint was pre-specified in the Protocol HPV-020. However, by investigating the confidence intervals of the VEs for the endpoints of PIN1, PIN2/3 or cancer, it appears that the vaccine effect may in fact be limited to the incidence of genital warts. Therefore, a post-hoc analysis was performed by me for testing the endpoint of condyloma only. The clinical relevance of this endpoint (incidence of HPV6-/11- related condyloma) should be determined by the clinical reviewer, Dr. Jeff Roberts.

VI. COMMENTS AND QUESTIONS TO APPLICANT

None