Statistical Review and Evaluation

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Subject STN: BL 125126/1895 Supplement
GARDASIL: Human Papillomavirus [Types 6, 11, 16 and 18] Recombinant Vaccine – Expanded Efficacy Indication for Prevention of Anal Intraepithelial Neoplasia (AIN) and Anal Cancer
Merck & Co, Inc.

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Executive Summary

On February 25, 2010, Merck & Co., Inc. submitted a supplemental Biologics License Application (sBLA) for human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine, (STN 125126, GARDASIL), which is a vaccine indicated for the prevention of cancer, precancerous or dysplastic lesions, genital warts caused by the Human Papillomavirus (HPV) types targeted by the vaccine. This submission provides the end-of-study results for Protocol 020 that are the basis for demonstrating the use of Gardasil to prevent anal intraepithelial neoplasia (AIN) and anal cancer.

Protocol 020 was designed to evaluate the efficacy of the qHPV vaccine against external genital lesions (EGLs) and persistent infection in young men, and included a substudy in men who have

sex with men (MSM), the objective of which was to evaluate efficacy of the vaccine against anal intraepithelial neoplasia (AIN). The primary analysis of the overall study of external genital lesions (EGLs) efficacy was presented in the original male qHPV vaccine submission (sBLA 125126/1297). The sBLA 125126/1297 supplemental application was approved by CBER on October 16, 2009 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.

Based on the results of the Protocol 020 MSM (men who have sex with men) substudy, the current application proposes the following new indications for the qHPV vaccine:

- qHPV vaccine is indicated in **individuals** 9 through 26 years of age for the prevention of AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16 and 18.
- qHPV vaccine is indicated in **individuals** 9 through 26 years of age for the prevention of anal cancer caused by HPV types 16 and 18.

The MSM substudy data presented in the current application support the proposed indications for the prevention of AIN 1+ and anal cancer in men; however, there are no study data provided to support the extension of these indications to women. This extension may be justified by the clinical reviewer based on physiopathological reasons.

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I. BACKGROUND

GARDASIL (referred to as the "qHPV vaccine" in this review) 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. 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 girls and women 9 through 26 years of age.

Protocol 020 was designed to evaluate the efficacy of the qHPV vaccine against external genital lesions (EGLs) and persistent infection in young men, and included a substudy in men who have sex with men (MSM), the objective of which was to evaluate efficacy of the vaccine against anal intraepithelial neoplasia (AIN). The primary analysis of the overall study of EGL efficacy was presented in the original male qHPV vaccine submission (sBLA 125126/1297). The supplemental application (sBLA 125126/1297) which was 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 was approved by CBER on October 16, 2009.

Based on the results of the Protocol 020 MSM substudy, the current application proposes the following new indications for the qHPV vaccine:

- qHPV vaccine is indicated in **individuals** 9 through 26 years of age for the prevention of AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16 and 18.
- qHPV vaccine is indicated in **individuals** 9 through 26 years of age for the prevention of anal cancer caused by HPV types 16 and 18.

The current submission provides analyses of the MSM substudy anal disease endpoint, in addition to updated analyses of the primary and secondary endpoints of efficacy against EGLs and persistent infection, as well as updated safety and immunogenicity data from the overall study.

II. CLINICAL STUDIES

II.1 Overview

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," was 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 number of lifetime sexual partners.

II.2 Study Design

A total of 4065 subjects were randomized into two 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 Objectives: (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 of study vaccine - No major protocol violations	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 being analyzed	A single population: - Received at least 1 dose of study Vaccine - Regardless of initial serology and PCR status
Case Counting	Starting after the Month 7 Visit	Starting after Day 1	Starting after Day 1

MSM Substudy Statistical methods

This study employed a fixed event design. The primary efficacy analysis was scheduled to be conducted when at least 32 cases of the primary endpoint had been observed and the MSM substudy efficacy analyses was scheduled to be conducted when at least 17 cases of the MSM substudy endpoint had been observed. For the MSM substudy, a **multiplicity adjustment** was applied to the tests of the MSM substudy efficacy hypothesis because the primary efficacy analysis was performed prior to the MSM substudy efficacy analysis and an interim summary of the MSM endpoint was conducted at the time of the primary efficacy analysis.

The MSM Substudy null hypothesis states that vaccine efficacy against HPV 6, 11, 16 or 18-related AIN or anal cancer is 0% or less. The alternative hypothesis is that vaccine efficacy against this endpoint is greater than 0%.

$$H_0: \lambda \leq 0 \text{ vs. } H_1: \lambda > 0$$

where λ is vaccine efficacy (defined as [1 – Relative Risk]*100%).

A point estimate for vaccine efficacy was provided together with an exact two-sided **95.1**% confidence interval. The corresponding 95.1% 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. A one-sided test of the null hypothesis that vaccine efficacy (VE) was $\leq 0\%$ at the $\alpha = 0.0245$ level of significance was used to address MSM endpoint hypotheses.

II.5 Efficacy Results

The efficacy and immunogenicity results presented in the current CSR use data obtained through Month 36, which corresponds to the end-of-study visit of the original Protocol 020 study. The analyses presented in the current CSR are based on all data from the day of the enrollment of the first study subject until completion of the last study visit on 31-Jul-2009.

Results for analyses of prophylactic efficacy of the qHPV vaccine are shown as follows:

- prophylactic efficacy with respect to anal disease and persistent infection
- prophylactic efficacy with respect to external genital disease and infection (updated results).

Prophylactic Efficacy With Respect to Anal Disease

The MSM substudy of Protocol 020 was designed to evaluate the efficacy of the qHPV vaccine against anal intraepithelial neoplasia (AIN) related to HPV types 6, 11, 16, and 18. A total of 602 MSM subjects were enrolled at selected sites to participate in the "Intensive Intra-anal Evaluation in MSM" substudy. The median duration of efficacy follow-up at the end of study was 32.2 months post-enrollment for the MSM study population.

The number of subjects who received at least one vaccination was 598. A summary of the number of MSM subjects who were randomized, vaccinated, who completed or discontinued during the vaccination period of the study, who entered the efficacy follow-up period of the study, and who completed or discontinued during the efficacy follow-up period of the study, by vaccination group, is provided in Table 2 (Table 2.7.3 – analdisease: 2).

Table 2 Subject Disposition Protocol 020 MSM Subjects

	qHPV		Placebo		Total	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES					99	
RANDOMIZED	301		301		602	
VACCINATED AT:						
Dose 1	299	(99.3)	299	(99.3)	598	(99.3)
Dose 2	286	(95.0)	286	(95.0)	572	(95.0)
Dose 3	278	(92.4)	277	(92.0)	555	(92.2)
VACCINATION PERIOD (Day 1 Through Month 7)						
ENTERED	299		299		598	
COMPLETED†	271	(90.6)	274	(91.6)	545	(91.1)
DISCONTINUED	28	(9.4)	25	(8.4)	53	(8.9)
WITH LONG-TERM FOLLOW-UP‡	4	(1.3)	3	(1.0)	7	(1.2)
Clinical AE	2	(0.7)	0	0.0	2	(0.3)
Other reasons	2	(0.7)	2	(0.7)	4	(0.7)
Uncooperative	0	0.0	1	(0.3)	1	(0.2)
WITHOUT LONG-TERM FOLLOW-UP§	24	(8.0)	22	(7.4)	46	(7.7)
Lost to follow-up	19	(6.4)	14	(4.7)	33	(5.5)
Moved	0	0.0	1	(0.3)	1	(0.2)
Other reasons	3	(1.0)	2	(0.7)	5	(0.8)
Protocol deviations	1	(0.3)	0	0.0	1	(0.2)
Withdrew consent	1	(0.3)	5	(1.7)	6	(1.0)
FOLLOW-UP PERIOD (After Month 7)						
ENTERED	275		277		552	
COMPLETED	210	(76.4)	222	(80.1)	432	(78.3)
DISCONTINUED	65	(23.6)	55	(19.9)	120	(21.7)
Lost to follow-up	51	(18.5)	39	(14.1)	90	(16.3)
Moved	6	(2.2)	2	(0.7)	8	(1.4)
Other reasons	4	(1.5)	4	(1.4)	8	(1.4)
Withdrew consent	4	(1.5)	10	(3.6)	14	(2.5)

† Subjects completed 3 doses of vaccinations and entered the long-term follow-up period.
‡ Subjects received fewer than 3 doses of vaccinations and entered the long-term follow-up period.
§ Subjects discontinued on or before Month 7 and did not enter the long-term follow-up period.
Status percentages are calculated based on the number of subjects who entered the respective time period.

Table 3 (Table 2.7.3-analdisease: 3) displays the demographic characteristics of MSM subjects randomized into the substudy, by vaccination group. The two vaccination groups were well balanced with respect to these demographics. The mean age of the MSM substudy cohort was 22.1 years. A substantial proportion of subjects had evidence of exposure to HPV or active HPV infection at the time of enrollment; in both vaccination groups, approximately **22.8**% of subjects were positive to a vaccine HPV type by serology, and approximately **30.5**% were positive by PCR.

Table 3 Summary of Subject Characteristics by Vaccination Group (Protocol 020 MSM Subjects)

	qHPV (N = 301)	Placebo (N = 301)	Total (N = 602)
	n (%)	n (%)	n (%)
Gender			
Male	301 (100)	301 (100)	602 (100)
Age (years)			
Mean	22.2	22.1	22.1
Standard Deviation	2.5	2.5	2.5
Median	22	22	22
Range	16 to 26	17 to 27	16 to 27
Race/Ethnicity			
Asian	15 (5.0)	18 (6.0)	33 (5.5)
Black	22 (7.3)	20 (6.6)	42 (7.0)
Hispanic American	72 (23.9)	77 (25.6)	149 (24.8)
White	185 (61.5)	178 (59.1)	363 (60.3)
Other	7 (2.3)	8 (2.7)	15 (2.5)
Region			
Asia-Pacific	45 (15.0)	44 (14.6)	89 (14.8)
Europe	61 (20.3)	61 (20.3)	122 (20.3)
Latin America	65 (21.6)	67 (22.3)	132 (21.9)
North America	130 (43.2)	129 (42.9)	259 (43.0)
Smoking Status			
Current smoker	121 (40.2)	120 (39.9)	241 (40.0)
Ex-smoker	26 (8.6)	30 (10.0)	56 (9.3)
Never smoked	153 (50.8)	150 (49.8)	303 (50.3)
Missing or Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Circumcision			
Yes	134 (44.5)	133 (44.2)	267 (44.4)
No	167 (55.5)	167 (55.5)	334 (55.5)
Missing or Unknown		1 (0.3)	1 (0.2)
HPV 6/11/16/18 PPE-Eligible			
yes	202 (67.1)	216 (71.8)	418 (69.4)

Percent calculated as 100*(n/N)
N = Number of subjects randomized.

The analysis of the MSM substudy endpoint was conducted after 17 cases were detected. Table 4 (Table 11-1 in P020) shows the results of the analysis of efficacy performed in the MSM PPE population to address the MSM substudy efficacy hypothesis. Success was achieved in the test of the MSM substudy efficacy hypothesis showing that vaccine efficacy against HPV 6/11/16/18-related AIN and anal cancer is above 0%. The vaccine efficacy against HPV 6/11/16/18-related AIN and anal cancer is 77.5% (95.1% CI: 39.6, 93.3). There were a total of 5 HPV 6/11/16/18-related AIN cases in the qHPV vaccine group and 24 cases in the placebo group. All of the cases in the qHPV vaccine group and the majority of the cases in the placebo group had positive PCR results for HPV types 6 and/or 16.

Table 4 Analysis of Efficacy against HPV 6/11/16/18-Related AIN and Anal Cancer† by HPV Type and Lesion Type (MSM Per-Protocol Efficacy Population) (Protocol 020)

	qHPV Vaccine (N=299)				Placebo (N=299)					
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‡
HPV 6/11/16/18-Related AIN and Anal Cancer	194	5	381.1	1.3	208	24	411.6	5.8	77.5	**(39.6, 93.3)**
By HPV Type										
HPV 6-Related AIN and Anal Cancer	141	3	275.2	1.1	144	10	298.5	3.4	67.5	(-26.4, 94.2)
HPV 11-Related AIN and Anal Cancer	141	0	279.2	0	144	6	298.2	2	100	(9.3, 100)
HPV 16-Related AIN and Anal Cancer	167	2	330.6	0.6	170	6	341.9	1.8	65.5	(-92.8, 96.6)
HPV 18-Related AIN and Anal Cancer	173	0	345.3	0	193	4	387.4	1	100	(-70.0, 100)
By Lesion Type										
AIN 1	194	4	383.1	1	208	16	413.8	3.9	73	(16.3, 93.4)
Condyloma Acuminatum	194	0	386.8	0	208	6	418.2	1.4	100	(8.2, 100)
Non-acuminate	194	4	383.1	1	208	11	416.7	2.6	60.4	(-33.5, 90.8)
AIN 2 or worse	194	3	383.9	0.8	208	13	417.2	3.1	74.9	(8.8, 95.4)
AIN 2	194	2	384.5	0.5	208	9	418.6	2.2	75.8	(-16.9, 97.5)
AIN 3	194	2	385.4	0.5	208	6	419.7	1.4	63.7	(-103.0, 96.4)
Anal Cancer	194	0	386.8	0	208	0	421.1	0	NA	NA

†Cases found from performing an HRA due to the presence of perianal external lesions are not included in this analysis to eliminate potential ascertainment bias.
‡ A 95.1% CI is reported for the HPV 6/11/16/18-related AIN and anal cancer endpoint. For all analyses by HPV type and lesion type, a 95% CI is reported. The CI reported for the HPV 6/11/16/18-related AIN and anal cancer endpoint differs from the other analyses due to the alpha adjustment applied.
N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the MSM substudy who have at least one follow-up visit after Month 7.
AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; HRA = High resolution anoscopy; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Reviewer's comments: VEs and the corresponding 95% CIs (95.1% for the HPV 6/11/16/18-related AIN and anal cancer endpoint) of VEs in Table 4 have been verified by me using SAS and StatXact programs.

Appendix Figure 1 (Figure 2.7.3-analdisease: 1) presents the cumulative incidence curve over time of HPV 6/11/16/18-related AIN and anal cancer by vaccination group for the MSM PPE population. The curve shows that after Month 24 the cumulative percentage of cases in the placebo group continues to rise while remaining constant in the qHPV vaccine group.

Table 5 (Appendix 2.7.3-analdisease: 1) and Table 6 (Appendix 2.7.3-analdisease: 2) show the results of efficacy analyses for the MSM Naïve to the Relevant HPV Type (HNRT) Population and the Full Analysis Set (FAS) populations, respectively. Efficacy in the HNRT population was comparable to that observed in the PPE population and efficacy was lower in the FAS population than in the PPE population. It is notable, however, that even in the FAS population, which included subjects who were baseline HPV positive for vaccine HPV types, the lower bound of

the 95% confidence interval for vaccine efficacy against HPV 6/11/6/18-related AIN 2 or worse was above 0%.

Table 5 Analysis of Efficacy against HPV 6/11/16/18-Related AIN and Anal Cancer by HPV Type and Lesion Type (MSM Naïve to the Relevant HPV Type Population) (Protocol 020)

	qHPV Vaccine (N=299)				Placebo (N=299)					
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
HPV 6/11/16/18-Related AIN and Anal Cancer	259	9	629.7	1.4	261	39	631.3	6.2	76.9	(51.4, 90.1)
By HPV Type										
HPV 6-Related AIN and Anal Cancer	198	4	478.3	0.8	190	19	477.4	4.0	79.0	(36.8, 94.8)
HPV 11-Related AIN and Anal Cancer	198	2	480.9	0.4	190	13	475.9	2.7	84.8	(32.7, 98.3)
HPV 16-Related AIN and Anal Cancer	228	2	563.9	0.4	218	8	547.8	1.5	75.7	(-21.7, 97.5)
HPV 18-Related AIN and Anal Cancer	237	1	588.7	0.2	242	7	603.6	1.2	85.4	(-14.0, 99.7)
By Lesion Type										
AIN 1	259	7	633.8	1.1	261	31	634.4	4.9	77.4	(47.7, 91.6)
Condyloma Acuminatum	259	2	639.4	0.3	261	16	645.0	2.5	87.4	(46.4, 98.6)
Non-acuminate	259	6	635.9	0.9	261	22	642.1	3.4	72.5	(30.0, 90.9)
AIN 2 or worse	259	7	635.9	1.1	261	19	646.6	2.9	62.5	(6.9, 86.7)
AIN 2	259	3	639.6	0.5	261	15	648.0	2.3	79.7	(28.4, 96.2)
AIN 3	259	5	637.3	0.8	261	10	649.9	1.5	49.0	(-63.7, 86.3)
Anal Cancer	259	0	641.9	0	261	0	656.2	0	NA	NA

N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the MSM substudy who have at least one follow-up visit after Day 1.
AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; HRA = High resolution anoscopy; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 6 Analysis of Efficacy against HPV 6/11/16/18-Related AIN and Anal Cancer by HPV Type and Lesion Type (MSM Full Analysis Set) (Protocol 020)

Endpoint	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (%)	95 HPV Type and Lesion Type (MSM Full Analysis Set) (Protocol 020)% CI
	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		
HPV 6/11/16/18-Related AIN and Anal Cancer	275	38	607.1	6.3	276	77	611.9	12.6	50.3	(25.7, 67.2)
By HPV Type										
HPV 6-Related AIN and Anal Cancer	275	18	644.8	2.8	276	47	645.3	7.3	61.7	(32.8, 79.1)
HPV 11-Related AIN and Anal Cancer	275	13	651.2	2.0	276	25	660.5	3.8	47.3	(-7.1, 75.2)
HPV 16-Related AIN and Anal Cancer	275	8	668.7	1.2	276	18	678.6	2.7	54.9	(-9.0, 83.0)
HPV 18-Related AIN and Anal Cancer	275	5	671.9	0.7	276	11	684.5	1.6	53.7	(-44.6, 87.4)
By Lesion Type										
AIN 1	275	31	619.3	5.0	276	62	624.1	9.9	49.6	(21.2, 68.4)
Condyloma Acuminatum	275	13	651.3	2.0	276	31	664.2	4.7	57.2	(15.9, 79.5)
Non-acuminate	275	27	636.0	4.2	276	48	641.3	7.5	43.3	(7.3, 66.0)
AIN 2 or worse	275	18	660.1	2.7	276	39	655.2	6.0	54.2	(18.0, 75.3)
AIN 2	275	11	668.0	1.6	276	29	671.5	4.3	61.9	(21.4, 82.8)
AIN 3	275	10	665.9	1.5	276	19	672.8	2.8	46.8	(-20.2, 77.9)
Anal Cancer	275	0	678.4	0.0	276	0	694.8	0	NA	NA

N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the MSM substudy who have at least one follow-up visit after Day 1.
AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; HRA = High resolution anoscopy; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Reviewer's comments: VEs and the corresponding 95% CIs of VEs in Tables 5 and 6 have been checked by me using SAS and StatXact programs.

Table 7 (Table 2.7.3-analdisease: 5) shows the results of the analysis of efficacy against AIN and anal cancer due to any HPV type in the MSM GHN population. Note that the vaccine efficacy against AIN and anal cancer due to any of non-vaccine HPV types is -35.1% and its corresponding 95% confidence interval includes 0%. There is thus insufficient evidence to conclude that the qHPV vaccine is efficacious in the anal canal against non-vaccine HPV types.

Table 7 Analysis of Efficacy against AIN and Anal Cancer Due to Any HPV Type (MSM Generally HPV-Naïve Population) (Protocol 020)

Endpoint	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (%)	95% CI
	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		
AIN and Anal Cancer Due to Any HPV Type	129	12	299.4	4	126	28	315.2	8.9	54.9	(8.4, 79.1)
HPV 6/11/16/18-Related AIN and Anal Cancer	129	2	305.4	0.7	126	20	317.2	6.3	89.6	(57.2, 98.8)
HPV 6-Related AIN and Anal Cancer	129	1	306.6	0.3	126	9	325.6	2.8	88.2	(14.8, 99.7)
HPV 11-Related AIN and Anal Cancer	129	0	308.0	0	126	8	321.3	2.5	100	(38.9, 100)
HPV 16-Related AIN and Anal Cancer	129	1	306.8	0.3	126	3	328.3	0.9	64.3	(-344.3, 99.3)
HPV 18-Related AIN and Anal Cancer	129	0	308.0	0	126	3	326.5	0.9	100	(-156.5, 100)
AIN and Anal Cancer related to any of 10 assay-identified HPV Types	129	5	304.7	1.6	126	4	329.4	1.2	-35.1	(-581.0, 70.9)
HPV 31-Related AIN and Anal Cancer	129	0	308.0	0	126	1	329.5	0.3	100	(-4072.8, 100)
HPV 33-Related AIN and Anal Cancer	129	0	308.0	0	126	0	329.5	0	NA	NA
HPV 35-Related AIN and Anal Cancer	129	0	308.0	0	126	0	329.5	0	NA	NA
HPV 39-Related AIN and Anal Cancer	129	0	308.0	0	126	1	329.5	0.3	100	(-4072.8, 100)
HPV 45-Related AIN and Anal Cancer	129	2	305.4	0.7	126	0	329.5	0	NA	NA
HPV 51-Related AIN and Anal Cancer	129	2	308.0	0.6	126	1	329.4	0.3	-113.9	(-12517.6, 88.9)
HPV 52-Related AIN and Anal Cancer	129	0	308.0	0	126	1	329.5	0.3	100	(-4072.8, 100)
HPV 56-Related AIN and Anal Cancer	129	0	308.0	0	126	0	329.5	0	NA	NA
HPV 58-Related AIN and Anal Cancer	129	0	308.0	0	126	0	329.5	0	NA	NA
HPV 59-Related AIN and Anal Cancer	129	1	307.3	0.3	126	0	329.5	0	NA	NA
AIN and Anal Cancer Not Related to any of 14 assay-identified HPV Types	129	7	297.9	2.3	126	6	308.2	1.9	-20.7	(-334.8, 65.3)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the MSM substudy who have at least one follow-up visit after Day 1.
AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 8 (Table 2.7.3-analdisease: 6) shows the results of the analysis of efficacy against AIN and anal cancer due to any HPV type in the MSM FAS population. The vaccine efficacy estimates for AIN and anal cancer related to any of the 10 assay identified HPV types and for AIN and anal cancer not related to any of the 14 assay identified HPV types are 11.8% (95% CI: -39.3, 44.4) and 5.0% (95% CI: -105, 56.3), respectively, in the MSM FAS. While the point estimates for these endpoints show a positive efficacy trend, there is insufficient evidence to conclude that the qHPV vaccine is efficacious against non-vaccine HPV types.

Table 8 Analysis of Efficacy against AIN and Anal Cancer Due to Any HPV Type (MSM Full Analysis Set) (Protocol 020)

	qHPV Vaccine (N=299)				Placebo (N=299)					
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
AIN and Anal Cancer Due to Any HPV Type	275	74	569.0	13.0	276	103	588.4	17.5	25.7	(-1.1, 45.6)
HPV 6/11/16/18-Related AIN and Anal Cancer	275	38	607.1	6.3	276	77	611.9	12.6	50.3	(25.7, 67.2)
HPV 6-Related AIN and Anal Cancer	275	18	644.8	2.8	276	47	645.3	7.3	61.7	(32.8, 79.1)
HPV 11-Related AIN and Anal Cancer	275	13	651.2	2.0	276	25	660.5	3.8	47.3	(-7.1, 75.2)
HPV 16-Related AIN and Anal Cancer	275	8	668.7	1.2	276	18	678.6	2.7	54.9	(-9.0, 83.0)
HPV 18-Related AIN and Anal Cancer	275	5	671.9	0.7	276	11	684.5	1.6	53.7	(-44.6, 87.4)
AIN and Anal Cancer related to any of 10 assay-identified HPV Types	275	38	635.4	6.0	276	44	648.8	6.8	11.8	(-39.3, 44.4)
HPV 31-Related AIN and Anal Cancer	275	7	675.1	1.0	276	8	687.1	1.2	11.0	(-181.0, 72.5)
HPV 33-Related AIN and Anal Cancer	275	1	677.8	0.1	276	2	690.9	0.3	49.0	(-879.0, 99.1)
HPV 35-Related AIN and Anal Cancer	275	3	675.2	0.4	276	5	687.6	0.7	38.9	(-214.1, 90.5)
HPV 39-Related AIN and Anal Cancer	275	6	670.8	0.9	276	8	689.3	1.2	22.9	(-153.3, 78.0)
HPV 45-Related AIN and Anal Cancer	275	5	671.2	0.7	276	7	686.4	1.0	27.0	(-167.3, 81.7)
HPV 51-Related AIN and Anal Cancer	275	9	674.0	1.3	276	9	683.7	1.3	-1.4	(-188.4, 64.3)
HPV 52-Related AIN and Anal Cancer	275	2	677.1	0.3	276	7	688.1	1.0	71.0	(-52.5, 97.1)
HPV 56-Related AIN and Anal Cancer	275	9	666.4	1.4	276	5	689.2	0.7	-86.1	(-607.0, 44.0)
HPV 58-Related AIN and Anal Cancer	275	5	672.4	0.7	276	6	686.1	0.9	15.0	(-234.4, 79.5)
HPV 59-Related AIN and Anal Cancer	275	11	667.9	1.6	276	9	687.8	1.3	-25.9	(-243.6, 52.6)
AIN and Anal Cancer Not Related to any of 14 assay-identified HPV Types	275	15	558.7	2.7	276	16	566.0	2.8	5.0	(-105.1, 56.3)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N = Number of subjects in the MSM substudy randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the MSM substudy who have at least one follow-up visit after Day 1.
AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Updated Results: External Genital Disease and Infection

Table 9 (Appendix 2.5: 16 in Clinical Overview) shows the updated results of analyses of efficacy performed in the PPE population to address the primary and secondary efficacy hypotheses. Vaccine efficacy against HPV 6/11/16/18-related EGL was 90.6% (95% CI: 70.1, 98.2). Since the previous analysis, there was a single additional case in the placebo group; this was an MSM placebo recipient with a diagnosis of HPV 16-related PIN 2/3. With this additional PIN case, the final data are favorable regarding efficacy of the qHPV vaccine against HPV-related penile malignancy. Updated efficacy against HPV 6/11/16/18-related persistent infection was 85.5% (95% CI: 77.0, 91.3). The supportive analyses in the HNRT and FAS populations were consistent with the primary analysis in the PPE population and support the previous conclusion that qHPV vaccine is efficacious against HPV 6/11/16/18-related EGL in males.

Table 9 Analysis of Efficacy Against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type, and Lesion Type (Per-Protocol Efficacy Population)

	qHPV Vaccine (N=2025)				Placebo (N=2030)					
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
HPV 6/11/16/18-Related EGL	1394	3	3109.2	0.1	1404	32	3106.0	1	90.6	(70.1, 98.2)
By Sexual Orientation										
HM Subjects	1200	2	2722.4	0.1	1196	26	2689.7	1	92.4	(69.6, 99.1)
MSM Subjects	194	1	386.9	0.3	208	6	416.3	1.4	82.1	(-47.8, 99.6)
By HPV Type										
HPV 6-Related EGL	1242	3	2779.8	0.1	1243	19	2790.3	0.7	84.2	(46.2, 97.0)
HPV 11-Related EGL	1242	1	2781.2	0	1243	11	2790.7	0.4	90.9	(37.2, 99.8)
HPV 16-Related EGL	1292	0	2883.5	0	1270	3	2841.1	0.1	100	(-138.4, 100)
HPV 18-Related EGL	1331	0	2978.0	0	1352	1	3013.4	0	100	(-3846.4, 100)
By Lesion Type										
Condyloma	1394	3	3109.2	0.1	1404	28	3108.0	0.9	89.3	(65.3, 97.9)
PIN 1 or worse	1394	0	3112.2	0	1404	4	3124.9	0.1	100	(-52.1, 100)
PIN 1	1394	0	3112.2	0	1404	2	3126.6	0.1	100	(-434.9, 100)
PIN 2/3 or Cancer	1394	0	3112.2	0	1404	2	3125.1	0.1	100	(-434.7, 100)
PIN 2/3	1394	0	3112.2	0	1404	2	3125.1	0.1	100	(-434.7, 100)
Penile/Perianal/Perineal Cancer	1394	0	3112.2	0	1404	0	3126.8	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; 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.

Quadrivalent HPV vaccine efficacy has been shown for up to 4.5 years Postdose 3 among young adult women. Data from Protocol 020 show that while incidence rates of disease in placebo recipients increased during the entire duration of study follow-up, rates in the vaccine group subjects remained low, providing evidence of sustained vaccine efficacy in young adult men over the 36 months of the study.

II.6 Immunogenicity Endpoints

The primary immunogenicity endpoint was anti-HPV 6, 11, 16, and 18 serum competitive Luminex immunoassay (cLIA) levels at Month 7 in the defined per protocol immunogenicity population. Serum samples were collected from all subjects at Months 0, 7, 24, and 36.

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.

Statistical Methods

The immunogenicity objective was addressed by computing:

(1) point estimates of the GMTs and the corresponding 95% confidence intervals for HPV types 6, 11, 16, and 18 at Month 7 in the PPI population;

(2) point estimates for the GMTs and the corresponding 95% confidence intervals for HPV types 6, 11, 16, and 18 at Months 24 and 36 in the PPI population, and observationally comparing the GMTs in the qHPV vaccine group to the corresponding GMTs at Month 7;

(3) point estimates of the seroconversion percentages and the corresponding 95% confidence intervals for HPV types 6, 11, 16, and 18 at Month 7 in the PPI population;

(4) point estimates of the seroconversion percentages and the corresponding 95% confidence intervals for HPV types 6, 11, 16, and 18 at Months 24 and 36 in the PPI population, and observationally comparing the seroconversion percentages in the qHPV vaccine group to the corresponding seroconversion percentages at Month 7; and

(5) the reverse cumulative distributions of anti-HPV 6, 11, 16, and 18 titers at Months 7, 24, and 36 in the PPI population for vaccine and placebo recipients.

II.8 Immunogenicity Results

Immunogenicity results at Months 7 and 24 were presented in the previous submission (sBLA 125126/1297). End of study data show that at Month 36, the GMTs in vaccinated subjects were lower than at Month 7 for all vaccine HPV types (Table 10 (Table 2.7.3-immunogenicity: 2)). Appendix Figure 2 (Figure 2.7.3-immunogenicity shows longitudinal plots of the anti-HPV 6, 11, 16, and 18 GMTs at Day 1 and Months 7, 24, and 36 in qHPV vaccine recipients. Similar to observations in the female studies, among all four vaccine HPV types, anti-HPV 18 antibodies show the highest rate of decline. Month 36 anti-HPV 18 GMTs were comparable to the estimated antibody level induced by natural infection; however, seroconversion percentages at Month 36 were comparable to the Month 24 rates for each of the vaccine types Table 11 (Table 2.7.3-immunogenicity: 3). Overall, the final immunogenicity findings from Protocol 020 are similar to the experience in the female qHPV vaccine efficacy studies.

Table 10 Summary of Anti-HPV Geometric Mean Titers by Vaccination Group (Per-Protocol Immunogenicity Population)

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=2025)			Placebo (N=2030)		
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	1092	< 7	(<7, <7)	1108	< 7	(<7, <7)
Month 07	1092	447.6	(422.6, 474.1)	1108	< 7	(<7, <7)
Month 24	941	79.8	(75.8, 84.1)	949	< 7	(<7, <7)
Month 36	847	71.5	(67.5, 75.8)	834	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1092	< 8	(<8, <8)	1107	< 8	(<8, <8)
Month 07	1092	624	(594.1, 655.4)	1107	< 8	(<8, <8)
Month 24	941	94.6	(90.0, 99.5)	948	< 8	(<8, <8)
Month 36	847	82.6	(78.3, 87.1)	833	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1135	< 11	(<11, <11)	1127	< 11	(<11, <11)
Month 07	1135	2,404.3	(2,272.2, 2,544.0)	1127	< 11	(<11, <11)
Month 24	979	342.7	(324.7, 361.7)	951	< 11	(<11, <11)
Month 36	877	293.3	(276.5, 311.2)	839	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1174	< 10	(<10, <10)	1202	< 10	(<10, <10)
Month 07	1174	402.3	(380.2, 425.7)	1202	< 10	(<10, <10)
Month 24	1011	38.4	(36.0, 41.0)	1010	< 10	(<10, <10)
Month 36	905	33.1	(30.9, 35.4)	882	< 10	(<10, <10)

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

Anti-HPV Response Study Time	qHPV Vaccine (N=2025)				Placebo (N=2030)			
		Seroconversion				Seroconversion		
	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 6 cLIA ≥ 20 mMU/mL								
Day 1	1092	0	0	(0.0%, 0.3%)	1108	0	0	(0.0%, 0.3%)
Month 07	1092	1080	98.9	(98.1%, 99.4%)	1108	18	1.6	(1.0%, 2.6%)
Month 24	941	855	90.9	(88.8%, 92.6%)	949	20	2.1	(1.3%, 3.2%)
Month 36	847	753	88.9	(86.6%, 90.9%)	834	26	3.1	(2.0%, 4.5%)
HPV 11 cLIA ≥ 16 mMU/mL								
Day 1	1092	0	0	(0.0%, 0.3%)	1107	0	0	(0.0%, 0.3%)
Month 07	1092	1083	99.2	(98.4%, 99.6%)	1107	23	2.1	(1.3%, 3.1%)
Month 24	941	900	95.6	(94.1%, 96.9%)	948	13	1.4	(0.7%, 2.3%)
Month 36	847	796	94.0	(92.2%, 95.5%)	833	19	2.3	(1.4%, 3.5%)
HPV 16 cLIA ≥ 20 mMU/mL								
Day 1	1135	0	0	(0.0%, 0.3%)	1127	0	0	(0.0%, 0.3%)
Month 07	1135	1121	98.8	(97.9%, 99.3%)	1127	20	1.8	(1.1%, 2.7%)
Month 24	979	970	99.1	(98.3%, 99.6%)	951	7	0.7	(0.3%, 1.5%)
Month 36	877	859	97.9	(96.8%, 98.8%)	839	18	2.1	(1.3%, 3.4%)
HPV 18 cLIA ≥ 24 mMU/mL								
Day 1	1174	0	0	(0.0%, 0.3%)	1202	0	0	(0.0%, 0.3%)
Month 07	1174	1143	97.4	(96.3%, 98.2%)	1202	21	1.7	(1.1%, 2.7%)
Month 24	1011	630	62.3	(59.2%, 65.3%)	1010	12	1.2	(0.6%, 2.1%)
Month 36	905	516	57.0	(53.7%, 60.3%)	882	9	1.0	(0.5%, 1.9%)

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.

Table 12 (Table 14-63 in V501, Reference P020) and Table 13 (Table 14-64 in V501, Reference P020) show the anti-HPV 6, 11, 16, and 18 GMTs in the PPI population at Day 1 and Months 7, 24, and 36 for HM and MSM subjects, respectively. In the MSM subgroup, the GMTs at Month 7 for all vaccine HPV types were lower than the corresponding GMTs in the HM subjects. At Months 24 and 36, the GMTs for HM and MSM subjects are comparable for HPV types 6, 11, and 18. For HPV type 16, the GMTs in the MSM subjects remain higher than the GMTs in the HM subjects for the Month 24 and 36 time points.

Table 12 Summary of Anti-HPV Geometric Mean Titers for HM Subjects by Vaccination Group (HM Per-Protocol Immunogenicity Population)

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=1726)			Placebo (N=1731)		
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	978	< 7	(<7, <7)	988	< 7	(<7, <7)
Month 07	978	473.9	(446.8, 502.7)	988	< 7	(<7, <7)
Month 24	851	81.6	(77.4, 86.1)	845	< 7	(<7, <7)
Month 36	792	73.4	(69.2, 77.8)	780	< 7	(<7, <7)
Anti-HPV 11						
Day 1	978	< 8	(<8, <8)	987	< 8	(<8, <8)
Month 07	978	651.5	(620.7, 683.7)	987	< 8	(<8, <8)
Month 24	851	94.9	(90.1, 100.0)	844	< 8	(<8, <8)
Month 36	792	83.8	(79.4, 88.5)	779	< 8	(<8, <8)
Anti-HPV 16						
Day 1	999	< 11	(<11, <11)	989	< 11	(<11, <11)
Month 07	999	2,622.10	(2,484.9, 2,766.9)	989	< 11	(<11, <11)
Month 24	869	355.7	(335.8, 376.7)	841	< 11	(<11, <11)
Month 36	811	309.3	(291.5, 328.1)	777	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1032	< 10	(<10, <10)	1043	< 10	(<10, <10)
Month 07	1032	439.3	(415.7, 464.3)	1043	< 10	(<10, <10)
Month 24	897	39.4	(36.8, 42.2)	882	< 10	(<10, <10)
Month 36	836	33.9	(31.6, 36.4)	813	< 10	(<10, <10)

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; HM = Heterosexual men; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 13 Summary of Anti-HPV Geometric Mean Titers for MSM Subjects by Vaccination Group (MSM Per-Protocol Immunogenicity Population)

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=299)			Placebo (N=299)		
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	114	< 7	(<7, <7)	120	< 7	(<7, <7)
Month 07	114	274.3	(222.5, 338.3)	120	< 7	(<7, <7)
Month 24	90	64.6	(53.7, 77.8)	104	< 7	(<7, <7)
Month 36	55	49.2	(37.3, 64.8)	54	< 7	(<7, <7)
Anti-HPV 11						
Day 1	114	< 8	(<8, <8)	120	< 8	(<8, <8)
Month 07	114	431.3	(348.2, 534.2)	120	< 8	(<8, <8)
Month 24	90	91.6	(76.7, 109.4)	104	< 8	(<8, <8)
Month 36	55	66.2	(51.8, 84.6)	54	< 8	(<8, <8)
Anti-HPV 16						
Day 1	136	< 11	(<11, <11)	138	< 11	(<11, <11)
Month 07	136	1,271.60	(996.0, 1,623.4)	138	< 11	(<11, <11)
Month 24	110	255.5	(219.5, 297.4)	110	< 11	(<11, <11)
Month 36	66	153	(116.1, 201.5)	62	< 11	(<11, <11)
Anti-HPV 18						
Day 1	142	< 10	(<10, <10)	159	< 10	(<10, <10)
Month 07	142	212.1	(170.0, 264.6)	159	< 10	(<10, <10)
Month 24	114	31.4	(25.9, 38.0)	128	< 10	(<10, <10)
Month 36	69	24.7	(19.0, 32.1)	69	< 10	(<10, <10)

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; HM = Heterosexual men; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 14 (Table 14-66 in V501, Reference P020) and Table 15 (Table 14-67 in V501, Reference P020) show the seroconversion percentages by vaccination group for vaccine HPV types 6, 11, 16, and 18 in the PPI population at Day 1 and Months 7, 24, and 36 for HM and MSM subjects, respectively. In the MSM subgroup, the seroconversion percentages in vaccine recipients at Month 7 for the HPV types 6 and 11 are comparable to the corresponding seroconversion percentages in the HM subjects. The seroconversion percentages in vaccine recipients at Month 7 for HPV types 16 and 18 in the MSM subgroup are slightly lower than the corresponding seroconversion percentages for HM subjects. At Months 24 and 36, the seroconversion percentages in vaccine recipients for the MSM subgroup are comparable to the seroconversion percentages for HM subjects.

Table 14 Summary of Anti-HPV Percent Seroconversion for HM Subjects by Vaccination Group (HM Per-Protocol Immunogenicity Population)

Anti-HPV Response Study Time	qHPV Vaccine (N=1726)				Placebo (N=1731)			
		Seroconversion				Seroconversion		
	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 6 cLIA ≥ 20 mMU/mL								
Day 1	978	0	0	(0.0%, 0.4%)	988	0	0	(0.0%, 0.4%)
Month 07	978	970	99.2	(98.4%, 99.6%)	988	12	1.2	(0.6%, 2.1%)
Month 24	851	777	91.3	(89.2%, 93.1%)	845	16	1.9	(1.1%, 3.1%)
Month 36	792	709	89.5	(87.2%, 91.6%)	780	22	2.8	(1.8%, 4.2%)
HPV 11 cLIA ≥ 16 mMU/mL								
Day 1	978	0	0	(0.0%, 0.4%)	987	0	0	(0.0%, 0.4%)
Month 07	978	972	99.4	(98.7%, 99.8%)	987	16	1.6	(0.9%, 2.6%)
Month 24	851	813	95.5	(93.9%, 96.8%)	844	8	0.9	(0.4%, 1.9%)
Month 36	792	747	94.3	(92.5%, 95.8%)	779	15	1.9	(1.1%, 3.2%)
HPV 16 cLIA ≥ 20 mMU/mL								
Day 1	999	0	0	(0.0%, 0.4%)	989	0	0	(0.0%, 0.4%)
Month 07	999	993	99.4	(98.7%, 99.8%)	989	13	1.3	(0.7%, 2.2%)
Month 24	869	862	99.2	(98.3%, 99.7%)	841	7	0.8	(0.3%, 1.7%)
Month 36	811	797	98.3	(97.1%, 99.1%)	777	13	1.7	(0.9%, 2.8%)
HPV 18 cLIA ≥ 24 mMU/mL								
Day 1	1032	0	0	(0.0%, 0.4%)	1043	0	0	(0.0%, 0.4%)
Month 07	1032	1016	98.4	(97.5%, 99.1%)	1043	12	1.2	(0.6%, 2.0%)
Month 24	897	564	62.9	(59.6%, 66.0%)	882	6	0.7	(0.3%, 1.5%)
Month 36	836	479	57.3	(53.9%, 60.7%)	813	7	0.9	(0.3%, 1.8%)

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; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table 15 Summary of Anti-HPV Percent Seroconversion for MSM Subjects by Vaccination Group (MSM Per-Protocol Immunogenicity Population)

Anti-HPV Response Study Time	qHPV Vaccine (N=299)				Placebo (N=299)			
		Seroconversion				Seroconversion		
	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 6 cLIA ≥ 20 mMU/mL								
Day 1	114	0	0	(0.0%, 3.2%)	120	0	0	(0.0%, 3.0%)
Month 07	114	110	96.5	(91.3%, 99.0%)	120	6	5.0	(1.9%, 10.6%)
Month 24	90	78	86.7	(77.9%, 92.9%)	104	4	3.8	(1.1%, 9.6%)
Month 36	55	44	80	(67.0%, 89.6%)	54	4	7.4	(2.1%, 17.9%)
HPV 11 cLIA ≥ 16 mMU/mL								
Day 1	114	0	0	(0.0%, 3.2%)	120	0	0	(0.0%, 3.0%)
Month 07	114	111	97.4	(92.5%, 99.5%)	120	7	5.8	(2.4%, 11.6%)
Month 24	90	87	96.7	(90.6%, 99.3%)	104	5	4.8	(1.6%, 10.9%)
Month 36	55	49	89.1	(77.8%, 95.9%)	54	4	7.4	(2.1%, 17.9%)
HPV 16 cLIA ≥ 20 mMU/mL								
Day 1	136	0	0	(0.0%, 2.7%)	138	0	0	(0.0%, 2.6%)
Month 07	136	128	94.1	(88.7%, 97.4%)	138	7	5.1	(2.1%, 10.2%)
Month 24	110	108	98.2	(93.6%, 99.8%)	110	0	0	(0.0%, 3.3%)
Month 36	66	62	93.9	(85.2%, 98.3%)	62	5	8.1	(2.7%, 17.8%)
HPV 18 cLIA ≥ 24 mMU/mL								
Day 1	142	0	0	(0.0%, 2.6%)	159	0	0	(0.0%, 2.3%)
Month 07	142	127	89.4	(83.2%, 94.0%)	159	9	5.7	(2.6%, 10.5%)
Month 24	114	66	57.9	(48.3%, 67.1%)	128	6	4.7	(1.7%, 9.9%)
Month 36	69	37	53.6	(41.2%, 65.7%)	69	2	2.9	(0.4%, 10.1%)

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; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Bridging Studies

Given that studying vaccine efficacy was not feasible in sexually naïve adolescent populations, an immuno-bridging approach to the basis of licensure in the target age group for vaccination was taken, that is demonstration of non-inferiority of GMTs and seroconversion rates in adolescents compared to adult males was accepted as the basis for efficacy in the target population.

Table 16 (Table 2.7.3-immunogenicity: 4) and Table 17 (Table 2.7.3-immunogenicity: 5) show that the GMTs and seroconversion rates in 9- to 15-year-old boys were non-inferior to GMTs and seroconversion rates in 16- to 26-year-old men respectively.

Table 16 Statistical Analysis of Month 7 Anti-HPV Geometric Mean Titers (GMT) 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 = 1,072)		16 to 26 Year-olds[2] (Comparison Group B) (N = 2,026)		Estimated Fold Difference Group A / Group B (95% CI)[3]
Assay	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	
Anti-HPV 6	884	1037.5	1093	447.8	2.32 (2.10, 2.56)
Anti-HPV 11	885	1386.8	1093	624.3	2.22 (2.03, 2.43)
Anti-HPV 16	882	6056.5	1136	2403.3	2.52 (2.27, 2.80)
Anti-HPV 18	887	1357.4	1175	402.6	3.37 (3.02, 3.76)

[1]9-15 year-old male subjects from Protocols 016 and 018. Of note, after database lock a transcription error was noted and one subject who was initially reported as male was confirmed as female.
[2]16-26 year-old male subjects from Protocol 020 and one 16 year old subject from Protocol 018.
[3]Parameter estimates, confidence intervals, and p-values are based on a statistical model with a term for age group.
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 17 Statistical Analysis of Month 7 Anti-HPV Seroconversion Rates Among Male Subjects Vaccinated with qHPV Vaccine Comparing Boys to Men (Per-Protocol Immunogenicity Population)

	9 to 15 Year-olds[1] (Comparison Group A) (N = 1,072)		16 to 26 Year-olds[2] (Comparison Group B) (N = 2,026)		Estimated Percent Point Difference Group A - Group B (95% CI)[3]
Anti-HPV Response	n	Estimated Response (%)	n	Estimated Response (%)	
HPV 6 cLIA .20 mMU/mL	884	99.9	1093	98.9	1.0 (0.4, 1.8)
HPV 11 cLIA .16 mMU/mL	885	99.9	1093	99.2	0.7 (0.1, 1.5)
HPV 16 cLIA .20 mMU/mL	882	99.8	1136	98.8	1.0 (0.3, 1.9)
HPV 18 cLIA .24 mMU/mL	887	99.8	1175	97.4	2.4 (1.5, 3.5)

[1]9-15 year-old male subjects from Protocols 016 and 018. Of note, after database lock a transcription error was noted and one subject who was initially reported as male was confirmed as female.
[2]16-26 year-old male subjects from Protocol 020 and one 16 year old subject from Protocol 018.
[3]Parameter estimates, confidence intervals, and p-values are based on methods developed by Miettinen and Nurminen
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

In general, GMTs and seroconversion rates in the MSM subgroup were equal to or lower than HM aged 16-26 years old (see Tables Table 12, Table 13, Table 14, and Table 15). Therefore, the demonstrated non-inferiority of immune responses in 9-15 year old boys to 16-26 year old men (HM and MSM) would also be true if the 9-15 year old boys had been compared to 16-26 year old MSM, the group in whom anal disease was assessed. It may therefore be concluded that the qHPV vaccine is efficacious in preventing HPV 6-, 11-, 16-, and 18-related anal intraepithelial neoplasia in boys and men 9 to 26 years of age.

II.9 Safety Assessments

The primary objective for safety was to demonstrate that qHPV, when administered at 0, 2, and 6 months, was generally well tolerated. The following measures were collected from each study subject to assess safety: (1) temperatures (oral or oral equivalent) 4 hours after vaccination and daily for the next 4 days; (2) all adverse experiences that occurred within 14 calendar days following vaccination; (3) all serious clinical adverse experiences that occurred within 14 days following vaccination; and (4) all serious clinical adverse experiences that resulted in the death of the subject or were determined to be related to the study vaccine or a study procedure that occurred at any time during the study. All subjects who received at least one injection and had safety follow-up data were included in the safety summary.

Since the reporting of safety results in the original CSR (sBLA 125126/1297), there were no new safety outcomes reported from Day 1 to 15 following any vaccination. In addition, no new serious adverse experiences were reported. The proportion of subjects with serious adverse experiences Day 1 to 15 following any vaccination visit was low, and was comparable in the qHPV vaccine group (0.3%) and the placebo group (0.1%). There were no subjects with serious vaccine-related adverse experiences at any time during the study. The proportion of subjects who reported one or more injection-site adverse experiences within 5 days following any vaccination was slightly higher in the qHPV vaccine group (59.9%) than in the placebo group (53.6%), but the proportion of subjects who reported a severe injection-site adverse experience within 5 days following any vaccination visit was comparable in the qHPV vaccine group (1.3%) and the placebo group (1%).

II.10 Gender, Age, and Other Subgroup Populations

Protocol 020 included only male subjects aged 16 to 27 years. Thus, subgroup analyses would not be applicable.

III. STUDY CONCLUSIONS

Efficacy Conclusion based on the MSM Substudy

The MSM substudy in Protocol 020 has demonstrated that prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is efficacious in preventing development of HPV 6/11/16/18-related AIN of any grade.

Efficacy Conclusion based on Protocol 020

The overall study data has demonstrated that prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is efficacious in preventing development of HPV 6/11/16/18-related external genital lesions.

Immunogenicity Conclusion based on Protocol 020

Immunogenicity data from Protocol 020 has demonstrated that 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 that result in a high level of protective efficacy through approximately 2.4 years following completion of the vaccination regimen.

Safety Conclusion based on Protocol 020

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

IV. RECOMMENDATION

The data presented in the current application support that: 1) qHPV vaccine is indicated in males 9 through 26 years of age for the prevention of AIN grades 1, 2, and 3 caused by HPV types 6, 11, 16 and 18; and 2) qHPV vaccine is indicated in males 9 through 26 years of age for the prevention of anal cancer caused by HPV types 16 and 18.

V. COMMENTS AND QUESTIONS TO CBER REVIEW COMMITTEE

- The MSM substudy data presented in the current application support the proposed indications for the prevention of AIN 1+ and anal cancer in men. However, the submission does not contain data to support extension of these indications to women. I defer to the clinical reviewer to decide whether these indications may be extended to women, based on physiopathological considerations.

VI. COMMENTS AND QUESTIONS TO APPLICANT

None

VII. APPENDIX

Figure 1 Analysis of Time to HPV 6/11/16/18-Related AIN and Anal Cancer (MSM Per-Protocol Efficacy Population) (Protocol 020)

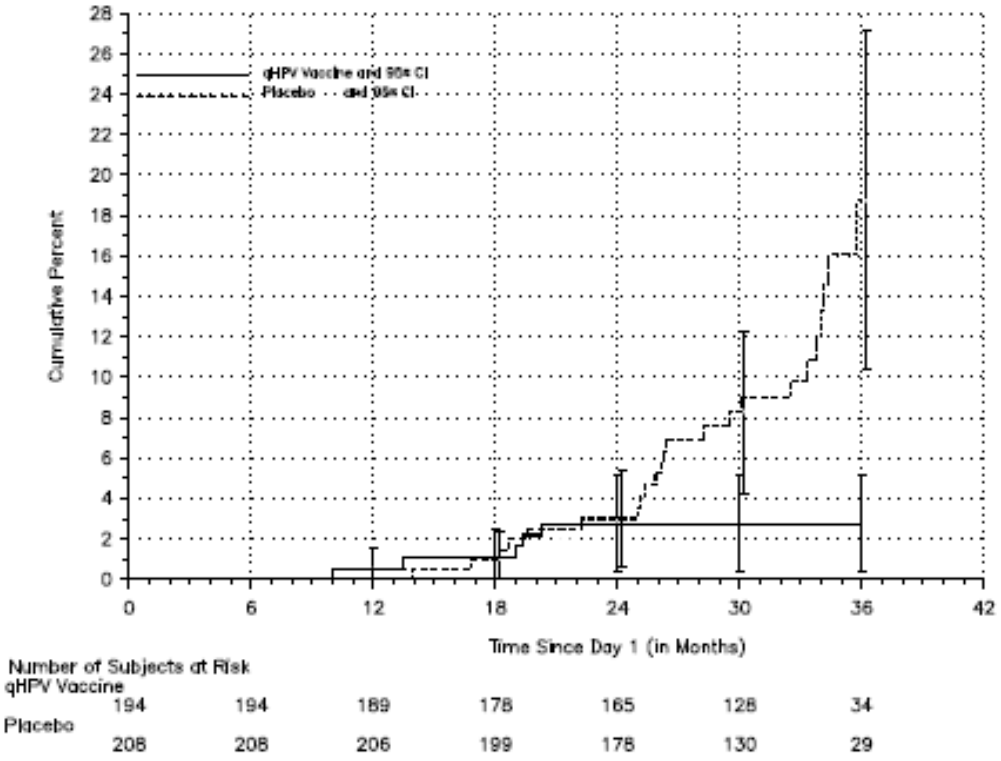

Figure 2 Longitudinal Plots of Anti-HPV Geometric Mean Titers in Vaccinated Subjects (Per-Protocol Immunogenicity Population)