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2.5.2 Overview of Biopharmaceutics

No traditional biopharmaceutic studies were conducted in support of this supplemental Application, as such studies are not applicable to vaccines. The quadrivalent HPV vaccine is an injectable recombinant vaccine that is immediately bioavailable. The bioavailability of the vaccine is confirmed by the development of serum anti-HPV responses to the component L1 VLP types.

2.5.3 Overview of Clinical Pharmacology

No clinical pharmacology studies of the qHPV vaccine were conducted in support of this supplemental Application. As noted in the Committee for Medicinal Products for Human Use (CHMP) "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005), clinical pharmacology studies are not routinely conducted as part of the evaluation of vaccines.

2.5.4 Overview of Efficacy and Immunogenicity

Protocol 020 contributed efficacy and immunogenicity data in young adult men ages 16 to 26 years and has provided clear evidence of the prophylactic efficacy of qHPV vaccine in the prevention of HPV-associated external genital lesions and persistent HPV infection in men [Sec. 2.7.3.2-exgenlesions]. Immunogenicity data in 9- to 15-year-old boys from Protocols 016 and 018 were utilized to immunobridge the efficacy results from men in Protocol 020 to boys [Sec. 2.7.3.4-Immunogenicity].

The current submission provides new data from analyses of the MSM substudy endpoint, as well as updated analyses of the primary and secondary endpoints of efficacy against external genital disease and persistent infection, and updated safety and immunogenicity data. As stated above, this section is focused primarily on the MSM substudy.

2.5.4.1 Clinical Efficacy

2.5.4.1.1 Definition of Populations Used in Analyses

Four different populations were used in vaccine efficacy analyses and the key elements for each population are summarized in [Appendix 2.5: 6] and [Appendix 2.5: 7].

- The per-protocol efficacy (PPE) population was used for the primary efficacy analysis. Briefly, PPE subjects were negative to the relevant HPV type at Day 1 and Month 7 and had no major protocol violations; case counting started after 4 weeks following completion of the vaccination series (i.e., after Month 7).
- The HPV-naïve to the Relevant Type (HNRT) population included subjects who were HPV-naïve at Day 1 to the vaccine HPV type being analyzed; case counting started after Day 1.
- The Generally HPV Naïve (GHN) population included subjects who were HPV-naïve at Day 1 to all 14 HPV types tested in the multiplex PCR assay (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) [Sec. 9.7.1.1.4] of [Ref. 5.3.5.1: P020]

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seronegative to HPV 6, 11, 16, 18, and had a negative anal Pap test at Day 1 (in the MSM); case counting started after Day 1.

- The Full Analysis Set (FAS) included all enrolled subjects who received at least one dose of vaccine; subjects with prevalent infection [i.e., HPV infection present at Day 1] and disease with any HPV type were therefore included; case counting started after Day 1.

Prophylactic Efficacy Analyses

Three populations were used in assessing the prophylactic efficacy of the qHPV vaccine: PPE, HNRT, and FAS. The primary efficacy analysis for the prophylactic efficacy of the qHPV vaccine against AIN utilized the PPE population, since this allowed measurement of the full benefit of qHPV vaccine in individuals who were naïve to the relevant vaccine HPV type through the completion of 3-dose vaccination regimen.

Supportive analyses in the HNRT and FAS population were performed. The HNRT population allows measurement of efficacy immediately after the first dose among subjects who are naïve to the relevant HPV type, thus providing supportive information about efficacy during the course of and after completion of the vaccination series. The FAS analysis population includes all HPV-naïve subjects, as well as subjects with evidence of prior exposure or active infection with a vaccine or non-vaccine HPV type at enrollment. Thus, the FAS analysis represents a mixture of prophylactic and therapeutic efficacy. Because this population includes virtually all study subjects, the FAS approximates the general population of sexually-active 16- to 26-year-old men. Evaluation of prophylactic efficacy impact was measured on vaccine-type disease only.

Population Benefit Analyses

The analysis of efficacy with respect to the population benefit endpoints (i.e., evaluation of the impact of qHPV vaccine on the incidence of any type anal disease) was performed using the GHN and the FAS populations.

The GHN population was designed to approximate a population of adolescent and young adult men who were either sexually-naïve or sexually-experienced but not yet been exposed to *any* HPV type. Given that it is impossible to evaluate the qHPV vaccine in the target population of boys prior to sexual debut, the GHN population is the most appropriate subpopulation of Protocol 020 to provide insight regarding the potential impact of vaccination of males when vaccinated in young adolescence, prior to HPV exposure. With cases being counted after the first dose of vaccine, efficacy for this population is anticipated to be lower than for the per protocol population. The FAS represents the general population of sexually-active 16- to 26-year-old men, and therefore includes subjects with prevalent HPV infection; only incident vaccine type disease was anticipated to be affected by the qHPV vaccine. Population impact analysis of the FAS population was for efficacy against any HPV type.

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2.5.4.1.2 Overall Study Subject Disposition, Subject Accounting, and Enrollment Characteristics

The final cut-off date for study visits was July 31, 2009. The median duration of efficacy follow-up at the end of study was 32.2 months post-enrollment for the MSM study population.

The primary efficacy analysis was conducted in the PPE population. Among the 4,055 subjects enrolled who received at least one injection in the study, 63%, 65%, and 68% were eligible for the PPE analyses related to HPV types 6/11, 16, and 18, respectively [Table 2.7.3-exgenlesions: 5]. The MSM substudy efficacy analysis was conducted in the PPE population. Among the 598 MSM subjects enrolled who received at least one injection in the study, 50%, 58%, and 63% were eligible for the MSM PPE analyses related to HPV types 6/11, 16, and 18, respectively. The most common reasons for exclusion from each of the HPV 6/11, HPV 16, and HPV 18 PPE populations were Day 1 through Month 7 positivity to the relevant HPV type (i.e., prevalent disease [Day 1] or incident disease before the full vaccination series take effect [through Month 7]), missing Day 1 or Month 7 swab PCR results, Day 1 or Month 7 swab samples not collected within the acceptable day range, and missing the 2nd and 3rd vaccinations. The numbers of subjects excluded within each vaccination group for each reason were generally comparable.

MSM subjects represented 14.8% of the overall study population and had a median age of 22 years, with a mean age of 22.1 [Section 10.5.1] of [Ref. 5.3.5.1: P020]. Baseline characteristics, including sexual history, were comparable between vaccine and placebo groups. Of the MSM subjects, 30.5% of subjects were PCR positive at Day 1 to a vaccine HPV type, 22.8% were seropositive to a vaccine HPV type, and 39.1% were positive to a vaccine HPV type by PCR or serology. Only 0.2% of subjects were HPV PCR positive to all 4 vaccine HPV types at Day 1. With regard to baseline prevalence of non-HPV anogenital infection, 9.4% of MSM subjects were positive for rectal chlamydia. Approximately 10% of baseline anal Pap tests were reported to have squamous intraepithelial lesions present.

2.5.4.1.3 Efficacy Results – Protocol 020

2.5.4.1.3.1 Prophylactic Efficacy With Respect to Anal Disease and Persistent Infection

Per Protocol Population Analyses of AIN and Intra-Anal Persistent Infection

The MSM substudy efficacy hypothesis was stated as follows: Administration of a 3-dose regimen of qHPV reduces the combined incidence of HPV 6-, 11-, 16-, and 18–related AIN or anal cancer in MSM who are seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV type, compared to placebo recipients. *(The statistical criterion for success required that the lower bound of the multiplicity-adjusted 95% confidence interval for vaccine efficacy exclude 0%.).*

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[Table 2.5: 1] and the associated time to event curve [Appendix 2.5: 8] show 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 significant vaccine efficacy against HPV 6/11/16/18-related AIN and anal cancer (p-value < 0.001). With 5 HPV 6/11/16/18-related AIN cases in the qHPV vaccine group and 24 cases in the placebo group, vaccine efficacy against this endpoint was 77.5% (95.1% CI: 39.6, 93.3). 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.

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Table 2.5: 1

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 (%)	CI‡	P-value§
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)	< 0.001
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	0.0	144	6	298.2	2.0	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	0.0	193	4	387.4	1.0	100	(-70.0, 100)	

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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) (Cont.)

Endpoint	qHPV Vaccine (N=299) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=299) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	CI‡	P-value§
By Lesion Type											
AIN 1	194	4	383.1	1.0	208	16	413.8	3.9	73.0	(16.3, 93.4)	
Condyloma Acuminatum	194	0	386.8	0.0	208	6	418.2	1.4	100	(8.2, 100)	
Non-acuminate	194	4	383.1	1.0	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	0.0	208	0	421.1	0.0	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.

§A p-value<0.0245 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 0% and supports the conclusion that the vaccine is efficacious against the given endpoint

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.

[Ref. 5.3.5.1: P020]

Having achieved success on the prespecified endpoint of HPV 6/11/16/18-related AIN, efficacy against high-grade AIN (AIN 2 or worse) was evaluated. Of the 24 cases in the placebo group, 13 were identified with diagnoses of AIN 2 or worse. In the vaccine group, there were 3 cases identified with diagnoses of AIN 2 or worse out of the total of 5 cases. Thus, the vaccine efficacy estimate for HPV 6/11/16/18-related high-grade AIN was 74.9% (95% CI: 8.8, 95.4), which indicates that the vaccine efficacy for this endpoint is above 0%. Although this was not a prespecified endpoint, the consistency of this observed vaccine effect with other demonstrations of qHPV vaccine efficacy against high-grade HPV-related disease provides support for the efficacy of the qHPV vaccine against high-grade AIN, the obligate precursor for anal cancer.

In order to further evaluate consistency of the effect, vaccine efficacy against high-grade AIN related to HPV types 16 and 18 was assessed. One (1) case was observed in the vaccine group and 8 cases were observed in the placebo group. Again, there was no a priori hypothesis test of efficacy against high-risk HPV type high-grade AIN; however the observed efficacy against 6/11/16/18-related AIN and this extension of the effect seen in prior demonstrations of qHPV vaccine efficacy provide further support for vaccine efficacy against HPV 16/18-related high-grade anal disease and therefore against anal cancer caused by these important types.

It is accepted that HPV-related premalignant and malignant disease does not develop in the absence of preceding persistent infection. Demonstration of type-specific vaccine efficacy against persistent infection in the relevant disease site therefore provides important supportive evidence that complements and strengthens disease efficacy findings. To support the MSM substudy efficacy analysis of AIN and anal cancer in the MSM PPE population, an analysis was performed to evaluate vaccine efficacy against HPV 6/11/16/18-related intra-anal persistent infection using only the intra-anal specimens from subjects in the MSM PPE population. [Table 2.5: 2] shows the results of the analysis of efficacy against HPV 6/11/16/18-related intra-anal persistent infection for the MSM PPE population. Vaccine efficacy for this population was 94.9% (95% CI: 80.4, 99.4). Notably, type-specific efficacy estimates against high-risk HPV type 16 and 18 infection were each over 90% and reached statistical significance. When considered in the context of the greater than 90% observed type-specific efficacy against persistent anal infection related to HPV 16 and 18, the strong trend in the disease endpoint analyses provides compelling support for efficacy of the qHPV vaccine against HPV 16/18-related high-grade anal disease.

Analysis of the Per Protocol Vaccine Group AIN Cases

Throughout the qHPV vaccine program, a conservative approach has been taken to the attribution of incident lesions to a causal HPV type. An endpoint of AIN related to HPV 6, 11, 16, or 18 is defined to occur if that HPV type is identified in an adjacent section from the same tissue block in which the lesion is diagnosed. Thus, a given lesion is attributed to the vaccine type, regardless of the presence of other high-risk types, even if infection with those types was present at baseline or preceded development of the lesion in the absence of any evidence of preceding infection with the vaccine type. Other less

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conservative approaches could have been taken, but this choice was made so as to avoid potential over-estimation of vaccine efficacy.

With this in mind, and in an effort to better understand the potential involvement of non-vaccine types in the development of the five AIN cases that occurred in the per protocol vaccine group subjects, these cases were reviewed with regard to the vaccine and non-vaccine HPV types identified in anogenital swabs and biopsy specimens before and subsequent to the diagnoses for which the subjects became cases. For each of the five subjects who became cases, the patterns of HPV detection suggest possible alternate explanations of the causal HPV type. See [Table 11-2] in [Section 11.1.1.1.1] of [Ref. 5.3.5.1: P020]. In each case, there was either more than one high-risk HPV type detected in the AIN lesion, or the subject was infected at baseline with an HPV type different from the type detected in the lesion.

To summarize the cases briefly, one subject who became a case of type 6-related AIN 1, AIN 2, and AIN 3 was infected at baseline and for most of the study with HPV 16, but the three AIN lesions were positive only for HPV 6, and thus the subject was counted as having type 6-related disease. The other vaccine group case of AIN 3 was counted as a type 16-related case; however, this subject was infected at baseline with types 6, 18, 45, 39, and 59, and had developed HPV 39-positive AIN 2 prior to becoming a case of AIN 3. Type 39 was also detected in the type 16-related biopsy for which the subject became a case. The subject with the second case of HPV 6-related AIN 2 was also positive for HPV 45, which was detected in the lesion as well as in subsequent intra-anal swabs for the duration of the study. The subject with the second case of type 6-related AIN 1 was infected at baseline with high-risk HPV types 45 and 51, as well as type 56, which was also detected in the AIN 1 lesion for which the subject became a case. The second case of type 16-related AIN 1 was also positive for type 45 in the lesion, as well in an adjacent biopsy for which pathology was read as negative. It is notable that in some of these cases, attribution to a vaccine HPV type was based on a single timepoint of detection of the given type, without evidence of persistent infection (as was seen with the non-vaccine types identified in the case lesions). The significance of detection of an HPV type in a lesion at a single timepoint is unknown, but in light of the observed detection patterns, does raise questions regarding attribution of causality. Additional details for each of these subjects were provided in the individual case narratives in the Protocol 020 Final CSR [Ref. 5.3.5.1: P020]. Despite these findings, these subjects were counted as cases in the group that received the qHPV vaccine, according to the prespecified case definition.

In addition to the patterns of HPV infection just described, the timing of disease occurrence in the vaccine as compared to the placebo group also suggests possible undetected prevalent disease in the vaccine cases. In contrast to the vaccine group, in which some cases occurred relatively early during post-vaccination follow-up, all of the cases in the placebo group occurred after Month 12, strongly suggesting that the placebo cases were related to new HPV infections that occurred following completion of the vaccination regimen. This finding is also supported by the observation that the median time to the development of AIN in the five per protocol population vaccine recipients was 1.00 years, compared to 1.82 years in the 24 placebo group subjects.

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Table 2.5: 2

Analysis of Efficacy Against HPV 6/11/16/18-Related Intra-Anal Persistent Infection by HPV Type (Per-Protocol Efficacy 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		
HPV 6/11/16/18-Related Intra-Anal Persistent Infection	193	2	385.6	0.5	208	39	381.2	10.2	94.9	(80.4, 99.4)
By HPV Type										
HPV 6-Related Intra-Anal Persistent Infection	140	1	277.9	0.4	144	13	286.8	4.5	92.1	(47.2, 99.8)
HPV 11-Related Intra-Anal Persistent Infection	140	0	279.4	0.0	144	5	295.6	1.7	100	(-15.5, 100)
HPV 16-Related Intra-Anal Persistent Infection	166	1	331.5	0.3	170	16	329.9	4.9	93.8	(60.0, 99.9)
HPV 18-Related Intra-Anal Persistent Infection	172	0	346.3	0.0	193	10	376.2	2.7	100	(51.5, 100)

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; HPV = Human papillomavirus; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

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Supportive Prophylactic Efficacy Analyses

Analyses of the MSM HNRT [Appendix 2.5: 9] and FAS [Appendix 2.5: 10] populations showed reductions in AIN due to HPV 6/11/16/18, supporting the efficacy findings in the PPE population. Efficacy in the HNRT population was comparable to that observed in the PPE population, despite the inclusion of cases that occurred after the first vaccination. As expected, given the inclusion of subjects irrespective of baseline HPV status, vaccine efficacy was lower in the FAS population than in the PPE population. It is notable, however, that even in this 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%. The associated time to event curve [Appendix 2.5: 11] in this population shows the separation of the vaccine and placebo groups as the rate of incident disease related to prevalent infections in the vaccine group declines, providing further support for the effect of HPV vaccination in this non HPV-naïve population.

Strength of Evidence for 6/11/16/18-related AIN 2/3 endpoint in the absence of a prespecified study hypothesis.

When considered individually, all grades of AIN demonstrated similar magnitudes of reduction, so the effect of the vaccine is not restricted to certain grades of AIN. Furthermore, there were sufficient cases of AIN 2/3 observed to demonstrate that the reduction in high-grade disease was in itself statistically significant.

While there was no prespecified hypothesis for the AIN 2/3 endpoint, the success of the primary endpoint and the consistency of the vaccine effect across all grades of AIN supports the clinical significance of reduction in high-grade disease related to HPV 6/11/16/18. Since assessment of the components of the primary substudy endpoint was done conditional upon success for the composite, it should not inflate the type I statistical error of chance findings from this substudy, and therefore no statistical multiplicity correction is warranted when assessing the components. Furthermore, these findings build upon results of previous studies demonstrating highly significant reductions in similar anogenital lesions; thus the specification of a 0% lower bound for vaccine efficacy for the primary AIN endpoint (and by extension, the AIN 2/3 endpoint) is considered appropriate.

Population Benefit – Prevention of Any Type AIN and Anal Cancer

[Appendix 2.5: 12] and [Appendix 2.5: 13] show the results of the analysis of efficacy against AIN and anal cancer due to any HPV type in the MSM GHN and FAS populations. [Appendix 2.5: 14] and [Appendix 2.5: 15] show the cumulative incidence over time for this endpoint in the same populations. The estimate of qHPV vaccine efficacy against AIN and anal cancer due to any HPV type in the MSM GHN population was 54.9% (95% CI: 8.4 to 79.1), supporting the potential of HPV vaccination to lower the overall burden of HPV-related anal disease in the population. With cases being counted after the first dose of vaccine, efficacy for this population is anticipated to be lower than for the per protocol population. Not unexpectedly, efficacy against this

endpoint in the FAS analysis did not reach statistical significance, given the contribution of disease from prevalent vaccine type and non-vaccine type infections in this population.

2.5.4.1.3.2 Updated Results: External Genital Disease and Infection

Prophylactic Efficacy With Respect to HPV 6/11/16/18-Related Infection and Disease

[Appendix 2.5: 16] 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) [Sec. 2.7.3.2.5 - exgenlesions]. The supportive analyses in the HNRT [Appendix 2.5: 17] and FAS [Appendix 2.5: 18] 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.

Population Benefit-Overall Rates of EGLs and Related Procedures

Final results of analyses of the impact of qHPV vaccine on the incidence of external genital procedures and therapy confirm the previous analyses, showing positive reductions in the incidence of external genital biopsies, external genital therapies overall, and surgical external genital therapies in the qHPV vaccine group compared to the placebo group.

2.5.4.1.3.2.1 Duration of Efficacy

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 vaccine group subjects remained low, providing evidence of sustained vaccine efficacy in young adult men over the 36 months of the study.

2.5.4.1.3.2.2 Efficacy Conclusions – Protocol 020

Based on the results of qHPV vaccine efficacy analyses of the primary study endpoint and the MSM substudy endpoint, the following conclusions can be made:

MSM Substudy Conclusions

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is highly efficacious in preventing the development of HPV 6/11/16/18-related high-grade AIN (AIN 2 or worse).
- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is highly efficacious in preventing development of HPV 6/11/16/18-related AIN of any grade.

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- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is highly efficacious in preventing development of 6/11/16/18 persistent anal infection.

Overall Study Conclusions

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is highly efficacious in preventing development of HPV 6/11/16/18-related external genital lesions.
- 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 persistent infection.
- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is efficacious in preventing detection of HPV 6/11/16/18 DNA at one or more visits.

2.5.4.2 Immunogenicity

2.5.4.2.1 Overview – Evaluation of the Immunogenicity of the qHPV Vaccine

Preclinical studies of L1 VLP vaccines showed antibody-associated protection against species-specific papillomavirus infection. These results supported the hypothesis that vaccine-induced systemic anti-HPV antibody responses should result in protection against HPV infection or disease. Based on this hypothesis, the qHPV clinical program has utilized vaccine type-specific anti-HPV neutralizing antibody serum levels as the primary means to measure the immunogenicity of the qHPV vaccine [Ref. 5.4: 327, 1929, 2010].

2.5.4.2.2 Design of the Immunogenicity Studies of qHPV Vaccine

2.5.4.2.2.1 Study Periods

As previously described, all studies in the clinical program for the qHPV vaccine were divided into a vaccination (Day 1 to Month 7-peak immune responses anticipated at approximately Month 7) and a persistence (beyond Month 7) phase for the purposes of immunogenicity evaluations.

2.5.4.2.2.2 Clinical Immunogenicity Endpoints and Primary Immunogenicity Analysis Population

The immunogenicity of the qHPV vaccine was measured using anti-HPV 6, 11, 16, and 18 competitive Luminex-based immunoassays (cLIAs). A detailed description of the HPV cLIA assay can be found in the CSR for P020 [Ref. 5.3.5.1: P020]. The immunogenicity endpoints for the clinical program have focused on anti-HPV levels (GMTs) and the proportion of subjects who became seropositive to vaccine HPV types at 4 weeks Postdose 3 [Ref. 5.4: 1134].

Immunogenicity analyses were conducted in the per-protocol immunogenicity (PPI) population, which was selected to measure the full benefit of 3 doses of qHPV vaccine in

healthy subjects with no evidence of prior HPV infection. This population is described in [Sec. 2.7.3.2.2.1-Immunogenicity] and [Ref. 5.3.5.1: P020].

2.5.4.2.3 Summary of Protocol 020 Results

Immunogenicity results at Months 7 and 24 were presented in the detail in the previous submission. 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 [Appendix 2.5: 19]. 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 [Appendix 2.5: 20]. No HPV 18-related AIN or EGL were observed among vaccinees in the PPE population of Protocol 020, supporting durability of efficacy despite waning antibody levels. Overall, the final immunogenicity findings from Protocol 020 are similar to the experience in the female qHPV vaccine efficacy studies.

2.5.4.2.4 Summary of Immunobridging

As described in the previous submission, immunobridging between adult and adolescent males was achieved by demonstrating non-inferiority of anti-HPV responses (Month 7 GMTs and seroconversion rates) in 9- to 15-year-old male subjects from previously conducted Protocols 016 and 018 with responses from 16- to 26 year old men in Protocol 020 [Table 2.7.3-immunogenicity: 4] and [Table 2.7.3-immunogenicity: 5] [Ref. 5.4: 2272]. Thus, it can be concluded that the qHPV vaccine is efficacious in preventing HPV 6-, 11-, 16-, and 18-related AIN and anal cancer in boys and men 9 to 26 years of age.

The parallel testing procedure was explained in detail in the previous submission; see [Sec. 2.7.3.2.4] in the original application for the male indication].

2.5.4.2.5 Conclusions Regarding the Immunogenicity of the qHPV Vaccine

Overall, the following conclusions can be made based on the immunogenicity findings of the clinical development program for qHPV vaccine presented in the supplemental Application:

- 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 36 months of study follow-up.
- Prophylactic administration of qHPV vaccine is highly immunogenic in all populations tested.
- Vaccine-induced anti-HPV levels in 9-15 year old boys are non-inferior to anti-HPV levels in 16-26 year old men.

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2.5.5 Overview of Safety

Published clinical literature about the qHPV vaccine was reviewed for consistency with the safety findings reported in this marketing application. These data support the safety of the qHPV vaccine in the target population [Ref. 5.4: 3242, 3243].

2.5.5.1 Summary of Safety Findings

This supplemental application contains updated safety data in a population of men 16 to 26 years of age from Protocol 020. Overall, the qHPV vaccine when administered to men 16 to 26 years of age was well-tolerated, and the clinical adverse experience (AE) profile exhibited was consistent with the previously described AE profile for the qHPV vaccine; no new safety issues were identified.

2.5.5.1.1 Protocol 020 Study Population

A total of 2025 subjects received at least 1 dose of qHPV vaccine and 2030 subjects received at least 1 dose of placebo in Protocol 020.

2.5.5.1.2 Analysis of Adverse Experiences in Protocol 020

Final safety data for subjects enrolled in Protocol 020 are summarized in detail in [Sec. 12] of the current CSR [Ref. 5.3.5.1: P020]. In Protocol 020, the following observations can be made from clinical adverse experiences reported by subjects at any time during the study. The proportions of subjects who reported at least one clinical adverse experience and who reported at least one injection-site adverse experience were 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, and the proportion of subjects who discontinued due to an AE was slightly higher in the placebo group than in the qHPV vaccine group.

A total of 19 subjects (8 in the qHPV vaccine group and 11 in the placebo group) reported serious adverse experiences over the entire duration of the study; none were vaccine-related. A total of 13 subjects died during the study (3 in the qHPV vaccine group and 10 in the placebo group); none of the deaths were considered to be vaccine related. Overall, the proportions of subjects who reported new medical conditions, including conditions potentially indicative of an autoimmune phenomenon, were comparable between vaccination groups.

2.5.5.2 Integrated Safety Data

Since this supplemental application supports the use of qHPV vaccine in boys and men 9 through 26 years of age, the new safety data in men have been integrated with safety data in 9- to 15-year-old boys from two studies, Protocol 016 (a safety and immunogenicity study in preadolescents and adolescents) and Protocol 018 (an ongoing safety, immunogenicity, and effectiveness study in preadolescents and adolescents) in order to present the adverse experience profile of the qHPV vaccine in all male subjects enrolled in the clinical development program. Safety data from Protocols 016 and 018 were

provided in the original application and previous supplemental applications. The data cutoff date for this supplemental application was 20-Sep-2004 for P016, 01-Jun-2007 for P018, 23-Jun-2009 for Protocol 019 (an ongoing efficacy, immunogenicity, and safety study in women 24 to 45 years of age), and 31-Jul-2009 for P020. Data are also included from P007 (an efficacy, immunogenicity, and safety study in 16- to 26-year-old female subjects), P013, P015 (Phase III pivotal efficacy studies in 16- to 26-year-old female subjects), all of which reached End-of-Study at the time of the current application.

In order to provide complete safety data in the categories of (1) serious adverse experiences resulting in death; (2) other serious adverse experiences, and (3) other significant adverse experiences, subjects from all studies of qHPV vaccine, including studies in female subjects 9 to 45 years of age and male subjects 9 to 26 years of age, are included in this submission. Data on common (non-serious) adverse experiences and new medical history in girls and women 9 to 45 years of age were provided in previous applications.

The approach to safety evaluation in the qHPV vaccine program was previously explained in detail, and is not covered here. All subjects in Protocols 016, 018, and 020 were followed using VRC-aided surveillance. Therefore, all tables presenting integrated common adverse experience data for these studies are provided for the detailed safety population. Listing tables displaying: (1) serious adverse experiences resulting in death; (2) other serious adverse experiences, and (3) other significant adverse experiences, are provided for the overall safety population, as these tables include subjects in Protocol 015 who were followed using the general surveillance method.

2.5.5.2.1 Study Population and Extent of Exposure

Overall, 3098 male subjects received at least 1 dose of qHPV vaccine in Protocols 016, 018 and 020 [Table 2.7.4: 2]. A total of 2305 male subjects received at least 1 dose of placebo. Information regarding subjects who were excluded from Protocol 020 safety summaries is presented in [Sec. 2.7.4.2.1].

2.5.5.2.2 Analysis of Adverse Experiences in Male Subjects

[Appendix 2.5: 21] presents an overall summary of adverse experiences (Day 1 through the entire study period) in male subjects in the detailed safety population of Protocols 016, 018, and 020. A larger proportion of subjects who received qHPV vaccine reported an adverse experience compared with subjects who received placebo, related to the higher proportion of qHPV vaccine compared to placebo recipients subjects who reported an injection-site adverse experience.

Serious adverse experiences were rare during the entire study period. The proportions of subjects who experienced a serious adverse experience were comparable between the vaccination groups, and there were no serious adverse experiences determined by the clinical investigator to be vaccine-related. Discontinuations due to an adverse experience were rare, and the proportions of subjects who discontinued the study due to an adverse experience were comparable between the vaccination groups.

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Consistent with prior applications, the proportion of subjects who reported an injection-site adverse experience was higher among vaccine compared with placebo recipients. The most common injection-site adverse experiences reported were pain, swelling, and erythema, most of which were judged by the study subjects to be mild or moderate in intensity. Although a higher proportion of girls and women reported injection-site adverse experiences compared with men and boys, the types of injection-site adverse experiences reported in both genders were comparable.

Consistent with prior applications, the proportions of subjects who reported a systemic adverse experience were comparable between the 2 vaccination group, the majority of which were judged to be mild or moderate in intensity. The proportions of subjects who reported a severe intensity systemic adverse experience were comparable between the vaccination groups. The most common systemic adverse experiences were headache and pyrexia. A higher proportion of girls and women reported one or more systemic clinical adverse experiences compared with men and boys, but the types of systemic clinical adverse experiences reported most commonly in both genders were comparable.

The proportions of subjects who reported an elevated temperature or who reported a maximum temperature ≥39.9°C were small and were comparable between the vaccination groups. Consistent with prior applications, data suggest that qHPV vaccine is associated with a modest increase in the incidence of transient low-grade fevers, compared with placebo.

Overall, the adverse experience profile in boys and men was generally comparable to the adverse experience profile in girls and women and is consistent with the adverse experience profile described in previous submissions.

2.5.5.2.3 Analysis of Adverse Experiences in the Safety Population of Males and Females

Cumulatively, a total of 39 subjects died at any time during the qHPV vaccine studies in males and females, including 21 qHPV vaccine (0.11%) and 18 placebo (0.13%) recipients. Of these 39 deaths, 13 occurred in Protocol 020 (3 subjects who received qHPV vaccine and 10 subjects who received placebo). None of the deaths in either vaccination group were determined by the investigator to be vaccine/placebo- or procedure-related.

A total of 129 subjects (0.8%) who received qHPV vaccine and 130 subjects (1.0%) who received placebo reported a serious systemic clinical adverse experience at any time during the studies. Serious systemic clinical or injection-site adverse experiences determined by the study investigator to be vaccine-related were reported in 6 subjects; all were in female subjects and have been described previously. The vaccination groups were also comparable with respect to the types of serious adverse experiences reported. [Appendix 2.7.4: 33] lists subjects in the safety population with serious clinical adverse experiences.

Overall, 70 subjects discontinued studies due to an adverse experience, including 36 (0.23%) subjects who received qHPV vaccine and 34 (0.25%) subjects who received

placebo. Of these 70 subjects, 19 subjects (5 subjects in the qHPV vaccine group and 14 subjects in the placebo group) were from Protocol 020. The proportions of subjects who reported new medical conditions, including conditions potentially indicative of an autoimmune phenomenon, were comparable between vaccination groups.

Overall, the adverse experience profile in boys and men appeared to be comparable to the adverse experience profile in girls and women, and consistent with the adverse experience profile described in previous submissions.

2.5.5.3 Limitations of the Safety Database for qHPV Vaccine

The qHPV vaccine has not been studied in children below 9 years of age. While the development program for qHPV vaccine enrolled approximately 25,000 women and children and 4000 men, the safety database is insufficiently sized to detect safety signals with respect to medical conditions occurring at a background rate of less than 1:10,000.

2.5.5.4 Postmarketing Safety Data

The postmarketing safety data are briefly summarized here. The detailed report is in [Sec. 2.7.4.6]. From the International Birthdate through 31-May-2009, over 50 million doses of the qHPV vaccine were distributed worldwide; there were no countries where marketing applications have been rejected, withdrawn, suspended, or revoked for safety reasons. The 6th 6 month Periodic Safety Update Report (PSUR) covering the time period of 01-Dec-2008 thru 31-May-2009 [Ref. 5.3.6: 2088] contains a list of 104 countries where the qHPV vaccine has received marketing approval up to 31-May-2009 [Ref. 5.4: 3226].

Overall, the post licensure experience with qHPV collected through passive reporting of spontaneous adverse experiences to Merck & Co., Inc. has confirmed the favorable safety profile of the vaccine, with a low proportion of reported serious adverse experiences; the benefit-risk ratio for the product remains favorable. Because the product has not been widely used in male patients the data from the post marketing environment is insufficient to draw conclusions regarding the safety profile of the vaccine relative to males. To date, however, the types of adverse experiences spontaneously reported in males do not suggest a unique safety concern for that gender.

In August, 2009, the U.S. Food and Drug Administration (FDA) and Centers for Disease Control (CDC) issued a statement on the safety of the qHPV vaccine, which stated that based on the review of available information, the qHPV vaccine continues to be safe and effective, and its benefits continue to outweigh its risks [Ref. 5.4: 3242]. A summary of data from the U.S. VAERS (Vaccine Adverse Event Reporting System) was also published in the same month, covering the 2.5 years following initial U.S. licensure of the qHPV vaccine in females [Ref. 5.4: 3243]. The conclusion from this review was that the postlicensure safety profile of the qHPV vaccine was broadly consistent with safety data from prelicensure trials.

Merck & Co., Inc will continue to the monitor the safety of the qHPV vaccine in the post-licensure period.

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2.5.5.5 Overdose

Information regarding overdoses during Protocol 020 was discussed in the original CSR, and subjects who received more than 3 doses of qHPV vaccine or placebo or ≥0.75 mL of vaccine or placebo in any one dose in other studies of qHPV vaccine were discussed in previous applications. In all studies, qHPV vaccine and placebo were generally well tolerated despite the increased volume and/or extra doses received.

2.5.5.6 Drug Abuse/Withdrawal and Rebound/Impairment of Mental Ability

The qHPV vaccine does not have properties associated with medications with abuse potential, and no occurrence of abuse, withdrawal or rebound has been reported in any of the clinical trials conducted to date. The qHPV vaccine does not have biologic properties or physiologic effects that could interfere with the ability to drive or operate machinery or impair mental abilities. Subjects who were involved in road traffic accidents, who attempted or completed suicide, or had other mental illness in qHPV vaccine studies have been discussed in previous Applications. The qHPV vaccine does not appear to have any adverse effects on the ability to drive or operate machinery, and does not appear to impair mental abilities.

2.5.5.7 Conclusions Regarding Safety of the qHPV Vaccine

The updated safety data presented in this supplemental application support the previous conclusions that qHPV vaccine is generally well tolerated and displays a favorable safety profile. Specifically, the following conclusions can be drawn:

With respect to Protocol 020:

- Prophylactic administration of a 3-dose regimen of qHPV vaccine is generally well tolerated in 16- to 26-year-old men.

With respect to the overall age range in boys and men:

- Administration of qHPV vaccine is generally well tolerated in 9- to 26-year-old boys and men.
- Boys and men 9 to 26 years of age who begin the 3-dose regimen of qHPV vaccine rarely discontinue vaccination due to a clinical adverse experience.
- Use of qHPV vaccine does not have any adverse health impact through approximately 36 months of follow-up in adolescent boys and young adult men.
- Use of qHPV vaccine does not appear to impact the ability to drive or operate machinery.

Overall, the safety profile observed in boys and men 9 to 26 years of age in Protocols 016, 018, and 020 is favorable and consistent with the safety profile observed in clinical studies in girls and women 9 to 26 years of age in Protocols 007, 013, 015, 016, 018, and 019. In addition, the safety profile is consistent with the current approved product circular.

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2.5.6 Benefits and Risks Conclusions

In the prior applications for the qHPV vaccine, the vaccine has been shown to be highly efficacious, immunogenic, and generally well-tolerated in girls and women 9 to 45 years of age. In addition, the vaccine has been shown to be immunogenic and generally well-tolerated in boys and men 9 to 26 years of age. Efficacy data in adult men was also successfully bridged to adolescent boys 9 to 15 years of age. The data presented in the current application support and extend the prior findings, and show the additional potential of the qHPV vaccine to address the important unmet medical need for prevention of HPV-related anal cancer in men and women. Therefore, the benefit to risk ratio of qHPV vaccination continues to be favorable.

2.5.6.1 Unmet Medical Need for HPV Vaccination Against Anal Cancer

HPV types contained in the vaccine are responsible for a substantial proportion of anal infection and disease. As described above, the similarity of anal and cervical cancers would suggest that prevention of anal cancer by screening and treatment of premalignant lesions could lead to lower anal cancer rates. However, there is currently no established screening for anal cancer, and results from this study suggest that in average-risk individuals, cytologic screening in the anal canal may not be as successful as in the cervix. Primary prevention of anal HPV infection is therefore the optimal approach, and the MSM substudy was designed to show the potential of qHPV vaccination to address this important unmet medical need.

2.5.6.2 New Information Presented in the Current Application; Efficacy Benefits of qHPV Vaccination

Administration of the qHPV vaccine to 16 to 26 year old MSM was highly efficacious in preventing persistent anal HPV 6/11/16/18 infection and HPV 6/11/16/18-related AIN. An analysis of efficacy against HPV 6/11/16/18-related high-grade AIN (AIN 2 or worse) although not prespecified, showed a statistically significant reduction of disease in the vaccine group. Similarly, the case split of vaccine to placebo cases of HPV 16/18-related high-grade AIN was strongly favorable and consistent with previous observations of qHPV vaccine efficacy. In the context of the greater than 90% observed type-specific efficacy against persistent anal infection related to HPV 16 and 18, the data provide compelling support for efficacy of the qHPV vaccine against HPV 16/18-related high-grade anal disease. Taken together, these data support the potential benefit of qHPV vaccination in the prevention of anal cancer related to high-risk vaccine HPV types.

The updated overall study analyses of EGL and persistent infection efficacy confirm the previous observations of the high efficacy of the qHPV vaccine against these endpoints, and demonstrate the durability of protection against EGLs and AIN through the entire follow-up of study subjects.

Immunogenicity data from Protocol 020 showed that the qHPV vaccine is highly immunogenic in men 16-26 years of age [Sec. 2.7.3 - Immunogenicity]. As qHPV vaccine is a prophylactic vaccine, targeting adolescents prior to sexual debut and HPV exposure is critical.

The favorable clinical adverse event profile observed upon final analysis of Protocol 020 is consistent with what has been previously observed for the qHPV vaccine [Sec. 2.7.4].

In summary, the qHPV vaccine is highly efficacious, immunogenic, and generally well-tolerated when administered to males 9 to 26 years of age.

2.5.6.3 Health Economic Modeling

At the population level, the value of qHPV vaccine in men and women is presented using results from health economic model analyses [Ref. 5.3.5.4: 2631]. The analysis was conducted with the purpose of projecting the health and economic impact of extending the current qHPV vaccine recommendation for girls and women in the US to boys and men [Ref. 5.3.5.4: 2631]. In brief, a previously developed mathematical model was utilized to evaluate the impact of a qHPV vaccination program in female and male persons 12 to 26 years of age in the US. This analysis extended the previous model by incorporating the most current vaccine efficacy results from the qHPV vaccine clinical trials (Protocols 007, 012, 020). In addition to a direct benefit to men, the model also evaluated if male qHPV vaccination could provide benefit to women through potentially impacting disease transmission. Besides cervical, vulvar, and vaginal HPV disease, the analysis included the impact of vaccination on genital warts and anal cancer in men and women. The analysis found that broadening the current qHPV vaccine recommendation for girls and women 12 to 26 years of age to boys and men 12 to 26 years of age would decrease the number of genital wart, CIN 2/3, cervical cancer, and anal cancer cases in the US by approximately 1,934,000, 169,600, and 5,100, and 1,500 respectively, 50 years following the introduction of the vaccine. The incremental cost-effectiveness ratio for the proposed male vaccination recommendation when added to the current female vaccination program would be approximately $54,000 per quality adjusted life year gained. This cost-effectiveness ratio falls within the range of cost-effectiveness ratios estimated for some other commonly accepted healthcare technologies typically regarded as cost-effective in the US. For example, the cost-effectiveness ratio for dialysis in end-stage renal disease in the US has been reported to range from $50,000 to $120,000 per quality adjusted life year (QALY) gained. Among vaccination programs, the estimated cost-effectiveness ratio was $88,000 per QALY gained for the recently recommended catch-up and routine vaccination of all US children 11-17 years of age with the meningococcal vaccine [Ref. 5.4: 2749].

2.5.6.4 Conclusion

As demonstrated in Protocol 020 and in published studies of HPV, there is a high burden of HPV–related vaccine-preventable genital infection and disease in men and a significant burden of anal disease in both men and women. Protocol 020 has demonstrated that, in addition to preventing external genital lesions, the qHPV vaccine is highly efficacious in preventing anal infection and disease. High-grade AIN is a precursor for anal cancer, but it is not routinely screened for, and although public health authorities recognize anal cancer as an important entity for which screening should be considered, Protocol 020 provides some evidence to suggest that anal cytologic screening may not be as effective as cytologic screening for cervical disease. **Primary prevention**

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through vaccination provides the potential to have a significant impact on this unmet medical need.

2.5.6.5 Limitations and Risks

The limitations and risks identified for male vaccination program are consistent with those identified and discussed in previous applications for the qHPV vaccine; no limitations and risks specific to males has been identified. Two key limitations of the data to date include: (1) The duration of protection induced by the qHPV vaccine remains to be determined; to provide additional data a sentinel cohort of adolescent boys and girls is being followed to assess vaccine effectiveness up to 10 years following study entry [Ref. 5.3.5.1: P018V1]. In addition, for evaluation of long term vaccine efficacy in the male population, Protocol 020 subjects will be enrolled in an extension for 10 years of follow-up from entry into the original study. (2) Although large, the qHPV vaccine safety database is insufficient to detect safety signals with respect to rare conditions (i.e., medical conditions occurring at a background rate of <1:10,000); to date the post-marketing safety experience with the qHPV vaccine is consistent with the safety profile observed in clinical trials. Merck & Co., Inc will continue to the monitor the safety of qHPV in the post-licensure period.

2.5.7 Overall Conclusions

The data presented in the current application strongly support and extend the main conclusions of the prior application, and show that the qHPV vaccine is efficacious across the entire spectrum of anogenital HPV infection and related disease in men and women.

The new data on the efficacy of the qHPV vaccine against AIN provide strong evidence of its potential impact on prevention of anal cancer, a disease that affects both men and women, and for which there is no established screening. The new data also further extend the evidence of the durability of protection provided by the qHPV vaccine, and confirm its favorable safety profile. The overall benefit to risk ratio of the qHPV vaccine is favorable, and on the basis of the data presented in the current supplemental application, these proposed new indications are justified:

- **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.**

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Appendix 2.5: 1

Rates of HPV Positivity in Anal Cancers (Includes only studies using PCR methodology with MY09/11 or GP5+/6+ primers *and* >20 cases)

Authors/Year	# of Cases	Overall HPV+	HPV16+	HPV18+	Non-16/18 HR HPV+	LR HPV+	Other
Wong 2009[§]	38	89.5%	68.4%	2.6%	21.1%	ND[†]	ND
Daling 2004[#]	179 Squamous	92.2%	76.0%	8.9%	ND	ND	ND
	41 Basaloid	97.6%	95.1%	0.0%	ND	ND	
Carter 2001	64	93.8%	79.7%	9.4%	6.2% (31+33+35+39)	Not separately tested for	10.8% (6+45+52+54+58+66+72+73+ unknown)
Frisch 1999[‡]	331 (206 if exclude perianal)	83.7% (92.2% if exclude perianal)	72.8%	5.7%	6.5%	4.5%	ND
Frisch 1997[¶]	388	87.6%	72.9%	5.7%	6.7% (31+33)	1.3% (6 only)	ND
Noffsinger 1995*	50	46.0%	38.0%	4.0%	ND	6.0% (6 only)	ND

[†]=Not Done
[§]Tested for 16/18/31/33/35/39/45/51/52/56/58/59/68
[#]Tested for 16/18 only
[‡]Tested for 16/18/31/33/35/39/45/51/52/56/58/59/66/68; LR types 6/11/40/42/43/44; type-specific for 16/18/31/33; perianal cases excluded
[¶]Tested for 16/18/31/33/35/39/45/51/52/56/58/59/66/68; LR types 6/11/40/42/43/44; type-specific for 6/11/16/18/31/33
*Tested for 6/16/18 only
PCR = Polymerase chain reaction, HR = high-risk, LR=low-risk

[Ref. 5.4: 385, 2499, 2696, 3175, 3176, 3178]

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Appendix 2.5: 2

Anal Cancer Risk in Patients with High Grade AIN

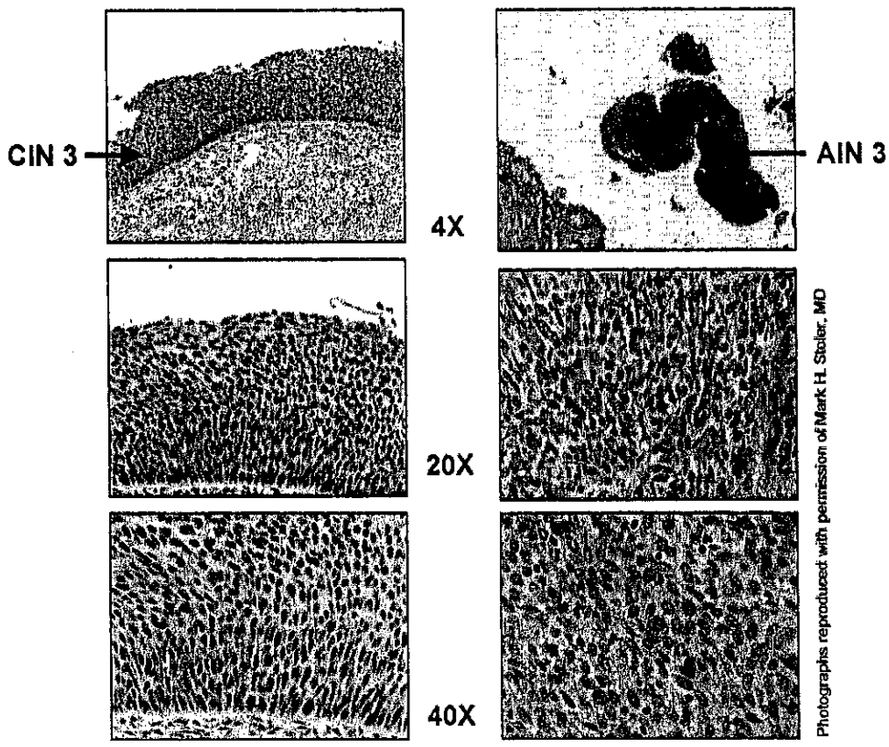
Study	Baseline diagnosis (Number of subjects)	Number of cases progressed to invasive anal cancer	Annualized incidence rate of invasive anal cancer
Watson et al, 2006	AIN 2 (10)	2	0.040
	AIN 3 (45)	6	0.027
	AIN 2/3 (55)	8	0.029
Sobhani et al, 2004	Condyloma (with or without AIN diagnosis) HIV-negative (141)	1	0.004
	HIV-positive (58)	6	0.054
Scholefield et al, 1994	AIN 3 (27)	8	0.178
Brown et al, 1994	High-grade AIN (46)	0	0
Scholefield et al, 2005	AIN 3 Immunocompetent (29)	0	0
	Immunosuppressed (6)	3	0.095
U.S. annual incidence rate, Johnson et al, 2004	General population	---	0.0000197

[Ref. 5.4: 2509, 2547, 2578, 2580, 2581, 3185]

Appendix 2.5: 3

CIN 3 and AIN 3 Histology

CIN 3 and AIN 3 are Histologically Identical



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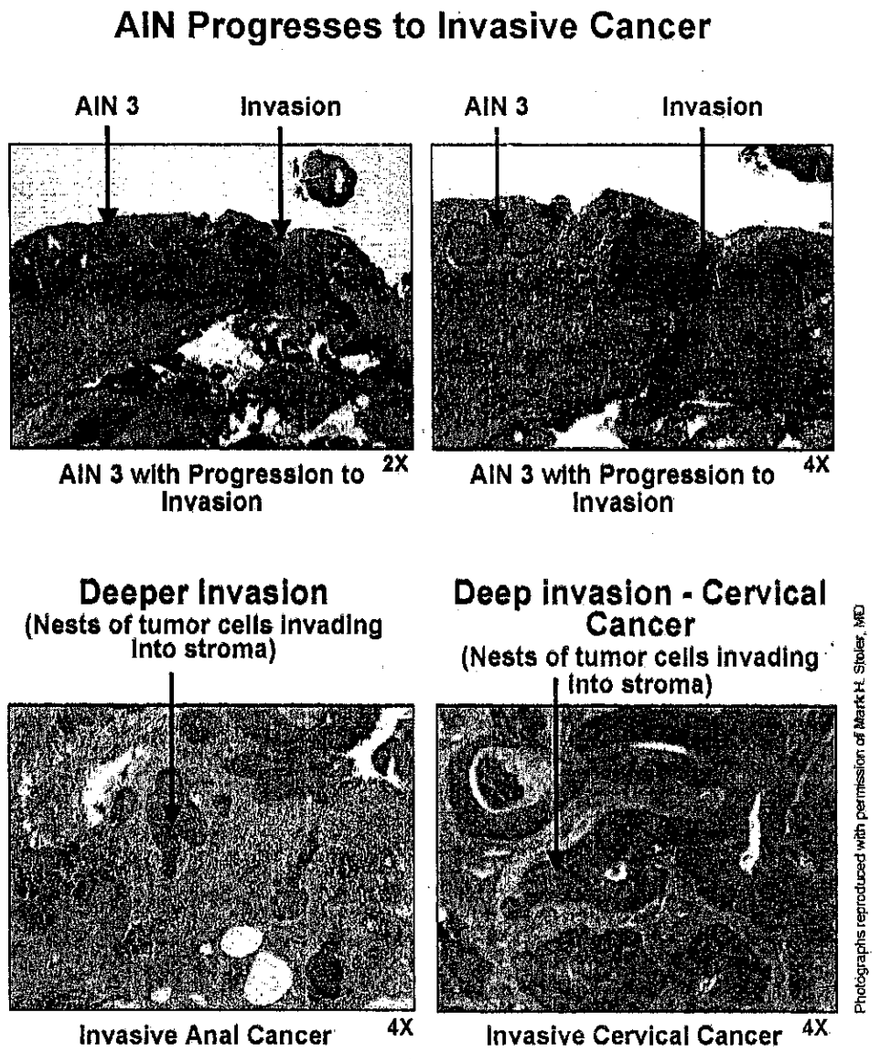
Appendix 2.5: 4

Progression of AIN 3 to Invasive Anal Cancer



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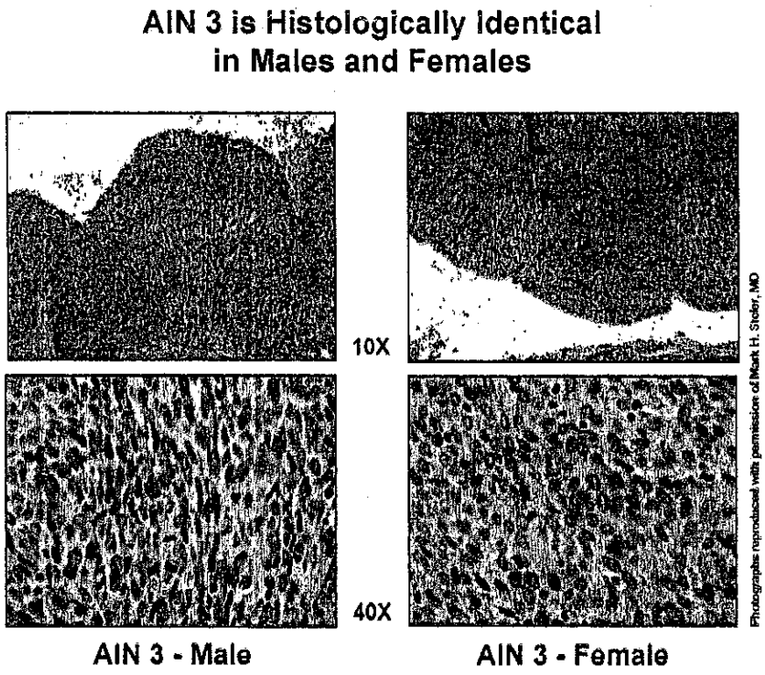
Appendix 2.5: 5

AIN 3 Histology in Males and Females



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Appendix 2.5: 6

Definitions of Populations Used in Prophylactic Efficacy Analyses in Protocol 020

Parameter	PPE	HNRT	FAS
Definition	Per-protocol efficacy (PPE): Included subjects who: (1) were sero- and PCR-negative at Day 1 and PCR-negative through Month 7 to the appropriate vaccine HPV types; (2) received all 3 vaccinations within a one year period; and (3) generally did not deviate from the protocol.	HPV-naïve to the relevant type (HNRT): Included subjects who: (1) were sero- and PCR-negative at Day 1 to the appropriate vaccine HPV types; and (2) received at least 1 vaccination.	Full analysis set (FAS): Included all subjects who received at least 1 vaccination.
Case Counting	Cases were counted starting after Month 7.	Cases were counted starting after Day 1.	Cases were counted starting after Day 1.
Relevant Endpoints	HPV 6-, 11-, 16-, and 18-Related External Genital Lesions HPV 6-, 11-, 16-, 18-related AIN or anal cancer HPV 6-, 11-, 16-, and 18-Related Persistent Infection HPV 6-, 11-, 16-, and 18-Related DNA Detection	HPV 6-, 11-, 16-, and 18-Related External Genital Lesions HPV 6-, 11-, 16-, 18-related AIN or anal cancer HPV 6-, 11-, 16-, and 18-Related Persistent Infection HPV 6-, 11-, 16-, and 18-Related DNA Detection	HPV 6-, 11-, 16-, and 18-Related External Genital Lesions HPV 6-, 11-, 16-, 18-related AIN or anal cancer HPV 6-, 11-, 16-, and 18-Related Persistent Infection HPV 6-, 11-, 16-, and 18-Related DNA Detection
Role in the Analysis Plan	Primary efficacy analysis population.	Supportive to primary efficacy analysis.	Supportive to primary efficacy analysis.
Value of Population in Evaluating Vaccine Efficacy	Measurement of the full benefit of qHPV vaccine in persons who were naïve to the relevant HPV type through the completion of 3-dose vaccination regimen.	Measurement of qHPV vaccine efficacy immediately after the first dose (including efficacy before anticipated full vaccine benefit) among subjects who are naïve to the relevant HPV type.	Measurement of vaccine impact on vaccine type disease in the general population of 16- to 26-year-old men, starting immediately after the first dose.
AIN = anal intraepithelial neoplasia; DNA = Deoxyribonucleic acid; HPV = Human papillomavirus; PCR = Polymerase chain reaction; qHPV vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.			

[Ref. 5.3.5.1: P020]

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Appendix 2.5: 7

Definitions of Populations Used in Population Benefit Analyses in Protocol 020

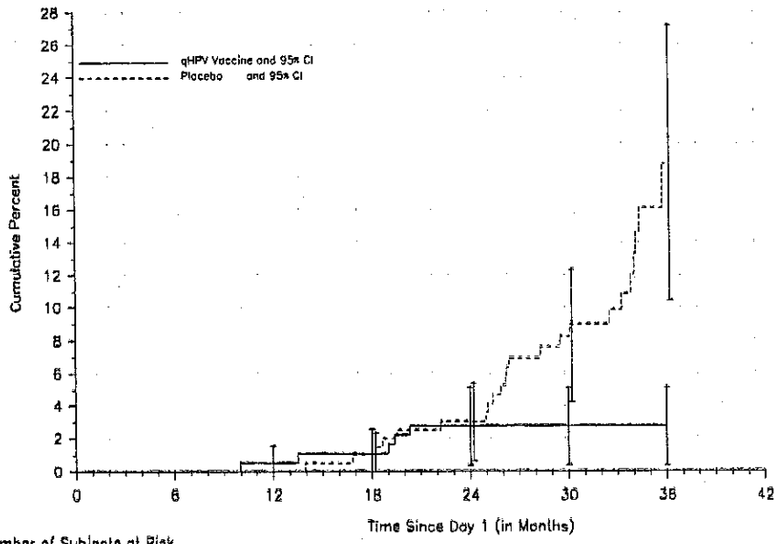
Parameter	GHN	FAS
Definition	Generally HPV-naïve (GHN): Included all subjects who: (1) were seronegative and PCR negative to all 4 vaccine HPV types at Day 1; (2) were PCR negative to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, *and* 59 at Day 1; (3) for MSM subjects, had a Pap test result at enrollment that was negative for SIL; and (4) received at least 1 vaccination.	Full analysis set (FAS): Included all subjects who received at least 1 vaccination.
Case Counting	Cases were counted starting after Day 1.	Cases were counted starting after Day 1.
Relevant Endpoints	External Genital Lesions caused by vaccine or non vaccine HPV types External Genital Lesion Procedures and Therapies AIN or anal cancer caused by vaccine and non-vaccine HPV types	External Genital Lesions (caused by vaccine or non vaccine HPV types) External Genital Lesion Procedures and Therapies AIN or anal cancer caused by vaccine and non-vaccine HPV types
Role in the Analysis Plan	Key analysis population for the evaluation of the population benefit of the qHPV vaccine.	For the evaluation of the population benefit of the qHPV vaccine, supportive population.
Value of Population in Evaluating Vaccine Efficacy	GHN population approximates a population of adolescent and young adult men who were either sexually-naïve or sexually-experienced and had not yet been exposed to *any* HPV type. This population provides insight on the potential impact of vaccination on males when vaccinated in young adolescence, prior to HPV exposure.	FAS population provides information on overall vaccine impact when used in a general population of sexually active 16- to 26- year old men.

DNA = Deoxyribonucleic acid: HPV = Human papillomavirus; MSM = Men having sex with men; Pap = Papanicolaou; PCR = Polymerase chain reaction; qHPV vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine; SIL = Squamous intraepithelial lesion.

[Ref. 5.3.5.1: P020]

Appendix 2.5: 8

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



Number of Subjects at Risk

qHPV Vaccine	194	194	189	178	165	128	34
Placebo	208	208	206	199	178	130	29

[Ref. 5.3.5.1: P020]

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Appendix 2.5: 9

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)

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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) (Cont.)

Endpoint	qHPV Vaccine (N=299) n	qHPV Vaccine (N=299) Number of Cases	qHPV Vaccine (N=299) Person-Years at Risk	qHPV Vaccine (N=299) Incidence Rate per 100 Person-Years at Risk	Placebo (N=299) n	Placebo (N=299) Number of Cases	Placebo (N=299) Person-Years at Risk	Placebo (N=299) Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
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	0.0	261	0	656.2	0.0	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; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

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Appendix 2.5: 10

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) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=299) 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	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)

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) (Cont.)

	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
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	0.0	NA	NA

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

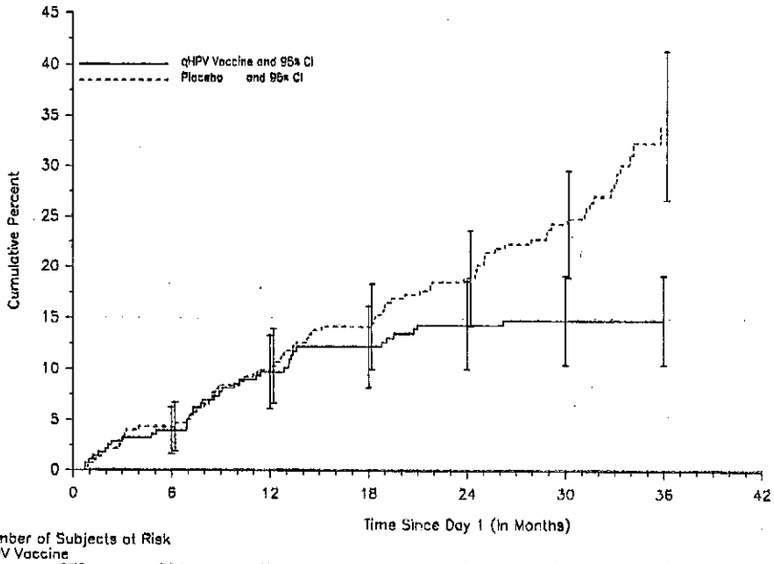
n = Number of subjects in the MSM substudy who have at least one follow-up visit after Day 1.

AIN = Anal intraepithelial neoplasia; CI = Confidence interval; HPV = Human papillomavirus; MSM = Men having sex with men; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

Appendix 2.5: 11

Analysis of Time to HPV 6/11/16/18-Related AIN and Anal Cancer
(MSM Full Analysis Set) (Protocol 020)



Number of Subjects at Risk

qHPV Vaccine	275	264	225	208	191	148	45
Placebo	276	263	236	218	192	146	38

[Ref. 5.3.5.1: P020]

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Appendix 2.5: 12

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) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=299) 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	129	12	299.4	4.0	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	0.0	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	0.0	126	3	326.5	0.9	100	(-156.5, 100)

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Analysis of Efficacy Against AIN and Anal Cancer Due to Any HPV Type (MSM Generally HPV-Naïve Population) (Protocol 020) (Cont.)

Endpoint	qHPV Vaccine (N=299) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=299) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
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	0.0	126	1	329.5	0.3	100	(-4072.8, 100)
HPV 33-Related AIN and Anal Cancer	129	0	308.0	0.0	126	0	329.5	0.0	NA	NA
HPV 35-Related AIN and Anal Cancer	129	0	308.0	0.0	126	0	329.5	0.0	NA	NA
HPV 39-Related AIN and Anal Cancer	129	0	308.0	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	0.0	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	0.0	126	1	329.5	0.3	100	(-4072.8, 100)
HPV 56-Related AIN and Anal Cancer	129	0	308.0	0.0	126	0	329.5	0.0	NA	NA
HPV 58-Related AIN and Anal Cancer	129	0	308.0	0.0	126	0	329.5	0.0	NA	NA
HPV 59-Related AIN and Anal Cancer	129	1	307.3	0.3	126	0	329.5	0.0	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.

[Ref. 5.3.5.1: P020]

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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)

Analysis of Efficacy Against AIN and Anal Cancer Due to Any HPV Type (MSM Full Analysis Set) (Protocol 020) (Cont.)

Endpoint	qHPV Vaccine (N=299) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=299) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
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.

[Ref. 5.3.5.1: P020]

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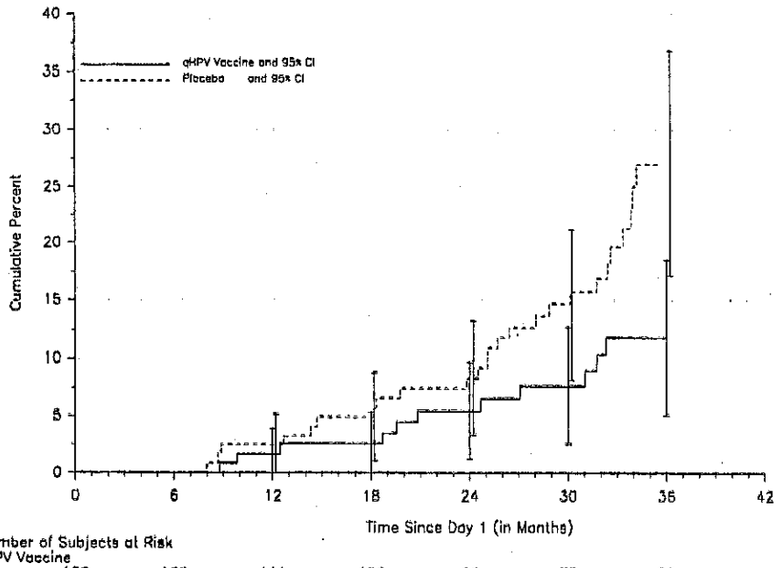
Analysis of Time to AIN and Anal Cancer Due to Any HPV Type
(MSM Generally HPV-Naïve Population) (Protocol 020)



Number of Subjects at Risk

qHPV Vaccine	129	129	111	103	92	72	26
Placebo	126	125	119	114	105	82	27

[Ref. 5.3.5.1: P020]

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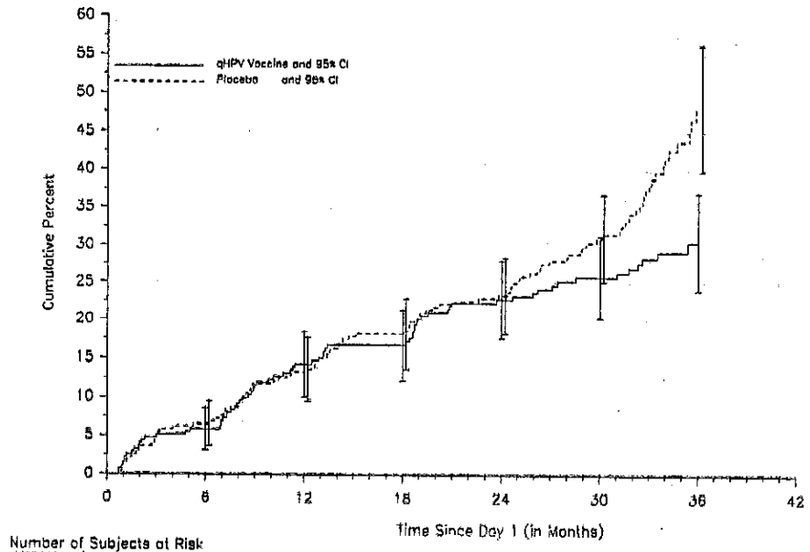
Analysis of Time to AIN and Anal Cancer Due to Any HPV Type
(MSM Full Analysis Set) (Protocol 020)



Number of Subjects at Risk

qHPV Vaccine	275	259	213	196	170	131	42
Placebo	276	257	228	210	183	136	34

[Ref. 5.3.5.1: P020]

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