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 current approved product circular.

2.5.6 Benefits and Risks Conclusions

In the prior Applications for qHPV vaccine, the vaccine was shown to be efficacious, immunogenic, and generally well-tolerated in girls and women 9 to 45 years of age. In addition, the vaccine was shown to be immunogenic and generally well-tolerated in boys 9 to 15 years of age. In this Application, efficacy, immunogenicity and safety of qHPV vaccine in men 16 to 26 years of age have been demonstrated. In addition, efficacy data among adult men was successfully bridged to adolescent boys 9 to 15 years of age. Therefore, the benefit to risk ratio is favorable and totality of the data supports broadening the qHPV vaccine indication to males 9 to 26 years of age.

2.5.6.1 Unmet Medical Need for HPV Vaccination in Men

As demonstrated in Protocol 020 and in published studies of HPV infections in men, anogenital HPV-related infection and diseases are common and associated with significant individual and public health burden [Ref. 5.3.5.1: P020V1] [Ref. 5.3.5.3: 2632, 2633]. HPV types contained in the vaccine constitute a substantial proportion of these diseases and infection and a vaccine highly efficacious in preventing such diseases and infection would provide significant benefit for the individual and public health in general.

HPV is the most common sexually transmitted infection, and HPV types contained in the qHPV vaccine constitute a substantial proportion of these infections in men. Consistent with previous published literature, in Protocol 020 approximately 9% of HM subjects had evidence of prevalent infection with at least one of the 4 vaccine HPV types. This rate is probably higher in the general population, as the study restricted enrollment to those with limited number of sexual partners. Furthermore, similar to findings in women, persistent infections were found to significantly predict development of EGL in men [Sec. 11.1.1.3.3] of [Ref. 5.3.5.1: P020V1]. Therefore, a vaccine that prevents persistent infection with HPV would also prevent the EGL that may occur subsequent to such infections.

There is no adequate protection method from anogenital HPV infections and diseases. Although circumcision and condom use have been suggested to be associated with reduced rates of infection, they do not provide complete protection. Analysis of data from placebo subjects in Protocol 020 showed that neither affords protective effect against prevalent or incident HPV infection [Ref. 5.3.5.3: 2633]. Thus, vaccination is the optimal method of HPV prevention.

Genital warts are the most common manifestation of HPV infection in men, and young adult men are at the highest risk for developing HPV-related anogenital diseases. Based on Protocol 020, in a general population of young heterosexual men, 1.5 out of 100 develops genital warts every year [Ref. 5.3.5.3: 2633]. Extrapolating this incidence rate

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to the US male population data suggests that approximately 314,000 new cases of genital warts occur every year among men 15-24 years of age. This incidence rate is higher than what has been reported in the literature for genital warts in the same age range, and signifies that burden of disease due to anogenital warts has been underestimated. Furthermore, these rates are substantially higher in at high-risk populations, such as MSM. However, this incident rate from Protocol 020 may still underestimate the true incidence of genital warts, because men with >5 sexual partners before enrollment were excluded.

Incidence of anogenital warts has been increasing significantly in recent years. This finding is corroborated by several sources in different countries. Warts-related direct health care cost alone is estimated $170 million to $225 million in the US. Patients experience pain, discomfort, pruritis, psychosocial burden, and stigmatization, and require multiple health care visits. Myriad of treatment methods, from topical to surgical, are not optimal in that they carry risks to varying degree for scarring, disfigurement, pain, and relapse.

Infection with high-risk HPV can also cause penile and anal cancers in men. More than 80% of anal cancers and 40-50% of penile cancers are due to HPV; HPV 16/18, which are contained in the qHPV vaccine, constitute most of the causal HPV type. As demonstrated in women, these HPV-related cancers are also preceded with high-grade intraepithelial neoplasia (i.e., PIN 2/3 and AIN 2/3). Data presented from Protocol 020 in this Submission had limited or no cases of high-grade lesions.

In summary, there is a strong public health rationale for immunization of men with qHPV. A vaccine to reduce the burden of vaccine-preventable HPV-related anogenital diseases in men would have significant individual and public health benefit.

2.5.6.2 New Information Presented in the Current Application and Benefits of qHPV Vaccination of Boys and Men 9-26 Years of Age

As demonstrated in Protocol 020, administration of qHPV vaccine to 16 to 26 year old men is highly efficacious in preventing HPV 6/11/16/18-related external genital lesions (external genital warts and penile/perineal/perianal intraepithelial neoplasia) [Sec. 2.7.3.1.2.5-exgenlesions]. qHPV vaccine reduced incidence of HPV 6/11/16/18-related external genital lesions by 90.4% (95% CI: 69.2, 98.1). Efficacy was high in both HM and MSM populations, and against any of the lesion types or any of the vaccine HPV types examined. These data confirm the benefit that the vaccine provides in preventing HPV 6/11/16/18-related external genital lesions in young men.

Data from Protocol 020 also demonstrated that there is significant reduction in overall burden of HPV-related external genital diseases through qHPV vaccination. This impact was consistently observed regardless of subpopulation examined, young men who are HPV-naïve or a general population of young men (including those who are HPV-naïve or infected) and across geographic regions. Population impact analysis showed that efficacy of the qHPV vaccine emerges soon after the vaccination series is completed.

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As presented in previously published studies, treatment modalities for genital warts can be costly and are an important public health burden [Ref. 5.3.5.3: 2632]. As demonstrated in Protocol 020, qHPV vaccine significantly reduces biopsies and therapies related to external genital lesions. Vaccine efficacy against external genital therapies was 47.9% (95% CI: 18.1, 67.5) in the GHN and 37.6% (95% CI: 18.2, 52.6) in the FAS populations [Sec. 11.1.2.2] of [Ref. 5.3.5.1: P020V1]. As demonstrated in Protocol 020, qHPV vaccine significantly reduces biopsies and therapies related to external genital lesions.

Quadrivalent HPV vaccine is also efficacious against HPV 6/11/16/18-related persistent infection and DNA detection at one or more visits [Sec. 2.7.3.1.2.5-exgenlesions]. As presented in the Protocol 020 report, persistent infection with HPV 6/11/16/18 significantly predicts development of external genital lesions; the high rate of reduction in persistent infection through vaccination is a major benefit and highly relevant to our understanding of how the vaccine prevents disease. qHPV vaccine also reduced HPV 6/11/16/18 DNA detection nearly by 45%.

Immunogenicity data from Protocol 020 showed that qHPV vaccine was highly immunogenic in men 16-26 years of age [Sec. 2.7.3.2.3-exgenlesions]. Vaccine-induced anti-HPV levels in 9-15 year old boys were non-inferior to anti-HPV levels observed in 16-26 year old men, inferring vaccine efficacy in this younger group as well [Sec. 2.7.3.2.4-exgenlesions], [Ref. 5.4: 2272]. As qHPV vaccine is preventative, targeting adolescents prior to sexual debut and HPV exposure is critical.

Administration of qHPV vaccine was shown to be generally well-tolerated in all populations in which it was evaluated [Sec. 2.7.4]. The proportions of subjects who reported serious adverse experiences, or who discontinued due to an adverse experience were low and comparable between vaccination groups. Injection-site adverse experiences were more common among subjects who received qHPV vaccine compared with placebo subjects, but most of these adverse experiences were mild or moderate in intensity. Overall, the proportions of subjects who reported new medical conditions, including conditions potentially indicative of an autoimmune phenomenon, were comparable between vaccination groups.

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

2.5.6.3 Health Economic Modeling

The population value of qHPV vaccine in men is presented using results from the 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. 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, cervical intraepithelial neoplasia (CIN), and cervical cancer cases in the US by 654,282, 71,783, and 721, respectively, 20 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 $78,086 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 $100,000 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]. In sensitivity analyses, male vaccination becomes more efficient (i.e., the cost-effectiveness ratio was lower) if coverage of the vaccine decreased to 50% or if vaccination did not protect against transmission. In contrast, the male vaccination program becomes less efficient if vaccine efficacy against infection increased in females, vaccine coverage increased in females, or the quality of life impact of genital warts and CIN was less.

In summary, the results from this model suggest that in a setting of organized cervical cancer screening, a prophylactic qHPV vaccine can reduce genital warts, CIN, cervical cancer, cervical cancer deaths and potentially be cost-effective when implemented as a strategy that combines vaccination of both females and males before age 12 with a 12 to 26 years of age catch up program compared to vaccinating females only before age 12 augmented by a female only 12 to 26 year old catch-up program.

2.5.6.4 Conclusion

As demonstrated in Protocol 020 and in published previous studies of HPV, there is a demonstrated high burden of incident HPV–related vaccine-preventable genital disease and infection, and consequently, an unmet medical need in men. Protocol 020 demonstrated that the vaccine is highly efficacious in preventing such diseases and infection in men 16-26 years of age and health economic analyses corroborate that vaccinating men will be a public health benefit. Making qHPV vaccine available to men meets an important 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 female qHPV vaccination; no limitations and risks specific to male subjects has been identified. Two of the risks and limitations are: (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 [Ref. 5.3.5.1: P018V1]; and (2) the safety database in the clinical development program for qHPV vaccine is insufficient to detect safety signals with respect to rare conditions (i.e. medical conditions occurring at a background rate of <1:10,000); overall, the post-marketing safety experience with qHPV vaccine is consistent with the safety profile seen in clinical trials. Merck & Co., Inc will continue to the monitor the safety of qHPV in the post-licensure period.

2.5.7 Overall Conclusion

The data obtained in the current supplemental Application strongly support the main conclusions of the prior Applications. There is strong evidence for efficacy in the study group that is representative of the population for which qHPV vaccine is intended, with a favorable safety profile. There is substantial vaccine preventable HPV infection and disease in boys and men. Administration of qHPV vaccine to male adolescents and adults is highly likely to induce protection through periods of high risk for acquisition of infection and disease with the vaccine HPV types. qHPV vaccine therefore addresses an unmet medical need and will significantly reduce the public health burden caused by the HPV types contained in the vaccine. Thus, the overall benefit to risk ratio in boys and men is favorable, and on the basis of the data presented in the prior Applications and the current supplemental Application, the indication in boys and men proposed below is justified:

> **qHPV vaccine is indicated in 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.**

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2.5.9 Appendix

Appendix 2.5: 1

Genital wart prevalence among men by age group
within a set of private health plans in the United States, 2000

[Ref. 5.4: 827]

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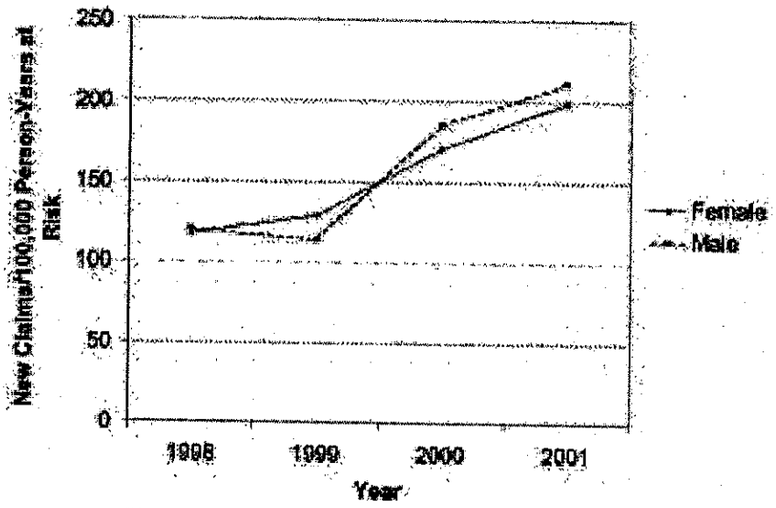
Appendix 2.5: 2

Rates of new claims per 100,000 person-years at risk between 1998-2001 age standardized to the 2001 privately insured US population



[Ref. 5.4: 2511]

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Appendix 2.5: 3

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-, 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-, 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-, 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 EGL in the general population of 16- to 26-year-old men, starting immediately after the first dose.

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: P020V1]

Appendix 2.5: 4

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	External Genital Lesions (caused by vaccine or non vaccine HPV types) External Genital Lesion Procedures and Therapies
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: P020V1]

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Appendix 2.5: 5

Analysis of Efficacy of qHPV Vaccine in the PPE Population
(Protocol 020)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) 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 EGL	1,397	3	2,830.9	0.1	1,408	31	2,812.2	1.1	90.4	(69.2, 98.1)	< 0.001
By Lesion Type											
Condyloma	1,397	3	2,830.9	0.1	1,408	28	2,813.9	1.0	89.4	(65.5, 97.9)	
PIN 1 or worse	1,397	0	2,833.3	0.0	1,408	3	2,824.5	0.1	100	(-141.2, 100)	
PIN 1	1,397	0	2,833.3	0.0	1,408	2	2,826.0	0.1	100	(-431.1, 100)	
PIN 2/3 or Cancer	1,397	0	2,833.3	0.0	1,408	1	2,824.7	0.0	100	(-3788.2, 100)	
PIN 2/3	1,397	0	2,833.3	0.0	1,408	1	2,824.7	0.0	100	(-3788.2, 100)	
Penile/Perianal/Perineal Cancer	1,397	0	2,833.3	0.0	1,408	0	2,826.2	0.0	NA	NA	
By HPV Type											
HPV 6-Related EGL	1,245	3	2,562.3	0.1	1,244	19	2,553.8	0.7	84.3	(46.5, 97.0)	
HPV 11-Related EGL	1,245	1	2,563.7	0.0	1,244	11	2,552.6	0.4	90.9	(37.7, 99.8)	
HPV 16-Related EGL	1,295	0	2,644.0	0.0	1,271	2	2,586.2	0.1	100	(-420.8, 100)	
HPV 18-Related EGL	1,335	0	2,723.3	0.0	1,354	1	2,726.6	0.0	100	(-3804.6, 100)	
HPV 6/11/16/18-Related Persistent Infection	1,390	15	2,549.4	0.6	1,400	101	2,469.3	4.1	85.6	(73.4, 92.9)	< 0.001
By HPV Type											
HPV 6-Related Persistent Infection	1,239	4	2,320.2	0.2	1,238	33	2,296.6	1.4	88.0	(66.3, 96.9)	
HPV 11-Related Persistent Infection	1,239	1	2,322.6	0.0	1,238	15	2,315.1	0.6	93.4	(56.8, 99.8)	
HPV 16-Related Persistent Infection	1,290	9	2,382.4	0.4	1,264	41	2,312.9	1.8	78.7	(55.5, 90.9)	
HPV 18-Related Persistent Infection	1,327	1	2,461.9	0.0	1,347	25	2,453.5	1.0	96.0	(75.6, 99.9)	

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Analysis of Efficacy of qHPV Vaccine in the PPE Population (Protocol 020) (Cont.)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) 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 DNA Detection	1,390	136	2,455.3	5.5	1,400	241	2,404.1	10.0	44.7	(31.5, 55.6)	< 0.001
By HPV Type											
HPV 6-Related DNA Detection	1,239	51	2,292.4	2.2	1,238	99	2,267.7	4.4	49.0	(27.9, 64.4)	
HPV 11-Related DNA Detection	1,239	16	2,311.7	0.7	1,238	37	2,300.5	1.6	57.0	(20.7, 77.6)	
HPV 16-Related DNA Detection	1,290	62	2,337.7	2.7	1,264	103	2,287.8	4.5	41.1	(18.5, 57.7)	
HPV 18-Related DNA Detection	1,327	25	2,441.3	1.0	1,347	66	2,440.6	2.7	62.1	(39.2, 77.1)	

[†] A 97.5% CI is reported for the HPV 6/11/16/18-related persistent infection endpoint. For all other analyses, a 95% CI is reported. The CI reported for the HPV 6/11/16/18-related persistent infection endpoint differs from the other analyses due to the Hochberg multiplicity adjustment applied.

[‡] A p-value<0.025 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 20% and supports the conclusion that the vaccine is efficacious against the given endpoint. The Hochberg multiplicity adjustment has been applied to the p-value reported for the HPV 6/11/16/18-related persistent infection and HPV 6/11/16/18-related DNA detection endpoints.

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

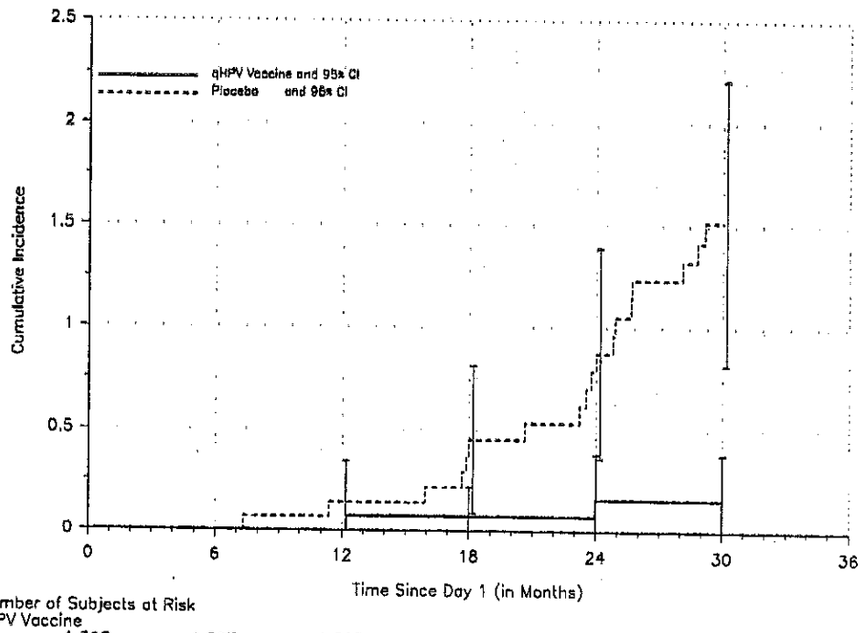
n = Number of subjects who have at least one follow-up visit after Month 7.

CI = Confidence interval; DNA = Deoxyribonucleic acid; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; PPE = Per-protocol efficacy; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020V1]

Appendix 2.5: 6

Analysis of Time to HPV 6/11/16/18-Related EGL
(Per-Protocol Efficacy Population) – Protocol 020



Number of Subjects at Risk

qHPV Vaccine	1,397	1,397	1,367	1,267	1,166	983
Placebo	1,408	1,408	1,374	1,267	1,149	949

CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020V1]

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Appendix 2.5: 7

Analysis of Efficacy of qHPV Vaccine in the HNRT Population (Protocol 020)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) 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	1,775	13	4,262.8	0.3	1,770	52	4,186.0	1.2	75.5	(54.3, 87.7)
By Lesion Type										
Condyloma	1,775	10	4,268.6	0.2	1,770	48	4,187.9	1.1	79.6	(59.1, 90.8)
PIN 1 or worse	1,775	4	4,274.0	0.1	1,770	4	4,223.5	0.1	1.2	(-430.5, 81.6)
PIN 1	1,775	2	4,278.9	0.0	1,770	3	4,225.0	0.1	34.2	(-474.7, 94.5)
PIN 2/3 or Cancer	1,775	2	4,276.1	0.0	1,770	1	4,223.9	0.0	-97.6	(-11555.6, 89.7)
PIN 2/3	1,775	2	4,276.1	0.0	1,770	1	4,223.9	0.0	-97.6	(-11555.6, 89.7)
Penile/Perianal/Perineal Cancer	1,775	0	4,280.9	0.0	1,770	0	4,225.4	0.0	NA	NA
By HPV Type										
HPV 6-Related EGL	1,603	10	3,904.8	0.3	1,607	36	3,866.3	0.9	72.5	(43.4, 87.8)
HPV 11-Related EGL	1,603	1	3,919.3	0.0	1,607	16	3,879.6	0.4	93.8	(60.2, 99.9)
HPV 16-Related EGL	1,674	1	4,060.0	0.0	1,649	3	3,961.7	0.1	67.5	(-305.1, 99.4)
HPV 18-Related EGL	1,713	2	4,146.9	0.0	1,715	1	4,107.4	0.0	-98.1	(-11587.0, 89.7)
HPV 6/11/16/18-Related Persistent Infection	1,669	58	3,865.2	1.5	1,664	175	3,697.2	4.7	68.3	(57.1, 76.9)
By HPV Type										
HPV 6-Related Persistent Infection	1,513	16	3,594.0	0.4	1,510	64	3,525.1	1.8	75.5	(57.1, 86.8)
HPV 11-Related Persistent Infection	1,513	3	3,614.9	0.1	1,510	22	3,576.4	0.6	86.5	(55.1, 97.4)
HPV 16-Related Persistent Infection	1,578	29	3,703.2	0.8	1,545	76	3,567.4	2.1	63.2	(42.9, 76.9)
HPV 18-Related Persistent Infection	1,610	13	3,799.6	0.3	1,614	42	3,744.0	1.1	69.5	(42.1, 85.0)

Analysis of Efficacy of qHPV Vaccine in the HNRT Population (Protocol 020) (Cont.)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) 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 DNA Detection	1,669	253	3,669.7	6.9	1,664	372	3,547.9	10.5	34.2	(22.7, 44.2)
By HPV Type										
HPV 6-Related DNA Detection	1,513	88	3,533.2	2.5	1,510	161	3,457.8	4.7	46.5	(30.2, 59.2)
HPV 11-Related DNA Detection	1,513	27	3,593.6	0.8	1,510	54	3,554.3	1.5	50.5	(20.1, 70.0)
HPV 16-Related DNA Detection	1,578	119	3,606.9	3.3	1,545	164	3,508.5	4.7	29.4	(10.1, 44.7)
HPV 18-Related DNA Detection	1,610	59	3,752.5	1.6	1,614	106	3,704.8	2.9	45.0	(23.7, 60.7)

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 Day 1.
CI = Confidence interval; DNA = Deoxyribonucleic acid; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HNRT = HPV-naïve to the relevant type; HPV = Human papillomavirus; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020V1]

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Analysis of Efficacy of qHPV Vaccine in the FAS Population (Protocol 020)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) 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	1,943	27	4,625.7	0.6	1,937	77	4,556.5	1.7	65.5	(45.8, 78.6)
By Lesion Type										
Condyloma	1,943	24	4,635.4	0.5	1,937	72	4,558.8	1.6	67.2	(47.3, 80.3)
PIN 1 or worse	1,943	6	4,658.7	0.1	1,937	5	4,628.2	0.1	-19.2	(-393.8, 69.7)
PIN 1	1,943	3	4,666.1	0.1	1,937	4	4,629.7	0.1	25.6	(-339.9, 89.1)
PIN 2/3 or Cancer	1,943	3	4,663.1	0.1	1,937	2	4,628.6	0.0	-48.9	(-1682.6, 82.9)
PIN 2/3	1,943	3	4,663.1	0.1	1,937	2	4,628.6	0.0	-48.9	(-1682.6, 82.9)
Penile/Perianal/Perineal Cancer	1,943	0	4,670.6	0.0	1,937	0	4,630.5	0.0	NA	NA
By HPV Type										
HPV 6-Related EGL	1,943	21	4,635.8	0.5	1,937	51	4,576.0	1.1	59.4	(31.2, 76.8)
HPV 11-Related EGL	1,943	6	4,663.7	0.1	1,937	25	4,606.6	0.5	76.3	(40.8, 92.0)
HPV 16-Related EGL	1,943	3	4,663.1	0.1	1,937	10	4,621.9	0.2	70.3	(-15.5, 94.7)
HPV 18-Related EGL	1,943	2	4,670.0	0.0	1,937	3	4,627.9	0.1	33.9	(-476.7, 94.5)
HPV 6/11/16/18-Related Persistent Infection	1,817	148	4,094.3	3.6	1,815	273	3,942.6	6.9	47.8	(36.0, 57.6)
By HPV Type										
HPV 6-Related Persistent Infection	1,817	63	4,213.8	1.5	1,815	112	4,139.4	2.7	44.7	(24.1, 60.1)
HPV 11-Related Persistent Infection	1,817	16	4,284.6	0.4	1,815	39	4,238.7	0.9	59.4	(25.7, 78.8)
HPV 16-Related Persistent Infection	1,817	71	4,199.5	1.7	1,815	131	4,112.7	3.2	46.9	(28.6, 60.8)
HPV 18-Related Persistent Infection	1,817	25	4,267.0	0.6	1,815	56	4,210.1	1.3	56.0	(28.2, 73.7)

Analysis of Efficacy of qHPV Vaccine in the FAS Population (Protocol 020) (Cont.)

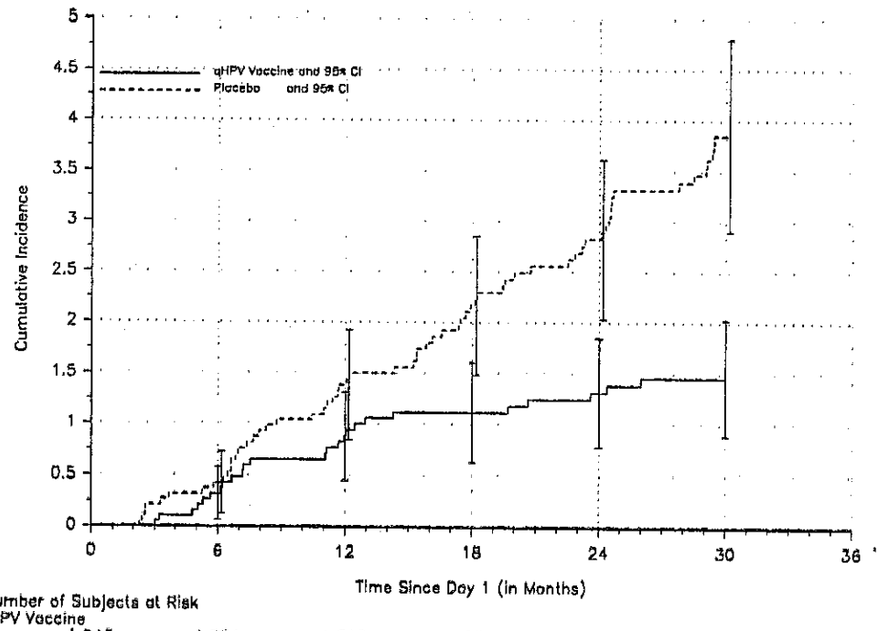
Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related DNA Detection	1,817	384	3,851.1	10.0	1,815	511	3,736.5	13.7	27.1	(16.6, 36.3)
By HPV Type										
HPV 6-Related DNA Detection	1,817	158	4,123.4	3.8	1,815	239	4,047.5	5.9	35.1	(20.3, 47.3)
HPV 11-Related DNA Detection	1,817	50	4,254.0	1.2	1,815	87	4,202.6	2.1	43.2	(18.7, 60.7)
HPV 16-Related DNA Detection	1,817	189	4,070.9	4.6	1,815	259	4,014.2	6.5	28.0	(12.9, 40.7)
HPV 18-Related DNA Detection	1,817	89	4,205.4	2.1	1,815	133	4,151.5	3.2	33.9	(13.0, 50.1)

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 Day 1.
CI = Confidence interval; DNA = Deoxyribonucleic acid; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; FAS = Full analysis set; HPV = Human papillomavirus; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020V1]

Appendix 2.5: 9

Analysis of Time to HPV 6/11/16/18-Related EGL
(Full Analysis Set) – Protocol 020



Number of Subjects at Risk

qHPV Vaccine	1,943	1,834	1,712	1,576	1,420	1,182
Placebo	1,937	1,829	1,699	1,546	1,391	1,140

CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020V1]

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Analysis of Efficacy Against EGL Due to Any HPV Type (Full Analysis Set) – Protocol 020

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
EGL Due to Any HPV Type	1,943	36	4,612.6	0.8	1,937	89	4,538.6	2.0	60.2	(40.8, 73.8)
HPV 6/11/16/18-Related EGL	1,943	27	4,625.7	0.6	1,937	77	4,556.5	1.7	65.5	(45.8, 78.6)
HPV 6-Related EGL	1,943	21	4,635.8	0.5	1,937	51	4,576.0	1.1	59.4	(31.2, 76.8)
HPV 11-Related EGL	1,943	6	4,663.7	0.1	1,937	25	4,606.6	0.5	76.3	(40.8, 92.0)
HPV 16-Related EGL	1,943	3	4,663.1	0.1	1,937	10	4,621.9	0.2	70.3	(-15.5, 94.7)
HPV 18-Related EGL	1,943	2	4,670.0	0.0	1,937	3	4,627.9	0.1	33.9	(-476.7, 94.5)
EGL Related to any of 10 Assay-identified HPV Types	1,943	9	4,655.0	0.2	1,937	17	4,613.5	0.4	47.5	(-24.4, 79.4)
HPV 31-Related EGL	1,943	0	4,670.6	0.0	1,937	5	4,625.5	0.1	100	(-8.1, 100)
HPV 33-Related EGL	1,943	1	4,670.6	0.0	1,937	3	4,627.0	0.1	67.0	(-311.3, 99.4)
HPV 35-Related EGL	1,943	1	4,669.6	0.0	1,937	0	4,630.5	0.0	NA	NA
HPV 39-Related EGL	1,943	0	4,670.6	0.0	1,937	1	4,630.5	0.0	100	(-3766.5, 100)
HPV 45-Related EGL	1,943	0	4,670.6	0.0	1,937	1	4,628.8	0.0	100	(-3765.1, 100)
HPV 51-Related EGL	1,943	1	4,668.5	0.0	1,937	4	4,627.7	0.1	75.2	(-150.4, 99.5)
HPV 52-Related EGL	1,943	3	4,664.9	0.1	1,937	3	4,624.3	0.1	0.9	(-640.1, 86.7)
HPV 56-Related EGL	1,943	2	4,666.3	0.0	1,937	1	4,630.1	0.0	-98.4	(-11607.8, 89.7)
HPV 58-Related EGL	1,943	0	4,670.6	0.0	1,937	3	4,626.0	0.1	100	(-139.7, 100)
HPV 59-Related EGL	1,943	2	4,668.0	0.0	1,937	1	4,630.0	0.0	-98.4	(-11603.4, 89.7)
EGL Not Related to any of 14 Assay-identified HPV Types	1,943	6	4,562.4	0.1	1,937	12	4,477.9	0.3	50.9	(-41.3, 84.9)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
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 Day 1.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020V1]

Appendix 2.5: 11

Summary of Anti-HPV Geometric Mean Titers by Vaccination Group
(Per-Protocol Immunogenicity Population) – Protocol 020

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=2,025) n	GMT (mMU/mL)	95% CI	Placebo (N=2,030) n	GMT (mMU/mL)	95% CI	P-value[1]
Anti-HPV 6							
Day 1	1,093	<7	(<7, <7)	1,110	<7	(<7, <7)	-
Month 7	1,093	447.0	(422.1, 473.5)	1,110	<7	(<7, <7)	<0.001
Month 24	906	80.3	(76.2, 84.6)	904	<7	(<7, <7)	-
Anti-HPV 11							
Day 1	1,093	<8	(<8, <8)	1,109	<8	(<8, <8)	-
Month 7	1,093	624.2	(594.4, 655.6)	1,109	<8	(<8, <8)	<0.001
Month 24	906	94.5	(89.8, 99.5)	902	<8	(<8, <8)	-
Anti-HPV 16							
Day 1	1,136	<11	(<11, <11)	1,128	<11	(<11, <11)	-
Month 7	1,136	2,402.5	(2,270.6, 2,542.0)	1,128	<11	(<11, <11)	<0.001
Month 24	937	347.8	(329.3, 367.4)	904	<11	(<11, <11)	-
Anti-HPV 18							
Day 1	1,175	<10	(<10, <10)	1,205	<10	(<10, <10)	-
Month 7	1,175	402.2	(380.2, 425.6)	1,205	<10	(<10, <10)	<0.001
Month 24	966	38.7	(36.2, 41.3)	952	<10	(<10, <10)	-

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

[Ref. 5.3.5.1: P020V1]

Appendix 2.5: 12

Summary of Anti-HPV Percent Seroconversion by Vaccination Group (Per-Protocol Immunogenicity Population) – Protocol 020

Anti-HPV Response Study Time	qHPV Vaccine (N=2,025) n	Seroconversion m	Percent	95% CI	Placebo (N=2,030) n	Seroconversion m	Percent	95% CI	P-value†
HPV 6 cLIA ≥ 20 mMU/mL									
Day 1	1,093	0	0.0	(0.0%, 0.3%)	1,110	0	0.0	(0.0%, 0.3%)	-
Month 7	1,093	1,081	98.9	(98.1%, 99.4%)	1,110	18	1.6	(1.0%, 2.6%)	<0.0001
Month 24	906	823	90.8	(88.8%, 92.6%)	904	19	2.1	(1.3%, 3.3%)	-
HPV 11 cLIA ≥ 16 mMU/mL									
Day 1	1,093	0	0.0	(0.0%, 0.3%)	1,109	0	0.0	(0.0%, 0.3%)	-
Month 7	1,093	1,084	99.2	(98.4%, 99.6%)	1,109	23	2.1	(1.3%, 3.1%)	<0.0001
Month 24	906	866	95.6	(94.0%, 96.8%)	902	11	1.2	(0.6%, 2.2%)	-
HPV 16 cLIA ≥ 20 mMU/mL									
Day 1	1,136	0	0.0	(0.0%, 0.3%)	1,128	0	0.0	(0.0%, 0.3%)	-
Month 7	1,136	1,122	98.8	(97.9%, 99.3%)	1,128	20	1.8	(1.1%, 2.7%)	<0.0001
Month 24	937	930	99.3	(98.5%, 99.7%)	904	7	0.8	(0.3%, 1.6%)	-
HPV 18 cLIA ≥ 24 mMU/mL									
Day 1	1,175	0	0.0	(0.0%, 0.3%)	1,205	0	0.0	(0.0%, 0.3%)	-
Month 7	1,175	1,144	97.4	(96.3%, 98.2%)	1,205	21	1.7	(1.1%, 2.7%)	<0.0001
Month 24	966	602	62.3	(59.2%, 65.4%)	952	10	1.1	(0.5%, 1.9%)	-

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

[Ref. 5.3.5.1: P020V1]

Appendix 2.5: 13

Clinical Adverse Experience Summary (Day 1 Through Entire Study Period† Following Any Vaccination Visit) Male Subjects 9 to 26 Years of Age in the Detailed Safety Population (Protocols 016, 018 and 020)

	qHPV Vaccine (N=3092)		Placebo (N=2303)	
	n	(%)	n	(%)
Subjects in analysis population	3092		2303	
Subjects without follow-up	89		84	
Subjects with follow-up	3003		2219	
Number (%) of subjects:				
with no adverse experience	786	(26.2)	794	(35.8)
with one or more adverse experiences	2217	(73.8)	1425	(64.2)
injection-site adverse experiences	1927	(64.2)	1177	(53.0)
systemic adverse experiences	1119	(37.3)	732	(33.0)
with vaccine-related‡ adverse experiences	2049	(68.2)	1284	(57.9)
injection-site adverse experiences	1927	(64.2)	1176	(53.0)
systemic adverse experiences	527	(17.5)	338	(15.2)
with serious adverse experiences	13	(0.4)	11	(0.5)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	4	(0.1)	10	(0.5)

Clinical Adverse Experience Summary (Day 1 Through Entire Study Period[†] Following Any Vaccination Visit)
Male Subjects 9 to 26 Years of Age in the Detailed Safety Population (Protocols 016, 018 and 020) (Cont.)

	qHPV Vaccine (N=3092)		Placebo (N=2303)	
	n	(%)	n	(%)
discontinued[§] due to an adverse experience	10	(0.3)	14	(0.6)
discontinued due to a vaccine-related adverse experience	4	(0.1)	3	(0.1)
discontinued due to a serious adverse experience	5	(0.2)	10	(0.5)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

[†] Entire study period includes visits through 20-Sep-2004 for Protocol 016, 01-Jun-2007 for Protocol 018, and 29-Aug-2008 for Protocol 020.
[‡] Determined by the investigator to be possibly, probably, or definitely related to the vaccine/placebo.
[§] Discontinued = Subject discontinued from therapy.
Percentages are calculated based on the number of subjects with follow-up.
N = Number of subjects who received 1, 2, or 3 doses of only the clinical material indicated in the give column.
n = Number of subjects within category.

[Ref. 5.3.5.1: 1464, 2050, 2083, P016V1, P016V2, P018V1, P020V1]

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2.5 Clinical Overview

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2.5.1 Product Development Rationale

2.5.1.1 Pharmacologic Class

Quadrivalent Human Papillomavirus (HPV) (Types 6,11,16,18) recombinant vaccine, referred to as the qHPV vaccine in the current document, is an aluminum adjuvanted recombinant protein particulate (virus-like particle [VLP]) vaccine manufactured by Merck & Co., Inc. (West Point, Pennsylvania, U.S.A.) for the prevention of cancer, dysplasia, genital warts, and persistent infection caused by HPV types targeted by the vaccine.

2.5.1.2 Chemical and Pharmaceutical Properties

The qHPV vaccine is prepared from the highly purified Virus Like Particles (VLPs) of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant and formulated with sodium chloride, L-histidine, polysorbate 80, sodium borate, and water. Each 0.5-mL quadrivalent dose is formulated to contain 20/40/40/20 µg of HPV 6/11/16/18 L1 proteins respectively. The final container product is a sterile suspension in a single-dose vial or prefilled syringe, each with a fill volume that permits administration of 0.5 mL of vaccine for intramuscular injection. The qHPV vaccine is not a live virus vaccine, and contains no viral deoxyribonucleic acid (DNA).

2.5.1.3 Proposed Indications

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.

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. **The efficacy data presented in this application strongly support and extend previous observations in the qHPV clinical trials program, establishing that the qHPV vaccine is efficacious across the entire spectrum of anogenital HPV infection and related disease in men and women.**

The original qHPV studies in young women provided the first demonstration that by preventing persistent cervical HPV infection with a high degree of type-specific efficacy, the qHPV vaccine prevents high-grade cervical intraepithelial lesion, the obligate precursor of cervical cancer. The qHPV vaccine was also shown to prevent the external genital lesions of vulvar intraepithelial neoplasia and vaginal neoplasia, the known precursors of HPV-related vulvar and vaginal cancers. The consistently high vaccine efficacy observed in women was then extended to young men, in whom type-specific prevention of persistent genital infection was shown to prevent the development of

genital warts, with favorable data on prevention of penile intraepithelial lesion, the precursor of HPV-related penile cancer. Final analyses of the male efficacy study have confirmed these findings.

Analyses of the Protocol 020 MSM substudy show that efficacy of the qHPV vaccine has now been demonstrated in the prevention of HPV 6/11/16/18-related anal intraepithelial neoplasia (AIN) [Ref. 5.3.5.1: P020]. The qHPV vaccine was also shown to reduce the incidence of HPV 6/11/16/18-related high-grade AIN (AIN 2 or worse). These efficacy findings are further supported by the strongly favorable case split of vaccine and placebo group (8 vs 1) HPV 16/18-related high-grade AIN. When considered in conjunction with the greater than 90% observed type-specific efficacy against persistent anal infection related to HPV 16 and 18, this 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.

When considered in light of the literature reviewed in the current application, which 1) supports the concept of high-grade AIN as the obligate precursor of anal cancer, 2) confirms the important role of HPV 16 and 18 infection in the pathogenesis of anal cancer as in other anogenital cancers in men and women, 3) supports the identical pathogenetic process of carcinogenesis from high-grade lesions in the anal canal of males and females, and 4) demonstrates the high incidence of HPV-related anal cancers in females, the data presented in this application establish the qHPV vaccine as having significant potential to reduce the incidence of HPV 6/11/16/18-related AIN and HPV 16/18-related anal cancer in all individuals regardless of gender.

Taken together, the totality of the qHPV vaccine clinical trials data supports the consistently high efficacy of the qHPV vaccine against persistent HPV infection and related premalignant lesions, irrespective of gender or location in the genital tract.

Accordingly, 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.**

2.5.1.4 Scientific Background

Since the new efficacy findings reported in this submission relate primarily to HPV-associated intra-anal disease, the following section provides detailed data on the burden of anal cancer in men and women, the role of HPV in anal cancer, anal HPV infection epidemiology and natural history, and the evidence of high-grade AIN as the obligate precursor of anal cancer. Detailed background information on external genital lesions was provided in the previous submission of Protocol 020 data.

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2.5.1.4.1 Anal Cancer

Burden of Anal Cancer in Men and Women

Worldwide, approximately 100,000 new cases of anal cancer are estimated to occur annually [Ref. 5.4: 2584]. In 2002, roughly 40% and 60% of these cases occurred in men and women respectively. In the United States, nearly 4500 new cases of anal cancer were reported in 2004; similarly, approximately 40% occurred in men. In the same year, there were 589 deaths attributed to anal cancer; 240 (41%) and 349 (59%) of which were males and females respectively [Ref. 5.4: 2525]. The burden of anal cancer in women is increasingly being recognized, and as these data show, the incidence of anal cancer in women is often reported to be higher than that in men, some studies demonstrating rates twice as high in females as in males [Ref. 5.4: 1993, 2504].

Epidemiologic studies show that anal cancer incidence has been increasing and continues to grow in several parts of the world. These increases in anal cancer rates have been observed in both males and females; in fact, rates appear to be rising more rapidly in females than in males [Ref. 5.4: 2486, 2504, 2509, 2512, 2689, 3171, 3183]. Analyses of SEER (Surveillance, Epidemiology and End Results) data from 1973 to 2000 showed that in the United States, the age-adjusted incidence of invasive anal cancer in men increased from 0.97 per 100,000 in 1973-1979 to 1.59 per 100,000 in 1994-2000, representing a 64% increase in ~2 decades. Over the same time period, the incidence rate in women increased from 1.27 to 1.84 per 100,000 [Ref. 5.4: 2509]. Similar analyses of time trends in SEER data up to 2004 have shown increases in anal cancer rates in both males and females; between 1992 and 2004, rates in the 13 SEER regions increased significantly, by 2.7% per year in males and 2.8% per year in females [Ref. 5.4: 2689]. It is particularly notable that rates in women ages 50-64 years increased by 4.7% per year in that time period. Estimates for 2009 were that 5,290 men and women (2,100 men and 3,190 women) would be diagnosed with, and 710 men and women (260/450 respectively) were expected to die of cancer of the anus, anal canal, and anorectum [Ref. 5.4: 3235]. Surveillance systems do not include data on sexual orientation; it is therefore not possible to know from population data, the relative proportion of anal cancers in heterosexual men (HM) and men having sex with men (MSM).

MSM and HIV-infected individuals are at particularly high risk of developing anal cancer. Before the HIV epidemic, the incidence of anal cancer in men with a history of receptive anal intercourse was estimated as 35 per 100,000, similar to cervical cancer rates before the introduction of cervical screening [Ref. 5.4: 2512]. Interestingly, the incidence of anal cancer has not declined during the HAART (Highly Active AntiRetroviral Therapy) era. Despite treatment, the prognosis of anal cancer is especially poor in HIV-infected patients [Ref. 5.4: 2526]. Anal HPV infection and anal intraepithelial neoplasia may be acquired in the absence of anal intercourse in HIV-infected men, likely reflecting their increased risk related to immunosuppression [Ref. 5.4: 727].

The median age at diagnosis of anal cancer is approximately 60 years [Ref. 5.4: 2521] and five-year survival rates are ~60% for men and 73% for women in the United States

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[Ref. 5.4: 2509]. Survival has been associated with age, stage of disease at diagnosis, race, and gender, with males being reported to have lower five-year relative survival than females for all stages of disease [Ref. 5.4: 2689]. Case control studies suggest infection with HPV 16 or HPV 18, history of cervical dysplasia or cancer, history of genital warts, history of receptive anal intercourse prior to age 30 or with multiple partners, lifetime number of sexual partners, having other sexually transmitted infections or history of sexual transmitted infection in a partner, smoking, and older age are all risk factors for anal cancer in both men and women [Ref. 5.4: 1156, 2491, 2496, 2499, 2504, 3174, 3175]. These risk factors are frequently noted as being similar to those for cervical cancer.

Due to lack of standardized screening and the asymptomatic nature of early disease, diagnosis of anal cancers in the later stages of disease is not uncommon. SEER data have shown that approximately 30% of cancers are diagnosed with either regional or distant spread [Ref. 5.4: 2689]. There is no established screening for anal cancer in the general population, but given the similarity of anal and cervical cancers, it follows that prevention by treatment of premalignant lesions detected through cytologic screening could lead to earlier detection of premalignant change and thus lower anal cancer rates. Reports on the sensitivity and specificity of anal cytology in healthy individuals have been variable. While some studies suggest that the sensitivities of anal and cervical cytology are similar, other studies suggest that the concordance between histologic and cytologic grades of abnormalities is poor, and that particularly in healthy individuals, anal cytology may underestimate the severity of anal neoplasia [Ref. 5.4: 3174, 3211, 3244]. It has also been shown that when HRA-guided biopsy is performed, the sensitivity of anal cytology is lower in immunocompetent as compared to immunocompromised individuals [Ref. 5.4: 3244, 3245].

Results from Protocol 020, in which a substantial number of the observed AIN cases were diagnosed at the mandatory end-of-study anoscopy, underscore these potential limitations of cytologic screening for anal premalignant and malignant disease in a generally healthy population. These data suggest that in average-risk individuals, cytologic screening of the anal canal may not be as successful as cervical screening in lowering anal cancer incidence rates. It has been shown that treatment of AIN lesions is feasible; however, in addition to high reported recurrence rates, therapy may be associated with side effects including post-operative pain, bleeding, and anal stenosis [Ref. 5.4: 1021, 3246]. **Primary prevention of anal HPV infection is therefore the optimal approach to anal cancer prevention, and the MSM substudy was designed to show the potential of qHPV vaccination to address this important unmet medical need.**

The Role of HPV in Anal Cancer

Detection of HPV in tumors is currently accepted as the best estimate of the etiologic fraction of potentially HPV-related cancers [Ref. 5.4: 3198]. On this basis, virtually 100% of cervical cancers are caused by HPV, with types 16 and 18 together responsible for approximately 70%. HPV is also strongly associated with anal cancer, and it is the minority of anal cancers in which this association is not observed. In fact, AIN and anal

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cancers resemble cervical intraepithelial neoplasia (CIN) and cancers of the cervix more than other anogenital cancers and precancers with regard to overall prevalence of HPV positivity [Ref. 5.4: 3177]. **As stated by Frisch et al, this high proportion of anal tumors with detectable HPV supports the role of HPV as a necessary cause of anal cancer [Ref. 5.4: 3178].**

Several authors report that approximately 90% of all anal cancers are caused by HPV [Ref. 5.4: 2689, 3178]. According to a meta-analysis, 84% of anal squamous cell cancers in men were HPV positive [Ref. 5.4: 2507]. Daling et al reported 87.9% HPV positivity of anal cancers in HM, compared to 88.4% in women and 97.7% in men who were not exclusively heterosexual [Ref. 5.4: 3175]. Similarly, in a case-control study of 394 anal cancer cases, 100% of men (11/11) reporting sexual activity with male partners had cancers that were positive for high-risk HPV types compared with 58% (38/66) of males who did not report same sex partners. In the same study, 90% (228/253) of women had high-risk HPV positive cancers [Ref. 5.4: 3178] [Appendix 2.5: 1].

In all populations, HPV 16 is consistently reported as the most common HPV type identified in anal cancers. In the meta-analysis described above, HPV 16 was the most common type (73%), followed by HPV 18 (5%) [Ref. 5.4: 2507]. Daling reported that 73% and 7% of all anal cancers examined were positive for HPV 16 and 18 respectively, regardless of gender [Ref. 5.4: 3175]. Overall, the literature suggests that HPV types 16 and 18 together account for approximately 70-90% of all anal squamous cancers, a larger proportion than for cervical cancers [Ref. 5.4: 385, 3175, 3176, 3177], strongly supporting the necessary role of these HPV types in anal cancer development. HPV types 6 and 11, classified as low-risk HPV types, are rarely identified in anal cancers, and are not considered an important cause of invasive disease or high-grade premalignant anal lesions [Ref. 5.4: 2688]. When low-risk HPV types are identified in anal cancers, high-risk types are frequently also present [Ref. 5.4: 3197].

As mentioned above, the risk factors for anal cancer in both males and females support the role of sexual transmission of HPV in anal carcinogenesis. These risk factors are notably similar to the well-known risk factors for cervical cancers, also supporting the etiologic role of HPV infection in anal carcinogenesis [Ref. 5.4: 2499, 3211].

The pathogenetic role of HPV in anal cancer is further supported by the observation that the vast majority of anal cancers are squamous cell carcinomas that are characterized by the same histologic patterns that are typically identified with other HPV-related cancers. In a large case-control study of anal cancer, for example, high-risk HPV types were associated with characteristics that are commonly associated with cervical cancers, including basaloid features, adjacent AIN, poor or absent keratinization, and predominance of small or medium neoplastic cells [Ref. 5.4: 2500]. Importantly, these histologic patterns are identical between the genders, supporting the same pathogenetic processes of anal cancer development in males and females [Ref. 5.4: 3178].

Frisch et al showed that there is similarity in the location of anal cancers in the anal canal in women and MSM compared with heterosexual males. In this study, increased high-risk HPV DNA positivity was associated with higher localization in the anal canal, with

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95% and 83% of cancers in the anal canal being HPV positive for high-risk types versus 80% and 28% of perianal skin cancers in women and men respectively [Ref. 5.4: 3178]. The similarities in localization of tumors and association with HPV may be reflective of similar modes of transmission in MSM and women [Ref. 5.4: 3174], which appear to differ from those in heterosexual males, for whom modes of anal HPV acquisition are less well understood.

Epidemiology and Natural History of Anal HPV Infection

The vast majority of studies of anal HPV in males have been done in MSM populations. An increasing body of literature has, however, demonstrated anal HPV infection in women to be more common than previously understood, findings that are consistent with the high rates of anal cancer that are observed in the female population. Women with a history of HPV-related genital tract disease are at particularly increased risk of anal HPV infection. For example, in a cross-sectional study of anal HPV infection in 102 women with histories of high-grade lower genital tract intraepithelial neoplasia or cancer, 47 of 92 evaluable subjects (51%) had detectable anal HPV. Of the 15 HPV types identified, 9 (60%) were high-risk types and 6 (40%) were low-risk or undetermined risk types [Ref. 5.4: 3181]. In some populations of women, including studies in healthy women, the prevalence of anal HPV infection is actually higher than the prevalence of cervical infection. In a cross-sectional study of 200 women for whom concurrent cervical and anal HPV PCR data were available, Palefsky et al showed higher prevalence of anal compared to cervical HPV in both HIV positive (79 vs 53%) and HIV negative women (43 vs. 24%) [Ref. 5.4: 1993]. There are data to suggest that anal HPV infections in women may clear more rapidly than cervical infections; however, some risk factors associated with delayed clearance, including tobacco smoking, are similar to those that contribute to persistence of infection in the cervix [Ref. 5.4: 3209]. Overall, the distribution of anal HPV types in women is similar to that of the cervix [Ref. 5.4: 3207].

In addition to epidemiologic data on HPV infection in women, there is evidence that heterosexual males are susceptible to HPV infection that can result in HPV-related anal cancers, albeit it at lower rates than in females and MSMs. In a cross-sectional study of HPV detection methodology in 18-40 year-old heterosexual males, anal canal HPV was detected in 17.6% of study subjects with complete sampling [Ref. 5.4: 3180], demonstrating that anal HPV infection in males is not limited to MSM. A subsequent study by the same authors, in 222 18-40 year-old non-HIV infected men with no history of sexual intercourse with men, overall prevalence of anal HPV infection was 24.8%. Of HPV infected subjects, 33.3% had a high-risk type [Ref. 5.4: 3199].

The risk factors for anal HPV infection in men and women reflect the risk factors for anal cancer that were described above [Ref. 5.4: 3199, 3211]. The natural history analysis of baseline data from Protocol 020 substudy placebo subjects was consistent with these findings, also demonstrating number of lifetime sex partners and use of tobacco products as risk factors for prevalent anal HPV detection. Notably, the analysis also identified older age as a risk factor for prevalent anal HPV infection, consistent with published reports of high prevalence rates of anal HPV in older MSMs [Ref. 5.3.5.3: 3239].

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The increased risk of high-grade AIN in individuals with persistent anal infection is well-documented [Ref. 5.4: 555, 2579], anal HPV infection being the most significant risk factor for AIN development in both males and females [Ref. 5.4: 3174, 3211]. In a prospective study, being HPV-positive for high and low-risk types was found to be associated with developing anal high-grade squamous intra-epithelial lesions among HIV-uninfected men (Odds Ratio=9.1, 95% CI: 3.3-352) [Ref. 5.4: 2579]. Detection of high-risk HPV type only was associated with high-grade lesions (Odds Ratio=4.0, 95% CI: 0.97-153). In another prospective study among HIV-uninfected men, developing anal high-grade intraepithelial neoplasia was 16.6 (95% CI 2.0-137) fold higher among those who had HPV types 16 or 18 detected [Ref. 5.4: 555].

Natural history data from placebo subjects in the MSM substudy are consistent with these findings. Notably, the incidence of AIN was higher in placebo subjects who were PCR positive at baseline to any of the four HPV vaccine types. The incidence of vaccine type-related AIN was highest among subjects who tested positive for both PCR and serology to any of the vaccine HPV types. Further type-specific analyses showed similar patterns of AIN incidence in subjects who were PCR positive, regardless of serology status, as well as in subjects who were seropositive only. Notably, the mean and median durations of anal HPV 16 and 18 infection were found to comparable to genital HPV infection duration in women, suggesting similar pathogenetic potential of HPV infection in these locations [Ref. 5.3.5.3: 3239]. **These data support the conclusion that type-specific prevention of persistent anal infection through qHPV vaccination will lead to prevention of subsequent AIN development.**

High-Grade AIN as the Obligate Precursor of Anal Cancer

The most important evidence supporting the premalignant potential of intraepithelial lesions is prospective natural history data showing evidence of progression from high-grade to invasive disease. The natural history of cervical neoplasia is well-established, and it is on the basis of the preponderance of evidence that high-grade CIN is a precursor of cervical cancer that prevention of CIN by vaccination was accepted as a basis for licensure of HPV vaccination for cervical cancer prevention [Ref. 5.4: 2936]. The data summarized in the following paragraphs demonstrate that similarly, while low-grade AIN is unlikely to progress to cancer, high-grade AIN (AIN 2 or worse) has significant malignant potential, and is a precursor for anal cancer. Analogous to CIN 3, which is cervical carcinoma in situ, AIN 3 is anal carcinoma in situ, which precedes invasive anal cancer. A more detailed summary of the literature is provided in the Integrated Summary Report: Summary of Literature Review on the Association between AIN and Anal Cancer [Ref. 5.3.5.3: 3240]. **Taken together, the evidence supports the use of high-grade AIN as an important and clinically relevant endpoint for anal cancer prevention in clinical studies and as the basis for an indication for the qHPV vaccine for the prevention of anal cancer.**

From an epidemiologic perspective, although documentation of the natural history of AIN continues to evolve, a review of the literature on anal cancer risk in patients with AIN demonstrated that virtually all studies showed a clearly elevated risk for anal cancer

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among both HIV-positive and HIV-negative patients with a history of high-grade AIN [Ref. 5.4: 2547, 2578, 2580]. The studies reviewed report annualized high-grade AIN to anal cancer progression rates ranging from 0.7% to 9.6% (or 700 to 9600 per 100,000 persons), which is dramatically increased compared to the 1.97 per 100,000 persons annual incidence of anal cancer in the general U.S. population [Ref. 5.4: 2509] [Figure 2.5: 1] and [Appendix 2.5: 2]. It should be noted that the sample sizes of these studies were often limited, some study populations were over-represented by HIV-positive patients, and the age distribution and demographic characteristics of study subjects may not reflect those in the general population; thus the reported data may not be directly comparable to general population data.

In the largest prospective study to date, which recruited 199 consecutive patients with recently treated anal condyloma (84% male; 72% HIV-positive), 7 (3.5%) of the patients developed invasive anal carcinoma (6 HIV-positive men aged 26-53 years and 1 62 year-old HIV-negative woman) over a median of 26 months (range 13-112 months after study entry). All 7 of the patients showed high-grade AIN prior to the development of carcinoma. Of 38 patients with high-grade lesions and of 7 patients with invasive carcinoma, 6 and 1, respectively, were HIV-uninfected; thus, 1 out of 6 HIV-uninfected patients with high-grade lesions developed invasive carcinoma. Having a high-grade lesion at baseline was significantly associated with developing invasive cancer (23% vs. 0.5%, $p<0.01$) [Ref. 5.4: 2547].

In another prospective study of 72 subjects with AIN 1, 2, or 3 (52 females/20 males), 8 subjects (2/10 subjects with AIN 2 and 6/45 subjects with AIN 3) developed invasive cancer over a median follow-up time of 60 months [Ref. 5.4: 2581]. The authors of this study concluded that "there is no reason to believe…that the conversion of intra-epithelial neoplasia to invasive cancer at any site should be different from any other", and "high-grade intra-epithelial neoplasia...in all anogenital sites can be a precursor to invasive malignancy…" **Taken together, these prospective data, in addition to the other studies summarized in the Integrated Summary Report on AIN progression [Ref. 5.3.5.3: 3240], suggest that individuals with a history of AIN are at a 400-1000-fold increased risk of developing anal cancer than the general population.**

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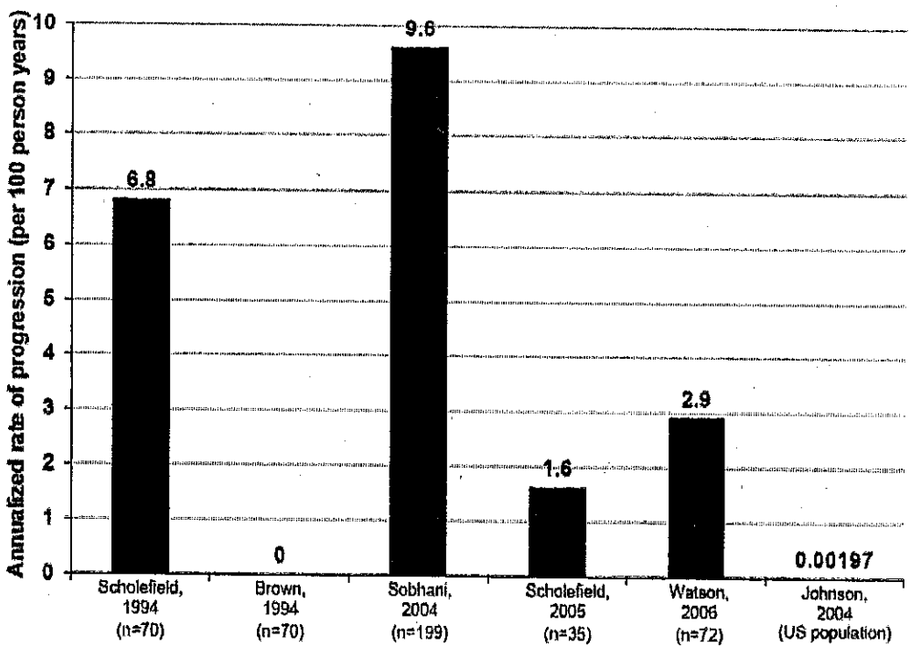
Figure 2.5: 1

Summary of the Literature on Annualized Progression Rates from AIN to Anal Cancer



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

The data supporting the relationship of high-grade AIN to anal cancer are further substantiated by convincing similarities between anal and cervical neoplastic disease. The anatomy of the anus and cervix are similar, both being characterized by a transformation zone, where the squamous and columnar linings of the anal or cervical canal meet, is characterized by immature metaplastic squamous epithelium that is highly susceptible to HPV infection and neoplastic change.

AIN 2/3 and CIN 2/3 share similar biological characteristics of progressively increasing proliferation and replacement of the normal epithelium by malignant cells with a basal morphology and large nuclear-cytoplasmic ratios, and mitoses in the more superficial cell layers [Ref. 5.4: 2476]. The two lesions are, in fact, essentially indistinguishable from a histologic standpoint [Appendix 2.5: 3]. Molecular changes such as p53 mutations and decreased apoptosis, are also shared between high-grade AIN and CIN, suggesting a common molecular pathway [Ref. 5.4: 396, 2545]. **High-grade AIN lesions are thus considered analogous to high-grade CIN [Ref. 5.4: 3233].**

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As commonly seen in cervical cancer, co-existent high-grade anal intraepithelial neoplastic changes are often identified adjacent to invasive anal cancers, showing histologic evidence of progression from the non-invasive AIN 3 (anal carcinoma in situ) to the invasive component of lesions [Appendix 2.5: 4]. As is observed with co-existent CIN and cervical cancers, studies have reported similar prevalence of high-risk HPV types in AIN and invasive anal carcinomas in surgical specimens containing both lesions. Studies of cervical and anal disease also report increasing HPV prevalence with increasing lesion severity. In a review of 111 anal surgical specimens, high-risk HPV types were detected in a progressively greater number of AIN lesions from low- to high-grade (from 56% in low-grade to 88% in high-grade) [Ref. 5.4: 3176]. As described by the study authors, this similarity in HPV prevalence between AIN and cancer, as well as the progressive increase in HPV positivity from low- to high-grade lesions is consistent with the observation that high-grade AIN is the true precursor of squamous carcinoma. When identified together, premalignant and invasive anal lesions also commonly share molecular changes [Ref. 5.4: 3178, 3179], providing further convincing evidence that AIN is equivalent to in situ carcinoma, and an obligate precursor of invasive anal cancer.

2.5.1.4.2 Rationale for Extension of Anal Indication to All Populations

The MSM substudy was performed in this population of males due to the significantly elevated risk of anal infection and disease related to sexual practices of MSM. Studying the AIN endpoint in the MSM subpopulation of the overall Protocol 020 study thus provided a higher likelihood of a successful efficacy demonstration within reasonable study timelines. As described in detail above, HPV infection and disease of the anal canal are not, however, limited to MSM. Furthermore, the pathogenesis, histopathologic, and clinical presentation of HPV-related anal disease are identical across genders and populations (women, HM, MSM). The anatomy and histology of the anal canal is identical in males and females, and there are no gender-specific characteristics of these lesions that differentiate AIN and anal cancers in men and women. AIN and anal cancer are in fact indistinguishable between the genders [Appendix 2.5: 5]. Importantly, as reviewed above, based on the clinical trials experience to date, there is no evidence that efficacy of the qHPV vaccine is gender-dependent. **Demonstration of qHPV vaccine efficacy against AIN should thus reflect efficacy in the general population.**

As reviewed in the detailed literature review on the association between AIN and anal cancer, most health authorities accept that AIN is a precursor to invasive anal carcinoma and recommend cancer prevention strategies including anal Pap smears or anoscopy in individuals at increased risk [Ref. 5.3.5.3: 3240]. Although there are no standardized guidelines, the American Society of Colon and Rectal Surgeons includes women with a history of genital warts or precancerous changes of the cervix, in addition to HIV positive men and MSMs, as being of particularly high risk for anal cancer.

Taken together, these considerations support a broadly applicable anal cancer indication in men and women.

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2.5.1.4.3 Approaches to the Evaluation of qHPV Vaccine in the Prevention of AIN and Anal Cancer

Introduction – Protocol 020 Substudy

Protocol 020 was a randomized, placebo-controlled, international, multicenter, double-blind safety, immunogenicity, and efficacy study operating under in-house blinding procedures. The "Intensive Intra-anal Evaluation in MSM" substudy enrolled 602 men having sex with men (MSM) ages 16-26 years. Substudy subjects were enrolled at selected sites with expertise in High Resolution Anoscopy, and all subjects were randomized in a 1:1 ratio to receive either qHPV vaccine or placebo at Day 1, Month 2, and Month 6.

Efficacy. The comprehensive design of the MSM substudy, with intra-anal Pap testing and anal sampling for HPV PCR detection at 6 month intervals, in addition to the use of high resolution anoscopy for evaluation of abnormal cytology, allowed for complete ascertainment of HPV-related anal disease in the MSM study population. In addition to external genital testing, MSM subjects also underwent anal swabbing for HPV PCR and Papanicolaou (Pap) testing at 6 month intervals. All anal lesions identified on physical examination or anoscopy that, in the opinion of the investigator, were possibly, probably, or definitely HPV-related, or whose relationship to HPV infection could not be determined, were biopsied. MSM subjects with abnormal anal Pap tests, defined as anal Pap test result of atypical squamous cells of undetermined significance (ASC-US) or worse, were referred to high resolution anoscopy (HRA). In addition, HRA was performed if the subject presented with perianal warts. All areas of abnormality were biopsied for histologic examination and HPV PCR testing.

The pathology infrastructure used in Protocol 020 was identical to the infrastructure used in the Phase II/III efficacy studies in Young Adult Women. All biopsies were processed through the program's central laboratory, which provided histopathologic diagnoses for the purposes of subject management. The blinded, independent Pathology Panel provided histopathologic diagnoses for the purpose of defining study endpoints [Sec. 9.5.2.2] and [App. 16.1.10.4] of [Ref. 5.3.5.1: P020]. HPV typing was performed using Thinsection PCR procedures at the program's central PCR laboratory. Laboratory personnel, the independent Pathology Panel, study investigators and site personnel, and subjects were blinded to the subjects' vaccination allocation throughout the entire study period. Thus, all personnel who were responsible for the ascertainment and confirmation of efficacy endpoints were blinded for the duration of the study.

The MSM substudy endpoint was AIN or anal cancer related to HPV 6, 11, 16 or 18. As pre-specified in the protocol, the fixed event design mandated that the analysis of the MSM substudy endpoint was to be conducted after 17 cases were observed. Because the target number of cases had not been observed at the time of the frozen file cut-off for the original Clinical Study Report, a summary of cases, with no analysis, was provided. The primary analysis was thus performed at the end of the study, at which time the median duration of post-vaccination 1 follow-up for the MSM study population was 32.2 months.

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Immunogenicity. Serum samples were collected on Day 1 prior to vaccination and at Months 7, 24, and 36, for the detection of anti-HPV antibodies. Immunogenicity data were used to bridge efficacy to adolescents evaluated in previous Phase III studies.

Safety. Subjects were observed for 30 minutes after each vaccination. All subjects were followed up for adverse experiences (AEs) using a vaccination report card (VRC). New medical history was collected throughout the study.

This clinical summary is focused on the analyses of the MSM substudy. Brief summaries of updated results for the primary analyses of vaccine efficacy (EGL endpoint), immunogenicity, and safety are also provided.

2.5.1.5 Overview of the Clinical Development Program for the qHPV Vaccine

Quadrivalent HPV vaccine efficacy was first studied among women 16 to 26 years of age. Efficacy was bridged to adolescent females by demonstrating non-inferiority of anti-HPV levels (geometric mean titers [GMTs] and seroconversion at 4 weeks Postdose 3) in female adolescents 9 to 15 years of age to anti-HPV levels in female adults. Following initiation of efficacy studies in women, Protocol 020, a clinical study to assess the efficacy, immunogenicity, and safety of qHPV vaccine in men 16 to 26 years of age, was implemented. Efficacy of the vaccine against HPV 6/11/16/18-related external genital lesions was demonstrated in the overall study, and was bridged to adolescent males by demonstrating non-inferiority of anti-HPV levels in male adolescents 9 to 15 years of age to anti-HPV levels in male adults.

Results from the MSM substudy of Protocol 020, and a summary of updated results from the primary efficacy, safety and immunogenicity analyses of the overall study are presented here.

2.5.1.6 Standard Research Procedures

The study methodology, subject selection, selection of endpoints, immunologic assays, and assessment of safety were in accordance with established practices for conducting vaccine studies. Key facets of Protocol 020 are described in [Sec. 2.5.1.4.3] and in the clinical study report (CSR) [Ref. 5.3.5.1: P020].

Statistical Analyses. Statistical analyses for Protocol 020 were pre-specified in the Statistical Analysis Plan (SAP) and Protocol 020-04, which are included in the CSR. The SAP was approved in 2007, before unblinding of data. All analyses were performed using standardized and validated methods.

2.5.1.7 Good Clinical Practices

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.

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