

Estudio no.: Ref. 4.2.3.5.2: TT037030 (cont.) (7/8)

6.7.5 Toxicidad reproductiva y del desarrollo: Efectos sobre el desarrollo embrionario y fetal

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	Grupo de control 1 (SSA)	Grupo de control 2 (AAM)	Grupo 1 con vacuna (2 dosis)	Grupo 2 con vacuna (4 dosis)
	Hembras F₁ (después del destete):			
No. evaluadas después del destete	44	43	44	42
No. muertas o sacrificadas moribundas	0	0	0	0
Observaciones clínicas	-	-	-	-
Cambio en el peso corporal antes del apareamiento (% ^a)	187	200	-6.5	-1.5
Peso corporal gestacional, el día 20 de la gestación (g)	421	441	411	434
Media de edad a la abertura vaginal (días)	32.7	32.7	32.4	31.9
Función sensorial	-	-	-	-
Actividad motora	-	-	-	-
Aprendizaje y memoria	-	-	-	-
No. medio de días antes del apareamiento (periodos de 4 días)	1.33	1.10	1.14	1.29
No. de hembras con esperma positivo	21	21	21	21
No. de hembras gestantes	21	21	21	21
No. medio de implantaciones	16.8	18.0	15.8	16.7
% de supervivencia después de la implantación (MC)	91.9	93.1	92.6	92.5

^a Los valores de control son la media de los aumentos absolutos de la semana 1 a la 8 después del destete. Los valores de los grupos con tratamiento son el cambio porcentual respecto al Control 2.

MC = media de la camada; SSA = solución salina amortiguada; AAM = adyuvante de aluminio de Merck (placebo de control).

- = sin hallazgos destacables.

**2.6.7.5 Toxicidad reproductiva y del desarrollo:
 Efectos sobre el desarrollo embrionario y fetal**

Estudio no.: Ref. 4.2.3.5.2: TT037030 (cont.) (8/8)

	Respuesta inmune a los antígenos de la vacuna															
	Grupo de control 1 (SSA)				Grupo de control 2 (AAM)				Grupo 1 con vacuna (2 dosis)				Grupo 2 con vacuna (4 dosis)			
	Media geométrica del título de anticuerpos específicos por serotipo (mUM/ml) ^a				Media geométrica del título de anticuerpos específicos por serotipo (mUM/ml) ^a				Media geométrica del título de anticuerpos específicos por serotipo (mUM/ml) ^a				Media geométrica del título de anticuerpos específicos por serotipo (mUM/ml) ^a			
	VPH-6	VPH-11	VPH-16	VPH-18	VPH-6	VPH-11	VPH-16	VPH-18	VPH-6	VPH-11	VPH-16	VPH-18	VPH-6	VPH-11	VPH-16	VPH-18
Antes de la prueba	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hembras F ₀	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cobertura (Día 1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hembras F ₀	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Día 21 G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hembras F ₀	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Día 21 G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fetos	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Día 21 G -	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Razón fetos/hembras F ₀	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Día posnatal 21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hembras F ₀	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Día posnatal 21	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Crias F ₁	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(1/sexo/carnada)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Día posnatal 21 -	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Razón fetos/hembras F ₀	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Día posnatal 77	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Crias F ₁	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(1/sexo/carnada)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
* Media geométrica de los títulos (todos los títulos se convirtieron en In(título)) = EXP (promedio [ln título]).																
- = por debajo del valor de corte (mUM/ml): VPH-6 = 20; VPH-11 = 16; VPH-16 = 20; VPH-18 = 24.																
G = de la gestación; N/A = no aplicable.																

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2.6.7.6 Tolerancia local (1/1)

Material de prueba: L-000931225

Especie/cepa	Método de administración	Dosis	Sexo y no. por grupo	Hallazgos destacables	Número del estudio
Conejo/blanco de Nueva Zelanda	IM (todos los conejos recibieron inyecciones separadas de cada material de prueba y de control)	0.5 ml por sitio de 40/80/80/40 µg/ml o bien 80/80/80/80 µg/ml o bien 160/160/80/160 µg/ml o bien 160/80/160/80 µg/ml de PPV de VPH de los tipos 6, 11, 16 y 18 Se administró una sola dosis, con un período de observación de 14 días (autopsias los días 4 y 14)	8H y 8M	El grado de reacción histomorfológica local observada estuvo dentro de los límites aceptables, y fue similar a los sitios de inyección del adyuvante de aluminio de control (usado como placebo). Nivel sin efectos adversos observados: 0.5 ml de 160/160/80/160 µg/ml o 160/80/160/80 µg/ml de PPV de VPH de los tipos 6, 11, 16 y 18	Ref. 4.2.3.6: TT992669

IM = intramuscular
H = hembra(s)
M = macho(s)

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2.6.7.7 Otros estudios de toxicidad (1/2)

Material de prueba: L-000931225

Especie/cepa	Método de administración	Duración de la administración	Dosis	Sexo y no. por grupo	Hallazgos destacables	Número del estudio
Ratas/ Sprague-Dawley	IM	2, 3 o 4 dosis en el curso de 25 semanas	0.2 ml por dosis de 40/80/80/40 µg/ml de PPV de VPH de los tipos 6, 11, 16 y 18	5 hembras por grupo Grupo de control 1: Adyuvante de aluminio de control (placebo) Grupo de control 2: Solución salina amortiguada con fosfato Grupo 1 con vacuna: Dos dosis, en las semanas 1 y 11 Grupo 2 con vacuna: Tres dosis, en las semanas 1, 4 y 14 Grupo con vacuna 3: Cuatro dosis, en las semanas 1, 4, 7 y 17	La vacuna fue generalmente bien tolerada durante un periodo de 25 semanas. No hubo muertes ni signos físicos relacionados con el tratamiento. Hubo una ligera reducción relacionada con el tratamiento en el incremento medio de peso corporal en las hembras que recibieron 4 dosis, en comparación con los grupos de control con placebo y con solución salina amortiguada. Después de la inmunización, en las ratas se produjeron anticuerpos contra las PPV del VPH de los tipos 6, 11, 16 y 18.	Ref. 4.2.3.7.7: TT027066

(Continúa)

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2.6.7.7 Otros estudios de toxicidad (2/2)

Material de prueba: L-000931225

Especie/cepa	Método de administración	Duración de la administración	Dosis	Sexo y no. por grupo	Hallazgos destacables	Número del estudio
Ratas/Sprague-Dawley	IM	2 dosis a intervalos de 3 semanas, con un período de observación de 5 semanas	0.2 ml por dosis de 40/80/80/40 µg/ml de PPV de VPH de los tipos 6, 11, 16 y 18	5 hembras por grupo	<p>Hallazgos destacables</p> <p>La administración intramuscular de dos dosis de GARDASIL®, la vacuna recombinante contra el VPH (tipos 6, 11, 16, 18), aplicadas a intervalos de 21 días en ratas hembra, fue bien tolerada. No hubo muertes, signos físicos ni efectos sobre el aumento de peso corporal. Las muestras de suero fueron positivas para anticuerpos contra el VPH de los cuatro serotipos presentes en la vacuna.</p>	Ref. 4.2.3.7.7: TT037036

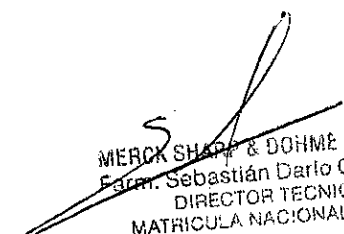
IM = intramuscular

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2.5 Clinical Overview


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Human Papillomavirus Quadrivalent [Types 6, 11, 16, 18] Vaccine, Recombinant - Efficacy in Men 1
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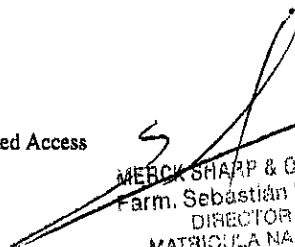
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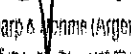
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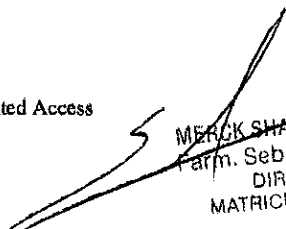
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2.5 Clinical Overview

2.5.1 Product Development Rationale

2.5.1.1 Pharmacologic Class

Quadrivalent Human Papillomavirus (HPV) (Types 6,11,16,18) recombinant vaccine, also referred to as qHPV vaccine, 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 infection caused by HPV types targeted by the vaccine. All protocols presented by number are protocols that studied qHPV vaccine.

2.5.1.2 Chemical and Pharmaceutical Properties

The qHPV vaccine is prepared from the highly purified 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. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection. Each 0.5-mL dose is formulated to contain 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein. The quadrivalent final container product is a sterile suspension for injection in a single-dose vial or a prefilled syringe. For each image, the fill volume permits administration of 0.5 mL of vaccine for intramuscular injection. The qHPV vaccine is not a live virus vaccine. It contains no viral deoxyribonucleic acid (DNA). It is incapable of causing infection.

2.5.1.3 Proposed Indications

The data presented in this supplemental Application demonstrate the efficacy of qHPV vaccine when administered to 16- to 26-year-old men [Sec. 2.7.3.1.2.5-exgenlesions]. Data further demonstrate that the immune response to qHPV vaccine in 9- to 15-year-old boys is non-inferior to the immune response in 16- to 26-year-old men [Ref. 5.4: 2272].

Accordingly, the current Application proposes the following indication for the qHPV vaccine in men and boys:

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.

2.5.1.4 Scientific Background

2.5.1.4.1 Public Health Burden of HPV-Related Clinical Disease and Infection in Young Men

HPV is one of the most common sexually transmitted infections. As in women, genital HPV acquisition in men appears to occur shortly after sexual debut with the prevalence and incidence of genital infection remaining constant through adulthood. HPV infection can result in anogenital diseases, including anogenital warts, intraepithelial neoplasia, and carcinoma of the penis and anus. These diseases are associated with substantial morbidity and mortality in men as summarized in a comprehensive literature review [Ref. 5.3.5.3: 2632] and corroborated by the data from placebo subjects in Protocol 020 ("A

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Study to Evaluate the Efficacy of qHPV Vaccine in Reducing the Incidence of HPV 6-, 11-, 16-, and 18-Related External Genital Warts, PIN, Penile, Perianal and Perineal Cancer, and the Incidence of HPV 6-, 11-, 16-, and 18-Related Genital Infection in Young Men", see [Sec. 2.5.1.4.4], [Ref. 5.3.5.3: 2633]. In addition, HPV causes recurrent respiratory papillomatosis (RRP) and is associated with head and neck cancers. Data in this Submission focus on external genital lesions (EGLs), which are mostly external genital warts (EGWs). Data on penile/perianal/perineal intraepithelial neoplasia (PIN) or anal intraepithelial neoplasia (AIN) and associated cancers provide important supportive information, but are not the focus of this file, due to small number of PIN cases and insufficient number of AIN endpoints to analyze efficacy against AIN. The burden of HPV disease in men is summarized briefly below.

Genital Warts. Condyloma acuminata, or anogenital warts, are the most common manifestation of HPV in men. About 1% of sexually active adults in the United States (US) have been estimated to have genital warts [Ref. 5.4: 1889]. Among men, about 80-95% of anogenital warts are positive for HPV 6 and/or 11 [Ref. 5.4: 1998, 2490, 2517, 2520, 2574]. Occurrence of genital warts peaks in young adulthood in men. For example, based on private health care claims data in the US, the highest prevalence was reported at ages 25-29 years, with prevalence of 5 per 1000 person years [Appendix 2.5: 1], [Ref. 5.4: 827].

While data are limited, the incidence of genital warts appears to be increasing. According to the US National Disease and Therapeutic Index, 422,000 initial visits due to genital warts occurred among men and women in 2006 [Ref. 5.4: 2630]. From 2005 to 2006 alone, the increase was by 18%. Incidence of new claims due to genital warts among privately insured 15 to 59 year old individuals in the US increased by 70% from 1998 (1.2 per 1000 person years) to 2001 (2.1 per 1000); rates increased in both genders [Appendix 2.5: 2], [Ref. 5.4: 2511]. Similar increasing trends were also observed in the United Kingdom [Ref. 5.4: 2502].

In Protocol 020, where a diverse group of men were enrolled, the annual incidence of genital warts among susceptible heterosexual men (HM) in the placebo group was 1.0 per 100 person years, and when HPV status at Day 1 was not considered, incidence was 1.5 per 100 person years [Ref. 5.3.5.3: 2633]. Extrapolating the latter incidence rate to the US male population of 16-26 years of age (2008 projection) suggests that approximately 350,000 new cases of genital warts occur every year among men in this age group. Among men having sex with men (MSM) in the placebo group, the incidence rate was almost three times higher (2.8 and 4.7 per 100 person years, among susceptible MSM and all MSM, respectively). Furthermore, these incidence rates from Protocol 020 may underestimate the true incidence of genital warts, because men with >5 sexual partners before enrollment were excluded. Neither condom use nor circumcision appeared to afford any protective effect against prevalent or incident HPV infection [Ref. 5.3.5.3: 2633].

Corroborating findings in the published studies, in Protocol 020 HPV 6 and 11 infections were significantly associated with development of genital warts. Of all external genital

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lesions, the majority of which were condyloma, 87% were HPV 6/11/16/18 positive. Within 12 months of an incident HPV 6 detection, 13.8% of HM subjects and 9.1% of MSM subjects developed an external genital wart; among subjects with incident HPV 11 detection, this progression was observed in 19.1% in HM and 21.1% in MSM. [Ref. 5.3.5.3: 2633].

Genital warts cause pain, discomfort, and pruritis, and they are highly infectious. They can also take the more aggressive form of giant condylomata (Buschke-Lowenstein tumors). Genital warts have been shown to cause significant social stigmatization and psychosocial burden in the patients [Ref. 5.4: 1512, 2586]. Myriad treatments are available, from prescription topical agents such as imiquimod, podophyllins, to more aggressive modalities such as intralesional interferon, cryotherapy, electrocautery, laser and surgical excision. These treatments are not optimal in that they carry risks to varying degree for scarring, disfigurement, pain, and relapse. Indeed, despite treatment, condyloma can recur at a rate of 10% to 90%, varying by treatment method [Ref. 5.4: 986] and multiple treatments are often required. Based on claims data from privately insured male patients in the US, on average, genital warts episodes last 102.6 (95% confidence interval (CI): 77.8-127.4) days, and patients have 3.1 (95% CI: 2.8-3.5) physician visits, with an estimated total cost of \$477 (95% CI: \$365-\$590) for health care [Ref. 5.4: 827]. Costs increase significantly for men with more recalcitrant cases of HPV infection, where repeat electro-, laser-, or cryosurgery or intralesional interferon may be required, and costs of intralesional interferon can exceed the \$2000-5000 range [Ref. 5.4: 2585], and the side effects include constitutional symptoms such as fever and malaise.

Conservative estimates of US national direct medical costs annually due to anogenital warts among both men and women have ranged between about \$170 million and \$225 million [Ref. 5.4: 2495, 2508]. These estimates have not included health care visits that could take place outside the health care systems analyzed (i.e., physicians with private practice or providers of privately insured patients), such as sexually transmitted disease (STD) clinics, family planning and college student health clinics. The indirect costs of social stigmatization and psychosocial burden are also not factored into these estimates. Studies of indirect costs related to anogenital warts are not available, meaning the true economic burden of genital warts is probably considerably higher than what has been estimated; however, the extent of actual difference is unknown.

Genital warts provide the commonest EGL identified in Protocol 020, and compelling data on vaccine efficacy are included in this application. However, HPV infection is associated with a variety of other conditions, including premalignant and malignant neoplasms, as well as other conditions such as RRP. While only limited or no data are provided in this application to support a role for vaccine efficacy in these conditions, these conditions (outlined below) provide other potential benefits of an HPV vaccine from a public health point of view.

Penile/Perianal/Perineal Cancer. In high-income countries, penile cancer is a relatively rare disease, but is associated with considerable morbidity and mortality in the patients.

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Human Papillomavirus Quadrivalent [Types 6, 11, 16, 18] Vaccine, Recombinant - Efficacy in Men

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About 40-50% of penile cancers are related to HPV [Ref. 5.4: 2498], similar to what has been reported for vulvar carcinoma. HPV 16 is the most frequently identified type; HPV 16 and 18 account for greater than 60% of HPV detected [Ref. 5.4: 1663, 2501, 2506, 2516]. In high-income countries, reported penile cancer incidence varies between 0.3 and 2.2 per 100,000 [Ref. 5.4: 2516]. In low-income countries, penile cancer is a larger public health problem. Reported incidence ranges between 3 to 8% from rural parts of India, Brazil, and Uganda [Ref. 5.4: 2513, 2515, 2528]. It is estimated that in 2002, globally about 26,000 cases of penile carcinoma occurred, of which ~6,600 were related to HPV 16/18 [Ref. 5.4: 2516].

Patients with penile carcinoma seek health care later than patients with other types of cancer, due to fear, embarrassment, ignorance, and/or neglect. Start of treatment can be delayed for >1 year in up to 50% of patients [Ref. 5.4: 2513]. In the US, fatality has been reported as 41% [Ref. 5.4: 2518]. Age, race, and stage of disease at diagnosis are associated with survival. Penectomy is associated with substantial sexual dysfunction and psychosocial burden [Ref. 5.4: 2497, 2629].

PIN 1 is low grade and PIN 2/3 are high grade dysplastic lesions. HPV positivity has been reported in up to 84% of PIN 1 cases [Ref. 5.4: 1018] and over 90% of PIN 3 cases [Ref. 5.4: 1018, 2540, 2541]. HPV 16 is the most common type detected. Erythroplasia of Queyrat (EQ), Bowen's disease (BD), and bowenoid papulosis (BP) are clinical presentations of high-grade PIN. As high as 33% of BD and EQ, has been associated with invasive cancer [Ref. 5.4: 2594, 2596]. BP rarely progresses to malignancy.

Anal Cancer. Anal cancers were estimated to be responsible for 40,000 new cases in men globally in 2002 [Ref. 5.4: 2501]. In the US, nearly 4500 new cases and 589 deaths due to anal cancer were reported in 2004, of these about 40% were among men [Ref. 5.4: 2525]. Studies suggest that anal cancer incidence has been increasing in several parts of the world [Ref. 5.4: 2486, 2509]. In the US, age-adjusted incidence of invasive cancer among men increased from 0.97 per 100,000 population in 1973-1979 to 1.59 per 100,000 population in 1994-2000, representing a 64% increase in ~2 decades [Ref. 5.4: 2509].

MSM and human immunodeficiency virus (HIV) infected individuals are at higher risk of developing anal cancer. Before the HIV epidemic, incidence of anal cancer among MSM was estimated as 35 per 100,000, similar to cervical cancer rates before introduction of cervical screening [Ref. 5.4: 2512]. In the highly active anti-retroviral therapy era, the incidence of anal cancer has not declined. Prognosis of anal cancer is poor in HIV-infected patients [Ref. 5.4: 2526].

The great majority of anal cancers are squamous cell carcinoma (SCC) and HPV infection is strongly associated with anal cancer [Ref. 5.4: 1156, 2499, 2500, 2523]. Anal canal SCCs were found HPV positive in 75% of cases in men [Ref. 5.4: 2507]. HPV 16 (73%) and HPV 18 (5%) are the most commonly associated types [Ref. 5.4: 2507]. The concept of high-grade AIN as a precursor of invasive anal SCC is supported by the association of high-risk HPV types with developing high-grade AIN, coexistence of high-

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grade AIN adjacent to invasive cancer, high-grade AIN showing biological and molecular characteristics that resemble anal cancer, and more importantly, by prospective studies assessing progression to invasive cancer among patients with high grade AIN [Ref. 5.4: 555, 2547, 2578, 2579, 2580, 2581].

Head and Neck Cancers. Approximately 560,000 new cases of head and neck squamous cell cancers (HNSCC) and 250,000 deaths due to HNSCC are reported annually worldwide. Overall, 2/3 of HNSCC cases occur in men. Oropharyngeal squamous cell carcinomas (OPSCC) that tend to occur in young, non-smoker/non-drinker men account for approximately 24-36% of OPSCCs worldwide. Oral HPV infection has been associated with a significantly elevated risk for development of OPSCC, with a reported odds ratio of 14 [Ref. 5.4: 2110]. Seropositivity for HPV type 16 L1 has been shown to be associated [Ref. 5.4: 384, 2110]. HPV 16 is detected in >90% of HPV-positive OPSCC cases [Ref. 5.4: 2439].

Recurrent Respiratory Papillomatosis. RRP is a rare, but severe disease that occurs both in children and adults. It is manifested by warts in the respiratory tract, most often in the larynx, and tends to recur despite repeated treatment efforts and can lead to death by blocking the airway. RRP is primarily caused by HPV types 6 and 11. Peak ages of disease occurrence are preschool age and young adulthood (20-40 years). A higher proportion of adult RRP patients are men [Ref. 5.4: 1628].

Role of Men in HPV Transmission to Women. HPV is a sexually transmitted virus. The role of men as vectors transmitting HPV has been suggested in prospective studies that identified an association between women's number of sexual partners and developing HPV infection and/or cervical neoplasia [Ref. 5.4: 775, 1828, 2533]. Other studies have shown the association between men's sexual behavior and cervical cancer, independent of sexual behavior of the women [Ref. 5.4: 381, 2488, 2492, 2493, 2522]. Several prospective studies have shown high level of HPV concordance between couples who recently became infected indicating transmission of HPV between the couples [Ref. 5.4: 2503, 2530, 2534]. These data consistently support the sexually transmitted nature of HPV and the role of men in infecting women, who subsequently can develop HPV-related anogenital cancers and warts. Although the SPONSOR is not seeking a claim for prevention of transmission with this application, based on these various lines of evidence it is expected that decreasing the risk of HPV infection in men through vaccination should decrease the risk of infection in their sexual partners, thereby providing additional public health benefit.

2.5.1.4.2 HPV Virology and Pathophysiology of HPV Infection

The Papillomavirus family has been organized into species groupings based on the major capsid protein, L1, sequence homologies. Members of the papillomavirus species share ~75% L1 gene sequence homology as well as a common pathophysiology. Individual types within a given HPV species may have up to 90% homology.

The 40 HPV types that infect the genital tract are classified as high-risk types that can cause cancer or low-risk types that cause dysplasia that rarely progresses to cancer [Ref.

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5.4: 685]. HPV 16 causes 50 to 55% of cervical cancers, nearly 75% of anal cancers and HPV 18 causes 15 to 20% of cervical cancers and 5% of anal cancers. Of HPV-related vulvar, vaginal, penile, and oropharyngeal cancers 60-95% have been associated with HPV 16/18. HPV 6 and HPV 11 are the most common low-risk HPV types, causing about 80 to 95% of genital warts [Ref. 5.4: 342, 1304, 1767, 2516].

2.5.1.4.3 Epidemiology of HPV Infection – Impact on Clinical Trial Design

Based on a limited number of studies conducted in the pediatric population, the prevalence and incidence of HPV-related genital diseases (such as cervical cancer and its precursors and genital warts) are virtually non-existent in children under the age of 10 years. Genital infection rises in adolescents soon after sexual debut. The median age of sexual debut is ~16 years in most countries [Ref. 5.4: 824, 1091, 1124]. By 5 years after sexual debut, ~50% of young women will have been infected with at least one of the 40 genital HPV types [Ref. 5.4: 1716, 1889]. Studies suggest a similar infection pattern in men [Ref. 5.4: 744]. The peak incidence of HPV infection occurs in young adults. Hence, the efficacy of the qHPV vaccine was first evaluated in 16- to 26-year-old women, followed by an efficacy evaluation in 16- to 26-year-old men.

The qHPV vaccine is meant to be a prophylactic vaccine. As efficacy trials in children are not feasible, immunogenicity studies were conducted in children below the age of 16 years. Vaccine efficacy in 9- to 15-year-old girls was inferred based on a demonstration of the robust immunogenicity of the qHPV vaccine among females in this age range and bridging immunogenicity data to studies in adult females. A similar approach of immunobridging has been followed for the male population in this Submission.

2.5.1.4.4 Approaches to the Evaluation of qHPV Vaccine in Young Men

2.5.1.4.4.1 Introduction – Protocol 020

Protocol 020 was a randomized, placebo-controlled, international, multicenter, double-blind safety, immunogenicity, and efficacy study operating under in-house blinding procedures. Approximately 4040 young men who met the eligibility criteria were to be enrolled in the study. These 4040 men were to include:

- Approximately 3450 HM aged 16 to 23 years;
- Approximately 590 MSM aged 16 to 26 years. These subjects were enrolled at selected sites to participate in the "Intensive Intra-anal Evaluation in MSM" substudy.

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. Protocol 020 was designed to accurately detect all HPV infection and HPV-related penile/perianal/perineal lesions in all subjects and, in addition, anal lesions in MSM. Subjects underwent genital inspection and collection of penile/perianal/perineal swabs for HPV polymerase chain reaction (PCR) at 6 month intervals. The MSM population also underwent anal swabbing for HPV PCR and Papanicolaou (Pap) testing

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at 6 month intervals. All anogenital lesions 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. This laboratory provided histopathologic diagnoses for the purpose 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: P020V1]. HPV typing was performed using Thinsection PCR procedures at the program's central PCR laboratory. For the purpose of endpoint determination, the laboratory personnel, the independent Pathology Panel, the investigators, the site personnel, and subjects were blinded to the subjects' vaccination allocation throughout the entire study period. Thus, all personnel who are responsible for the ascertainment and confirmation of efficacy endpoints are blinded for the duration of the study.

Protocol 020 uses the following primary endpoint for evaluation of efficacy of the qHPV vaccine:

- 1. External genital warts, penile/perineal/perianal/perineal intraepithelial neoplasia, or penile/perianal/perineal cancer related to HPV 6, 11, 16 or 18 (primary endpoint)

In addition, the following secondary endpoints are being evaluated:

- 1. Persistent HPV 6, 11, 16, or 18 infection - DNA detection at two consecutive visits 6 months apart.
- 2. HPV 6, 11, 16, or 18 DNA detection at one or more visits

The study employed a fixed event design. A single primary analysis of efficacy was performed after at least 32 cases of the primary efficacy endpoint had been observed, of which 23 must have occurred outside of the MSM substudy.

The endpoint for the MSM substudy is:

- 1. Anal intraepithelial neoplasia or anal cancer (in MSM) related to HPV 6, 11, 16 or 18 (MSM substudy endpoint).

The analysis of the MSM substudy endpoint will be conducted after 17 cases have been observed. As pre-specified in the protocol, since the target was not met at the time of the primary analysis, the analysis of the MSM substudy endpoint will be the subject of a separate report [Ref. 5.4: 2599]. Laboratory personnel, pathology panel members, site investigators and personnel, and study subjects will remain blinded to treatment assignments throughout the study. Thus, any investigators or technicians who are

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responsible for the ascertainment and confirmation of efficacy endpoints will remain blinded and the integrity of the MSM substudy endpoint will not be compromised.

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. In addition, 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). In addition, new medical history was collected throughout the study.

The findings presented in this clinical summary represent the primary analyses of vaccine efficacy, immunogenicity, and safety.

2.5.1.4.4.2 Study Endpoints in Efficacy Studies of qHPV Vaccine in Young Men

The primary efficacy endpoint is the incidence of HPV 6-, 11-, 16-, and 18-related external genital warts, penile/perianal/perineal intraepithelial neoplasia, and/or penile, perianal, or perineal cancer (i.e., external genital lesions). The study's secondary endpoints are the incidence of HPV 6-, 11-, 16-, or 18-related persistent infection and detection of HPV 6, 11, 16 or 18 DNA on at least 1 post vaccination visit. These endpoints were chosen based on the following considerations:

- Genital warts represent the most common clinical manifestation of HPV infection in men. The rates of genital warts appear to be increasing. While these lesions are generally benign, they cause a significant amount of pain, embarrassment, and discomfort. They are highly infectious. Furthermore, treatment of these lesions is costly, painful, and often unsuccessful.
- Although rare, penile cancer is associated with significant morbidity and mortality. As with other HPV related anogenital cancers, they are considered to be preceded by precancerous lesions.
- In general persistent infection with high-risk HPV types in the anogenital area has been associated with progression to genital warts and precancerous lesions.
- At the time of study design, natural history of HPV infection in men had not been well-defined. Some data had indicated that duration of HPV infection in men might be shorter than that observed in women. In order to better understand the course of HPV infection in men, and vaccine impact on HPV DNA detection with shorter than 6 months duration (i.e., the planned visit interval in the study), the analysis of DNA detection on at least one visit was included.

2.5.1.4.4.3 Issues Surrounding the Study of qHPV Vaccine in Young Men

Several studies had been conducted to detect HPV in men, sampling different areas in the anogenital region, using various devices [Ref. 5.4: 449, 527, 923, 925, 1076, 1878]. Protocol V501-017 was a probe study to evaluate anogenital specimen collection techniques in MSM aged 18 to 80 years. The study included collection of serum for

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detection of HPV antibodies, urine, semen, specimens from the penis, scrotum, perianal and anal region, examination for external genital lesions, anal cytology, and high-resolution anoscopy (if indicated). No vaccinations were administered. Two instruments were used in combination as a single device to collect specimens from each anogenital region. The first instrument was a sterilized LACROSS™ nail file. The second instrument was a DACRON™ swab wetted with sterile saline. The file was used first, followed by the DACRON™ swab. The combination device of the file/swab was only used on the penile shaft, scrotum, coronal sulcus, and perianal region. For specimen collection within the foreskin, the wetted swab was used alone. The sampling technique using file and swab was found to be effective in detection of HPV DNA in the anogenital region of MSM. Information obtained from this study [Ref. 5.3.5.4: 2598], along with supportive data from the literature formed the basis of the sampling technique used in Protocol 020.

2.5.1.5 Overview: Clinical Development Program for 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) among female adolescents 9 to 15 years of age to anti-HPV levels among female adults. Following initiation of efficacy studies in women, a clinical study to assess the efficacy, immunogenicity, and safety of qHPV vaccine in men 16 to 26 years of age (Protocol 020) was implemented. The required number of cases had been accrued in study visits in which swab specimens were collected as of 30-May-2008 and biopsy specimens were collected as of 29-Aug-2008, with data available as of 11-Oct-2008. In addition, anti-HPV levels (GMTs and seroconversion at 4 weeks Postdose 3) from adolescent boys 9-15 years of age were compared with anti-HPV levels in men 16-26 years of age with the purpose of immunobridging. Results from these analyses are presented herein.

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 the established practices for conducting vaccine studies. Key facets of Protocol 020 are described in [Sec. 2.5.1.4.4.1] and in the clinical study report (CSR) [Ref. 5.3.5.1: P020V1].

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

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treatment of human subjects that were in place at the time the trials were performed.

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. 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 describing the pharmacokinetic and pharmacodynamic properties of qHPV vaccine were conducted in support of this supplemental Application. Clinical pharmacology studies are not routinely conducted as part of the evaluation of vaccines as mentioned in the Committee for Medicinal Products for Human Use (CHMP) "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

2.5.4 Overview of Efficacy and Immunogenicity

Protocol 020 contributes efficacy and immunogenicity data in young adult men ages 16 to 26 years and provides clear evidence of the prophylactic efficacy of qHPV vaccine in the prevention of HPV-associated EGL in men [Sec. 2.7.3.1.2.5-exgenlesions], [Sec. 2.7.3.2.3-exgenlesions]. In order to immunobridge the efficacy results from men in Protocol 020 to boys, immunogenicity data in 9- to 15-year-old boys from Protocols 016 and 018 were utilized [Sec. 2.7.3.2.4-exgenlesions].

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: 3] and [Appendix 2.5: 4].

- 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 the case count 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 and the case count 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. 9.5.4.1.1] of [Ref. 5.3.5.1: P020V1] seronegative to HPV 6, 11, 16, 18, and had a negative anal Pap test at Day 1 (in the MSM). The case count started after Day 1.

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- The Full Analysis Set (FAS) included everyone randomized into the study (including those with prevalent infection [i.e. HPV infection present at Day 1] and disease with any HPV type) and received at least one dose of vaccine. The case count started after Day 1.

2.5.4.1.1.1 Populations Used in Prophylactic Efficacy Analyses

Three populations were used in assessing prophylactic efficacy of the qHPV vaccine: PPE, HNRT, and FAS. The primary efficacy analysis for the prophylactic efficacy of the qHPV vaccine utilized the PPE population since this allowed measurement of the full benefit of qHPV vaccine in persons who were naïve to the relevant vaccine HPV type through the completion of 3-dose vaccination regimen. Full vaccine benefit is not expected until after the 3-dose vaccination series is completed (i.e. starting after 4 weeks following dose 3).

Analyses in the HNRT and FAS population were supportive of the primary analysis in the PPE population. The HNRT population allows measurement of efficacy immediately after the first dose among subjects who are naïve to the relevant HPV type. HNRT analysis is a supportive analysis, since vaccine efficacy is not expected to be maximal until after completion of the 3-dose vaccine regimen, and provides information about efficacy during the course and after the completion of the vaccination series.

The FAS analysis is also a supportive analysis of prophylactic efficacy. Compared with the main analysis populations, the FAS also included subjects who had prior exposure or were currently infected with a vaccine or non-vaccine HPV type at Day 1. Because this population includes virtually everyone in the study, the FAS approximates the general population of sexually-active 16- to 26-year-old men. Evaluating prophylactic efficacy impact was measured on vaccine-type disease only (and hence representing a mix of prevalent and incident vaccine-type disease, only the latter of which would be expected to be affected by qHPV vaccine). This analysis shows vaccine impact on vaccine type EGL in the general population of 16- to 26-year-old men, starting immediately after the first dose.

2.5.4.1.1.2 Populations Used in 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 disease caused by vaccine and non-vaccine HPV types and external genital procedures and therapies) was performed among the GHN and the FAS.

The GHN population was designed to approximate 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. Given that it is impossible to evaluate the qHPV vaccine in boys prior to sexual debut (i.e. the intended target for vaccination), the SPONSOR believes that the GHN population is the correct subpopulation in Protocol 020 to provide insight on the potential impact of vaccination on males when vaccinated in young adolescence, prior to HPV exposure.

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As mentioned previously, FAS represents the general population of sexually-active 16- to 26-year-old men. Different from prophylactic efficacy, when evaluating population benefit on overall EGL reduction, impact on endpoints due to any HPV type (both vaccine and non-vaccine types, both prevalent and incident infection and disease) was measured, with only the incident vaccine type disease anticipated to be substantially affected by the qHPV vaccine.

2.5.4.1.2 HPV Clinical Program in Young Men

2.5.4.1.2.1 Overview – Protocol 020

Protocol 020 was designed to demonstrate the efficacy, immunogenicity, and safety of qHPV vaccine in men 16 to 26 years of age. The data cut-off date for this supplemental Application was 30-May-2008 for the study visits in which swab specimens were collected and 29-Aug-2008 for study visits in which biopsy specimens were collected, with data available as of 11-Oct-2008.

2.5.4.1.2.2 Subject Disposition and Subject Accounting

The mean duration of efficacy follow-up post-enrollment was approximately 2.4 years. At the time of the visit cutoff for the study's primary analysis, a total of 74%, 67%, and 56% of study subjects completed their Month 24, Month 30, and Month 36 visits, respectively [Sec. 10.6.2] of [Ref. 5.3.5.1: P020V1].

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 analysis related to HPV types 6/11, 16, and 18, respectively [Table 2.7.3-exgenlesions: 4]. 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.

2.5.4.1.2.3 Enrollment Characteristics

Median age of subjects enrolled was 20 years [Table 2.7.3-exgenlesions: 5]. Of all subjects, 14.8% were MSM. Overall, at Day 1, 12.2% of subjects were PCR positive to a vaccine HPV type (suggestive of ongoing infection), 7.6% were seropositive to a vaccine HPV type (suggestive of prior infection), and 17.3% were positive to a vaccine HPV type by PCR or serology ([Section 10.5.4] of [Ref. 5.3.5.1: P020V1]). Baseline characteristics were comparable between vaccine and placebo groups. Vaccinees and placebo recipients were also comparable regarding sexual history.

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2.5.4.1.2.4 Efficacy Results – Protocol 020

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

[Table 2.5: 1] and [Appendix 2.5: 5] show the results of analyses of efficacy performed in the PPE population to address the primary and secondary efficacy hypotheses. The vaccine efficacy against HPV 6/11/16/18-related EGL was 90.4% (95% CI: 69.2, 98.1). Success was achieved in the test of the primary efficacy hypothesis showing that vaccine efficacy against HPV 6/11/16/18-related EGL is above 20% with a p-value < 0.001. With respect to the secondary hypotheses, the vaccine efficacy against HPV 6/11/16/18-related persistent infection was 85.6% (97.5% CI: 73.4, 92.9) and against HPV 6/11/16/18-related DNA detection was 44.7% (95% CI: 31.5, 55.6). Success was achieved in the test of both secondary hypotheses showing that vaccine efficacy against HPV 6/11/16/18-related persistent infection and HPV 6/11/16/18-related DNA detection is above 20% with a p-value < 0.001.

[Appendix 2.5: 6] shows the cumulative incidence curve over time of HPV 6/11/16/18-related EGL by vaccination group for the PPE population. This plot is truncated at Month 30 due to lack of follow-up information beyond this time point since the study is still ongoing. While the incidence rate in the placebo group increased during the entire duration of follow-up shown, the incidence rate in the vaccine group remained low indicating persisting vaccine-induced protection against HPV 6/11/16/18 EGL through a mean duration of approximately 2 years Postdose 3.

The supportive analyses in the HNRT [Appendix 2.5: 7] and FAS [Appendix 2.5: 8] populations were consistent with the primary analysis in the PPE population and support the conclusion that qHPV vaccine is efficacious in males in preventing HPV 6/11/16/18-related EGL.

[Table 2.5: 1] and [Appendix 2.5: 7] display the results of analyses of efficacy in the HNRT population. Efficacy was observed with respect to each endpoint, although the point estimates of efficacy were lower than those observed in the PPE populations. EGL cases due to HPV infection between Day 1 and Month 7 (4 weeks Postdose 3) accounted for this lower efficacy. This is similar to the phenomenon that occurred in efficacy trials of the qHPV vaccine among young-adult and adult women, where, in populations in which case counting started Postdose 1, efficacy at earlier time periods was lower compared to efficacy at later time periods due to the influence of HPV infection that started between Day 1 and Month 7.

[Table 2.5: 1] and [Appendix 2.5: 8] display the results of analyses of efficacy against vaccine types in the FAS. As was the case in the studies in young-adult and adult women, the inclusion of endpoints caused by prevalent infections that were present at vaccination onset (endpoints that will not be impacted by prophylactic vaccines such as

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the qHPV vaccine) reduced the estimate of vaccine efficacy. Across the study duration cumulative incidence in placebo subjects increased and in vaccinees the rates nearly plateaued or remained significantly lower than in the vaccine group as illustrated in [Appendix 2.5: 9].

To assess the clinical importance of the persistent infection and DNA detection endpoints, the value of HPV 6/11/16/18-related persistent infection and DNA detection as predictors of external genital disease was evaluated [Sec. 2.7.3.1.2.5-exgenlesions]. Results indicate that persistent infection with HPV 6/11 is a significant predictor of condyloma, and HPV 6/11/16/18-related persistent infection is a significant predictor of PIN, bearing in mind that the number of PIN cases in the analysis was small. The DNA detection endpoint is a weaker predictor of external genital disease when compared to persistent infection, and the predictive value of DNA detection is driven by the cases of persistent infection, which are a subset of the DNA detection cases. Overall, these data indicate that persistent infection with vaccine types predicts development of external genital disease.


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Table 2.5: I

Analysis of Efficacy of qHPV Vaccine Against HPV 6/11/16/18-Related EGL, Persistent Infection and DNA Detection in the PPE, HNRT, and FAS Populations

Endpoint	qHPV Vaccine (N=2,025)				Placebo (N=2,030)				Observed Efficacy (%)	CI [†]	P-value [‡]
	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 EGL By Population	PPE	1,397	3	2,830.9	0.1	1,408	2,812.2	1.1	90.4	(69.2, 98.1)	< 0.001
	HNRT	1,775	13	4,262.8	0.3	1,770	4,186.0	1.2	75.5	(54.3, 87.7)	
	FAS	1,943	27	4,625.7	0.6	1,937	4,556.5	1.7	63.5	(45.8, 78.6)	
HPV 6/11/16/18-Related Persistent Infection By Population	PPE	1,390	15	2,549.4	0.6	1,400	2,469.3	4.1	85.6	(73.4, 92.9)	< 0.001
	HNRT	1,669	58	3,865.2	1.5	1,664	3,697.2	4.7	68.3	(57.1, 76.9)	
	FAS	1,817	148	4,094.3	3.6	1,815	3,942.6	6.9	47.8	(36.0, 57.6)	
HPV 6/11/16/18-Related DNA Detection By Population	PPE	1,390	136	2,455.3	5.5	1,400	2,404.1	10.0	44.7	(31.5, 55.6)	< 0.001
	HNRT	1,669	253	3,669.7	6.9	1,664	3,547.9	10.5	34.2	(22.7, 44.2)	
	FAS	1,817	384	3,851.1	10.0	1,815	3,736.5	13.7	27.1	(16.6, 36.3)	

[†] A 97.5% CI is reported for the PPE 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 Condylomata, PIN, or Penile/Perianal/Perineal Cancer; FAS = Full analysis set; HNRT = HPV-Native to the relevant type; HPV = Human papillomavirus; PPE = Per-protocol efficacy; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020V1]

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2.5 Clinical Overview

2.5.4.1.2.4.2 Efficacy in Subjects Immunologically Experienced With Vaccine HPV Types

A pre-specified analysis was conducted to determine whether, among subjects who showed evidence of current or previous HPV infection by serology and PCR assessment at Day 1, administration of qHPV vaccine reduced the incidence of disease, compared with placebo. Results of these analyses are in [Sec. 11.1.3.4] of [Ref. 5.3.5.1: P020V1].

Subjects who, at Day 1, had a prevalent infection without a history of prior infection were examined. Vaccine efficacy against HPV 6/11/16/18-related EGL among subjects who were seronegative and PCR positive to the relevant HPV vaccine type(s) at Day 1 was 23.2% (95% CI: -57.8, 63.4). Consistent with prior observations in the young adult women, there is no evidence to suggest that the qHPV vaccine is beneficial for subjects who have prevalent infection at the time the first vaccination of the qHPV vaccine is administered.

Subjects who were both seropositive and PCR positive at Day 1 were likely to represent a subset of the general population whose infection persisted despite a humoral response; such subjects would be unlikely to benefit from additional boosting of anti-HPV levels. There were a total of 3 cases of HPV 6/11/16/18-related EGL observed among subjects who were seropositive and PCR positive to the relevant vaccine HPV type(s) at Day 1. All of these cases were in the placebo group, but due to the small sample size and small number of cases in this population, no inference can be made with regard to this endpoint.

In subjects who clear an HPV infection, natural immunity may wane, resulting in a potential risk for recurrence. There were no HPV 6/11/16/18-related EGL cases observed among subjects who were seropositive and PCR negative to the relevant vaccine HPV type(s) at Day 1 in either the qHPV vaccine or placebo groups.

2.5.4.1.2.4.3 Population Benefit - Overall Rates of Genital Disease and Related Procedures and Therapy

The public health benefit of qHPV vaccine in men will be measured in terms of the impact of the vaccine on a man's risk for developing genital warts, penile, perineal, perianal neoplasia and cancers and the public health burden related to treating these clinical HPV diseases. Regarding clinical HPV diseases, this Submission focuses primarily on EGL, as there are limited or no data presented on precancerous or cancerous lesions. Therefore, population benefit is measured through assessing impact of qHPV vaccine on reducing incidence of EGL due to any HPV type and incidence of external genital procedures and therapies. Impact is assessed on two study populations which represent different male populations in real life that could be targeted for qHPV vaccination. The first population is GHN; as discussed in [Sec. 2.5.4.1], it is designed to

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approximate a population of adolescent and young adult men who are either sexually-naïve or sexually-experienced and have not yet been exposed to any HPV type. The second population is the FAS; it approximates the general population of sexually-active 16- to 26-year-old men, being a combination of both HPV- infected and uninfected individuals.

Results of analyses of efficacy against EGL due to any HPV type are in [Sec. 11.1.2.1] of [Ref. 5.3.5.1: P020V1]. In the GHN population, the vaccine efficacy for EGL due to any HPV type was 83.8% (95% CI: 61.2, 94.4), signifying a substantial efficacy of qHPV vaccine in reducing the incidence of overall EGL in the population that approximates HPV-naïve adolescents or young adult men. High efficacy against EGL due to any HPV type is expected, since vaccine HPV types are the predominant types in EGL.

The vaccine efficacy against EGL due to any HPV type was 60.2% (95% CI: 40.8, 73.8) in the FAS [Appendix 2.5: 10]. Due to EGL occurring as a result of infections prevalent at the onset or early phase of vaccination series, vaccine efficacy in this population is expected to be lower than the GHN population. However, the observed efficacy against EGL due to any HPV type in the FAS highlights the benefit of vaccinating a general population of 16- to 26-year old men, even though they may be sexually active. Furthermore, the efficacy would increase and the vaccine impact would be more apparent over time, as new vaccine-type infections are prevented beginning immediately after the 3-dose vaccination regimen is completed.

Results of analyses of the impact of qHPV vaccine on the incidence of external genital procedures and therapy are in [Sec. 11.1.2.2] of [Ref. 5.3.5.1: P020V1]. In both the GHN population and the FAS, there were 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. Vaccine efficacy against external genital therapies was 47.9% (95% CI: 18.1, 67.5) in the GHN population and 37.6% (95% CI: 18.2, 52.6) in the FAS. For external genital biopsies, vaccine efficacy was 57.0% (95% CI: 31.3, 73.7) in the GHN population and 45.5% (95% CI: 27.9, 59.1) in the FAS. The data indicate the potential benefit of qHPV vaccination in the reduction of external genital biopsies and therapies, and the cost associated with them.

EGL therapies in this analysis include all therapies that could potentially be associated with HPV-related EGL (i.e., surgical therapies included procedures such as surgical excision, laser ablation, cauterization, coagulation, and cryotherapy, and non-surgical therapies included topical treatments, including chemical ablation). In addition, investigators were instructed to collect biopsies from any lesion that could possibly, probably or definitively be associated with HPV or whose relationship to HPV could not be determined, to increase sensitivity of EGL detection. Therefore, these procedures and therapies are not necessarily associated with a diagnosis of condyloma or PIN (as determined by the pathology panel), or detection of HPV in the lesion. As they may include therapies or procedures that are associated with non-HPV related EGL or other external genital diseases, the specificity of these endpoints and vaccine efficacy estimates

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for them are expected to be lower than what has been observed against vaccine type HPV-related EGL.

2.5.4.1.2.4.4 Impact of Baseline Characteristics on the Efficacy of qHPV vaccine

Analyses of the efficacy of qHPV vaccine against HPV 6/11/16/18-related EGL, persistent infection, and DNA detection in the PPE population, by categories of pre-specified covariates for Protocol 020 are provided in [Sec. 11.1.1.1.4] of [Ref. 5.3.5.1: P020V1]. Covariates include age at start of vaccination, race/ethnicity, geographic region, and at Day 1, smoking status, circumcision status, presence of other sexually transmitted diseases, serostatus, and PCR status. For all baseline characteristics where there was enough information to conduct an analysis of vaccine efficacy, the vaccine efficacy estimates were comparable for all categories within a particular characteristic. The incidence rates by these baseline characteristics were also comparable given that the number of subjects for each category of a particular characteristic can vary substantially. The analysis indicates that there were no baseline covariates with sufficient data to estimate vaccine efficacy that had a significant impact on the efficacy estimates.

2.5.4.1.2.4.5 Duration of Efficacy

Quadrivalent HPV vaccine efficacy has been shown for up to 4.5 years Postdose 3 among young adult women. In men, Protocol 020 provides a shorter follow-up period (mean duration of approximately 2 years Postdose 3). Low incidence rate of HPV 6/11/16/18-related EGL observed among men in the vaccine group indicates sustained efficacy over this time period, as seen in women.

2.5.4.1.2.5 Efficacy Conclusions – Protocol 020

Based on the results of qHPV vaccine efficacy analysis among PPE population, with supportive, consistent analyses results from the HNRT and FAS populations, the following conclusions can be made:

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is efficacious in preventing development of HPV 6/11/16/18-related external genital lesions.
- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 16 to 26 year old men is efficacious in preventing development of HPV 6/11/16/18-related 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 with L1 VLP vaccines demonstrated that: (1) administration of L1 VLP vaccines protected animals from species-specific papillomavirus infection; (2) this protective efficacy was associated with virus-neutralizing antibody; and (3) unvaccinated

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animals that were given serum from vaccinated animals became protected from infection/disease. These results supported the hypothesis that induction of systemic anti-HPV antibody responses to HPV L1 VLP vaccine should result in protection against HPV infection or disease [Ref. 5.4: 327, 1929, 2010]. Based on the results of the preclinical studies, the clinical program has utilized vaccine type-specific anti-HPV neutralizing antibody serum levels as the primary means to measure the immunogenicity of the HPV L1 VLP vaccines.

The minimal anti-HPV response that provides protection against HPV infection and disease is not known for the following reasons: (1) the dependence of the HPV viral life cycle on terminal differentiation of epithelial cells has precluded the development of *in vitro* functional assays to demonstrate that vaccine-induced anti-HPV responses can neutralize live virions; and (2) due to the high efficacy of the qHPV vaccine and low number of cases among vaccinees it has not been possible to correlate vaccine failure with vaccine-induced anti-HPV levels. Similar to qHPV vaccine trials among women, in Protocol 020, the data from cases in the vaccine group do not indicate a serologic correlate of protection. Despite lack of a correlate of protection, demonstrated efficacy even at low antibody levels and anamnestic immune response after a fourth qHPV vaccine dose in women suggest immune memory is generated.

2.5.4.2.2 Design of the Immunogenicity Studies of qHPV Vaccine

2.5.4.2.2.1 Study Periods

All studies in the clinical program for the qHPV vaccine were divided into 2 parts for the purposes of immunogenicity evaluations:

- The period between Day 1 and the Month 7 visit was considered to be the studies' vaccination phase. Immunogenicity evaluations conducted during this phase were designed to demonstrate the peak anti-HPV responses generated by the qHPV vaccine (the Month 7 visit approximated the time during which peak vaccine-induced immune responses were anticipated).
- The period after the Month 7 visit was termed the studies' persistence phase. Immunogenicity evaluations conducted during this phase were designed to define the duration of vaccine-induced immune responses and to explore potential immune correlates of vaccine efficacy.

2.5.4.2.2.2 Clinical Immunogenicity Endpoints

The immunogenicity of qHPV vaccine was measured using anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 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: P020V1].

The immunogenicity endpoints for the clinical program have focused on 2 parameters: (1) anti-HPV levels (GMTs), which is a standard summary measure of immunogenicity; and (2) the proportion of subjects who became seropositive to vaccine HPV types at 4 weeks Postdose 3 [Ref. 5.4: 1134].

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2.5.4.2.2.3 Primary Immunogenicity Population

Immunogenicity analyses were conducted in the per-protocol immunogenicity (PPI) population of the relevant studies. The PPI population was selected for the immunogenicity analysis to measure the full benefit of 3 doses of qHPV vaccine in healthy subjects who had no evidence of HPV infection prior to onset of vaccination. The PPI population is described in [Sec. 2.7.3.2.2.2.1-exgenlesions] and [Ref. 5.3.5.1: P020V1].

2.5.4.2.3 Summary of Results of Protocol 020

[Appendix 2.5: 11] presents a summary of anti-HPV geometric mean titers by vaccination group in the PPI population of Protocol 020. [Appendix 2.5: 12] presents a summary of the percent seroconversion by vaccination group in the PPI population.

Anti-HPV Results at Month 7. The seroconversion percentages at 4 weeks post-dose 3 (Month 7) for vaccine recipients are 98.9%, 99.2%, 98.8%, and 97.4% for the vaccine HPV types 6, 11, 16, and 18, respectively.

In the qHPV vaccine group, measurable immune responses, well above the lower limit of quantitation (LLOQ), were induced by the 3-dose vaccination at 4 weeks Postdose 3 (Month 7) for each vaccine HPV type. Although there is no formal immunogenicity hypothesis for this study, Wilcoxon rank sum tests were performed to compare the anti-HPV titers in the qHPV vaccine and placebo groups at Month 7. These tests showed that the GMT for vaccine recipients was significantly higher than for placebo recipients for each vaccine HPV type.

Persistence of Anti-HPV Responses. At Month 24, the seroconversion percentages for vaccine recipients decreased for all vaccine HPV types with the exception of HPV type 16. The estimates of percent seroconversion dropped, 8.1, 3.6, and 35.1 percentage points for HPV types 6, 11, and 18, respectively. The GMTs in vaccinated subjects at Month 24 were lower than at Month 7 for all vaccine HPV types. For anti-HPV 6, 11, and 16 GMTs, levels at Month 24 remained above levels obtained from natural infection (placebo subjects who were seropositive and PCR negative at Day 1) for each HPV type. For anti-HPV 18, the GMT at Month 24 was not significantly different from GMT among subjects with natural infection.

Similar decline in anti-HPV levels were observed after Month 7 in qHPV vaccine trials among women 16- to 26- years of age. However, decline in anti-HPV levels are not correlated with increased disease incidence. There are no serologic correlates of protection, and low anti-HPV levels or seronegativity is not indicative of vaccine failure. Additionally, previous studies have shown that a 4th dose given approximately 4.5 years after dose 3 induced strong anamnestic response, even in those who became seronegative between doses 3 and 4 [Ref. 5.4: 2177].

Among all four vaccine HPV types, HPV 18 has had the highest rate of decline in both female and male studies. No HPV 18-related EGL was observed among vaccinees in the PPE population of Protocol 020. Female studies with longer period of follow up have

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shown that efficacy against HPV 18-related diseases continued to remain high in the presence of high attack rates in the placebo groups [Ref. 5.4: 2577].

2.5.4.2.4 Summary of Results of Comparison of Anti-HPV Titers in 16- to 26-Year-Old Men (Protocol 020) and 9- to 15-Year-Old Boys (Protocols 016 and 018)

Bridging of Immune Response between Adult and Adolescent Males

As with female HPV vaccination, vaccination of male adolescents prior to sexual debut is of utmost importance. However, efficacy studies are not feasible among sexually naïve adolescent populations. Therefore, immunobridging between adult and adolescent males was targeted by comparing anti-HPV levels and demonstrating that GMTs and seroconversion rates among adolescent males are not inferior to what is observed among men. Anti-HPV responses (Month 7 GMTs and seroconversion rates) among 9- to 15-year-old male subjects from previously conducted Protocols 016 and 018 were compared with responses from 16- to 26 year old men in Protocol 020. As presented in [Table 2.7.3-exgenlesions: 17] and [Table 2.7.3-exgenlesions: 18], respectively, GMTs and seroconversion rates in 9- to 15-year-old boys were non-inferior to GMTs and seroconversion rates in 16- to 26-year-old men [Ref. 5.4: 2272]. Thus, it can be concluded that qHPV vaccine is efficacious in preventing HPV 6-, 11-, 16-, and 18-related external genital lesions in boys and men 9 to 26 years of age.

Parallel Testing

Since sera from Protocols 016 and 018 subjects were tested approximately 4 years prior to testing of Protocol 020 sera, a parallel testing procedure was undertaken in samples from a total of 490 vaccinated subjects (240 adult men and 250 boys) to provide support for the comparison of immunogenicity between the Protocol 016 and 018 data and the Protocol 020 data [Ref. 5.4: 2270]. The sample size was selected to ensure sufficient statistical power to address the immunobridging hypotheses. In order to assess whether testing in parallel would provide similar results to what was observed in the immunobridging study, sera from a random sample of 9- to 15- year old boys in Protocols 016 and 018 were tested in parallel with a random sample of sera from 16- to 26-year old men from Protocol 020. Results of the analysis indicate that anti-HPV responses (Month 7 GMTs and seroconversion rates) in the randomly selected 9- to 15-year-old boys were non-inferior to anti-HPV responses in the randomly selected 16- to 26-year-old men. So, non-inferiority of vaccine-induced anti-HPV response in adolescents compared to adult men was also demonstrated when samples were tested in parallel [Ref. 5.4: 2270].

2.5.4.2.5 Conclusions Regarding the Immunogenicity of 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

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responses that result in a high level of protective efficacy through approximately 2 years following completion of the vaccination regimen.

- 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.

2.5.5 Overview of Safety

2.5.5.1 Protocol 020

This supplemental Application contains new safety data in a population of men 16 to 26 years of age from Protocol 020. To evaluate tolerability, adverse experiences were collected on a VRC on the day of vaccination and for 14 days following each vaccination. Serious adverse experiences occurring after the 15-day reporting period were collected if the event resulted in death or was determined by the investigator to be vaccine- or study procedure-related [Ref. 5.3.5.1: P020V1]. In addition, medical history was collected at Day 1. At subsequent visits, new medical history that occurred since the last study visit was recorded. Overall, qHPV vaccine when administered to men 16 to 26 years of age was well-tolerated, and the clinical adverse experience profile exhibited was consistent with the previously described adverse experience profile for qHPV vaccine; no new safety issues were identified.

2.5.5.1.1 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. In the study, 4 subjects were enrolled more than one time by providing false information regarding their identities to the study sites. Three (3) of these subjects were enrolled twice and were assigned 2 allocation numbers each. These subjects received a total of 4, 6, and 3 doses of vaccine/placebo, respectively. One (1) subject was enrolled 3 times and was assigned 3 allocation numbers. This subject received a total of 6 doses of vaccine/placebo. None of these subjects reported adverse experiences related to overdose. Furthermore, 2 non-study participants presented themselves to study sites as study participants. These 11 allocation numbers are excluded from all tables, including [Table 2.7.4: 2], in the Summary of Clinical Safety (see [Sec. 10.1] and [Sec. 10.2] of [Ref. 5.3.5.1: P020V1] for a complete discussion regarding these subjects).

2.5.5.1.2 Analysis of Adverse Experiences

Safety data for subjects enrolled in Protocol 020 are summarized in detail in [Sec. 12] of the CSR [Ref. 5.3.5.1: P020V1]. In Protocol 020, the following observations can be made from clinical adverse experiences reported by subjects at any time during the study:

- The proportion of subjects who reported at least one clinical adverse experience was slightly higher in the qHPV vaccine group than in the placebo group;

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- The proportion of subjects who reported at least one injection-site adverse experience was slightly higher in the qHPV vaccine group than in the placebo group;
- The proportion of subjects who reported at least one systemic adverse experience was generally comparable between the vaccine and placebo groups;
- Few subjects discontinued the study due to an adverse experience. The proportion of subjects who discontinued the study due to an adverse experience was slightly higher in the placebo group than in the qHPV vaccine group.
- A total of 19 subjects reported serious adverse experiences. None were vaccine-related. Of these subjects, 8 were in the qHPV vaccine group and 11 were in the placebo group. In addition, a serious adverse experience of overdose was reported in 3 subjects, who were enrolled more than once (see [Sec. 2.7.4.5.5]).
- A total of 13 subjects died during the study. The proportion of subjects who died was higher in the placebo group than in the qHPV vaccine group. A total of 3 subjects died in the qHPV vaccine group and a total of 10 subjects died in the placebo group. None of the deaths were vaccine related.
- Overall, the proportions of subjects who reported new medical conditions, including conditions potentially indicative of an autoimmune phenomenon, Post Month 7 were comparable between vaccination groups. No case of Guillain Barre Syndrome was reported in Protocol 020.

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 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. 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.

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 supplemental Application. 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.

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In all of the clinical trials conducted as part of the clinical development plan for qHPV vaccine, safety was evaluated using VRC-aided surveillance for 14 days after each injection of HPV vaccine or placebo. However, in one study (Protocol 015 – a Phase III pivotal efficacy study in 16- to 26-year-old female subjects), only a subset of subjects was followed using VRC-aided surveillance, and the remainder of the subjects used a general surveillance methodology. Serious adverse experiences occurring after the 15-day reporting period were collected if the event resulted in death or was determined by the investigator to be vaccine- or study procedure-related. In addition, medical history was collected at Day 1. At subsequent visits, new medical history that occurred since the last study visit was recorded.

Two (2) general populations were considered for evaluations of safety:

Safety Population: includes all subjects who received qHPV vaccine or placebo (aluminum or non-aluminum), regardless of surveillance method.

Detailed Safety Population: includes all subjects who received qHPV vaccine or placebo (aluminum or non-aluminum) who were followed using the VRC-aided surveillance method.

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.

All published clinical literature about qHPV vaccine was reviewed for consistency with the safety findings reported in this supplemental Application. The data presented in this supplemental Application are comparable to the data presented in prior Applications and demonstrate that qHPV vaccine is generally well tolerated in all populations studied. References are provided in Module 5 [Ref. 5.3.5.1: 2025, 2027] [Ref. 5.4: 1193, 2096, 2098, 2099, 2149, 2151, 2152, 2173, 2177].

The data cutoff date for this supplemental Application was 01-Jun-2007 for P018, 13-Jul-2007 for Protocol 019 (an ongoing efficacy, immunogenicity, and safety study in women 24 to 45 years of age), and 29-Aug-2008 for P020. P007 (an efficacy, immunogenicity, and safety study in 16- to 26-year-old female subjects), P013 (a Phase III pivotal efficacy study in 16- to 26-year-old female subjects), P015, and P016 reached End-of-Study at the time of the current Application.

2.5.5.2.1 Study Population and Extent of Exposure

Overall, 3097 male subjects received at least 1 dose of qHPV vaccine in Protocols 016, 018 and 020, as shown in [Table 2.7.4: 2]. A total of 2305 male subjects received at least 1 dose of placebo. Subjects who received protocol non-compliant vaccination regimens (mixed regimens of vaccine and placebo) are excluded from the clinical adverse

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experience summaries included in this Summary of Clinical Safety. A total of 7 subjects (5 randomized to receive qHPV vaccine and 2 randomized to receive placebo) received protocol non-compliant vaccination regimens [Sec. 2.7.4.1.2]. Information regarding subjects who were excluded from Protocol 020 safety summaries is presented in [Sec. 2.7.4.1.2].

2.5.5.2.2 Analysis of Adverse Experiences

[Appendix 2.5: 13] 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. This finding was caused by an increase in the proportion of subjects in the group that received qHPV vaccine who reported an injection-site adverse experience compared with the placebo group.

In the detailed safety population during the entire study period:

- serious adverse experiences were rare;
- the proportion of subjects who experienced a serious adverse experience were comparable between the vaccination groups;
- 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.

Note that no protocol-specified laboratory safety tests were performed and, therefore, no laboratory adverse experiences were assessed in the clinical development program for qHPV vaccine.

2.5.5.2.3 Analysis of Common Adverse Experiences in Detailed Safety Population

Injection-Site Adverse Experiences. Consistent with prior Applications, the proportion of subjects who reported an injection-site adverse experience was higher among subjects who received qHPV vaccine compared with subjects who received placebo. Most injection-site adverse experiences were judged by the study subjects to be mild or moderate in intensity. The most common injection-site adverse experiences reported were pain, swelling, and erythema.

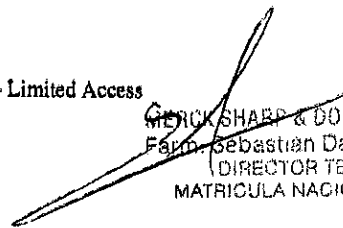
Although a higher proportion of girls and women reported one or more injection-site adverse experience compared with men and boys, the types of injection-site adverse experiences reported in both genders were comparable. Overall, the adverse experience profile in boys and men was generally comparable to the adverse experience profile in girls and women and consistent with the adverse experience profile described in previous submissions.

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Systemic Clinical Adverse Experiences. Consistent with prior Applications, the proportions of subjects who reported a systemic clinical adverse experience were comparable between the 2 vaccination groups. The great majority of these adverse experiences were judged to be mild or moderate in intensity. Severe intensity systemic adverse experiences were more common than severe intensity injection-site adverse experiences. However, 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 (12.3% and 11.2% in the vaccine and placebo groups, respectively) and pyrexia (8.2% and 6.5% in the vaccine and placebo groups, respectively).

Although a higher proportion of girls and women reported one or more systemic clinical adverse experiences compared with men and boys, the types of systemic clinical adverse experiences reported most commonly in both genders were comparable (with the exception of reproductive disorders, such as dysmenorrhea, which occur only in the female population). 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.

Elevated Temperatures. Temperature values were recorded daily for 5 days after vaccination for all subjects in the detailed safety population. Elevated temperature (fever) was defined as a temperature ($\geq 100^{\circ}\text{F}$ [$\geq 37.8^{\circ}\text{C}$], oral or oral equivalent). The proportions of subjects who reported an elevated temperature or who reported a maximum temperature $\geq 39.9^{\circ}\text{C}$ 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.

2.5.5.2.4 Analysis of Adverse Experiences in Safety Population

Deaths were rare. Cumulatively, a total of 36 subjects died at any time during the studies (18 subjects [0.11%] who received qHPV vaccine and 18 subjects [0.13%] who received placebo). Of these 36 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 127 subjects (0.81%) who received qHPV vaccine and 129 subjects (0.95%) who received placebo reported a serious clinical adverse experience at any time during the studies. Narratives for all subjects in Protocol 020 who reported a serious clinical adverse experience are in [Ref. 5.3.5.1: P020V1]. Serious systemic clinical or injection-site adverse experiences determined by the study investigator to be vaccine-related were reported in 6 subjects. None of the 6 subjects were enrolled in Protocol 020; all of the serious vaccine-related clinical adverse experiences were reported in female subjects and were described in previous Applications. The vaccination groups were also comparable with respect to the types of serious adverse experiences reported. [Appendix 2.7.4: 42] lists subjects in the safety population with serious clinical adverse experiences.

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Overall, 70 subjects discontinued from their respective study 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.

2.5.5.2.5 New Medical History in the Safety Population

Medical History at Day 1 was recorded for all subjects. Any acute or chronic medical conditions that occurred during the year prior to study entry were recorded. After Day 1, any medical history or conditions or procedures that occurred since the last study visit were recorded. New medical conditions were not considered adverse experiences when they occurred outside the safety follow-up period (Day 1 through Month 7) and/or were not considered by the study investigators to be vaccine/placebo related.

[Table 2.7.4: 13] presents a cumulative summary of the number and percentage of male subjects in Protocols 016, 018, and 020 with new medical conditions (incidence ≥5% in one or more vaccination groups) by system organ class and vaccination group during the follow-up period (Post Month 7). Overall, 1568 subjects reported one or more new medical conditions (887 recipients of qHPV vaccine [34.6%] and 681 recipients of placebo [32.7%]). In the group that received qHPV vaccine, the most common medical conditions include infections (pharyngitis, upper respiratory tract infection, and nasopharyngitis). In the placebo group, the most common medical conditions also include infections (upper respiratory tract infection, pharyngitis, and fungal skin infection).

[Table 2.7.4: 14] presents a summary of new medical conditions potentially indicative of an autoimmune phenomenon among all male subjects in Protocols 016, 018, and 020 reported Post Month 7 by vaccination group. Overall, 51 subjects reported one or more new medical conditions potentially indicative of an autoimmune phenomenon Post Month 7 (23 recipients of qHPV vaccine [0.9%] and 28 recipients of placebo [1.3%]). The most common new medical condition potentially indicative of an autoimmune phenomenon was arthralgia (0.6% in the qHPV vaccine group and 0.6% in the placebo group), followed by vitiligo (0.1% in the qHPV vaccine group and 0.2% in the placebo group).

Overall, the proportions of subjects who reported new medical conditions, including conditions potentially indicative of an autoimmune phenomenon, Post Month 7 were comparable between vaccination groups. Use of qHPV vaccine does not have any adverse health impact through approximately 2 years following the completion of the vaccination regimen in adolescent boys and young adult men.

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. Trials of qHPV vaccine in immunocompromised subjects and trials to evaluate the concomitant use of qHPV vaccine with vaccines other than hepatitis B vaccine are ongoing. While the development program for qHPV vaccine enrolled approximately 25,000 women and children and 4000 men, the safety database was insufficiently sized to detect safety

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signals with respect to medical conditions occurring at a background rate of less than 1:10,000. However, data from over 20,000,000 doses of qHPV vaccine distributed in the US since licensure further inform the safety profile of the vaccine [Sec. 2.5.5.4].

2.5.5.4 Postmarketing Safety Data

From the International Birthdate through 30-Sep-2008, approximately 40,952,912 doses of qHPV vaccine were distributed worldwide; there were no countries where marketing applications have been rejected, withdrawn, suspended, or revoked for safety reasons. The 4th 6-month Periodic Safety Update Report (PSUR) covering the time period of 01-Dec-2007 thru 31-May-2008 [Ref. 5.3.6: 2597] contains a list of 97 countries where qHPV has received marketing approval up to 31-May-2008.

To permit safety surveillance for its products, Merck & Co., Inc. maintains the New Worldwide Adverse Experience System (NWAES) database. Postmarketing safety surveillance is a worldwide, passive, spontaneous, and voluntary reporting system. At Merck & Co. Inc., the NWAES database contains all spontaneous AE reports from the marketed environment, serious reports from clinical trials, and reports from the medical literature. This is a dynamic database, and adverse experience information is updated continuously. The retrieval of data is provided as a snapshot in time. The data are compiled and reviewed on a periodic basis and reported in a PSUR.

All of the reports are entered into NWAES and are coded using the terminology of the reporter. The Medical Dictionary for Regulatory Activities (MedDRA) is the dictionary used to code AE terms in the NWAES database. Inclusion of the report in the database implies only a temporal association and not necessarily a causal association. Each report represents one individual who may experience one or more AEs. Since each AE is coded to a body system, one report may contain multiple AEs in the same or different body systems.

Routine Pharmacovigilance practices include continuous monitoring of the safety profile of approved products. Data from the NWAES database are routinely reviewed as individual reports and in aggregate. The purpose of the review is to evaluate adverse experience reports for possible safety signals, to determine if further investigation is warranted to clarify the safety profile of the product, and to ensure completeness of safety information in worldwide package circulars. This approach is in line with generally accepted pharmacovigilance approaches including the European Union (EU) requirements.

A query of the NWAES database performed on 16-Oct-2008 revealed that 23,792 spontaneous reports have been received from product launch through 30-Sep-2008; 2,439 reports (10%) were considered serious. The 5 most frequently reported adverse experiences included no adverse effect (4961), inappropriate schedule of drug administration (4611), drug exposure during pregnancy (2160), syncope (1909), and dizziness (1807).

Additionally, a second query of the NWAES database, performed on 16-Oct-2008, revealed that 154 spontaneous reports involving male patients have been received from

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product launch through 30-Sep-2008; 6 reports (4%) were considered serious. The 5 most frequently reported adverse experiences which involved male patients included off label use (76), no adverse event (67), inappropriate schedule of drug administration (22), wrong drug administered (21), and accidental exposure (16). The 6 serious reports included 10 serious adverse experiences as follows: convulsion (2), anaphylactic reaction (1), Guillain Barre Syndrome (1), hypersensitivity (1), inappropriate schedule of drug administration (1), periorbital edema (1), rash (1), swelling face (1), and tendon rupture [secondary to trauma] (1).

Overall, the post licensure experience with qHPV vaccine 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 any conclusions regarding the safety profile of the vaccine relative to males.

In addition, the following postmarketing epidemiologic studies or surveillance conducted by the SPONSOR include safety monitoring: 1) Surveillance for general safety as well as autoimmune conditions and pregnancy exposures to qHPV vaccine in approximately 44,000 females aged 9 to 26 years in a managed care organization setting in the US (Protocol 031); 2) Pregnancy registry monitoring outcomes in inadvertently vaccinated pregnant women; 3) Measuring vaccine impact on HPV-related genital diseases, as well as the congenital anomalies of babies born to mothers with inadvertent exposure to qHPV vaccine during pregnancy among general population in four Nordic countries (Denmark, Iceland, Norway, and Sweden) (Protocol 33); 4) Long-term follow-up of vaccinated women to measure vaccine effectiveness and monitor certain health outcomes (Protocol 15-20) [Ref. 5.4: 2184]; and 5) Long-term follow-up of adolescent vaccinees for persistence of immunogenicity, vaccine effectiveness and vaccine-related serious adverse experiences (Protocol 18-10) [Ref. 5.4: 2109].

Merck & Co., Inc will continue to the monitor the safety of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine, in the post-licensure period.

Over 20,000,000 doses of qHPV vaccine have been distributed in the US. To date, assessment based on the Vaccine Adverse Events Reporting System (VAERS) and Vaccine Safety Datalink (VSD) project suggest that the postlicensure safety data continue to support the benefit-risk profile of the qHPV vaccine [Ref. 5.4: 2748, 2750, 2751]

2.5.5.5 Overdose

For HPV vaccine and placebo, overdose was defined as a subject receiving >3 doses (0.5 mL per dose) of vaccine or placebo throughout the study or receiving ≥0.75 mL of vaccine or placebo in any one dose. Overdose was reported for three (3) subjects in Protocol 020 who received >3 doses of vaccine or placebo. These 3 subjects enrolled more than once into Protocol 020 by providing false information regarding their identities to the study sites [Sec. 2.7.4.5.5.1]. No subjects in Protocol 020 received ≥0.75-mL dose

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of qHPV vaccine. Subjects who received >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

No abuse of qHPV vaccine was reported in any of the clinical trials conducted to date. qHPV vaccine does not have properties associated with medications with abuse potential.

No occurrence of withdrawal or rebound was reported in any of the clinical trials conducted to date. 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.

Two (2) subjects in Protocol 020 were involved in fatal road traffic accidents. One subject received qHPV vaccine and the other subject received placebo. Two (2) subjects in Protocol 020 completed suicide. Both subjects received placebo. Other subjects who were involved in road traffic accidents, who attempted or completed suicide, or had other mental illness in other studies of qHPV vaccine were discussed in previous Applications.

Thus, qHPV vaccine does not appear to have any adverse effects on the ability to drive or operate machinery. Also, qHPV vaccine does not appear to impair mental abilities.

2.5.5.7 Conclusions Regarding the Safety of qHPV vaccine

The safety data presented in this supplemental Application support the conclusion that qHPV vaccine is generally well tolerated and displays a favorable safety profile similar to that shown in the original Application and Safety Update Report (SUR). Specifically, the following conclusions can be drawn:

With respect to Protocol 020:

- 1. 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:

- 1. Administration of qHPV vaccine is generally well tolerated in 9- to 26-year-old boys and men.
- 2. 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.
- 3. Use of qHPV vaccine does not have any adverse health impact through ~2 years following the completion of the vaccination regimen in adolescent boys and young adult men.
- 4. Use of qHPV vaccine does not appear to impact the ability to drive or operate machinery.

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