EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gardasil

human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)

Procedure No.: EMEA/H/C/000703/WS/0029

Silgard

human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)

Procedure No.: EMEA/H/C/000732/WS/0029

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Gardasil/Silgard is a quadrivalent recombinant Human Papillomavirus (HPV, Types 6, 11, 16 and 18) vaccine (qHPV) that was licensed 24 September 2006.

The current indication is based on the demonstration of efficacy of qHPV vaccine in adult females 16 to 45 years of age and on the demonstration of immunogenicity of qHPV vaccine in 9- to 15-year old children and adolescents:

"Gardasil/Silgard is a vaccine for use from the age of 9 years for the prevention of:
– premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types
– external genital warts (condyloma acuminata) causally related to specific HPV types"

The evaluation procedure started as a variation application EMEA/H/C/703/II/WS/0029 for Gardasil and EMEA/H/C/732/II/ WS/0029 for Silgard, to extend the indication to include premalignant anal lesions and anal cancer in section 4.1.

This application concerns the following medicinal products:

Medicinal product:	**Common name:**	**Presentations:**
Gardasil	human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	See Annex A
Silgard	human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	See Annex A

Within this variation the results from the analysis of Protocol 020, the efficacy study of qHPV vaccine administered to young men (16 to 26 years of age) were submitted and assessed. Study 020 was designed to evaluate efficacy of the qHPV vaccine in the prevention of HPV 6/11/16/18-related external genital lesions (genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), and penile, perianal or perineal cancer) and the AIN Substudy of study 020 including men who have sex with men (MSM) was designed to evaluate vaccine efficacy in the prevention of HPV 6/11/16/18-related persistent anal infection, anal intraepithelial neoplasia (AIN) and anal cancer.

In order to extend the indication to boys 9-15 years of age immunogenicity bridging studies, Protocols 016 and 013 were used to compare antibody responses to HPV in male subjects from the pivotal efficacy trial to boys 9-15 years of age.

The final clinical study report (CSR) of Protocol 020 included in the present type II variation fulfils FUM 015 for Gardasil/Silgard.

The changes of the indication initially proposed by the MAH included:

- The qHPV vaccine is indicated in boys and men 9 through 26 years of age for the prevention of **external genital lesions including genital warts** (condyloma acuminata) caused by HPV types 6, 11, 16, and 18.

- The qHPV vaccine is indicated in individuals 9 through 26 years of age for the prevention of **premalignant anal lesions** caused by HPV types 6, 11, 16 and 18.
- The qHPV vaccine is indicated in individuals 9 through 26 years of age for the prevention of **anal cancer** caused by HPV types 6, 11, 16 and 18.
- The qHPV vaccine is indicated in boys and men 9 through 26 years of age for the prevention of **persistent infection** due to HPV types 6, 11, 16, and 18.

The CHMP concluded that the expected very limited benefit in the general population with respect to prevention of anal cancer is not expected to outweigh potential safety issues, therefore the extension of the indication to include premalignant anal lesions and anal cancer was not considered as approvable.

The CHMP also decided not to approve the inclusion of persistent infection in the indication since the relevance of preventing persistent infection in males is less clear in cancer prevention than it is in females.

However, following the two rounds of assessment the CHMP concluded that the preventive vaccine effect against genital warts was of clinical relevance and recommended revising the indication external genital lesions to genital warts.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision P/13/2010.

The PDCO issued an opinion on compliance.

1.2. Toxico-pharmacological aspects

In support of the male indication, a study on male fertility has been performed in rats. The rats were given a full human dose. Two different dosing schemes were tested. One group (30 rats) were given the vaccine 6 weeks, 3 weeks, and 3 days prior to cohabitation. A second group was immunized 3 days prior to cohabitation. There were no unscheduled deaths during the study, and no treatment-related physical signs, changes in mean body weight gain or food observations. There were no treatment-related effects on reproductive performance including fertility, sperm count, and sperm motility. There were no treatment-related gross or histomorphologic changes and no treatment-related effects on testes weights. qHPV induced the expected antibody response to HPV Types 6, 11, 16, and 18 following 1 or 3 intramuscular injections.

In the initial dossier, single-dose, repeat-dose and local tolerance studies were performed on both genders. To support the extension of indication, this fertility study in male rats was submitted. Taking into account the clinical use, the protocol was adequate (treatment dose and duration). An antibody response was obtained in all animals receiving the vaccine, thus proving the relevance of the chosen species and the exposure of treated animals.

In conclusion, the results of the study raised no concerns regarding effects on male reproductive function. The results of the study are adequately described in section 5.3. Preclinical safety data of the SmPC, and the wording regarding the administered dose was modified. In addition, section 4.6

Fertility, Pregnancy and Lactation was modified as well. The update of these sections of the SmPC was endorsed by the CHMP.

1.3. Clinical aspects

The clinical program for quadrivalent HPV (qHPV) vaccine in young men 16 to 26 years of age included one pivotal study, Protocol 020 and two smaller immunogenicity bridging studies, Protocols 016 and 018. Protocols 016 and 018 were submitted in support of the extension of indication to include boys 9-15 years of age (these studies were assessed in the original marketing authorisation application - MAA) and are covered in the Immunogenicity section below and are also discussed regarding their contribution to the overall safety database in males. An overview of the relevant studies is shown in Table 1.

Table 1. Overview of clinical qHPV studies in males 9-26 years of age

Study number	Type of study	Primary efficacy objective	Number of subjects	Treatment groups
Protocol 020 Phase III pivotal efficacy and safety in males	Randomized (1:1), double blind, placebo-controlled, multicenter study	Demonstrate reduced incidence of HPV 6/11/16/18- related EGL (PIN; penile, perianal, and perineal cancer; and genital warts) in males MSM substudy: Demonstrate reduced combined incidence of HPV 6/11/16/18 related AIN or anal cancer	Total: 4065 males 16-26 years of age qHPV vaccine: 2032 Placebo: 2033 Total subset: 598 MSM subjects qHPV vaccine: 299 Placebo:299	qHPV vaccine 0.5mL IM dose Placebo: 0.5mL IM dose of placebo (with adjuvant; 225 mcg of aluminum as AAHS) Vaccine schedule: Day 1, Mo 2, Mo 6 Each subject was to be followed for a total of 36 months.
Protocol 016 Phase III immunogenicity and tolerability	Double-blind, multicenter international study	Demonstrate similar anti-HPV titers in males and females 10-15 years of age compared with females 16-23 years of age	510 males (10-15 years of age) 506 females (10-15 years of age) 513 females (16-23 years of age)	All 3 groups received qHPV vaccine 0.5mL IM on Day 1, Mo 2, and Mo 6
Protocol 018 Phase III immunogenicity and tolerability	Randomized (2:1), double blind, placebo-controlled, multicenter study	Demonstrate similar anti-HPV titers in males 9-15 years of age compared with females 9-15 years of age	Total : 939 females and 842 males 9-15 years of age qHPV vaccine: 567 males, 617 females Placebo : 275 males, 322 females	qHPV vaccine 0.5mL IM dose Placebo: 0.5mL IM dose of placebo (normal saline without adjuvant) Vaccine schedule: Day 1, Mo 2, Mo 6

Protocol 020

Protocol 020 (P020) was a randomized, double-blind, placebo-controlled, multicenter safety, efficacy and immunogenicity study. The study included 4065 males of whom 3463 subjects (85%) were heterosexual males (HM) aged 16 to 23 years and 602 subjects (15%) were men who have sex with men (MSM) aged 16 to 26 years. All subjects were screened on Day 1 and randomized 1:1 to receive qHPV or placebo on Day 1, Month 2 and Month 6. Subjects were recruited at 71 study sites in 18 different countries - Australia, Brazil, Canada, Costa Rica, Croatia, Finland, Germany, Mexico,

Netherlands, Norway, Peru, Philippines, Portugal, South Africa, Spain, Sweden, Taiwan, and the United States.

The primary objective of P020 was to determine whether administration of a 3-dose regimen of qHPV vaccine to men who were naïve to HPV 6, 11, 16 and/or HPV 18 at baseline would reduce their risk of external genital lesions (EGLs) (penile/perianal/perineal intraepithelial neoplasia (PIN), penile/perianal/perineal cancer and genital warts) caused by vaccine HPV types. In the MSM substudy, which was embedded within P020, the efficacy of 3 doses of qHPV vaccine against HPV 6/11/16/18-related anal intraepithelial neoplasia (AIN) and anal cancer was assessed in MSM who were naïve to the respective type at baseline.

P020 was designed to be unblinded for primary efficacy analysis when at least 32 cases of primary endpoints had accrued. The required number of cases was accrued and the study was unblinded on October 11, 2008. The median duration of follow-up as of cut-off date for the overall, HM, and MSM study populations were 34.3, 35.2, and 19.0 months respectively.

P020 was completed, and the current variation includes end-of-study results from all visits through July 31, 2009 (database frozen October 21, 2009). Median durations of follow-up at study completion for the overall, heterosexual men (HM) and MSM study populations were 35.3, 35.4, and 32.2 months, respectively. The mean post-month 7 follow-up in HPV naïve subjects was 29.7 months (overall study population).

The data analysed in this variation correspond the second and final end of clinical study report (CSR) for the original Protocol 020 study. This CSR included the analyses of the MSM substudy and updated primary efficacy and immunogenicity results of the overall study.

Study design

Study procedures

P020 was designed to detect all HPV infection and HPV-related penile/perianal/perineal lesions in all subjects. All subjects underwent external genital lesion inspection and swabbing for HPV detection at Day 1 and Months 7, 12, 18, 24, 30, and 36. The study procedures included anogenital examinations as well as sampling from the penis, scrotal, penile/perineal/perianal region in all subjects and with intra-anal Pap testing, high resolution anoscopy (HRA) and anal sampling for HPV detection in MSM at 6 month intervals. These procedures allowed for complete ascertainment of HPV-related extragenital disease in the P020 study population and anal disease in the MSM substudy population. The mandatory HRA at the final study visit further enhanced the detection of anal disease.

Study objectives

Protocol 020 was specifically designed to evaluate the efficacy of the qHPV vaccine in reducing the incidence of HPV 6, 11-, 16-, and 18-related external genital lesions (EGLs), genital warts, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal and perineal cancer), persistent infection (PI), and anal intraepithelial neoplasia (AIN) in 16- to 26-year old men (AIN Substudy of Protocol 020).

Primary safety objective: To demonstrate that a 3-dose regimen of qHPV, when administered at 0, 2 and 6 months, is generally well tolerated in young men.

Primary efficacy objective: To demonstrate that qHPV when given in a 3-dose regimen reduces the incidence of HPV 6-, 11-, 16- or 18-related external genital warts, PIN, penile, perianal or perineal cancer in young men who are naïve to the relevant HPV type, compared with placebo.

MSM Substudy efficacy objective: To investigate the impact of administration of a 3-dose regimen of qHPV on the combined incidence of HPV 6/11/16/18-related AIN or anal cancer in MSM subjects who are naïve to the relevant HPV type.

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

Immunogenicity objective: To evaluate the vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in young men.

Outcomes/endpoints

Primary endpoint

The primary endpoint was HPV 6/11/16/18-related EGL (external genital warts, PIN and penile, perianal or perineal cancer). An EGL endpoint occurred if on a single biopsy or excised tissue block, the following conditions were met:

- the Pathology Panel consensus diagnosis was condyloma acuminata (genital warts), PIN 1, PIN 2/3, penile, perianal, or perineal cancer *and,*
- at least one of HPV types 6, 11, 16, or 18 was detected by Thin section polymerase chain reaction (PCR) in an adjacent section from the same tissue block.

This endpoint was evaluated in both HM and MSM subjects. In the primary analysis of this endpoint, cases were counted beginning at 4 weeks post-dose 3 (i.e., after Month 7).

MSM Substudy endpoint

The efficacy endpoint within the MSM substudy is HPV 6/11/16/18-related AIN or anal cancer. This endpoint occurred if, on a single biopsy or excised tissue block, the following conditions were met:

- the Pathology Panel consensus diagnosis was condyloma acuminata, AIN 1, AIN 2, AIN 3, or anal cancer, and
- at least one of HPV types 6, 11, 16, or 18 was detected by Thin section PCR in an adjacent section from the same tissue block.

Secondary endpoints

- The secondary efficacy endpoint was the incidence of persistent HPV 6/11/16/18-related infection at two consecutive visits 6 months (+/- 1 month) apart.
- A further secondary efficacy endpoint is HPV 6/11/16/18-related DNA detection.

The following AIN Substudy endpoints were evaluated:

- Persistent intra-anal HPV 6, 11, 16, or 18 infection at two consecutive visits 6 months (+/- 1 month) apart.
- HPV 6, 11, 16, or 18 intra-anal DNA detection at one or more visits

Immunogenicity endpoints

The immunogenicity endpoints include GMTs, Percentage of subjects who seroconverted for the vaccine HPV types and Study populations

Definition of efficacy populations

The study populations used in vaccine efficacy analyses are as follows:

Prophylactic Efficacy Populations

- Per-protocol efficacy (PPE) population was used for the primary efficacy analysis. The PPE included subjects who: (1) were sero- and PCR-negative at Day 1 and PCR-negative through Month 7 to the appropriate vaccine HPV types; (2) received all 3 vaccinations within a one year period; and (3) generally did not deviate from the protocol. Cases were counted starting after Month 7.
- HPV-Naïve to the Relevant Type (HNRT) population was supportive to primary efficacy analysis. The HNRT included subjects who: (1) were sero- and PCR-negative at Day 1 to the appropriate vaccine HPV types; and (2) received at least 1 vaccination. Cases were counted starting after Day 1.
- The Full Analysis Set (FAS) population was supportive to primary efficacy analysis. The FAS included everyone randomized into the study (including those with prevalent infection and disease with any HPV type) and received at least 1 dose of vaccine. Cases for this population were counted starting after Day 1.

Population benefit efficacy populations

- Generally HPV Naïve (GHN) population included all subjects who: (1) were seronegative and PCR negative to all 4 vaccine HPV types at Day 1; (2) were PCR negative to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 at Day 1 and (3) for MSM subjects, had an anal Pap test result at enrolment that was negative for squamous intraepithelial lesion (SIL); and (4) received at least 1 vaccination. Cases were counted starting after Day 1.
- Full analysis set (FAS); as above

When analyses were performed for endpoints related to the MSM substudy, the populations above were used as defined, but restricted to MSM subjects only.

The defined efficacy populations are the same as those used previously in the female clinical trials and are considered appropriate.

Definition of immunogenicity populations

Per-Protocol Immunogenicity (PPI) Population

The per-protocol population for immunogenicity (PPI) analysis generally included subjects who received all 3 injections; had a Day 1 serum sample and (for all subjects except those <16 years of age in Protocols 016 and 018) Day 1 PCR samples within acceptable day ranges of the first vaccination and were seronegative to the appropriate vaccine HPV types before the first injection and (for all subjects except those <16 years of age in Protocols 016 and 018) PCR-negative to the appropriate vaccine HPV types through Month 7.

All Naïve Subjects with Serology (ANSS):

The supportive analyses of immunogenicity were conducted using the ANSS population. This population included subjects who received at least one dose of study vaccine; provided serology data and were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to the relevant HPV types.

The defined immunogenicity populations are the same as those used previously in the female clinical trials and are considered appropriate.

Sample size

To determine the sample size needed to obtain 32 endpoint cases, several assumptions were made. In the HM population, it was assumed that (i) rates of pre-positivity to HPV 6/11, 16, and 18 were 15%, 18%, and 10%, respectively and in MSM 36%, 18%, and 10%, respectively and (ii) attrition rates were 5% annually. Under these assumptions and with a sample size of 4040, approximately 2500 subjects were expected to complete the study through Month 36 and be eligible for the primary analysis for each of the 4 vaccine HPV types. Some 330 additional eligible subjects were expected to drop out post-Month 7 and were to contribute an average of half the follow-up time. Assuming that 6500 person-years would be accrued by the end of the follow-up period, the incidence rate for the primary endpoint is 1% per year, and the vaccine is highly efficacious, 32 cases were expected to occur by the end of the follow-up period in the placebo group. With 32 cases observed across both treatment groups, 9 or fewer cases in the vaccine group would result in a conclusion that the vaccine is efficacious.

Approximately 590 subjects were expected to be enrolled into the evaluation in MSM substudy. In this subgroup, it was assumed that (i) rates of pre-positivity to HPV 6/11, 16, and 18 were 36%, 18%, and 10%, respectively; (ii) the incidence rate of vaccine type AIN was 5.5% annually; (iii) attrition rates were 5.5% annually. Under these assumptions, it was expected that 24 cases of HPV 6/11/16/18-related AIN would occur at Month 36. A minimum of 17 cases of HPV 6/11/16/18 related AIN would be required in order to achieve at least 90% power for the MSM substudy hypothesis, assuming the true efficacy of the vaccine is 85%. If there was equal follow-up in the vaccine and placebo groups, among the 17 endpoint cases, 4 or fewer cases in the vaccine group would result in a conclusion that the vaccine is efficacious.

It was expected that 107 cases of the secondary endpoint persistent HPV 6, 11, 16, or 18 infection would be observed between Month 7 and Month 36. This assumed annual incidence rates for persistent infection (PI) with HPV 6/11, 16, and 18 of 4%, 4%, and 2%, respectively, among the evaluation of MSM sites; and of 1%, 1%, and 0.2% respectively, among the remaining sites. If there was equal follow-up in the vaccine and placebo groups, among the 107 cases of HPV 6,11,16, or 18 infections, 35 or fewer cases in the vaccine group would result in a conclusion that the vaccine is efficacious. By definition, there were more cases of the secondary endpoint HPV 6, 11, 16 or 18 DNA detection than PI cases. Therefore, it was expected that more than 107 cases of HPV detection would be observed between Month 7 and Month 36. The power for the secondary efficacy hypothesis, incorporating the multiplicity adjustment, was 99.9% assuming true vaccine efficacy of 80%.

Interim analyses

No interim analyses were performed for the primary or secondary efficacy endpoints in this study. The primary efficacy analysis was conducted when 32 primary efficacy cases were observed. Conclusions regarding the success of the study were drawn from the result of this analysis. Estimates of VE and immunogenicity were updated after Month 36 follow-up was completed in all subjects, since the primary analysis was conducted at an earlier time.

An interim summary of the MSM substudy endpoint was performed at the time of the primary analysis since the case target of 17 in the MSM substudy was not achieved prior to unblinding. Although no inference was made regarding the MSM substudy endpoint based on this interim summary, a Haybittle-Peto group sequential interim analysis plan was used for the interim summary and substudy efficacy analysis.

Analyses conducted but not pre-specified in the SAP

1) Analysis of VE against HPV 6/11/16/18-related intra-anal persistent infection. This analysis was performed to support the MSM substudy analysis of vaccine efficacy against HPV 6/11/16/18-related AIN and anal cancer. This analysis was planned after unblinding occurred.

2) Summary of rates of new sexual partners. This analysis was conducted for the purpose of providing a measure of the risk of acquisition of HPV infection or disease in the vaccine and placebo groups. This analysis was planned prior to unblinding.

Study population/ Main inclusion and main exclusion criteria

The study subjects were healthy 16- to 26-year-old men. (For HM: 16 years to 23 years and for MSM: 16 years to 26 years). Subjects were enrolled in community health centres, college campuses, and at primary health care provider sites. There was no pre-screening visit for HPV.

A main inclusion criterion was: HM who have experienced sexual debut but have had no more than 5 lifetime sexual partners.

HIV infection was an exclusion criterion.

Randomisation and treatment

Subjects were randomized in a 1:1 ratio to qHPV vaccine or placebo, in each region and within each age stratum. Each subject received an allocation number (AN) and was randomised to vaccination group within each centre.

Study Results

Study population

A total of 4076 young men were randomized in the study. Of these, 11 allocation numbers for subjects with randomization issues were excluded from all analyses. These 4065 men (qHPV 2032/placebo 2033) included 3463 heterosexual male (HM) subjects aged 16 to 23 years; and 602 men who have sex with men (MSM) aged 16 to 26 years. The MSM subjects were enrolled at selected sites to participate in the Intra-anal Evaluation in the MSM substudy.

Subject disposition

Overall, 91.2% of all subjects completed the vaccination phase and 81.4% completed the follow-up phase (Table 2). The proportions of subjects who discontinued during the vaccination period and follow-up and the reasons for discontinuation within this period were generally well balanced between the 2 vaccination groups. Few subjects discontinued due to clinical adverse events. Discontinuation rates in the vaccination period and follow-up period were similar in the HM and MSM populations.

Table 2. Subject disposition (All subjects -Protocol 020

	qHPV vaccine n (%)	Placebo n (%)	Total n (%)
Screening failures			99
Randomized	2032	2033	4065
Vaccinated Dose 1	2025 (99.7)	2030 (99.9)	4055 (99.8)
Vaccinated Dose 2	1936 (95.3)	1929 (94.9)	3865 (91.2)
Vaccinated Dose 3	**1860 (91.5)**	**1846 (90.8)**	**3706 (91.2)**
Vaccination period (Day 1 through Month 7)			
Entered	2025	2030	4055
Completed	1818 (89.8)	1814 (89.4)	3632 (89.6)
Discontinued	**207**	**216**	**423 (10.4)**
With long-term follow-up	4	7	11
Clinical AEs	2	4	6
Other reasons	2	2	4
Without long-term follow-up	203	209	412
Lost to follow-up	11 (5.5)	112 (5.5)	223 (5.5)
Moved	20	21	41
Withdrew consent	64	69	133 (3.3)
Other reasons	5	5	10
Follow-up period (after Mo 7)			
Entered	1822	1821	3643
Completed	**1487 (81.6)**	**1479 (81.2)**	**2966 (81.4)**
Discontinued	**335 (18.4)**	**342 (18.8)**	**677 (18.6)**
Clinical AEs	3	10	13
Lost to follow-up	232 (12.7)	226 (12.4)	458 (12.6)
Moved	40	36	76
Other reasons	10	9	19
Withdrew consent	50	61	111 (3.0)

Subject Accounting

Among the 4,055 subjects belonging to the FAS, 2,551 (63%), 2,630 (65%), and 2,755 (68%) were eligible for the PPE analysis related to HPV types 6/11, 16, and 18, respectively.

The MSM Substudy primary efficacy analysis was conducted in the PPE population. Among the 598 substudy subjects enrolled who received at least one injection in the study, 50%, 58%, and 63% were eligible for the AIN PPE analyses related to HPV types 6/11, 16, and 18, respectively.

The most common reasons for exclusion from each of the HPV 6/11, HPV 16, and HPV 18 PPE populations were Day 1 through Month 7 positivity to the relevant HPV type (i.e., prevalent disease or incident disease before the full vaccination series take effect), 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.

Table 3 shows the number of subjects who were eligible for the HPV type-specific PPE analyses and who had follow-up during the efficacy phase (i.e., after Month 7) for the endpoints of EGL, persistent infection, DNA detection, and, in MSM subjects, HPV 6/11/16/18-related AIN and anal cancer.

Table 3. Number of subjects with efficacy phase follow-up in PPE population by vaccination group

	qHPV vaccine N=2032	Placebo N=2033	Total N=4065
HPV 6/11/16/18 PPE-Eligible	**1429**	**1448**	**2877**
With Follow up for HPV 6/11/16/18 related EGL	1394	1404	2798
With Follow up for HPV 6/11/16/18 related persistent infection	1390	1402	2792
With Follow up for HPV 6/11/16/18 related DNA detection	1390	1402	2792
HPV 6/11/16/18 MSM PPE-Eligible	**292**	**216**	**418**
With Follow up for HPV 6/11/16/18 related AIN and anal cancer	194	208	402

Baseline demographics

P020 enrolled subjects from racially and geographically diverse populations. Only 12.2% of the study subjects originated from Europe. The median age of enrolled subjects was 20 years. MSM Substudy subjects represented 14.8% of the overall study population and had a median age of 22 years. A total of 187 subjects (4.6%) <18 years of age were enrolled.

The two vaccination groups were well balanced with respect to the demographics in all study populations (All subjects, HM, and MSM subjects).

Sexual demographics

Overall 99.5% of all subjects had experienced sexual debut at study entry. For all subjects, the median age at first intercourse among non-virgins was 17 years and the median number of lifetime sex partners was 3. Approximately 43.3% of subjects reported a new sexual partner within the 6 months prior to study start. The proportion of subjects who used condoms at enrollment was comparable between the vaccination groups.

Among MSM subjects, 96.2% had experienced sexual debut with a male partner and 25.2% had experienced sexual debut with a female partner. Among MSM subjects, the median age at first intercourse with a male partner was 18 years. For HM subjects, the median age at first intercourse with a female partner was 17 years. Approximately 60.3% of MSM subjects reported a new male sexual partner within the 6 months prior to study start, while ~2.4% of HM subjects had reported a new female sexual partner within the 6 months prior to study start.

In general, the proportions of history of sexually transmitted infection (STI) at enrolment were comparable between the two vaccination groups for all subjects, as well as for the HM and MSM populations.

HPV 6, 11, 16, and 18 Serostatus and DNA Detection at Day 1

In both vaccination groups, ~8% of subjects (23% MSM) were positive to a vaccine HPV type by serology, and ~ 12% (MSM 30.5%) were positive by PCR. Across both vaccination groups, the proportion of subjects who were HPV positive by serology and by PCR was higher in the MSM population (~39%) when compared to the HM population (~17%).

The proportions of subjects found to be anti-HPV 6, anti-HPV 11, anti-HPV 16, or anti- HPV 18 seropositive were comparable between the two vaccination groups. Day 1 anti-HPV 6 seropositivity was the most common.

Overall, 25% (45 of 178) and 19% (12 of 62) of subjects who at Day 1 were anti-HPV 6 and anti-HPV 11 seropositive, respectively, were also PCR positive to the same HPV type at Day 1. The corresponding proportions for HPV 16 and 18 were comparable to those for HPV 6 and 11. Overall,

34% (32 of 93) and 20% (9 of 44) of subjects who were seropositive at Day 1 to HPV types 16 and 18, respectively, were also PCR positive to the same type.

For each vaccine HPV type, the proportion of seropositive subjects who were also PCR positive to the same HPV type at Day 1 were higher in the MSM population than in the HM population as follows: HM subjects: 11%, 4%, 16%, and 12% for HPV 6, 11, 16, and 18, respectively; and MSM subjects: 42%, 29%, 57%, and 26% for HPV 6, 11, 16, and 18, respectively.

Case assignment analysis of the per-protocol vaccine group AIN cases

Methodology: Throughout the qHPV vaccine program, an endpoint of AIN related to HPV 6, 11, 16, or 18 is defined to occur if that HPV type is identified in an adjacent section from the same tissue block in which the lesion is diagnosed, regardless of the presence of non-vaccine high-risk HPV types. In an effort to better understand the potential involvement of non-vaccine types in the development of the AIN cases in the PPE population, these cases were all reviewed with regard to the vaccine and non-vaccine HPV types identified in anogenital swab specimens before the diagnoses for which the subjects became cases. Vaccine type-related AIN cases in which more than one HPV type was found were assessed for evidence of preceding infection with a non-vaccine high-risk HPV type. For these cases, the presence of HPV types in swab samples from the two preceding visits was evaluated. If an HPV type was detected in at least one swab sample from at least one of the two visits as well as in the lesion, that type was considered to be causal. More than one HPV type could be considered causal. If none of the HPV types detected in the lesion were found in either of the two preceding swab samples, the lesion was attributed to the lesional HPV types.

Prevention of any HPV type AIN and anal cancer

The analysis of efficacy with respect to evaluation of the impact of qHPV vaccine on the incidence of any type anal disease was performed using the MSM GHN and the MSM FAS populations.

EFFICACY RESULTS

Primary endpoint analysis: Efficacy against HPV 6/11/16/18-related EGL

PPE Population

The vaccine efficacy (VE) against HPV 6/11/16/18-related EGL in the PPE population was 90.6% (Table 4). There were a total of 3 EGL cases in the vaccine group and 32 cases in the placebo group. All of the cases in the vaccine group and the majority of the cases in the placebo group had positive PCR results for HPV types 6 and/or 11 and were from diagnoses of condyloma. Of the 32 cases in the placebo group, 4 were due to diagnoses of PIN 1 or worse, with 2 cases of PIN 2/3 identified. No cases of cancer were detected during the study.

The two vaccine subjects, who were cases of HPV 6-related EGL, had anti-HPV 6 titers at Month 7 that were comparable to the GMTs among per-protocol subjects who received the qHPV and were naïve to HPV type 6 during the vaccination period. The vaccine subject who was diagnosed with an EGL related to HPV types 6 and 11 had anti-HPV 6 and 11 titers at Month 7 that were considerably above the levels observed among per-protocol HPV-naïve recipients as well as those who had evidence of prior infection of types 6 or 11 at Day 1. Thus, these results do not suggest a failure of efficacy related to low antibody titers.

Table 4. Analysis of efficacy against HPV 6/11/16/18-related EGL by sexual orientation, HPV type and lesion type (PPE population)

Endpoint	qHPV vaccine N=2025		Placebo N=2030		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 EGL	**1,394**	**3**	**1,404**	**32**	**90.6**	**(70.1, 98.2)**
By sexual orientation						
HM subjects	1,200	2	1,196	26	92.4	(69.6, 99.1)
MSM subjects	194	1	208	6	82.1	**(-47.8, 99.6)**
By HPV type						
HPV 6-related EGL	1,242	**3**	1,243	**19**	**84.2**	**(46.2, 97.0)**
HPV 11-related EGL	1,242	**1**	1,243	**11**	**90.9**	**(37.2, 99.8)**
HPV 16-related EGL	1,292	0	1,270	3	100	(-138.4, 100)
HPV 18-related EGL	1,331	0	1,352	1	100	(-3846.1, 100)
By lesion type						
Condyloma	**1,394**	**3**	**1,404**	**28**	**89.3**	**(65.3, 97.9)**
P1N 1 or worse	1,394	0	1,404	4	100	(-51.1, 100)
PIN 1	1,394	0	1,404	2	100	(-24.9, 100)
PIN 2/3 or cancer	**1,394**	**0**	**1,404**	**2**	**100**	**(-434.7, 100)**
PIN 2/3	1,394	0	1,404	2	100	(-434.7, 100)
Cancer	1,394	0	1,404	0	NA	NA

A cumulative incidence curve over time of vaccine type EGL by vaccination group showed that the incidence rate in the placebo group increased during the entire duration of follow-up while, the incidence rate in the vaccine group remained low indicating persisting vaccine-induced protection against HPV 6/11/16/18 EGL over the 36 months of the study.

HNRT and FAS population

Vaccine efficacy was 76.3% in the HNRT population and 66.7% in the FAS population. As expected, VE was lower for the EGL endpoint in the FAS and HNRT populations. The analyses of the HNRT and FAS populations generally support the primary PPE analysis of efficacy against HPV 6/11/16/18-related EGL.

HNRT population

Any cases that occurred after the first vaccination were included in this analysis. VE for this population was 76.3%, which is lower than the VE in the PPE population.

A cumulative incidence curve over time of HPV 6/11/16/18-related EGL by vaccination group for the HNRT population showed that in the placebo group cases occurred evenly over the duration of follow-up. For the vaccine group, the time-to-event plot showed that many of the cases occurred early in the follow-up period, before the Month 12 visit. After the Month 12 visit, the cumulative incidence curve for vaccine recipients begins to plateau. This suggests that most of the cases in the vaccine group occurred before the full benefit of the 3-dose vaccination regimen took effect.

FAS population

Vaccine efficacy for this population was 66.7% (Table 5). VE was lower for the EGL endpoint in the FAS than in the PPE and HNRT populations. Similar to the PPE and HNRT populations, a majority of the endpoint cases for the FAS are due to HPV types 6 and/or 11 and had a diagnosis of condyloma.

Table 5. Analysis of efficacy against HPV 6/11/16/18-related EGL by sexual orientation, HPV type and lesion type (FAS population)

Endpoint	qHPV vaccine N=2025		Placebo N=2030		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV6/11/16/18 EGL	**1,943**	**27**	**1937**	**80**	**66.7**	**(48.0, 79.3)**
By sexual orientation						
HM subjects	1,653	21	1648	57	63.8	(39.3, 79.1)
MSM subjects	290	6	289	23	74.0	(34.4, 91.4)
By HPV type						
HPV 6	1,943	21	1,937	52	60.1	(32.5, 77.1)
HPV 11	1,943	6	1,937	26	77.2	(43.2, 92.3)
HPV 16	1,943	3	1,937	11	72.9	(-2.6, 95.1)
HPV 18	1,943	2	1,937	3	33.7	(-478.8, 94.5)
By lesion type						
Condyloma	**1,943**	**24**	**1,937**	**74**	**68.1**	**(48.8, [illegible])**
PIN 1 or worse	1,943	6	1,937	6	0.3	(-272.[illegible])
PIN1	1,943	3	1,937	4	25.3	(-34[illegible])
PIN 2/3 or cancer	**1,943**	**3**	**1,937**	**3**	**0.4**	**(-643.4, 86.7)**
PIN 2/3	1,943	3	1,937	3	0.4	(-643.4, 86.7)
Cancer	1,943	0	1,937	0	NA	NA

Secondary efficacy endpoint analysis

- **Efficacy against HPV 6/11/16/18-related persistent infection**

PPE Population

Vaccine efficacy against HPV 6/11/16/18-related persistent infection (PI) (6-month definition) was 85.5% in the PPE population (Table 6).

Table 6. Analysis of efficacy against HPV 6/11/16/18-related persistent infection by sexual orientation, and HPV type (PPE population)

Endpoint	qHPV vaccine N=2025		Placebo N=2030		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 persistent infection	**1,390**	**21**	**1,402**	**140**	**85.5**	**77.0, 91.3**
By sexual orientation						
HM subjects	1,196	16	1,194	99	84.5	(73.5, 91.5)
MSM subjects	194	5	208	41	88.0	(69.5, 96.3)
By HPV type						
HPV 6	1,238	5	1,242	50	90.1	(75.3, 96.9)
HPV 11	1,238	1	1,242	18	94.4	(64.7, 99.9)
HPV 16	1,288	13	1,268	61	79.3	(61.9, 89.6)
HPV 18	1,327	2	1,350	33	93.9	(76.3, 99.3)

Source: Adapted from Module 5 Clinical Study report, V501 -P020V1 – Table 11-16

There were 21 cases in the vaccine group and 140 cases in the placebo group. The majority of the cases of PI in the vaccine and placebo groups were due to HPV types 6 and 16.

The cumulative incidence curve over time showed that the PI events occurred most frequently at the points during follow-up when scheduled visits occurred, i.e. Month 12, 18, 24, and 30 because the swab samples are obtained at these visits. The rate of increase in the cumulative incidence around these time points was much higher in the placebo group when compared to the vaccine group.

HNRT Population

VE for this population was 70.8% and is lower than that in the PPE population. Any cases that occurred after Day 1 were included in this analysis and it is expected that the VE in this population is lower. The majority of the PI cases in both the vaccine and placebo groups were related to HPV types 6 and 16 as in the PPE population.

The cumulative incidence curve over time showed that the incidence of PI was lower in the vaccine group than in the placebo group. In the vaccine group, the largest increase in the rate of cases of HPV 6/11/16/18-related PI was between Month 6 and Month 7. These cases of PI likely began before the full benefit of the 3-dose vaccine regimen took effect.

FAS population

VE for this population was 52.2% (95% CI: 42.0, 60.7) (Table 7). Efficacy for HPV 6/11/16/18-related PI was lower in the FAS than in the PPE and HNRT populations. This is expected due to the inclusion of infections that were present at Day 1.

The cumulative incidence curve over time of HPV 6/11/16/18-related PI by vaccination group for the FAS showed that as in the HNRT population, there were many cases of PI that began between Month 6 and Month 7 in both the vaccine and placebo groups. In the vaccine group, the largest increase in the rate of cases of PI occurred within this time interval. After Month 7, the cumulative incidence increases at a faster rate in the placebo group than in the vaccine group.

Table 7. Analysis of efficacy against HPV 6/11/16/18-related persistent infection by sexual orientation, and HPV type (FAS population)

Endpoint	qHPV vaccine N=2025		Placebo N=2030		Observed efficacy %	95% CI
	N	Number of cases	N	Number of cases		
HPV 6/11/16/18 persistent infection	**1818**	**161**	**1817**	**321**	**52.2**	**42.0, 60.7**
By sexual orientation						
HM subjects	1543	99	1541	204	53.4	40.4, 63.7
MSM subjects	275	62	276	117	52.0	34.2, 65.3
By HPV type						
HPV 6	1818	68	1817	137	51.4	34.5, 64.2
HPV 11	1818	17	1817	49	65.7	39.4, 81.5
HPV 16	1818	80	1817	161	51.5	36.3, 63.4
HPV 18	1818	30	1817	70	57.8	34.3, 73.4

- **Efficacy against HPV 6/11/16/18-related DNA detection**

The secondary endpoint referred to as DNA detection was defined as the detection of HPV 6, 11, 16, or 18 DNA by PCR in anogenital specimens collected on at least one visit. By definition, this endpoint includes cases of HPV-related persistent infection, external disease and intra-anal disease, in addition to cases where a subject is PCR positive on at least one swab or biopsy specimen, but not a case of disease or persistent infection. DNA detection can be considered a composite of these single endpoints.

PPE population

The VE against HPV 6/11/16/18-related DNA detection was 51.0% (Table 8). There were 153 cases in the vaccine group and 303 cases in the placebo group. The majority of the cases in both treatment groups were due to HPV types 6 and 16.

The cumulative incidences in the vaccine and placebo groups were similar around Month 12. As follow-up continued the cumulative incidence in the vaccine group did not increase as quickly as the cumulative incidence in the qHPV placebo group.

Table 8. Analysis of efficacy against HPV 6/11/16/18-related DNA at 1 or more visits by sexual orientation, and HPV type (PPE population)

Endpoint	qHPV vaccine N=2025		Placebo N=2030		Observed efficacy %	95% CI
	N	Number of cases	N	Number of cases		
HPV 6/11/16/18 DNA	**1,390**	**153**	**1,402**	**303**	**51.0**	**(40.3, 59.9)**
By sexual orientation						
HM subjects	1,196	125	1,194	229	47.3	(34.1, 57.9)
MSM subjects	194	28	208	74	62.1	(40.7, 76.1)
By HPV type						
HPV 6	1,238	59	1,242	115	49.1	(29.7, 63.4)
HPV 11	1,238	20	1,242	49	59.2	(33.0, 77.0)
HPV 16	1,288	69	1,268	143	53.0	(37.0, 65.3)
HPV 18	1,327	29	1,350	79	63.2	(43.1, 76.9)

HNRT and FAS population

Similar analyses were conducted in the HNRT and FAS populations and VE estimates were lower than that for the PPE population. VE for the HNRT was 40.5% (95% CI: 30.7, 49.0) and for the FAS was 32.1% (95% CI: 22.8, 40.3). The number of cases in the vaccine and the placebo group was 275 vs. 444 (HNRT) and 410 vs. 581 (FAS).

Efficacy results AIN substudy in MSM

Subject disposition

A total of 602 subjects were randomized into the substudy. The number of subjects who received at least one vaccination was 598. Overall, 91.1% of all subjects completed the vaccination phase. The proportions of subjects who completed the vaccination phase were comparable between the group that received vaccine and the placebo group. During the vaccination period, 6 subjects (1%) withdrew consent and 2 subjects (0.3%) discontinued due to an AE. Overall 432 subjects (78.3%) completed the follow-up phase. Ninety subjects (16.3%) were lost to follow-up, 14 subjects (2.5%) withdrew consent and none discontinued due to an adverse experience.

The mean duration of follow-up at the time of the analysis of the AIN Substudy endpoint was ~2.0 years for the PPE population (post-Month 7) and approximately 2.4 years for the HNRT population (post-Day 1) in the substudy population.

Efficacy against HPV 6/11/16/18-related AIN and anal cancer

MSM PPE Population

The PPE population included a total of 402 subjects. Efficacy against HPV 6/11/16/18-related AIN was 77.5% (95% CI: 39.6, 93.3) (Table 9). There were a total of 5 AIN cases in the vaccine group and 24 cases in the placebo group. All of the cases in the vaccine group and the majority of the cases in the placebo group had positive PCR results for HPV types 6 and/or 16 (see below). Success was achieved

in the test of the AIN substudy efficacy hypothesis showing that VE against HPV 6/11/16/18-related AIN was above 0% with a p-value <0.001.

Of the 24 cases in the placebo group, 13 were identified with diagnoses of AIN 2 or worse. In the vaccine group, there were 3 cases identified with diagnoses of AIN 2 or worse out of the total of 5 cases. The VE estimate for HPV 6/11/16/18-related AIN 2 or worse was 74.9%, (95% CI: 8.8, 96.4), which indicates that the VE for this endpoint is statistically significant with a lower bound above 0%. There were a total of 9 cases of HPV 16/18-related AIN 2 or worse. Of these, 1 case was in the vaccine group and 8 were in the placebo group. No cases of cancer were detected during the study.

Table 9. Efficacy against HPV vaccine type related AIN and anal cancer by HPV type and lesion type (MSM PPE population)

Endpoint	qHPV vaccine N=299		Placebo N=299		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 AIN	**194**	**5**	**208**	**24**	**77.5**	**39.6, 93.3**
By HPV type						
HPV 6	141	3	144	10	67.5	-26.4, 94.2
HPV 11	141	0	144	6	100	9.3, 100
HPV 16	**167**	**2**	**170**	**6**	**66.5**	**-92.8. 96.6**
HPV 18	**173**	**0**	**193**	**4**	**100**	**-70.0, 100**
By lesion type						
AIN 1	194	4	208	16	73.0	**16.3, 93.4**
Condyloma acuminatum	194	0	208	6	100	8.2, 100
Non-aciuminate	194	4	208	11	60.4	-33.5, 90.8
AIN 2 or worse	**194**	**3**	**208**	**13**	**74.9**	**8.8, 95.4**
AIN 2	194	2	208	9	75.8	-16.9, 97.5
AIN 3	194	2	208	6	63.7	-103.0, 96.4
Anal cancer	194	0	208	0	NA	NA

The case assignment methodology led to the re-assignment of 3 of the HPV 6/11/16/18-related AIN lesions in the vaccine group and none of the lesions in the placebo group, resulting in a 2/24 vaccine/placebo case split (compared to 5/24 in the original analysis) and efficacy of 91.1% (95% CI: 64.2%, 99.0%), compared to efficacy of 77.5% (95% CI: 39.6, 93.3) in the original analysis (Table 10). The vaccine/placebo case split for vaccine type related high-grade AIN was now 1/13 (compared to 3/13 in the original analysis), resulting in efficacy of 91.7% (95% CI: 44.6, 99.8%).

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

Table 10. Efficacy against HPV vaccine type related AIN and anal cancer by HPV type and lesion type after removing cases attributed to non-vaccine HPV types (MSM PPE population)

Endpoint	qHPV vaccine N=299		Placebo N=299		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 AIN	**194**	**2**	**208**	**24**	**91.1**	**64.2, 99.0**
By HPV type						
HPV 6	141	1	144	9	88.0	13.7, 99.7
HPV 11	141	0	144	6	100	9.3, 100
HPV 16	167	1	170	6	65.5	-41.3, 96.6
HPV 18	173	0	193	4	100	-70.0, 100
By lesion type						
AIN 1	194	2	208	16	86.6	43.0, 98.6
Condyloma acuminatum	194	0	208	6	100	8.2, 100
Non-aciuminate	194	2	208	11	80.4	10.0, 97.9
AIN 2 or worse	**194**	**1**	**208**	**13**	**91.7**	**44.6, 99.8**
AIN 2	194	1	208	9	87.9	1[illegible]0. 99.7
AIN 3	194	1	208	6	81.9	**-79.4,** 99.6

MSM HNRT Population

The VE against HPV 6/11/16/18-related AIN and anal cancer for this population is 76.9% (95% CI: 51.4, 90.1). The VE is comparable to that shown in the MSM PPE population even though any cases that occurred after the first vaccination were included in the HNRT analysis and the full benefit of the 3-dose vaccination does not occur until after the third dose.

The cumulative incidence curve over time of HPV 6/11/16/18-related AIN and anal cancer in HNRT showed that cases in the placebo group occurred evenly over the duration of follow-up. For the vaccine group, the time-to-event plot shows that all of the cases occurred in the first half of the follow-up period. Between the Month 18 and Month 24 visit, the cumulative incidence curve for vaccine recipients begins to plateau, while the curve in the placebo group continues to increase.

MSM FAS population

The FAS population included a total of 551 subjects. VE for this population was 50.3% (95% CI: 25.7, 67.2) (Table 11). Efficacy was lower for the AIN endpoint in the MSM FAS than in the PPE and HNRT populations. Similar to the MSM PPE and MSM HNRT populations, the 95% CI for VE against HPV 6/11/16/18-related AIN 2 or worse remains above 0%.

Table 11. Efficacy against HPV vaccine type related AIN and anal cancer by HPV type and lesion type (MSM FAS population)

Endpoint	qHPV vaccine N=299		Placebo N=299		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 AIN	**275**	**38**	**276**	**77**	**50.3**	**25.7, 67.2**
By HPV type						
HPV 6	275	18	276	47	61.7	(32.8, 79.1)
HPV 11	275	13	276	25	47.3	(-7.1, 75.2)
HPV 16	275	8	276	18	54.9	**(-9.0, 83.0)**
HPV 18	275	5	276	11	53.7	**(-44.6, 87.4)**
By lesion type						
AIN 1	275	31	276	62	49.6	(21.2, 68.4)
Condyloma acuminatum	275	13	276	31	57.2	(15.9, 79.5)
Non-aciuminate	275	27	276	48	43.3	(7.3, 66.0)
AIN 2 or worse	**275**	**18**	**276**	**39**	**54.2**	**18.0, 75.3)**
AIN 2	275	11	276	29	61.9	(21.4, 82.8)
AIN 3	275	10	276	19	46.8	**(-20.2,** 77.9)
Anal cancer	275	0	276	0	NA	NA

The cumulative incidence curve over time of HPV 6/11/16/18-related AIN and anal cancer by vaccination group for the AIN Substudy FAS population showed separation of the vaccine and placebo groups as the rate of incident disease related to prevalent infections in the vaccine group declines, providing further support for the effect of HPV vaccination in this non HPV-naïve population.

Efficacy against HPV 6/11/16/18-related intra-anal persistent infection (PI) – Post-hoc analysis

To support the MSM substudy efficacy analysis of AIN and anal cancer in the MSM PPE population, an analysis was performed to evaluate VE against HPV 6/11/16/18-related intra-anal PI. This analysis is similar to the secondary efficacy analysis performed for the PI endpoint, but here only intra-anal specimens from subjects in the MSM PPE population were used to assess the efficacy of the vaccine on PI in the intra-anal region.

MSM PPE population

VE against HPV 6/11/16/18-related intra-anal PI (6-month definition) for the MSM PPE population was 94.9% (95% CI: 80.4, 99.4) (Table 12). There were a total of 2 cases in the vaccine group and 39 cases in the placebo group. The qHPV vaccine demonstrated to be efficacious against HPV 6/11/16/18-related intra-anal PI, and importantly also against those related to HPV 16 (VE: 93.8%) and HPV 18 (VE: 100%).

Table 12. Efficacy against HPV vaccine type related persistent infection and anal cancer by HPV type and lesion type (MSM PPE population)

Endpoint	qHPV vaccine N=299		Placebo N=299		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 persistent anal infection	**193**	**2**	**208**	**39**	**94.9**	**80.4, 99.4**
By HPV type						
HPV 6	140	1	144	13	92.1	47.2, 99.8
HPV 11	140	0	144	5	100	-15.5, 100
HPV 16	166	1	170	16	**93,8**	**60.0, 99.9**
HPV 18	172	0	193	10	**100**	**51.5, 100**

Population benefit analyses

An important public health question in the evaluation of the qHPV vaccine is whether vaccination reduces the overall incidence of intra-anal and external genital disease and health care resource utilization.

Population benefit was measured through assessing impact of qHPV vaccine on reducing incidence of EGL and intra-anal disease due to any HPV type and incidence of intra-anal and external genital procedures and therapies. Two populations were used 1) GHN: this population was designed to represent HPV-naïve boys and men and 2) FAS population, which approximates the general population of sexually-active 16- to 26-year-old men. Subjects in the GHN population were required to be DNA negative to all 14 HPV types tested at Day 1 and Se negative for the Vaccine HPV types and MSM subjects were also required to have a negative intra-anal Pap test on Day 1.

Incidence of overall EGLs

GHN population

In the GHN population, the disease reduction of EGL due to any HPV type was 81.5% (95% CI: 58.0, 93.0). High efficacy against EGL due to any HPV type is expected, given that vaccine HPV types are the predominant types in EGL. The VE estimates for EGL related to any of the 10 non-vaccine HPV types and for EGL not related to any of the 14 assay-identified HPV types in the GHN population were 67.1% (95% CI: -83.9, 96.8) and 41.5% (95% CI: -201, 90.9), respectively. VE against genital warts due to any HPV type was 85.2% (95%CI: 61.8, 95.5). This result is similar to the VE estimate for GWs due to vaccine HPV types (89.3%) since the predominant HPV types are 6 and 11. No significant VE was observed against PIN 1 or worse due to any HPV type (50.7% (95% CI: -244.3, 95.5) or against PIN 2/3 due to any HPV type (100% (95% CI:-425.5, 100).

FAS population

The disease reduction of EGL due to any HPV type was 59.3% (95% CI: 40.0, 79.2) in the FAS. Although VE was lower than in the GHN population, the observed reduction of EGL due to any HPV type in the FAS is of clinical relevance.

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. The VE estimates for EGL

related to any of the 10 non-vaccine HPV types and for EGL not related to any of the 14 assay-identified HPV types in the GHN population were non-significant as the lower bound of CIs were <0%.

The VE estimates for EGL related to any of the 10 non-vaccine HPV types and for EGL not related to any of the 14 assay-identified HPV types were 50.3% (95% CI: -16.5, 80.3) and 34.5% (95% CI: -74.3, 76.8), respectively, in the FAS. VE against genital warts due to any HPV type was 61.8% (95% CI: 42.3, 75.3) in the FAS. The VE against PIN 1 or worse due to any HPV type was -13.9% (95% CI: -269, 63.9) and against PIN 2/3 or cancer due to any HPV type is 0.4% (95% CI: -643, 86.7) in the FAS.

Incidence of external genital procedures and therapies

In the analyses of EGL therapies all therapies were included that could potentially be associated with HPV-related EGL (i.e., surgical therapies including excision, laser ablation, cauterization, coagulation, and cryotherapy, and non-surgical therapies including topical treatments, chemical ablation).

In both the GHN and the FAS, there were positive reductions in the incidence of EGL biopsies, EGL therapies overall and surgical external genital therapies in the vaccine group compared to the placebo group. Reduction of EGL therapies was 47.7% (95% CI: 18.4, 47.1) in the GHN population and 38.1% (95% CI: 19.4, 52.6) in the FAS. Reduction of EGL biopsies was 54.2% (95% CI: 28.3, 71.4) in the GHN population and 45.7% (95% CI: 29.0, 58.7) in the FAS. There was however, insufficient evidence in both study populations to conclude that the vaccine has a positive effect on the incidence of non-surgical procedures.

MSM GHN population

The estimate of disease reduction of AIN due to any HPV type in the MSM GHN population was 54.9% (95% CI: 8.4 79.1) which was statistically significant (lower bound CI was above 0 estimates against AIN related to any of the 10 assay-identified non-vaccine HPV types and against AIN not related to any of the 14 assay-identified HPV types were negative (VE: -35.1% and -20.7%, respectively). Of note the numbers of cases related to non-vaccine HPV types were low because of the limited sample size in the MSM GHN population.

The results of the analysis of efficacy against AIN 1 (intra-anal condyloma acuminatum and non-acuminate AIN 1) due to any HPV type showed VE of 67.2% (95% CI: 14.5, 89.3). The lower bound of the CI is above 0%, indicating positive VE for this endpoint. However, the VE estimates for the individual endpoints intra-anal condyloma acuminatum due to any HPV type and nonacuminate AIN 1 due to any HPV type did not reach statistical significance. For intra-anal condyloma due to any HPV type, the disease reduction (82.3% (95% CI -46.0, 99.6) was of similar magnitude as that observed for extragenital condyloma, but only a trend was observed.

No statistically significant efficacy against AIN 2 or worse (AIN 2, AIN 3, or anal cancer) due to any HPV type was observed (VE 52.5% (95% CI: -14.8, 82.1).

MSM FAS population

Reduction of disease against AIN due to any HPV type, AIN related to any of the 10 assay-identified non-vaccine HPV types and AIN and anal cancer not related to any of the 14 assay-identified HPV types in the FAS analysis did not reach statistical significance. Negative efficacy was observed for two of non-vaccine types, i.e. HPV 56 and 59 with somewhat more cases in the vaccine group than in the placebo group (9 vs. 5 and 11 vs. 9, respectively).

In the analyses (GHN nor FAS) there was insufficient evidence to conclude that the qHPV vaccine was efficacious against non-vaccine HPV types.

The result of the analysis of efficacy against AIN 1 due to any HPV type was not statistically significant (VE: 30.0% (95% CI: -1.1, 49.3). However, the VE estimates for the individual endpoint intra-anal condyloma acuminatum due to any HPV type reached statistical significance with VE of 55% (95% CI: 15.2, 77.3). For AIN 2/3 due to any HPV type only a trend was seen.

Reduction in the incidence of intra-anal procedures

Intra-anal procedures in these analyses include all therapies that could potentially be associated with HPV-related AIN and anal cancer (i.e., surgical and non-surgical therapies). As they may include therapies or procedures that are associated with non-HPV related intra-anal lesions or other intra-anal diseases, the specificity of these endpoints and VE estimates for them are expected to be lower than what has been observed against vaccine type HPV-related AIN and anal cancer.

The percent incidence reduction was positive for intra-anal biopsies, intra-anal therapies overall, and surgical intra-anal therapies in the vaccine group compared to the placebo group; however, it was not statistically significant and thus, there was insufficient evidence to conclude that the qHPV vaccine has a positive effect on the incidence of these procedures. There was not enough information to estimate the percent incidence reduction for non-surgical intra-anal therapies due to the low number of cases accrued.

Immunogenicity

Primary Analysis: Summaries of vaccine-type anti-HPV responses in the Per-Protocol Immunogenicity (PPI) Population

Summary of GMTs

Table 11-40 shows the anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs for the qHPV vaccine and placebo groups in the PPI population at Day 1, Month 7, Month 24, and Month 36 as measured by cLIA. In the vaccine group, measurable immune responses, well above the lower limit of quantitation (LLOQ), were induced by the 3-dose vaccination at 4 weeks post-dose 3 (Month 7) for each HPV vaccine type. At Months 24 and 36, the GMTs in vaccinated subjects were lower than at Month 7 for all vaccine HPV types. For anti-HPV 6, 11, and 16 GMTs, levels at Months 24 and 36 remained above the estimated antibody levels induced by natural infection for each HPV type. For anti-HPV 18, the GMT at Months 24 and 36 were comparable to the estimated antibody level induced by natural infection. In the placebo group, the GMTs were below the LLOQ of the assay for all vaccine HPV types at all time points evaluated.

Table 11-40

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

Assay (cLIA) Study time	qHPV Vaccine (N=2,025) n	GMT (mMU/mL)	95% CI	Placebo (N=2,030) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	1,092	< 7	(<7, <7)	1,108	< 7	(<7, <7)
Month 7	1,092	447.6	(422.6, 474.1)	1,108	< 7	(<7, <7)
Month 24	941	79.8	(75.8, 84.1)	949	< 7	(<7, <7)
Month 36	847	71.5	(67.5, 75.8)	834	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1,092	< 8	(<8, <8)	1,107	< 8	(<8, <8)
Month 7	1,092	624.0	(594.1, 655.4)	1,107	< 8	(<8, <8)
Month 24	941	94.6	(90.0, 99.5)	948	< 8	(<8, <8)
Month 36	847	82.6	(78.3, 87.1)	833	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1,135	< 11	(<11, <11)	1,127	< 11	(<11, <11)
Month 7	1,135	2,404.3	(2,272.2, 2,544.0)	1,127	< 11	(<11, <11)
Month 24	979	342.7	(324.7, 361.7)	951	< 11	(<11, <11)
Month 36	877	293.3	(276.5, 311.2)	839	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,174	< 10	(<10, <10)	1,202	< 10	(<10, <10)
Month 7	1,174	402.3	(380.2, 425.7)	1,202	< 10	(<10, <10)
Month 24	1,011	38.4	(36.0, 41.0)	1,000	< 10	(<10, <10)
Month 36	905	33.1	(30.9, 35.4)	882	< 10	(<10, <10)

The estimated GMTs and associated CIs are calculated using an ANOVA model with a term for vaccination group.

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

n = Number of subjects contributing to the analysis.

ANOVA = Analysis of variance; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

In the MSM subgroup, the GMTs at Month 7 for all vaccine HPV types were lower than the corresponding GMTs in the HM subjects (Table 13). At Months 24 and 36, the GMTs for HM and MSM subjects are generally comparable for HPV types 6, 11, and 18. For HPV type 16, the GMTs in the HM subjects remain higher than the GMTs in the MSM subjects for the Month 24 and 36 time points. Note that the sample sizes in the MSM subgroup are low.

Table 13. Summary of anti-HPV GMTs for HM and MSM subjects (PPI Population)

Assay (cLIA v2) Study time	HM subjects qHPV vaccine (n=1726)			MSM subjects qHPV vaccine (n=299)		
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	978	<7	(<7, <7)	114	< 7	(<7, <7)
Month 7	978	473.9	(446.8, 502.7)	114	**274.3**	(<7, <7)
Month 24	851	81.6	(77.4, 86.1)	90	**64.9**	(<7, <7)
Month 36	792	73.4	(69.2, 77.8)	44	**49.2**	(<7, <7)
Anti-HPV 11						
Day 1	978	<8	(<8, <8)	114	< 8	(<8, <8)
Month 7	978	651.5	(620.7, 683.7)	114	**431.3**	(<8, <8)
Month 24	851	94.9	(90.1, 100.0)	90	91.6	(<8, <8)
Month 36	792	83.6	(79.4, 88.5)	44	**66.2**	(<8, <8)
Anti-HPV 16						
Day 1	999	<11	(<11, <11)	136	< 11	(<11, <11)
Month 7	999	2622.1	(2484.9, 2766.9)	136	**1271.6**	(<11, <11)
Month 24	869	357.7	(335.8, 376.7	110	**253.**	(<11, <11)
Month 36	811	309.3	(291.5, 328.1)	66	**153.0**	(<11, <11)
Anti-HPV 18						
Day 1	1032	<10	(<10, <10)	142	< 10	(<10, <10)
Month 7	1032	439.3	(415.7, 464.3)	142	**212.1**	(<10, <10)
Month 24	897	39.4	(36.8, 42,2)	114	**31.4**	(<10, <10)
Month 36	836	33.9	(31.6, 36.4)	69	**24.7**	(<10, <10)

Summary of seroconversion

The percent seroconversion by vaccination group for vaccine HPV types 6, 11, 16, and 18 at Day 1 and Months 7, 24, and 36 in the PPI population was presented. The seroconversion percentages at 4 weeks post-dose 3 (Month 7) for vaccine recipients were 98.9%, 99.2%, 98.8%, and 97.4% for the vaccine HPV types 6, 11, 16, and 18, respectively. 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, 8.0, 3.6, and 35.1 percentage points for HPV types 6, 11, and 18, respectively. In the vaccine group, the Month 36 seroconversion percentages were comparable to the Month 24 seroconversion percentages for each of the vaccine types. In the placebo group, seroconversion percentages were at most 3.1% for all vaccine HPV types at Months 7, 24, and 36.

In the MSM subgroup, the seroconversion percentages in vaccine recipients at Month 7 for the HPV types 6 and 11 were comparable to the corresponding percentages in the HM subjects. The seroconversion percentages in vaccine recipients at Month 7 for HPV types 16 and 18 in the MSM subgroup were slightly lower than the corresponding seroconversion percentages for HM subjects (94.1% vs. 99.4% and 89.4% vs. 98.4%, respectively): At Months 24 and 36, the seroconversion percentages in vaccine recipients for the MSM subgroup were generally comparable to the seroconversion percentages for HM subjects. The anti-HPV 18 seroconversion percentage at Month 36 was 53.6% in MSM subjects vs. 57.6% in HM subjects.

The immunogenicity results in the All Naïve Subjects with Serology (ANSS) population supported those in the PPI population.

Comparison and analyses of results across studies

Bridging Studies

As with female HPV vaccination, prophylactic vaccination of males prior to sexual debut is critical in achieving prevention of HPV infection and disease. Given that studying efficacy is not feasible in sexually naïve adolescent populations, an immunobridging approach to the basis of licensure in the target age group for vaccination was taken, whereby demonstration of non-inferiority of GMTs and seroconversion rates in adolescents compared to adult males was utilized as the basis for efficacy in the target population.

The criteria for non-inferiority were as follows: For the null hypothesis that the GMTs Boys/GMTs Men $\leq$0.5 (2-fold decrease), a p-value <0.025 supports a conclusion that the specific type anti-HPV response in boys is non-inferior to that in adult young men. As regards seroconversion, for the null hypothesis that %boys/%men <0.05, a p-value <0.025 supports a conclusion that the specific type seroconversion rate in boys is non-inferior to that in men.

Immune responses among 9- to 15-year-old male subjects from the previously conducted Protocols 016 and 018 were compared with responses from 16- to 26-year-old men in Protocol 020. The GMTs and seroconversion rates in 9- to 15-year-old boys were non-inferior to GMTs and seroconversion rates in 16- to 26-year-old men. Thus, it can be concluded that the qHPV vaccine is efficacious in preventing HPV 6/11/16/18-related EGLs in boys and men 9 to 26 years of age. The results also show persistence phase anti-HPV responses (GMTs and seroconversion rates, respectively) through Month 36 in 9- to 15-year-old and 16- to 26-year-old male subjects.

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

Parallel Testing

Since sera from Protocols 016 and 018 subjects were tested ~4 years prior to testing of P020 sera, a parallel testing procedure was undertaken to provide support for the comparison of immunogenicity between the P016 and P018 data and the P020 data. The non-inferiority of vaccine-induced anti-HPV response in adolescents compared to adult men was also demonstrated when samples were tested in parallel.

Anti-HPV Responses by Gender

Anti-HPV responses (Month 7 GMTs and seroconversion rates) were compared between 16- to 26-year-old men in Protocol 020 and 16- to 26-year-old women in Protocols 007, 013, 015, 016, and 019. GMTs for HPV type 16 were comparable. GMTs were slightly lower in young adult males than in young adult females for HPV types 6, 11, and 18. GMTs in men were between 82% - 100% of the female GMTs, by type. Seroconversion rates were high in both groups and generally comparable. According to the MAH, given the high efficacy against persistent infection and disease observed in both females and males, the gender difference in GMTs appears to have limited clinical relevance.

1.4. Results and Discussion

Efficacy Results:

The efficacy claim in males is based on one randomized, placebo-controlled phase III efficacy study, Protocol 020 (P020) and the MSM Substudy, which was embedded within P020. Median durations of post-dose 1 follow-up at study completion for the overall, HM, and MSM study populations were 35.3, 35.4, and 32.2 months, respectively.

Two smaller immunogenicity bridging studies, Protocols 016 and 018 were submitted in support of the extension of indication to include boys 9-15 years of age.

Primary EGL endpoint: In P020, administration of the qHPV vaccine to 16 to 26 year old men was shown to be highly efficacious in preventing HPV 6/11-related external genital warts. Although vaccine efficacy against the combined endpoint of HPV 6/11/16/18-related EGL was significant (VE: 90.6% (95%CI: 70.1, 98.2)), the vast majority of cases contributing to the combined endpoint were HPV 6/11-related genital warts. Efficacy against condyloma was 89.3% (95%CI: 65.3, 97.9) in the PPE population and 68.1% (95%CI: 48.8, 80.7) in the FAS population. Data from P020 also demonstrated that there is significant reduction in the overall burden of HPV-related external genital warts through qHPV vaccination. There were not sufficient numbers of PIN (n=4) or PIN 2/3 (n=2) cases in the PPE or FAS analysis to conclude on efficacy against these endpoints

In the secondary efficacy endpoints, persistent infection (PI) and DNA detection, significant results were obtained. Vaccine efficacy against HPV 6/11/16/18-related PI was 85.5% (95%CI: 77.0, 91.3) in the PPE analysis and 52.2% (95%CI: 42.0, 60.7) in the FAS analysis Efficacy against PI related to oncogenic vaccine HPV types was also statistically significant in both population, with VE of 79.5% (95%CI: 61.9, 89.6) for HPV 16 and 93.9% (95%CI: 76.3, 99.3) for HPV 18 in the PPE analysis. However, the relevance of preventing persistent infection in males is less clear in cancer prevention than it is in females. Due to the limitation of data this issue cannot be resolved at the present time.

MSM substudy AIN endpoint: Overall there were few cases of AIN (qHPV n=5, placebo n=24) detected in the PPE population after a mean follow-up of slightly more than 2 years. Efficacy against HPV 6/11/16/18-related AIN was 77.5% (95%CI: 39.6, 93.3) in the PPE population and 50.3% (95%CI: 25.7, 67.2) in the FAS population. Consistency of the vaccine effect across all grades of AIN was seen, although there were very few cases of AIN 2 or worse (qHPV n=3, placebo n=13). VE against HPV 6/11/16/18- related AIN 2/3 was 74.9% with very wide CIs (95% CI: 8.8, 96.4) due to the small number of cases. There were only a total of 9 cases of HPV 16/18-related AIN 2/3, one case in the vaccine group and 8 cases in the placebo group (VE: 86.6% (95%CI: 0.0, 99.7). When efficacy was analyzed by HPV type, no statistical significance was achieved for either HPV 16 or HPV 18. No cases of anal cancer were detected in the MSM substudy.

The analysis of intra-anal PI was a post-hoc analysis not pre-specified in the study protocol. As this analysis occurred after unblinding it can only be considered supportive not allowing any definite conclusions. The qHPV vaccine was demonstrated to be highly efficacious against HPV 6/11/16/18-related intra-anal PI (VE: 94.9% (95%CI: 80.4, 99.4)) in the PPE population, and importantly also against PI related to HPV 16 (VE: 93.8% (95%CI: 60.0, 99.9)) and HPV 18 (VE: 100% (95%CI: 51.5, 100)). Persistent infection by high-risk HPV types is generally considered a prerequisite for developing progressive genital disease.

Discussion and conclusion on the AIN endpoint:

The evidence supporting that the qHPV vaccine is efficacious against AIN 2/3 in the MSM population included the consistency of efficacy against all grades of anal disease severity and in all populations including the FAS, the high level of efficacy against intra-anal persistent infection related to HPV 16 and HPV18 and, considering the close parallels between anal and cervical disease/cancer, the efficacy data on CIN 2/3 in women. The extrapolation of data from MSM to healthy heterosexual men and women are considered justified by the supportive data provided from the literature and the fact that the anatomic location, the histologic and molecular characteristics of AIN/cancer are identical between the genders, supporting the same role of HR HPV in the pathogenetic processes of cancer development. Moreover, based on clinical trial data on qHPV vaccine, there is no evidence that efficacy of the vaccine is gender specific and the estimates obtained in MSM would be applicable to women and HM.

The issue on surrogacy of AIN 2/3 for anal cancer was resolved on the basis of the literature data available, although limited, and the striking similarities between CIN and AIN as regards natural history, pathogenesis, histological appearance, spectrum of lesions and high-risk HPV types providing strong evidence that AIN2/3, in the same way as CIN 2/3, is a precursor of invasive HPV-related cancer and could be considered as a surrogate marker of invasive cancer.
The conclusions of the ad-hoc expert group on these issues are in agreement with the CHMP position.
In conclusion, the extrapolation of the relative efficacy in preventing AIN 2/3 from the MSM to the general population is considered as acceptable, but considering the low incidence of anal cancer in the general population, the absolute benefit is questionable.

All other concerns were resolved. As regards the issue of anal persistent infection, it seems reasonable to assume that the pathogenesis of HPV-related genital cancers is the same regardless of gender and anatomic region, at least with respect to anal and cervical regions, and thereby that the general concept of persistent high-risk HPV infection being a prerequisite for developing progressive disease is also valid for anal disease. However, the data available at present are too limited to allow any conclusion on this issue. Since intra-anal persistent infection was only analysed after unblinding, the data should be interpreted with caution. The ad-hoc HPV expert group, on January 27, 2011, stated that at the present time there is lack of evidence to support the view that intra-anal persistent infection is a prerequisite for progressive disease (AIN2/3 and anal cancer).

Discussion and Conclusions on immunogenicity

The vaccine-induced immune responses in men aged 16-26 years were robust, and generally comparable to those in women aged 16-26 years. However, anti-HPV GMTs appeared somewhat lower in males than those in women, whereas in the younger age ranges 9-15 years, the opposite pattern was observed. The immune responses in MSM were lower than those observed in HM. The consequence of these lower antibody responses in young men and MSM for long-term efficacy is not known, since no minimum anti-HPV level that confers protection has been defined. The low persistence of GMTs and seropositivity for HPV 18 at Month 36 did not translate into loss of efficacy, but will have to be closely monitored in the future. The data in HIV-infected subjects suggest that the vaccine-induced immune responses are substantially lower than those observed in immunocompetent subjects and MSM and may indicate that an alternate vaccination schedule should be used in this population.

The same approach was taken as in the clinical program for females i.e. efficacy was bridged to adolescent males by demonstrating non-inferiority of antibody responses among male adolescents 9 to 15 years of age compared to male adults. On the basis of immunogenicity bridging, using Protocols 016 and 018, protection against genital warts in adult males can be inferred in 9-15 year old males.

The MAH has committed to conduct a 10-year follow-up of P020 to evaluate long term immunogenicity in men. In addition, Protocol 018, which includes males and females 9-15 years of age, has immunogenicity follow-up to 10 years. These data will also be indicative for a possible future booster dose of the vaccine. In addition, the 10-year extension of study 020 and the Adolescent Vaccine Effectiveness Study will provide long-term safety data.

Safety results

New safety data were presented for the qHPV vaccine administered in men 16 to 26 years of age. A total of 3,092 males 9-26 years of age who received the qHPV vaccine and 2,303 males 9-26 years of age who received placebo were included in the Detailed Safety Population analyses. The total safety data base in males includes 5402 subjects.

Number (%) of Male Subjects With New Medical Conditions (Incidence ≥5% in One or More Vaccination Groups) by System Organ Class (During the Follow-up Period, Post Month 7) in the Safety Population (Protocols 016, 018, and 020) (Cumulative Data)

	qHPV (N= 2564†)		Placebo (N= 2082)	
	n	(%)	n	(%)
Subjects in analysis population	2564		2082	
Subjects with one or more new Medical History	917	(35.8)	711	(34.1)
Subjects with no new secondary diagnosis	1647	(64.2)	1371	(65.9)
Gastrointestinal Disorders	133	(5.2)	115	(5.5)
Infections And Infestations	554	(21.6)	432	(20.7)
Injury, Poisoning And Procedural Complications	213	(8.3)	143	(6.9)
Skin And Subcutaneous Tissue Disorders	135	(5.3)	96	(4.6)

† Protocol 018, AN 70028 is a female subject who is erroneously transcribed in the locked database as a male subject and is included in all Protocol 018 tables as a male.
Percentages are calculated based on the number of subjects in analysis population.

Although a subject may have had two or more new Medical History, the subject is counted only once within a category. The same subject may appear in different categories.
Medical conditions terms are from MedDRA Version 11.1.

N= Number of subjects who received 1, 2, or 3 doses of only the clinical material indicated in the given column.
n = Number of subjects who reported specific new medical condition.

The most commonly reported injection-site AEs were mild or moderate pain, swelling, and erythema. Severe systemic AEs were more common than severe injection-site AEs. The most commonly observed systemic AEs were headache and pyrexia. The data suggest that the qHPV vaccine is associated with a modest increase of transient low-grade fevers, compared with placebo. No vaccine related local or systemic SAEs were reported in study 020.

Thirteen deaths occurred in Protocol 020; 3 subjects in qHPV group (0.2%), and 10 subjects in the placebo group (0.5%). None of the deaths were determined to be vaccine/placebo-or procedure-related.

Five subjects in the qHPV vaccine group and 14 subjects in the placebo group discontinued due to an AE in Protocol 020.

The most common new medical conditions in both vaccination groups include infections (qHPV group: pharyngitis, upper respiratory tract infection, and nasopharyngitis; placebo group: upper respiratory tract infection, pharyngitis, and fungal skin infection). The most common new medical condition potentially indicative of an autoimmune phenomenon, which occurred in both vaccination groups was arthralgia followed by vitiligo. Important potential risks which should be considered are syncope and autoimmune reactions including Guillian Barré Syndrome. Conditions which are more applicable to male population are ankylosing spondylitis and Crohn´s disease although no such cases were observed. The follow up period is still less than three years and further observation is needed in order to identify possible related autoimmune conditions.

Overall, a higher proportion of girls and women reported injection-site adverse events as well as systemic clinical adverse experiences (AEs) than men and boys although the AE profile is comparable between genders.

1.5. Efficacy Conclusions:

During the assessment of this procedure major objections and other concerns were identified.

The major objection contained 5 issues to be addressed. Regarding the *first issue*, the CHMP position was accepted that the claim with respect to EGL other than genital warts could not be supported. Therefore the proposed inclusion of external genital lesions could not be accepted and the wording was revised.

The *second issue* concerned the documentation on HPV16/18-related AIN 2/3, which was considered, limited to allow any firm conclusion on protective efficacy. All supportive data providing evidence that the qHPV vaccine is efficacious against HPV related anal diseases were reviewed, i.e. the consistency of efficacy against all grades of anal disease severity and in all populations including the FAS, the high level of efficacy against intra-anal persistent infection related to HPV 16 and HPV18 as well as the consideration of the close parallels between anal and cervical disease/cancer, the efficacy data on CIN 2/3 in women. Based on the limited vaccine efficacy data available in men, the claim for AIN 2/3 and the proposed addition of premalignant anal lesion in the indication cannot be accepted.

The *third issue* was the proposed extrapolation of data from anal disease to anal HPV infection and related disease in the general population (including women). All literature data were reviewed to support this concept. It is evident that the MSM is a very special population with a high risk for anal disease, whereas healthy heterosexual men (HM) and women constitute low-risk populations. Published data suggest some differences between these populations in transmission routes, distribution of HPV types and age prevalence of anal HPV infection, 70-90% of anal cancers have consistently been observed to be caused by HPV 16 and 18 in all populations and in both genders. According to the scientific literature (Frisch et al: N Eng J Med 1997;337(19):1350-8, Palefsky et al: Obstet Gynecol Clin North Am 2009;36:187-200.), the anatomic location, the histologic and molecular characteristics of AIN/cancer are identical between the genders, supporting the role of HPV in the pathogenetic processes of cancer development. Moreover, based on clinical trial data on qHPV vaccine, there is no evidence that efficacy of the vaccine is gender specific and the estimates obtained in MSM would be applicable to women and HM. In addition, the immune responses to qHPV vaccine were lower in MSM than in HM and young women, and therefore if MSMs are protected it is likely that the effect is preserved in other populations. Taken all these data into consideration, the proposed extrapolation of data from anal disease in MSM to anal HPV related disease in the general population (including women) could be considered as acceptable. The same position was taken by the ad-hoc HPV expert group

meeting on 27 January, 2011. However, it remains necessary to point out the absolute benefit in terms of prevention of anal cancer in the general population needs to be established.

The *fourth issue* concerned the surrogacy of AIN 2/3 for anal cancer, which was questioned by the CHMP. Supportive data in the literature and relevant statements from established scientific societies/organisations were reviewed. Although the similarities between CIN and AIN as regards natural history, pathogenesis, histological appearance, spectrum of lesions and high-risk HPV types, The issue on surrogacy of AIN 2/3 for anal cancer was resolved on the basis of the literature data available, although limited, and the striking similarities between CIN and AIN as regards natural history, pathogenesis, histological appearance, spectrum of lesions and high-risk HPV types, providing strong evidence that AIN2/3, in the same way as CIN 2/3, is a precursor of invasive HPV-related cancer and could be considered as a surrogate marker of invasive cancer.
The conclusions of the ad-hoc expert group on these issues are in agreement with the CHMP position.
In conclusion, the extrapolation of the relative efficacy in preventing AIN 2/3 from the MSM to the general population is considered as acceptable.
It can be concluded that the evidence to corroborate the progression from AIN to invasive carcinoma is very limited at the present time. However, the study data available are consistent and point in the same direction that AIN2/3 if left untreated can progress to invasive cancer. This is in line with the conclusion of the ad-hoc HPV expert group meeting on 27 January 2011.

The *fifth issue* concerned the absolute benefit in terms of prevention of anal cancer in the general population has not been established. Considering that in order to prevent the disease, vaccination of all boys before the sexual debut would be indicated, the benefit/risk in the proposed target population needed further discussion. The absolute benefit in terms of prevention of anal cancer in the general population has not been established which represents a major concern. However, the data provided has to some extent added to the understanding of the medical need for decrease and possible prevention of the rising prevalence and risks for anal HPV infection and consequently the incidence of anal cancer and the precursor lesions in women as well as in MSW (men who have sex with women) and MSM. Data from the substudy of Protocol 020, in HPV naïve MSM demonstrated efficacy against anal persistent infection due to HPV 16 and 18 and that the qHPV vaccine induces protection against high-grade anal HPV disease (AIN 2/3), consequently encompassing anal cancer. Although extrapolation of data from anal disease in MSM to anal HPV infection and related disease in heterosexual men and women was recommended by an EMA Expert Panel Meeting, it should be noted that the study comprised a limited number of individuals.
The overall expected benefit of the qHPV vaccine in sexually experienced MSM may be lower than in the HM population, due to substantially higher baseline level of sero-/PCR positivity. In the HPV naïve male population, benefit of vaccination in terms of prevention of anal cancer will be highest in boys that later will come out as MSM. Thus, in order to prevent the disease, vaccination of all boys before the sexual debut would seem to be indicated. Epidemiologic studies show that anal cancer incidence has increased several fold over the past decades among both males and females. Rates are rising more rapidly in females than in males and at the present time more than 60% of anal cancer cases occur in women. Overall, in the EU, the annual incidence rate of anal cancer is estimated to vary between 0.3 and 1.2 per 100,000 in men and between 0.5 and 2.9 per 100,000 in women. In comparison the incidence rate of anal cancer in HIV negative MSM is estimated to be ~35 per 100,000 and in HIV positive MSM up to 80 per 100,000. There are very limited data on the incidence of anal cancer in HM. If it is assumed that healthy heterosexual men constitute 90% of the male population, the incidence rate of anal cancer in HM in the EU would be in the range of 0.17 and 0.67 per 100,000. Thus, anal cancer is a rather uncommon, although serious disease. There are some potential benefits that also need to be taken into consideration. Given that anogenital HPV is an infectious agent transmitted between sexual partners and the qHPV vaccine very effectively prevents persistent HPV 6/11/16/18-

related infections that can lead to anogenital disease, it is reasonable to assume that qHPV vaccination of males is likely to have some impact on reduction of HPV 6/11/16/18 prevalence in the population, and thus less transmission to female sexual partners. The feasibility of evaluating the impact of vaccination in controlled studies is limited. It is difficult to accurately define HPV infection status in all potential partners at baseline and throughout the study in order to avoid misclassification of the source of new HPV infections, to control for HPV exposures outside the partners in the study, and the ethics of using a placebo control group. Evaluation of reduction of transmission will best be accomplished in population-based epidemiological observational studies such as those being conducted in Australia where female vaccination coverage rates are very high. Similar studies by public health authorities in other countries where high female vaccination coverage is being achieved may help to provide more information on this issue over time. Reduction of the incidence of HPV related lesions in men after extensive vaccinations in females in the Australian study may be an indication of, but does not prove, a preventive effect due to reduced transmission. Since no quantitative estimations based on the available data on anal cancer incidence in Europe and the US has been provided, it is difficult to assess the absolute benefit of vaccinating all boys/adolescents prior to sexual debut.
The long term duration of protection by the qHPV vaccine remains to be determined. The 10-yr extension of study 020 and the Adolescent Vaccine Effectiveness Study will provide long-term safety data and further information regarding the possible protective effect against anal cancer by the vaccine.
The MAH has provided some calculations concerning the number needed to vaccinate (NNV). According to the calculations, the NNV to prevent a case of HPV 16/18-related anal cancer in men by vaccinating 12 year old boys ranged from 265 to 1,961 depending on sexual orientation, geographic region (European Union vs. United States of America), and vaccine efficacy (80% to 100%). However, these calculations were based on the assumption that the duration of vaccine protection is life-long. The MAH also stated that the NNV estimate to prevent a case of any HPV 16/18/6/11-related disease in men by vaccinating 12 year old boys will be less than the NNV estimate to prevent a case of HPV 6/11-related genital warts in men (8-11) due to the cumulative impact of anal cancer prevention in addition to genital warts prevention that will result in an overall NNV for prevention of both anal cancer and genital warts that is less than the NNV for genital warts alone.

Even though this might be true, the current indication already covers the prevention of HPV 6/11-related genital warts in men and the numbers of interest is indeed the NNV for prevention of anal cancer which is considered as rather high. Thus, the calculations provided are not considered to change the previous CHMP conclusion (April 2011 CHMP RSI) concerning the benefit/risk balance in the general population.

The data in HIV-infected subjects suggest that the vaccine-induced immune responses are substantially lower than those observed in immune-competent subjects and may indicate that an alternate vaccination schedule should be used in this population. Further studies, ideally an efficacy study are warranted in HIV-infected subjects. As regards the issue of anal persistent infection, it seems reasonable to assume that the pathogenesis of HPV-related genital cancers is the same regardless of gender and anatomic region, at least with respect to anal and cervical regions, and thereby that the general concept of persistent high-risk HPV infection being a prerequisite for developing progressive disease is also valid for anal disease. However, the data at present are too limited to allow any conclusion on this issue. Since intra-anal persistent infection was only analysed after unblinding, the data should be interpreted with caution. For these reasons, the vaccine efficacy against intra-anal persistent infection should not be mentioned in the SmPC. The ad-hoc HPV expert group, on January 27, 2011, stated that at the present time there is lack of evidence to support the view that intra-anal persistent infection is a prerequisite for progressive disease (AIN2/3 and anal cancer).

1.6. Safety Conclusions:

No safety signals or adverse events differing from the safety profile of qHPV vaccine observed in vaccinated females have so far been reported. Specific identified adverse events such as autoimmune reactions including arthralgia, vitiligo, ankylosing spondylitis and MB Crohn should be closely monitored and reported on in future PSURs. Another potential risk to be considered is HPV replacement with oncogenic non-vaccine HPV types. There are no data of qHPV vaccine use in populations with high risk for HPV infection such as immunosuppressed patients or HIV infected individuals. This issue is considered as not solved and the MAH should make an effort to provide estimations of the absolute benefits of preventing anal cancer in the general population and also provide estimations of other potential benefits, such as reductions of genital warts and HPV transmission. This should be weighed against estimations of the potential risks possibly induced by vaccinating all pre-pubertal boys.

The qHPV vaccine when administered to men 16 to 26 years of age was well-tolerated, and the clinical AE profile exhibited was consistent with the previously described AE profile in both genders, except for AEs affecting only the female reproductive system. No new or significant safety issues were identified. All autoimmune reactions including arthralgia and vitiligo should be continuously closely monitored and reported on in future PSURs.

The qHPV vaccine safety database is insufficient to detect safety signals with respect to rare conditions (i.e., medical conditions occurring at a background rate of <1:10,000). In addition, the 10-year extension of study 020 and the Adolescent Vaccine Effectiveness Study will provide long-term safety data.

1.7. Pharmacovigilance system

1.7.1. Risk Management Plan

Version 6 of the RMP for Gardasil/Silgard provides relevant information for Risk Management under the current indication for qHPV vaccination in men 9-26 years.

The Safety Specification does not bring any new identified or potential risks in relation to what is included in the RMP for the approved indication in women (except syncope with falls and risk of injury).

However, also for qHPV vaccinations in men there is a need to provide information on long-term effectiveness (incidence of persisting HPV-related infections, and of genital warts), long-term immunogenicity and long-term general safety (hospitalisations and emergency care) and pre-specified disorders (autoimmune, endocrine and neurological disorders). To address these safety issues, the MAH has described two ongoing trial extension studies for up to 10 years follow-up of the targeted male population, including hetero- and homosexual men. Also, a large observational health data base study in the US is proposed for follow-up of pre-specified conditions and general health. The planned 10 year follow-up of P020 as outlined in the RMP is considered critical to assess long-term durability of immunogenicity and efficacy in males and to clarify if and when a booster dose will be needed in the future.

1.8. Benefits:

Demonstrated benefits

In Protocol 020, administration of the qHPV vaccine in a 3-dose vaccination regimen to 16 to 26 year old men was shown to be highly efficacious in preventing HPV 6/11-related external genital warts in the primary analysis**.** The end-of study results showed maintenance of vaccine efficacy over a median duration of follow-up of 35.3 months for the overall study population. Data from study 020 also demonstrated that there is a significant reduction in the overall burden of HPV-related external genital warts through qHPV vaccination resulting in statistically significant reductions of biopsies and therapies related to EGLs.
The magnitude of vaccine efficacy against genital warts in males was comparable to that previously shown for females. HPV 6 and HPV 11 seem to play a more important role in young men than in young women. The burden of genital warts is significant in males. Although they are usually benign, genital warts cause pain, discomfort, and pruritus, are highly infectious and result in social stigmatization and psychosocial burden in affected patients.

In the MSM substudy of Protocol 020, there were few cases of anal premalignant lesions (AIN 2/3) but significant efficacy was demonstrated. Also for the most relevant endpoint HPV 16/18-related AIN 2/3, efficacy was high (86.6% (95%CI: 0.0, 99.7), although statistical significance was barely reached. Supporting evidence was the consistency of the vaccine effect across all severity grades of AIN and all populations. In addition, a *post-hoc* analysis in HPV naïve MSM showed high efficacy against anal persistent infection due to HPV 16 and 18 (VE 95% and 100%, respectively). Extrapolation of data from anal disease in MSM to anal HPV infection and related disease in heterosexual men and women is accepted.

The vaccine-induced immune responses in men aged 16-26 years were robust, and generally comparable to those in women aged 16-26 years. As in females, the low persistence of GMTs and seropositivity as measured by cLIA for HPV 18 at Month 36 did not translate into loss of efficacy, but will have to be closely monitored in the future. On the basis of immunogenicity bridging, using Protocols 016 and 018, protection against genital warts in adult males can be inferred in 9-15 year old males

The qHPV vaccine when administered to men 16 to 26 years of age was well-tolerated, and the clinical AE profile exhibited was consistent with that in females. No new or significant safety issues were identified.

Potential benefits

To date there are no effective preventive strategies against extragenital or anal disease in men available. No standardised screening for HPV infection or early detection premalignant genital/anal disease is employed in men apart from certain high risk groups. Thus, there may be an unmet medical and public health need. However, since the incidence of anal cancer in the overall population is very low, the absolute benefit of vaccinating all boys/adolescents prior to sexual debut is likely to be very limited.

Studies support the important role of men in the transmission of HPV to women. Published studies have shown the association between men's sexual behaviour and cervical cancer in women and also indicate high prevalence of HPV-associated PIN in sexual partners of women with CIN. In the pivotal

study 020, data demonstrated that the qHPV vaccine was efficacious in preventing HPV 16/18-related persistent infection.

Risks and uncertainties

The anti-HPV immune responses in MSM were lower than those observed in heterosexual men. The consequence of these lower antibody responses in MSM for long-term efficacy is not known, since no minimum anti-HPV level that confers protection has been defined.

The limitations and risks identified for the male vaccination program are consistent with those identified in previous variations for the qHPV vaccine. Two key limitations of the data to date include

(1) The long-term duration of protection induced by the qHPV vaccine remains to be determined; to provide additional data a sentinel cohort of adolescent boys and girls is being followed to assess vaccine effectiveness up to 10 years following study entry. In addition, for evaluation of long term vaccine efficacy in the male population, Protocol 020 subjects will be enrolled in an extension for 10 years of follow-up from entry into the original study. These data will also indicate the possible need for a booster dose of the vaccine.

(2) The qHPV vaccine safety database is insufficient to detect safety signals with respect to rare conditions (i.e., medical conditions occurring at a background rate of < 1:10,000); to date the post-marketing safety experience with the qHPV vaccine is consistent with the safety profile observed in clinical trials.

The 10-yr extension of study 020 and the Adolescent Vaccine Effectiveness Study will provide long-term safety data. Although the types of adverse experiences reported in males do not suggest a unique safety concern for that gender, the risks have to be further evaluated in the post-marketing program as outlined in the RMP to allow a firm conclusion to be drawn.

All autoimmune reactions including arthralgia and vitiligo should be continuously closely monitored and reported on in future PSURs.
HPV type replacement with oncogenic non-vaccine HPV types is considered as an important potential risk and a detailed plan to address this issue is included in the RMP.
There are no data for use in populations at high risk for HPV infection, such as immunosuppressed patients including HIV-infected individuals. Any use of qHPV vaccine in these populations may not provide satisfactory protection or there will an obvious risk for breakthrough infections.

1.9. Balance conclusion:

Gardasil/Silgard is currently approved for use from the age of 9 years for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic HPV types and prevention of genital warts causally related to specific HPV types. Even though this indication is based on data from the female population, the use in boys/men to prevent genital warts is not contraindicated even though it has been stated in the SmPC section 5.1 that "*Immunogenicity and safety of Gardasil/Silgard have been demonstrated in 9- to 15-year-old boys. Protective efficacy has not been evaluated in males*".

The purpose of this variation was to add prevention of "premalignant anal lesions and anal cancer" in the indication including the general population of both men and women as well as reflect the current experience in males in sections 4.8 and 5.1 of the SmPC. In support of the extension of the indication results in MSM in study 020 were assessed. It has been agreed that the results can be extrapolated from the MSM population to the general population, including both heterosexual men as well as

females. The rates of anal infection and anal disease are higher in the MSM compared to the general population. However, since sexual identity will not be evident until after sexual debut, implicating a possible high prevalence of prevalent HPV infection, it has been considered that the maximum effect of vaccination would be obtained in virginal (or at least pre-pubertal) boys.

Overall, in the EU, the annual incidence rate of anal cancer is estimated to vary between 0.3 and 1.2 per 100,000 in men and between 0.5 and 2.9 per 100,000 in women. Thus, the incidence of anal cancer in the general population of men and women is lower relative to the incidence in MSM, and the overall number of cases of anal cancer that occur annually is lower than for other common HPV-related malignancies. This implicates that, in the general population, the vaccine may be offered without any benefit as regards the indication to prevent anal cancer.

At the oral explanation, the MAH presented estimations of reduction of cases of anal cancer over 50 years (n=1840) if males would be vaccinated, but it was unclear how many males would have to be vaccinated to achieve this goal. Even though the safety profile in males is not believed to be different compared to females, and it is agreed that based on current knowledge, the safety profile seems innocuous, unexpected adverse events always constitutes an uncertainty and therefore, the CHMP concluded that the expected very limited benefit in the general population with respect to prevention of anal cancer, is not expected to outweigh potential safety issues. Therefore, the extension of the indication to include premalignant anal lesions and anal cancer is therefore not considered as approvable.

Vaccine efficacy against genital warts has been convincingly demonstrated in both the PPE and FAS populations and the qHPV indication for males should focus on these lesions. Thus, the CHMP recommended revising the initial proposed indication external genital lesions to genital warts during the procedure.

The preventive effect against genital warts is considered to be of clinical relevance; therefore section 5.1 of the SmPC includes a description of study 020 with main focus on results in the main study in support of the revised indication. A short and balanced description of the results of the MSM study was also included in 5.1.

The planned 10 year follow-up of P020 as outlined in the RMP is considered critical to assess long-term durability of immunogenicity and efficacy in males and to clarify if and when a booster dose will be needed in the future.

Based on the above consideration, the CHMP concluded that the following MAH's proposed change is endorsed for the following change in section 4.1 of the SmPC with the agreed revision

- The qHPV vaccine is indicated in boys and men 9 through 26 years of age for the prevention of ~~**external genital lesions including**~~ **genital warts** (condyloma acuminata) caused by HPV types 6, 11, 16, and 18.

The CHMP further concluded that the following MAH's proposed changes are not endorsed for the following changes in section 4.1 of the SmPC and related section of the PL:

- The qHPV vaccine is indicated in individuals 9 through 26 years of age for the prevention of premalignant anal lesions caused by HPV types 6, 11, 16 and 18.
- The qHPV vaccine is indicated in individuals 9 through 26 years of age for the prevention of anal cancer caused by HPV types 6, 11, 16 and 18.
- The qHPV vaccine is indicated in boys and men 9 through 26 years of age for the prevention of persistent infection due to HPV types 6, 11, 16, and 18.

1.10. Changes to the Product Information

The detailed changes can be found in the final approved highlighted SmPC / PL attached to this report.

Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH:

1) Changes in section 4.1 Indication were accepted with revisions (see section 3.9 of this report);

2) Changes in section 4.2 Posology and method of administration were accepted without revisions;

3) 4.4 Special warnings and precautions for use: changes were accepted;

4) 4.6 Fertility, Pregnancy and lactation: changes were accepted without revisions (see section 3.2 of this report);

5) 4.8 Undesirable effects: changes were accepted without revisions;

6) 5.1 Pharmacodynamics properties: changes in this section were partially accepted and required revisions (see section 3.9 of this report);

7) 5.3 Preclinical safety data: changes were accepted without revisions (see section 3.2 of this report);

1.11. Significance of paediatric studies

The CHMP is of the opinion that study P020, which is contained in the agreed Paediatric Investigation Plan and has been completed after 26 January 2007, is considered significant.

1.12. Follow-up measures (FUMs) following the Marketing Authorisation

Area	Description
Clinical	Long-term Follow-up Study in Males (P020-20) (10 years of follow-up from base study enrolment date) to evaluate vaccine immunogenicity and safety, and (data permitting) vaccine effectiveness. Follow-up safety data from Protocol 020-20 will be provided with special reference to autoimmune reactions

2. Conclusion

On 23 June 2011 the CHMP considered this Type II variation following a worksharing procedure according to Article 20 of the Commission Regulation (EC) No 1234/2008 to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Furthermore, the CHMP reviewed the available paediatric data subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate the Package Leaflet.

In accordance with Article 45(3) of Regulation EC(No)1901/2006 as amended, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation.