EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2014
EMA/415775/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gardasil	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)
Silgard	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)

Procedure No. EMEA/H/C/xxxx/WS/0523

Note

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

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List of abbreviations

AIN	Anal intraepithelial Neoplasia
ANSM	Agence National De Sécurité Du Médicament Et Des Produits De Santé (France)
CDC	Center For Disease Control And Prevention
cLIA	Competitive Luminex immunoassay
CVG	Catch up Vaccination Group
EGL	External Genital Lesion
EVG	Early Vaccination Group
FAS	Full Analysis Set
GBS	Guillain-Barre Syndrome
HPV	Human Papillomavirus
MSM	Men who have Sex with Men
NNH	Number Needed To Harm
NNV	Number Needed To Vaccinate
PIN	Penile/perianal/perineal Intraepithelial Neoplasia
PPE	Per-Protocol Efficacy
qHPV	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine
SAE	Serious Adverse Event
SNIIRAM	Système National d'Informations Inter-régimes de l'Assurance Maladie (France)
SRC	Safety Review Committee
US	United States
VLP	Virus-Like Particle
VE	Vaccine efficacy
VTE	Venous Thromboembolism

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme Limited submitted to the European Medicines Agency on 8 January 2014 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	**Common name:**	**Presentations:**
Silgard	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)	See Annex A
Gardasil	HUMAN PAPILLOMAVIRUS VACCINE [TYPES 6, 11, 16, 18] (RECOMBINANT, ADSORBED)	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The WSA applied for an extension of the indication to include prevention of premalignant anal lesions and anal cancer. Consequently, the MAH proposed the update of section 5.1 of the SmPC.

The Package Leaflet was proposed to be updated accordingly.

The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Appointed Rapporteur for the WS procedure: Kristina Dunder

1.2. Steps taken for the assessment

Submission date:	8 January 2014
Start of procedure:	25 January 2014
Rapporteur's preliminary assessment report circulated on:	21 March 2014
CHMP opinion:	25 April 2014

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 PIP is completed.

The PDCO issued an opinion on compliance.

2. Scientific discussion

2.1. Introduction

Gardasil/Silgard is a quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine. It is an aluminium adjuvanted recombinant protein particulate (virus-like particle [VLP]) vaccine for the prevention:

- pre-malignant lesions (cervical, vulvar and vaginal) and cervical cancer, causally related to human papillomavirus (HPV) types 16 and 18;
- genital warts (condyloma acuminate causally related to HPV types 6 and 11).

The current worksharing application was submitted to extend the indication to include pre-malignant anal lesions and anal cancer.

Burden of anal cancer in men and women

Approximately 27,000 new cases of anal cancer are estimated to occur annually around the world. In Europe, it is estimated that 6,800 new anal cancer cases occur each year among which about 75-80% are attributable to HPV types 16 and 18. According to population-based studies, anal cancers are more frequent in women than in men, with over 60% of cases occurring in women. Among men, even though the incidence of anal cancer is higher among men who have sex with men (MSM), a substantial proportion of cases still occur in heterosexual men, at the population level. For example, a population based study estimated that 53% of anal cancers in males occurred in heterosexual men.

In Europe, the annual age-standardized incidence rates of anal cancer are estimated to vary between 0.1 and 1.4 per 100,000 in men and between 0.1 and 2.2 per 100,000 in women. This incidence has been continuously increasing over recent decades, both amongst men and women, in industrialized countries, in general, and in Europe, in particular. The reason for this increasing incidence is not well understood, but may, at least partially, reflect changes in sexual behaviour in the latter half of the twentieth century that increased the risk of exposure to HPV in the anal canal.

The incidence of anal cancer is particularly high among MSM and immunosuppressed men and women. Risk factors for anal cancer are lifetime number of sexual partners, history of receptive anal intercourse, a history of genital warts or other HPV related cancers/pre-cancerous lesions, and cigarette smoking. Although identified as a risk factor, history of receptive anal intercourse has not been shown consistently to be a significant risk factor for high-risk anal HPV infection in women, suggesting that other sexual and non-sexual routes of transmission are possible, including contamination from cervix/vagina, non-penetrative sex or inoculation through fingers. The median age at diagnosis of anal cancer is approximately 60 years and five-year survival rates are ~60% for men and 73% for women. In addition to gender, survival from anal cancer has been associated with age, race, and stage of disease at diagnosis.

The role of HPV in anal cancer

Overall, published data suggest that approximately 90% of all anal cancers are caused by HPV. According to a meta-analysis, 84% of anal squamous cell cancers in men were HPV positive. Daling et al reported 87.9% HPV positivity of anal cancers in heterosexual men (HM), compared with 88.4% in women and 97.7% in men who were not exclusively heterosexual. In all populations, HPV 16 is consistently reported as the most common HPV type identified in anal cancers and AIN 2/3 lesions. HPV 16 was reported to be present in between 73% to 81% of anal cancers, followed by HPV 18 in about 3% to 5% of anal cancers. Daling reported that 73% and 7% of all anal cancers examined were positive for HPV 16 and 18 respectively, regardless of gender. Overall, the literature suggests that HPV

types 16 and 18 together account for approximately 75-80% of all anal squamous cancers, a larger proportion than for cervical cancers, strongly supporting the necessary role of these HPV types in anal cancer development. This is also supported by the results from a recent study on 496 anal cancer samples worldwide, in which HPV prevalence in anal cancers was reported to be about 90% (after adjustment for several parameters, including region of the world, period of diagnosis, age at diagnosis and gender). In this study, the contribution of the qHPV vaccine types to HPV-related anal cancer was estimated to be 87.2%, after taking multiple infections into account.

Data provided in the current application

In addition to the results from Protocol 020 that established the efficacy for prevention of pre-cancerous anal lesions and anal cancer and the immunogenicity of qHPV vaccine (assessed in EMEA/H/C/703/WS/0029), the new results presented in this variation application are issued from the following studies:

- For long-term protection and safety, new data issued from the long-term follow-up studies of the Gardasil clinical trials are available:

  a) Protocol 020-21 (P020-21) – Long-term effectiveness, immunogenicity, and safety study of Gardasil in young men: 6 years of follow-up [submitted through post-authorisation measures MEA 070 and MEA 069 respectively];

  b) Protocol 018-11 (P018-11) – Long-term immunogenicity, safety and effectiveness study of Gardasil among girls and boys who received Gardasil at 9-18 years of age: 8 years of follow-up [submitted in post-authorisation measure MEA 020.4];

  c) Protocol 015-21 (P015-21) – Long-term effectiveness, immunogenicity, and safety study of Gardasil in young adult women: 8 years of effectiveness and safety, 9 years of immunogenicity [submitted through post-authorisation measure MEA019.3];

- in order to address questions on potential uncertainties on qHPV vaccine safety, including rare conditions, the results of the following post-marketing observational studies in women and men are available:

three studies are part of the Risk Management Plan (RMP):

1. Protocol 031 (P031) - Post-licensure safety surveillance program in females: final report : [submitted through follow-up measure FU2 028.3]
2. Protocol GDS03F – Final report on Analysis of Gardasil and autoimmune disorders using the Pharmacoepidemiologic General Research eXtension (PGRx) Information System.
3. Protocol 070 (P070) – Post-licensure safety surveillance program in males: First interim report.

- Other data source available:

  d) Three independent studies (one in France, one in the US, and one in the Nordic countries)

  e) The analysis of post-marketing spontaneous adverse event reports in males (in comparison with reports for females)

  f) In addition, in order to anticipate discussions about possible associations when vaccinating adolescent boys in Europe and to help interpreting post-licensure surveillance data, the background incidence rates of potential adverse events likely to be temporally associated with qHPV vaccination in adolescent boys were computed and compared to those observed in adolescent girls.

Finally, the qualitative and quantitative evaluation of the benefit/risk balance of Gardasil vaccination for the prevention of premalignant anal lesions and anal cancer was performed by the MAH using complementary methods:

a) First, the MAH has estimated the absolute benefit of preventing anal cancer with Gardasil using the number needed to vaccinate (NNV) method and, in the perspective of a Benefit/Risk evaluation, has balanced it with estimations of the absolute risk of vaccinating the general population for this indication, using the number needed to harm (NNH) calculation

b) Then, the MAH has used the 'problem, objectives, alternatives, consequences, trade-offs, uncertainty, risk attitude, linked decisions' (PrOACT-URL) and the multi criteria decision analysis' (MCDA) approaches, which are two similar and well-structured approaches to estimate the overall benefit-risk balance, both on a qualitative (PrOACT and MCDA) and a quantitative (MCDA) point of view. These two approaches allow taking into consideration all the potential benefits and all the potential risks within a single evaluation.

2.2. Non-clinical aspects

No new non clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4. Clinical Efficacy

2.4.1. Main studies

The pivotal study for this application is study protocol 020, which was fully assessed in the variation application EMEA/H/C/703/WS/0029. In addition, results from Protocol 020-21, 018-11 and 015-21 were also provided.

2.4.2. Results

2.4.2.1. Protocol 020

Protocol 020 (P020) was a randomized, double-blind, placebo-controlled, multicentre 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-matched 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 these HPV types 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).

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

PPE Population

Vaccine efficacy (VE) against HPV 6/11/16/18-related EGL in the PPE population was 90.6% (Table 1). 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 titres 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 titres 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 titres.

Table 1. 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, 98.1)
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	(-3846.4, 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	(-52.1, 100)
PIN 1	1,394	0	1,404	2	100	(-434.9, 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.

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. Overall 432 subjects (78.3%) completed the follow-up phase.

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 2). 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. Success was achieved in the test of the AIN sub-study 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 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 2. Efficacy against HPV vaccine type related AIN and anal cancer by HPV type and lesion type (MMS 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**	**77.2**	**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**	**65.5**	**-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-accuminate	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	1	208	0	NA	NA

MSM HNRT Population

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 results are comparable to that observed 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). 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%.

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.

2.4.2.2. Protocol 020-21

This is a long-term effectiveness, immunogenicity, and safety study of Gardasil in young men with a 6 years follow-up**.** Protocol 020-21 was added to the original base study to provide information on the long-term immunogenicity, safety, and effectiveness of the qHPV vaccine among these men up to 10 years post-vaccination overall. Subjects who received at least 1 dose of the qHPV vaccine during either the base study (i.e. early vaccination group, EVG) or the first extension study (i.e. those who received placebo during the base study and the qHPV vaccine afterwards (i.e. catch-up vaccination group, CVG) were eligible to enter this long-term follow-up extension of the study.

Results

Subject Disposition

A total of 4055 study subjects were randomized in a 1:1 ratio and vaccinated with either qHPV vaccine (N=2025) or placebo (N=2030), in the context of the V501-020 base study.

The V501-020-10 extension offered vaccination to all subjects worldwide who had received placebo or an incomplete series of vaccinations in the base study. A total of 1088 subjects who had originally received placebo (54%) received one or more doses of qHPV vaccine in this extension. In study 020-21 the Early vaccination group consisted of 936 subjects, the Catch-up vaccination group of 867 subjects.

Table 3. Accumulated Follow-Up Time in Base Study and Extension

Follow-Up Time (Years) Since Day 1			
Base Study	N	Median	Mean
qHPV Group	2025	2.97	2.45
Placebo Group	2030	2.92	2.43
Follow-Up Time (Years) Since qHPV Dose 1			
020-21 Extension	N	Median	Mean
Early Vaccination Group	936	6.45	6.34
Catch-Up Vaccination Group	867	2.07	1.96

Effectiveness (PP population)

Incidence of HPV 6/11-Related Genital Warts

Table 4 displays the cumulative incidence of HPV 6/11-related genital warts, from the start of the base study through all visits completed before 01-Jun-2012, in the EVG Per-Protocol population. Three cases of this endpoint were observed in this group during the base study. In follow-up visits to date, no additional cases of this endpoint have occurred.

Table 4. Effectiveness of qHPV Vaccine in Men 16 to 26 Years Against HPV 6/11-Related Genital Warts Cumulative Incidence, Day 1 through June 1, 2012 (Per-Protocol Efficacy Population)

Endpoint	Early vaccination group (N=2,025)				
	n	Number of cases	Person-years at risk	Incidence rate per 100 person-years at risk	(95% CI)
HPV 6/11-related genital warts	1,243	3	4,962.8	0.1	(0.0, 0.2)
By sexual orientation					
HM	1.102	2	4,539.8	0.1	(0.0, 0.2)
MSM	141	1	423.0	0.2	(0.0, 1.3)
By period from dose 1					
Base study period	1,240	3	2,775.1	0.1	(0.0, 0.3)
Post-base study period	640	0	2,187.6	0.0	(0.0, 0.2)
By HPV Type					
HPV 6-related genital warts	1,243	3	4,962.8	0.1	(0.0, 0.2)
HPV 11-related genital warts	1,243	1	4,970.3	0.0	(0.0, 0.1)

N = Number of subjects in the indicated group who received at least 1 dose qHPV vaccine
n = Number of subjects in the indicated analysis population.
CI = Confidence interval.
HM = Heterosexual men; MSM = Men having sex with men; HPV = Human papillomavirus; qHPV = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Incidence of HPV 6/11/16/18-Related External Genital Lesions

In the PP population the incidence of HPV 6/11/16/18 - related external genital lesions coincides with the condyloma results presented above (Table 4).

Incidence of HPV 6/11/16/18-Related AIN

There were 5 cases of HPV 6/11/16/18-related AIN in the EVG MSM Per-Protocol population during the base study. In follow-up visits to date, no additional cases of this endpoint have occurred. Incidence of this endpoint remains low during the extension period.

Incidence of HPV 31/33/35/39/45/51/52/56/58/59-Related External Genital Lesions

Of the total 5 cases of HPV 31/33/35/39/45/51/52/56/58/59 - related external genital lesions, in the EVG HNRT population for this endpoint, all cases have been reported in the context of the base study.

In follow-up visits to date, no additional cases of this endpoint have occurred. Incidence of this endpoint remains low during the extension period.

Incidence of AIN Related to Any HPV Type

Of the total 12 cases of HPV any - related AIN in the EVG GHN population no additional case has been reported subsequent to the base study. Incidence of this endpoint remains low during the extension period.

Immunogenicity

Persistence of Antibody Response in the Per-Protocol Immunogenicity Analysis Population

Table 5 displays the geometric mean titre (GMT) levels of subjects in the PPI population, EVG, through Month 72 from first vaccination, as measured by the competitive Luminex assay (cLIA). Timepoints Day 1 through Month 36 were part of the base study. Titres observed at Month 48 through Month 72 are comparable to those at Month 36, indicating no further diminution of titres in

extension period.

The small group of subjects who commenced their long term follow-up in time for a Month 48 visit were all MSM subjects. As noted in the base study, MSM subjects demonstrated lower titres than HM subjects.

Table 5 includes all subjects, both HM and MSM. Thus, the Month 48 GMTs are numerically lower than other time points.

Table 5 also displays the proportion of subjects seropositive to HPV 6, 11, 16 and 18 by time point, within EVG in the PPI population, through Month 72 from first vaccination, as measured by cLIA. Time points Day 1 through Month 36 were part of the base study. Titres observed at follow-up visits (Month 48, Month 60 and Month 72) are comparable to those at Month 36, indicating no further diminution of SPR in extension period. As noted in previous studies, and in the base study Protocol 020, the proportion of subjects seropositive to HPV 18 by the cLIA declines over time. From Month 48 through Month 72, the overall SPR is approximately 50%, whereas for HPV 6, 11 and 16, the SPR is maintained at approximately 85% or higher. Of note, no cases of HPV 18-related disease have been observed in the EVG PPE population, during the base study or follow-up to date.

Table 5. Summary of Anti-HPV cLIA Immunogenicity Responses by Time from Vaccination Dose 1 (Per-Protocol Immunogenicity Population)

Assay (cLIA) Time Point†	Early Vaccination Group (N=2,025)			
	n	GMT (mMU/mL) (95% CI)	n	SPR (%) (95% CI)
Anti-HPV 6				
Day 1 (qHPV)	1,090	<7 (<7,< 7)	1,090	0.0% (0.0%, 0.3%)
Month 07	1,090	447.7 (415. 9, 481.9)	1,090	98.9% (98.1%, 99.4%)
Month 24	939	79.8 (7.7, 85.2)	939	90.8% (88.8%, 92.6%)
Month36	845	71.5 (66.7, 76.7)	845	88.9% (86.6%, 90.9%)
Month 48	24	43.2 (28.1, 66.4)	24	79.2% (57.8%, 92.9%)
Month 60	133	61.8 (50.5, 75.6)	133	85.7% (78.6%, 91.2%)
Month 72	411	57.0 (51.4, 63.2)	411	84.4% (80.6%, 87.8%)
Anti HPV 11				
Day 1 (qHPV)	1,090	< 8 (<8, <8)	1,090	0.0% (0.0%, 0.3%)
Month 07	1,090	624.4 (588.4, 662.6)	1,090	99.2% (98.4%, 99.6%)
Month 24	939	94.6 (88.5, 101.1)	939	95.6% (94.1%, 96.8%)
Month36	845	82.5 (77.0, 88.5)	845	94.0% (92.1%, 95.5%)
Month 48	24	49.6 (33.7, 73.1)	24	87.5% (67.6%, 97.3%)
Month 60	133	77.6 (64.3, 93.6)	133	91.7% (85.7%, 95.8%)
Month 72	411	5 8.7 (52.5, 65. 6)	411	86.9% (83.2%, 90.0%)
Anti HPV 16				
Day 1 (qHPV)	1,133	<11 (<11, <11)	1,133	0.0% (0.0%, 0.3%)
Month 07	1,133	2,406. 1(2, 245.0, 2,578	1,133	98.8% (97.9%, 99.3%)
Month 24	977	343.1 (319.0, 368.9)	977	99.1% (98.3%, 99.6%)
Month36	875	293. 6 (27.6, 31.4)	875	97.9% (96.8%, 98.8%)
Month 48	30	199.7 (116.1, 343.3	30	96.7% (82.8%, 99.9%)
Month 60	148	2 8 4.2(232.3, 347.9)	148	95.9% (91.4%, 98.5%)
Month 72	423	242.7 (215.3, 273.6)	423	97.4% (95.4%, 98.7%)
Anti HPV 18				
Day 1 (qHPV)	1,171	<1 0 (<10, <10)	1,171	0.0% (0.0%, 0.3%)
Month 07	1,173	402.8 (373.9, 433.9)	1,173	97.4% (96.3%, 98.2%)
Month 24	1,010	38.4 (35.2, 41.9)	1,010	62.4% (59.3%, 65.4%)
Month36	904	33.2 (30.2, 36.4)	904	57.1% (53.8%, 60.3%)
Month 48	34	24.0 (14.6, 39.7)	34	47.1% (29.8%, 64.9%)
Month 60	156	33.4 (26.6, 41.9)	156	55.8% (47.6%, 63.7%)
Month 72	435	24.0 (21.1, 27.4)	435	48.3% (43.5%, 53.1%)

†The indicated time point is relative to day of injection of dose 1 of the qHPV vaccine.
N = Number of subjects in the indicated group who received at least 1 dose of the qHPV vaccine.
n = Number of subjects with non-missing titer in the indicated analysis population.
CI = Confidence interval; HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric Mean Titer; SPR = seropositivity rate; mMU/mL = Milli Merck units per milli-liters; qHPV = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

2.4.2.3. Protocol 018-11 (P018-11)

Long-term immunogenicity, safety and effectiveness study of Gardasil among girls and boys who received Gardasil at 9-18 years of age: 8 years of follow-up.

Background

The V501 Protocol 018 was a Phase III, randomized, placebo-controlled study of the qHPV vaccine that enrolled 1794 boys and girls 9 to 15 years of age. Enrolment was stratified in order to achieve a ratio of 1:1 by gender and a ratio of 2:1 (9- to 12-year-old and 13- to 15-year-old, respectively) by age group across all centres. Once enrolled, subjects were randomized to receive either the qHPV vaccine or non-aluminium-containing placebo in a 2:1 ratio at each study site.

The V501-018-11 study did not have a placebo group. The group vaccinated with the qHPV vaccine in the base study is referred to as the "Early Vaccination Group" (EVG). The group vaccinated with placebo in the base study were vaccinated with a 3-dose regimen of the qHPV vaccine starting at Month 30 (relative to study Day 1 of the base study) during the first extension of the base study (V501-018-05/06) and are referred to as the "Catch-up Vaccination Group" (CVG). Because there is

no placebo group, vaccine efficacy cannot be measured. In lieu of efficacy measurements, effectiveness of vaccination with the qHPV vaccine is assessed by calculating the incidence of endpoints in each of the EVG and CVG and comparing these rates with those observed in groups vaccinated in previous efficacy studies within the MAH qHPV vaccine program. This long-term follow-up study started on Month 42 (relative to study Day 1 of the base study) and will be completed at Month 126 (approximately 7.5 years later).

Results

Subject disposition

A total of 1,781 study subjects were randomized approximately 2:1 to receive the qHPV vaccine (N=1,184) or placebo (N=597) during the V501-018-00 base study. Among these, a total of 1,661 (EVG = 1,179; CVG = 482) received at least 1 dose of the qHPV vaccine and were eligible to participate in the V501-018-11 long-term follow-up study.

A total of 1,575 subjects (EVG = 1,116; CVG = 459) had follow-up post dose 3 of the qHPV vaccine. The median (mean) follow-up time post dose 3 of the qHPV vaccine was 6.8 (5.2) years in the EVG and 4.7 (3.5) years in the CVG.

Immunogenicity Follow-up: A total 1,127 subjects (EVG = 798; CVG = 329) had at least one immunogenicity follow-up during the time period covering the Month 42 (i.e., the start of the LTFU study) through Month 96 study visits.

Effectiveness Follow-up

For an individual subject, study procedures related to the qHPV vaccine effectiveness evaluation (i.e., detection of HPV DNA through PCR testing) commenced after that subject reached 16 years of age. Thus, follow-up time related to the effectiveness assessment differs from follow-up time post dose 3 of the qHPV vaccine.

A total of 590 subjects (EVG = 388; CVG = 202), representing 36% (EVG = 33%; CVG = 42%) of the 1,661 subjects who received at least 1 dose of the qHPV vaccine had at least one follow-up visit with effectiveness data starting after Month 72 through Month 96. The median (mean) follow-up time related to the effectiveness assessment was 4.1 (3.8) years in the EVG and 3.9 (3.6) years in the CVG. Because study procedures related to effectiveness evaluations were performed only in the context of the V501-018-11 long term follow-up study, the follow-up time for effectiveness evaluations was similar in the EVG and the CVG even though the EVG has longer follow-up time post dose 3 of the qHPV vaccine compared to the CVG. Table 4-3 shows the number of subjects with effectiveness follow-up during the time period covering the Month 42 through Month 96 study visits for each of the EVG and CVG, separately for males and females.

Incidence of HPV 6/11/16/18-related Persistent Infection and Disease among Females

Table 5 shows the estimates of incidence rate (per 100 person-years) of the co-primary endpoint of HPV 6/11/16/18-related persistent infection and disease among females in the EVG and CVG in the Per-Protocol Effectiveness (PPE) population.

No cases of HPV 6/11/16/18-related CIN (any grade) were observed in either the EVG or CVG; no cases of HPV 6/11/16/18-related EGL were observed in either the EVG or CVG; while two cases of HPV 6/11/16/18-related persistent infection, both related to HPV 16, were observed in the EVG and one case of HPV 6/11/16/18-related persistent infection, related to HPV 16, was observed in the CVG.

The 2 cases of HPV 16-related persistent infection observed in the EVG over 645.3 person-years of follow-up represent an incidence of 0.3 per 100 person-years (95% CI: 0.0 to 1.1) while the single

case of the same type persistent infection observed in the CVG over 212.7 person-years of follow-up has an incidence of 0.5 per 100 person-years (95% CI: 0.0 to 2.6). Such incidences observed in Protocol 018 are comparable to the corresponding incidences observed in the qHPV vaccine group in the per-protocol populations of other V501 efficacy studies among females. There are five more endpoint cases of persistent infection identified in CVG group in the FAS population, one related to HPV 16 and four related to HPV 18. One case of CIN 1 is also observed in the CVG group in FAS population.

Table 6. Effectiveness of qHPV Vaccination in Females Against HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL (Per-Protocol Effectiveness Population)

	Early Vaccination Group (N=614)					Catch-up Vaccination Group (N=262)				
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	95% CI	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	95% CI
HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL	246	2	645.3	0.3	(0.0, 1.1)	84	1	212.7	0.5	(0.0, 2.6)
By HPV Type										
HPV 6-Related Persistent Infection, CIN, or EGL	243	0	644.0	0.0	(0.0, 0.6)	79	0	199.5	0.0	(0.0, 1.8)
HPV 11-Related Persistent Infection, CIN, or EGL	243	0	644.0	0.0	(0.0, 0.6)	79	0	199.5	0.0	(0.0, 1.8)
HPV 16-Related Persistent Infection, CIN, or EGL	244	2	639.2	0.3	(0.0, 1.1)	77	1	192.8	0.5	(0.0, 2.9)
HPV 18-Related Persistent Infection, CIN, or EGL	244	0	641.6	0.0	(0.0, 0.6)	81	0	208.6	0.0	(0.0, 1.8)
By Endpoint Type (HPV 6/11/16/18-related)										
Persistent Infection	230	2	557.8	0.4	(0.0, 1.3)	79	1	179.5	0.6	(0.0, 3.1)
HPV 6-related Persistent Infection	227	0	556.6	0.0	(0.0, 0.7)	74	0	170.1	0.0	(0.0, 2.2)
HPV 11-related Persistent Infection	227	0	556.6	0.0	(0.0, 0.7)	74	0	170.1	0.0	(0.0, 2.2)
HPV 16-related Persistent Infection	228	2	553.3	0.4	(0.0, 1.3)	73	1	164.4	0.6	(0.0, 3.4)
HPV 18-related Persistent Infection	228	0	555.7	0.0	(0.0, 0.7)	76	0	175.4	0.0	(0.0, 2.1)
CIN (any grade)	196	0	529.6	0.0	(0.0, 0.7)	65	0	163.1	0.0	(0.0, 2.3)
EGL	246	0	640.1	0.0	(0.0, 0.6)	84	0	210.1	0.0	(0.0, 1.8)

N = Number of subjects in the indicated group who received at least 1 dose of the qHPV vaccine.
n = Number of subjects who have at least one effectiveness follow-up visit.
CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; EGL = External genital lesions; HPV = Human papillomavirus; qHPV = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.

Incidence of HPV 6/11/16/18-related Persistent Infection and Disease among Males

- No cases of HPV 6/11/16/18-related EGL were observed in either the EVG or CVG;
- 2 cases of HPV 6/11/16/18-related persistent infection, one related to HPV 6, the other related to HPV16, were observed in the EVG;
- 1 case of HPV 6/11/16/18-related persistent infection, related to HPV 6, was observed in the CVG.

The 2 cases of persistent infection observed in the EVG over 459.8 person-years of follow-up represent an incidence of 0.4 per 100 person-years (95% CI: 0.1 to 1.6) while the single case of persistent infection observed in the CVG over 161 person-years of follow-up represents an incidence of 0.6 per 100 person-years (95% CI: 0.0 to 3.5). Such incidences observed in Protocol 013 are comparable to the corresponding incidences observed in the qHPV vaccine group in the per-protocol populations of other V501 efficacy studies among males.

There are no endpoints identified in the FAS analysis additional to the endpoint cases of persistent infection among males already identified in the PPE analysis.

Immunogenicity

Anti-HPV as measured by both the cLIA and the IgG LIA were consistent with the observed efficacy of the qHPV vaccine that provides continued protection against HPV 6/11/16/18-related persistent infection or disease for up to at least eight years following vaccination in adolescents.

The percentage of subjects who were seropositive at Month 96 visit was high for all HPV types. For HPV 18, 88.8% of EVG subjects were seropositive as measured by the IgG LIA compared with 64.1% as measured by the cLIA assay. Despite the lower seropositivity for HPV type 18 over time, when measured with the cLIA, there were no cases of either HPV type 18-related persistent infection or disease.

2.4.2.4. Protocol 015-21 (P015-21)

Long-term effectiveness, immunogenicity, and safety study of Gardasil in young adult women: 8 years of effectiveness and safety, 9 years of immunogenicity.

Background

Protocol V501-015 was a pivotal Phase III, efficacy, immunogenicity, and safety study that supported the initial licensure of the qHPV vaccine. The study included 5493 women in Denmark, Iceland, Norway, and Sweden, randomized in a 1:1 ratio and received either qHPV vaccine or placebo in 2002 to 2003. Participation and retention in these countries was very high with approximately 95% of study participants in both Cohort 1 and Cohort 2 completing the Month 48 visit. Subject-level data are being collected from:

Cohort 1: Approximately 2700 subjects who received qHPV vaccine at the start of Protocol V501-015 and will contribute approximately 14-years of follow-up after vaccination (4-years within Protocol V501-015 and 10-years within the LTFU study).

Cohort 2: Approximately 2100 subjects who received placebo at the start of Protocol V501-015 and qHPV vaccine prior to entry into the LTFU. These subjects will contribute 10 years of follow-up after vaccination of qHPV vaccine

The LTFU of Protocol V501-015 subjects will be accomplished in 2 ways: 1) registry based follow-up for effectiveness data as well as safety data including but not limited to deaths, cancers, and

hospitalizations; 2) active follow-up for blood collection for immunogenicity assessments at Years 5 and 10 of the LTFU study.

Effectiveness and safety analyses will occur approximately 2 years following completion of Protocol V501-015 and approximately every 2 years thereafter for 10 years. A 10 year registry follow-up (14 years total) means that 16- to 23-year-old women (Nordic Region enrolment age) will be followed until they are 30 to 37 years old. This period covers the period of peak incidence of CIN 2/3 and AIS, and the onset of the period of highest risk for cervical cancer. Immunogenicity analyses will occur after the Year 5 and Year 10 study visits are completed.

The V501-015-21 Long-Term Follow-Up (LTFU) Study report was based on available data collected from national healthcare registries in Denmark, Iceland, Norway and Sweden. The data covered the period from 02 March 2009 through 01 March 2011; which represents approximately 4 to 8 years of post-vaccination follow-up. The final clinical study report is estimated to be in 2019.

Results

Subject disposition

A total of 5493 subjects in Denmark, Iceland, Norway, and Sweden were vaccinated with either qHPV vaccine or placebo in the Protocol V501-015 base study. Of these, 4847 received at least one dose of qHPV vaccine, either during the vaccination phase of the study or during the extension for vaccination of subjects who initially received placebo, and were eligible to participate in the Nordic LTFU extension study (Protocol V501-015-21).

Primary Effectiveness Objective: Analysis of Effectiveness in the Per-Protocol Efficacy (PPE) Population

There were zero (0) cases of HPV 16/18-related CIN 2 or worse observed in Cohort 1. There were 1724 subjects out of 2650 eligible subjects in the PPE population who contributed a total of 5144.1 person-years of follow-up since their exit from the base study.

The estimated baseline incidence rate of HPV 16/18-related CIN 2 or worse in this vaccinated cohort is 0.287/1,000 person-years if vaccine efficacy is maintained at 90%. Based on the 5144.1 person-years of follow-up time accrued, 1 case is expected if vaccine efficacy is maintained at 90%. As of 01 March 2011, no cases were observed.

Based on the number of eligible subjects in this population, a minimum of 2634 person years of follow-up time are necessary in any given interval of time since Day 1 in order to draw conclusions from the results of this analysis. A total of 3077.2 person-years have been accrued over the period from 4 to 6 years following vaccination in the Cohort 1 per-protocol population, which is a sufficient amount of follow-up time to conclude that effectiveness has been maintained beyond the initial 4 years follow-up period of the base study up to 6 years.

2.4.3. Discussion on clinical efficacy

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 consistent 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 HPV in the pathogenesis 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 whether or not AIN 2/3 lesions can be considered a surrogate marker for anal cancer is resolved on the basis of the literature data available, albeit limited, and also based on the striking similarities between CIN and AIN as regards natural history, pathogenesis, histological appearance, spectrum of lesions and high-risk HPV types, which overall provide strong evidence that AIN 2/3 lesions are a precursor of invasive HPV-related cancer and could be considered as a surrogate marker of invasive cancer, in the same way as CIN 2/3 lesions are a surrogate marker for cervical cancer.

In conclusion, the extrapolation of the relative efficacy in preventing AIN 2/3 from the MSM to the general population is considered acceptable, but, because of the low incidence of anal cancer in the general population, the absolute benefit is considered small.

2.4.4. Conclusion on clinical efficacy

Efficacy against premalignant anal lesions is considered demonstrated, and can be extrapolated to anal cancer. The data can also be extrapolated to a general population. However, the absolute benefit of protection against anal cancer in the general population is considered small due to the low incidence of anal cancer in the general population.

2.5. Clinical Safety aspects

2.5.1. Methods – analysis of data submitted

In addition to the results from Protocol 020 that established the efficacy, immunogenicity and safety of the qHPV vaccine for the prevention of pre-cancerous anal lesions and anal cancer, new safety data from the following long-term follow-up studies of qHPV clinical trials are now available:

a) Protocol 020-21 (P020-21) – Long-term effectiveness, immunogenicity, and safety study of GARDASIL in young men;

b) Protocol 018-11 (P018-11) – Long-term immunogenicity, safety and effectiveness study of GARDASIL among girls and boys who received GARDASIL at 9-18 years of age;

c) Protocol 015-20 (P015-21) – Long-term effectiveness, immunogenicity, and safety study of GARDASIL in young adult women.

These three long-term follow-up safety studies have collected data for 7,714 subjects (Table 7).

Table 7. Summary of subjects included in the long-term follow-up studies, P020-21, P018- 11 and P015-21

	P020 (enrolled 16 to 26 year-old males)		**P018** (enrolled 9 to 15 year-old females and males)		**P015** (enrolled 16 to 23 year-old females)	
Base study	**qHPV**	**Placebo**	**qHPV**	**Placebo**	**qHPV**	**Placebo**
Number of subjects who received ≥1 injection	2,025	2,030	1,184	597	2,750	2,097
Extension study	**EVG***	**CVG****	**EVG***	**CVG****	**Cohort 1#**	**Cohort 2##**
Number of subjects who consented to safety follow-up [$]	936	867	1,116	459	2,448	1,888
Follow-up duration (mean)	7 years		6 years		8 years	

* EVG= early vaccination group, i.e. subjects who received at least 1 dose of the qHPV vaccine during the base study
** CVG= catch-up vaccination group, i.e subjects who received placebo during the base study and the qHPV vaccine afterwards
# Cohort 1= subjects who received at least 1 dose of the qHPV vaccine during the base study (equivalent to EVG)
Cohort 2= subjects who received placebo during the base study and the qHPV vaccine afterwards (equivalent to CVG) $ at the cut-off date for the most recent analyses

The following new safety data from post-marketing experience have also been made available:

- Protocol 031-02 (P031-02) – Post-licensure safety surveillance program in females;
- Protocol GDS03E – Analysis of Gardasil and autoimmune disorders using the Pharmacoepidemiologic General Research eXtension (PGRx) Information System;
- Protocol 070 (P070) – Post-licensure safety surveillance program in males: first interim report
- Three independent studies (one in France, one in the US and one in the Nordic countries).

Furthermore, an analysis of post-marketing spontaneous adverse event reports in male (in comparison with reports for females) was provided.

Patient exposure

Safety data for qHPV vaccination in men: Protocol 020

In protocol 020, men aged 16 to 26 years were randomized to receive three doses of qHPV vaccine or three doses of placebo. A total of 4055 study subjects were randomized in a 1:1 ratio and vaccinated with either qHPV vaccine (N=2025) or placebo (N=2030). Data for tolerability and safety were collected on a Vaccination Report Card (VRC) for 14 days following each vaccination. Serious adverse events occurring after this reporting period were collected if the event resulted in death or was judged by the investigator to be vaccine- or study related. The medical histories of all subjects were collected on Day 1. At subsequent visits, new medical history that had occurred since the previous study visit was recorded.

Long-term follow-up safety data in men: Protocol 020-21

A long-term follow-up extension protocol 020-21 was added to the original base study to provide information on the long-term immunogenicity, safety, and effectiveness of the qHPV vaccine among these men up to 10 years post vaccination. Subjects who received at least one dose of the qHPV vaccine during either the base study (i.e., early vaccination group, EVG) or the first extension study (i.e., those who received placebo during the base study and the qHPV vaccine afterwards (i.e. catch-up vaccination group, CVG) were eligible to enter this long-term follow-up extension of the study.

The first interim report was submitted in June 2013. Out of the 2,966 subjects who completed the Protocol 020 base study, 1,805 subjects participated in the long-term study as of the data cut-off date of the first interim report (01 June 2012). Among these subjects, the median follow-up time Post-Dose 3 was 5.8 years in the EVG. The range of follow-up was 3.1 to 6.8 years.

The Protocol 020-21 study safety objective is to describe the incidence of vaccine- or procedure-related serious adverse events (SAEs), SAEs resulting in death and pre-specified medical conditions. The assessment related to the study's safety objective was conducted on the Full Analysis Set (FAS), which included all subjects who received at least one dose of the qHPV vaccine.

Long-term safety data of qHPV vaccine in girls and boys: Protocol 018- 11

A total of 1,781 study subjects were randomized approximately 2:1 to receive the qHPV vaccine (N=1,184) or placebo (N=597) during the V501-018-00 base study. Among these, 1,661 (EVG = 1,179; CVG = 482) received at least one dose of qHPV vaccine and were eligible to participate in the

V501-018-11 long-term follow-up study. The median age at time of injection of dose 1 of the qHPV vaccine was 12 years in the EVG and 15 years in the CVG. The V501-018-11 study safety objective was to describe the incidence of deaths and serious adverse experiences deemed by the study investigators to be vaccine- or procedure-related. The assessment related to the study's safety objective was conducted on the Full Analysis Set, which included all subjects who received at least one dose of the qHPV vaccine. The Month 96 interim analysis database was based on follow-up data from 1,575 subjects, accumulated up to the data cut-off date of 18th May 2012.

Long-term safety data of qHPV vaccine in women: Protocol 015-21

In the Protocol V501-015 base study, 5493 subjects in Denmark, Iceland, Norway, and Sweden were vaccinated with either qHPV vaccine or placebo. Of these, 4847 received at least one dose of qHPV vaccine, either during the vaccination phase of the study (Cohort 1) or during the extension for vaccination of subjects who initially received placebo (Cohort 2), and were eligible to participate in the Nordic LTFU extension study (Protocol V501-015-21). Most of the eligible subjects had consented to the passive follow-up portions of the LTFU study (Total n= 4,336; Cohort 1=2,448; Cohort 2=1,888) as part of the original protocol and additional country-specific consent was obtained for collection of long-term safety data. The Nordic Cancer Registries were searched for deaths, cancers, hospitalizations and other safety outcomes (including, but not limited to, incident cases of: systemic lupus erythematosus (SLE), rheumatoid arthritis, Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and multiple sclerosis (MS)) as measures of long-term safety in the vaccinated group. Data are available for new medical history conditions to measure long-term safety in subjects vaccinated with the qHPV vaccine in Cohorts 1 and 2 up to the data cut-off date of 1st March 2011; this represents about four to eight years of post-vaccination follow-up.

US: post-licensure safety surveillance study in females: Protocol 031-02

This study is a post-licensure regulatory commitment to the FDA and the EMA; it is part of the Gardasil RMP. The study was sponsored by Merck and conducted by two large managed care organizations, Kaiser Permanente North California (KPNC) and Kaiser Permanente South California (KPSC) using their electronic health records. A total of about 190,000 females who received at least 1 dose of qHPV vaccine ('Secondary Study Population') were enroled in the study, including about 44,000 females aged 9 to 26 years who received three doses of qHPV vaccine per protocol ('Primary Study Population'). Safety was measured by assessing:

a) general safety (emergency room visits and hospitalization) on day 0 (day of vaccination), and from day 1 to 60)

b) Pregnancy safety

c) Occurrence of 16 pre-specified autoimmune (AI) conditions within six months of qHPV vaccination.

France: post-licensure safety surveillance study for pre-specified autoimmune diseases in females: Protocol GDS03E

Protocol GDS03E was an investigator-initiated study that was funded by Sanofi Pasteur MSD as part of the risk management plan for qHPV vaccine in France. The risk management plan targeted the surveillance for the following six groups of AI conditions:

- idiopathic thrombocytopenic purpura (ITP),
- connective tissue disorders (CTD) (undifferentiated connective tissue disorder, lupus erythematosus, rheumatoid arthritis/juvenile arthritis, myositis and dermatomyositis),
- central demyelination and multiple sclerosis (CDMS),

- Guillain-Barré syndrome,
- type 1 diabetes mellitus,
- autoimmune thyroid disorders (ATDs) including Grave-Basedow and Hashimoto's disease.

PGRx (pharmacoepidemiologic general research program) is an on-going research platform that prospectively recruits cases of AI disorders to clinical registries in France using a network of centres specialized in research on AI disorders and representative pools of patients from general practice for the selection of controls. The recruitment is independent of any exposure to drugs or vaccines.

The objective of Protocol GDS03E was to assess if exposure to qHPV vaccine was associated with an increased risk of developing pre-specified AI conditions or ATDs. For this study, case and control females aged 14 to 26 years who lived in France, could read, and could respond to a telephone interview (parents could be interviewed for participants under 18 years of age) were selected from these registries from December 2007 to April 2011. Vaccination with qHPV was first recommended by the French health authorities for this age group in 2006. Case definitions were based on internationally-accepted definitions for each disorder. Diagnoses were classified as definite, possible or rejected to allow patients to be recruited at early stages of the diseases. If confirmation of the diagnosis was needed, the patients were followed for up to one year.

The exposure to qHPV vaccine and to risk factors was documented through interviews of the patients or of their parents (proxies). A total of 92% of cases and 84% of reported referents were interviewed. Objective confirmation for reported qHPV use (copy of prescription, copy of medical record, vaccine batch number, and vaccine package) was obtained for 97.4% patients. Potential risk factors for AI disorders were documented, including age (continuous variable), region of residence and of birth of the patient (or of the patient's parent), oral contraceptive use (within two years before the index date), smoking, alcohol consumption, exposure to a vaccine other than qHPV in the two years before the index date, occupation, presence of chronic comorbidities, number of drug used. A priori suspected risk factors and those found associated with disease status were summarized in a multivariate risk score. First-degree familial or personal history of autoimmune disorder (f/pHAID) was shown to be more frequent in cases than in controls (12.3% vs. 5.7% respectively).

Cases and controls were randomly matched for age, region of residence and date of recruitment. Only controls with no history of AI disorders were selected as potential controls. A mean of four controls were matched to each case. Controls were selected for each of the six AI disorders and then different controls were selected for the combined analyses of all AI disorders. The multivariate risk score was applied to each patient for all multivariate studies, which were all controlled for the familial or personal history of autoimmune disorders. In addition, stratified analyses were done according to f/pHAID status.

A total of 269 definite and possible cases and 1096 controls were recruited. The cases were not statistically different from the controls for all variables, except for oral contraceptive use within 24 months of the index data (more frequent in controls; 49.4% vs. 58.6%; p=0.01), personal or family history of AI disorders (more frequent in cases;14.1%vs. 5.6%; p >0.001). Overall, the exposure to qHPV was consistent with estimates from French prescription data: 33.5% vs. 32.0% expected for the age-structure of the population.

The planned primary analysis was for each AI conditions separately. Only patients with confirmed disease diagnosis and only confirmed exposure to qHPV in the primary time window at risk before the index date defined for each disease were included. The index date was the date of first symptom in the cases, applied to their matched controls. The primary time window at risk was 24 months for CTD, CDMS and ATD, 6 months for ITP and 2 months for GBS. Adjusted odds ratios (ORs) were estimated using conditional logistic regression.

Protocol 070 (P070): post-licensure observational study of the safety of qHPV in males

Protocol 070-01, "Post-Licensure Observational Study of the Safety of Gardasil in Males" is ongoing. This post-licensure observational study is conducted as a regulatory commitment to the FDA to assess the general safety of qHPV vaccine in males. This study is included in the risk management plan.

The objective of the study is to assess the safety of qHPV vaccine in the general population of males who receive the vaccine during the course of routine clinical practice, with accrual of subjects starting at the date of initial licensure in the US for males (October 2009). The study is being conducted using a database from a large managed care organization in the United States, Kaiser Permanente. An external safety review committee (SRC) composed of experts in adolescent medicine, vaccine safety, autoimmune conditions, and pharmacoepidemiology has been established to review and evaluate the safety data emerging from the study.

For the general safety analysis the incidence of medical events resulting in hospitalization or emergency room visit in the first 60 days after vaccination, relative to a self-comparison reference period will be analysed. The incidence of selected pre-specified events on the day of vaccination will also be analysed. In addition, it is also planned to follow subjects for six months after each vaccine dose to evaluate the occurrence of new onset cases of 20 specific autoimmune diseases (ADs). The study population will consist of either 44,000 males completing the 3-dose regimen of qHPV vaccine, 135,000 males receiving at least 1 dose of qHPV vaccine, or the number of males accrued up to six years after study start.

Prior to accrual of a pre-specified sample size (22,000 males), interim annual reports include only counts of outcome diagnosis codes, not incidence rates (IRs) or relative risks (RRs). The first interim report was submitted in August 2013 with the PSUR covering the period from 1st June 2012 to 31st May 2013. To be included, the subjects had to have been enrolled for at least 12 months in Kaiser Permanente. Among those who had been enrolled for ≥12 months, from October 2009 to December 2011, 12,609 males had received ≥one dose of qHPV vaccine (38.4% had received two dose; 10.7% had received all three doses). A total of 18,805 doses were administered. The low number of males is explained by the study period analysed for this report, during which the accrual of males occurred mainly prior to the Advisory Committee on Immunization Practices (ACIP) universal recommendation (25 October 2011, published on 23 December 2011).

France: Cohort study by ANSM on SNIIR-AM (French National Social Security) database

To complement the European risk management plan (RMP) for HPV vaccines, the French drug safety agency, ANSM, has implemented a cohort study to study the risk of ADs in young girls exposed and not exposed to either bivalent or quadrivalent HPV vaccine. The study used data from the French National Social Security database (SNIIR-AM). In 2007, a cohort of young girls was established from those born between 1983 and 1996 (subjects were aged between 11 and 24 years) and followed for three years. To avoid possible bias due to girls changing from the general to a student social security system during the study, only girls aged 11 to 15 were included.

Young girls with no reimbursement for a HPV vaccine (unexposed) and those with reimbursement for up to three HPV vaccines (exposed) and who had a long-term disorder recorded as an AD were eligible for inclusion. During the three-year period of the study the database was searched for new notifications for ADs; the date of notification was taken as the date of symptom onset.

US: Centres for Disease Control and Prevention (CDC)-sponsored study to evaluate safety of qHPV vaccine in females

This observational study sponsored by the CDC involved 9-26 year-old females who received qHPV in one of seven large managed care organizations. The Vaccine Safety Datalink (VSD) is a collaboration

of managed care organizations that collects medical information on more than 9 million people every year. They have developed a real-time surveillance system to monitor potential adverse events following the licensure of new vaccines called Rapid Cycle Analysis (RCA). Between August 2006 and October 2009 600,558 doses of qHPV were administered. Weekly sequential analyses were performed to detect associations between qHPV exposure and pre-specified outcomes, identified by ICD-9 codes. The outcomes evaluated were: Guillain-Barre syndrome (GBS); seizures; new onset seizures; syncope; appendicitis; stroke; venous thromboembolism (VTE); anaphylaxis; and other allergic reactions. For comparison, background rates were calculated using historical data for the less common outcomes (<150 cases per 100,000 person/years) and a concurrent unexposed comparison group for more common outcomes.

Denmark and Sweden: Register-based cohort study to evaluate the safety of qHPV vaccine in females

A register-based cohort study, sponsored by the Swedish Foundation for Strategic Research and the Danish Medical Research Council, included nearly 1 million adolescent girls aged between 10 and 17 years in Denmark and Sweden among whom 29.8% had received at least one dose of qHPV vaccine in the first four years after its licensure. Among the vaccinated girls, 80.4% had received the second dose and 54.2% had received the third. Overall 696 420 doses of qHPV vaccine were administered. A total of 53 pre-defined outcomes (AI conditions, neurological conditions and VTE) were assessed using ICD-10 codes. For the AI conditions and neurological outcomes the period at risk was defined as 180 days after exposure to vaccine and for VTE the period at risk was defined as 90 days. To be considered as a safety signal, the lower bound of the 95% CI of the rate ratio for an outcome with at least five qHPV vaccine-exposed cases had to be >1.0. Three criteria were considered as signal strengthening: analysis based on ≥20 qHPV exposed cases (reliability); a rate ratio of ≥3.0 (strength of association); and significantly increased rate ratios in both countries when analysed separately (consistency).

2.5.2. Results

Adverse events

Safety data for qHPV vaccination in men: Protocol 020

Table 8 displays a summary of clinical adverse experiences reported by subjects at any time during the study through visit cut-off date.

The percentages of subjects who reported

- at least one clinical adverse experience
- at least one injection-site adverse experience

were slightly higher in the qHPV vaccine group than in the placebo group.

The percentage of subjects who reported at least one systemic adverse experience was comparable between the qHPV vaccine and placebo groups. Few subjects discontinued the study due to an adverse experience; the percentage of subjects was slightly higher in the placebo group than in the qHPV vaccine group.

Table 8. Clinical Adverse Experience Summary (Days 1 to 9999 Following Any Vaccination Visit) (All Vaccinated Subjects) (Protocol 020)

	qHPV	Placebo
Subjects in analysis population (N)	2020	2029
Subjects without follow-up	75	79
Subjects with follow-up	1945	1950
Number (%) of subjects:		
With no adverse experience	599 (30.8)	698 (35.8)
With ≥ 1 adverse experience	1346 (69.2)	1252 (64.2)
Injection site adverse experience	1169 (60.1)	1046 (53.6)
Systemic adverse experiences	617 (31.7)	622 (31.9)
With vaccine† related adverse experience	1242 (63.9)	1134 (58.2)
Injection site adverse experience	1169 (60.1)	1046 (53.6)
Systemic adverse experiences	275 (14.1)	283 (14.5)
With serious adverse experiences§	8 (0.4)	11 (0.6)
With serious vaccine related adverse experiences	0 (0.0)	0 (0.0)
Who died	3 (0.2)	10 (0.5)
Who discontinued‡ due to an adverse experience	5 (0.3)	14 (0.7)
Who discontinued due to vaccine related adverse experience	2 (0.1)	3 (0.2)
Who discontinued due to serious adverse experience	3 (0.2)	10 (0.5)
Who discontinued due to serious vaccine related adverse experience	0 (0.0)	0 (0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
‡ Discontinued = Subject discontinued from therapy.
§ Three (3) subjects enrolled more than once and were excluded from this table. AN 72648, AN 73819, AN 73858 each had an SAE of overdose.
Percentages were calculated based on the number of subjects with follow-up.

US: post-licensure safety surveillance study in females: Protocol 031-02

All diagnosis codes listed for the hospitalizations or emergency room visits were grouped by healthcare cost and utilization project (HCUP) categories. Increases for Day 0 events were seen for three HCUP categories: epilepsy/convulsions, allergic events, and syncope. There were three events in both the epilepsy/convulsions and allergic events categories. The independent Safety Review Committee (SRC), consisted of five experts who were external to the investigator's team conducting the study and to the sponsor. The SRC included: a general paediatrician/ clinical epidemiologist, a perinatologist / teratologist, a vaccinologist, a paediatric rheumatologist and a pharmacoepidemiologist. They concluded that there was no evidence of an association with qHPV for any of these Day 0 cases of epilepsy/convulsions and allergic events. There were 23 syncope cases that occurred on Day 0 in either the emergency room or hospital setting. The SRC stated that recipients of qHPV are at increased risk for syncope occurring on the day of vaccination.

Based on the results of the general safety analysis and the subsequent chart review results, the SRC found no safety signals for diagnoses from emergency room visits or hospitalizations, with the exception of syncope on Day 0 and possibly, cellulitis, in the Day 1-14 risk period.

Serious adverse events and deaths

Safety data for qHPV vaccination in men: Protocol 020

Serious adverse events

A total of 19 subjects reported serious adverse experiences. Eight occurred in the qHPV vaccine group and 11 in the placebo group. This included the 13 deaths described in the section below. The remaining six subjects (five in the qHPV group and one in the placebo group) experienced nonfatal serious clinical adverse experiences during the study. None of these events were vaccine-related.

Deaths

A total of 13 subjects died during the study. The percentage of subjects who died was higher in the placebo group than in the qHPV vaccine group (Table 8). Three subjects in the qHPV vaccine group and ten subjects in the placebo group died. None of the deaths were vaccine related.

New medical conditions

Overall, the proportions of subjects who reported new medical conditions, including conditions potentially indicative of an autoimmune phenomenon, Post Month 7 were comparable between the qHPV and placebo groups at the end of the base study.

Long-term follow-up safety data in men: Protocol 020-21

At the time of latest report, two SAEs had been reported; neither of them was vaccine-related. Subject AN 74389 had a subarachnoid haemorrhage with a fatal outcome. Subject AN 72841 had a myocardial infarction with a fatal outcome.

New medical conditions

More than 99% of all subjects reported no new medical conditions; less than 1% of all subjects had at least one new medical condition reported in the long-term extension study period. The new medical conditions reported were: vitiligo; psoriasis; hyperthyroidism; and type 1 diabetes mellitus. There was no specific pattern of new medical conditions in either group.

Long-term safety data of qHPV vaccine in girls and boys: Protocol 018- 11

There were three SAEs reported as occurring since Month 37 (relative to base study Day 1). Two were assessed as not vaccine-related and one case of VII nerve paralysis that occurred 131 days post-dose 3, was assessed as vaccine-related by the investigator.

Long-term safety data of qHPV vaccine in women: Protocol 015-21

New medical conditions

Approximately 47% and 45% of subjects in Cohort 1 and Cohort 2, respectively, had at least one new medical history condition during the first 4 years of the long-term follow-up. For Cohort 1, approximately 23% had at least one new medical history condition during the second reporting interval, and for Cohort 2 it was approximately 24%. The most common new medical conditions included delivery in the pregnancy, puerperium and perinatal conditions SOC and perineoplasty in the surgical and medical procedures SOC. The number of subjects with cancers, conditions with a potential autoimmune aetiology, or who died, was minimal. Due to the low number of subjects with these conditions, comparison of the rates of these outcomes to published rates in the general population was not necessary. Overall, there was no specific pattern of new medical conditions within or between the two cohorts.

In the base study, there were four subjects who had multiple sclerosis (MS). Two of the subjects had prevalent MS at enrolment (ANs 41573, 45062) and were subsequently vaccinated with qHPV vaccine and 2 subjects (ANs 44905, 49818) developed MS during the study. Both of the latter subjects were diagnosed with MS during the base study, had received placebo and did not receive qHPV vaccine subsequently. During the second reporting interval, there were two subjects who had a new medical history condition of MS. This brings the total number of subjects in the LTFU study with a new medical condition of MS to 3 (ANs 41025, 41376, 55090). These observed cases of MS are within the expected incidence for subjects of this age.

US: post-licensure safety surveillance study in females: Protocol 031-02

Autoimmune conditions

The study population for AI conditions surveillance included 189 629 women of all ages who received ≥ 1 dose between August 2006 and March 2008. The women were followed for 180 days after each dose of qHPV to identify pre-specified AI conditions:

a) Rheumatologic/Autoimmune: immune thrombocytopenia (ITP), autoimmune haemolytic anemia (AHA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and juvenile rheumatoid arthritis (JRA);

b) Endocrine: insulin dependent diabetes mellitus (i.e., type 1 diabetes), Hashimoto's and Graves' disease;

c) Neurologic/Ophthalmologic: multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), other demyelinating diseases of the CNS, vaccine associated demyelination, Guillain-Barre syndrome (GBS), neuromyelitis optica, optic neuritis, and uveitis.

A total of 149,306 of the 189,629 women meet the analysis inclusion criteria of having at least 12-month KP membership and 719 potential new-onset AI diagnoses were identified in these women. A total of 318 were sampled for review by the case review committee (CRC). For each condition, the number of cases in the vaccinated KP Northern Californian (NC) population (actual number or projected number from the simulation) was small. Estimated incidence rates in the vaccinated KP Southern Californian (SC) population ranged from 1.14 per 100,000 person-years for 'other demyelinating diseases of the CNS' to 104.82 per 100,000 person years for Hashimoto's disease. The 'background' incidence rates of the autoimmune conditions in the non-vaccinated female population aged 9–26 years old were estimated to be comparable with those the observed in the vaccinated women, using the population at KPSC only. For the non-vaccinated population, incidence rates ranged from 1.60 to 81.10 per 100,000 person-years for the same conditions. The incidence estimates in the non-vaccinated population and in the vaccinated population were considered to be significantly different if the rate ratio confidence interval excluded 1.0. For optic neuritis, multiple sclerosis (MS), immune thrombocytopenia (ITP), systemic lupus erythematosus (SLE) and Hashimoto's disease, the estimated rate ratio was higher than 1.0, but the difference was statistically significant for Hashimoto's disease only. An additional sensitivity analysis for Hashimoto's disease was undertaken, in which the main analysis was repeated but the background population was limited to individuals with at least one KPSC health care encounter in 2005 (i.e., the year prior to qHPV licensure). The resulting RR (CI) was also increased. For ITP results for six cases confirmed as new onset after vaccination at KPSC. For juvenile rheumatoid arthritis (JRA) and insulin-dependent diabetes mellitus (IDM), the incidence rates were significantly lower in the vaccinated population. For the remaining four conditions, the rate ratio was less than 1.0, but not significantly decreased.

France: post-licensure safety surveillance study for pre-specified autoimmune diseases in females: Protocol GDS03E

Autoimmune conditions

In three groups of autoimmune diseases studied, exposures of cases and controls to qHPV were very similar and the odds ratios estimates were close to 1:

- For idiopathic thrombocytopenic purpura (ITP), 6 (15.0%) out of 40 definite cases and 33 (18.0%) out of 183 controls were exposed to qHPV during the primary time window (6 months). The matched adjusted odds ratio was 0.96 (95% CI 0.35, 2.64). In patients without f/pHAID, the adjusted odds ratio was 1.17 (95% CI 0.36, 3.76). All cases were definite and none of the secondary analyses or sensitivity analyses displayed any different result.
- For Type 1 diabetes mellitus (T1DM), 9 (23.7%) out of 38 definite cases and 41 (20.3%) out of 202 controls were exposed to qHPV during the primary time window (24 months). The

matched adjusted OR for qHPV exposure was 1.21 (95% CI 0.38, 3.58). In patients without f/pHAID, the adjusted OR was 1.06 (95% CI 0.36, 3.10). Two cases were possible and none of the secondary or sensitivity analyses displayed any different result.

- For connective tissue disorders (CTD), 6 (12.2%) out of 49 definite cases and 37 (18.5%) out of 200 controls were exposed to qHPV during the primary time window (24 months). The matched adjusted OR for qHPV exposure was 0.83 (95% CI 0.29, 2.37). In patients without f/pHAID, the adjusted OR was 0.60 (95% CI 0.15, 2.40). The subgroup analyses for lupus and inflammatory arthritis were in opposite directions; OR= 0.41 (95% CI 0.08 - 2.20) and OR=1.52 (95% CI 0.32 - 7.15), respectively but the number of cases was very small.
- For a fourth disorder, Guillain-Barré syndrome, the observed incidence was within the expected limits; the absence of qHPV exposure is likely to be explained by chance, considering the small number of cases involved:
- 0 (0.0%) out of 15 definite cases of Guillain- Barré Syndrome (GBS) and 7 (7.7%) out of 91 controls were exposed to qHPV during the primary time window (8 weeks). Odds ratios were not calculable. However, the absence of exposure in cases was within statistical expectations considering the small number of cases and the short time window considered: the 95% confidence interval of the probability to be exposed in the case population was [0-0.218], which translates in terms of number of cases, to [0- 3.27]. The expected number of exposed cases, assuming an OR of 1, is 1, which is included in the 95% CI.
- For two disorders, the observed exposure of cases to qHPV vaccine was lower than that of controls:
    - For central demyelination or multiple sclerosis, 4 (4.8%) out of 83 definite cases and 48 (16.6%) out of 290 controls were exposed to qHPV vaccine during the primary time window (24 months). The adjusted OR for qHPV vaccine exposure was 0.28 (95% CI [0.09 - 0.89]) overall and 0.53 (95% CI 0.17, 1.77) in patients without f/pHAID. No clear explanation was found for these results; the differences in the odds ratios for the overall and stratified analysis by familial or personal history of AI disorders, leaves the possibility of some uncontrolled residual confounding.
    - For autoimmune thyroid disorders (AITD), 39.1% of the 46 reported cases had been rejected initially by the clinical algorithm (73.7% for autoimmune thyroiditis and 14.8% for Grave-Basedow disease). Among the 46 cases reported, 44 cases were eligible incident cases; 42 of these cases could be interviewed (38 definite cases and 4 possible cases). The main analysis showed that 1 (2.6%) was exposed to qHPV vaccine during the primary time window (24 months) whereas 34 (20.1%) out of 169 controls were exposed. Adjusted odds ratios were not calculable. These observations should be considered cautiously because of the difficulties to diagnose AITD.

In the combined analysis using definite cases of all studied AID, the matched adjusted OR for qHPV exposure was 0.72 (95% CI 0.45, 1.18). In patients without reported f/pHAID, the adjusted OR for qHPV vaccine exposure was 0.63 (95% CI 0.36, 1.09); in patients who reported f/pHAID, it was 0.64 (95% CI 0.16, 2.49). When AITD was not considered in the combined analysis, the adjusted odds ratio was 0.90 (95% CI 0.54, 1.49).

Protocol 070 (P070): post-licensure observational study of the safety of qHPV in males

Because accrual was less than 22,000 for this first interim report, it is limited to counts of claim codes. For the general safety analysis a variety of codes were identified in both the risk and comparison (i.e. control) periods. The HCUP categories with the highest combined ER/hospital outcome counts between

the Day 1 and Day 60 post-vaccination risk interval for all doses combined were similar to those in the post-vaccination self-comparison period.

The identification of no events related to syncope, epilepsy/convulsions, head trauma and allergic reactions on Day 0 is reflective of the rarity of these outcomes.

For the AI conditions analysis, 12 potential cases with an unconfirmed diagnosis of new-onset autoimmune disease were electronically identified in the cohort of males who had received the qHPV vaccine (n= 4,898) and 17 were identified in a matched comparison cohort of males who had not receive the qHPV vaccinate (n= 4,898). Medical record review and adjudication are currently being conducted for potential autoimmune cases and findings will be presented in future annual reports.

During the Days 1-60 post-vaccination risk interval for all doses combined, 7 VTE outcomes were identified among males in the general safety cohorts, and 3 VTE outcomes were identified during the post-vaccination self-control period. Claims-profile review and medical record review will be conducted for potential VTE cases identified among the general safety cohort.

Two deaths were identified from claims codes in the cohort of males who received the qHPV vaccine. The cause and timing of death relative to vaccination will be summarized and provided in the next study report.

France: Cohort study by ANSM on SNIIR-AM (French National Social Security) database

A total of 1,774,622 girls aged from 11 to 15 years were included in the study cohort; 33.8% had been reimbursed for at least one HPV vaccine. The mean age of the first reimbursement was 15 years. After three years of follow-up, 1,103 subjects had received specific cover for an AD. In November 2011, and interim analysis showed that the incidence rate for all ADs was not significantly different between those who had been exposed to HPV vaccination and those who had not. There were 2.01/10,000 patients/years in those exposed to HPV versus 2.09/10,000 patient/years for those unexposed to HPV; HR = 1.08 [0.91 – 1.29].

US: Centres for Disease Control and Prevention (CDC)-sponsored study to evaluate safety of qHPV vaccine in females

The publication reported data from 164 weeks during which time 600,558 doses of qHPV vaccine were administered in the VSD population: 416,942 to youths and 183,616 to adults. The risk of seizures, new-onset seizures, allergic reactions or syncope were not statistically significant increased for either the youth or adult populations. Only one of the 27 cases of anaphylaxis observed was confirmed as being qHPV vaccine related after medical record review; the estimated rate of anaphylaxis was 1.7 cases per million doses (95% CI: 0.004, 9.3).

Eight cases of VTE were identified compared with the expected number of four. Five of the cases were confirmed as VTE by medical record review; all five had other risk factors. Two of the other cases were miscoded and the last case was ruled out after diagnostic testing. A signal for appendicitis in youths was observed, however investigations showed that coding practices for appendicitis at one of the sites had changed due to a modification of the electronic medical record system that lead to a lower background rate. No significant clusters were observed and a logistic regression analysis showed a non-significant association (OR=1.13; 95% CI: 0.84-1.26). In addition, case-centred analyses showed no association between vaccination and subsequent appendicitis.

There was one case of GBS among the adults but medical record review showed this was not an incident case. Two cases of stroke were observed among the adults, with a non-statistically significant RR of 1.33. There was no statistically significant increased risk for appendicitis or VTE among the adults.

Denmark and Sweden: Register-based cohort study to evaluate the safety of qHPV vaccine in females

A total of 29 of the 53 assessed outcomes satisfied the criterion for further analysis (≥5 qHPV vaccine-exposed cases). The rate ratios for the five neurological outcomes analysed were not significantly increased; the rate ratios were significantly decreased for epilepsy and paralysis. The rate ratio for VTE was 0.86 (95% CI: 0.55-1.36). The rate ratios for 20 of the 23 AI conditions were not significantly increased. Each of the three AI conditions with a statistically increased rate ratio satisfied only one of the signal strengthening criteria:

- ≥20 qHPV-exposed cases: Raynaud's disease and type-1 diabetes
- rate ratio ≥3.0: Behcet's syndrome

The rate ratios for these three events were similar in the period starting on day 181 after qHPV vaccine exposure to those in the period up to 180 days. In addition, the temporal distribution of the cases showed a random pattern (this was inconclusive for Behcet's disease as there were only five cases). Thus, there is no consistent evidence for a plausible association for these three AI conditions.

Post marketing experience

a) Worldwide safety data for males and females

An aggregate analysis tool (METEOR) has been used to review the worldwide safety data, by gender, (male compared with female/ unknown gender excluded) included in marketed case adverse events (AEs) reported by healthcare providers (HCP) and entered into Merck's safety data base (MARRS) as temporally related to the administration of qHPV vaccine from the time of market introduction (01st June 2006) up to 31st May 2013. Since it is unknown what percentage of the doses distributed have been used to vaccinate males vs. females, it is not possible to reliably estimate a reporting rate of adverse events for each group. However, the distribution and percentage of AEs by SOC in males can be viewed in comparison to the overall distribution of AEs by SOC in females.

Aggregate data at the SOC level displaying the number of distinct case reports for each SOC as well as the percentage of the total number of case reports included in each SOC by gender was provided. The three SOCs with the highest percentage of total reports for both genders include:

- general disorders and administration site conditions;
- injury, poisoning and procedural complications;
- nervous system disorders.

Over the period of this analysis (1st June 2006 up to 31st May 2013), there have been 56,784 AE reports received from HCPs in the marketed environment temporally associated with the receipt of qHPV vaccine worldwide; 13% of these reports were serious. A total of 48,065 (85%) of the reports involved females; 1807 (3.2%) of the reports involved males; the gender was unknown in the remaining reports. The number of doses distributed worldwide cumulative to 31 May 2013 is approximately 127,234,506. The percentage of doses administered to males and females is unknown.

The distribution of case reports by SOC is similar for both genders as demonstrated by the top three SOCs with the highest percentage of reports being the same for both: general disorders and administration site conditions (46.6% female / 48.7% male); injury, poisoning and procedural complications (33.2% female / 31.8% male); and nervous system disorders (33.2% female / 39.0% male). The most frequently reported events for each of the three SOCS are also similar for males and females with the exception of those that occur in the injury, poisoning and procedural complications

SOC. The most marked difference in this SOC is the report of exposure to vaccine during pregnancy in the female group.

There were 1,313 and 32,231 AEs in the general disorders and administration site conditions SOC, for males and females, respectively. The 10 most frequently reported terms accounted for 69% of the events in this SOC for males and 66% for females. Therefore, the distribution of the AEs within the general disorders and administration site conditions SOC is similar for males and females. The preferred terms (PTs) asthenia, fatigue, injection site reactions, malaise, and pyrexia are included in the Company Core Data Sheet (CCDS).

There were 702 and 18,360 AEs in the injury, poisoning and procedural complications SOC for males and females, respectively. The 10 most frequently reported terms accounted for 76% of the events in this SOC for males and 84% for females. Therefore, the distribution of the AEs within this SOC is similar for males and females. The main difference is the number of pregnancy exposures in the female group. The majority of reports of fall in both males (63%) and females (66%) and reports of head injury in males (71%) also include the terms of syncope and/or dizziness.

There were 1,051 and 25,691 AEs in the nervous system disorder SOC, for males and females, respectively. The 10 most frequently reported terms accounted for 81% of the events in this SOC for males and 76% for females. Therefore, the distribution of the AEs within this SOC is similar for males and females. The PTs of dizziness, headache, pre-syncope, and syncope are included in the CCDS.

In conclusion, the AE profile for males is similar to that for females and comparable, with males and females having the same three most commonly affected SOCs (the general disorders and administration site conditions SOC, the injury, poisoning and procedural complications SOC, and the nervous system disorders SOC). The main difference between the males and females appeared to be in terms of the top 10 PTs that were reported in the injury, poisoning and procedural complications SOC for each gender. This is primarily due to the reports of 'exposure to vaccine during pregnancy' that are reported in for females.

<u>b) Background incidence rates of potential adverse events in adolescent boys vs. adolescent girls– assessment of temporal associations</u>

A literature review was conducted in order to identify the background incidence rates of potential adverse events likely to be temporally associated with Gardasil vaccination (auto-immune disease and allergic events) in adolescent boys.

Results

Overall, in Europe, one study describing the background incidence rate of several auto-immune diseases in adolescent boys (10-17 years old) was found. The background incidence rates of auto-immune diseases within the same age-group (10-17 years old) were also described for females, allowing for comparisons. Another Danish study described the male vs. female ratio within the target age-group of vaccination (12-15 year old) for several diseases, likely to be temporally associated to vaccination in adolescents. Among industrialized countries, one study in the US provides the background incidence rate of auto-immune diseases in adolescent boys and girls (10-17 years old). Finally, an Australian study described the background incidence rate of several events likely to be temporally associated to vaccination in adolescent boys.

Overall, the background rates of auto-immune diseases tended to be either lower or non-statistically different in adolescent boys compared to adolescent girls.

The only events for which the background incidence rates were found to be statistically higher in adolescent boys compared to adolescent girls were:

- Type 1 diabetes mellitus.

In the 2 Danish studies, incidence of Type 1 diabetes mellitus was higher in adolescent boys compared to adolescent girls:

- Incidence in boys: 27.48 (95% CI: 26.12 to 28.90) per 100 000 vs. 23.98 (95% CI : 22.69 to 25.34) per 100 000 in girls aged 10-17 years old;
- F/M incidence rate ratio of 0.71 (95% CI: 0.60 -0.84).

The same observation was not made in the US study, where incidence rates between adolescent boys and girls were not statistically significant (27.7 [95% CI: 21.9 to 34.5] per 100 000 in boys 10-17 years old vs. 28.2 [95% CI: 22.4- 35.2] per 100 000 in girls aged 10-17 years old):

- Allergic rhinitis: F/M incidence ratio = 0.77 (95% CI: 0.69 - 0.86);
- Allergic conjunctivitis: F/M incidence ratio = 0.69 (95% CI: 0.54 - 0.89);
- Death from unknown cause: 0.76 (95% CI: 0.55 to 1.02) per 100 000 vs. 0.26 (95% CI: 0.14 to 0.44) per 100 000 in adolescent boys vs. adolescent girls, respectively.

Also, the study of Clothier summarized the number of events expected to occur by chance following the introduction of boys' vaccination in Australia. Assuming a 80% vaccination rate with three doses per person in the population of 12 to 16 years old boys in Australia – which equates to approximately to 480 000 boys vaccinated per year within the first two year of vaccination - it was expected that about 2.4 episodes of Guillain-Barré syndrome would be expected within 6 weeks of vaccination. In addition, it was expected that about 3.9 episodes of seizures and 6.5 of acute allergy presentations would be expected to occur within 1 day of vaccination, including 0.3 episodes of anaphylaxis.

2.6. Additional data provided

Number Needed to Vaccinate (NNV) / Number Needed to Harm (NNH) -Brief overview of results

Introduction

The applicant has estimated the absolute benefit of preventing anal cancer with qHPV vaccine through the Number Needed to Vaccinate (NNV) methodology, and has balanced these NNV estimates with estimations of the absolute risks of vaccinating the general population in the perspective of this indication, through the Number Needed to Harm (NNH) methodology.

The objectives of the analysis were:

- To evaluate the Benefit/Risk balance of qHPV vaccine vaccination in the perspective of anal cancer prevention in the general population in the EU using the NNV/NNH methodology;
- To put into perspective the NNV estimates for anal cancer with the NNV estimates for other HPV-related diseases (genital warts and cervical cancer).

The NNV/NNH are widely used in clinical practice because they are simple to calculate and to interpret for a single event or a single disease. Still, they present a number of limitations, which limit their use for decision making purposes and for which they have been heavily criticized: they are highly dependent on the baseline incidence of developing a disease (or "risk at baseline") in a population and of the time horizon considered, as such, they cannot be seen as a property of an intervention and a result obtained in a given population may not be applicable in to a population with a different level of risk for the condition of interest; they do not allow to account for several benefits and several harms in

a single evaluation, which may be particularly a problem for decision making regarding a vaccine; finally, they do not account by themselves for clinical relevance, severity , utility or for the perceived "value of the benefit" or "value of the risk" and may lead to logically unsound decisions by focusing on probability differences only.

Method overview

NNV were defined as NNV = 1 / (r0–rV) where r0 and rV represents the risk of the disease over a fixed period of time in absence of vaccination and with vaccination, respectively; rV was defined as rV = r0 * (1–VE); where VE represents the effectiveness of the vaccine in reducing the disease over the fixed period of time. VE for HPV16/18 related anal cancer was considered to vary between 70 to 100%. The target population for vaccination considered was 12 year-old boys and/or 12 year-old girls living in the EMA territory and the time horizon considered was the remaining life span of this cohort. NNV were primarily estimated for anal cancer (boys and/or girls) but also for genital warts (boys and/or girls) and cervical cancer (girls).

The lifetime risk of developing HPV16/18 related anal cancer, r0, was based on the incidence rates currently observed, which is mainly driven by subjects currently in an age group at risk of developing anal cancer (mean age = 60 years old). This therefore requires a correction to take into account the increasing incidence trend consistently observed in the EMA territory over recent decades; this trend is likely to persist and to affect the incidence rate that will be observed when subjects being vaccinated now (12 years old) are at an age at risk of developing anal cancer. Based on recent EU literature data, several assumptions of future increasing trends have been suggested, ranging between 34% and 100% increase within 40 years. In addition, even if unlikely, the assumption of 0% increase of anal cancer incidence was considered too, in order to provide a global overview of the possible results.

NNH for potential adverse events were defined as NNH = 1 / (rV – r0), where r0 and rV represents the incidence rate of the event of interest in the placebo group/control group and in the vaccinated group, respectively. The choice of potential adverse events relied on concerns that were raised initially at licensure, disregardful of the results of post-licensure studies. The potential adverse events chosen were serious adverse events (SAE), syncope, auto-immune diseases (AID) and hypersensitivity. These events were considered within the period defined as being at risk after vaccination in the studies, i.e., 1 day for syncope and hypersensitivity (Day 0), 14 days for SAE and 6 months for AID. Data source used were either the pooled Gardasil clinical trial data, when power was sufficient, or large observational post-authorization safety studies in which incidence rates were available.

Results overview

Depending on the assumption used regarding VE (70% to 100%) and the expected increase in anal cancer incidence within the next 40 years (0% to 100%), between 571 and 1 631 individuals aged 12 year-old would need to be vaccinated in order to prevent one case of HPV16/18 related anal cancer (see Table 9 for detailed results by assumption). When considering males only, depending on the assumption used, between 798 and 2 279 boys aged 12 year-old would need to be vaccinated in order to prevent one case of HPV16/18 related anal cancer (see Table 10 for detailed results by assumption). In addition, between 8 and 10 boys aged 12 year-old would need to be vaccinated in order to prevent an episode of genital warts.

Table 9. NNV to prevent one anal cancer case* – vaccination of 12 year-old boys and girls in 2013

	Number Needed to Vaccinate			
	VE=70%	VE=80%	VE=90%	VE=100%
No increase in incidence	1 631	1 427	1 268	1 142
34% increase in incidence over 40 years	1 098	1 001	921	852
50% increase in incidence over 40 years	951	878	815	761
100% increase in incidence over 40 years	672	634	601	571

Assuming lifelong duration of protection
*Prevention of 16/18 HPV-related anal cancer cases

Table 10. NNV to prevent one anal cancer case* – vaccination of 12 year-old boys in 2013

	Number Needed to Vaccinate			
	VE=70%	VE=80%	VE=90%	VE=100%
No increase in incidence	2 279	1 994	1 773	1 595
34% increase in incidence over 40 years	1 534	1 399	1 287	1 191
50% increase in incidence over 40 years	1 330	1 227	1 140	1 064
100% increase in incidence over 40 years	938	886	840	798

Assuming lifelong duration of protection
*Prevention of 16/18 HPV-related anal cancer cases

NNH were evaluated for SAE, syncope, hypersensitivity and AID. The NNH point estimate for SAE was less than 0 (-716) based on the pooled data of all qHPV vaccine clinical trial. The NNH point estimate for syncope varied between 91 and over 12 000, depending on the data source used. The NNH point estimated for hypersensitivity was less than 0 (-699) based on a large post-authorization safety study in females but the variability of the respective incidence rates among vaccinated (rV) and non-vaccinated (r0) was compatible with a null absolute difference and thus an infinite NNH. The NNH point estimate for AID varied from 49 505 to less than 0 (- 4 760) depending on the data source used. When looking at each individual AID, either no statistically significant difference was observed between the vaccine and the control group, or the difference was not judged clinically relevant, leading to think that the actual risk difference is most probably close to 0 for each individual auto-immune disease, and thus, that the NNH for AID is most probably close to infinity.

Based on these results, the NNH was only clinically relevant for syncope, for which between 91 and over 12 000 individuals depending on the study considered would need to be vaccinated to experience it. It is to be noted that syncope is common to any vaccination procedures and thus is not-specific of qHPV vaccine. Besides, syncope may be avoided by close post-vaccination surveillance. For all other

potential adverse events studied, a negative NNH point estimate was part of the possible results, so the absence of detrimental effect of qHPV vaccine on the safety parameter of interest could not be excluded. Also, the wide variability of NNH, including either positive or negative values depending on the study for the same event, and the possibility that the actual risk difference (rV-r0) could be null or close to 0 leads to think that an infinite NNH cannot be excluded for these events. For all these reasons, we interpret this as qHPV vaccine having no detrimental effect compared to placebo/absence of vaccination on SAE, hypersensitivity and AID.

MAH Conclusions

The absolute benefits of qHPV vaccine for the prevention of anal cancer in the general population, particularly in males, is substantial and would help addressing an increasing medical need. In comparison, the only adverse event for which a clinically relevant harm could be identified is syncope, which is frequently observed after all vaccination procedures and is avoidable. For all other possible adverse events considered, the absence of difference between the vaccine and the control group, resulting in an infinite number of subjects that would need to be vaccinated to experience it and in the absence of harm of qHPV vaccine could not be excluded. For all these reasons, the Benefit/Risk balance of qHPV vaccine in the prevention of anal cancer in the general population, and in males in particular, was found to be positive, as the potential risks do not outweigh the important determined benefits.

Multi-criteria Decision analysis (MCDA and PrOACT-URL)

Introduction

In order to overcome some of the NNV/NNH approach limitations, the MAH has used another complementary approach to evaluate the Benefit/Risk balance: the Multi-criteria decision analysis (MCDA) and PrOACT-URL framework. Given the differences between males and females in both the choice of the effects and the data sources to be used, as well as the specific interest of the benefit risk (BR) assessment for males, a model for males only was developed. The benefit/risk profile of qHPV vaccine in females is widely recognized as being positive and is not questioned. Including a new indication for females would only improve this Benefit/Risk profile.

MCDA is an eight-step procedure. The main purpose of MCDA is to bring together evaluations of options on different criteria into one overall evaluation. It does this through two separate processes: scoring and weighting. Scoring is the process of measuring the value of options, one criterion at a time, using scaling techniques. Weighting ensures that the units of value on all the criteria are comparable, which is necessary for combining the scales into one overall scale. MCDA solves the problem of comparing benefits and risks by providing a common unit of value so that the added value of favourable effects can be compared to the loss of value from the unfavourable effects.

In the first step, an assessment using the PrOACT/MCDA approach was made based on internal expertise only. This internal assessment served as the basis for the second step, which relied upon input from a number of external experts. This report summarizes the BR assessment based upon the external expert input (step 2). Six experts from the United Kingdom, France, Austria and Spain were chosen for their expertise in HPV related diseases, or in HPV vaccination or in qualitative and quantitative BR methodology.

The assessment compares qHPV vaccine to 'no vaccination' as the sole alternative option. A large value tree taking into account all the relevant effects (benefits/risks) applicable to qHPV vaccine, including those of females, was trimmed down to a simpler value tree. The trimming took out those effects that were either not applicable to the male population or for which the available data showed no difference between qHPV vaccine and control. Whereas the criteria serious adverse events (SAEs) and auto

immune disease (AIDs) could also have been taken out on the basis of no observed difference in several studies, these criteria were left in, for transparency sake.

The final value tree included three benefits effects (anal cancer, genital warts and HPV transmission) and six risk effects (adverse events AE, serious adverse events as adverse effect observed in clinical trials; syncope and hypersensitivity as identified risks; auto immune diseases as potential risks; and unanticipated safety signal as potential for non-demonstrated additional risk).

Two effects tables were built: one for the criteria reflecting the benefits and one for the criteria reflecting the risks. Studies that closely reflect the expected use of qHPV vaccine in the general male population (adolescent boys) and are of sufficient sample size were taken as preferred data sources. For criteria with no or insufficient data in the young male population, studies from older males or from females were selected. The effects were expressed in absolute measures to allow comparison of the benefits and risks.

The observed effects of the different criteria were measured on a scale that ranges from the best to the worst anticipated extremes. Extremes were chosen close to the actual observed effects so as to best discriminate between the two options. Where possible, the range between the two extremes was kept constant across the different criteria. The respective scores of the options within these scales were transformed into values ranging from 0 to 100 using a linear value function.

A survey and a consensus meeting were held among the 6 external experts on the relative weights to be assigned to the criteria and groups of criteria in the value tree. Experts weighted the prevention of anal cancer among the benefits and the potential risk of SAEs among the risks as the two most important effects in the BR model.

Several sensitivity analyses were undertaken in order to see if any criterion could drive to a preference of no vaccination if given a different weight. In addition to sensitivity analyses within the primary model, five alternative models were construed as additional sensitivity analyses.

Results

The primary BR assessment model suggested a superior benefit-risk score for qHPV vaccine compared to no vaccination (scores of 66 and 46 for qHPV vaccine and no vaccination, respectively). The effects that contributed most to the difference between the two alternatives were genital warts and anal cancer among the benefits and AEs and AIDs among the potential risks.

In all of the alternative models used, qHPV vaccine maintained a better benefit-risk profile compared to no vaccination. In the analysis most challenging to qHPV vaccine, the BR scores difference between the two options decreased to 5 points, compared to the primary model with a difference of 20 points. In this analysis only study 018 was used as source data for SAEs.

MAH Conclusion

The assessment showed qHPV vaccine to have a positive BR profile with prevention of anal cancer and genital warts as the most important beneficial effects. The result was robust to changes to the individual weights on the criteria or nodes. qHPV vaccine was also the preferred option when using the lower limit of the efficacy against AIN, or when using less favourable assumptions on the rates of hypersensitivity and SAEs following qHPV vaccine.

2.7. Discussion on additional data provided

The NNV/NNH analysis was considered inappropriate as a tool to determine the benefit risk balance for qHPV vaccine in the prevention of anal cancer. The methodology itself did not allow a weighting of risks and benefits, and is therefore not considered sufficient. However, the NNV figures were

considered of interest in the overall benefit risk evaluation. It was noted that the NNV for cervical cancer was much lower compared to the NNV for anal cancer, which was expected.

MCDA is a method considered to be useful as a complementary and supportive tool. Through a number of steps the purpose is to bring together evaluations of options on both benefits and risks into one overall evaluation taking into account what is considered best current evidence. It was noted that subjective assessments are also needed.

Overall, the MCDA analysis was considered of interest. The model has been discussed in the Benefit-risk methodology project Work package 2 report, issued by EMA. The results appear to be consistently in favour of qHPV vaccine over no vaccination using several different sensitivity analyses.

2.8. Update to the Product Information

The MAH proposed the following changes to the SmPC sections 4.1, 4.4 and 5.1 and to the package leaflet (PL), to which the CHMP agreed (new text is marked underlined and deleted text marked as strikethrough):

4.1 Therapeutic indications

Gardasil/Silgard is a vaccine for use from the age of 9 years for the prevention of:

– premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, ~~and~~ cervical ~~and anal~~ cancers and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types

– genital warts (condyloma acuminata) causally related to specific HPV types.

See sections 4.4 and 5.1 for important information on the data that support this indication.

The use of Gardasil should be in accordance with official recommendations.

4.4 Special warnings and precautions for use

Long-term follow-up studies are currently ongoing to determine the duration of protection ~~The duration of protection is currently unknown. Sustained protective efficacy has been observed for 4.5 years after completion of the 3-dose series. Longer-term follow-up studies are ongoing~~ (see section 5.1).

5.1 Pharmacodynamic properties

Mechanism of Action

HPV 16 and HPV 18 are estimated to be responsible for approximately 70% of cervical cancers and 75-80% of anal cancers; 30% of adenocarcinoma in situ (AIS); 45-70% of high-grade cervical intraepithelial neoplasia (CIN 2/3); 25% of low grade cervical intraepithelial neoplasia (CIN 1); approximately 70% of HPV related high-grade vulvar (VIN 2/3) and vaginal (VaIN 2/3) intraepithelial neoplasia and 80% of HPV related high-grade anal (AIN 2/3) intraepithelial neoplasia. HPV 6 and 11 are responsible for approximately 90% of genital warts and 10% of low grade cervical intraepithelial neoplasia (CIN 1). CIN 3 and AIS have been accepted as immediate precursors of invasive cervical cancer.

The term "premalignant genital lesions" in section 4.1 corresponds to high-grade cervical intraepithelial neoplasia (CIN 2/3), high-grade vulvar intraepithelial neoplasia (VIN 2/3) and high-grade vaginal intraepithelial neoplasia (VaIN 2/3).

The term "premalignant anal lesions" in section 4.1 corresponds to high-grade anal intraepithelial neoplasia (AIN 2/3).

Efficacy in men 16 through 26 years

Efficacy was evaluated against HPV 6-, 11-, 16-, 18-related external genital warts, penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3, and persistent infection.

///

The duration of protection against anal cancer is currently unknown. In the long-term extension study of Protocol 020 for 16-26 year old men, in the PPE population of men vaccinated with

Gardasil/Silgard in the base study, no cases of HPV diseases (HPV types 6/11 related genital warts, HPV 6/11/16/18 external genital lesions and HPV 6/11/16/18 AIN any grade in MSM) were observed up to approximately 6 years.

Persistence of Immune Response of Gardasil/Silgard in Clinical Studies
///
Men vaccinated with Gardasil/Silgard at 16-26 years of age in Protocol 020 base study will be followed up to 10 years in an extension study. Depending on HPV type, 48-97% and 82-100% of subjects were seropositive by cLIA and IgG LIA, respectively, 6 years after vaccination. ~~In the Phase III study in men 16 through 26 years, after a median follow-up of 2.9 years, 88.9 %, 94.0%, 97.9 % and 57.1% of individuals who received Gardasil/Silgard in the per protocol immunogenicity population were anti HPV 6, anti HPV 11, anti HPV 16 and anti HPV 18 seropositive in the cLIA, respectively.~~

Package leaflet

1. What Gardasil/Silgard is and what it is used for

These diseases include ~~cervical cancer~~; pre-cancerous lesions of the female genital (cervix, vulva, and vagina); pre-cancerous lesions of the anus and genital warts in males and females; cervical and anal cancers. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases, 75-80 % of anal cancer cases; and 70% of HPV-related pre-cancerous lesions of the vulva and vagina; 75 % of HPV related pre-cancerous lesions of the anus. HPV types 6 and 11 are responsible for approximately 90% of genital wart cases.

2.9. 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.

3. Benefit-risk Balance

Benefits

Beneficial effects

The data regarding protection against anal cancer were already assessed in variation EMA/H/C/00703-732/WS/0029. The conclusions regarding anal cancer and premalignant anal lesions that were made in variation EMA/H/C/00703-732/WS/0029 are still valid and indicate that significant efficacy has been demonstrated:

"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, i.e. HPV 16/18-related AIN 2/3, vaccine efficacy was high (86.6% (95%CI: 0.0, 99.7), although statistical significance was barely reached. Supporting evidence was the consistent vaccine efficacy across all severity grades of AIN in all populations studied. 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 data in adult males, using Protocols 016 and 018, protection against genital warts can be inferred in 9-15 year old

males."

In the data presented in the current variation, the duration of protection has been followed for up to 7 years in the long-term follow-up Protocol 020-21. The study was descriptive, but there was no sign of waning protection against the more common outcomes (e.g. condyloma). The more uncommon outcomes AIN2/3 and cancer were only reported during the base study, no cases were reported during the extended follow-up phase of the study.

Results from extension studies provided immunogenicity follow-up data up to 8 years in girls and boys who received qHPV vaccine at 9-18 years of age. The immune responses reached a plateau value approximately 24 month after vaccination and thereafter the decline was slow.

Uncertainty in the knowledge about the beneficial effects

The absolute benefit of protection against anal cancer is considered limited, because the incidence of anal cancer is low in the general population. The MAH has argued that the incidence is increasing, but there are uncertainties as to the magnitude of this increase.

The duration of protection against premalignant anal lesions and anal cancer is currently unknown. It is considered to be the same as the duration of protection against cervical lesions, but the incidence of anal cancer most likely peaks at a higher age. However, the cause of anal cancer, i.e. HPV infection, is likely to occur within 5-20 years of vaccination in most cases and there is no reason to believe that the acquisition pattern of HPV differs substantially between men and women. Considering that the duration of follow-up has been extended by approximately 3 years, and that the immune responses appear to decline slowly once a plateau value has been reached, the uncertainties regarding duration of protection are now considered reduced compared to what was known previously.

Risks

Unfavourable effects

Male subjects who received HPV vaccination experienced local injection site reactions which were mild or moderate in intensity. Overall, the injection site adverse experience profile in boys and men was generally comparable to the profile in girls and women. Review of post-marketing data reveal that males have reported similar adverse events after vaccination compared to females, including episodes of syncope, dizziness, headache and loss of consciousness.

Overall, the review of supportive long-term studies does not reveal a significantly increased risk for autoimmune conditions after receipt of vaccination.

Uncertainty in the knowledge about the unfavourable effects

There are non-statistically significant associations with certain autoimmune conditions and/or adverse events of interest (for example venous thromboembolism), which could potentially suggest that a small increase in risk cannot be ruled out. On the other hand, for other conditions there is no association or there is lower incidence in patients exposed to qHPV vaccine. The relevance of these findings is unknown but the uncertainties regarding rare unknown adverse events are now considered smaller compared to what was known previously.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

There is currently no screening program for early detection of anal cancer/premalignancies, and no effective means of preventing anal cancer. Anal cancer is still a relatively rare condition, with an incidence of 0.1 to 1.4 per 100 000 in men and 0.1 to 2.2 in women, but some data indicate that the incidence may progressively increase in the future. Currently, approximately 27,000 new cases of anal cancer are estimated to occur annually around the world. In Europe, it is estimated that 6,800 new anal cancer cases occur each year, among which about 75-80% are attributable to HPV types 16 and 18. Anal cancer is considered a serious condition, and therefore, the preventive effect of qHPV vaccines is considered to be of high importance. For women, the inclusion of prevention of anal cancer to the indication is unlikely to change the use of qHPV vaccines either at a population or individual level, considering the already approved indication for protection against cervical malignancies. However, for men, the inclusion of prevention of anal cancer could be more important, as the only other benefit of qHPV vaccines is protection against genital warts.

The data assessed in this and in previous procedures demonstrate that the vaccine is efficacious against anal cancer and premalignant anal lesions across all severity grades of AIN in all populations studied. In addition, a post-hoc analysis in HPV naïve MSM showed high efficacy against anal persistent infection due to HPV 16 and 18. Extrapolation of data from anal disease in MSM to anal HPV infection and related disease in heterosexual men and women is acceptable. In the studies presented in the current variation for the first time, the duration of protection has been followed for up to 7 years showing no sign of waning protection against the more common outcomes.

The safety profile of qHPV vaccines is considered acceptable with regard to the achievable benefits in men and women. The safety profile is likely to be similar in boys/men vs. girls/women.

Benefit-risk balance

The benefit risk balance is considered positive.

Discussion on the Benefit-Risk Balance

During the previous assessment of the anal cancer indication there were mainly four limitations in the data provided:

1) there was uncertainty on the long-term duration of protection induced by qHPV vaccine,
2) there was uncertainty on qHPV vaccine safety in terms of rare conditions,
3) there was absence of post-marketing safety data in males,
4) the incidence of anal cancer in the general population was considered to be low and therefore the expected benefit was considered to be limited.

1) Uncertainty in the long-term duration of protection

The follow-up of effectiveness against AIN in men in the extension of study 020, and other clinical endpoints in men and women in the extension studies 015 and 018 has been extended to up to 8 years. At the time of the previous assessment the immunogenicity follow- up was up to 5 years and effectiveness data were available up to nearly 4 years. There is currently no indication on waning efficacy, and further follow-up is ongoing. Thus, there is greater knowledge regarding duration of protection compared to the previous application.

2) Uncertainty regarding qHPV vaccine safety in terms of rare conditions

The post-marketing experience is currently three years longer, and the number of exposed subjects

has increased. There were 10 million estimated subjects exposed in the most recent PSUR with a reporting period between 1 June 2012 and 31 May 2013; this represents almost 25% of the cumulative exposure of 42 million subjects since marketing authorisation. In addition, safety follow-up is included in the ongoing extension studies, post-authorisation safety surveillance and registry-based studies are now available. In conclusion, the risks of rare conditions are considered very small, and no consistent increased risk has been identified. Compared to the previous application the uncertainty regarding unknown risks is considered smaller based on the additional safety data.

3) Absence of post-marketing data in males

More post-marketing data in males became available compared to that from the previous application. However, it is not possible to estimate how many doses have been given to males globally. The post-marketing safety data available includes results from the first interim report P070, and an analysis of post-marketing spontaneous adverse event reports in males.

4) The incidence of anal cancer in the general population was considered to be low

There is no reason to believe that the incidence of anal cancer in the general population has changed since the previous assessment. The overall risk is considered low, but not non existent. There is also uncertainty regarding future developments, i.e. increasing incidence over time.

Thus, the overall amount of follow-up data, both with respect to duration of protection and safety, has increased since the previous application, and the data obtained so far are reassuring. Efficacy was considered demonstrated, and there is currently no indication of waning efficacy, or need for further booster doses. The post-marketing experience has increased substantially, and the risks of rare serious unknown events are considered very small. Therefore the opinion of the CHMP is that the benefit/risk balance for Gardasil and Silgard in the newly proposed indication is positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variations acceptable and therefore recommends by majority the variation to the terms of the Marketing Authorisations, concerning the following change:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of the indication to include prevention of premalignant anal lesions and anal cancer. Consequently sections 4.1, 4.4 and 5.1 of the SmPC are updated.

The Package Leaflet is updated accordingly.

The requested variation worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Divergent positions are presented in Appendix 1.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/13/2010 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, in the Package Leaflet.

Appendix to CHMP opinion

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting the extension of the indication for Gardasil/Silgard:

"Gardasil/Silgard is a vaccine for use from the age of 9 years for the prevention of:

- *premalignant genital lesions (cervical, vulvar and vaginal), **premalignant anal lesions**,—cervical cancers **and anal cancer** causally related to certain oncogenic Human Papillomavirus (HPV) types*
- *genital warts (condyloma acuminata) causally related to specific HPV types*

See sections 4.4 and 5.1 for important information on the data that support this indication.

The use of Gardasil/Silgard should be in accordance with official recommendations".

The reasons for divergent opinion were as follows:

An extension of the indication with premalignant anal lesions and anal cancer is not endorsed. Anal cancer is a very uncommon cancer. Women have a higher incidence rate in age groups greater than 50 years but men dominate in the age ranges between 20 and 50 years old. In men and women, common risk factors are e.g. receptive anal sex, lifetime number of sexual partners and genital warts.

Taking into consideration that

- at this time, no validated screening algorithm for early detection of premalignant genital/anal disease in populations at risk is available,
- the incidence of anal cancer in the overall population is very low,

the number boys/adolescents prior to sexual debut to be vaccinated to prevent one case of anal (pre)malignancy is considered too high, making the yield of population based vaccination most likely extremely limited.

The benefit-risk balance of the proposed variation is considered negative.

London, 25 April 2014