EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Evaluation of Medicines for Human Use

CHMP variation assessment report

Invented name/Name: Gardasil
International non-proprietary name/Common name: human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)

Type II Variation: EMEA/H/C/000703/II/0026

Indication summary (as last approved):	Prevention of cancer, precancerous or dysplastic lesions, genital warts and infections caused by HPV types targeted by the vaccine
Marketing Authorisation Holder:	Sanofi Pasteur MSD, SNC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Gardasil is a quadrivalent (HPV Types 6, 11, 16 and 18) recombinant HPV (qHPV) vaccine licensed on 24 September 2006.

Gardasil is indicated in the prevention of premalignant genital lesions (cervical, vulvar and vaginal), cervical cancer and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.

The current indication is based on the demonstration of efficacy of qHPV vaccine in adult females 16 to 26 years of age and on the demonstration of immunogenicity of qHPV vaccine in 9- to 15-year old children and adolescents.

In November 2008 the MAH submitted a type II variation to extend the age of indication for women up to 45 years old, based on submission of efficacy, immunogenicity and safety of the qHPV vaccine in female subjects 24 to 45 years of age from a phase III study (Protocol 019) after a median duration follow-up of 2.2 years. Following a major objection the MAH accepted to limit the application to an update of SmPC sections 4.2, 4.4, 4.5, 4.6. 4.8, and 5.1 to reflect the study results obtained in mid-adult women (MAW). This type II variation received a positive CHMP opinion 23 July 2009.

The present type II variation containing the end-of-study data on efficacy, immunogenicity and safety from the clinical study conducted in mid-adult women 25-45 year of age (Protocol 019) aims to modify sections 4.1, 4.4, 4.6, 4.8 and 5.1 of the SmPC and section 1 of the PL. The median duration of follow-up for this study was 4.0 years.

The proposed modification by the MAH of the current indication of the SmPC is as follows:

Gardasil is a vaccine for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), cervical cancer and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18 ~~(see section 5.1).~~
~~The indication is based on the demonstration of efficacy of Gardasil in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males (see section 5.1).~~

See sections 4.4 and 5.1 for important information regarding vaccine efficacy and immune responses to vaccination in different age groups from 9 years of age onwards and study populations and by gender.

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

The final clinical study report (CSR) of Protocol 019 included in the present type II variation fulfils FUM 014 at the same time.

The HPV attack rate is high in sexually active adults and women remain at risk for acquisition of new infections throughout their sexual lives. The incidence of HPV disease peaks within 10 years after sexual debut. However, social changes (e.g. later marriage, increasing divorce rate) have increased

the risk in women in their late 20s, 30s and 40s. The literature review provided by the MAH showed that HPV incidence rates in mid-adult women (MAW) varied by country, in general decreased with increasing age, but were still noticeable at older ages. The published data suggest that at least 60% of MAW will remain susceptible to vaccine HPV type infection and can potentially benefit from the qHPV vaccine. Therefore, the MAH has conducted this efficacy study in MAW.

1.2 Clinical efficacy

1.2.1 Protocol 019

1.2.1.1 Methods

The claim of efficacy in mid-adult women (MAW) is based on one randomized controlled efficacy trial Protocol 019 (summarized in table 1) including 3819 healthy sexually active 24- to 45-year old women.

The study was designed to demonstrate the efficacy in MAW with respect to the composite co-primary endpoints of HPV 6/11/16/18- and HPV 16/18-related persistent infection and clinical disease (CIN, AIS and EGLs).

Randomisation was stratified by age in approximately 1:1 ratio into 2 groups, those 24 to 34 years and those 35 to 45 years. Within each age stratum subjects were randomized in 1:1 ratio to qHPV vaccine or placebo.

Table 1: Summary of study P019

Study Protocol	**No. of study centres / locations/dates**	**Study vaccine No/study arm**	**No subjects and age group**	**Primary Endpoint**	**Duration Post-7 mo FU**
P019 Phase III **FUTURE III**	US, Europe (France, Germany, Spain), Colombia, Thailand (n=38 sites) 18 Jun 2004 – 30 April 2009	qHPV vaccine n=1910 Placebo (n=1907)	N=3819 24-45 year-old women Mean 34.3 years Age stratification (1:1): 24-34 years: 35 to 45 years of age	<u>Co-primary endpoint:</u> - the incidence of HPV 6/11/16/18-related persistent infection, CIN, AIS, cervical cancer or EGLs (genital warts, VIN, VaIN or vulvar/vaginal cancer) - the incidence of HPV 16/18-related persistent infection, CIN, AIS, cervical cancer or EGLs	Mean: 3.8 years Median 4.0 years

Study participants

The study subjects were healthy 24 to 45-year-old women. The studies did not include pre-screening visit for HPV status. Thus, both naïve individuals and individuals who had been exposed to HPV prior to enrolment were included. All subjects had at inclusion:

- Serum anti-HPV testing for vaccine types, HPV 6, 11, 16, 18
- Pap test
- Cervicovaginal sampling for PCR HPV DNA typing
- Colposcopy if Pap test showed some abnormalities

To enrich the population with HPV naïve subjects, intact cervix (i.e. those without hysterectomy) was used as screening criterion. Subjects who had surgical treatment (such as conisation, LEEP, laser cervical cryotherapy) or subjects who had a cervical biopsy taken within 5 years were not eligible for further evaluation.

Populations

The following populations were considered for the HPV-specific efficacy analysis:

Per-protocol efficacy:

- Received all 3 doses of study vaccine
- Were seronegative to relevant vaccine HPV type(s) at Day 1
- Were PCR negative to relevant vaccine HPV type(s) Day 1 to Month 7
- Did not have general protocol violations
- Cases counted starting 30 days postdose 3 (Month 7).

The Per-Protocol Efficacy (PPE) population was used as the primary efficacy population.

HPV-Naïve to the Relevant-HPV-Type (HNRT) population*

- Received at least 1 vaccination
- Were seronegative to relevant vaccine HPV type(s) Day 1
- Were PCR negative to relevant vaccine HPV type(s) Day 1
- Cases counted starting after Day 1

(*This population was similar to the Modified Intention to Treat-2 (MITT-2) population for young adult women (YAW) (used in P005, P007, P013, P015) but for MITT-2, cases counted starting after Day 30)
The HNRT population was used as a supportive population

Full Analysis Set (FAS)*

- Received at least 1dose of study vaccine
- Regardless of PCR status at Day 1
- Had at least one follow-up visit after Day 1
- Cases counted starting after Day 1

(*This FAS population is similar to the MITT-3 population in studies in YAW. In the MITT-3 population, cases were counted started after Day 30)
The FAS population represents the general (female) population (ITT) in this age group.

For the analyses that were not HPV-vaccine-type specific (population benefit analyses) the following populations were defined:

Generally HPV-naïve (GHN) population*

- Received at least 1 vaccination
- Were seronegative and PCR negative to all 4 vaccine HPV types at Day 1;
- Were PCR negative to non-vaccine HPV type for which testing were available (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) at Day 1,
- Had a negative-for-SIL Pap test result at Day 1;
- Had at least one follow-up visit following Day 1.
- Cases were counted starting after Day 1

(*For studies conducted in YAW, the generally HPV-naïve (GHN) population was referred to as the RMITT-2 population. In the RMITT-2 population, cases were counted starting after Day 30 instead of after Day 1)

The GHN population represents the primary analysis population

HPV-naïve to the relevant type (HNRT)

- Received at least 1 vaccination
- Were sero- and PCR-negative at Day 1 to the appropriate vaccine HPV type (HPV 6, 11, 16, 18); were PCR-negative at Day 1 to the appropriate non-vaccine HPV type for which PCR assays were available (31, 33, 35, 39, 45, 51, 52, 56, 58, or 59), or had a negative Day 1 Pap test result;
- Cases were counted starting after Day 1.

The HNRT population is a supportive population

Full Analysis Set (FAS)

General population (ITT) as defined above.

Treatments

Subjects were randomised 1:1 to receive either quadrivalent HPV VPL vaccine (20/40/40/20mcg + 225mcg amorphous aluminium hydroxyphosphate sulphate (AAHS) adjuvant) or placebo (225mcg Aluminium adjuvant in normal saline) at Day 1, Month 2 and Month 6.

Objectives

The primary efficacy study objectives were to demonstrate that administration of the HPV vaccine would reduce the combined incidence of:

- HPV6/11/16/18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, AIS, and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline.

- HPV16/18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, AIS, and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline.

The secondary efficacy study objectives were to demonstrate that administration of the HPV vaccine would reduce the combined incidence of:

- HPV6/11-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, AIS, and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline.

- HPV 31/33/35/52/58-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, AIS, and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline.

Outcomes/endpoints

Primary efficacy endpoint

First co-primary endpoint: the combined incidence of HPV 6, 11, 16, and 18-related persistent infection CIN (any grade), AIS, or EGLs.

The definition of the persistent infection endpoint for the first primary endpoint encompassed:

- Persistent vaccine-type infection without confirmed CIN – defined as detection of HPV positivity for the same HPV type by the HPV 6/11/16/18 PCR assay in 2 or more consecutive cervicovaginal specimens obtained at least 6 months apart (within ± 4-week windows).

- Vaccine-type HPV infection with confirmed CIN – defined as a consensus Pathology Panel diagnosis of CIN 1, CIN 2, CIN 3, AIS or cervical cancer plus detection of the corresponding HPV vaccine type in specimens obtained from the same lesion, plus detection of HPV vaccine type on the routine visit immediately prior to colposcopy visit in which the biopsy showing CIN, AIS or cervical cancer was obtained.

Second co-primary endpoint: the combined incidence of persistent HPV 16 and HPV 18 infection and HPV 16- and 18-related CIN (any grade), AIS or EGLs.

Secondary efficacy endpoint

- The number of subjects in the PPE population who developed a HPV 6- and HPV 11-related persistent infection, external genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN (any grade), AIS, and cervical cancer.
- The number of subjects in the PPE population who developed a HPV 31/33/35/52/58-related persistent infection, external genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN (any grade), AIS, and cervical cancer.

1.2.1.2 Results

A total of 3819 subjects were enrolled in the study. At End-of-Study (EOS), the median follow-up time was 4.0 years per study participant (mean follow-up time was 3.8 years). A total of 89.7% and 88.6% of study subjects completed their Month 36 and Month 48 visits, respectively

Thirty-eight study centers located in 7 countries in France, Germany, Spain, Columbia, Philippines, Thailand and the US conducted the study. The 3 countries with the highest number of recruitment were Colombia (43% of study population), Thailand (20%) and the US (14%). Europe enrolled 12.6% of the study population.

Overall, 96.7% of all subjects completed the vaccination phase and 90.7% completed the follow-up phase. The proportions of subjects who discontinued during the vaccination period and follow-up and the reasons for discontinuation within this period were generally well balanced between the 2 vaccination groups. Few subjects discontinued due to clinical adverse events.

Baseline data

The 2 vaccination groups were well balanced with respect to baseline demographics.

Sexual demographics were comparable between vaccination groups. Overall, 99.9% of subjects had experienced sexual debut. The median age at first intercourse among non-virgins was 18 years and the median number of lifetime sex partners was 2.

In both vaccination groups approximately 30% of subjects were positive to a HPV vaccine type by serology and approximately 8% were positive by PCR. Altogether 67% of the population was seronegative and PCR negative to all vaccine HPV types 6, 11, 16 and 18 (64.6% of 24 to 34 year-olds; 69% of 35 to 45 year-olds). By age, the proportion of subjects who were PCR positive was lower in the 35 to 45 year-old stratum than in the 24 to 34 year-olds (5.6% vs. 10.2%) whereas with respect to serology the proportions were similar (28.8% vs. 30.7%).

The vaccination groups were comparable with respect to the overall proportions of subjects with detectable vaccine HPV type DNA at baseline.

Efficacy against HPV 6/11/16/18-related persistent infection, CIN and EGL

PPE-population

Results with respect to the primary and secondary efficacy endpoints in the primary efficacy population (PPE) are displayed in Table 2. The results were statistically significant in all three analyses ($p<0.001$) and were generally comparable within each of the two protocol-defined age strata.

Efficacy against HPV 11-related endpoints could not be confirmed, due to the fact that too few and no cases, respectively, were observed.

Table 2: Analysis of efficacy against HPV 6/11/16/18-related persistent infection (PI), CIN or EGL (PPE population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI, CIN or EGL	**1601**	**10**	**1599**	**86**	**88.7**	**78.1, 94.8**
By age						
24 to 34 year-olds	785	5	790	56	91.3	78.4, 97.3
35 to 45 year-olds	816	5	809	30	83.8	57.9, 95.1
HPV 16/18 PI, CIN or EGL	**1587**	**8**	**1571**	**51**	**84.7**	**67.5, 93.7**
By age						
24 to 34 year-olds	777	5	772	35	86.0	64.0, 95.7
35 to 45 year-olds	810	3	799	16	81.8	36.3 96.6
HPV 6/11 PI, CIN or EGL	**1316**	**2**	**1316**	**38**	**94.8**	**79.0, 99.4**
By age						
24 to 34 year-olds	630	0	651	24	100	83.2, 100
35 to 45 year-olds	686	2	665	14	86.2	40.0, 98.5
By HPV type (all ages)						
HPV 6	1316	2	1316	35	94.4	78.0, 99.3
HPV 11	1316	0	1316	4	100	-51.5, 100
HPV 16	1337	8	1325	39	79.9	56.4, 91.9
HPV 18	1508	0	1512	13	100	67.4, 100

Of the 96 HPV 6/11/16/18-related endpoint cases, 10 cases occurred in the vaccine group. Of these 3 were identified during the 2007 endpoint driven analysis. Of the 7 new cases observed during the additional follow-up, 5 cases had infections of high risk non-vaccine HPV prior to detection of persistent HPV 16 infection. Two cases had HPV 6-related persistent infection. None of the 7 cases observed during additional follow-up were cases of HPV 6/11/16/18-related CIN or EGL.

HNRT population

Results for this population are presented in table 3. Vaccine efficacy was 79.9% (95% CI 69.4, 87.3).

VE was lower in the older age stratum versus the younger stratum (VE: 71.3% vs. 83.7).

Compared to the previous 2007 analysis (20 cases) there were 7 additional cases of HPV 6/11/16/18 PI, CIN or EGL in the vaccine arm observed in the end-of study analysis. All these cases were detected in the PPE analysis.

Table 3: Analysis of efficacy against HPV 6/11/16/18-related PI, CIN or EGL (HNRT)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI, CIN or EGL	**1841**	**27**	**1833**	**130**	**79.9**	**69.4, 87.3**
By age						
24 to 34 year-olds	914	15	920	90	83.7	71.7, 91.3
35 to 45 year-olds	927	12	913	40	71.3	44.1, 86.3
HPV 16/18 PI, CIN or EGL	**1823**	**19**	**1803**	**85**	**78.3**	**64.0, 87.5**
By age						
24 to 34 year-olds	904	13	901	60	78.7	60.7, 89.2
35 to 45 year-olds	919	6	902	25	77.0	42.6, 92.3
HPV 6/11 PI, CIN or EGL	**1514**	**8**	**1514**	**50**	**84.2**	**66.5, 93.5**
By age						
24 to 34 year-olds	735	2	770	35	94.1	77.1, 99.3
35 to 45 year-olds	779	6	744	15	62.2	-3, 88.0
By HPV type (all ages)						
HPV 6	1514	8	1514	47	83.2	64.2, 93.2
HPV 11	1514	0	1514	4	100	-51.2, 100
HPV 16	1554	18	1524	64	72.7	53.4, 84.8
HPV 18	1741	1	1726	23	95.7	73.6, 99.9

FAS population

Vaccine efficacy against the HPV 6/11/16/18-related endpoint was much lower in the FAS population (VE: 47.2%) (Table 4). Compared to the 2007 end-point driven analysis, VE in the HPV 16/18-related endpoint at EOS was statistically significant (VE: 41.6% (95% CI: 24.3, 55.2).

Table 4: Analysis of efficacy against HPV 6/11/16/18-related PI, CIN or EGL (FAS population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI, CIN or EGL	**1886**	**116**	**1883**	**214**	**47.2**	**33.5, 58.2**
By age						
24 to 34 year-olds	937	75	944	134	44.1	25.3, 58.5
35 to 45 year-olds	949	41	939	80	51.2	28.0, 67.3
HPV 16/18 PI, CIN or EGL	**1886**	**95**	**1883**	**160**	**41.6**	**24.3, 55.2**
By age						
24 to 34 year-olds	937	95	944	100	39.6	16.0, 56.9
35 to 45 year-olds	949	60	939	60	28.9	13.4, 64.1
HPV 6/11 PI, CIN or EGL	**1886**	**27**	**1883**	**69**	**61.3**	**38.8, 76.2**
By age						
24 to 34 year-olds	937	18	944	44	58.6	26.9, 77.5
35 to 45 year-olds	949	9	939	25	65.2	22.9, 85.7
By HPV type (all ages)						
HPV 6	1886	24	1883	65	63.5	40.9, 78.1
HPV 11	1886	3	1883	5	40.1	-207.9, 90.7
HPV 16	1886	78	1883	121	**36.3**	14.6, 52.7
HPV 18	1886	20	1883	46	56.9	25.6, 75.8

Exploratory statistical analysis (N-weighted average efficacy analysis in the FAS)

An exploratory statistical analysis was conducted whereby the expected value of VE in the FAS was computed to account for the anticipated VE-by- Day 1 HPV status interaction.

Results relating to the analysis of the HPV 6/11/16/18-, HPV16/18- and HPV 6/11-endpoint related persistent infection and disease endpoint that takes into account the subjects' Day 1 HPV infection status are displayed in table 5.

Table 5: Analysis of efficacy against HPV 6/11/16/18-related PI, CIN or EGL (FAS population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI, CIN or EGL	**1886**	**116**	**1883**	**214**	**47.2**	**33.5, 58.2**
Day 1 HPV-naïve to all 6/11/16/18	1243	16	1249	90	82.7	70.3, 90.5
Day 1 HPV non-naïve to any of 6/11/16/18	643	100	634	124	21.5	-3.0, 40.3
N-weighted average efficacy					70.7	57.9, 79.6
HPV 16/18 PI, CIN or EGL	**1886**	**95**	**1883**	**160**	**41.6**	**24.3, 55.2**
Day1 HPV naïve to all 16/18	1472	17	1447	73	77.4	61.4, 87.5
Day1 HPV non-naïve to any of 16/18	414	78	436	87	6.1	-28.9, 31.8
N-weighted average efficacy					68.6	52.5, 79.3
HPV 6/111 PI, CIN or EGL	**1886**	**27**	**1883**	**69**	**61.3**	**38.8, 76.2**
Day1 HPV naïve to all 6/11	1514	8	1514	50	84.2	66.5, 93.5
Day1 HPV non-naïve to all HPV 6/11	372	19	369	19	-0.4	-100.4, 49.7
N-weighted average efficacy					77.2	58.0, 87.7

These results confirm the anticipated existence of VE-by-Day 1 HPV status interaction with respect to the HPV 6/11/16/18-related persistent infection, CIN, or EGL. The N-weighted analysis provides a

reasonable estimate of vaccine efficacy in a population with unknown HPV status at the time of vaccination and constitutes an appropriate complementary analysis of the FAS population.

Efficacy against HPV vaccine type related persistent infection

PPE population

Results of analysis of efficacy against HPV 6/11/16/18-related persistent infection (table 6) are similar to the results of analysis of efficacy against the composite HPV 6/11/16/18-related persistent infection and disease endpoint because persistent infection comprises the majority of the composite persistent infection and disease endpoint. Most of the persistent infection endpoints in the qHPV vaccine group were HPV 16-related.

Efficacy estimates with regard to HPV 16/18- and 6/11-related persistent infection within each of the 2 protocol-defined age strata were comparable. No HPV 18- related persistent infections were observed in the qHPV vaccine group.

Table 6: Efficacy against HPV vaccine type-related persistent infection (PI) (PPE-population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI	**1581**	**9**	**1586**	**85**	**89.6**	**79.3, 95.4**
By age						
24 to 34 year-olds	774	5	787	56	91.1	77.9, 97.2
35 to 45 year-olds	807	4	799	29	86.7	62.0, 96.6
By severity						
PI without HPV-related disease	1581	9	1586	82	89.2	78.5, 95.2
PI with HPV-related disease	1581	0	1586	5	100	-9.8, 100
HPV 16/18 PI	**1568**	**7**	**1559**	**50**	**86.2**	**69.4, 94.7**
By age						
24 to 34 year-olds	767	5	769	35	85.7	63.3, 95.6
35 to 45 year-olds	801	2	790	15	87.1	44.5, 98.6
By severity						
PI without HPV-related disease	1568	7	1559	49	85.9	68.8, 94.6
PI with HPV-related disease	1568	0	1559	1	100	-3794.5. 100
HPV 6/11 PI	**1299**	**2**	**1304**	**38**	**94.7**	**79.7, 99.4**
By age						
24 to 34 year-olds	622	0	648	24	100	82.7, 100
35 to 45 year-olds	677	2	656	14	86.3	40.2, 98.5
By severity						
PI without HPV-related disease	1299	2	1304	35	94.3	77.8, 99.3
PI with HPV-related disease	1299	0	1304	4	100	-53.0, 100
By HPV type (all ages)						
HPV 6	1299	2	1304	35	94.3	77.8, 99.3
HPV 11	1299	0	1304	4	100	-52.5, 100
HPV 16	**1299**	**7**	**1304**	**38**	**82.0**	**59.1,93.2**
HPV 18	1299	0	1304	13	100	67.1, 100

An exploratory analysis of efficacy against HPV16/18-related PI was conducted. The estimate of VE against HPV 16/18-related persistent infection of ≥12 months duration was somewhat lower to the estimate of VE against persistent infection based on the protocol defined duration of ≥6 months (±1 month) (77.2% vs. 86.2%).

VE against persistent HPV 6/11 infection was 95%. The clinical relevance of this finding was questioned in the previous 2007 procedure. However, at EOS there are more clear indications that the HPV 6/11 persistent infection results in the development of lesions. The likelihood ratios used in the study to measure the value of persistent infection as a predictor of subsequent progression to disease were very high (LR+=37.2), which support the use of PI due to HPV 6/11 as a surrogate for condyloma.

HNRT population

The efficacy estimates were lower in the HNRT population compared to the PPE population (see table 7). The findings with respect to persistent infection were similar to the results of analyses of efficacy against the composite HPV 6/11/16/18-related endpoint.

Table 7: Efficacy against HPV vaccine type related persistent infection (HNRT-population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI	**1811**	**26**	**1808**	**129**	**80.4**	**69.9, 87.7**
By age						
24 to 34 year-olds	893	15	906	90	83.5	71.3, 91.1
35 to 45 year-olds	918	11	902	39	73.0	46.3, 87.5
By severity						
PI without HPV-related disease	1811	25	1808	124	80.4	69.6, 87.8
PI with HPV-related disease	1811	1	1808	8	87.5	6.7, 99.7
HPV 16/18 PI	**1793**	**18**	**1778**	**84**	**79.1**	**64.9, 88.2**
By age						
24 to 34 year-olds	883	13	887	60	78.4	60.2, 89.1
35 to 45 year-olds	910	5	891	24	80.1	46.8. 94.1
By severity						
PI without HPV-related disease	1793	17	1778	83	80.0	66.1, 88.9
PI with HPV-related disease	1793	1	1778	1	0.5	-7711.6, 98.7
HPV 6/11 PI	**1497**	**8**	**1496**	**50**	**84.1**	**66.3, 93.5**
By age						
24 to 34 year-olds	723	2	758	35	94.0	76.7, 99.3
35 to 45 year-olds	774	6	738	15	62.3	-2.8, 89.6
By severity						
PI without HPV-related disease	1497	8	1496	44	81.9	61.2, 92.7
PI with HPV-related disease	1497	0	1496	7	100	30.5,100
By HPV type (all ages)						
HPV 6	1497	8	1496	47	83.1	64.0, 93.1
HPV 11	1497	0	1496	4	100	-51.6, 100
HPV 16	**1528**	**17**	**1502**	**63**	**73.9**	**54.8, 85.7**
HPV 18	1711	1	1703	23	95.7	73.4, 99.9

FAS population

Overall vaccine efficacy estimates were substantially lower in this population compared with the PPE population, as could be explained by the inclusion of subjects with infections that were present at vaccination onset (table 8). Compared with the 2007 endpoint driven analysis, the estimate of efficacy against the HPV 16/18-related endpoint has increased from 23.9% (-1.7, 43.2) to 44.8 % (25.5, 56.3) during the additional follow-up time. Also as regards HPV 16 and 18-related persistent infection statistically significant results were observed at end-of study.

Table 8: Efficacy against HPV vaccine type related persistent infection (FAS-population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI	**1856**	**110**	**1857**	**211**	**49.0**	**35.5 59.9**
By age						
24 to 34 year-olds	916	71	929	133	46.2	27.8,60.3
35 to 45 year-olds	940	39	928	78	52.4	29.2, 68.4
By severity						
PI without HPV-related disease	1856	99	1857	190	48.9	34.5, 60.3
PI with HPV-related disease	1856	12	1857	24	50.0	-4.0, 77.2
HPV 16/18 PI	**1856**	**91**	**1857**	**157**	**42.8**	**25.5, 56.3**
By age						
24 to 34 year-olds	916	58	929	99	40.6	17.0, 57.8
35 to 45 year-olds	940	33	928	58	45.3	14.7, 65.5
By severity						
PI without HPV-related disease	1856	80	1857	140	43.6	25.3, 57.7
PI with HPV-related disease	1856	11	1857	17	35.3	-46.5, 72.6
HPV 6/11 PI	**1856**	**24**	**1856**	**69**	**65.6**	**44.5, 79.3**
By age						
24 to 34 year-olds	916	15	929	44	65.2	36.2, 82.0
35 to 45 year-olds	940	9	927	25	65.4	23.4, 85.6
By severity						
PI without HPV-related disease	1856	23	1856	63	63.8	40.8, 78.6
PI with HPV-related disease	1856	1	1856	7	85.7	-11.2, 99.7
By HPV type (all ages)						
HPV 6	1856	22	1856	65	66.5	44.9, 80.3
HPV 11	1856	2	1856	5	60.1	-144.0, 96.2
HPV 16	***1856***	***74***	***1856***	***118***	***37.9***	***16.2, 54.2***
HPV 18	***1855***	***20***	***1855***	***45***	***55.7***	***23.5, 75.2***

Exploratory statistical analysis (N-weighted average efficacy analysis in the FAS)

When analysed separately for each of the Day 1 HPV-naïve and Day 1 HPV-non-naïve cohorts within the FAS, results were different. In the Day 1 HPV-naïve cohort, the estimate of VE against HPV 6/11/16/18-related persistent infection was 82.6% (95% CI: 70.2, 90.5). In the Day 1 HPV-non-naive cohort, the estimate of VE against HPV 6/11/16/18- related persistent infection was 23.9% (95% CI: -0.5, 42.5).

The estimate of the expected value of VE in the FAS against the HPV 6/11/16/18- related persistent infection endpoint was 71.0% (95% CI: 58.3, 79.9); against the HPV 16/18-related persistent infection endpoint was 69.7% (95% CI: 53.7, 80.2) and against the HPV 6/11-related persistent infection endpoint is 78.1% (95% CI: 59.4, 88.1).

Efficacy against persistent infection related to any of 10 non-vaccine HPV types

The results of analysis of efficacy against persistent infection related to the 10 non-vaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) showed no statistically significant VE in the qHPV vaccine group (relative to placebo) in any of the study populations.

Efficacy against vaccine HPV type-related CIN

PPE population

The results of the PPE analysis of efficacy against HPV 6/11/16/18-related CIN showed VE of 94.1%, with 1 case in the vaccine group versus 17 cases in the placebo group (Table 9). The one case of HPV 16-related CIN 2 in the vaccine group was already detected in the 2007 endpoint-driven analysis. During additional study follow-up through EOS, no cases of HPV 6/11/16/18-related CIN (or worse) was observed in the vaccine group, while additional 8 cases were observed in the placebo group.

Table 9: Efficacy against HPV vaccine type related CIN (PPE-population)

	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy	
Endpoint	**n**	**Number of cases**	**n**	**Number of cases**	**%**	**95% CI**
HPV 6/11/16/18 CIN	**1581**	**1**	**1584**	**17**	**94.1**	**62.5, 99.9**
By age						
24 to 34 year-olds	772	0	785	8	100	39.9, 100
35 to 45 year-olds	809	1	799	9	89.1	21.7, 99.8
By severity						
CIN 1	1581	0	1584	15	100	72.1,100
CIN 2/3 or AIS	***1581***	***1***	***1584***	***6***	***83.3***	***-37,6, 99.6***
CIN 2	1581	1	1584	4	75.0	-153.0, 99.5
CIN 3	1581	0	1584	1	100	-3804.1, 100
AIS	1581	0	1584	1	100	-3804.3, 100
Cervical cancer	1581	0	1584	0	NA	NA
By HPV type (all ages)						
HPV 6	1300	0	1305	4	100	-52.2, 100
HPV 11	1300	0	1305	3	100	-143.2, 100
HPV 16	***1325***	***1***	***1313***	***12***	***91.8***	***44.4, 99.8***
HPV 18	1490	0	1491	1	100	-3807.0, 100
HPV 16/18 CIN	**1568**	**1**	**1558**	**13**	**92.1**	**49.1. 99.8**
By age						
24 to 34 year-olds	765	0	768	6	100	-13.5, 100
35 to 45 year-olds	803	1	790	7	86.1	-8.1, 99.7
By severity						
CIN 1	1568	0	1558	11	100	60.4, 100
CIN 2/3 or AIS	***1568***	***1***	***1558***	***6***	***83.4***	***-36.7, 99.6***
CIN 2	1568	1	1558	4	75.1	-151.4, 99.5
CIN 3	1568	0	1558	1	100	-3779.2, 100
AIS	1568	0	1558	1	100	-3779.2, 100
HPV 6/11 CIN	**1300**	**0**	**1305**	**6**	**100**	**14.7, 100**
By age						
24 to 34 year-olds	621	0	647	4	100	-59.2, 100
35 to 45 year-olds	679	0	658	2	100	-413.3, 99.8

Statistical significance was not reached in the CIN 2/3+ endpoint, but clear numerical reductions were seen and an estimate in the range of that seen for CIN (any grade). The study was not powered to demonstrate VE against the CIN 2/3+ endpoint. The case of HPV 16-related CIN 2/3 in the vaccine group was already observed in the previous 2007 analysis.

HNRT population

In the HNRT analysis, VE was 89.0% (table 10).

There were 3 cases of HPV 6/11/16/18 CIN in the vaccine group that was observed already in the 2007 endpoint-driven analysis.

Table 10: Efficacy against HPV vaccine type related CIN (HNRT-population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 CIN	**1817**	**3**	**1812**	**27**	**89.0**	**64.1, 97.9**
By age						
24 to 34 year-olds	896	2	908	15	86.3	41.1, 98.5
35 to 45 year-olds	921	1	904	12	92.0	45.8, 99.8
By severity						
CIN 1	1817	1	1812	23	95.7	73.4, 99.9
CIN 2/3 or AIS	***1817***	***3***	***1812***	***8***	***62.7***	***-55.4, 93.6***
CIN 2	1817	3	1812	4	25.3	-341.3, 89.1
CIN 3	1817	1	1812	2	50.2	-855.8, 99.2
AIS	1817	0	1812	2	100	-429.9, 100
Cervical cancer	1817	0	1812	0	NA	NA
By HPV type (all ages)						
HPV 6	1502	0	1499	6	100	15.2, 100
HPV 11	1502	0	1499	3	100	-141.7, 100
HPV 16	**1534**	**3**	**1505**	**19**	**84.6**	**45.7, 97.1**
HPV 18	1717	0	1707	2	100	-429.2, 100
HPV 16/18 CIN	**1799**	**3**	**1782**	**21**	**85.9**	**52.7, 97.3**
By age						
24 to 34 year-olds	886	2	889	11	81.4	14.9, 98.0
35 to 45 year-olds	913	1	893	10	90.4	32.7, 99.8
By severity						
CIN 1	1799	1	1782	17	94.2	62.9, 99.9
CIN 2/3 or AIS	***1799***	***3***	***1782***	***8***	***62.9***	***-54.6, 93.7***
CIN 2	1799	3	1782	4	25.8	-338.8, 89.1
CIN 3	1799	1	1782	2	50.5	-850.3, 99.2
AIS	1799	0	1782	2	100	-426.8, 100
HPV 6/11 CIN	**1502**	**0**	**1499**	**8**	**100**	**41.5, 100**
By age						
24 to 34 year-olds	725	0	760	6	100	9.9, 100
35 to 45 year-olds	777	0	739	2	100	-401.9, 100

During additional study follow-up through EOS, no cases of HPV 6/11/16/18-related CIN 2/3+ was observed in the vaccine group, while additional 4 cases were observed in the placebo group. At EOS, the estimate of VE against HPV 6/11/16/18- related CIN 2/3+ is 62.7% (95% CI: –55.5, 93.6). The estimate of VE against HPV 16/18-related CIN 2/3+ is similar to the estimate of VE against HPV 6/11/16/18-related CIN 2/3+, as most of the cases of vaccine-HPV type related CIN 2/3+ were related to HPV type 16.

FAS population

Efficacy against the HPV 6/11/16/18-related CIN (or worse) endpoint was demonstrated at EOS with an estimate of VE of 47.5% (95% CI: 16.3, 67.7). (Table 11) Compared with the 2007 endpoint driven analysis, 4 additional cases occurred in the vaccine group (all HPV 16-related; 2 CIN1 and 2 CIN3) at EOS and 14 cases in the placebo group (1 HPV 6-, 2 HPV 11- and 12 HPV 16-related).

Table 11: Efficacy against HPV vaccine type related CIN (FAS-population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 CIN	**1862**	**29**	**1861**	**55**	**47.5**	**16.3, 67.7**
By age						
24 to 34 year-olds	919	22	931	33	31.5	-21.1 61.9
35 to 45 year-olds	943	7	930	22	69.3	25.6, 88.9
By severity						
CIN 1	1862	17	1861	37	54.3	16.8, 75.9
CIN 2/3 or AIS	***1862***	***21***	***1861***	***27***	***22.4***	***-42.5, 58.3***
CIN 2	1862	11	1861	11	0.2	-153.7, 60.8
CIN 3	1862	16	1861	18	0.4	-84.1 57.7
AIS	1862	0	1861	2	100	-430.9, 100
Cervical cancer	1862	0	1861	2	100	-430.9, 100
By HPV type (all ages)						
HPV 6	1862	3	1861	7	57.3	-87.1, 92.9
HPV 11	1862	1	1861	3	66.8	-314.0, 99.4
HPV 16	1862	24	1861	44	43.4	5.5, 66.8
HPV 18	1862	3	1861	4	25.3	-341.8, 89.1
HPV 16/18 CIN	**1862**	**28**	**1861**	**48**	**46.9**	**5.6, 64.9**
By age						
24 to 34 year-olds	919	21	931	29	25.6	-35.1, 59.7
35 to 45 year-olds	943	7	930	19	64.4	11.6, 87.4
By severity						
CIN 1	1862	156	1861	30	46.9	-0.5, 73.0
CIN 2/3 or AIS	***1862***	***21***	***1861***	***27***	***22.4***	***-42.5, 58.3***
CIN 2	1862	11	1861	11	0.2	-153.7, 60.8
CIN 3	1862	16	1861	18	11.4	-84.1, 57.7
AIS	1862	0	1861	1	100	-430.9, 100
Cervical cancer	1862	0	1861	2	100	-430.9, 100
HPV 6/11 CIN	**1862**	**4**	**1861**	**9**	**55.7**	**-58.8, 90.0**
By age						
24 to 34 year-olds	919	4	931	6	31.3	-189.8, 85.7
35 to 45 year-olds	943	0	930	3	100	-133.8, 100

The estimate of VE against HPV 16/18-related CIN (or worse) at EOS was 46.9% (95% CI: 5.6, 64.9) overall. By comparison, during the endpoint-driven analysis conducted in 2007, the estimate of VE without accounting for Day 1 HPV 16/18 infection status was 33.6% (95% CI: –14.3, 62.1).

Exploratory statistical analysis (N-weighted average efficacy analysis in the FAS)

In the analysis of efficacy against HPV 6/11/16/18-related CIN by baseline HPV status showed VE of 95.2% (95%CI: 70.4, 99.9) in the Day 1 HPV-naïve and VE of 18.9% (95% CI:-37.7, 52.6 in the Day 1 HPV-non-naïve cohorts within the FAS. The estimate of the expected value of VE in the FAS against the HPV 6/11/16/18-related CIN was 87.6% (95%CI: 52.5, 96.7).

The results of analysis of VE against HPV 16/18-related CIN (or worse) separately for each of the Day 1 HPV-naïve and Day 1 HPV-non-naïve cohorts within the FAS showed VE of 85.3% (50.3, 97.2) and 6.9% (-65.5, 48.0) respectively. The estimate of the expected value of VE in the FAS against the HPV 16/18-related CIN (or worse) is 77.6% (95% CI: 42.2, 91.3).

Efficacy against CIN (or worse) related to any of 10 non-vaccine HPV types

No statistically significant efficacy was observed in the qHPV vaccine group (relative to placebo) against the CIN endpoint related to the 10 non-vaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) in any of the populations studied.

In the FAS population 65 cases (vaccine = 40, placebo = 25) of CIN 2/3+ related to non-vaccine HPV types were observed. This imbalance between the two study groups was observed in the 2007 endpoint-driven analysis and was due to an imbalance in Day 1 prevalent infections. There was no imbalance in acquisition of non-vaccine HPV type CIN 2/3+ in the vaccine and placebo groups during the additional follow-up through EOS.

Efficacy against any CIN (or worse) (regardless of HPV type)

In the assessment of efficacy against the endpoint Any CIN (or worse) regardless of HPV type, the PPE and HNRT analysis populations are undefined because the PPE and HNRT populations are comprised of subjects who are naïve to the specific HPV type to which a particular endpoint is related. The "HPV-naïve" population that is relevant in the assessment of efficacy against CIN (or worse) regardless of HPV type is the generally HPV-naïve (GHN) population. The GHN population is comprised of subjects who were Day 1 HPV-naïve to all 14 tested HPV types (i.e., 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59).

No statistically significant results were obtained in any of the study populations, except for as expected CIN related to the 4 vaccine types in both populations. The VE against Any CIN regardless of HPV type over all age groups was 34.5% (95% CI: –12.5, 62.5) in the GHN population and 5.5% in the FAS population. The estimates of VE in the CIN 2/3 endpoint were lower and even negative in the FAS population.

Efficacy against vaccine HPV type-related EGL

PPE-population: There were 7 cases (vaccine = 0, placebo = 7) of HPV 6/11/16/18- related EGL observed in the PPE population at EOS. All 7 cases were HPV 6-related condyloma (vulvar n=6, vaginal n=2). At EOS, the estimate of VE against HPV 6-related condyloma (100%; 95% CI: 30.7, 100) was statistically significant, while not so during the endpoint driven analysis conducted in 2007 (VE 100% (95%CI: -49.2, 100). There was no high grade HPV 6/11/16/18-related VIN or VaIN (i.e., grades 2/3) nor vulvar or vaginal cancers observed in the PPE population.

HNRT-population: There were 13 cases (vaccine = 2, placebo = 11) of HPV 6/11/16/18-related EGL observed in the HNRT population at EOS. All 11 placebo group cases were HPV 6-related genital warts (1 also with VaIN 1). The 2 cases in the qHPV vaccine group had prevalent infection of high risk HPV type at Day 1. The estimate of VE against HPV 6/11/16/18-related EGL (81.9%; 95% CI: 17.2, 98.1) was statistically significant. There was no high-grade HPV 6/11/16/18-related VIN or VaIN (i.e., grades 2/3) nor vulvar or vaginal cancers observed in the HNRT population.

FAS population: There were a total of 23 cases (vaccine = 11, placebo = 12) of HPV 6/11/16/18-related EGL observed at EOS. Of these, 9 cases (vaccine = 8, placebo = 1) were due to Day 1

prevalent infections and 13 (vaccine = 2, placebo = 11) were due to incident infections and 1 case of HPV 6-related genital warts in the vaccine group with unknown HPV 6 PCR status at Day 1. In the FAS (pooled population), the estimate of efficacy of the qHPV vaccine against HPV 6/11/16/18-related EGL is 8.5% (95% CI: –126.6, 63.4).

The estimate of the expected value of VE in the FAS (that accounts for HPV infection status at Day 1) against the HPV 6/11/16/18-related EGL is 61.1% (95% CI: –67.0, 90.9).

Other efficacy Analyses - Evaluation of population benefit of the vaccine

No significant efficacy results were obtained in the population benefit endpoints. No efficacy against the overall burden of cervical or external genital HPV disease could be demonstrated. The qHPV vaccine was efficacious in preventing HPV 16/18-related Pap abnormalities of ASC-US positive for high-risk HPV probe or worse in all study populations, but no significant efficacy could be shown against Pap abnormalities due to any HPV type or in the reduction in the incidence of cervical or external genital procedures. The number of endpoints was insufficient to detect a statistically significant effect.

Therapeutic efficacy

Clearance of prevalent infection related to vaccine HPV types

The impact of a 3-dose vaccination regimen on the clearance of vaccine HPV type DNA among subjects who were PCR-positive at Day 1 to the relevant HPV type was analysed.

The current analysis at EOS again shows a higher clearance of HPV 16 DNA in the placebo group versus the vaccine group (percent incidence reduction 54.8 % (95% CI: 018.6, 75.5)) among subjects who were Day 1 PCR positive and seronegative (table 12).

Table 12: Clearance of HPV DNA among subjects PCR positive at Day 1

	qHPV vaccine N=1910		Placebo N=1907		Percent incidence reduction %	95% CI
	n	Number of cases	n	Number of cases		
Day 1 PCR positive (PCR+/RT)						
Clearance of HPV 6 infection	28	23	33	25	6.1	-72.4, 49.1
Clearance of HPV 11 infection	4	4	5	5	-36.4	-533.8, 72.9
Clearance of HPV 16 infection	79	38	63	38	33.1	-7.8, 58.4
Clearance of HPV 18 infection	35	19	34	18	-7.8	-117.8, 46.4
Day 1 PCR positive/seronegative (S0P1)						
Clearance of HPV 6 infection	12	12	18	14	-73.2	-303.4, 26.8
Clearance of HPV 11 infection	3	3	2	2	-37.8	-1549.9, 84.2
Clearance of HPV 16 infection	**41**	**20**	**43**	**32**	**54.8**	**18.6, 75.5**
Clearance of HPV 18 infection	26	15	24	13	-6.1	.-142.3, 52.9
Day 1 PCR positive/seropositive (S1P1)						
Clearance of HPV 6 infection	**16**	**11**	**15**	**11**	**36.7**	**-61.0, 75.1**
Clearance of HPV 11 infection	1	1	3	3	-423.2	-6416.3, 90.0
Clearance of HPV 16 infection	38	18	20	6	-84.9	-468.9, 29.7
Clearance of HPV 18 infection	9	4	10	5	-1.7	-372.4, 79.8

A time-to-clearance analysis of HPV infection showed that in the cohort with co-infection at any time from Day 1 to EOS some subjects in the vaccine group compared to placebo exhibited delay in

clearance of prevalent HPV 16 infection whereas in the cohort of subjects without co-infection there was no difference between vaccine and placebo groups with respect to HPV 16 clearance.

Recurrent infection and acquisition of disease related to vaccine HPV types among subjects seropositive and PCR negative to the relevant HPV type

Table 13 shows the results of analysis of efficacy against HPV 6/11/16/18-related persistent infection and disease among subjects seropositive and PCR negative to the relevant HPV type at Day 1.

The estimate of VE at EOS against HPV 6/11/16/18-related persistent infection that is of ≥6 months duration over consecutive visits 6 (±1) months apart among subjects who were seropositive and PCR-negative to the relevant HPV type at Day 1 was 66.8% (95% CI: 3.8, 90.5). Among the 35 to 45 year-old seropositive and PCR-negative subjects, the estimate of VE was 81.3% (95% CI: 14.4, 98.0).

Table 13: Analysis of efficacy against HPV 6/11/16/18-related persistent infection and disease in subjects who were PCR negative and seropositive for the relevant vaccine HPV type(s) at Day 1

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
	n	Number of cases	n	Number of cases		
HPV 6/11/16/18 PI, CIN or EGL	**506**	**5**	**513**	**15**	**66.9**	**4.3, 90.6**
Persistent infection	***496***	***5***	***505***	***15***	***66.8***	***3.8, 90.5***
CIN (any grade) or EGL	506	0	513	0	NA	NA
By HPV type and Age group						
HPV 6/11/16/18 PI	496	5	505	15	66.8	3.8, 90.5
24 to 34 year-olds	258	3	248	4	27.4	-329.0, 89.4
35 to 45 year-olds	***258***	***2***	***257***	***11***	***81.3***	***14.4, 98.0***
HPV16/18 PI	284	3	312	11	70.3	-12.5, 94.7
24 to 34 year-olds	145	2	154	3	28.1	-528.1, 94.0
35 to 45 year-olds	139	1	158	8	86.2	-2.7, 99.7

There were no cases of HPV 6/11/16/18-related CIN (any grade) or EGL observed among subjects who were seropositive and PCR-negative to the relevant HPV type at Day 1 during the course of the study.

In a post hoc analyses of individuals (who received at least one vaccination) with evidence of a prior infection with a vaccine HPV type (seropositive) no longer detectable (PCR negative) at vaccination onset the efficacy of Gardasil to prevent conditions due to the recurrence of the same HPV type was 100% (95% CI: 62.8, 100.0; 0 vs. 12 cases [n = 2572 from pooled studies in young women]) against HPV 6-, 11-, 16-, and 18-related CIN 2/3, VIN 2/3, VaIN 2/3, and genital warts in women 16 to 26 years. Efficacy was 68.2% (95% CI: 17.9, 89.5; 6 vs. 20 cases [n= 832 from studies in young and adult women combined]) against HPV 16- and 18-related persistent infection in women 16 to 45 years.

1.2.1.3 Discussion

The main goal of the study was to provide data to support that efficacy in MAW was comparable to that shown in young adult women (YAW). The study was designed to demonstrate the efficacy in MAW with respect to the composite co-primary endpoints of HPV 6/11/16/18- and HPV 16/18-related persistent infection and clinical disease (CIN, AIS and EGLs). The scientific basis for these endpoints constituted the natural history of HPV and the results of the clinical program in YAW. The original licensure of the

qHPV vaccine was based on histologically-confirmed efficacy endpoints, i.e. HPV 16/18-related CIN 2/3 and AIS, as surrogates for cervical cancer. Subsequent to the demonstration of robust efficacy in this endpoint in YAW, a virological endpoint was applied in the study of MAW. Persistent HPV infection is recognised as a necessary pre-requisite for the development of cervical cancer. Comparable efficacy against HPV 16/18-related persistent infection and CIN 2/3 was demonstrated in the YAW studies. The CHMP´s ad-hoc expert HPV meeting on December 3rd 2009 recommended the use of persistent infection due to oncogenic HPV types of 6 months duration as a surrogate endpoint for cervical cancer in efficacy trials of HPV vaccines. The MAH conducted an exploratory analysis of efficacy against HPV16/18 persistent infection based on duration of >12 months and results showed a similar VE to the protocol defined definition of 6 months. In this study (P019), the likelihood ratios of persistent infection as a predictor of type-specific mediated disease due to HPV 6/11/16/18, HPV 16/18 and HPV 6/11 were high in MAW. Based on all these findings the use of 6 months persistent infection is considered justified including for HPV 6/11.

Regarding baseline HPV status, it was demonstrated that 67% of the mid-adult women (64.6% of the 24- to 34-year-olds and 69% of the 35- to 45-year-olds) were seronegative and PCR negative to HPV 6, 11, 16 and 18 at Day 1 and thus, susceptible to all 4 vaccine HPV types at study entry. The corresponding percentage in YAW was 73%. However, as a reflection of the higher cumulative exposure of HPV and the lower number of new sexual partners in older women, the MAW had lower baseline HPV DNA prevalence and higher seroprevalence than YAW. Within the MAW, HPV DNA prevalence was lowest in the 35- to 45-year-olds (5.2%) compared with the 24- to 34-year-olds (10.2%) whereas the seroprevalence was comparable (~30%). Overall, the HPV sero-/DNA-prevalence data observed in P019 are consistent with literature estimates. However, in the integrated summary report of natural history in P019, it was shown that HPV sero-/DNA- prevalence varied greatly by countries/continents, which has to be considered in the evaluation of efficacy results.

Efficacy:

PPE population: The findings at end of study confirm the efficacy of the qHPV vaccine in MAW in the PPE population demonstrated in the 2007 endpoint driven analysis. The qHPV vaccine was highly efficacious in the PPE population with respect to the relevant endpoints, persistent infection, CIN and EGL. Efficacy was observed overall and in each age stratum. High efficacy was observed with respect to HPV 6, 16 and 18 individually; with respect to persistent infection alone and with respect to disease endpoints (CIN, AIS, or EGL) alone. There were no cases of HPV 11 infection or disease observed in the PPE population due to the rarity of this HPV type. VE was 88.7% against HPV 6/11/16/18-related persistent infection (PI)/disease, 84.7% against HPV 16/18-related PI/disease, 94.7% against HPV6/11-related PI/disease and 94.1% against vaccine type related CIN, which is generally comparable to VE obtained in the YAW studies. No statistical significance was reached in the HPV 16/18-related CIN 2/3 endpoint (VE 83.4%; 95%CI: -36.7, 99.6). There were 7 new endpoint cases (5 HPV16 PI and 2 HPV6 PI) in the vaccine group and 46 new cases in the placebo group detected during the additional follow-up since the 2007 analysis. All of these 7 cases of persistent infection had preceding infections with multiple non-vaccine HPV types. There were no new cases of HPV 6/11/16/18-related CIN or EGL reported in the qHPV group since the first analysis. In contrast there were 8 new cases of HPV 6/11/16/18-related CIN (any grade), 2 new cases of HPV 6/11/16/18-related CIN 2/3 or worse and 3 new cases of EGL in the placebo group during the same period.

HNRT population: During the assessment of the 2007 endpoint-driven report concerns were raised since the number of CIN 2/3 cases in the vaccine group was the same as in the placebo group (3 vs. 4 cases). It was clarified that all cases in the vaccine group had non-vaccine HPV types at baseline and

had very early detection of HPV 16-related disease suggesting the presence of prevalent HPV 16 infection at baseline. At EOS no new cases of HPV 16/18-related CIN 2/3 were observed in the vaccine group, while additional 4 cases were observed in the placebo group. The estimate of VE against HPV 16/18-related CIN 2/3+ was 63% (95% CI -54.6, 93.7). No HPV 18-related CIN lesion was detected.

For all endpoints, efficacy was somewhat lower in the HNRT population. The lower efficacy was a function of the presence of infections with onset detected at the Month 7 visit (such infections were acquired between Day 1 and Month 7 and not a result of waning immunity. The observed efficacy in P019 followed the same pattern for similar endpoints seen in YAW for a similar duration of follow-up and that efficacy continues to increase over time.

FAS (ITT) population: Improved efficacy results were demonstrated during the additional follow-up since the 2007 analysis with VE against HPV 6/11/16/18-related PI/disease of 47.2% (33.5, 58.2). Four new cases of HPV 6/11/16/18-related CIN were detected in the vaccine group of FAS during the additional follow-up through EOS. It is noted that at least three of these cases also were infected by non-vaccine serotypes. VE in the more important HPV 16/18-related PI/disease endpoint now reached statistical significance (VE: 41.6% (24.3, 55.2). These point estimates are lower than those observed among YAW. With respect to HPV 16/18 CIN2/3 only an efficacy trend was observed (VE: 22.4% (-42.5, 58.3), but the estimate was improved relative to the 2007 analysis (VE: 9.9%). There were no new cases of HPV 16/18-related CIN 2/3+ in the vaccine group since the 2007 analysis. There were a total of 48 (qHPV=21, placebo =27) cases of vaccine type related CIN 2/3 in the FAS population. An exploratory statistical analysis N-weighted analysis was conducted whereby the expected value of VE in the FAS was computed to account for the anticipated VE-by- Day 1 HPV status interaction. This analysis gave higher efficacy estimates than the pooled analysis and provides a reasonable estimate of vaccine efficacy in a population with unknown HPV status at the time of vaccination and constitutes an appropriate complementary analysis of the FAS population.

Other efficacy populations:

Day 1 PCR positive and seronegative: The observation of a significantly higher clearance of HPV 16 DNA in the placebo group versus the vaccine group in the first 2007 analysis remained and was even stronger at end of study (percent incidence reduction 54.8% (95% CI: 18.6, 75.5) among subjects who were Day 1 PCR positive and seronegative to HPV 16. A two-fold higher prevalence of co-infection in the vaccine group compared to the placebo group probably explains the longer persistence of HPV 16. A time-to-clearance analysis of HPV infection showed that in the cohort with co-infection at any time from Day 1 to EOS some subjects in the vaccine group compared to placebo exhibited delay in clearance of prevalent HPV 16 infection whereas in the cohort of subjects without co-infection there was no difference between vaccine and placebo groups with respect to HPV 16 clearance. The imbalance in co-infections likely explains the unexpected reverse therapeutic efficacy observed. Moreover, it is difficult to understand by which mechanism the qHPV vaccine would exert a negative effect on on-going HPV infections.

Day 1 seropositive and PCR negative: Analysis of efficacy against the recurrence of persistent HPV 6/11/16/18 infection among subjects who were seropositive and PCR negative to the relevant HPV type at baseline showed statistically significant results. The estimate of VE at EOS against HPV 6/11/16/18-related persistent infection that is of ≥6 months duration over consecutive visits 6 (±1) months apart was 66.8% (95% CI: 3.8, 90.5). Among the 35 to 45 year-old seropositive and PCR-negative subjects, the estimate of VE was 81.3% (95% CI: 14.4, 98.0). Based on these data, which are consistent with and similar to data from the efficacy studies in young women that show efficacy against both CIN and EGL, as well as persistent infection, the MAH has a claim of protection against recurrent HPV infection

in the Day 1 seropositive and PCR negative population and section 5.1 of the SmPC was updated with data from the post hoc analyses performed by the MAH.

No significant efficacy results were obtained in the population benefit endpoints. No efficacy against the overall burden of cervical or external genital HPV disease could be demonstrated. The qHPV vaccine was efficacious in preventing HPV 16/18-related Pap abnormalities of ASC-US positive for high-risk HPV probe or worse in all study populations, but no significant efficacy could be shown against Pap abnormalities due to any HPV type or in the reduction in the incidence of cervical or external genital procedures. The number of endpoints was insufficient to detect a statistically significant effect.

Non-vaccine serotypes:

There was no imbalance in acquisition of non-vaccine HPV type CIN 2/3+ in the vaccine and placebo groups during the additional follow-up through EOS. The original imbalance observed in the 2007 endpoint-driven analysis was due to an imbalance in prevalent infection at Day 1 between the two groups. The 65 cases (vaccine = 40, placebo = 25) of CIN 2/3+ related to non-vaccine HPV types observed in the FAS: i) do not represent evidence suggesting that the qHPV vaccine allows non-vaccine HPV type disease to replace vaccine HPV type-related disease in vaccinated subjects; and ii) do not support a view that the qHPV vaccine accelerates progression of existing non-vaccine HPV type-related infection to pre-cancerous lesions in subjects vaccinated with the qHPV vaccine. No cross-protective could be demonstrated, probably due to the sample size and the relative lack of power to detect a significant result.

The collection of data on possible HPV type replacement in the MAW population will only be performed in the 019 study in Columbia. The conditions are not ideal since the Columbian cohort is very limited and there will be no population-based data on background HPV types available. However, the observed HPV types after vaccination will be compared with data from another population in Bogota. This approach will probably be informative. In addition, HPV type replacement will be studied in the YAW population in two large studies from which data to some degree may be extrapolated to the MAW population. It is noted that an overview on how the MAH plans to assess the potential occurrence of type replacement following vaccination with qHPV vaccine is detailed in the current risk management plan. An updated version of the RMP will be submitted in June 2010. The type replacement issue will therefore be the subject of further discussion.

In conclusion the results at end of study of Protocol 019 confirmed the efficacy of the qHPV vaccine in mid-adult women 24 to 45 years of age. Long-term follow up of efficacy for a duration of at least 10 years will be performed in the Colombian cohort of study 019

1.3 Immunogenicity

Protocol 019 included the immunogenicity evaluation. The study enrolled a total of 3819 subjects in 2 approximately equal age strata (24- to 34-year-olds and 35- to 45-year-olds). All subjects were to undergo serology testing for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 levels at Day 1, and Months 7, 12, 24, 36, and 48. The primary immunogenicity evaluations were to be conducted in the per-protocol immunogenicity (PPI) population. The 2007 endpoint driven analysis presented results from all visits through 13-July-2007 (corresponding primarily to the Day 1, Month 7 and Month 24 visits). The new results presented in this end-of-study report pertain to immunogenicity responses at Months 12, 36, and 48 and maternal transfer of anti-HPV (exploratory immunogenicity objective).

1.3.1 Methods

The below characteristics are specific for the immunogenicity analysis.

Study population

Per-Protocol immunogenicity (PPI) population

The per-protocol population for immunogenicity (PPI) analysis generally included subjects who were seronegative and PCR negative to the relevant HPV type(s) at Day 1, remained HPV PCR negative through 1 month post dose 3 (month 7), received all 3 vaccinations within pre-specified time intervals, and no deviation from the study protocol.

Exploratory immunogenicity populations

Day 1 seronegative and PCR positive (S0P1)

Day 1 seropositive and PCR negative (S1P0)

Day 1 seropositive and PCR positive (S1P1)

Objectives

The immunogenicity objectives were:

To evaluate the kinetics and age dependence of anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of qHPV vaccine

To observationally compare anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of qHPV vaccine among HPV-naïve women 24 to 45 years of age enrolled in P019 and HPV-naïve women 16 to 23 years of age from P011, P012 (substudies of P013) and the Consistency Lot substudy of P015.

The immunogenicity of the HPV vaccines was measured using the method competitive Luminex-based immunoassay (cLIA). The method was requalified as cLIA version 2.

Outcomes/endpoints

The immunogenicity endpoints for the clinical program have focused on 2 parameters:

Anti-HPV levels (geometric mean titers [GMTs]),

The proportion of subjects who became seropositive to each of the 4 HPV antigens 4 weeks after the third dose.

The immunogenicity time points of interest were:

Month 7: The primary immunogenicity endpoint was anti-HPV 6, 11, 16 and 18 serum cLIA levels at Month 7 in the defined PPI population, as this time point reflected the time frame during which peak vaccine-induced immune responses were expected.

Persistence time points. Depending on the protocol, subjects underwent serology testing at 6- to 48-month intervals following the Month 7 visit. The data collected at these time points were used to evaluate the durability of vaccine-induced anti-HPV responses.

1.3.2 Results

GMTs

Table 14 shows the anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 geometric mean titers (GMTs) for each of the vaccine group and placebo group in the per-protocol immunogenicity (PPI) population at Day 1, Month 7, Month 12, and every 12 months thereafter through Month 48.

For each of the vaccine HPV types, and at all the time points evaluated, the GMTs in the placebo group were below the lower limit of quantitation (LLOQ) of the assay.

In the vaccine group for each vaccine HPV type, measurable immune responses well above the LLOQ were induced by a 3-dose vaccination of qHPV vaccine at Month 7 (table 14). For each of anti-HPV-6, -11, -16, and -18, the GMTs declined from Month 7 through Month 24. The Month 24 GMTs were then sustained through Month 48.

Table 14: Summary of anti-HPV GMTs by vaccination group (PPI Population)

Table 14

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

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=1,910) n	GMT (mMU/mL)	95% CI	Placebo (N=1,907) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	1,249	< 7	(<7, <7)	1,244	< 7	(<7, <7)
Month 07	1,249	416.2	(395.6, 438.0)	1,244	< 7	(<7, <7)
Month 12	1,225	155.1	(148.8, 161.8)	1,231	< 7	(<7, <7)
Month 24	1,207	70.3	(66.8, 73.9)	1,202	< 7	(<7, <7)
Month 36	1,169	80.8	(76.9, 85.0)	1,169	< 7	(<7, <7)
Month 48	1,152	60.9	(57.8, 64.2)	1,165	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1,249	< 8	(<8, <8)	1,244	< 8	(<8, <8)
Month 07	1,249	551.2	(525.3, 578.3)	1,244	< 8	(<8, <8)
Month 12	1,225	176.9	(170.1, 184.0)	1,231	< 8	(<8, <8)
Month 24	1,207	77.6	(74.0, 81.4)	1,202	< 8	(<8, <8)
Month 36	1,169	81.0	(77.7, 84.5)	1,169	< 8	(<8, <8)
Month 48	1,152	65.9	(63.0, 68.8)	1,165	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1,269	< 11	(<11, <11)	1,249	< 11	(<11, <11)
Month 07	1,269	2,225.9	(2,113.4, 2,344.4)	1,249	< 11	(<11, <11)
Month 12	1,236	719.6	(692.6, 747.6)	1,235	< 11	(<11, <11)
Month 24	1,225	278.9	(264.0, 294.5)	1,211	< 11	(<11, <11)
Month 36	1,190	285.7	(272.5, 299.5)	1,177	< 11	(<11, <11)
Month 48	1,172	202.1	(192.3, 212.3)	1,178	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,430	< 10	(<10, <10)	1,419	< 10	(<10, <10)
Month 07	1,430	356.9	(340.0, 374.6)	1,419	< 10	(<10, <10)
Month 12	1,387	79.2	(75.6, 83.0)	1,405	< 10	(<10, <10)
Month 24	1,378	28.3	(26.8, 29.9)	1,371	< 10	(<10, <10)
Month 36	1,331	29.4	(27.9, 31.0)	1,329	< 10	(<10, <10)
Month 48	1,313	23.1	(21.9, 24.3)	1,324	< 10	(<10, <10)

The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.
The estimated GMTs and associated CIs are calculated using an ANOVA model with a term for vaccination group.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
ANOVA = Analysis of variance; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; PCR = Polymerase chain reaction; qHPV = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Seroconversion

Table 15 shows the percent seropositivity in the vaccination groups.

Table 15

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

Anti-HPV Response / Study Time	qHPV Vaccine (N=1,910)				Placebo (N=1,907)			
		Seroconversion				Seroconversion		
	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 6 cLIA ≥ 20 mMU/mL								
Day 1	1,249	0	0.0	(0.0%, 0.3%)	1,244	0	0.0	(0.0%, 0.3%)
Month 7	1,249	1,229	98.4	(97.5%, 99.0%)	1,244	38	3.1	(2.2%, 4.2%)
Month 12	1,225	1,209	98.7	(97.9%, 99.3%)	1,231	50	4.1	(3.0%, 5.3%)
Month 24	1,207	1,078	89.3	(87.4%, 91.0%)	1,202	42	3.5	(2.5%, 4.7%)
Month 36	1,169	1,070	91.5	(89.8%, 93.1%)	1,169	57	4.9	(3.7%, 6.3%)
Month 48								
HPV 11 cLIA ≥ 16 mMU/mL								
Day 1	1,249	0	0.0	(0.0%, 0.3%)	1,244	0	0.0	(0.0%, 0.3%)
Month 7	1,249	1,225	98.1	(97.2%, 98.8%)	1,244	27	2.2	(1.4%, 3.1%)
Month 12	1,225	1,210	98.8	(98.0%, 99.3%)	1,231	18	1.5	(0.9%, 2.3%)
Month 24	1,207	1,115	92.4	(90.7%, 93.8%)	1,202	31	2.6	(1.8%, 3.6%)
Month 36	1,169	1,116	95.5	(94.1%, 96.6%)	1,169	14	1.2	(0.7%, 2.0%)
Month 48	1,152	1,060	92.0	(90.3%, 93.5%)	1,165	14	1.2	(0.7%, 2.0%)
HPV 16 cLIA ≥ 20 mMU/mL								
Day 1	1,269	0	0.0	(0.0%, 0.3%)	1,249	0	0.0	(0.0%, 0.3%)
Month 7	1,269	1,254	98.8	(98.1%, 99.3%)	1,249	45	3.6	(2.6%, 4.8%)
Month 12	1,236	1,232	99.7	(99.2%, 99.9%)	1,235	21	1.7	(1.1%, 2.6%)
Month 24	1,225	1,182	96.5	(95.3%, 97.4%)	1,211	48	4.0	(2.9%, 5.2%)
Month 36	1,190	1,175	98.7	(97.9%, 99.3%)	1,177	39	3.3	(2.4%, 4.5%)
Month 48	1,172	1,141	97.4	(96.3%, 98.2%)	1,178	46	3.9	(2.9%, 5.2%)

Anti-HPV Response / Study Time	qHPV Vaccine (N=1,910)				Placebo (N=1,907)			
		Seroconversion				Seroconversion		
	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 18 cLIA ≥ 24 mMU/mL								
Day 1	1,430	0	0.0	(0.0%, 0.3%)	1,419	0	0.0	(0.0%, 0.3%)
Month 7	1,430	1,392	97.3	(96.4%, 98.1%)	1,419	31	2.2	(1.5%, 3.1%)
Month 12	1,387	1,174	84.6	(82.6%, 86.5%)	1,405	13	0.9	(0.5%, 1.6%)
Month 24	1,378	753	54.6	(52.0%, 57.3%)	1,371	21	1.5	(1.0%, 2.3%)
Month 36	1,331	739	55.5	(52.8%, 58.2%)	1,329	19	1.4	(0.9%, 2.2%)
Month 48	1,313	629	47.9	(45.2%, 50.6%)	1,324	13	1.0	(0.5%, 1.7%)

The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.
Percent is calculated as 100*(m/n).
The CIs are computed based on exact methods.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
m = Number of subjects who seroconverted to the indicated HPV type at the indicated time point.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; qHPV = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

The percent seroconversion at Month 7 was at least 97% for each of the vaccine HPV types.

For each of anti-HPV-6, -11, and -16, the percent seropositive at Month 7 declined by no more than 10 percentage points through Month 48.

For anti-HPV 18, the percent seroconversion at Month 7 declined by approximately 50 percentage points through Month 48 and the percentage seropositive was 47.9%.

Vaccine-type anti-HPV responses by age group in the HPV naïve population

When analysed by age strata no significant differences in the distribution of anti-HPV GMTs or seroconversion rates were observed. The antibody decay profile by time was similar in both age groups. Overall the distribution of HPV titers was slightly lower in the 35 to 45 year-olds compared to 24 to 34 year-olds. At Month 48, 50.7% of the younger women and 45% of the older remained seropositive to HPV 18.

Comparison of 16 to 23 year-olds and 25 to 45 year-olds

The vaccine-induced anti-HPV GMTs were lower (except for anti-HPV 16) in MAW compared with the younger women, both at Month 7 and Month 24. The GMTs decreased as the age progressed and were lowest in the 35 to 45 age stratum. At the current stage, the clinical relevance of the decreased GMTs in MAW is not known, since no immunological correlate of protection has been identified.

The seroconversion rate for each HPV vaccine type was generally comparable in all age groups at Month 7, but was somewhat lower at Month 24 in the older age groups. For HPV 18, the seropositivity rate at Month 48 was 61% in women 16 to 23 years of age, 51% in women 23 to 34 years of age and 45% in women 35 to 45 years of age.

Vaccine HPV type anti-HPV responses in populations with prior HPV exposure

Seropositive/PCR negative population (S1P0)

At Day 1 anti-HPV GMTs were comparable in the two vaccination groups. At Month 7 the GMTs in the vaccine group increased at greater magnitude compared to those in the HPV-naïve, S1P1 and S0P1 populations. In general, for each of HPV types 6, 11, 16, and 18, the distribution of anti-HPV in this population declined from Month 7 through Month 24, and the distribution of anti-HPV at Month 24 was sustained through Month 48. The antibody levels were higher than those in the HPV naïve women at all time points. However, the sample size was very small compared to the sample size of the HPV naïve population.

Seropositive/PCR positive population (S1P1)

The number of evaluable patients was limited. In the placebo group GMTs were somewhat higher than those observed in the seropositive/PCR negative group. The results showed that the antibody levels were higher than those in HPV naïve women at all times.

Seronegative/PCR positive population(S0P1)

The number of evaluable patients was small. In general the anti-HPV GMTs were lower than those observed in the seropositive populations. It is to be noted that the trends observed are not necessarily robust due the very small sample size of the Day 1 seronegative and PCR positive population.

Analysis of maternal transfer of Anti-HPV

This investigation aimed at characterising the titer of anti-HPV type 6/11 in both peripartum maternal blood and in cord blood of infants born to women who received blinded therapy in P019 in Thailand and the Philippines. It was a pre-specified exploratory immunogenicity objective in P019. There were a total of 44 subjects with mother-infant serology data of which 24 originated from the vaccinated group and 20 from the placebo group. The maternal serum and cord blood samples were obtained at a median time of 28 months post-dose 3.

The results showed that for each of HPV types 6, 11, 16 and 18 maternal anti-HPV was detected in cord blood samples. Moreover, HPV titers in cord blood samples were highly positively correlated with maternal HPV titers.

1.3.3 Discussion

The vaccine induced a significant Month 7 immune response to all HPV 6, 11, 16 and 18 types in MAW and seroconversion rate was above 97% for each of the vaccine HPV types. The strongest responses were demonstrated against HPV 16 and the weakest response to HPV 18. At Month 24 the GMTs had decreased substantially, in particular with respect to anti-HPV 18 (GMT: 28mMU/mL), but then remained stable until Month 48 including for anti-HPV 18 (23 mMU/mL). The antibody level for HPV18 at Month 24-48 is below that measured in naturally infected subjects (37 mMU/mL). The percent seroconversion was maintained above 91% through Month 48 for anti-HPV 6, 11 and 16. In contrast

for HPV 18, only 48% of the subjects were still seropositive at Month 48. Despite the nominal loss of seropositivity, no cases of HPV 18 infection or disease were observed in the PPE population during the 4 year follow-up period. In the HNRT population, there was one case of HPV 18 persistent infection that started during the vaccine period Day 1 and Month 7.

In the previous 2007 procedure the MAH addressed the issue regarding the choice of serological testing methodology. The currently used serological cLIA assay may not be the optimal method to measure long-term vaccine induced HPV immunity. This assay might be too specific measuring only antibodies against a single type-specific neutralizing epitope on L1 VLPs and not all relevant neutralizing antibodies. Therefore, the MAH have committed to perform serological studies using broader neutralization assays, i.e. pseudo-neutralization assays (see letter of undertaking), and submitted the validation protocol and final results using the newly developed assay measuring the VLP-specific total IgG.

When analysed by the two pre-specified age strata, no significant differences in the distribution of anti-HPV GMTs or seroconversion rates were observed. The antibody decay profile by time was similar in both age groups. Overall the distribution of HPV titers was slightly lower in the 35 to 45 year-olds compared to 24 to 34 year-olds. At Month 48, 50.7% of the younger women and 45% of the older remained seropositive to HPV 18.

The study demonstrated that administration of the vaccine to baseline HPV vaccine-type naïve 24- to 45-year-old women resulted in anti-HPV 6/11/16/18 responses at Month 7 that were lower than those observed in 16- to 23- year-old (non-overlapping 95% CIs up to Month 24). The exception was anti-HPV 16 GMTs that were comparable between the two age groups. The GMTs decreased as the age progressed and were lowest in the 35 to 45 age stratum. At the present time, the clinical relevance of the decreased GMTs in MAW is not known, since no immunological correlate of protection has been identified. The seroconversion rate for each HPV vaccine type was generally comparable in all age groups at Month 7, but was somewhat lower at Month 24 in the older age groups. For HPV 18, the seropositivity rate at Month 48 was 61% in women 16 to 23 years of age, 51% in women 23 to 34 years of age and 45% in women 35 to 45 years of age.

Subjects who were positive to the relevant HPV type at baseline had substantially higher GMTs. These data suggest the qHPV vaccine induces an anamnestic response in individuals seropositive as a result of prior natural infection.

In an exploratory analysis maternal-infant transfer of anti-HPV antibodies was demonstrated at a median of 28 months postdose 3 and showed high correlation coefficients for all HPV types. The clinical significance of the antibody titers measured in the cord blood of infants is not known since immunological correlates of protection have not been established.

In conclusion the vaccine-induced immune responses in MAW seem robust, but were lower than those observed in younger 16- to 23- year-old women. The consequence of these lower antibody responses in MAW for long-term efficacy is not known since no minimum anti-HPV level that confers protection has been defined. The low persistence of GMTs and seropositivity for HPV 18 at end-of-study did not translate into loss of efficacy, but will have to be closely monitored in the future. The MAH has committed to conduct a 10-year follow-up of Protocol 019 in Columbia to evaluate long term immunogenicity and efficacy in mid-adult women, which is satisfactory. The MAH has also committed to apply broader neutralization assays to further characterize the vaccine induced immune responses.

1.4 Clinical safety

The post-marketing experience with qHPV vaccine is summarised from the International Birthdate (1 June 2006) in 6-monthly PSUR's. More than 51,000,000 doses of this vaccine were distributed as of 31 May 2009, data lock point of the most recent PSUR. The post licensure experiences with the vaccine collected through passive reporting of spontaneous adverse experiences to the MAH has shown a low frequency of reported serious adverse experiences.

The MAH submitted complete summaries for all new fatal and nonfatal SAEs and discontinuations due to an adverse experience not reported in the Protocol 019 CSR for safety data (interim report) and new medical history collected through 23 June 2009. In addition, the complete summaries for pregnancies and lactation outcomes were provided.

1.4.1 Protocol 019

Patient exposure

The Safety Population is defined as all subjects who were enrolled in P019 and who received at least one vaccination. This population included 3810 subjects (1908 subjects who received qHPV vaccine and 1902 subjects who received placebo).

The new data in the current submission are adverse events reported during the follow-up period till end of the study i.e. from July 14, 2007 till June 23, 2009.

The final study visit associated with the end-of-study (i.e. the last visit in which last subject who required follow-up for an HPV-related abnormality observed on an end-of study visit) occurred on 30 April 2009. The last date in which pregnancy outcomes data were collected was 23 June 2009.

Adverse events

A total of 14 (0.7%) subjects who received qHPV vaccine and 16 (0.8%) of subjects who received placebo experienced a Serious Adverse Experience at any time during the study.

During the period 13 July 2007 until 23 June 2009, there was 1 non-related SAE's in the 1 vaccine group and 2 in the placebo group. There were no Serious Adverse Experiences judged by the study investigator to be vaccine-related. The vaccination groups were also comparable with respect to the types of serious adverse experiences reported. The most common serious adverse experiences in both vaccination groups were infections and pregnancy complications. Overall, 9 subjects discontinued from the study due to an adverse experience. Of these subjects 7 (0.4%) received qHPV vaccine and 2 (0.1%) received placebo.

Serious adverse events and deaths

Deaths

A total of 8 deaths have been reported in Protocol 019 as of 23 June 2009. A total of 7 deaths (0.4%) have been reported in the qHPV group and 1 death (0.1%) has been reported in the placebo group. All deaths in the study were determined by the investigator to be "definitely not" related to the vaccine. Since the interim CSR for Protocol 019, there are 3 additional subjects with fatal adverse experiences. All 3 were in the qHPV group. In none of the described 3 additional fatal events which occurred in connection with a history of administration of qHPV vaccine was a close temporal relationship to administration of dose 3 and the fatal events were considered not to be related to study therapy.

Serious adverse events

In addition to the 8 fatalities, 24 subjects (9 in the qHPV group and 15 in the placebo group) experienced nonfatal serious clinical adverse experiences during the entire study period. Since the endpoint-driven CSR, there have been 3 additional subjects with nonfatal serious clinical adverse experiences. One is in the group that received qHPV (cervical bleeding) and 2 are in the group that received placebo (cervical bleeding and vaginal bleeding). The described adverse events were all considered to be related to study procedure i.e. cervical biopsies as part of the study protocol but not to the study therapy.

New medical history in the safety population

The most commonly reported new medical conditions during the Day 1 to Month 7 and the post Month 7 follow-up period, respectively were infections such as bacterial vaginosis, nasopharyngitis, and upper respiratory tract infection; with similar incidence in both groups.

Safety in special groups

The proportions of subjects who reported new medical history consistent with potential autoimmune phenomena were comparable between the vaccination group.

The AE non-specific arthritis/arthropathy is specifically addressed in section 4.8 of the SmPC. Two new cases of arthritis were reported in the qHPV vaccination group and 1 new case in the placebo group. Although listed such events should be continuously monitored and reported on in future PSURs,

Pregnancy

Overall, 499 subjects (~13% of the study population) reported at least one pregnancy from Day 1 to 23 June 2009. At the time of the closing of the study database for this EOS analyses, outcomes were available for 95.3% of pregnancies in the qHPV vaccine group and 96.0% of pregnancies in the placebo group.

The proportions of pregnancies resulting in fetal loss were comparable between the 2 vaccination groups. A total of 12 congenital anomalies were reported for pregnancies (live births, fetal losses) in subjects in Protocol 019. Of these, 6 were in infants and 2 in a fetus of subjects in the group that received qHPV vaccine and 5 were in infants and 1 in a fetus of subject in the group that received placebo. New congenital anomalies were reported in 4 infants and 1 fetus of subjects who received qHPV vaccine (1 infant each with ankyloglossia, Meckel's diverticulum, mesenteric cyst, syndactyly,

and trisomy 21). New congenital anomalies were reported in 3 infants and 1 fetus of subjects who received placebo (1 each of inguinal hernia, patent ductus arteriosus, pulmonary artery stenosis, and trisomy 13, Turner's syndrome). None of these observed congenital anomalies, however, indicated any safety signal which could be considered related to the study therapy.

Since the primary endpoint analysis in 2007 (interim report), 246 new pregnancies were reported in 194 subjects (97 in the qHPV group and 97 in the placebo group. During the whole study, a slightly smaller proportion of subjects in the qHPV vaccine group became pregnant compared with the placebo group (12.4% vs. 13.8% respectively). The proportions of pregnancies resulting in live birth and fetal loss were comparable in the group that received qHPV vaccine compared with the placebo group (78.9% versus 76.9%, and 18.8% versus 21.4% for subjects receiving qHPV vaccine and placebo, respectively).

The proportions of pregnancies with natural outcomes that ended in a negative outcome were 19.1% (49/257) in the group that received qHPV vaccine and 20.3% (56/276) in the placebo group.

Administration of qHPV vaccine to lactating women

No SAEs were reported among subjects who were breast-feeding during the study.

Discussion

The present safety data support the conclusion that qHPV vaccine is generally well tolerated in 24-45 year old women. There were no new vaccine-related serious adverse experiences. No safety signals have been identified with the exception of the previously observed increased incidences of transient injection-site adverse experiences and low-grade fever following vaccination. Use of qHPV vaccine did not impact overall pregnancy outcomes. Administration of qHPV vaccine to nursing mothers did not affect the health of the mother or the nursing child. The additional data obtained in the follow-up of Protocol-019 further confirm the profile observed before.

Additionally the MAH committed to update the CHMP with regard to the feasibility of extending to 45 years of age the ongoing PGRx studies. The objective of the ongoing PGRx studies is to assess whether the use of Gardasil is associated with a modified risk for 8 autoimmune diseases in females aged 14-26 years old, residing in France (see letter of undertaking).

1.5 Pharmacovigilance system

1.5.1 Risk Management Plan

The MAH has submitted a revised Risk Management Plan (version 4) in December 2009. The revised RMP has been adequately updated in relation to the extension of the indication to mid-adult women, including a commitment to perform a long-term observational study on viral type replacement, long-term effectiveness/immunogenicity and long-term safety in Columbia. The assessment of the outline of this study protocol is ongoing. Furthermore the MAH has submitted a further revision of the RMP that is under evaluation.

1.6 Overall discussion and benefit-risk assessment

The results at end of study confirmed and extended the efficacy of the qHPV vaccine in MAW demonstrated in the 2007 endpoint driven analysis. The qHPV vaccine was highly efficacious in the PPE population with respect to the relevant endpoints, persistent infection, CIN and EGL. High efficacy was observed with respect to HPV 16 and HPV 18 individually, with respect to persistent infection alone and with respect to disease endpoints (CIN, AIS, or EGL) alone. There were no new cases of HPV 6/11/16/18-related CIN or EGL reported in the qHPV group since the first analysis. Hence, the results in study 019 showed significant vaccine efficacy in HPV naïve MAW and in similar magnitude as that shown in YAW. In the FAS population improved efficacy results were demonstrated during the additional 2-year follow-up. The efficacy estimates against HPV 16/18-related PI/disease endpoint now reached statistical significance. There were a total of 48 (qHPV=21, placebo =27) cases of vaccine type related CIN 2/3 in the FAS population with no new cases in the vaccine group since the first analysis. The issues raised during the previous regulatory procedure, which included efficacy against HPV 16/18-related persistent infection by duration of infection (6 or 12 months), relevance of the HPV 6/11-related persistent infection endpoint, poor vaccine efficacy in the FAS population, delayed clearance of HPV 16 infection in the Day 1 PCR positive and seronegative population of the vaccine group, and the potential of vaccine-induced acceleration of disease and of replacement by non-vaccine types, were properly addressed.

The vaccine-induced immune responses in MAW were robust, but lower than those observed in younger 16- to 23- year-old women. The consequence of these lower antibody responses in MAW for long-term efficacy is not known since no minimum anti-HPV level that confers protection has been defined. The low persistence of GMTs and seropositivity for HPV 18 at end-of-study did not translate into loss of efficacy, but need to be closely monitored in the future. The MAH has already committed to conduct a 10-year follow-up of Protocol 019 in Columbia to evaluate long term immunogenicity and efficacy in mid-adult women, which is satisfactory. The MAH has also already committed to apply broader neutralization assays to further characterize the vaccine induced immune responses (see letter of undertaking).

Administration of qHPV vaccine is generally well tolerated in 24- to 45-year-old women. The present safety data support the conclusion that qHPV vaccine is well tolerated and displays a safety profile similar to that shown in previous submissions. No safety signals have been identified with the exception of increased incidences of transient injection-site adverse experiences and low-grade fever following vaccination. There were no new vaccine-related serious adverse experiences in the present report. Additionally the MAH committed to update the CHMP with regard to the feasibility of extending to 45 years of age the ongoing PGRx studies (see letter of undertaking).

The revised RMP version 4 in relation to the extension of the indication to mid-adult women has been adequately updated, including a commitment to perform a long-term observational study on viral type replacement, long-term effectiveness/immunogenicity and long-term safety in Columbia (see letter of undertaking). The assessment of the outline of the study protocol is on going. Annex II was updated with the revised version of the RMP.

The overall expected benefit of the qHPV vaccine in mid-adult women is lower than in the young adult women population, due to the higher level of baseline sero-/PCR-positivity and the much lower risk of acquiring of new HPV infection at older ages. However, based on the result in Protocol 019 it is evident that efficacy in HPV naïve older women is of the same magnitude as that in young adult women. Since the overall expected benefit of the qHPV vaccine in mid-adult women is lower than in the young adult women population the CHMP considered important to alert the prescribers that HPV exposure and potential benefit should be considered in the decision to vaccinate an individual adult women. Further

important information for prescribers already mentioned in the product information include statements that the vaccine does not protect against all HPV types and therefore it is critical that the women continue to attend routine cervical screening according to local recommendations and that Gardasil is for prophylactic use only and has no effect on active HPV infections or established clinical disease.

The product information was updated to reflect these data as detailed in section 3.7 and the above mentioned commitments were included in the letter of undertaking.

1.7 Changes to the product information

Further to the assessment of the different proposals of the MAH to amend the Product Information and in the light of the assessment of the submitted data, the Product Information was revised as follows:

Summary of Product Characteristics

Section 4.1 "Therapeutic indication"
The MAH's applied to extend the age of the indication for women up to 45 years old, based on submission of 4 years data of study 019. Furthermore the CHMP took the opportunity of this variation to simplify the wording of the indication and to harmonise it between the HPV vaccines.

Since statistically significant efficacy results in the primary HPV16/18-related endpoint were demonstrated in the ITT population at end-of study (the general mid-adult population that will be vaccinated in clinical practice) the indication was revised to include the vaccination of women from the age of 9 years on wards.

To harmonise the indication between the HPV vaccines and to simplify the wording of the indication the vaccine HPV types were replaced by "certain oncogenic HPV types" since for both vaccines some cross protection against related non-vaccine HPV types have been demonstrated. The CHMP included the word "certain" to make prescribers aware that the vaccine does not protect against all HPV oncogenic types. The information on the different HPV types is covered by a cross reference to section 5.1 where these data are presented.

The paragraph detailing the basis for the indication: "the indication is based on the demonstration of efficacy of Gardasil in females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males." was amended with the new data up to 45 years and moved to section 5.1. This paragraph was not considered necessary any longer in the indication since data were submitted for mid adult women and since a cross reference to sections 4.4 and 5.1 for important information on the data that support this indication was included in this section.

Therefore the new indication is as follows:

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

Section 4.4 "Special warnings and precautions for use"
Since the data at end-of study after 4 years of follow-up now demonstrate statistically significant vaccine efficacy in the FAS population for mid-adult women the relevant sentence based on the 2007 endpoint driven analysis was removed from this section.

Since the overall expected benefit of the qHPV vaccine is lower in sexually experienced women than in HPV naïve children/adolescents and substantially lower in mid-adult women than in the young adult women population the CHMP considered important to alert prescribers that HPV exposure and potential benefit should be considered in the decision to vaccinate an individual adult women. Therefore, the following sentence was modified and moved to the beginning of this section: "the decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination".

Section 4.6 "Pregnancy and lactation"
The MAH proposal to revise the numbers of women in the clinical development program that reported pregnancy was endorsed by the CHMP.

Section 4.8 "Undesirable effects"
The CHMP endorsed the update of the numbers in the safety population.

Section 5.1 "Pharmacodynamic properties"
The following paragraph: "the indication is based on the demonstration of efficacy of Gardasil in females 16 to 45 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males." was moved from section 4.1 to this section and updated based on new data.

Efficacy in woman 24 through 45 years was updated with results from the PPE and FAS analyses after a follow up of 4 years.

Data from post-hoc analyses of efficacy against recurrent infection in women (16 to 45 years) with evidence of a prior infection with a vaccine HPV type (seropositive) that was no longer detectable at vaccination onset (PCR negative) were introduced.

The data on immunogenicity were updated.

In addition, the Marketing Authorisation Holder (MAH) took the opportunity to introduce other minor changes to the SmPC.

Package Leaflet
The PL was updated to reflect the change in the indication.

Annex II was updated with the new version of the risk management plan.

2. Conclusion

On 24 June 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.