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CHMP VARIATION ASSESSMENT REPORT

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

TYPE II VARIATION: EMEA/H/C/000732/II/0018

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

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Table of contents

I. SCIENTIFIC DISCUSSION

1.1. Introduction

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

Silgard 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.

The present type II variation application aimed to extend the therapeutic indication to women up to 45 years old, based on submission of data on efficacy, immunogenicity, and safety of the qHPV vaccine in female subjects 24 to 45 years of age from an on-going phase III study (Protocol 019). The MAH proposed amendments of the age range in section 4.1 of the SPC is as follows:

Gardasil /Silgard 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/Silgard in adult females 16 to ~~26~~ **45** years of age and on the demonstration of immunogenicity of Gardasil/Silgard in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males (see section 5.1).*

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

This variation also aimed to update all relevant sections of the SPC (sections 4.5, 4.6. 4.8 and 5.1) and PL (sections 1, 3 and 4) to reflect the study results obtained in mid-adult women.

Following CHMP major objections to extend the age range of woman up to age of 45, which could not be overcome by the MAH, the MAH agreed not to pursue with the extension of indication and limited this application to the update of sections 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1.

1.2 Clinical efficacy

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 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 mid-adult women (MAW).

The main goal of the study was to provide data to support that efficacy was comparable to that shown in young adult women (YAW) and thereby allowing the inclusion of a statement in the indication that efficacy against premalignant genital lesions, cervical cancer and genital warts has been demonstrated in women up to the age of 45 years. 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 recognized 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.

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. Randomization 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 - 13 Jul 2007 (on-going)	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	Co-primary endpoints: - 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: 19 months** **(Ongoing planned follow-up 4 years)**

Study participants
The study subjects were healthy 24 to 45-year-old women. The studies did not include pre-screening visit for HPV. 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
- Pap test
- Cervicovaginal sampling for HPV 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 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. However, 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:

- HPV 6/11/16/18-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.

Statistical methods

Study 019 employed a fixed event design. Hypothesis testing was planned on 3 endpoints, HPV6/11/16/18- (co-primary), HPV 16/18- (co-primary) and HPV 6/11- (secondary) -related persistent infection and disease. The testing of the endpoints was to be performed in a priority order, where testing of the successive endpoints would only proceed if success was achieved in the previous

endpoint. The testing was to take place when at least 25 subjects had developed a case of HPV6/11/16/18-related endpoint and at least 14 subjects had developed a case of HPV 16/18-related endpoint in the PPE population. For the secondary HPV 6/11-related endpoint, 19 subjects were the target number. The study was powered for the two co-primary endpoints, but not to detect statistically significant efficacy with respect to the individual components of the composites. The stipulated number of primary and secondary endpoints was reached as of 13 Jul-2007, after 2.2 years of follow-up post-enrollment. The statistical methods are considered acceptable.

1.2.1.2 Results

A total of 3819 subjects were enrolled in the study. Protocol 019 is ongoing and therefore, a large number of subjects are continuing in the efficacy follow-up period. The mean duration of follow-up post-enrollment was 2.2 years. Final analyses are planned for End-of-Study (through 4.0 years of follow-up post-enrollment).

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, 96.8% of all subjects completed the vaccination phase. The proportions of subjects who completed the vaccination phase were comparable between the vaccine and the placebo group. Altogether, 2.5% of the subjects discontinued participation in the study during the vaccination period and 1.0% discontinued participation in the study in the follow-up period.

Baseline data
The 2 vaccination groups were well balanced with respect to baseline demographics. The mean age was 34.3 years. The majority of subjects were Hispanic American (43%). Europe contributed only 12.6% of study subjects.

Sexual demographics were comparable between vaccination groups. Overall 99.9% of subjects had experienced sexual debut. The median first intercourse was 18 years (range: 4 to 39) and the median number of lifetime sex partners was 2 in both groups and in both age strata.

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. The vaccination groups were comparable with respect to the overall proportions of subjects with detectable vaccine HPV type DNA at baseline. 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 (29.8% vs. 30.7%).

Pap test results showed that SIL was present in 7.5% of subjects. The proportions of subjects reporting a SIL-related diagnosis were comparable between the 2 vaccination groups. When analysed by age stratum, higher occurrence of an abnormal Pap test was reported in the 24 to 34 year age group compared with the 35 to 45 year old women (6.8% vs. 2.6% in the respective vaccine group and 5.9% vs. 4.0% in the placebo groups).

Efficacy against HPV 6/11/16/18-related persistent infection, CIN and EGL
The results presented in the tables were analysed using 6-month persistent infection.

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 comparable within each of the two protocol-defined age strata.

Efficacy against HPV 18- and 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	**1615**	**4**	**1607**	**41**	**90.5**	**73.7, 97.5**
By age						
24 to 34 year-olds	792	2	792	24	91.8	67.1, 99.1
35 to 45 year-olds	823	2	815	17	88.6	51.9, 98.7
HPV 16/18 PI, CIN or EGL	**1601**	**4**	**1579**	**23**	**83.1**	**50.6, 95.8**
By age						
24 to 34 year-olds	784	2	774	13	85.0	33.8, 98.4
35 to 45 year-olds	817	2	805	10	80.6	9.1, 97.9
HPV 6/11 PI, CIN or EGL	**1329**	**0**	**1323**	**19**	**100**	**79.0, 100**
By age						
24 to 34 year-olds	636	0	653	12	100	63.7, 100
35 to 45 year-olds	693	0	670	7	100	33.6, 100
By HPV type (all ages)						
HPV 6	1329	0	1323	19	100	79.0, 100
HPV 11	1329	0	1323	0	NA	NA
HPV 16	1347	4	1325	18	78.0	34.1, 94.7
HPV 18	1522	0	1512	5	100	-7.1, 100

Of the 45 HPV 6/11/16/18-related endpoint cases, 4 cases occurred in the vaccine group. There were 3 cases of HPV 16 persistent infection (6-month definition) and 1 case of HPV 16-related CIN 2 (positive for HPV types 16 and 51 at a month 18 biopsy).

All of the 4 cases occurred early in the follow-up, 5 and 11 months after completion of the 3-dose series. All of these cases had satisfactory anti-HPV 16 responses at Month 7 including two of them having evidence of an anamnestic response with very high antibody levels at Month 7.

Vaccine efficacy against HPV 6/11/16/18-related related persistent infection, CIN and EGL–was also calculated excluding the endpoint HPV 6 and 11- related persistent infection in PPE population. Vaccine efficacy was 86.0% (95% CI: 60.0, 96.4).

The MAH further calculated this primary combined endpoint using 12-month persistent infection. For HPV 16/18-related persistent infection, CIN and EGL vaccine efficacy was 84.5% (95% CI: 47.4, 97.1) using 12-month persistent infection.

HNRT population

Results for this population are presented in table 3. Vaccine efficacy was 74.6% (95% CI 58.1, 85.3). Twenty (20) cases were observed in the vaccinated arm (16 new cases compared with the PPE population). Ten (10) of these new cases were HPV 16/18-related.

VE was lower in the older age stratum versus the younger stratum (VE: 62.3% vs. 79.8%).

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**	**20**	**1833**	**77**	**74.6**	**58.1, 85.3**
By age						
24 to 34 year-olds	914	11	920	54	79.8	61.0, 90.5
35 to 45 year-olds	927	9	913	23	62.3	15.1, 84.6
HPV 16/18 PI, CIN or EGL	**1823**	**14**	**1803**	**48**	**71.6**	**47.6, 85.5**
By age						
24 to 34 year-olds	904	9	901	33	73.0	42.2, 88.6
35 to 45 year-olds	919	5	902	15	68.0	7.3, 90.9
HPV 6/11 PI, CIN or EGL	**1514**	**6**	**1514**	**30**	**80.2**	**51.7, 93.3**
By age						
24 to 34 year-olds	735	2	770	22	90.6	61.7, 98.9
35 to 45 year-olds	779	4	744	8	5.8	-76.1, 89.6
By HPV type (all ages)						
HPV 6	1514	6	1514	30	80.2	51.7, 93.3
HPV 11	1514	0	1514	0	NA	NA
HPV 16	1554	13	1524	37	65.8	34.2, 83.3
HPV 18	1741	1	1726	12	91.8	44.5, 99.8

FAS population

Vaccine efficacy against the HPV 6/11/16/18-related endpoint was much lower in the FAS population (VE: 30.9%) (Table 4). As regards the HPV 16/18-related endpoint only a numerical reduction was seen (lower bound of the 95% CI <0%).

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**	**108**	**1883**	**154**	**30.9**	**11.1, 46.5**
By age						
24 to 34 year-olds	937	71	944	94	23.7	-4.9, 44.7
35 to 45 year-olds	949	37	939	60	40.7	9.2, 61.7
HPV 16/18 PI, CIN or EGL	**1886**	**90**	**1883**	**115**	**22.6**	**-2.9, 41.9**
By age						
24 to 34 year-olds	937	57	944	70	17.7	-18.4, 43.0
35 to 45 year-olds	949	33	939	45	28.9	-13.9, 56.1
HPV 6/11 PI, CIN or EGL	**1886**	**24**	**1883**	**45**	**47.1**	**11.4, 69.2**
By age						
24 to 34 year-olds	937	17	944	28	38.4	-16.5, 68.4
35 to 45 year-olds	949	7	939	17	60.1	-1.3, 86.0
By HPV type (all ages)						
HPV 6	1886	22	1883	44	50.5	15.6, 71.7
HPV 11	1886	2	1883	1	-99.0	-11641.1, 89.6
HPV 16	1886	72	1883	89	19.8	-10.6, 42.1
HPV 18	1886	19	1883	30	37.2	-15.3, 66.6

Vaccine efficacy against HPV 6/11/16/18-related related persistent infection, CIN and EGL–was calculated excluding the endpoint HPV 6 and 11- related persistent infection in FAS population. No statistical significant efficacy was demonstrated [23.7% (95% CI: -0.1, 42.0)].

Efficacy against HPV vaccine type related persistent infection
The results presented in the tables were analysed using 6-month persistent infection.

PPE population
The analysis of efficacy against HPV 6/11/16/18-related persistent infection gave similar results as that of the composite HPV 6/11/16/18-related endpoint, since persistent infection comprised the majority of the composite persistent infection and disease endpoint (Table 5).

Efficacy estimates against the HPV 16/18-related persistent infection were similar in both age strata. All the persistent infection endpoints in the vaccine group, and majority of those in the placebo group, were HPV 16-related. With regard to HPV 6/11-related persistent infection there were no cases in the vaccine group (VE: 100%).

Table 5: Efficacy against HPV vaccine type-related persistent infection (PI) (PPE-population)

Endpoint	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy	
	n	Number of cases	n	Number of cases	%	95% CI
HPV 6/11/16/18 PI	**1593**	**3**	**1592**	**40**	**92.6**	**76.9, 98.5**
By age						
24 to 34 year-olds	780	2	788	24	91.7	66.4, 99.0
35 to 45 year-olds	813	1	804	16	94.0	61.1, 99.9
By severity						
PI without HPV-related disease	1593	3	1592	38	92.2	75.5, 98.5
PI with HPV-related disease	1593	0	1592	3	100	-140.3, 100
HPV 16/18 PI	**1580**	**3**	**1565**	**22**	**86.7**	**55.6, 97.4**
By age						
24 to 34 year-olds	773	2	770	13	84.7	32.5, 98.3
35 to 45 year-olds	807	1	795	9	89.3	33.8, 99.8
By severity						
PI without HPV-related disease	1580	3	1565	22	86.7	55.6, 96.8
PI with HPV-related disease	1501	0	1565	0	NA	NA
HPV 6/11 PI	**1310**	**0**	**1311**	**19**	**100.0**	**78.7, 100**
By age						
24 to 34 year-olds	627	0	650	12	100	62.9, 100
35 to 45 year-olds	683	0	661	7	100	33.6, 100
By severity						
PI without HPV-related disease	1310	0	1311	16	100	74.2, 100
PI with HPV-related disease	1310	0	1311	3	100	-141.5, 100
By HPV type (all ages)						
HPV 6	1310	0	1311	19	100	78.7, 100
HPV 11	1310	0	1310	0	NA	NA
HPV 16	1333	3	1319	17	82.7	40.2, 96.8
HPV 18	1501	0	1498	5	100	-7.8, 100

The MAH further presented the results using 12-month persistent infection. For HPV 16/18-related persistent infection, VE was 80.4% (8.0, 97.9).

HNRT population

The efficacy estimates were lower in the HNRT population compared to the PPE population (see table 6). 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.

A single case of persistent HPV 18 infection was observed in the vaccine group, which started between Day 1 and Month 7.

Table 6: 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**	**19**	**1807**	**76**	**75.5**	**59.0, 86.0**
By age						
24 to 34 year-olds	893	11	906	54	79.6	60.5, 90.4
35 to 45 year-olds	918	8	901	22	65.1	18.6, 86.6
By severity						
PI without HPV-related disease	1811	18	1807	71	75.1	58.8, 86.0
PI with HPV-related disease	1811	1	1807	6	83.4	-36.7, 99.6
HPV 16/18 PI	**1793**	**13**	**1777**	**47**	**73.0**	**49.2, 86.6**
By age						
24 to 34 year-olds	883	9	887	33	72.7	41.7, 88.5
35 to 45 year-olds	910	4	890	14	71.7	13.0,93.5
By severity						
PI without HPV-related disease	1793	12	1777	47	74.0	52.2, 87.9
PI with HPV-related disease	1793	1	1777	0	NA	NA
HPV 6/11 PI	**1497**	**6**	**1496**	**30**	**80.1**	**51.4, 93.2**
By age						
24 to 34 year-olds	723	2	758	22	90.5	61.2, 98.9
35 to 45 year-olds	774	4	738	8	52.8	-76.4, 89.6
By severity						
PI without HPV-related disease	1497	6	1496	24	75.1	37.5, 91.7
PI with HPV-related disease	1497	0	1496	6	100	15.1, 100
By HPV type (all ages)						
HPV 6	1497	6	1496	30	80.1	51.4, 93.2
HPV 11	1497	0	1496	0	NA	NA
HPV 16	1528	12	1501	36	67.5	36.1, 84.6
HPV 18	1711	**1**	1702	12	91.8	44.3, 99.8

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 7). Only trends were observed for the majority of endpoints. With respect to HPV 6/11-related infections less impact was seen than that of HPV 16/18-related endpoint, due the lower baseline prevalence of HPV 6/11 and the shorter duration of this infection.

Table 7: 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**	**102**	**1856**	**151**	**33.2**	**13.6, 48.6**
By age						
24 to 34 year-olds	916	67	929	93	26.7	-1.5, 47.3
35 to 45 year-olds	940	35	927	58	42.0	10.2, 63.0
By severity						
PI without HPV-related disease	1856	91	1856	130	30.8	8.6, 47.6
PI with HPV-related disease	1856	12	1856	22	45.6	-14.7, 75.5
HPV 16/18 PI	**1856**	**86**	**1856**	**112**	**23.9**	**-1.7, 43.2**
By age						
24 to 34 year-olds	916	55	929	69	18.8	-17.4, 44.1
35 to 45 year-olds	940	31	927	43	30.2	-13.2, 57.6
By severity						
PI without HPV-related disease	1856	75	1856	96	23.5	-5.9, 43.5
PI with HPV-related disease	1856	11	1856	16	32.6	-57.0, 71.3
HPV 6/11 PI	**1856**	**21**	**1856**	**45**	**53.6**	**20.5, 73.8**
By age						
24 to 34 year-olds	916	14	929	28	48.9	-0.4, 75.1
35 to 45 year-olds	940	7	927	17	60.2	-1.1, 86.0
By severity						
PI without HPV-related disease	1856	20	1856	39	49.0	10.4, 71.8
PI with HPV-related disease	1856	1	1856	6	83.4	-37.1, 99.6
By HPV type (all ages)						
HPV 6	1856	20	1856	44	54.8	21.8, 74.8
HPV 11	1856	1	1856	1	0.0	-7727, 98.7
HPV 16	1856	68	1856	87	22.3	-8.0, 44.3
HPV 18	1855	19	1855	29	34.8	-20.2, 65.5

The MAH further presented the results using 12-month persistent infection. For HPV 16/18-related persistent infection, no statistical significant efficacy was shown [14.6% (-24.3, 41.6)].

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 90.1%, with 1 case in the vaccine group versus 10 cases in the placebo group (Table 8). Efficacy against HPV 16/18-related CIN 2/3 or AIS was not statistically significant with one case in the vaccine group and 4 cases in the placebo group (VE: 75.2% (95% CI: -150.6, 99.5)). The one case in the vaccine group was a case of HPV 16-related CIN 2 (positive for HPV types 16 and 51 at Month 18 biopsy).

Table 8: Efficacy against HPV vaccine type related CIN (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 CIN	**1595**	**1**	**1592**	**10**	**90.1**	**30.3, 99.8**
By age						
24 to 34 year-olds	779	0	787	5	100	-10.[illegible] 100
35 to 45 year-olds	816	1	805	5	80.5	-75.9, 99.6
By severity						
CIN 1	1595	0	1592	7	100	31.2, 100
CIN 2/3 or AIS	***1595***	***1***	***1592***	***4***	***75.2***	***-150.6, 99.5***
CIN 2	1595	1	1592	3	66.9	-311.8, 99.4
CIN 3	1595	0	1592	0	NA	NA
AIS	1595	0	1592	1	100	-3768.0, 100
Cervical cancer	1595	0	1592	0	NA	NA
HPV 16/18 CIN	**1582**	**1**	**1566**	**8**	**87.7**	**8.3, 99.7**
By age						
24 to 34 year-olds	772	0	770	4	100	-51.5, 100
35 to 45 year-olds	810	1	796	4	75.8	-144.6, 99.5
By HPV type (all ages)						
HPV 6	1313	0	1312	3	100	-140.8, 100
HPV 11	1313	0	1312	0	NA	NA
HPV 16	1335	1	1320	6	83.6	-35.2, 99.6
HPV 18	1504	0	1499	2	100	-427.1, 100

HNRT population

In the HNRT analysis, VE was 81.4% (table 9).

The number of CIN 2/3 cases in the vaccine group was almost the same as that in the placebo group (3 vs. 4 cases), but by severity it was worse with the only case of CIN 3 in the vaccine group. VE against HPV 16/18-related CIN 2/3 or AIS was only 25.4% (95% CI: -340.8, 89.1). Two of the CIN 2/3 cases in the vaccine group were detected early in the follow-up, at Month 8 and Month 9, despite that the subjects were HPV-naïve at baseline.

Table 9: 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**	**16**	**81.4**	**34.9, 96.5**
By age						
24 to 34 year-olds	896	2	908	10	79.5	4.0, 97.8
35 to 45 year-olds	921	1	904	6	83.9	-32.5, 90.7
By severity						
CIN 1	1817	1	1812	13	92.4	43.1, 99.8
CIN 2/3 or AIS	***1817***	***3***	***1812***	***4***	***25.4***	***-340.8, 89.1***
CIN 2	1817	3	1812	3	0.6	-642.3, 86.7
CIN 3	1817	1	1812	0	NA	NA
AIS	1817	0	1812	1	100	-3777, 100
Cervical cancer	1817	0	1812	0	NA	NA
HPV 16/18 CIN	**1799**	**3**	**1782**	**12**	**75.3**	**8.5, 95.9**
By age						
24 to 34 year-olds	886	2	889	7	71.0	-52.4, 97.1
35 to 45 year-olds	913	1	893	5	80.8	-71.8, 99.6
By HPV type (all ages)						
HPV 6	1502	0	1499	5	100	-8.8, 100
HPV 11	1502	0	1499	0	NA	NA
HPV 16	1534	3	1505	10	70.6	-14.4, 94.8
HPV 18	1717	0	1707	2	100	-427.8, 100

FAS population
As presented in table 10, no efficacy against HPV vaccine type-related CIN could be confirmed in the FAS population (VE: 39% (95% CI: -2.2, 64.6)). A similar number of new cases were added to the vaccine and placebo group (22 vs. 25 cases), in addition to those detected in the HNRT population.

Table 10: 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**	**25**	**1861**	**41**	**39.3**	**-2.2, 64.6**
By age						
24 to 34 year-olds	919	19	931	26	25.2	-40.5, 60.9
35 to 45 year-olds	943	6	930	15	61.3	-5.7, 87.7
By severity						
CIN 1	1862	15	1861	26	42.6	-12.5, 71.7
CIN 2/3 or AIS	***1862***	***19***	***1861***	***21***	***9.9***	***-76.1, 51.2***
CIN 2	1862	10	1861	10	0.3	-106.9, 62.8
CIN 3	1862	14	1861	14	0.4	-125.1, 56.0
AIS	1862	0	1861	1	100	-378.8, 100
Cervical cancer	1862	0	1861	2	100	-4990.4, 100
HPV 16/18 CIN	**1862**	**24**	**1861**	**36**	**33.6**	**-14.3, 62.1**
By age						
24 to 34 year-olds	919	18	931	23	1[illegible]	-55.1, 59.3
35 to 45 year-olds	943	6	930	13	5[illegible]	-26.2, 86.1
By HPV type (all ages)						
HPV 6	1862	3	1861	6	50.2	-133.3, 91.9
HPV 11	1862	1	1861	0	NA	NA
HPV 16	1862	21	1861	32	34.7	-16.9, 64.2
HPV 18	1862	3	1861	4	25.3	-341.7, 89.1

With respect to the CIN 2/3 or AIS endpoint not even an efficacy trend was observed (VE: 9.9%). The number of CIN 2 and CIN 3 cases was exactly the same in the vaccine group as in the placebo group.

The MAH provided the details on these cases and clarified that in each of the vaccine and placebo groups, the 10 cases of CIN 2 and the 14 cases of CIN 3 do not represent 24 unique subjects because some subjects were cases of both CIN 2 and CIN 3. These cases correspond to 40 cases (vaccine = 19, placebo = 21). The breakdown of the 40 cases of HPV 6/11/16/18-related CIN 2/3 revealed that the majority of cases (n=33) were due to prevalent disease, which would not be expected to be prevented by the vaccine. The remaining 7 cases were incident infections (vaccine=3 and placebo =4). Of the 3 vaccine cases, one was confounded by co-infection with an oncogenic non-vaccine HPV type (HPV 51) and one had a very early HPV 16 infection (CIN 1 at Month 1) suggesting a baseline infection. The third case with a baseline infection with HPV 56 had a very rapid progression to HPV 16-related CIN 3 diagnosed at Month 8.

Efficacy against vaccine HPV type-related EGL
PPE-population: In the PPE-population, too few cases of HPV 6/11/16/18-related EGL were observed to detect a statistically significant efficacy (VE: 100%; 95% CI: -49.2 to 100%). All 4 cases were HPV 6-related condyloma and all were observed in the placebo group.

HNRT-population: The breakdown of cases of HPV 6/11/16/18-related EGL in the HNRT population showed 8 cases in the placebo group and all were HPV 6-related condylomas. One (1) case of HPV 16-related VaIN 1 was observed in the qHPV vaccine group at 7 months Postdose 3 (or 13 months after Day 1). The subject was PCR-positive to HPV 56 at Day 1 and to HPV 16 at Month 7.

FAS population: The following cases were observed among subjects in the group that received qHPV vaccine in the FAS efficacy analysis in addition to the 1 case of HPV 16-related VaIN 1 already noted among subjects eligible for the HNRT analysis of efficacy:

- 6 cases of HPV 6-related condyloma (5 of 6 were Day 1 HPV 6 PCR-positive; 1 of 6 was Day 1 HPV 18 seropositive with unknown Day 1 HPV 6 status);
- 1 case of HPV 6-related VIN 1 (Day 1 HPV 6 and 16 PCR-positive)
- 1 case of HPV 18-related VaIN 2 (Day 1 HPV 18 PCR-positive).

Efficacy against vaccine-HPV-type related CIN (any grade) or EGL

The efficacy against disease endpoints (CIN+EGL) is shown in the Table 11. Efficacy against the different components of the vaccine was similar and in the same direction as the efficacy observed against the combined endpoint. However, the number of endpoints was too limited in many of the analyses to detect statistically significant efficacy.

The number of new cases added to the vaccine group in the FAS-analysis compared with the HNRT analysis was higher in the vaccine group (n=30) than in the placebo group (n=26), which could suggest a negative impact of the vaccine on baseline HPV infections (see 3.2.1.3 Discussion).

Table 11: Analysis of efficacy against HPV 6/11/16/18-related CIN or EGL

	qHPV vaccine N=1910		Placebo N=1907		Observed efficacy %	95% CI
HPV 6/11/16/18 CIN or EGL	**n**	**Number of cases**	**n**	**Number of cases**		
PPE-population	**1615**	**1**	**1607**	**13**	**92.4**	**49.6, 99.8**
By age						
24 to 34 year-olds	792	0	792	8	100	42.0, 100
35 to 45 year-olds	823	1	815	5	80.4	-77.9, 99.6
By HPV type (all ages)						
HPV 6	1329	0	1323	6	100	16.2, 100
HPV 11	1329	0	1323	0	NA	NA
HPV 16	1346	1	1325	6	83.6	-34.8, 99.6
HPV 18	1522	0	1512	2	100	-423.9, 100
HNRT population	**1841**	**4**	**1833**	**22**	**82.0**	**47.0, 95.5**
By age						
24 to 34 year-olds	914	3	920	16	81.1	33.8, 96.5
35 to 45 year-olds	927	1	913	6	83.8	-33.3, 99.6
By HPV type (all ages)						
HPV 6	1514	0	1514	11	100	60.5, 100
HPV 11	1514	0	1514	0	NA	NA
HPV 16	1514	4	1514	10	60.8	-36.0, 91.0
HPV 18	1514	0	1514	2	100	-426.3, 100
FAS population	**1886**	**34**	**1883**	**48**	**29.7**	**-11.4, 56.1**
By age						
24 to 34 year-olds	937	26	944	32	17.5	-42.8, 2.8
35 to 45 year-olds	949	8	939	16	51.5	-20.2, 82.0
By HPV type (all ages)						
HPV 6	1886	10	1883	13	23.4	-89.0, 69.9
HPV 11	1886	1	1823	0	NA	NA
HPV 16	1886	22	1883	32	31.8	-21.1, 62.2
HPV 18	1886	4	1823	4	100	-434.0, 81.5

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 number of events, and the total person-years of follow-up in each vaccination group were small and therefore, do not allow any firm conclusions to be drawn. However, it is of note that among subjects who were PCR-positive and seronegative to HPV 16, the clearance of HPV 16 DNA was higher in the placebo group compared to the vaccine group (table 12). The opposite pattern was observed in PCR-/sero-positive group (see below).

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		
PCR positive and seronegative Day 1						
Clearance of HPV 6 infection	12	10	18	12	-69.4	-327.9, 34.4
Clearance of HPV 11 infection	3	2	2	1	-83.7	-1078.9, 90.4
Clearance of HPV 16 infection	**41**	**14**	**24**	**10**	**47.3**	**0.4, 73.0**
Clearance of HPV 18 infection	26	14	24	10	-43.5	-261.0, 40.7
PCR positive and seropositive Day 1						
Clearance of HPV 6 infection	16	8	15	9	69.2	-77.7, 79.6
Clearance of HPV 11 infection	1	1	3	3	433.2	-6416, 90.0
Clearance of HPV 16 infection	38	14	21	6	-28.4	-386.9, 44.6
Clearance of HPV 18 infection	9	4	10	4	-12.9	-506.0, 79.0

The MAH performed re-analyses that led to a change in percent incidence reduction from 47.3% (95% CI: 0.4, 73.0) i.e. to 46% (95% CI: -2.7, 72.4) a statistically non-significant result. The result of the original analysis was inaccurate due to a mistake in case counts.

An additional analysis (life table analysis of time-to-clearance of HPV 6 and HPV16 infection) was performed, comparing the vaccine and placebo groups of MAW who were Day 1 PCR-positive (regardless of sero-status at Day 1) with respect to the instantaneous probability of clearing infection related to HPV 6 and 16. Results showed no relevant difference between the vaccine and placebo groups. Inconsistent results were observed in the PCR positive group depending on its serostatus.

In addition, the MAH was requested to provide data on the timing of detection of CIN 2/3 in the vaccine and placebo group in the FAS population to clarify whether the qHPV vaccine has a negative impact accelerating disease progression (see figures 1 and 2 below).

Figure 1: Cumulative Incidence of HPV 6/11/16/18-Related CIN 2/3 or Worse (Full Analysis Set)

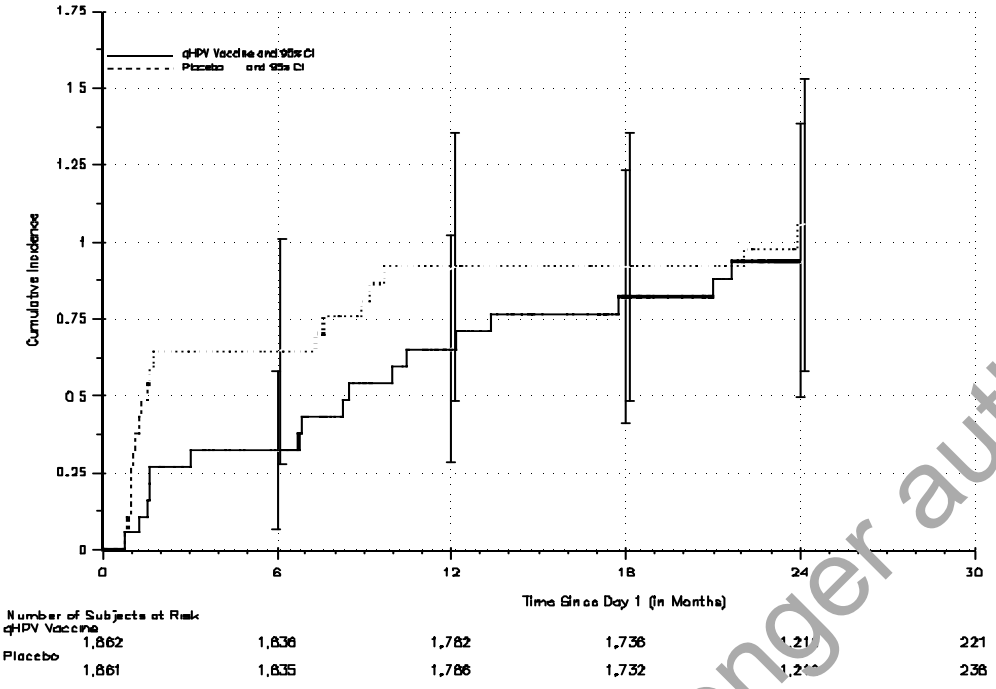
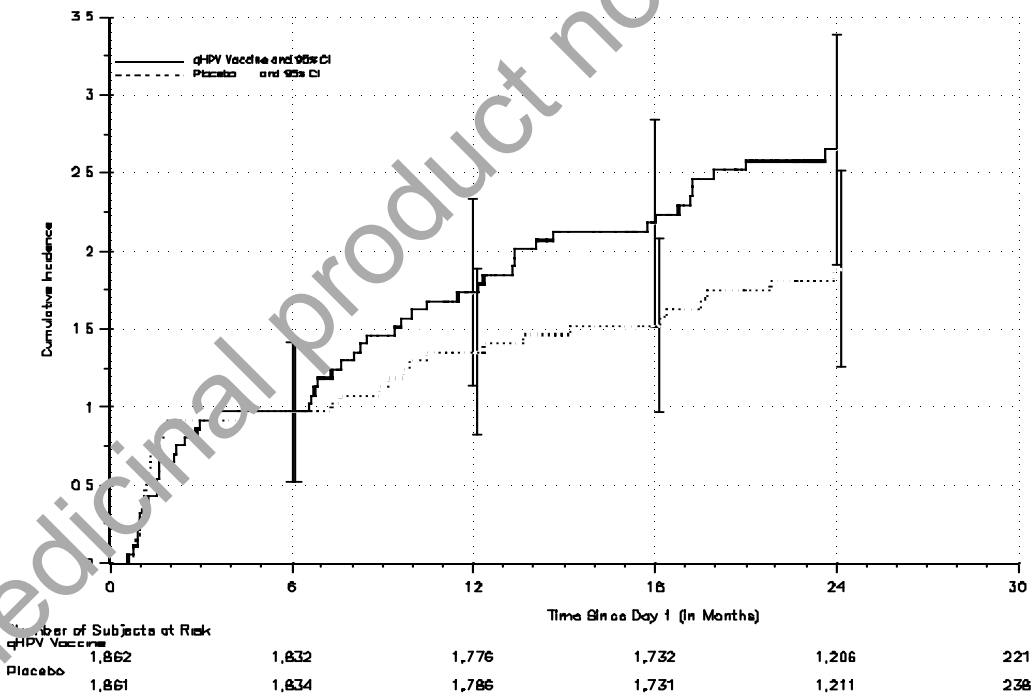


Figure 2: Cumulative Incidence of CIN 2/3 or Worse due to Any HPV Type (Full Analysis Set)



Upon CHMP request the MAH has provided further analysis in non vaccine types to respond to the issue of negative impact of the vaccine with respect to acceleration of disease progression and type replacement.

As regards, the observed higher proportion of non-vaccine HPV-type related CIN2/3 or worse endpoints in the vaccine group compared to placebo (figure 2), the provided new data revealed imbalances in baseline HPV DNA positivity related to HPV types 33, 39, 51 and 58. The increased incidence of CIN 2/3 related to these 4 HPV types in the vaccine group (Table 13) was correlated with the increased incidence of baseline HPV DNA positive in that group compared to placebo.

For each of HPV types 45, 56 and 59 the number of excess cases of CIN 2/3 or worse in the qHPV vaccine group compared to placebo was only 2 (table 13). The case histories revealed that in the majority of CIN 2/3 or worse diagnoses, co-infections with other high-risk HPV types at baseline of unknown duration confounded the causality assessment.

Table 13: Analysis of efficacy against CIN 2/3, AIS, or cervical cancer due to vaccine and non-vaccine types (FAS)

Endpoint	qHPV vaccine n=1910				Placebo N=1907					95% CI
	n	N cases	PY at risk	Incidence rate/100 PY at risk	n	N cases	PY at risk	Incidence rate/100 PY at risk	Observed efficacy %	
CIN 2/3 due to <u>any</u> HPV type	**1,862**	**52**	**4,009.2**	**1.3**	**1,861**	**36**	**4,037.9**	**0.9**	**-44.3**	**(-127.1, 7.5)**
HPV 6, 11, 16 ,18 – related CIN 2/3	1,862	19	4,022.5	0.5	1,861	21	4,007.6	0.5	9.9	(-76.1, 54.2)
HPV 6	1,862	1	4,026.0	0.0	1,861	1	4,012.4	0.0	0.3	(-7723.1, 98.7)
HPV 11	1,862	0	4,026.1	0.0	1,861	0	4,012.5	0.0	NA	NA
HPV 16	1,862	16	4,023.6	0.4	1,861	21	4,007.6	0.5	24.1	(-52.6, 63.0)
HPV 18	1,862	3	4,025.0	0.1	1,861	0	4,012.5	0.0	NA	NA
CIN 2/3 due to any of the 10 typeable HPV types	**1,862**	**34**	**4,014.5**	**0.8**	**1,861**	**19**	**4,008.0**	**0.5**	**-78.7**	**(-231.6, 0.9)**
HPV 31	1,862	6	4,024.7	0.1	1,861	6	4,009.8	0.1	0.4	(-272.7, 73.4)
HPV 33	**1,862**	**4**	**4,025.8**	**0.1**	**1,861**	**0**	**4,012.5**	**0.0**	**NA**	**NA**
HPV 35	1,862	0	4,026.1	0.0	1,861	1	4,012.5	0.0	100	(-3786.8, 100)
HPV 39	**1,862**	**6**	**4,024.2**	**0.1**	**1,861**	**1**	**4,012.2**	**0.0**	**-498.2**	**(-27416.3, 27.4)**
HPV 45	**1,862**	**2**	**4,026.1**	**0.0**	**1,861**	**0**	**4,012.5**	**0.0**	**NA**	**NA**
HPV 51	**1,862**	**9**	**4,022.1**	**0.2**	**1,861**	**3**	**4,012.2**	**0.1**	**-199.3**	**(-1619.0, 25.3)**
HPV 52	1,862	6	4,025.4	0.1	1,861	7	4,011.4	0.2	14.6	(-196.8, 76.3)
HPV 56	**1,862**	**5**	**4,023.6**	**0.1**	**1,861**	**3**	**4,012.3**	**0.1**	**-66.2**	**(-970.3, 67.7)**
HPV 58	**1,862**	**6**	**4,025.0**	**0.1**	**1,861**	**1**	**4,012.5**	**0.0**	**-498.1**	**(-27412.8, 27.4)**
HPV 59	**1,862**	**2**	**4,025.9**	**0.0**	**1,861**	**0**	**4,012.5**	**0.0**	**NA**	**NA**
CIN2/3 <u>not</u> related to any of the 14 HPV types	**1,862**	**6**	**3,916.9**	**0.2**	**1,861**	**5**	**3,897.2**	**0.1**	**-19.4**	**(-394.6, 69.6)**

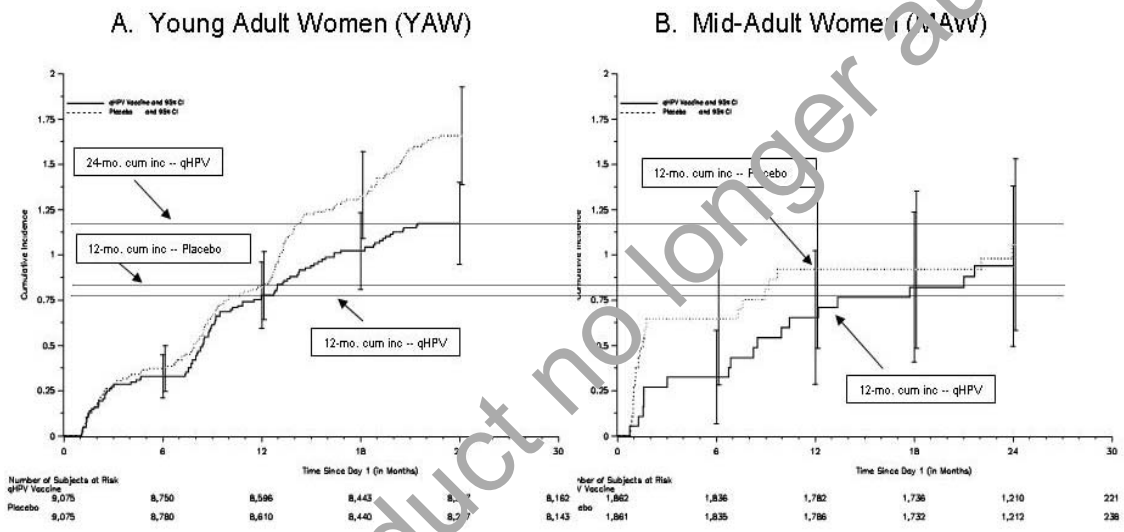
In the analyses of non-vaccine HPV types, the incidence of CIN 2/3 cases was higher in the vaccine group compared to the incidence in the placebo group. The data were supplemented with analyses of the cumulative incidence of HPV 31/33/35/39/45/51/52/56/58/59-related CIN 2/3 or worse and CIN 2/3 related to non-typeable non-vaccine HPV types in the FAS population and also by age groups. The incidence of cases were markedly higher in the vaccine group (34 cases vs. 19 cases in the placebo group). The cumulative incidence of HPV 31/33/35/39/45/51/52/56/58/59-related CIN 2/3 was also higher in the vaccine group vs. the placebo group.

The breakdown of the 53 cases of HPV 31/33/35/39/45/51/52/56/58/59-related CIN 2/3 or worse (vaccine n=34; placebo n=19) revealed that the majority of cases (vaccine n=25; placebo n=17)) were due to prevalent disease. According to the MAH all these cases were diagnosed with a baseline HPV infection that was of the same type as that detected in the CIN 2/3 lesion. The remaining 11 cases were incident infections (vaccine n=9; placebo n=2). Of the 9 vaccine cases, 5 were confounded by baseline co-infection with other oncogenic HPV type(s) and the other two had a very early diagnosis of CIN 2/3 suggesting a baseline infection. The two remaining cases, judged as incident infections, were diagnosed with HPV 58-related CIN 2/3 at Month 13 and HPV 56-related CIN 2 at Month 19. In the

placebo group one case was confounded by an infection with HPV 39 at Day 1 and the other case was diagnosed with CIN 2 related to HPV 16 and 51 at Month 30. These few cases of incident infection preclude any conclusions to be drawn.

The side-by-side comparison of plots of cumulative incidence of HPV 6/11/16/18-related CIN 2/3 in the ITT population of MAW versus YAW was presented. At Month 12 the separation in the cumulative incidence distributions between the vaccine and placebo group were greater in MAW compared to YAW, In contrast, the Month 24 results in MAW showed that there was no difference in the cumulative incidence plots between the vaccine and placebo group (figure 3). This could likely be explained by the smaller number of subjects resulting in low incidence of new infections in the placebo group and short-term follow-up time. Some 500 MAW subjects per group are still to contribute to the Month 24 estimate. The end-of study results at Month 48 of P019 will be critically important to reveal whether the separation between the vaccine and placebo groups will be of the same magnitude as that observed in the younger women.

Figure 3: Cumulative incidence of HPV 6/11/16/18-related CIN 2/3 or worse through 24 Months (MITT-3 for YAW / Full Analysis Set for MAW



Recurrence of HPV 6/11/16/18-related persistent infection

Analysis of efficacy against the recurrence of persistent HPV 6/11/16/18-related infection among subjects who were seropositive and PCR-negative to the relevant HPV type at baseline did not reveal any statistically significant results.

Of note in the vaccine group, there were 3/233 cases of persistent HPV 16 infection among women who were seropositive and PCR negative to HPV 16 at Day 1 compared with 6/250 cases in the placebo group leading to an efficacy of 45.1% (CI 95%:-156.9, 91.1).

1.2.1.3 Discussion

Efficacy endpoints

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).

Success was achieved in the primary and secondary efficacy study objectives.

The statistical methods are considered acceptable.

Persistent infection

The MAH provided data to support that persistent HPV infection of 6 months duration (±1 month) was as predictive of HPV 16/18-related CIN 2/3 as persistent infection of longer duration based on the data in young adult women. The proposed definition of persistent infection can be accepted with respect to HPV 16/18 and cervical endpoints. Upon CHMP request the MAH provided data on the proportion of women with a CIN or EGL who had prior persistent infection in comparison with women without a lesion. Overall the number of disease endpoints in study 019 was too limited to ensure reliability of the data. The predictive values achieved in the HNRT analyses did not vary significantly by age group or by testing interval of persistent infection. However, the lower PPV value obtained in the analysis of persistent infection of 12 months duration is not consistent with the results presented in the paper by Koshiol et al (2008). This is a systematic meta-analysis of 41 studies including 22000 women. Results indicate that persistent infection of 12 months duration appears to be the most valid endpoint to be used in clinical trials as a surrogate marker for cervical cancer. Also the data from a recent study (Rodriguez et al. JNCI, 2008) indicate that 12 month persistent infection is a more reliable predictor of CIN 2/3+. Although the large Koshiol meta-analysis has some limitations, data on the natural course of HPV disease suggest that the 12-month persistent infection is a more reliable and robust predictor of progression to CIN 2/3+ than the 6-month persistent infection. Therefore, the CHMP considers that in future study reports, data on 12 month persistent infection should also be included. The MAH provided results of the analyses of study 019 using a 12 month persistent infection. Results showed that efficacy estimates against HPV 16/18-related persistent infection and against the combined primary endpoint were in the same order of magnitude, although with wider confidence intervals, as the results of the analyses using the 6-month persistent infection.

The CHMP questioned, the correlation between HPV 16/18-related persistent infection and VIN 2/3 and VaIN 2/3. In response, data on duration of HPV infection were provided for the cases of HPV 16/18-related VIN/VaIN 2/3. The data submitted by the MAH showed that all cases of VIN 2/3, except one, were preceded by persistent HPV 16/18 infection, whereas none of the cases of VaIN 2/3. Furthermore, there was only one case of HPV 18-related high-grade vulvar disease. The analyses and calculations were therefore based on HPV 16-related persistent infection and VIN 2/3. Overall it must be stated that the number of disease endpoints was too limited (n=7) to ensure reliability of the data. Furthermore, the MAH provided statistical analysis of the value of HPV 16-related persistent infection for predicting HPV 16-related VIN 2/3 or VaIN 2/3 (for P012, on MITT-2 and MITT-3 populations). It can be agreed that the data give some evidence to support the association between HPV 16-related persistent infection and HPV 16-related high-grade vulvar disease. Since persistent infection with high-risk HPV has been established as a requirement for progression of cervical disease to pre-/cancer it is likely that the same applies for vulvar as well as vaginal disease and also for HPV 18. Biological plausibility and the provided data support the use of HPV 16/18-related persistent infection as a surrogate marker for high-grade vulvar and vaginal disease (VIN 2/3 and VaIN 2/3) and as a clinical efficacy endpoint in P019.

The CHMP questioned the clinical relevance of persistent HPV 6/11 infection, used as a secondary efficacy endpoint in P019, The MAH was requested to justify this endpoint and present data to support its correlation with clinical disease. The data provided from the qHPV vaccine studies in YAW (P012) showed that the majority of genital warts occurred without preceding persistent HPV 6/11 infection questioning the clinical relevance of the persistent infection endpoint for HPV6/11 in study 019. Since there are no valid data to support the use of persistent infection related to HPV 6/11 as an efficacy endpoint, the results obtained in study 019 were re-analysed excluding all data on HPV 6/11-related persistent infection. For the primary combined endpoint vaccine efficacy decreased from 90.5% (73.7, 97.5) to 86.0% (60.0, 96.4) in the PPE population and from 30.9% (11.1, 46.5) to 23.7 (-0.1, 42.0) in the FAS population when this endpoint was excluded.

The inclusion of vaginal and vulvar cancers in the composite endpoints as proposed by the MAH is not accepted by the CHMP, since the surrogacy of VIN 2/3 and VaIN 2/3 for these cancers has not been proven. All text on these cancers in the SPC were removed since it could falsely be perceived as vaccine efficacy has been demonstrated against vulvar cancer and vaginal cancer.

Study populations
The primary efficacy population (PPE) was defined similarly to that in all previous studies in YAW, as the per-protocol population who received all 3 vaccinations and was naïve to the relevant HPV type(s) at Day 1 prior to vaccination through 1 month postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit. Two further populations were defined that resembled the MITT-2 and MITT-3 populations used in the YAW studies; the HNRT population included baseline HPV-naïve women, but case-counting started immediately after the Day 1 visit. The third population (FAS) included all women enrolled in the trial regardless of Day 1 HPV status, i.e. also those already infected or with clinical disease at baseline, and with case-counting starting after the Day 1 visit.

In the first assessment the CHMP identified two major objections. The first objection concerned the indication of the qHPV vaccine, which covers all women regardless of HPV status and therefore the ITT (FAS) population was considered the most representative population for MAW. The primary efficacy population, the HPV naïve (PPE) population does not reflect the general population of MAW that will be vaccinated in clinical practice. The poor efficacy results observed in the FAS population did not support the MAH´s proposal to include a statement in the indication that efficacy had been demonstrated in 27-45 year old women.

In the response the MAH reiterated the approach to bridge the MAW results to the prophylactic efficacy results against clinical disease obtained in the YAW. Study 019 was powered to demonstrate significant prophylactic efficacy (i.e in the HPV naive population) and in the composite efficacy endpoints (persistent infection and disease), The CHMP agreed that for demonstration of prophylactic efficacy, the PPE population is the optimal population. The results in study 019 showed significant vaccine efficacy in HPV naïve mid-adult women and in similar magnitude as that shown in young adult women. However, this target HPV naïve population is difficult to identify among sexually experienced MAW and many non-naïve women will be vaccinated deriving little if any benefit. Therefore, the MAH was asked to evaluate the usefulness of possible pre-screening approaches.
The MAH´s response addressed the possible tools that could be used to select a susceptible population and their limitations. The MAH discussed the use of baseline characteristics as well as laboratory testing, such as cytological testing (Pap smear). Serological testing, HPV DNA testing (Hybride capture 2 test (HC2) and genotyping as a pre-screening tool to target HPV naïve women. According to the MAH its usefulness for pre-screening of HPV DNA status is very limited. The MAH evaluation of HPV status gave meagre positive incremental yield with respect to identifying women who would benefit from vaccination with the qHPV vaccine.
The CHMP accepted the MAH's response. In the future, with the increasing use of HPV testing in cervical screening programmes and availability of validated tests, the public health authorities might reconsider the use of various pre-screening strategies of HPV vaccination.

Since pre-screening is not feasible the CHMP considered critical to update the SPC and PL to make it very clear to the prescribers and patients that vaccine efficacy cannot be expected in non-naïve women. In the indication, the statement that efficacy has been demonstrated in women 16-26 years of age is retained. In section 4.4 it is stated that the vaccine is for prophylactic use only and that the vaccine is not effective against already established HPV infection/disease prior to vaccination, and that no vaccine efficacy has been shown in the ITT population of study 019. Moreover, it is mentioned that continued attendance to cervical screening program is critical.

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. Overall the region-by-region analyses did not allow any firm conclusions to be drawn. However, the incidence of the composite HPV endpoints in the vaccine and placebo group in the PPE populations did not differ substantially by region suggesting that prophylactic efficacy was similar in all locations. In the FAS populations differences were noted, with the lowest efficacy and the highest incidence of HPV infections seen in Europe, whereas the reverse was observed for the Asia Pacific region. Moreover, with respect to disease endpoints (CIN), it was noted that more cases were seen in the vaccine group than in the placebo group in the EU population, which was not the case in Latin America or Asia-Pacific. Although the EU population was limited in

size, these data raised some concern. These findings suggest that a lower magnitude of efficacy and a reduced benefit of the vaccine would be obtained in the EU ´real world´ female population than in the populations of the other regions. The end-of study results of P019 at Month 48 are awaited to show whether vaccine efficacy increases with time, as observed in YAW.
Based on the above section 4.4 of the SPC was revised to inform prescribers that the use of Silgard in adult women should take into consideration the variability of HPV type prevalence in different geographical areas and in the general population of 24- to 45-year-old women, and that no significant efficacy against HPV 16/18-related persistent infection and clinical disease has been demonstrated. The decision to vaccinate an individual woman 24-45 years old should take into account her risk for previous HPV exposure and her potential benefit from vaccination. Furthermore, the SPC was revised to make it clear that vaccine efficacy cannot be expected in women already infected with vaccine HPV types at baseline and results in the ITT population, in particular with respect to HPV 16/18-related persistent infection, were included in section 5.1.

PPE population
In this population VE was 90.5% against HPV 6/11/16/18-related persistent infection (PI)/disease, 83.1% against HPV 16/18-related PI/disease and 100% against HPV 6/11-related PI/disease. With respect to the HPV 16/18 endpoint, lower efficacy was observed in the 35- to 45-year-olds (VE: 80.6%) than in the younger age stratum (VE: 85%). There were 4 HPV 16-related endpoint cases in the vaccine group (3 PI and 1 CIN 2) vs. 41 in the placebo group. The 4 cases occurred relatively early in the follow-up, despite that all subjects developed a satisfactory anti-HPV 16 responses. The MAH was requested to address the grounds for "vaccine failure". The issue of the 4 "vaccine failure" cases were addressed as follows. One case with CIN 2 had a baseline infection with a non-vaccine type (HPV 56) and a co-infection with another HPV type (HPV 51 + HPV 16) at the time of diagnosis Month 18. Therefore the causal role of HPV 16 in the CIN 2 lesion could be questioned. According to the MAH the two early cases of HPV 16 persistent infection might be due to an active infection already present at baseline against which the vaccine would not be expected to protect.

Overall, the point efficacy estimates in MAW were lower than those among YAW, and in particular, with respect to the most important HPV 16/18 endpoint (VE 83.1% vs. 95-99% in YAW). It was clarified that the disease attack rates differed among the young and older women with lower rates in the placebo group of MAW, but that the incidence of vaccine HPV type-related persistent infection and disease among vaccinated MAW and YAW were similar.

P019 was powered to demonstrate vaccine efficacy against composite endpoints of persistent infection/disease in the HPV naïve population and not against vaccine type-related clinical disease (i.e. HPV 16/18-related CIN 2/3). No statistical significant efficacy was shown against HPV 16/18-related CIN 2/3, vaccine efficacy was 75.2% (95% CI: -150.6, 99.5).

HNRT population
In the HNRT population vaccine efficacy was lower; 74.6% (58.1, 85.3) against HPV 6/11/16/18-related persistent infection (PI)/disease, 71.6% (47.6, 85.5) against HPV 16/18-related PI/disease and 80.2% (51.7, 93.3) against HPV 6/11-related PI/disease. Vaccine efficacy was also lower than that seen in the MITT-2 population of YAW. A contributing factor is the different time point for case-counting, which started earlier in the HNRT vs. the MITT-2 population. Among the 16 new cases observed in the HNRT analysis (compared to PPE), 10 were HPV 16/18-related. These infections occurred during the vaccination course, which suggest that the vaccine did not provide protection prior to the completion of the 3 dose series, which is in contrast to that seen in YAW.
The MAH provided details on these cases. The immune responses induced by the qHPV vaccine appeared satisfactory in all cases (except low anti-HPV 18 GMTs response observed in two subjects (<10 and 72 mMU/ml)). The case narrative was provided for the HPV 18-related persistent infection and this subject was shown to have achieved an acceptable antibody response to HPV 18 at Month 7. Most infections were related to HPV 16 (n=9) and HPV 6 (n=6). The majority of women did not have any new sexual partner reported at 6 months prior to Day 1. It is of note that two-thirds of the cases had co-infections with oncogenic non-vaccine HPV types at baseline, which might explain the early infections seen.
Although not powered for CIN 2/3 or AIS, VE was only 25.4%, with 3 cases (one CIN 3) in the vaccine group and 4 cases (3 CIN 2 and 1 AIS) in the placebo group. This finding raised concerns on a

potential negative impact of the vaccine and the MAH was asked to provide all details and the timing of disease in these cases. In the group that received vaccine all three women had non-vaccine HPV types at baseline and two had very early detection of HPV 16-related disease, at Month 1 (CIN 1 progressing to CIN 2 at Month 22)) and at Month 8 (CIN 3). It seems likely that both these subjects were infected at baseline (despite a negative PCR) and therefore it is not possible to judge if the vaccine had any negative impact on the course of the HPV 16 infections. The third case had CIN 2 diagnosed at Month 18, but due to co-infection with HPV 51, the role of HPV 16 is difficult to interpret. All placebo cases were diagnosed with CIN 2/3 at later time points; Months 18, 24, 27 and 30. It is noted that two of the four CIN 2 cases in the placebo group were co-infected with non-vaccine HPV types. In conclusion, based on the data provided there is no clear evidence of a negative impact of vaccination with qHPV vaccine in women with baseline infection. This issue is further discussed under the therapeutic efficacy header. Overall, the efficacy results in the HNRT-analysis versus MITT-2 analysis in YAW suggest that the vaccine is somewhat less efficacious in MAW. However, longer duration of follow-up is needed to get conclusive data.

FAS (ITT) population

In the FAS (ITT) population, very low efficacy was noted for the HPV 6/11/16/18 related PI/disease endpoint (VE: 30.9%) and for the more important HPV 16/18-related PI/disease endpoint only nominal reductions were seen (VE: 22.6% (-2.9, 41.9)). Efficacy for the HPV 6/11-related endpoint was 47% (11.4, 69.2).

These point estimates are much lower than those observed among YAW and the results in the two populations cannot be considered comparable. With respect to CIN 2/3 no efficacy at all was observed, not even a trend (VE: 9.9%). However, the study was not powered to show statistically significant efficacy in the FAS population. Furthermore, the different efficacy estimates observed between MAW and YAW studies could be explained by the differences in sample size, study duration and exposure risk of acquiring infection. The consequence of the lower exposure risk in MAW is that it will take much longer time to demonstrate public health benefit in this population in comparison with the YAW population.

The number of cases vaccine type related CIN in the vaccine group, 10 CIN 2 and 14 CIN 3 (table 10), was exactly the same as in the placebo group. The CHMP requested all details on these cases, including the time course of the disease in order to exclude a negative impact of the qHPV vaccine, in particular with respect to HPV 16 infection. The MAH provided the details on these cases. The breakdown of the 40 cases of HPV 6/11/16/18-related CIN 2/3 revealed that the majority of cases (n=33) were due to prevalent disease, which would not be expected to be prevented by the vaccine. The remaining 7 cases were incident infections (vaccine=3 and placebo=4). Of the 3 vaccine cases, one was confounded by co-infection with an oncogenic non-vaccine HPV type (HPV 51) and one had a very early HPV 16 infection (CIN 1 at Month 1) suggesting a baseline infection. The third case with a baseline infection with HPV 56 had a very rapid progression to HPV 16-related CIN 3 diagnosed at Month 8. However, this single case does not allow any general conclusions to be drawn as regards any impact of the vaccine on the course of disease.

The hypothesis that the qHPV vaccine causes acceleration of CIN 2/3 or worse due to any HPV type issue is discussed under therapeutic efficacy.

Furthermore, the vaccinated MAW population should be the subject of long-term follow-up to monitor duration of vaccine efficacy and to evaluate the need for a booster dose. This is important considering the lower immune responses obtained in older women, which might suggest shorter duration of immunity compared to young adult women. The consequence of these lower antibody responses in the MAW population for the durability of efficacy is not known since no immunological correlate of protection has been defined. The MAH has committed to submit the study synopsis of a sentinel cohort of P019.

Overall, very low efficacy results were achieved in the FAS-population. Since there is no positive benefit risk in the general population, the indication remained unchanged in section 4.1 of the SPC. The data is reflected in sections 4.4 and 5.1 of the SPC to inform prescribers that the use of Silgard in adult women should take into consideration the variability of HPV type prevalence in different geographical areas. Moreover, a statement was included in the SPC that in the general population of

24- to 45-year-old women, no significant efficacy against HPV 16/18-related persistent infection and clinical disease has been demonstrated. The decision to vaccinate an individual woman 24-45 years old should take into account her risk for previous HPV exposure and her potential benefit from vaccination and that Silgard is not effective in women already infected/diseased at the start of vaccination.

Therapeutic efficacy

The observation of a significantly higher clearance of HPV 16 DNA in the placebo group versus the vaccine group (percent incidence reduction 47.3 (95% CI: 0.4, 73.0)) among subjects who were Day 1 PCR positive and seronegative to HPV 16, raised major concerns and was identified in the first assessment as a second major objection. The study population was limited, but together with the efficacy results in the FAS/HNRT populations with respect to CIN 2/3, the data could indicate that the vaccine has a negative impact on ongoing HPV infections. Moreover, a similar finding was seen initially in one of the pivotal YAW studies (P013), where data suggested that the vaccine aggravated disease in baseline HPV positive subjects. In response the MAH performed re-analyses due to the fact that inaccurate case/non-case definitions were used originally. The re-analyses led to a change in percent incidence reduction to 46% (95% CI: -2.7, 72.4) a statistically non-significant result. Inconsistent results were observed in the PCR positive group depending on its serostatus. In addition, the life table analysis of time-to-clearance of HPV 6 and HPV 16 infection showed no relevant difference between the vaccine and placebo groups. The "similar" finding in the YAW study 013 was only seen in one study, in one subset (not in PCR positive/seronegative) and did not extend to the MAW population. Moreover, the vaccine efficacy results in MAW with respect to HPV16/18-related CIN 2/3 in PCR positive/seronegative subjects did not corroborate the negative therapeutic efficacy trend with respect to clearance of HPV 16 infection. Furthermore, there is no plausible mechanism for a negative effect of the vaccine on on-going HPV infections. From the above the CHMP concluded that the overall pattern is not consistent with a negative impact of the vaccine on prevalent HPV infections.

The MAH provided data on the cumulative incidence of HPV 6/11/16/18-related CIN 2/3, which was lower in the vaccine group than in the placebo group suggesting no acceleration of vaccine HPV type-related disease progression (see figure 1). However, the lack of separation of the cumulative incidence plots on HPV 16/18-related CIN 2/3 in the FAS-population between vaccine and placebo group at Month 24 raised concern. However, due to the small sample size (500 subjects in each group still to be included in the 24 month time point) these curves are not fully representative. The lower number of subjects at Month 24 would result in a lower incidence of new infections in the placebo group, a likely explanation for the flattened incidence curve. The results at Month 48 will be important to reveal whether the cumulative incidence plots will separate between the vaccine and placebo groups in a similar way as that observed in the young adult women

In contrast, to the findings for vaccine HPV types, figure 2 showed the opposite pattern with higher incidence of CIN 2/3 due to any HPV type and a steeper curve by time in the vaccine group. These findings raised a major concern since it could suggest an accelerated progression of CIN 2/3 due to any HPV type among vaccinated subjects compared with those in the placebo group. In response the MAH provided relevant data for FAS population to clarify this issue including narratives for all CIN2/3 cases observed.

The breakdown of cases of CIN 2/3 in the FAS population by prevalent and incident cases showed in the MAH´s reasoning that there were only 2 cases of incident infection in the vaccine group (out of 9 putative incident cases) and 1 case in the placebo group (out of 2 putative incident cases). However, the exclusions made by the MAH were not fully supported, resulting in 4 cases of incident infection in the vaccine group versus 1 case in the placebo group. It is important to mention here that the presence of prevalent or pre-existing HPV infection due to non-vaccine HPV types in the FAS population complicates the analysis. The baseline imbalances observed between the vaccine and placebo groups were addressed by the MAH. This analysis showed that the higher incidence of CIN 2/3 related to four non-vaccine HPV types (33, 39, 51 and 58) among vaccines is likely to be attributed to the baseline imbalance in prevalent infection corresponding to the relevant HPV type. For three further non-vaccine HPV types (HPV 45, 56 and 59) with higher incidence of CIN 2/3 in the vaccine group, the case histories do not suggest that qHPV vaccine accelerates progression of disease related to the relevant HPV type.

For CIN 2/3 not related to any of the typeable 14 HPV types, the cumulative incidence in the vaccine group was higher than in the placebo group, although not statistically significantly different. However there were too few cases (6 in the vaccine group vs. 5 in the placebo group) to draw conclusions. The end-of-study results at Month 48 are important in order to show whether a larger difference between groups will be discernable.

Moreover, it is difficult to hypothesize a plausible mechanism for a negative effect of the vaccine on on-going HPV infections.

The time to event data on CIN 2/3 are not possible to be evaluated in cases with baseline infections since the duration of prevalent HPV infection prior to vaccination is not known. The MAH has provided results of analysis of efficacy of the qHPV vaccine against CIN 2/3 related to any of the 10 non-vaccine HPV types in the cohort of women who were PCR positive at Day 1 to the relevant HPV type, i.e., women infected at baseline with the relevant HPV type and the results of comparison of the qHPV vaccine group and placebo group with respect to the cumulative incidence of CIN2/3 related to any of the 10 non-vaccine HPV types in the same cohort of women. The results do not suggest a clinically significant acceleration of disease progression in the vaccine group compared to the placebo group.

Overall, the data provided, do not suggest that the qHPV vaccine accelerates progression of disease related to vaccine HPV types. At the present time there is no indication of the occurrence of HPV type replacement disease in the vaccine group. However, these issues must be closely monitored during longer term follow-up and must be addressed again in the end-of-study report of Protocol 019.

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 did not reveal any statistically significant result. The data at the current stage are too limited to allow any firm conclusion on this matter. However, there were 3 cases with persistent HPV 16 infection in the vaccine group (vs. 6 cases in the placebo group), which suggest that the vaccine might not be effective against recurrences. Vaccine efficacy against persistent HPV 16 infection in the seropositive/PCR negative subset could not be demonstrated in either the TATV or MAW population, (although efficacy was observed for HPV 16 CIN in the young adult women).

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 PPI population. The study is ongoing. The current application includes results from all visits through 13-July-2007 (corresponding primarily to the Day 1, Month 7, and Month 24 visits).

In addition to the new immunogenicity data from P019, an integrated immunogenicity analysis of the immune response over the entire range of 9 to 45 years of age was provided.

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.

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 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 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 24-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

1.3.2.1 Protocol 19

GMTs
Table 13 shows the anti-HPV 6, 11, 16, and 18 GMTs for the vaccine group and placebo group in the PPI population at Day 1, Month 7 and Month 24. 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 quantification (LLOQ) of the assay. In the vaccine group measurable immune responses well above the LLOQ were induced at 4 weeks Postdose 3. At Month 24, the anti-HPV 6, 11, 16, and 18 GMTs were lower, in particular with respect to anti-HPV 18. For anti-HPV 18 the GMT at Month 24 was approximately 50% of the baseline GMT among subjects who were anti-HPV 18 seropositive/PCR negative at baseline.

Table 13: Summary of anti-HPV GMTs by vaccination group (PPI 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	1,262	< 7	(<7, <7)	1,251	< 7	(<7, <7)
Month 07	1,262	417.5	(396.9, 439.2)	1,251	< 7	(<7, <7)
Month 24	1,218	70.4	(66.9, 74.0)	1,203	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1,262	< 8	(<8, <8)	1,251	< 8	(<8, <8)
Month 07	1,262	552.4	(526.7, 579.5)	1,251	< 8	(<8, <8)
Month 24	1,218	77.5	(73.9, 81.3)	1,203	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1,279	< 11	(<11, <11)	1,256	< 11	(<11, <11)
Month 07	1,279	2,234.7	(2,122.4, 2,353.0)	1,256	< 11	(<11, <11)
Month 24	1,235	279.6	(264.9, 295.2)	1,213	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,444	< 10	(<10, <10)	1,427	< 10	(<10, <10)
Month 07	1,444	358.7	(341.9, 376.4)	1,427	< 10	(<10, <10)
Month 24	1,390	**28.4**	(26.9, 30.0)	1,370	< 10	(<10, <10)

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

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

n = Number of subjects contributing to the analysis.

ANOVA = Analysis of variance; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units;

Seroconversion

The percentage of seroconversion in each of the vaccine HPV types at all time points evaluated were less than 5% in the placebo group (Table 14). In the vaccine group, the percentage seroconversion at Month 7 was at least 97% for each of the vaccine HPV types. At Month 24 the percententage seroconversion had dropped by <10% for each of HPV types 6, 11, and 16. For HPV 18, the percentage seroconversion at 4 weeks postdose 3 dropped by 43 percentage points at Month 24 and the percentage seropositive was 54.7%.

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

Anti-HPV response	qHPV Vaccine (N=1910)				Placebo (n=1907)			
		Seroconversion				Seroconversion		
Study time	n	M*	Percent	95% CI	n	M*	Percent	95% CI
Anti-HPV 6 ≥20 mMU/ml								
Day 1	1262	0	0.0	0.0, 0.3	1251	0	0.0	0.0, 0.3
Month 7	1262	1242	98.4	97.6, 99.0	1251	38	3.0	2.2, 4.1
Month 24	1218	1,087	89.2	87.4, 90.9	1,203	42	3.5	2.5, 4.7)
Anti- HPV 11 ≥16 mMU/ml								
Day 1	1,262	0	0.0	0.0, 0.3	1,251	0	0.0	0.0, 0.3
Month 7	1,262	1,238	98.1	97.2, 98.8	1,251	27	2.2	1.4, 3.1
Month 24	1,218	1,126	92.4	90.8, 93.9	1,203	31	2.6	1.8, 3.6
Anti- HPV 16 ≥20 mMU/ml								
Day 1	1,279	0	0.0	0.0, 0.3	1,256	0	0.0	0.0, 0.3
Month 7	1,279	1,264	98.8	98.1, 99.3	1,256	45	3.6	2.6, 4.8
Month 24	1,235	1,192	96.5	95.3, 97.5	1,213	48	4.0	2.9, 5.2
Anti- HPV 18 ≥24 mMU/ml								
Day 1	1,444	0	0.0	0.0, 0.3	1,427	0	0.0	0.0, 0.3
Month 7	1,444	1,406	97.4	96.4, 98.1	1,427	31	2.2	1.5, 3.1
Month 24	1,390	760	**54.7**	52.0, 57.3	1,370	22	1.6	1.0, 2.4

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

Comparison of 24 to 34 year-olds and 35 to 45 year-olds
Anti-HPV GMTs at Months 7 and 24 were somewhat lower among 35- to 45-year-old women compared with 24- to 34-year-old women, though the difference was not statistically significant (i.e., the CIs were overlapping).

For each of the vaccine HPV types, the percent seroconversion at Month 7 and Month 24 was similar between the 2 age groups.

Comparison of 16 to 23 year-olds and 25 to 45 year-olds
The anti-HPV 6, anti-HPV 11 and anti-HPV 18 GMTs at Month 7 and Month 24 were significantly higher in the 16 to 23 year-olds compared to those in the 24 to 45 year-olds (95% CIs not overlapping). Anti-HPV 16 GMTs were comparable between the age groups at Month 7, but were significantly higher in the 16 to 23 year-olds at Month 24.

The percent seroconversion for each of the 4 vaccine HPV types at Month 7 was comparable between age groups. At Month 24, the percent seroconversion for each of the 4 vaccine HPV types was higher in the 16 to 23 year-old age group compared to that in the 24 to 45 year-old age group (95% CIs do not overlap).

Comparison of 16 to 23 year-olds, 24 to 34 year-olds and 35 to 45 year-olds
Month 7
For anti-HPV 6, 11 and 18 GMT at Month 7 was highest in the 16 to 23-old age group and lowest in the 35 to 45 year old. In general the GMTs in each of the 3 age groups were different (95% CIs of the GMTs did not overlap), and decreased as the age progressed.

- Among 24 to 34 year-olds anti-HPV 6, 11, 16 and 18 GMTs were 82%, 79%, 102% and 87%, respectively, of the corresponding anti HPV GMTs among 16 to 23 year-olds.

- Among 35 to 45 year-olds anti-HPV 6, 11, 16 and 18 GMTs were 74%, 67%, 93% and 71%, respectively, of the corresponding anti-HPV GMTs among 16 to 23 year-olds.

- The percent seroconversion for each of the 4 vaccine HPV types was comparable in all 3 age groups.

Month 24
In general the anti-HPV GMTs for each of the 4 vaccine types at Month 24 was lower compared to the GMTs at Month 7 and the Month 24 GMTs decreased as age progressed.

- Among 24 to 34 year-olds anti-HPV 6, 11, 16 and 18 GMTs were 64%, 57%, 63% and 60%, respectively, of the corresponding anti-HPV GMTs among 16 to 23 year-olds.

- Among 35 to 45 year-olds anti-HPV 6, 11, 16 and 18 GMTs were 62%, 51%, 59% and 50%, respectively, of the corresponding anti-HPV GMTs among 16 to 23 year-olds.

- The percent seroconversion for each of the 4 vaccine HPV types was higher in the 16 to 23 year-olds compared to that in the other 2 older age groups.

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

Seropositive/PCR negative population
At Day 1 anti-HPV GMTs were comparable in the vaccine and placebo group. At Month 7 the GMTs in the vaccine group increased at greater magnitude in the baseline HPV seropositive subjects compared to those in the HPV-naïve population. At Month 24 the GMTs were lower than at Month 7, but were higher in the baseline seropositive subjects than the GMTs in the PPI population. In the placebo group there was a steady decline in GMTs.

Seropositive/PCR positive population
The number of evaluable patients was small. In the placebo group GMTs were somewhat higher than those observed in the seropositive/PCR negative group. In the vaccine group, the anti-HPV GMTs at Months 7 and 24 were higher in the seropositive/PCR positive subjects than those in the PPI population.

Seronegative/PCR positive population
The number of evaluable patients was small. In the placebo group anti-HPV 6, anti-HPV 11 and anti-HPV 16 seroconversion was observed. At Month 7, 41.2%, 100% (one subject), 23.9% and 4.3% of subjects who were HPV 6, HPV 11, HPV 16 and HPV DNA-18 positive had seroconverted in the placebo group. The anti-HPV 6, 11 and 18 GMTs at Months 7 and 24 in the vaccine group were somewhat higher in the baseline PCR positive subjects than those in the PPI population, whereas anti-HPV 16 levels were slightly lower.

1.3.2.2 Integrated review

The integrated review of the immunogenicity of qHPV vaccine includes data from the following protocols: P007 (Phase II dose ranging study of in YAW) ; P013 (Phase III efficacy study in YAW; substudies P011 and P012); P015 (Phase III efficacy study in YAW); P016 (Phase III adult-adolescent immunogenicity bridging study); P018 (Phase III immunogenicity and safety study in pre-adolescents and adolescents); and P019 (Phase III efficacy, safety, and immunogenicity study in mid-adult women).

Baseline characteristics seem to exert some influence on the Month 7 immune response with age as the strongest predictor for all vaccine HPV types, The decreases in Month 7 anti-HPV natural log titers associated with one year´s increase in enrolment age were calculated and corresponded to 2.9%, 2.6%, 2.8% and 3.5% decrease in anti-HPV 6, 11, 16 and 18 GMTs, respectively. Some variability in response was seen by race/ethnicity and by geographic region, but no significant pattern was evident.

The integrated review of immunogenicity showed that age influenced significantly on Month 7 and Month 24 anti-HPV titres for all vaccine HPV types. The type-specific GMTs were highest in 9- to 17-year-olds and decreased with an increase in the enrolment age, being the lowest in the 35- to 45-year-olds. The age-related decline in GMTs was most pronounced over the 9- to 17-year old age range, whereafter it was more gradual between ages 18 to 45. The Month 7 GMTs were 2 to 3 fold lower in the 35- to 45 year-olds compared with those in 9- to 17-year-olds.
At Month 24, the GMTs of the 4 vaccine HPV types had decreased substantially from the peak at Month 7 in all vaccine recipients across age groups. The GMTs for HPV 18 were low in all age groups, but in particular in the MAW population, where the antibody levels had declined below those in subjects naturally infected. The proportions of subjects who were anti-HPV 6, 11 and 16 seropositive at Month 24 remained above 89% in all age groups; the seropositivity rates being 3 to 6 percentage points lower in the 35- to 45 year-olds than in the 18- to 26-year-olds. With respect to HPV18, only 55% of MAW remained seropositive as opposed to 85% of 9- to 17-year-olds.

1.3.3 Discussion

The version 2 of the HPV-4 cLIA assay was appropriately validated.

Protocol 019, at month 7, the qHPV vaccine induced an immune response to all four HPV types. Seroconversion rates for all HPV type were comparable (>97%). As regards persistence of immune response, for all HPV types, anti-HPV GMTs declined between Month 7 and Month 24. Anti-HPV 6, anti-HPV 11, anti-HPV 16 remained above the baseline levels, while for anti-HPV 18 the level was below that of baseline and somewhat lower than that observed up to 4 years post enrollment in young women (see variation II/19) [28.4 mMU/ml) (95%CI: 26.9, 30.0) vs. 33.9 mMU/ml (32.0, 35.9)].

The study demonstrated that administration of the qHPV 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

significantly lower than those observed in 16- to 23- year-old (non-overlapping 95% CIs). The exception was anti-HPV 16 GMTs that were comparable between the two age groups. When analyzed by the two age strata of MAW, the lowest responses were observed in the 35- to 45-year-olds. It can be concluded that the magnitude of antibody response to the qHPV vaccine was related to age, with the highest response achieved in the younger women. The most robust responses were demonstrated against HPV 16 and the weakest response to HPV 18. At Month 24, the anti-HPV GMTs for all 4 vaccine types had decreased substantially.

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.

From the integrated analyses it can be concluded that the vaccine-induced immune responses in MAW were inferior to those seen in adolescents and young women. The consequence of these lower antibody responses in the MAW population for the durability of efficacy is not known, since no immunological correlate of protection has been defined. The low Month 24 GMTs and seropositivity rates for HPV 18 raised concern. The data demonstrated that cLIA seems not to be the optimal test to measure long-term vaccine induced HPV immunity (since protection in YAW was sustained despite seronegativity to HPV 18). 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 has committed to perform serological studies using broader neutralization assays, i.e. pseudo-neutralization assays, as well as to submit the validation protocol and final results using the newly developed assay measuring the VLP-specific total IgG. The MAH submitted the relevant study reports in April 2009 and they are currently under assessment, as a follow up measure.

In addition, the long-term surveillance of disease outcomes in young adult women will reveal the significance of the seronegativity to HPV 18. However considering the lower immune response observed in vaccinated mid-adult women it is critical to determine whether this translates to shorter duration of immunity and necessitates an earlier booster dose. At the current stage after a relatively short duration of follow-up (2.2 years) in study 019, no obvious breakthrough infections have been documented. However, long-term follow-up of efficacy and immunogenicity in MAW is mandatory. The MAH has committed to submit a study synopsis on a long term follow up of vaccine efficacy, immunogenicity and safety in MAW and a Protocol.

Baseline characteristics seemed to exert some influence on the Month 7 immune response with age as the strongest predictor for all vaccine HPV types. In the multifactor models, BMI was found to be a significant predictor for Month 7 anti-HPV 18 titers and for Month 24 anti-HPV 11, 16 and 18 titers in 18-26 year old female. Unfortunately, BMI was not included in the modeling for the MAW. This factor is of interest since the qHPV vaccine is similar to the recombinant Hep B vaccine, for which BMI is a well-known factor associated with a reduced immune response. The results of the modeling exercise were difficult to interpret, since the significant predictors of Month 7 and Month 24 anti-HPV responses varied by HPV type and by age group in an inconsistent pattern. The MAH was requested to clarify whether there are any baseline characteristics that are associated with a decreased immune response to qHPV vaccine that deserve to be mentioned in the SPC. It was shown that multiple factors influenced on the anti-HPV titres. Overall age is the most important predictor of titer response with the strongest immune responses observed in youngest subjects below 12 years of age. Importantly, no particular subgroup has been identified with poor responses to the vaccine. Moreover, the factors evaluated have not so far been identified to impact on short-term efficacy. Whether the lower response associated with some of the factors will affect the durability of immunity is not known at present, but will be shown in the on-going long-term surveillance studies.

The subjects who were seropositive to the relevant HPV type(s) at baseline had much higher GMTs than those who were seronegative to the same HPV type(s) at Day 1, suggesting the induction of an anamnestic response in naturally infected subjects. Among MAW who were seropositive to vaccine HPV types at Day 1, vaccine induced immune response to the types for which they were positive were comparable to those observed among YAW who were seropositive to the same type at Day 1.

Mild to moderate deviations (+1 month with administration of Dose 2 and +2 months with administration of Dose 3) from the current dosing schedule of a 3-vaccine injection series at Day 1, Month 2 and Month 6 did not have a major impact on the Month 7 or Month 24 anti-HPV immune responses.

In conclusion, section 5.1 of the SPC reflects the study results and was endorsed by the CHMP with minor changes. Furthermore, a paragraph concerning persistent of immune response was included upon CHMP request to add the percentages of MAW vaccinated women per subtype that remained seropositive after a follow up of 2.2 years.
The MAH submitted the relevant study reports to measure long-term vaccine induced HPV immunity test in April 2009 that are currently under assessment as a follow up measure.

1.4 Clinical safety

The MAH has provided the safety analysis of study 019 conducted in 3819 healthy 24 to 45 year-old women enrolled in 38 sites in 7 countries. The data are obtained from the start of the study through the visit cut-off date of 13-Jul-2007. The cut-off date for SAEs reported to the WAES was 16-May-2008.
Furthermore, the MAH has submitted an integrated overview of safety data in the population of subjects 9 to 45 years (including studies P007, P013, P015, P016, P018 and P019) across the entire age range. In addition integrated safety data is presented by age, in order to provide a comparison between the age groups (9 to 17 years, 18 to 26 years, 27 to 34 years and 35 to 45 years). Protocol 019 contributes all subjects in the categories of 27 to 34 years and 35 to 45 years. All safety data in clinical trials of qHPV vaccine in studies of subjects 9 to 26 years of age have been submitted previously in the EU to the CHMP in the context of the MAA and subsequent Type II variations.
Furhermore, the MAH proposes the deletion of "Injection-site bruising" from section 4.8 of the SPC.

1.4.1 Protocol 019

Patient exposure
Overall, 3819 subjects were enrolled in this study, two (2) subjects were randomised but not vaccinated (resulting in 3817 vaccinated subjects). A total of 1910 subjects received at least one dose of qHPV vaccine and 1907 subjects received at least one dose of placebo.

The mean age was 34.3 years in both groups. Thirty-one percent (31%) of subjects were Asian, 43% were Hispanic American and 20% were white. Approximately 13% of the subjects originated from Europe, 13% from North- America, 42% from Latin-America and 31% from Asia.

Adverse events
From Protocol 019 the following observations can be made:

- The proportions of subjects who reported at least one clinical AE was somewhat higher in the group that received qHPV vaccine (87.1%) than in the placebo group (81.3%).
- The proportion of subjects who reported at least one injection site AE was somewhat higher in the group that received qHPV vaccine (76.8%) than in the placebo group (64.3%).
- The proportion of subjects who reported at least one systemic AE was generally comparable between the two vaccination groups (59.3% in the qHPV group and 60.1% in the placebo group).
- Few subjects discontinued the study due to an AE (0.4% in the qHPV group and 0.1% in the placebo group) or a vaccine related AE (0.3% in the qHPV group and 0.1% in the placebo group).
- A total of 11 subjects who received qHPV vaccine (0.6%) and a total of 15 subjects who received placebo (0.8%) reported a serious clinical adverse experience (SAE) at any time during the study. None of the SAEs were determined by the investigator to be related to study vaccine/placebo.
- There were 5 deaths: one in the placebo group (0.1%) and 4 in the vaccine group (0.2%). The deaths occurred at least 4 months after vaccination and were not determined to be related to study vaccine.

Injection site Adverse Experiences: The most common injection site AEs in both the vaccine and the placebo group, respectively, were pain (75.3% and 62.0%), swelling (18.7% and 11.3%) and erythema (14.5% and 10.5). In general the proportion of subjects who reported specific injection site AEs was higher in the qHPV group than in the placebo group.

Systemic Clinical Adverse Experiences: In both the vaccine and placebo groups, respectively, the most common clinical AEs were headache (27.8% and 27.5%), pyrexia (11.6% and 12.3%), influenza (5.2% and 5.4%), nasopharyngitis (4.2% and 4.7%), and dizziness (4.2% and 4.3%). In general the proportion of subjects who reported a systemic AE was comparable between the vaccination groups. The exception was pain in the extremity where the proportion of subjects was higher in the qHPV vaccine group than in the placebo group (4.7% vs 2.2%).

Elevated temperatures: The percentage of subjects in the qHPV vaccine group who had maximum temperature >37.8 º C was comparable to that in the placebo.

Serious adverse events and deaths

Deaths
At the time of the closing of the study database for the current analysis 5 subjects (4 in the qHPV vaccine group and 1 in the placebo group) died during the study.
The deaths occurred at least 4 months after vaccination. None of the deaths was determined to be related to study vaccine.

Serious adverse events
A total of 11 subjects in the qHPV vaccine group (0.6% of the 1903 subjects) and a total of 15 subjects in the placebo group (0.8 % of the 1902 subjects) reported a SAE at any time during the study. None of the SAEs was determined to be related to study vaccine/placebo.The most common SAEs in both vaccination groups were pregnancy related (premature labour, ectopic pregnancy). The most common non-pregnancy related SAE was pelvic inflammatory disease. The incidences were comparable between the vaccination groups.

New medical history in the safety population
The MAH presented the new medical conditions with an incidence > 1% in either treatment group during the vaccination period (Day 1 through Month 7). The most common new medical conditions reported were headache (3.3% vs. 4.1%), nasopharyngitis (2.6% vs. 2.1%), and bacterial vaginitis (2.0% vs. 1.6%). The proportion of subjects reporting new medical conditions was generally comparable between the two vaccination groups.
Among nervous system disorders headache prevailed. No other unlisted neurological symptoms were specifically described.

The number and percentage of new medical conditions potentially indicative of an autoimmune phenomenon among all subjects in the safety population reported post month 7 by vaccination group shows that the most common diagnosis was hypothyroidism (0.4% in the qHPV group and 0.5% in the placebo group). Overall the reporting of potential autoimmune conditions was comparable between vaccination groups.

Safety in special groups
The initial MAA included safety summaries by concomitant medications including systemic, immunosuppressive, anti-inflammatory or antipyretic formulations or contraceptives. The MAH anticipated no differences in safety profiles in this respect in subjects 27 to 45 years of age as compared to subjects 9 to 26 years and therefore did not conduct such analysis in study P019.

Pregnancy outcomes
Pregnancy outcomes were generally comparable between the two vaccination groups.

Congenital anomalies
A total of 5 congenital anomalies were reported for pregnancies (live births, foetal losses). Of these, 2 were in an infant (with ventricular septal defect and adrenal neoplasm) and one in a foetus (with bilateral renal agenesis) born to subjects in the qHPV vaccine group and 2 were in infants (with hypochondroplasia and congenital hydronephrosis) born in the placebo group. No specific anomaly could be possibly related to vaccination.

Analysis of pregnancy outcomes in subsets of subjects in protocol 019
Analyses were conducted to evaluate the impact of the qHPV vaccine on pregnancy outcomes among subjects whose estimated date of conception (ECDn) calculated by last menstrual period occurred within 30 days of receiving a dose of study vaccine (Proximate Pregnancies).
The outcome of pregnancies that occurred within 30 days of a vaccination reported 1 case in the placebo group but none in the qHPV group. In the group of subjects whose EDCn greater than 30 days following any vaccination were 3 cases of congenital anomalies reported in the qHPV group but 1 in the placebo group.

Analysis of pregnancy outcomes in subsets of subjects in the phase III clinical program for qHPV vaccine
A total of 14 infants born to 14 subjects in the qHPV vaccine group experienced a SAE. None was judged to be vaccine related. A total of 14 infants born to 14 subjects in the placebo group experienced a SAE.

Serious adverse experiences reported in women who reported pregnancies
Twelve (12) SAEs were reported by subjects during pregnancy. None of these SAEs were determined to be vaccine/placebo related.

Administration of qHPV vaccine to lactating women
No SAEs were reported among subjects who were breast-feeding during the study. Data were provided in cumulative tabulations of the combined protocols as described below.

1.4.2 Protocols 013, 015, 016, 018 and 019 combined

Patient exposure
For the integrated summaries, 2 safety populations were specified (as for the initial MAA and previous Type-II variations).

- Safety population: includes all subjects who were enrolled in Protocols 007, 013, 015, 016, 018 and 019 who received only qHPV vaccine or placebo (aluminium or non-aluminium), regardless of surveillance method. This population included 25,274 subjects; 13,686 subjects who received qHPV vaccine (as the subjects who received qHPV vaccine in the extension to Protocol 007 are not included), and 11,588 subjects who received placebo.
- Detailed Safety Population: includes all subjects who were enrolled in protocols 007, 013, 015, 016, 018 and 019 who received only qHPV vaccine or placebo (aluminium or non-aluminium) who were followed using the VRC-aided surveillance method. This population included 14,034 subjects; 8,068 subjects who received qHPV vaccine and 5,966 subjects who received placebo. All subjects in Protocol 019 were followed using VRC-aided surveillance.

Overall the proportion of subjects 9 to 45 years of age who were randomised to receive qHPV vaccine in the integrated database consisted of 25% of subjects 9 to 17 years of age, 63% of subjects 18 to 26 years of age, 5% of subjects 27 to 34 years of age and 7% 35 to 45 years of age. The proportions for subjects randomised to receive placebo were 15% of subjects 9 to 17 years of age, 71% of subjects 18 to 26 years of age, 6% of subjects 27 to 34 years of age and 8% of subjects 35 to 45 years of age.

A higher percentage of subjects in the integrated data set who received qHPV vaccine (49.1%) reported an injection site experience than subjects who received placebo (37.1%). The rates of discontinuation were not impacted.

In the detailed safety population the frequency by age of injection site reactions were higher in the younger age groups (9-17 years old) with more erythema and swelling.

The proportions of subjects reporting a systemic AE were comparable between the vaccination groups. The most common systemic AEs were headache, pyrexia, nausea and nasopharyngitis. A great majority of systemic AEs were mild or moderate in intensity both in the vaccine and placebo groups.

In the qHPV group the proportions of subjects reporting systemic AEs were generally comparable across age groups. The only exception was a higher frequency of pain in the extremity in the older age category.

The most common SAEs in both vaccination groups were pregnancy related. None of the SAEs was determined to be related to study vaccine or placebo.

New medical conditions potentially consistent with autoimmune phenomena reported post-month 7 among all subjects by vaccination group showed proportions of such reported events comparable between the vaccine and placebo groups.

Overall data from the combined study protocols showed that the proportions of pregnancies with natural outcome that ended in a negative outcome were comparable between the vaccination groups. A total of 70 cases of congenital anomaly included 40 cases in the qHPV vaccine group and 30 cases in the placebo group. The proportions of live births resulting congenital anomalies were comparable: 2.6% (38/1447) in the qHPV vaccine group and 1.9% (27/1424) in the placebo group. The number of pregnancies resulting in congenital anomaly was within the incidence rate of 3% to 4% in large health care systems. No specific medical conditions could be related to any of the vaccine groups.
The follow-up of breast-fed infants of mothers vaccinated identifies more SAEs in the qHPV group compared to the placebo group. There were no patterns or trends in the types of serious adverse experiences reported in infants who were breastfed during the vaccination phase of clinical studies. No safety signals of clinical concern were identified among these infants.

1.4.3 Discussion

No new or significant safety signals were identified with the exception of increased incidences of transient injection-site adverse experiences and low-grade fever following vaccination in the new Medical History safety data from P019 or the Protocols 013, 015, 016, 018 and 019 combined. The proportions of subjects who reported SAEs or who discontinued due to a SAE were low and comparable between the vaccination groups. Vaccine-related SAEs occurred in <1% of the subjects. Reporting frequency of adverse events was similar in the different age ranges except for the higher frequency of pain in the extremity in older subjects and somewhat higher frequency of erythema and swelling in the younger age range.

The MAH proposed to delete the “Injection-site bruising” from section 4.8 of the SPC. The tabulation of subjects with Injection Site Adverse Experiences (>1% in one or more vaccination groups) indicate that the AE “Injection Site Bruising” occurs in 2,1% reports in the qHPV group and in 2.2% of the non-aluminium containing placebo vs 2.3% of the aluminium containing placebo. The injection site adverse reactions may be well covered by the remaining PTs. “Bruising” is most likely associated with the injection procedure rather than the nature of the injected product and would thus be considered to be an adverse effect of vaccination although very rarely occurring. Therefore, the CHMP considers that “bruising” should remain listed.

The follow-up of breast-fed infants of mothers vaccinated identifies more SAEs in the qHPV group compared to the placebo group. However, the excess of AEs in the qHPV group was not specific and not considered related to vaccination.

Use of qHPV vaccine did not impact overall pregnancy outcomes. Nor did administration of qHPV vaccine to nursing mothers affect the health of the mother or the nursing child. Rates of foetal loss

were slightly lower among subjects who received qHPV vaccine compared with the placebo groups. Slightly more foetuses/infants with congenital anomalies were observed in subjects who became pregnant in the qHPV vaccine group compared to the placebo group. However, the congenital anomalies that were observed were diverse and deemed to be highly unlikely related to the vaccine.

A comprehensive description of the reported arthritis/arthropathia cases has been provided. A causal relationship between these diagnoses and qHPV vaccination could not be proven in any of the cases. According to the cases narratives one case of arthritis was autoimmune in nature and one case was considered as reactive arthritis caused by an infection. One case reporting a low grade inflammatory arthropathy was an onset of rheumatoid arthritis and one case of "inflammatory joint" was later clarified as chondromalacia patellae. The present data do not indicate a direct connection between qHPV vaccination and arthritis/arthropathy. However, as these conditions may be considered as autoimmune reactions continuous close monitoring and cumulative presentation of such adverse events should be performed and all cases should be presented and discussed in future PSURs.

Among the systemic SAEs determined to be caused by the qHPV vaccine in the combined group and previously reported in MAA and Type II variations were vaginal haemorrhage and ulcerative colitis. However, only one case of gastroenteritis was reported as a related SAE in study 019. The possible mechanisms for these reactions have not been discussed.

Adverse experiences recommended for close monitoring shall be cumulatively reported on in the future PSURs. All autoimmune phenomena (including ulcerative colitis) as well as the events of the vaginal haemorrhage and gastroenteritis should be closely monitored. Vaccine safety in mid-adult women should be specifically addressed in future PSURs.

Regarding pregnancy, close safety surveillance is continuously ongoing as the MAH maintains pregnancy registries in the US, Canada and France. Nordic countries collect data on exposures to qHPV during pregnancy. Standardised incidence ratios on congenital anomalies will be calculated by comparing the observed and expected cases of congenital anomaly in women with inadvertent exposure to qHPV vaccine during pregnancy.
Studies in HIV infected children and adults are ongoing.

In conclusion, there was no new significant safety signal identified associated with the administration of the qHPV vaccine in mid-adult women in study 019, nor in the combined protocols safety analyses.

1.5 Pharmacovigilance system

1.5.1 Risk Management Plan

The MAH was requested by the CHMP to commit to perform long-term PMS surveillance in MAW.
The MAH committed to provide the study synopsis and to submit the study protocol.
A sentinel cohort of Protocol 019 participants is considered the best option for conducting long-term post-marketing surveillance in a cohort that has been vaccinated some years ago.
The CHMP acknowledged that this cohort study is the most relevant for follow-up of qHPV vaccine efficacy and immunogenicity.

The MAH committed to provide a revised RMP in December 2009.

In addition, there is a need to have an appropriate safety follow-up in the EU for the MAW population. Therefore, the MAH should continuously and cumulatively report vaccine safety in older women in future PSURs (see follow up measures).

1.6 Overall discussion and benefit-risk assessment

Efficacy

The claim of efficacy in MAW is based on one randomized controlled phase III efficacy trial (Protocol 019) including 3819 healthy sexually active 24- to 45-year old women. The median duration of follow-up for this study was 2.2 years. The main goal was to provide data to support that efficacy was comparable to that shown in young adult women (YAW). The MAH applied to extend the indication to MAW, including a statement in the indication that efficacy against premalignant genital lesions, cervical cancer and genital warts has been demonstrated in women up to the age of 45 years. Study 019 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) and one secondary endpoint HPV 6/11-related persistent infection and clinical disease. 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 in YAW was based on histologically-confirmed efficacy endpoints, i.e. HPV 16/18-related CIN 2/3 and AIS as surrogates for cervical cancer, whereas in P019 a virological endpoint, persistent infection (6-month) was used. The primary efficacy population (PPE) (HPV naïve) was defined similarly to that in all previous studies in YAW. Two further populations were defined that resembled the MITT-2 and MITT-3 populations used in the YAW studies: the HNRT and FAS population, respectively. The FAS (ITT) population included all women enrolled in the trial regardless of Day 1 HPV status, i.e. also those already infected or with clinical disease at baseline. No prescreening for HPV status was performed before study enrollment. At baseline 67% of MAW subjects were HPV naïve and, thus, susceptible to all 4 vaccine HPV types at study entry. Approximately 8% of MAW were infected (HPV DNA positive) with HPV 6, 11, 16 and/or HPV 18 at baseline.

In the HPV naïve PPE population vaccine efficacy was 90.5% (95% CI: 73.7, 97.5) against HPV 6/11/16/18-related persistent infection (PI)/disease, 87.1% (50.6, 95.8) against HPV 16/18-related PI/disease and 100% (79.0, 100) against HPV 6/11-related PI/disease. Efficacy against CIN 2/3 could not be shown in the PPE population due to few cases (1 vs. 4 placebo cases) (VE: 75.2% (95% CI -150.6, 99.5). In the HNRT population vaccine efficacy was lower 74.6% (58.1, 85.3), 71.6% (47.6, 85.5) and 80.2% (51.7, 93.3), respectively. Although P019 was not powered for disease endpoints (CIN 2/3), efficacy was only 25% in the HNRT population with 3 cases in the vaccine group and 4 cases in the placebo group. In the FAS (ITT) population, very low efficacy was noted for the HPV 6/11/16/18-related PI/disease endpoint (VE: 30.9% (11.1, 46.5) and for the more important HPV 16/18-related PI/disease endpoint only nominal reductions were seen (VE: 22.6% (-2.9, 41.9). Efficacy for the HPV 6/11 related endpoint was 47.1% (11.4, 69.2). With respect to vaccine HPV type-related CIN 2/3, no efficacy at all was observed, not even a trend (VE; 9.9%). The number of cases in the vaccine group was the same as in the placebo group.

In the initial assessment of this type II variation, two major objections were identified. The first objection concerned the indication of the qHPV vaccine, which covers all women regardless of HPV status and therefore the ITT (FAS) population was considered the most representative population for MAW. The primary efficacy population, the HPV naïve (PPE) population does not reflect the general population of MAW that will be vaccinated in clinical practice. The poor efficacy results observed in the FAS population did not support the MAH´s proposal to include a statement in the indication that efficacy had been demonstrated in 27-45 year old women. A second objection (safety) was also raised with respect to the results observed in the PCR positive/seronegative subpopulation suggesting a negative impact of the vaccine on on-going HPV infection/disease. In addition, several other concerns were raised in the RSI.

In the MAH´s response to the CHMP´s first Request for Supplementary Information the CHMP agreed that for demonstration of prophylactic efficacy, the PPE population is the optimal population. The results in study 019 showed significant efficacy in HPV naïve MAW and in similar magnitude as that shown in young adult women. However, this target HPV naïve population is difficult to identify among sexually experienced MAW and many non-naïve women will be vaccinated without deriving

little if any benefit. Therefore, the CHMP considered critical that the SPC and PI make it very clear to the prescribers and patients that efficacy cannot be expected in non-naïve women. In the indication referral should be made to section 4.4 (and section 5.1) where it should be stated that the vaccine is for prophylactic use only and that the vaccine is not effective against already established HPV infection/disease prior to vaccination. Furthermore, the MAH was requested to discuss all possible tools on which to select the target population and to discuss the possibility and usefulness of screening for HPV DNA status prior to vaccination.

With respect to the safety objection the MAH performed re-analyses and complementary analyses. Overall, the most significant finding was the inconsistent results observed in the PCR positive group depending on its serostatus, which would not be expected, other than as a result of multiple analyses on subgroups with small sample size. Importantly it is difficult to hypothesize a plausible mechanism for a negative effect of the vaccine on on-going HPV infections. In addition, the life table analysis of time-to-clearance of HPV 6 and HPV 16 infection showed no conspicuous difference between the vaccine and placebo groups. The "similar" findings in the young adult women as regards HPV 16/18-related CIN 2/3 in study 013 seemed to be an isolated event only seen in one study and one subset of the Day 1 PCR positive population and did not extend to the MAW population. It was concluded that the overall pattern was not consistent with a negative impact of the vaccine on prevalent HPV infections.
The issue whether the vaccine has a negative impact accelerating disease progression was further investigated in the FAS population. Data on the cumulative incidence of HPV 6/11/16/18-related CIN 2/3 was lower in the vaccine group than in the placebo group suggesting no acceleration of vaccine HPV type-related disease progression. In contrast, the opposite pattern was shown for CIN 2/3 due to any HPV type with higher incidence and a steeper curve by time in the vaccine group. This increase in the vaccine group could indicate the occurrence of type replacement disease. The findings raised major objections and the MAH was requested to scrutinise all relevant data and to perform formal statistical analyses to clarify this issue.

In the MAH´s response to the CHMP´s second Request for Supplementary Information, the major objection was only partly resolved. The higher incidence of CIN 2/3 or worse related to any HPV type in the qHPV vaccine group compared with the placebo group could be likely attributed to the baseline imbalance in prevalent infection related to non-vaccine HPV types. The data did not lend support to the hypothesis that the qHPV vaccine accelerates progression of disease. However, further analysis was requested as regards non-vaccine HPV types to fully clarify this issue. The results did not suggest type replacement disease due to the qHPV vaccine, but this issue needs to be closely monitored on a longer-term basis.
In response to the `other concerns´ it became clear that the MAH has no valid data to support the use of persistent infection related to HPV 6/11 as an efficacy endpoint. Therefore the MAH was requested to re-analyse results obtained in study 019 excluding all data on the HPV 6/11-related persistent infection.
Based on recent data, including the Koshiol et al meta analysis, persistent infection of 12 months duration appears to be the most valid endpoint to be used in clinical trials as a surrogate marker for cervical cancer. The MAH was further requested to address this issue and to provide available P019 data on 12 month persistent infection related to HPV 16/18.
The MAH´s evaluation of usefulness of possible pre-screening approaches of HPV status gave meagre positive incremental yield with respect to identifying women who would benefit from vaccination with the qHPV vaccine. The MAH was requested to address the issue of HPV vaccination resulting in missed cancers in mid-adult women due to false security of being protected against cervical cancer and subsequent failing attendance to the routine cervical screening. At the present time, with the increasing use of HPV assays it is not unreasonable that genotyping could be used as a pre-screening tool before vaccination of women above 30 years of age in countries where validated type-specific HPV techniques are available, to target vaccination to HPV 16/18 naïve MAW. The MAH was requested to address this issue.

The CHMP considered that efficacy has to be shown in the total population or it has to be possible to define the population which benefits in clinical practice. No efficacy was shown in the general population and pre-screening will be apparently a difficult option in clinical practice. Furthermore

vaccination of women who do not benefit is not acceptable and might lead to a false sense of security. Therefore, the CHMP considered that the indication should not be changed. CHMP recommended to revise sections 4.4 and 5.1 of the SPC to inform prescribers of the study results and that the use of Silgard in adult women should take into consideration the variability of HPV type prevalence in different geographical areas in the general population of 24- to 45-year-old women, and that no significant efficacy against HPV 16/18-related persistent infection and clinical disease has been demonstrated. The decision to vaccinate an individual woman 24-45 years old should take into account her risk for previous HPV exposure and her potential benefit from vaccination. The SPC was also revised to inform that Silgard is not effective in women already infected/diseased at the start of vaccination.

In the MAH´s response to the CHMP´s third Request for Supplementary Information, the major objection was resolved with the submission of supplementary data on cumulative incidence of CIN2/3 or worse related to 10 non-vaccine HPV types in women who were PCR positive to the relevant HPV type at Day 1. These results do not suggest a clinically significant acceleration of disease progression in the vaccine group compared to the placebo group, however this issue will be readdressed at end of study, month 48 results. The issue of pre-screening of women ≥30 years of age for HPV16/18 positivity prior to vaccination was resolved, since the low prevalence of these types (~2.6%) in older women makes this strategy highly cost-ineffective. The SPC already gives a clear message that continued attendance of cervical screening programs is critical. Furthermore, several paragraphs have been amended informing the prescribers that the qHPV vaccine is for prophylactic use only, that prevalence of HPV types and the women´s risk for previous HPV exposure should be taken into account in the decision to vaccinate mid-adult women. In addition, the indication remains unchanged and states that efficacy has only been demonstrated in young women 16 to 26 years of age. The CHMP considers these measures provide the necessary relevant information to prescribers. The reanalysis of the results of study P019 excluding the data on HPV 6/11 persistent infection showed that efficacy estimates decreased in the combined primary endpoint from 90.5% to 86.0%. Although the large Koshiol meta-analysis has some limitations, data on the natural course of HPV disease suggest that the 12-month persistent infection is a more reliable and robust predictor of progression to CIN 2/3+ than the 6-month persistent infection. Therefore in future study reports, the CHMP considered that data on 12 month persistent infection should also be included. The results of the analyses of study 019 using a 12 month persistent infection showed that efficacy estimates against HPV 16/18-related persistent infection and against the combined primary endpoint were in the same order of magnitude, although with wider confidence intervals, as the results of the analyses using the 6-month persistent infection.

Overall, the CHMP considered that efficacy has to be shown in the total population or it has to be possible to define the population which benefits in clinical practice. Since no statistically significant efficacy was shown in the general population and pre-screening will be a difficult option in clinical practice, the CHMP did not endorse the MAH´s extension of indication to include a statement in section 4.1 of the SPC that efficacy had been demonstrated in 27-45 year old women. With the indication remaining unchanged and with the SPC revisions reflecting the results of study 019 and providing the relevant information to prescribers to decide on the vaccination of individual woman 27 to 45 years old the CHMP considered that the major objections were resolved,

Immunogenicity

The immunogenicity data in study 019 showed that the vaccine-induced immune responses in MAW were inferior to those observed in adolescents and young women, with a 2 to 3 fold lower GMTs postdose 3 in MAW. The low Month 24 GMTs and seropositivity rate for HPV 18 raise concern. The consequence of these lower antibody responses in the MAW population for the durability of vaccine efficacy is not known, since no immunological correlate of protection has been defined. Among MAW who were seropositive to vaccine HPV types at Day 1, vaccine induced immune response to the types for which they were positive were comparable to those observed among YAW who were seropositive to the same type at Day 1. These results suggest that adult women can mount anamnestic responses that appear as robust as those observed in YAW. Such anamnestic responses are critical to the durability of the efficacy of vaccines in general, but whether the immune memory induced by the qHPV vaccine will be sufficient to protect against HPV infection in subjects who have lost seropositivity, remains to be shown. At the current stage after a relatively short duration of follow-up

(2.2 years), no obvious breakthrough infections in study 019 have been documented. However, long-term follow-up of efficacy and immunogenicity in MAW is mandatory. The MAH has committed to conduct a long-term follow-up study of immunogenicity and vaccine efficacy in a sentinel cohort (n=1600) in study 019. Furthermore, section (section 5.1) of the SPC was modified to inform prescribers on results for anti-HPV 18 seropositivity.
In the MAH`s response to the CHMP Request for Supplementary Information, the majority of immunogenicity concerns were resolved. However, it was clarified that the currently used serological cLIA assay might 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 has committed to perform serological studies using broader neutralization assays, i.e. pseudo-neutralization assays, as well as to submit the validation protocol and final results using the newly developed assay measuring the VLP-specific total IgG. Relevant study reports were submitted on April 28, 2009 and are currently under assessment.

Safety
According to the new information presented in the current application the administration of qHPV vaccine was found to be generally well tolerated across all populations.

The proportions of subjects who reported SAEs or who discontinued due to a SAE were low and comparable between the vaccination groups. Vaccine-related SAEs occurred in <1% of the subjects. No safety signals were identified with the exception of increased incidences of transient injection-site adverse experiences and low-grade fever following vaccination. Reporting adverse events was similar in the different age ranges except for the higher frequency of pain in the extremity in older subjects and somewhat higher frequency of erythema and swelling in the younger age range. The MAH proposed to delete “Injection-site bruising” from section 4.8 of the SPC since the incidence of this AE was shown to be low and very rarely occurring. Bruising most likely is associated with the injection procedure rather than the nature of the injected product and though is considered to be an adverse effect of vaccination. Therefore, the CHMP considers that “bruising” should remain listed in the SPC.
The follow-up of breast-fed infants of mothers vaccinated identifies more SAEs in the qHPV group compared to the placebo group. However the excess of AEs in the qHPV group was not specific and not considered related to vaccination.
Use of qHPV vaccine did not impact overall pregnancy outcomes. Nor did administration of qHPV vaccine to nursing mothers affect the health of the mother or the nursing child. Rates of foetal loss were slightly lower among subjects who received qHPV vaccine compared with the placebo groups. Slightly more foetuses/infants with congenital anomalies were observed in subjects who became pregnant in the qHPV vaccine group compared to the placebo group. However, the congenital anomalies that were observed were diverse and deemed to be highly unlikely related to the vaccine.
In conclusion all autoimmune phenomena (including ulcerative colitis) as well as the events of vaginal haemorrhage and gastroenteritis should be closely monitored and cumulatively reported on in the future PSURs.

The most frequently reported new medical condition potentially indicative of an autoimmune phenomenon as well as arthritis/arthropathy in temporal relationship with qHPV should be specifically watched over. Furthermore, concerning pregnancy, close safety surveillance is continuously ongoing as the MAH maintains pregnancy registries in the US, Canada and France. Nordic countries collect data on exposures to qHPV during pregnancy. Standardised incidence ratio on congenital anomalies should be analysed and calculated by comparing the observed and expected cases of congenital anomaly in women with inadvertent exposure to qHPV vaccine during pregnancy.

In conclusion, the benefit risk balance of Silgard remains favorable in the current therapeutic indication, and the changes of the SPC reflect relevant study results in mid-adult woman for prescribers.

1.6 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:

SPC

Section 4.1 "Therapeutic indication"
The MAH's initially proposed to extend the age of indication for women up to 45 years old, based on submission of study 019.
The claims for the requested indication were not accepted by the CHMP and were withdrawn by the MAH. This section remains unchanged.

Section 4.2 "Posology and method of administration"
The CHMP requested to replace the wording "not recommended" by "there is no experience" to better reflect the information on children below 9 years of age.

Section 4.4 "Special warnings and precautions for use"

This section was revised upon CHMP request to reinforce the message that Silgard is for prophylactic use only and has no effect on active HPV infections or established clinical disease and to make clear that Silgard does not prevent lesions due to a vaccine HPV type in women already infected with that HPV type at the time of vaccination. A cross reference to section 5.1 was included.

Furthermore a paragraph was included to guide prescribers on the decision to vaccinate an individual woman 27 to 45 years old as follows:
The use of Silgard in adult women should take into consideration the variability of HPV type prevalence in different geographical areas. In the clinical study of adult women (24 to 45 years of age), no statistically significant vaccine efficacy was observed after 2.2 years of follow-up in the full analysis set that includes women regardless of baseline HPV status (see section 5.1). The decision to vaccinate an individual woman 27 to 45 years old should take into account her risk for previous HPV exposure and her potential benefit from vaccination.

Section 4.5 "Interaction with other medicinal products and other forms of interaction"
The MAH proposal to update the numbers on MAW using hormonal contraceptives was endorsed by the CHMP.

Section 4.6 "Pregnancy and lactation"
The MAH proposal to update 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.
The inclusion of the adverse reaction pain in the extremity as common was endorsed by the CHMP.
The CHMP did not endorse the MAH proposal to delete "Injection-site bruising".

Section 5.1 "Pharmacodynamic properties"
<u>Efficacy in woman 24 through 45 years.</u>
The wording was revised taking into consideration the following:
The proposed paragraph on vaccine efficacy in MAW in line with the young adult women was revised to mention the efficacy results in HPV naïve women and in the overall population women (ITT). The ITT population is the most representative population targeted in the indication. Data on efficacy results in the two co-primary endpoints were included of which the HPV 16/18-related infection and disease endpoint is considered the most important.
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The number of women included in P019 was included as well as the duration of follow-up.

Reference to vulvar and vaginal cancers were removed since vaccine efficacy in these cancers has not been demonstrated.

Immunogenicity
Since the CHMP considered important to inform prescribers on results for anti-HPV 18 seropositivity, a paragraph was introduced to include the observed reduced percentage of vaccinated individuals who remained seropositive (analysed per subtype) after a median follow up of 2.2 years.

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

PL
The PL was updated with minor linguistic changes.

The MAH has agreed with the changes as proposed by the CHMP.

IV. CONCLUSION

On 23 July 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet, based of the additional commitments undertaken as clarified below.

VI. GLOSSARY

1. AAHS – Amorphous Aluminum Hydrxyphosphate Sulfate
2. AE – Adverse event
3. AIS – Cervical Adenocarcinoma in situ
4. CHMP – Committee for medical products for human use
5. CIN – Cervical Intraepithelial Neoplasia
6. CI – Confidence Interval
7. cLIA – Competitive Luminex Assay
8. EGL – External genital lesions
9. EMEA – European Medicines Agency
10. FAS – Full Analysis Set
11. FUTURE – Females United To Unilaterally Reduce Endo/Ectocervical Disease
12. HPV – Human Papilloma virus
13. HNRT – HPV-Naïve to the Relevant-HPV-Type
14. LEEP – Loop Electrosurgical Excision Procedure
15. LLOQ – Lower Limit Of Quantification
16. MAA – Marketing authorisation application
17. MAH – Marketing authorisation holder
18. MAW– Mid-Adult Women
19. mMU/ml – Milli-Merck Units per millilitre.
20. Pap – Papanicolau´s test
21. PCR – Polymerase chain reaction
22. PI – Persistent Infection
23. PL – Package Leaflet
24. PPE – Pre-protocol Efficacy
25. PPI – Per-Protocol immunogenicity
26. qHPV – Quadrivalent HPV vaccine
27. SIL – Squamous Intraepithelial Lesion
28. SPC – Summary of Product Characteristics
29. STD – Sexual transmitted diseases
30. VaIN – Vaginal intraepithelial neoplasia
31. VE – Vaccine efficacy
32. VIN – Vulvar intraepithelial neoplasia
33. VLP – Virus-like particles
34. YAW – Young Adult Woman
35. LR – Likelihood ratio
36. PPV – Positive predictive value.
37. MITT – Modified Intention to Treat-
38. SAES – Serious adverse events
39. PTS – Preferred terms
40. AES –Adverse events
41. RSI – Request for Supplementary information
42. FUM – Follow up measure