European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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**ASSESSMENT REPORT**
**FOR**
**SILGARD**

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

**Procedure No: EMEA/H/C/000732/II/0012**

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

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# I. SCIENTIFIC DISCUSSION

## 1.1 Introduction

Silgard is a quadrivalent (HPV Types 6, 11, 16 and 18) recombinant HPV vaccine (qHPV) that was licensed on 24 September 2006 for the prevention of high-grade cervical and vulvar dysplasia, cervical cancer and external genital warts causally related to the vaccine HPV types. The dose schedule includes 3 intramuscular 0.5 ml doses administered at 0, 2, 6 months. The approval was based on two pivotal phase III trials after a mean follow-up of two years. The approved indication in 2006 is as follows:

*"Silgard is a vaccine for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.*

*The indication is based on the demonstration of efficacy of Silgard in adult females 16 to 26 years of age and on the demonstration of immunogenicity of 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 Silgard should be in accordance with official recommendations."*

The present type II variation application concerns an extension of the indication to include protection against:

- vulvar and vaginal cancer;
- low-grade vulvar (VIN 1) dysplasia;
- high-grade and low-grade vaginal (VaIN 1/2/3) dysplasia;
- low-grade cervical dysplasia (CIN 1);

based on updated efficacy and safety data (3-year data) from the pivotal phase III studies (FUTURE I and II) as well as post-marketing experience. Compared with the database that supported the marketing authorisation application (MAA), this application includes ~ 1 more year of follow-up in the phase III program.

The present application has the following objectives:

- Update vaccine efficacy (VE) with respect HPV6/11/16/18-related cervical, vulvar and vaginal dysplasia
- Update VE with respect HPV16/18-related VaIN 2/3
- Update the rationale for inclusion of CIN 1 in the therapeutic indication
- Update VE with respect HPV16/18-related cervical, vulvar and vaginal cancer (via surrogate markers)
- Update the duration of VE with respect to HPV6/11/16/18-related cervical, vulvar and vaginal pre-cancerous lesions
- Evaluate HPV type replacement

## 1.2 Clinical aspects

HPV infection is the most common sexually transmitted disease worldwide. Approximately 50% of sexually active adults become infected with HPV during their lifetime. HPV infection can cause pre-cancerous dysplastic lesions and cancer of the cervix, vagina, vulva, anus, and external genital skin, as well as benign genital and respiratory tumors (condyloma acuminata and Recurrent Respiratory Papillomatosis (RRP), respectively). An overview is given below concerning the new proposed indications by the MAH.

**Cervical Cancer**
Cervical cancer is the second most common cause of cancer deaths in women worldwide resulting in approximate 493,000 new cases and 274,000 deaths each year. HPVs are judged to be the primary cause of cancer, detected in over 99% of cervical cancers. In the year 2004 the International Agency for Research on Cancer estimated that cervical cancer was diagnosed in approximately 34 300 women in the 27 member states of the European Union and about 16 300 women died from the disease. It is estimated that within the European population each year there are ~33,000 women diagnosed with cervical cancer and 15,000 deaths from this disease. Organised cervical cancer screening programs have reduced cancer rates by ~75% in the developed world. The success of Pap testing has shifted the burden associated with HPV disease from managing the morbidity and mortality of cervical cancer to managing a large number of premalignant and other HPV-associated lesions (Cervical Intraepithelial Neoplasia (CIN) grades 1, 2, 3).

**Low-grade cervical dysplasia (CIN 1)**
CIN 1 is the most frequent HPV-related dysplastic lesion of the cervix. The potential for CIN 1 to progress to CIN 2/3 or cervical cancer is low, but the health and economic consequences of these lesions are substantial. The lifetime risk of acquiring CIN 1 (17 %) is four times that of CIN 2/3 or AIS (4%) in places where cervical cancer screening programs are established. In all of Europe, it is estimated that 817,000 women are newly diagnosed with low grade cervical lesions (CIN 1) each year. Most CIN 1 lesions regress to normal but it is not possible to differentiate those lesions that will persist and progress to CIN 2/3 from those that will regress. All women with CIN 1 require close follow-up, including repeated diagnostic biopsies.

**Other HPV related cancers**
Other HPV-related cancers include vulvar and vaginal cancers that occur predominantly in young women and result in ~1600 deaths in the US each year. They are preceded by dysplastic lesions (vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN). In men, anal cancer is the most common HPV-related cancer with 5000 cases reported annually in the US. Also penile and certain oral cancers are caused by the virus. Other benign HPV-associated conditions include condyloma acuminata (genital warts) located in the genital or perianal region and juvenile RRP primarily located in the larynx. RRP is thought to occur by transmission of the virus from an infected mother to her child.

**Vulvar cancer and vulvar intraepithelial neoplasia (VIN)**
Vulvar cancer accounts for 3 to 5% of all gynecologic cancer cases. Data on the exact burden of vulvar cancer in Europe are not presently available, but in the US in 2005, it has been estimated that approximately 3870 women would be diagnosed with vulvar cancer and 870 women would die from the disease. Up to 90% of vulvar cancers are squamous cell carcinomas. Vulvar cancer can be HPV-Related (typically occurs in women under the age of 65) and non-HPV-Related (typically occurs in women >65 years).
HPV-related vulvar cancer accounts for 15 to 50% of cases of vulvar cancer.

**Vaginal cancer and vaginal intraepithelial neoplasia (VaIN)**
Vaginal cancer accounts for 1 to 2% of all gynecologic cancer cases. In the US in 2005, ~2140 women were estimated to be diagnosed with vaginal cancer and 800 women would die from the

disease. Data on the exact burden of vaginal cancer in Europe is not presently available. In 2005, in the UK there were 223 new diagnoses of vulvar cancer and 100 deaths from this disease.

### 1.2.1 Clinical efficacy

The clinical development program for Silgard was designed to measure the impact of the vaccine on the cervical cancer risk using a composite endpoint of CIN 2/3, adenocarcinoma in situ (AIS) and cervical cancer. The primary goal was to evaluate vaccine impact on the incidence of HPV 16/18-related CIN 2/3, AIS or cervical cancer. A secondary goal was to evaluate vaccine impact on the overall incidence of CIN 2/3, AIS or cervical cancer.

## Main studies

The clinical efficacy program for Silgard included 4 randomised, double-blind, placebo-controlled phase II and phase III clinical studies (for details about studies see table 1). Phase II studies included protocol 005 (evaluated the HPV 16 component of Silgard) and protocol 007. Phase III studies, included FUTURE I (Protocol 013) and FUTURE II (Protocol 015). Altogether these 4 studies randomised 20,887 16- to 26-year-old adolescent and young adult women, of whom 20,845 subjects received at least one dose of study vaccine (Silgard, HPV 16 L1 VLP vaccine component of Silgard, or placebo). Protocol 005 was complete at the time of the marketing authorisation. Protocols 007-10, 013, and 015 were ongoing in the efficacy follow-up phase at the time of the marketing authorisation.

**Table 1: Overview of clinical efficacy studies**

| 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 |
|---|---|---|---|---|---|
| **P005**<br>Phase IIb | USA (n=16 sites)<br><br>1998 - 2004 | HPV 16 L1 VLP vaccine (40mcg)/ placebo<br><br>(1193 / 1198) | N=2,409<br><br>16- to 23-year-old women | 1. Safety and tolerability of vaccine<br>2. Efficacy in prevention of persistent HPV 16 infection vs placebo | Mean: 3.1 years<br><br>Median: 3.9 years |
| **P007**<br>Phase IIb<br>Dose-ranging study | USA, Europe Latin America<br>(n=23 sites)<br><br>2000 - 2004 | qHPV VLP vaccine (20/40/40/20mcg 40/40/40/20mcg 80/80/40/20mcg) / placebo<br><br>Part A n=52<br>Part B n=1106 | N=1,158<br><br>16- to 23-year-old women | *Part A:* General tolerability<br>*Part B:*<br>1. Identify formulations with acceptable type specific anti-HPV responses<br>2. Efficacy in prevention of persistent HPV 6,11, 16, 18 infection and clinical disease cf placebo<br>3. General tolerability | Mean: 2.4 years<br>Median: 3.0 years<br>Prot. 7-10<br>Mean: 4.5 years<br>Median: 4.9 years |
| **P013**<br>Phase III<br><br>**FUTURE I** | North America, Latin America, Europe, Asia-Pacific<br>(n=32 sites)<br><br>2001 - 2005 | qHPV VLP vaccine 20/40/40/20mcg / Placebo<br><br>(2717 / 2725) | N=5,455<br><br>16- to 23-year-old women | Co-primary endpoints:<br>i) External genital lesion: efficacy in reducing HPV 6,11,16,18-related EGL (=genital warts, VIN, VaIN, vulvar or vaginal cancer) cf placebo<br>ii) Cervical endpoint: efficacy in reducing the incidence of HPV 6,11, 16,18-related CIN (any grade), AIS or cervical cancer cf placebo<br>- Safety and tolerability | Mean: 1.7 years<br>Median: 2.4 years<br><br>Updated Mean: 2.4 years<br>Median: 2.9 years |
| **P015**<br>Phase III<br><br>**FUTURE II** | North America, Latin America, Europe, Asia-Pacific<br>(n=90 sites)<br><br>2002 - 2005 | qHPV VLP vaccine 20/40/40/20mcg / Placebo<br><br>(6082 / 6075) | N=12,167<br><br>16- to 26 -year-old women | Primary Cervical endpoint: efficacy in reducing the incidence of HPV 6,11,16,18-related CIN 2/3, AIS or invasive cervical cancer in HPV naïve subjects | Mean: 1,4 years<br>Median: 2.0 years<br><br>Updated Mean: 2.4 years<br>Median: 2.9 years |

**Study populations**

Per-protocol efficacy (PPE) population:

- 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 at Day 1 and at Month 7
- Did not deviate from the protocol
- Cases counted starting 30 days post-dose 3 (Month 7)

The Per-protocol efficacy (PPE) population was used as the primary analysis population for efficacy and includes subjects naïve to relevant vaccine HPV types.

MITT-populations (modified intention to treat populations):

- MITT-2 population
- Restricted MITT-2 (R-MITT2)
- MITT-3 population: general population (ITT)

Two MITT populations were used for the analysis of efficacy with respect to the population benefit endpoints (i.e., evaluation of the impact of Silgard on the incidence of disease caused by vaccine or non-vaccine HPV types). Importantly, these populations differ from those in the marketing authorisation application with respect to the extent of HPV type testing. This updated report, include additional testing for 10 common non-vaccine HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) in all swabs and tissue specimens obtained during the phase II studies.

MITT-2 population

- Received at least one dose of study vaccine
- Were seronegative and PCR-negative to all 4 vaccine HPV types at Day 1
- Were PCR-negative at Day 1 to the appropriate non-vaccine HPV type (31, 33, 35, 39, 45, 51, 52, 56, 58, or 59) or had a negative Day 1 Pap test result
- Had at least one follow-up visit after 1 month following the first injection
- Cases were counted starting after Day 30

This population represents virginal HPV naïve young women but who could be infected with HPV before or after the completion of the vaccination period.

Restricted MITT-2 (R-MITT2)

- Received at least one dose of study vaccine
- Were seronegative and PCR negative to all 4 vaccine HPV types at Day 1
- Were PCR negative to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 at Day 1 and had a negative Pap test result at Day 1
- Had at least one follow-up visit after 1 month following the first injection
- Cases were counted starting after Day 30

The RMITT-2 was designed to approximate a population of adolescent and young adult women who were either sexually-naïve or sexually-experienced and had not yet been exposed to *any* HPV type but who could be infected with HPV before or after the completion of the vaccination period.

MITT-3 population: general population (ITT)

- Received at least one dose of study vaccine
- Regardless of PCR status at Day 1
- Cases counted starting 30 days after Day 1

Compared with the main analysis populations, the MITT-3 population also includes subjects who were already infected with a vaccine or non-vaccine HPV type at Day 1 and subjects who had evidence of CIN at Day 1 (e.g., an abnormal Pap test at Day 1). Such a population approximates the general population of sexually-active 16- to 26-year-old girls and provides a real world estimate of efficacy in the vaccinated population.

### 1.2.1.1 Protocol 13

**Cervical lesions**

➢ ***Primary efficacy analysis***

Efficacy results obtained in the primary analyses with respect to HPV 6/11/16/18-related CIN (any grade), AIS or cervical cancer in the different studied populations are shown in Table 2. No cases of cervical cancer were reported in study 013.

**Table 2: Analysis of efficacy against HPV 6/11/16/18-related CIN by study population (P013)**

| Study population<br>Endpoint | Silgard N=2717 | | Placebo N=2725 | | Observed efficacy % | 95% CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **PPE** | | | | | | |
| **HPV 6/11/16/18 CIN** | **2241** | **0** | **2258** | **65** | **100.0** | **94.2, 100** |
| *By HPV type* | | | | | | |
| HPV 6 | 1961 | 0 | 1975 | 12 | 100.0 | 64.0, 100 |
| HPV 11 | 1961 | 0 | 1975 | 4 | 100.0 | 52.7, 100 |
| HPV 16 | 1888 | 0 | 1847 | 39 | 100.0 | 90.3, 100 |
| HPV 18 | 2102 | 0 | 2120 | 16 | 100.0 | 74.1, 100 |
| *By disease severity* | | | | | | |
| CIN 1 | 2241 | 0 | 2258 | 49 | 100.0 | 92.2, 200 |
| ***CIN 2 or worse*** | ***2241*** | ***0*** | ***2258*** | ***32*** | ***100.0*** | ***87.8, 100*** |
| CIN 2 | 2241 | 0 | 2258 | 21 | 100.0 | 80.7, 100 |
| CIN 3 | 2241 | 0 | 2258 | 17 | 100.0 | 75.7, 100 |
| AIS | 2241 | 0 | 2258 | 6 | 100.0 | 14.8, 100 |
| **MITT-2** | | | | | | |
| **HPV 6/11/16/18 CIN** | **2557** | **2** | **2573** | **89** | **97.8** | **91.7, 99.7** |
| *By HPV type* | | | | | | |
| HPV 6 | 2280 | 1 | 2305 | 17 | 94.1 | 62.5, 99.9 |
| HPV 11 | 2280 | 0 | 2305 | 7 | 100.0 | 30.6, 100 |
| HPV 16 | 2158 | 0 | 2170 | 53 | 100.0 | 92.8, 1000 |
| HPV 18 | 2423 | 1 | 2450 | 22 | 95.5 | 71.9, 99.9 |
| *By disease severity* | | | | | | |
| CIN 1 | 2557 | 2 | 2573 | 68 | 97.1 | 89.0, 99.7 |
| ***CIN 2 or worse*** | ***2557*** | ***0*** | ***2573*** | ***43*** | ***100.0*** | ***91.0, 100*** |
| CIN 2 | 2557 | 0 | 2573 | 28 | 100.0 | 85.9, 100 |
| CIN 3 | 2557 | 0 | 2573 | 24 | 100.0 | 83.9, 100 |
| AIS | 2557 | 0 | 2573 | 6 | 100.0 | 15.1, 100 |
| **MITT-3** | | | | | | |
| **HPV 6/11/16/18 CIN** | **2607** | **69** | **2611** | **154** | **55.8** | **40.9, 67.2** |
| *By HPV type* | | | | | | |
| HPV 6 | 2607 | 5 | 2611 | 26 | 80.9 | 49.5, 94.3 |
| HPV 11 | 2607 | 0 | 2611 | 11 | 100.0 | 60.6, 100 |
| HPV 16 | 2607 | 57 | 2611 | 106 | 46.7 | 25.8, 62.1 |
| HPV 18 | 2607 | 8 | 2611 | 32 | 75.2 | 45.0. 90.1 |
| *By disease severity* | | | | | | |
| CIN | 2607 | 43 | 2611 | 117 | 63.7 | 48.2, 75.1 |
| ***CIN 2 or worse*** | ***2607*** | ***52*** | ***2611*** | ***80*** | ***35.4*** | ***7.3, 55.3*** |
| CIN 2 | 2607 | 36 | 2611 | 51 | 29.9 | -9.6, 55.5 |
| CIN 3 | 2607 | 39 | 2611 | 44 | 11.8 | -38.9, 44.2 |
| AIS | 2607 | 1 | 2611 | 6 | 83.4 | -36.5, 99.6 |

Efficacy against HPV 6/11/16/18-related CIN (any grade) was 100% in the PPE population. Altogether, there were 17 CIN 3 cases and 6 AIS cases in the placebo group versus none in the vaccine group resulting in efficacy of 100% for both these high-grade lesion types and with the lower bound of the 95% CIs above 0%. Efficacy was comparable across HPV types. The results in the MITT-2 population supported the PPE analysis. The case of HPV 18-related CIN 1 in the vaccine group of the MITT-2 population was described in the MAA.

The efficacy estimates in the MITT-3 population were substantially lower, which could be expected since this population included cases already infected at baseline. The variations in percent reductions for disease by HPV 6, 11, 16 or HPV 18 were correlated with the baseline prevalence of infection with individual HPV type. The lowest effect was observed for HPV 16, which was most prevalent among the vaccine HPV types. Vaccine efficacy against HPV 6/11//16/18-related CIN 2/3, AIS was increased compared to the MAA, 35% (95% CI: 7, 55) vs. 23% (95% CI: <0, 48). However, by lesion type, statistical significance with respect to efficacy against CIN 2 or CIN 3 lesions was not reached (lower 95% CIs were <0%).

➢ ***Secondary efficacy analysis***

The efficacy of the vaccine against the combined incidence of HPV 16- or HPV 18-related CIN or AIS is shown in Table 3.

**Table 3: Analysis of efficacy against HPV 16/18-related CIN (of any grade) or AIS (PATC)**

| | Silgard N=2717 | | Placebo N=2725 | | | |
|---|---|---|---|---|---|---|
| **Study population Endpoint** | **n** | **Number of cases** | **n** | **Number of cases** | **Observed efficacy %** | **95 % CI** |
| **PPE** | | | | | | |
| **HPV 16/18 CIN** | **2201** | **0** | **2222** | **52** | **100.0** | **92.6, 100** |
| *By HPV type* | | | | | | |
| HPV 16 | 1888 | 0 | 1847 | 39 | 100.0 | 90.3, 100 |
| HPV 18 | 2102 | 0 | 2120 | 16 | 100.0 | 74.1, 100 |
| *By disease severity* | | | | | | |
| CIN 1 | 2102 | 0 | 2222 | 38 | 100.0 | 89.8, 200 |
| ***CIN 2/3 or worse*** | ***2102*** | ***0*** | ***2222*** | ***30*** | ***100.0*** | ***86.9, 100*** |
| CIN 2 | 2102 | 0 | 2222 | 20 | 100.0 | 79.7, 100 |
| CIN 3 | 2102 | 0 | 2222 | 16 | 100.0 | 74.0, 100 |
| AIS | 2102 | 0 | 2222 | 6 | 100.0 | 14.7, 100 |
| **MITT-2** | | | | | | |
| **HPV 16/18 CIN** | **2518** | **2** | **2538** | **71** | **98.6** | **91.9, 100** |
| *By HPV type* | | | | | | |
| HPV 16 | 2158 | 0 | 2176 | 53 | 100.0 | 92.8, 1000 |
| HPV 18 | 2423 | 1 | 2450 | 22 | 95.5 | 71.9, 999 |
| *By disease severity* | | | | | | |
| CIN 1 | 2518 | 1 | 2538 | 51 | 98.0 | 88.6, 100 |
| ***CIN 2/3 or worse*** | ***2518*** | ***0*** | ***2538*** | ***41*** | ***100.0*** | ***90.6, 100*** |
| CIN 2 | 2518 | 0 | 2538 | 26 | 100.0 | 84.8, 100 |
| CIN 3 | 2518 | 0 | 2538 | 24 | 100.0 | 83.4 100 |
| AIS | 2518 | 0 | 2538 | 6 | 100.0 | 15.0, 100 |
| **MITT-3** | | | | | | |
| **HPV 16/18 CIN** | **2607** | **65** | **2611** | **128** | **49.7** | **31.7, 63.3** |
| *By HPV type* | | | | | | |
| HPV 16 | 2607 | 57 | 2611 | 106 | 46.7 | 25.8, 62.1 |
| HPV 18 | 2607 | 8 | 2611 | 32 | 75.2 | 45.0. 90.1 |
| *By disease severity* | | | | | | |
| CIN 1 | 2607 | 39 | 2611 | 92 | 58.1 | 38.4, 71.9 |
| ***CIN 2/3 or worse*** | ***2607*** | ***52*** | ***2611*** | ***77*** | ***32.9*** | ***3.3, 53.7*** |
| CIN 2 | 2607 | 36 | 2611 | 48 | 25.5 | -17.3, 53.0 |
| CIN 3 | 2607 | 39 | 2611 | 44 | 11.8 | -38.9, 44.2 |
| AIS | 2607 | 1 | 2611 | 6 | 83.4 | -36.5, 99.6 |

In the secondary analysis of efficacy against HPV 16/18-related CIN lesions, high efficacy (100%) against CIN of all grades was demonstrated in the PPE population. However, in the MITT-3 population, the vaccine estimates were substantially lower; VE against CIN 2/3 was 33% (95% CI: 3.3, 53.7). By lesion, for CIN 2, CIN 3 and AIS only numerical reductions were seen.

The vaccine estimates were comparable between the current and MAA report and there was no evidence of waning immunity.

**External genital lesions**

➢ ***Co-primary efficacy analysis-HPV 6/11/16/18-related EGL***

The co-primary efficacy analysis with respect to HPV 6/11/16/18-related external genital lesions is shown in Table 4.

**Table 4: Analysis of efficacy against HPV6/11/16/18-related EGL (P013)**

| Study population Endpoint | Silgard N=2717 | | Placebo N=2725 | | Observed efficacy % | 95% CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **PPE** | | | | | | |
| **HPV 6/11/16/18 EGL** | **2261** | **0** | **2279** | **60** | **100.0** | **93.7, 100** |
| *By HPV type* | | | | | | |
| HPV 6 | 1978 | 0 | 1991 | 41 | 100.0 | 90.6, 100 |
| HPV 11 | 1978 | 0 | 1991 | 12 | 100.0 | 63.[illegible], 100 |
| HPV 16 | 1890 | 0 | 1855 | 12 | 100.0 | 6[illegible].7, 100 |
| HPV 18 | 2120 | 0 | 2136 | 3 | 100.0 | -[illegible]3.[illegible], 100 |
| *By disease severity* | | | | | | |
| Condyloma | 2261 | 0 | 2279 | 48 | 100.0 | 92.0, 100 |
| Vulvar condyloma | 2261 | 0 | 2279 | 47 | 100.0 | 91.8, 1000 |
| Vaginal condyloma | 2261 | 0 | 2279 | 6 | 100.0 | 14.4, 100 |
| VIN 1 or VaIN 1 | 2261 | 0 | 2279 | 9 | 100.0 | 49.0, 100 |
| VIN 1 | 2261 | 0 | 2279 | 4 | 100.0 | -52.8, 100 |
| VaIN 1 | 2261 | 0 | 2279 | 5 | 100.0 | -10.0, 100 |
| VIN 2/3 or VaIN 2/3 | 2261 | 0 | 2279 | 9 | 100.0 | 48.9, 100 |
| VIN 2/3 | 2261 | 0 | 2279 | 5 | 100.0 | -10.0, 100 |
| VaIN 2/3 | 2261 | 0 | 2279 | 4 | 100.0 | -52.8, 100 |
| **MITT-2** | | | | | | |
| **HPV 6/11/16/18 EGL** | **2620** | **4** | **2628** | **81** | **95.1** | **86.9, 98.7** |
| *By HPV type* | | | | | | |
| HPV 6 | 2334 | 2 | 2352 | 53 | 96.2 | 86.9, 98.7 |
| HPV 11 | 2334 | 1 | 2352 | 17 | 94.1 | 62.3, 99.9 |
| HPV 16 | 2215 | 1 | 2215 | 17 | 94.1 | 62.5, 99.9 |
| HPV 18 | 2480 | 0 | 2502 | 8 | 100.0 | 41.0, 100 |
| *By disease severity* | | | | | | |
| Condyloma | 2620 | 3 | 2628 | 67 | 95.9 | 86.4, 99.1 |
| Vulvar condyloma | 2620 | 2 | 2628 | 65 | 96.9 | 88.5, 99.6 |
| Vaginal condyloma | 2620 | 1 | 2628 | 8 | 87.5 | 6.5, 99.7 |
| VIN 1 or VaIN 1 | 2620 | 2 | 2628 | 11 | 81.8 | 16.4, 98.0 |
| VIN 1 | 2620 | 2 | 2628 | 4 | 49.8 | -250.4, 95.5 |
| VaIN 1 | 2620 | 0 | 2628 | 7 | 100.0 | 30.4, 100 |
| VIN 2/3 or VaIN 2/3 | 2620 | 1 | 2628 | 11 | 90.9 | 37.2, 99.8 |
| VIN 2/3 | 2620 | 1 | 2628 | 6 | 83.3 | -37.9, 99.6 |
| VaIN 2/3 | 2620 | 0 | 2628 | 5 | 100.0 | -9.6, 100 |
| **MITT-3** | | | | | | |
| **HPV 6/11/16/18 EGL** | **2671** | **27** | **2668** | **102** | **73.8** | **59.7, 83.6** |
| *By HPV type* | | | | | | |
| HPV 6 | 2671 | 19 | 2668 | 70 | 77.0 | 62.2, 86.0 |
| HPV 11 | 2671 | 2 | 2668 | 19 | 89.5 | 56.5, 98.8 |
| HPV 16 | 2671 | 6 | 2668 | 22 | 72.8 | 30.9, 91.0 |
| HPV 18 | 2671 | 1 | 2668 | 9 | 88.9 | 20.0, 99.7 |
| *By disease severity* | | | | | | |
| Condyloma | 2671 | 20 | 2668 | 86 | 77.0 | 62.2, 86.6 |
| Vulvar condyloma | 2671 | 18 | 2668 | 82 | 78.3 | 63.5, 87.7 |
| Vaginal condyloma | 2671 | 2 | 2668 | 10 | 80.0 | 6.4, 97.9 |
| VIN 1 or VaIN 1 | 2671 | 6 | 2668 | 16 | 62.6 | -0.6, 88.0 |
| VIN 1 | 2671 | 5 | 2668 | 7 | 28.7 | -161.0, 82.2 |
| VaIN 1 | 2671 | 1 | 2668 | 9 | 88.9 | 20.0, 99.7 |
| VIN 2/3 or VaIN 2/3 | 2671 | 5 | 2668 | 13 | 61.6 | -14.7. 89.3 |
| VIN 2/3 | 2671 | 5 | 2668 | 8 | 37.6 | -116.3, 83.9 |
| VaIN 2/3 | 2671 | 0 | 2668 | 6 | 100.0 | 15.2, 100 |

This longer term results showed sustained and high vaccine efficacy against EGL lesions caused by the vaccine HPV types and in all study populations. It is important to note that the majority of lesions

reported were condyloma acuminata of vulvar origin. HPV 6 was the predominant HPV type. Since HPV 6 and 11 cause the majority of genital warts (>95%) high vaccine efficacy was also observed in the MITT-3 population. There were few VIN and VaIN lesions in all populations, although all endpoint cases occurred in the placebo group in the PPE population. In the MITT-3 population, VE was not significant for the combined endpoint of VIN 2/3 or VaIN 2/3.

➢ ***Efficacy analysis-HPV 16/18-related VIN 2/3 and VaIN 2/3***

Analysis of efficacy with respect to the composite endpoint of HPV 16- or HPV18-related VIN 2/3 and VaIN 2/3 is presented in Table 5.

**Table 5: Analysis of efficacy against HPV 16/18-related VIN 2/3 or VaIN 2/3 (P013)**

| | **Silgard N=2717** | | **Placebo N=2725** | | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **n** | **Number of cases** | **n** | **Number of cases** | **Observed efficacy %** | **95% CI** |
| **PPE** | | | | | | |
| **VIN 2/3 or VaIN 2/3** | **2219** | **0** | **2239** | **7** | **100.0** | **30.0, 100** |
| HPV 16 | 1890 | 0 | 1855 | 5 | 100.0 | [illegible]3, 100 |
| HPV 18 | 2120 | 0 | 2136 | 2 | 100.0 | -463.9, 100 |
| **MITT-2** | | | | | | |
| **VIN 2/3 or VaIN 2/3** | **2620** | **1** | **2628** | **10** | **90.0** | **29.4, 99.8** |
| HPV 16 | 2215 | 1 | 2215 | 8 | 87.5 | 6.6, 99.7 |
| HPV 18 | 2480 | 0 | 2502 | 3 | 100.0 | -143.9, 100 |
| **MITT-3** | | | | | | |
| **VIN 2/3 or VaIN 2/3** | **2671** | **5** | **2668** | **11** | **54.6** | **-41.7, 87.6** |
| HPV 16 | 2671 | 5 | 2668 | 9 | 44.5 | -84.3, 85.4 |
| HPV 18 | 2671 | 0 | 2668 | 3 | 100.0 | -141.6, 100 |

There were few cases of HPV 16/18-related high-grade vulvar and vaginal neoplasia and the majority were caused by HPV 16. Only in the combined analysis of HPV 16/18-related VIN/VaIN 2/3, vaccine estimates were statistically significant in the PPE and MITT 2 populations. No statistically significant efficacy was seen in the MITT-3 population.

As for cervical lesions, the current results with respect to HPV6/11/16/18-related EGL, were similar to those in the MAAand there was no evidence of waning immunity.

- **Updated Exploratory efficacy analyses - evaluation of population impact**

Exploratory analyses to estimate the impact of vaccination on the overall burden of cervical, vaginal or vulvar disease (caused by vaccine or non-vaccine HPV types) were conducted. These analyses were performed in the redefined MITT-2 and RMITT-2 population, as well as in the MITT-3 population.

➢ ***CIN due to <u>any</u> HPV type***

In the RMITT-2 population Silgard reduced the rates of CIN (any grade) or AIS by 31.0% and of CIN 2/3 or AIS by 41.6% (Table 6).

**Table 6: Analysis of efficacy against CIN (of any grade) or AIS due to <u>any</u> HPV type (P013)**

| Endpoint | Silgard N=2717 | | Placebo N=2725 | | Observed efficacy % | 95%CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **RMITT-2** | | | | | | |
| **CIN due to any HPV type** | **1429** | **92** | **1441** | **132** | **31.0** | **9.3, 47.7** |
| CIN 1 | 1429 | 81 | 1441 | 122 | 34.2 | 12.1, 50.9 |
| ***CIN 2/3 or worse*** | ***1429*** | ***24*** | 1441 | ***41*** | ***41.6*** | ***1.1, 66.3*** |
| CIN 2 | 1429 | 16 | 1441 | 29 | 45.0 | -4.7, 72.1 |
| CIN 3 | 1429 | 8 | 1441 | 17 | 53.0 | -14.9, 82.4 |
| AIS | 1429 | 0 | 1441 | 2 | 100.0 | -43.8, 100 |
| **MITT-2** | | | | | | |
| **CIN due to any HPV type** | **2602** | **214** | **2607** | **276** | **23.6** | **8.3, 36.4** |
| CIN 1 | 2602 | 178 | 2607 | 240 | 26.8 | 10.8, 40.1 |
| ***CIN 2/3 or worse*** | ***2602*** | ***67*** | ***2607*** | ***85*** | ***21.7*** | ***-9.1, 44.0*** |
| CIN 2 | 2602 | 46 | 2607 | 62 | 26.3 | -9.6, 50.8 |
| CIN 3 | 2602 | 32 | 2607 | 37 | 13.9 | -42.0, 48.1 |
| AIS | 2602 | 0 | 2607 | 6 | 100.0 | 15.6, 100 |
| **MITT-3** | | | | | | |
| **CIN due to any HPV type** | **2607** | **338** | **2611** | **412** | **19.7** | **7.0, 30.7** |
| CIN 1 | 2607 | 271 | 2611 | 355 | 25.3 | 12.2,36.4 |
| ***CIN 2/3 or worse*** | ***2607*** | ***142*** | ***2611*** | ***153*** | ***7.8*** | ***-16.6, 27.2*** |
| CIN 2 | 2607 | 102 | 2611 | 114 | 11.2 | -17.0, 32.7 |
| CIN 3 | 2607 | 79 | 2611 | 72 | -9.2 | -52.4, 21.7 |
| AIS | 2607 | 1 | 2611 | 6 | 83.4 | -36.5, 99.6 |

Analyses in the RMITT-2 represent the best available population to examine overall vaccine impact on the rate of CIN (any grade) or AIS due to incident infection (i.e. infection following onset of vaccination). In the general population (MITT-3), the effect of Silgard against CIN of any grade due to any HPV type was 20%, which was largely due to reductions in low-grade lesions CIN 1. For CIN 2/3 or AIS, no significant vaccine efficacy was demonstrated (VE: 7.8%) and was even negative (-9.2%) against CIN 3.

➢ ***EGL due to <u>any</u> HPV type***

The reductions with respect to the incidence of EGLs were greater than those observed for cervical lesions. In the RMITT-2 and MITT-3 populations Silgard reduced the rate of any vulvar or vaginal lesion regardless of HPV type by 49.5% and 34.4%, respectively. With respect to VIN and VaIN, both low and high-grade lesions, only numerical reductions were seen (lower 95% CIs <0%) in all study populations.

The comparison of current results with the MAA is only possible for the MITT-3 population since the definition of the RMITT-2 and MITT-2 populations have changed with the additional testing of 10 non-vaccine HPV types. The comparison MITT-3 shows that the rates of detection of CIN and EGL lesions over the additional follow-up period (5.1/100 person-years at risk (PYR) and 1.7/100 PYR) were lower than those observed in the MAA (6.1 and 2.3, respectively). In general, the magnitude of benefit was somewhat higher in the updated results.

### 1.2.1.2 Protocol 15

**Cervical lesions**

➢ ***Primary efficacy analysis***

Results of the primary efficacy analyses are shown in Table 7. No cases of cervical cancer were reported in study 015. The observed vaccine efficacy against HPV 16/18-related CIN 2/3 in the PPE population was 97.6%.

The results in the MITT-2 analysis were supportive of the results in the PPE-population. In the MITT-3 population vaccine efficacy was substantially lower, 44%. The majority of MITT-3 endpoint cases occurred in subjects who were seropositive or PCR positive at Day 1. Due to the higher prevalence of HPV 16 at baseline, VE against HPV 16-related CIN 2/3 was lower than that against HPV 18-related CIN 2/3.

**Table 7: Analysis of efficacy against HPV16/18-related CIN 2/3 or worse (P015)**

| | Silgard N=6082 | | Placebo N=6075 | | Observed efficacy % | 95%CI |
|---|---|---|---|---|---|---|
| **Study population Endpoint** | **n** | **Number of cases** | **n** | **Number of cases** | | |
| **PPE** | | | | | | |
| **HPV 16/18 CIN 2/3** | **5305** | **1** | **5260** | **42** | **97.6** | **85.6, 100** |
| *By HPV type* | | | | | | |
| HPV 16 | 4559 | 1 | 4408 | 35 | 97.2 | 83.6, 99.9 |
| HPV 18 | 5055 | 0 | 4970 | 11 | 100.0 | 60.9, 100 |
| *By lesion type* | | | | | | |
| CIN 2 | 5305 | 0 | 5260 | 28 | 100.0 | 86.1, 100 |
| CIN 3 | 5305 | 1 | 5260 | 2[illegible] | 96.9 | 79.5, 99.9 |
| AIS | 5305 | 0 | 5260 | 1 | 100.0 | 14.7, 100 |
| **MITT-2** | | | | | | |
| **HPV 16/18 CIN 2/3** | **5738** | **3** | **5766** | **62** | **95.2** | **85.2, 99.0** |
| *By HPV type* | | | | | | |
| HPV 16 | 4951 | 3 | 4[illegible]59 | 51 | 94.1 | 81.8, 98.8 |
| HPV 18 | 5479 | 0 | 5508 | 16 | 100.0 | 74.0, 100 |
| *By lesion type* | | | | | | |
| CIN 2 | 5738 | 1 | 5766 | 40 | 97.5 | 85.2, 99.9 |
| CIN 3 | 5738 | 2 | 5766 | 43 | 95.3 | 82.1, 99.5 |
| AIS | 5738 | 0 | 5766 | 4 | 100.0 | -51.9, 100 |
| **MITT-3** | | | | | | |
| **HPV 16/18 CIN 2/3** | **5950** | **83** | **5974** | **148** | **43.8** | **26.0, 57.6** |
| *By HPV type* | | | | | | |
| HPV 16 | 5950 | 77 | 5974 | 132 | 41.5 | 22.0, 56.4 |
| HPV 18 | 5950 | 6 | 5974 | 29 | 79.3 | 49.2. 93.0 |
| *By lesion type* | | | | | | |
| CIN 2 | 5950 | 40 | 5974 | 96 | 58.3 | 39.0, 71.9 |
| CIN 3 | 5950 | 57 | 5974 | 104 | 45.1 | 23.4, 61.0 |
| AIS | 5950 | 5 | 5974 | 7 | 28.4 | -162.0, 82.1 |

Vaccine efficacy against HPV 16/18-related CIN 2/3 remained high in the PPE-population, with one single case of CIN 3 in the vaccine group. This lesion was possibly related to a non-vaccine HPV type since HPV 16 was only detected once, whereas HPV 52 was detected on several occasions. In the MITT-3 population VE against HPV 16/18-related CIN 2/3 was 44%, which is higher than that observed in the MAA (VE: 39%). It is of note that VE estimates against CIN 3, which is the most relevant marker, were significant in all study populations ranging from 97% to 45% in the PPE- and MITT-3 population, respectively, For AIS there were too few endpoint cases to allow any conclusions.

➢ ***Secondary efficacy analysis***

In the PPE population, administration of Silgard reduced the combined incidence of HPV 6/11/16/18-related CIN (any grade) or AIS by 93 % and that of HPV 16/18-related CIN by 91% (See Table 8).

**Table 8: Analysis of efficacy against HPV 6/11/16/18-related CIN by study population (P015)**

| | Silgard N=6082 | | Placebo N=6075 | | | |
|---|---|---|---|---|---|---|
| **Study population Endpoint** | **n** | **Number of cases** | **n** | **Number of cases** | **Observed efficacy %** | **95%CI** |
| **PPE** | | | | | | |
| **HPV 6/11/16/18 CIN** | **5387** | **6** | **5372** | **80** | **92.6** | **83.1, 97.4** |
| *By HPV type* | | | | | | |
| HPV 6 | 4726 | 0 | 4642 | 18 | 100.0 | 77.8, 100 |
| HPV 11 | 4726 | 0 | 4642 | 3 | 100.0 | -136.4, 100 |
| ***HPV 16/18 CIN*** | ***5305*** | ***6*** | ***5260*** | ***65*** | ***90.9*** | ***79.1, 96.8*** |
| HPV 16 | 4559 | 5 | 4408 | 52 | 90.7 | 77.0, 97.1 |
| HPV 18 | 5055 | 1 | 4970 | 20 | 95.1 | 69.1, 99.9 |
| *By disease severity* | | | | | | |
| CIN 1 | 5387 | 5 | 5372 | 60 | 91.7 | 79.6,97.4 |
| CIN 2 or worse | 5387 | 1 | 5372 | 43 | 97.7 | 86.4. 99.9 |
| CIN 2 | 5387 | 0 | 5372 | 29 | 100.0 | 86.5, 100 |
| CIN 3 | 5387 | 1 | 5372 | 29 | 96.6 | 79.4, 100 |
| AIS | 5387 | 0 | 5372 | 1 | 100.0 | -3771.4, 100 |
| **MITT-2** | | | | | | |
| **HPV 6/11/16/18 CIN** | **5813** | **10** | **5844** | **124** | **91.9** | **84.7, 96.2** |
| *By HPV type* | | | | | | |
| HPV 6 | 5136 | 0 | 5150 | 22 | 100.0 | 81.8, 100 |
| HPV 11 | 5136 | 1 | 5150 | 6 | 83.4 | -37.1, 99.6 |
| HPV 16/18 CIN | 5738 | 9 | 5766 | 106 | 91.6 | 83.4, 96.3 |
| HPV 16 | 4951 | 7 | 4959 | 84 | 91.7 | 82.1, 96.8 |
| HPV 18 | 5479 | 2 | 5508 | 31 | 93.5 | 74.6, 99.2 |
| *By disease severity* | | | | | | |
| CIN 1 | 5813 | 7 | 5844 | 94 | 92.6 | 84.0, 97.1 |
| CIN 2 or worse | 5813 | 3 | 5844 | 63 | 95.2 | 85.4, 99.0 |
| CIN 2 | 5813 | 1 | 5844 | 42 | 97.6 | 86.0, 99.9 |
| CIN 3 | 5813 | 2 | 5844 | 43 | 95.3 | 82.1, 99.5 |
| AIS | 5813 | 0 | 5844 | 4 | 100.0 | -52.4, 100 |
| **MITT-3** | | | | | | |
| **HPV 6/11/16/18 CIN** | **5950** | **120** | **5974** | **249** | **51.9** | **40.0, 61.7** |
| *By HPV type* | | | | | | |
| HPV 6 | 5950 | 8 | 5974 | 33 | 75.7 | 46.4, 90.3 |
| HPV 11 | 5950 | 5 | 5974 | 10 | 49.9 | -60.8, 86.6 |
| HPV 16/18 CIN | 5950 | 110 | 5974 | 224 | 51.0 | 38.1, 61.3 |
| HPV 16 | 5950 | 100 | 5974 | 190 | 47.4 | 32.6, 59.1 |
| HPV 18 | 5950 | 13 | 5974 | 54 | 75.9 | 55.3, 87.9 |
| *By disease severity* | | | 5974 | | | |
| CIN 1 | 5950 | 59 | 5974 | 167 | 64.7 | 52.3, 74.31 |
| CIN 2 or worse | 5950 | 84 | 5974 | 151 | 44.3 | 28.8, 57.8 |
| CIN 2 | 5950 | 41 | 5974 | 99 | 58.5 | 39.7, 71.9 |
| CIN 3 | 5950 | 57 | 5974 | 106 | 46.1 | 25.0, 61.7 |
| AIS | 5950 | 5 | 5974 | 7 | 28.4 | -162.0, 82.1 |

Vaccine efficacy against HPV 6/11/16/18-related low-grade CIN remained at the same high level as that observed in the MAA. Against CIN 1, VE ranged from 92% to 65% in the different study populations.

**External genital lesions**

The efficacy of Silgard against EGLs remained high across all efficacy populations (Table 9). Efficacy also remained high for the combined incidence of HPV 6-, 11-, 16-, or 18-related VIN 2/3 or VaIN 2/3. No cases of vulvar or vaginal cancer were observed in the study.

**Table 9: Analysis of efficacy against HPV6/11/16/18-related EGL (P015)**

| Study population | Silgard | | Placebo | | Observed efficacy % | 95%CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **PPE** | | | | | | |
| **HPV 6/11/16/18 EGL** | **5403** | **2** | **5388** | **126** | **98.4** | **94.2, 99.8** |
| *By HPV type* | | | | | | |
| HPV 6 | 4739 | 2* | 4654 | 104 | 98.1 | 83.1, 99.8 |
| HPV 11 | 4739 | 0 | 4654 | 17 | 100.0 | 76.3, 100 |
| HPV 16 | 4564 | 0 | 4412 | 21 | 100.0 | 81.5, 100 |
| HPV 18 | 5069 | 0 | 4981 | 9 | 100.0 | 50.3, 100 |
| *By disease severity* | | | | | | |
| Condyloma | 5403 | 2 | 5388 | 109 | 98.2 | 93.3, 99.8 |
| Vulvar condyloma | 5403 | 2* | 5388 | 105 | 98.1 | 93.0, 99.8 |
| Vaginal condyloma | 5403 | 0 | 5388 | 9 | 100.0 | 49.6, 100 |
| VIN or VaIN 1 | 5403 | 0 | 5388 | 14 | 100.0 | 70.0, 100 |
| VIN 1 | 5403 | 0 | 5388 | 11 | 100.0 | 60.4, 1000 |
| VaIN 1 | 5403 | 0 | 5388 | 3 | 100.0 | -14[illegible] |
| ***VIN 2/3 or VaIN 2/3*** | ***5403*** | ***0*** | ***5388*** | ***10*** | ***100.0*** | ***[illegible]*** |
| VIN 2/3 | 5403 | 0 | 5388 | 6 | 100.0 | [illegible] |
| VaIN 2/3 | 5403 | 0 | 5388 | 4 | 100.0 | [illegible] |
| **MITT-2** | | | | | | |
| **HPV 6/11/16/18 EGL** | **5875** | **7** | **5898** | **175** | **96.0** | **91.6, 98.4** |
| *By HPV type* | | | | | | |
| HPV 6 | 5194 | 6 | 5196 | 137 | [illegible] | 90.3, 98.4 |
| HPV 11 | 5194 | 0 | 5196 | 26 | [illegible] | 84.8, 100 |
| HPV 16 | 5003 | 1 | 5002 | 35 | [illegible] | 83.0, 99.9 |
| HPV 18 | 5540 | 0 | 5559 | 15 | [illegible] | 72.0. 100 |
| *By disease severity* | | | | | | |
| Condyloma | 5875 | 7 | 5898 | 145 | 95.2 | 89.8, 98.1 |
| Vulvar condyloma | 5875 | 6 | 5898 | 137 | 95.6 | 90.2, 98.4 |
| Vaginal condyloma | 5875 | 1 | 5898 | 14 | 92.8 | 52.8, 99.8 |
| VIN or VaIN 1 | 5875 | 0 | 5898 | 22 | 100.0 | 81.7, 100 |
| VIN 1 | 5875 | 0 | 5898 | 15 | 100.0 | 72.0, 100 |
| VaIN 1 | 5875 | 0 | 5898 | 7 | 100.0 | 30.3, 100 |
| ***VIN 2/3 or VaIN 2/3*** | ***5875*** | ***0*** | ***5898*** | ***20*** | ***100.0*** | ***79.7, 100*** |
| VIN 2/3 | 5875 | 0 | 5896 | 15 | 100.0 | 72.0, 100 |
| VaIN 2/3 | 5875 | 0 | 5898 | 5 | 100.0 | -9.7, 100 |
| **MITT-3** | | | | | | |
| **HPV 6/11/16/18 EGL** | **6016** | **45** | **6029** | **213** | **79.0** | **70.9, 85.1** |
| *By HPV type* | | | | | | |
| HPV 6 | 6016 | 39 | 6029 | 172 | 77.4 | 67.9, 84.5 |
| HPV 11 | 6016 | 2 | 6029 | 28 | 92.8 | 71.6, 99.2 |
| HPV 16 | 6016 | 6 | 6029 | 40 | 85.0 | 64.3, 94.8 |
| HPV 18 | 6016 | 1 | 6029 | 17 | 94.1 | 62.3, 99.9 |
| *By disease severity* | | | | | | |
| Condyloma | 6016 | 41 | 6029 | 177 | 76.9 | 67.4, 84.0 |
| Vulvar condyloma | 6016 | 38 | 6029 | 169 | 77.6 | 68.0, 84.7 |
| Vaginal condyloma | 6016 | 3 | 6029 | 16 | 81.2 | 34.3, 96.5 |
| VIN or VaIN 1 | 6016 | 6 | 6029 | 27 | 77.7 | 44.9, 92.5 |
| VIN 1 | 6016 | 3 | 6029 | 18 | 83.3 | 42.7, 96.8 |
| VaIN 1 | 6016 | 3 | 6029 | 9 | 66.5 | -34.1, 94.2 |
| ***VIN 2/3 or VaIN 2/3*** | ***6016*** | ***4*** | ***6029*** | ***22*** | ***81.8*** | ***46.3, 94.5*** |
| VIN 2/3 | 6016 | 3 | 6029 | 16 | 81.2 | 34.3, 96.5 |
| VaIN 2/3 | 6016 | 2 | 6029 | 6 | 66.5 | -87.1, 96.7 |



***** Two cases of HPV 6-related condyloma acuminata were detected in subjects who received Silgard within the PPE population. These cases are described as follows:

1. AN 57819: This case was reported in the P015 CSR submitted as part of the MAA. This case of HPV 6-related genital warts occurred in an 18-year-old Caucasian woman. She was negative at Day 1 by PCR to all 14 HPV types for which testing was conducted. At Month 8, she was found to have an HPV 6-related condyloma. She had mounted a strong anti-HPV 6 response at Month 7.

2. AN 40727: This case of HPV 6-related genital warts occurred in a 16-year-old Caucasian woman. She was negative at Day 1 by PCR to all 14 HPV types for which testing was conducted. At Month 36, she was found to have genital warts. A biopsy obtained at that time confirmed this diagnosis. The lesion was positive for

HPV 6 and HPV 59 DNA. The subject did not participate in the Consistency Lot substudy and, thus, did not undergo serology testing after Day 1.

**Table 10: Analysis of efficacy against HPV 16/18-related VIN 2/3 or VaIN 2/3 (P015)**

| | Silgard N=6082 | | Placebo N=6075 | | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **n** | **Number of cases** | **n** | **Number of cases** | **Observed efficacy %** | **95%CI** |
| **PPE** | | | | | | |
| **VIN 2/3 or VaIN 2/3** | **5321** | **0** | **5273** | **8** | **100.0** | **42.1, 100** |
| HPV 16 | 4564 | 0 | 4412 | 8 | 100.0 | 43.5, 100 |
| HPV 18 | 5069 | 0 | 4981 | 0 | NA | NA |
| **MITT-2** | | | | | | |
| **VIN 2/3 or VaIN 2/3** | **5800** | **0** | **5818** | **18** | **100.0** | **77.2,100** |
| HPV 16 | 5003 | 0 | 5002 | 18 | 100.0 | 77.3, 100 |
| HPV 18 | 5540 | 0 | 5559 | 0 | NA | NA |
| **MITT-3** | | | | | | |
| **VIN 2/3 or VaIN 2/3** | **6016** | **4** | **6029** | **19** | **78.9** | **36.3, 94.6** |
| HPV 16 | 6016 | 5 | 6029 | 9 | 84.2 | 44.7, 97.0 |
| HPV 18 | 6016 | 0 | 6029 | 0 | NA | NA |

Efficacy results in this large study were similar to those obtained in study 013, i.e. with a predominance of condyloma among disease categories and HPV 6 among vaccine types. Vulvar and vaginal lesions were rarely detected and all the HPV 16/18-related high grade lesions were caused by HPV 16. A consistent pattern was that all VIN/VaIN cases regardless of grade in the PPE- and MITT-2 analyses were reported in the placebo group. Significant efficacy against HPV 16/18-related VIN 2/3 or VaIN 2/3 was seen in all study populations.

The current results were similar to those in the MAA and there was no evidence of waning immunity over the 3 year follow up period.

- **Updated Exploratory efficacy analyses - evaluation of population impact**

➢ ***CIN due to any HPV type***

In the RMITT-2 population Silgard reduced the combined rates of CIN (any grade) or AIS by 28.6%, of CIN 2/3 by 49.4% and CIN 3 by 55.3% (Table 11). In the MITT-2 population observed efficacy was lower (19.5%) although significant for all disease severities.

In the MITT-3 population CIN was reduced by 14%, CIN 2/3 by 16.8% with the lower 95% CI barely above 0% (0.1%). For CIN 3 only a numerical reduction of 20.9% (95% CI <0 to 37.8%) was noted.

Compared with the RMITT-2 population, a total of 378 and 415 cases of the composite endpoint CIN/AIS were added to the vaccine and placebo groups, respectively in the MITT-3 population. Among these 349 (92%) and 375 (90%) of cases in the respective group, occurred among women who were PCR-positive to one of the 14 tested HPV types at Day 1.

**Table 11: Analysis of efficacy against CIN (of any grade) or AIS due to any HPV type (P015)**

| Endpoint | Silgard N=6082 | | Placebo N=6075 | | Observed efficacy % | 95%CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **RMITT-2** | | | | | | |
| **CIN due to any HPV type** | **3187** | **99** | **3234** | **140** | **28.6** | **6.9, 45.4** |
| CIN 1 | 3187 | 92 | 3234 | 122 | 21.9 | -3.4., 41.2 |
| **CIN 2 or worse** | **3187** | **28** | **3234** | **41** | **49.4** | **19.0., 69.1** |
| CIN 2 | 3187 | 21 | 3234 | 29 | 49.4 | 12.6, 71.5 |
| **CIN 3** | **3187** | **15** | **3234** | **17** | **55.3** | **15.8, 77.4** |
| AIS | 3187 | 0 | 3234 | 2 | NA | NA |
| **MITT-2** | | | | | | |
| **CIN due to any HPV type** | **5936** | **267** | **5962** | **332** | **19.5** | **5.1, 31.7** |
| CIN 1 | 5936 | 222 | 5962 | 273 | 18.6 | 2.4, 32.1 |
| **CIN 2 or worse** | **5936** | **95** | **5962** | **137** | **30.5** | **9.1, 47.1** |
| CIN 2 | 5936 | 65 | 5962 | 96 | 32.1 | 6.[illegible], 5[illegible]3 |
| CIN 3 | 5936 | 50 | 5962 | 83 | 39.6 | 13.2, 58.4 |
| AIS | 5936 | 0 | 5962 | 4 | 100.0 | -51.3, 100 |
| **MITT-3** | | | | | | |
| **CIN due to any HPV type** | **5950** | **477** | **5974** | **555** | **14.0** | **2.6, 24.0** |
| CIN 1 | 5950 | 377 | 5974 | 440 | 14.3 | 1.4, 25.5 |
| **CIN 2 or worse** | **5950** | **219** | **5974** | **264** | **[illegible]** | **0.1, 30.8** |
| CIN 2 | 5950 | 148 | 5974 | 190 | [illegible] | 2.7, 37.4 |
| **CIN 3** | **5950** | **127** | **5974** | **161** | **[illegible]** | **-0.4, 37.8** |
| AIS | 5050 | 5 | 5974 | 8 | 37.4 | -117.2, 83.9 |

The overall benefit of Silgard with respect to CIN was low in the MITT-3 analysis, although higher than in the MAA.

➢ ***EGL due to <u>any</u> HPV type***

In the RMITT-2, MITT-2 and MITT-3 populations Silgard reduced the rates EGLs by 88.3%, 75.9% and 57.9% respectively. The higher efficacy noted for EGL compared to CIN/AIS can be explained by the inclusion criteria and by the fact that a large proportion of EGLs are due to vaccine HPV types.

#### 1.2.1.3 Combined analysis of study protocols

As in the MAA the two pre-planned pooled analyses were performed and updated with the additional follow-up data at 3 years:
1) integrated summary of efficacy: includes P007, P013 and P015.
2) combined phase II/III efficacy analysis: includes P005 (16-related endpoints only), P007, P013 and P015.

The efficacy for HPV 16/18 related CIN 2/3 or AIS is based on data from protocols 005, 007, 013, and 015. The efficacy for all other endpoints is based on protocols 007, 013, and 015.

##### 1.2.1.3.1 Combined protocols 007, 013 and 015 Update of the integrated summary of efficacy

Protocol 007, 013 and 015 were included in the updated integrated summary of vaccine efficacy against CIN, EGL, Pap abnormality endpoints and cervical procedures in this report. Altogether 18,174 women aged 16 to 26 years were randomised across the 3 study protocols.

➢ ***Efficacy with respect to HPV 6/11/16/18-related CIN (any grade), AIS or cervical cancer***

There was no case of cervical cancer in any of the studies. The estimates of efficacy within each of the 3 protocols were consistent with the overall estimates of VE across the protocols. The vaccine efficacy in the MITT-2 population (VE: 94.5%) was similar to efficacy in the PPE population (VE: 96%), whereas lower estimates were noted in the MITT-3 population (VE: 53.9%). In the PPE population, there was 1 new case of HPV 18-related CIN 1 and a single case of HPV 16-related CIN 3 in the group that received Silgard reported since the MAA.

Efficacy was observed for each vaccine HPV type of the composite HPV 6-, HPV 11-, HPV 16- or HPV 18-related CIN (any grade) or AIS endpoint and was similar to that reported in the MAA. Efficacy against HPV 6/11/16/18-related CIN 2/3 was 98.7%, 97.2% and 42.1% in the PPE-, MITT-2 and MITT-3 population, respectively. Corresponding efficacy for CIN 1 was 95.5%, 94.6% and 64.5%.

In the placebo group within the MITT-2 population, the cumulative incidence of HPV 6/11/16/18-related CIN (any grade) or AIS through approximately 3 years of follow-up was 2.7%. The risk of developing an endpoint was reduced from 1 in 40 in the placebo group to 1 in 719 in the group that received Silgard.

In the MITT-3 population, administration of Silgard resulted in a 54% reduction in the incidence of HPV 6/11/16/18-related CIN (any grade) or AIS, compared with placebo. In the MAA, a 46% (95% CI: 35 to 56%) reduction was observed. The hazard of becoming a case of HPV 6/11/16/18-related CIN in the placebo group increased over time compared to the group vaccinated with Silgard. Hence, the percent reduction in the incidence of HPV 6/11/16/18-related CIN in the vaccinated group compared with placebo increased over time.

The vaccine efficacy against HPV 6/11/16/18-related CIN (any grade) was maintained through an additional year of follow-up with comparable efficacy in the PPE- and MITT-2 populations. It is reassuring that VE against CIN 2/3, and in particular against CIN 3, which is the most relevant surrogate marker for cervical cancer, was significant in all study populations including the MITT-3. The single case of HPV 16-related CIN 3 that occurred in the vaccine group (PPE population) was most likely caused by HPV 52. Also for adenocarcinoma in situ (AIS) VE was demonstrated in the PPE- and MITT-2 analyses, although there were few cases. All AIS cases were detected in the placebo group.

The efficacy results are comparable to those obtained in the MAA. The difference between the vaccine and placebo group in the incidence of CIN lesions, increased during the additional year of follow-up. Almost all of the new cases in the Silgard group (MITT-3 population) were in subjects who had evidence of prior HPV exposure, whereas those in the placebo group were true new infections.

- ***Efficacy with respect to HPV 6/11/16/18 18-related EGL***

Efficacy results against HPV 6/11/16/18-related EGL in the combined analysis are presented in Table 12. There were no cases of vaginal/vulvar cancer observed in any of the studies. The efficacy of Silgard was 99% in the PPE population (2 vs. 189 cases). The MITT-2 analysis supported the primary analysis in the PPE population.
In the MITT-3 population, administration of Silgard resulted in a 77.6% (95% CI: 71.0, 82.9%) reduction in the incidence of HPV 6/11/16/18-related EGL compared with placebo. The hazard of becoming a case of HPV 6/11/16/18-related EGL in the placebo group increased over time compared to the group vaccinated with Silgard. Hence, the percent reduction in the incidence of HPV 6/11/16/18-related EGL in the vaccinated group compared with placebo increased over time.

The integrated analysis of vaccine efficacy against EGL by HPV vaccine type showed that estimates were similar across the different HPV type-related EGLs and significant for each type in all 3 study populations. There were 2 cases of HPV 6-related vulvar condyloma in the vaccine group of the PPE-population. The single case of VIN 2/3 in the MITT-2 population was HPV 16-related. In the MITT-population the estimates of efficacy were consistent across the different disease severities.

**Table 12: Analysis of efficacy against HPV6/11/16/18-related EGL (Protocols 007, 013, 015)**

| Study population | HPV L1 VLP vaccine | | Placebo | | Observed efficacy % | 95%CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **PPE** | | | | | | |
| **Combined protocols** | **7899** | **2** | **7900** | **189** | **99.0** | **96.2, 99.9** |
| *By HPV type* | | | | | | |
| HPV 6 | 6931 | 2 | 6854 | 147 | 98.7 | 95.1, 99.8 |
| HPV 11 | 6931 | 0 | 6854 | 30 | 100.0 | 87.1, 100 |
| HPV 16 | 6653 | 0 | 6465 | 34 | 100.0 | 88.9, 100 |
| HPV 18 | 7413 | 0 | 7341 | 12 | 100.0 | 64.4, 100 |
| *By disease severity* | | | | | | |
| Condyloma | 7899 | 2 | 7900 | 160 | 98.8 | 95.4, 99.9 |
| Vulvar condyloma | 7899 | 2 | 7900 | 155 | 98.7 | 95.3, 99.8 |
| Vaginal condyloma | 7899 | 0 | 7900 | 15 | 100.0 | 72.1, 100 |
| VIN 1 or VaIN 1 | 7899 | 0 | 7900 | 23 | 100.0 | 82.6, 100 |
| VIN 1 | 7899 | 0 | 7900 | 15 | 100.0 | 72.1, 100 |
| VaIN 1 | 7899 | 0 | 7900 | 8 | 100.0 | 41.[illegible], 100 |
| VIN 2/3 or VaIN 2/3 | 7899 | 0 | 7900 | 19 | 100.0 | [illegible], 100 |
| VIN 2/3 | 7899 | 0 | 7900 | 11 | 100.0 | [illegible], 100 |
| VaIN 2/3 | 7899 | 0 | 7900 | 8 | 100.0 | 41.[illegible], 100 |
| **MITT-2** | | | | | | |
| **Combined protocols** | **8760** | **11** | **8787** | **260** | **95.8** | **92.3, 97.9** |
| *By HPV type* | | | | | | |
| HPV 6 | 7769 | 8 | 7788 | 192 | 95.[illegible] | 91.7, 98.2 |
| HPV 11 | 7769 | 1 | 7788 | 44 | 9[illegible] | 86.6, 99.9 |
| HPV 16 | 7443 | 2 | 7444 | 54 | 96.3 | 86.0, 99.6 |
| HPV 18 | 8272 | 0 | 8312 | 23 | 100.0 | 82.5, 100 |
| *By disease severity* | | | | | | |
| Condyloma | 8760 | 10 | 8787 | 215 | 95.4 | 91.3, 97.8 |
| Vulvar condyloma | 8760 | 8 | 8787 | 205 | 96.1 | 92.2, 98.3 |
| Vaginal condyloma | 8760 | 2 | 8787 | 22 | 90.9 | 62.9, 99.0 |
| VIN 1 or VaIN 1 | 8760 | 2 | 8787 | 33 | 93.9 | 76.2, 99.3 |
| VIN 1 | 8760 | 2 | 8787 | 19 | 89.4 | 56.2, 98.8 |
| VaIN 1 | 8760 | 0 | 8787 | 14 | 100.0 | 69.7, 100 |
| VIN 2/3 or VaIN 2/3 | 8760 | 1 | 8787 | 32 | 96.9 | 81.2, 99.9 |
| VIN 2/3 | 8760 | 1 | 8787 | 22 | 95.4 | 71.8, 99.9 |
| VaIN 2/3 | 8760 | 0 | 8787 | 10 | 100.0 | 55.2, 100 |
| **MITT-3** | | | | | | |
| **Combined protocols** | **8954** | **72** | **8964** | **319** | **77.6** | **71.0, 82.9** |
| *By HPV type* | | | | | | |
| HPV 6 | 8954 | 58 | 8964 | 244 | 76.3 | 68.4, 82.5 |
| HPV 11 | 8954 | 4 | 8964 | 48 | 91.7 | 77.2, 97.8 |
| HPV 16 | 8954 | 12 | 8964 | 64 | 81.2 | 64.9, 90.8 |
| HPV 18 | 8954 | 2 | 8964 | 26 | 92.3 | 69.2, 99.1 |
| *By disease severity* | | | | | | |
| Condyloma | 8954 | 61 | 8964 | 266 | 77.2 | 69.8, 83.0 |
| Vulvar condyloma | 8954 | 56 | 8964 | 254 | 78.1 | 70.6, 83.9 |
| Vaginal condyloma | 8954 | 5 | 8964 | 26 | 80.7 | 49.0, 94.2 |
| VIN 1 or VaIN 1 | 8954 | 12 | 8964 | 43 | 72.1 | 46.1, 86.6 |
| VIN 1 | 8954 | 8 | 8964 | 25 | 67.9 | 26.7, 87.5 |
| VaIN 1 | 8954 | 4 | 8964 | 18 | 77.7 | 32.4, 94.5 |
| VIN 2/3 or VaIN 2/3 | 8954 | 9 | 8964 | 36 | 75.0 | 47.0, 89.4 |
| VIN 2/3 | 8954 | 8 | 8964 | 25 | 67.9 | 26.7, 87.5 |
| VaIN 2/3 | 8954 | 2 | 8964 | 12 | 83.3 | 25.0, 98.2 |

***Condyloma:*** In the PPE population, efficacy was 98.7% for HPV 6- or 11-related condyloma. When comparing the PPE population and MITT-2 population, an additional 7 subjects in the group that received Silgard and 53 subjects in the placebo group were found to have an HPV 6- or HPV 11-related condyloma in the MITT-2 population. Thus, there is evidence that the vaccine is already efficacious during the course of the vaccination regimen. The impact of Silgard in the MITT-3 population was lower than the efficacy observed in the PPE population and MITT-2 population due to the presence of disease that was caused by infections that were already present at Day 1.

The updated integrated efficacy results are consistent with those obtained in the MAA.

➢ ***Vaccine efficacy against HPV 16/18-related EGL***

In the integrated efficacy analysis significant vaccine efficacy against both HPV 16/18-related VIN 2/3 and VaIN 2/3 was demonstrated in all study populations, supporting the claim of the MAH to include VaIN 2/3 in the indication. VE for VaIN 2/3 was 100% in the PPE population and 81.8% in the MITT-3 population. In the separate studies, no VE could be shown due to the sparseness of cases with high-grade vulvar and vaginal lesions. However, the pattern was consistent across protocols with almost all endpoint cases in the placebo group. The majority of VIN/VaIN 2/3 lesions were caused by HPV 16 (64% in the placebo group). This finding and the higher incidence of VIN 2/3 compared with VaIN 2/3 are consistent with published data.

With regard to low-grade lesions, vaccine efficacy was demonstrated against VaIN 1 in all study populations, whereas for VIN 1 no significant efficacy was shown. The knowledge about these low-grade lesions is limited and the terminology for vaginal/vulvar lesions is not as established as that for cervical lesions. The ISSVD society has recommended the abolition of VIN 1 due to low reproducibility. The proportion of these low-grade lesions caused by oncogenic HPV types need to be clarified. At this stage the MAH´s claim for VIN 1 and VaIN 1 in the indication cannot be considered justified.

- **Overall impact on invasive cervical procedures**

In the RMITT-2 population, the combined incidence of cervical diagnostic and therapeutic procedures was reduced in the group that received Silgard compared with the placebo group with respect to the incidence rates of colposcopy, cervical biopsy, and cervical definitive therapy (Table 13). Results observed in the MITT-3 population were lower but consistent with those in the RMITT-2 population.

**Table 13: Vaccine impact on invasive cervical procedures (P007, P013, P015 combined)**

| Study population | Silgard N=9075 | | Placebo N=9075 | | | |
|---|---|---|---|---|---|---|
| **Restricted MITT-2** | **n** | **Number of cases** | **n** | **Number of cases** | **Percent Reduction** | **95%CI** |
| Colposcopy | 4696 | 592 | 4754 | 748 | **20.3** | 11.1, 28.5 |
| Cervical biopsy | 4696 | 500 | 4754 | 636 | 21.5 | 11.6, 30.3 |
| Definitive therapy | 4696 | 82 | 4754 | 138 | **40.1** | 20.7, 55.0 |
| **MITT-3** | | | | | | |
| Colposcopy | 8820 | 2084 | 8849 | 2302 | 10.5 | 5.0, 15.7 |
| Cervical biopsy | 8820 | 1709 | 8849 | 1991 | 11.0 | 5.1, 16.6 |
| Definitive therapy | 8820 | 466 | 8849 | 582 | **20.0** | 9.4, 29.3 |

The reductions observed with regard to definitive therapy (40% (RMITT-2) and 20% (MITT-3)) seen are considered clinically relevant.

- **Therapeutic efficacy**

An analysis was conducted to determine whether, among subjects who showed evidence of infection with a vaccine HPV type at Day 1, administration of Silgard reduced the proportion of subjects who were found to have progressed to clinical disease due to that type, compared with placebo.

The combined data do not provide adequate evidence that Silgard has therapeutic efficacy against HPV type-related CIN or EGL endpoints for the non-HPV-naïve populations. The analyses did not have sufficient power to allow any firm conclusions to be drawn with regard to therapeutic vaccine efficacy.

### 1.2.1.3.2 Protocols P005, P007, P013, P015 Updated combined efficacy results

The efficacy for HPV 16/18 related CIN 2/3 or AIS is based on data from protocols 005, 007, 013, and 015.

➢ ***Efficacy with respect to HPV 16- or HPV 18-related CIN 2/3 or AIS***

The results are presented in the table 14 below.

**Table 14: Analysis of efficacy against HPV16/18-related CIN 2/3 or AIS (Combined protocols 005, 007, 013 and 015)**

| Study population | Silgard N=10268 | | Placebo N=10273 | | Observed efficacy % | 95%CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **PPE** | | | | | | |
| **Combined protocols** | **8492** | **1** | **8462** | **85** | **98.8** | **93.3, 100** |
| ***By study protocol*** | | | | | | |
| P005 | 755 | 0 | 750 | 12 | 100.0 | 65.1, 100 |
| P007 | 231 | 0 | 230 | 1 | 100.0 | <0.0, 100 |
| P013 | 2201 | 0 | 2222 | 30 | 100.0 | 86.9, 100 |
| P015 | 5305 | 1 | 5260 | 42 | 97.6 | 86.2, 100 |
| *By HPV type* | | | | | | |
| HPV 16 | 7401 | 1 | 7203 | 73 | 98.7 | 92.4, 100.0 |
| HPV 18 | 7381 | 0 | 7314 | 18 | 100.0 | 77.5, 100 |
| *By disease severity* | | | | | | |
| CIN 2/3 or worse | 8492 | 1 | 8462 | 85 | 98.8 | 93.3, 100 |
| CIN 2 | 8492 | 0 | 8462 | 56 | 100.0 | 93.3, 100 |
| CIN 3 | 8492 | 1 | 8462 | 51 | 98.1 | 88.7, 100 |
| AIS | 8492 | 0 | 8462 | 7 | 100.0 | 30.5, 100 |
| **MITT-2** | | | | | | |
| **Combined protocols** | **9344** | **3** | **9400** | **121** | **97.5** | **92.6, 99.5** |
| ***By study protocol*** | | | | | | |
| P005 | 834 | 0 | 843 | 16 | 100.0 | 74.3, 100 |
| P007 | 254 | 0 | 253 | 2 | 100.0 | <0, 100 |
| P013 | 2518 | 41 | 2538 | 41 | 100.0 | 90.6, 100 |
| P015 | 5738 | 3 | 5766 | 62 | 95.2 | 85.2, 99.0 |
| *By HPV type* | | | | | | |
| HPV 16 | 8162 | 2 | 8195 | 103 | 97.1 | 91.3, 99.4 |
| HPV 18 | 8147 | 0 | 8204 | 25 | 100.0 | 84.1,100 |
| *By disease severity* | | | | | | |
| CIN 2/3 or worse | 9344 | 3 | 9400 | 121 | 97.5 | 92.6., 99.5 |
| CIN 2 | 9344 | 1 | 9400 | 77 | 98.7 | 92.5, 100 |
| CIN 3 | 9344 | 2 | 9400 | 75 | 97.3 | 90.0, 99.7 |
| AIS | 9344 | 0 | 9400 | 10 | 100.0 | 55.3, 100 |
| **MITT-3** | | | | | | |
| **Combined protocols** | **9834** | **142** | **9897** | **255** | **44.3** | **31.4, 55.0** |
| P005 | 1017 | 5 | 1050 | 23 | 77.9 | 40.6, 93.4 |
| P007 | 260 | 2 | 262 | 7 | 71.7 | <0.0, 97.1 |
| P013 | 2607 | 2 | 2611 | 77 | 32.9 | 3.3, 53.7 |
| P015 | 5950 | 83 | 5974 | 148 | 43.8 | 26.0, 57.6 |
| *By HPV type* | | | | | | |
| HPV 16 | 9834 | 134 | 9897 | 232 | 42.2 | 28.2, 53.6 |
| HPV 18 | 8817 | 8 | 8847 | 42 | 81.0 | 59.0, 92.3 |
| *By disease severity* | | | | | | |
| CIN 2/3 or worse | 9834 | 142 | 9897 | 255 | 44.3 | 31.4, 55.0 |
| CIN 2 | 9834 | 81 | 9897 | 163 | 50.3 | 34.8, 62.4 |
| CIN 3 | 9834 | 99 | 9897 | 162 | 38.9 | 21.0, 52.9 |
| AIS | 9834 | 6 | 9897 | 13 | 53.9 | -30.0, 85.6 |

The results obtained in this combined efficacy analyses were comparable to those observed in the MAA, but now based on a larger number of CIN 2/3 cases (86 vs. 53, PPE population) increasing the precision of the vaccine estimates. The single case in the vaccine group was an HPV 16-related CIN 3 case in Month 25. The subject was positive to HPV 52 at baseline and in 5 histology specimens (both biopsy and LEEP). HPV 16 was detected in one histology sample. The efficacy estimates against HPV 16/18-related CIN 3 and AIS, the most relevant surrogate markers for cervical cancer, were both significant, with VE of 98% and 100%, respectively in the PPE-population and 97% and 100% in the MITT-2. There were only 7 cases AIS in the PPE- and 10 cases in the MITT-2 population, but all occurred in the placebo group.
The efficacy estimate in the MITT-3 population was increased to 44% compared to 39% in the MAA. With respect to CIN 3, VE was 39% (21, 53), which did not fulfil the statistical criterion of the analysis (lower bound of 95% CI >25%).

### 1.2.1.3.3 Protocols P013, P015 combined

➢ ***Combined efficacy results with respect to CIN 2/3 or AIS caused by vaccine and non-vaccine HPV types***

The efficacy results with respect to CIN 2/3 or AIS due to any HPV type by severity are presented in the table 15 below. In the MITT-2 population a combined efficacy of 27.1% was obtained. In the most restricted population RMITT-2, corresponding to a sexually naïve population, VE was 46.1% against CIN 2/3, AIS and 54.5% against CIN 3 which is clinically relevant. This estimate is, however, lower than the expected (70%), but might be explained by baseline high-risk HPV infections that were not detected by Pap test or the current HPV testing methods.
The overall benefit of Silgard against any CIN 2/3 or AIS regardless of causal HPV type was limited in the general population (MITT-3). The observed efficacy was only 13.5% (18% (95% CI: 6 to 28) if P005 and P007 was included in the analysis). When analysed by disease severity, no significant efficacy against CIN 3 was documented (lower 95% CI <0%)

**Table 15: Analysis of efficacy against CIN 2/3 or AIS due to any HPV type by severity**

| | Silgard N=8750 | | Placebo N=8800 | | | |
|---|---|---|---|---|---|---|
| **Study population** | **n** | **Number of cases** | **n** | **Number of cases** | **Observed efficacy %** | **95%CI** |
| ***MITT-2*** | | | | | | |
| **CIN 2/3+ due to any HPV type** | **8538** | **162** | **8569** | **222** | **27.1** | **10.3, 40.9** |
| CIN 2 | 8538 | 111 | 8569 | 158 | 29.8 | 9.8, 45.5 |
| CIN 3 | 8538 | 82 | 8569 | 120 | 31.6 | 8.6, 49.1 |
| AIS | 8538 | 0 | 8569 | 10 | 100.0 | 55.1, 100.0 |
| **CIN 2/3+ not related to HPV 6/11/16/18** | **8538** | **160** | **8569** | **167** | **4.3** | **-19.7, 23.5** |
| CIN 2 | 8538 | 111 | 8569 | 118 | 6.0 | -23.0, 28.2 |
| CIN 3 | 8538 | 80 | 8569 | 82 | 2.4 | -34.6, 29.3 |
| AIS | 8538 | 0 | 8569 | 4 | 100.0 | 52.7, 100.0 |
| ***R-MITT-2*** | | | | | | |
| **CIN 2/3+ due to any HPV type** | **4616** | **52** | **4675** | **97** | **46.1** | **23.6, 62.3** |
| CIN 2 | 4616 | 37 | 4675 | 71 | 47.5 | 20.7, 65.8 |
| CIN 3 | 4616 | 23 | 4675 | 51 | 54.5 | 24.1, 73.5 |
| AIS | 4616 | 0 | 4675 | 2 | 100.0 | -443.3, 100 |
| **CIN 2/3+ not related to HPV 6/11/16/18** | **4616** | **52** | **4675** | **70** | **25.3** | **-8.7, 48.9** |
| CIN 2 | 4616 | 37 | 4675 | 54 | 30.9 | -7.1, 55.9 |
| CIN 3 | 4616 | 23 | 4675 | 34 | 31.8 | -19.5, 61.7 |
| AIS | 4616 | 0 | 4675 | 1 | 100.0 | -3914, 100 |
| **MITT-3** | | | | | | |
| **CIN 2/3+ due to any HPV type** | **8557** | **361** | **8585** | **417** | **13.5** | **0.1, 25.1** |
| CIN 2 | 8557 | 250 | 8585 | 304 | 17.8 | 2.5, 30.8 |
| CIN 3 | 8557 | 206 | 8585 | 233 | 11.6 | -7.2, 27.1 |
| AIS | 8557 | 6 | 8585 | 14 | 57.2 | -19.1, 86.6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **CIN 2/3+ <u>not</u> related to HPV 6/11/16/18** | **8557** | **282** | **8585** | **295** | **4.5** | **-12.9, 19.2** |
| CIN 2 | 8557 | 195 | 8585 | 216 | 9.8 | -10.1, 26.1 |
| CIN 3 | 8557 | 152 | 8585 | 149 | -2.0 | -28.9, 19.2 |
| AIS | 8557 | 1 | 8585 | 7 | 85.7 | -11.8, 99.7 |

Over time the benefit of the vaccine was shown to increase relative to placebo. However, the incidence of CIN 2/3 also increased substantially in the vaccinated population, suggesting an important role of non-vaccine HPV types.

➢ ***Combined efficacy results with respect to CIN 1 due to any HPV type***

Vaccine efficacy against CIN 1 due to <u>any</u> HPV type was 27.9% (95% CI: 12.0, 41.0) in the RMITT-2 population, 22.3% (95% CI: 11.2, 32.0) in the MITT-2 population and 19.0% (95% CI: 10.0, 27.0) in the MITT-3 population of the combined studies 013 and 015.

➢ ***Efficacy against VIN 2/3 and VaIN 2/3 due to any HPV type***

This analysis was conducted in the pooled dataset of Protocols 013 and 015 (not including P007). The results are shown in table 16.

**Table 16: Analysis of efficacy against VIN 2/3 and VaIN 2/3 due to any HPV type (P013, P015 combined)**

| | **Silgard n=8799** | | **Placebo n=8800** | | **Observed efficacy** | |
|---|---|---|---|---|---|---|
| **Study population** | **n** | **Number of cases** | **n** | **Number of cases** | **%** | **95%CI** |
| **MITT-2** | | | | | | |
| VIN 2/3 or VaIN 2/3 due to any HPV type | | | | | | |
| VIN 2/3 | **8667** | **8** | **8680** | **29** | **72.4** | **38.1, 89.1** |
| VaIN 2/3 | 8667 | 11 | 8680 | 18 | 38.8 | -36.8, 73.9 |
| **RMITT-2** | | | | | | |
| VIN 2/3 or VaIN 2/3 due to any HPV type | | | | | | |
| VIN 2/3 | **4688** | **2** | **4732** | **16** | **87.4** | **46.4, 98.6** |
| VaIN 2/3 | 4688 | 4 | 4732 | 9 | 55.3 | -60.2, 89.9 |
| **MITT-3** | | | | | | |
| VIN 2/3 or VaIN 2/3 due to any HPV type | | | | | | |
| **VIN 2/3** | **8687** | **16** | **8697** | **32** | **49.9** | **6.0, 74.3** |
| VaIN 2/3 | 8687 | 12 | 8697 | 21 | 42.9 | -21.6, 74,4 |

Vaccine efficacy against VIN/ 2/3 due to any HPV type was demonstrated in all study populations and was high in the HPV naïve women, 87% in RMITT-2 population and 72% in the MITT-2 population supporting the important role of vaccine HPV types in this condition. In the MITT-3 population it was lower, 49.9%. For VaIN 2/3 only numerical reductions were observed in all study populations.

➢ ***Efficacy with respect to external genital lesions due to any HPV type***

The higher efficacy in the RMITT-2 population (VE: 74.1%) compared with the MITT-2 population (VE: 65.2%) is likely a reflection of the fact that only subjects who were negative to <u>all</u> 14 tested HPV types and who had a normal Pap test result at Day 1 were included in the RMITT-2 population, whereas the MITT-2 population included any subject who was negative to at least 1 tested HPV type (Table 17). The more stringent RMITT-2 inclusion criteria identify a population of women who are less likely to have been exposed to any vaccine or non-vaccine HPV type compared with the MITT-2 population. The reductions observed in the MITT-3 populations were more modest (VE: 49.0%).

**Table 17: Analysis of efficacy against EGL due to <u>any</u> HPV type by severity of disease (P013, P015 combined)**

| Study population | Silgard N=8799 | | Placebo N=8800 | | Observed efficacy % | 95%CI |
|---|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | | |
| **MITT-2** | | | | | | |
| EGL due to any HPV type | **8667** | **120** | **8680** | **342** | **65.1** | **57.0, 71.9** |
| *By disease severity* | | | | | | |
| Condyloma | 8667 | 57 | 8680 | 254 | 77.7 | 57.0, 71.9 |
| Vulvar condyloma | 8667 | 54 | 8680 | 239 | 77.5 | 70.1, 83.5 |
| Vaginal condyloma | 8667 | 4 | 8680 | 27 | 85.2 | 69.7, 83.6 |
| VIN 1 or VaIN 1 | 8667 | 54 | 8680 | 83 | 34.9 | 57.4, 96.2 |
| VIN 1 | 8667 | 17 | 8680 | 31 | 45.0 | 7.1, 54.6 |
| VaIN 1 | 8667 | 37 | 8680 | 52 | 28.7 | -2.4, 71.5 |
| VIN 2/3 or VaIN 2/3 | 8667 | 19 | 8680 | 47 | 59.5 | -10.8, 54.5 |
| VIN 2/3 | 8667 | 8 | 8680 | 29 | 72.4 | 29.7, 77.6 |
| VaIN 2/3 | 8667 | 11 | 8680 | 18 | 38.7 | -37.0, 73.9 |
| **Vulvar cancer** | 8667 | 1* | 8680 | 0 | NA | NA |
| **RMITT-2** | | | | | | |
| EGL due o any HPV type | **4688** | **49** | **4732** | **189** | **74.1** | **64.4, 81.5** |
| *By disease severity* | | | | | | |
| Condyloma | 4688 | 26 | 4732 | 144 | 81.9 | 72.4, 88.6 |
| Vulvar condyloma | 4688 | 24 | 4732 | 136 | 82.3 | 72.5, 89.0 |
| Vaginal condyloma | 4688 | 2 | 4732 | 15 | 86.5 | 42.1 ,98.5 |
| VIN 1 or VaIN 1 | 4688 | 19 | 4732 | 44 | 56.5 | 23.9, 76.0 |
| VIN 1 | 4688 | 4 | 4732 | 14 | 71.2 | 8.2, 93.1 |
| VaIN 1 | 4688 | 15 | 4732 | 30 | 49.6 | 3.3, 74.8 |
| VIN 2/3 or VaIN 2/3 | 4688 | 6 | 4732 | 25 | 75.8 | 39.6, 91.9 |
| VIN 2/3 | 4688 | 2 | 4732 | 16 | 87.4 | 46.4, 98.6 |
| VaIN 2/3 | 4688 | 4 | 4732 | 9 | 55.1 | -60.8, 89.9 |
| **Vulvar cancer** | 4688 | 1* | 4732 | 0 | NA | NA |
| **MITT-3** | | | | | | |
| EGL due o any HPV type | **8687** | **213** | **8697** | **415** | **49.0** | **39.6, 56.9** |
| *By disease severity* | | | | | | |
| Condyloma | 8687 | 125 | 8697 | 308 | 59.6 | 50.1, 67.4 |
| Vulvar condyloma | 8687 | 114 | 8697 | 289 | 60.7 | 51.0, 68.6 |
| Vaginal condyloma | 8687 | 12 | 8697 | 33 | 63.6 | 27.6, 82.9 |
| VIN 1 or VaIN 1 | 8687 | 82 | 8697 | 108 | 24.0 | -2.3, 43.6 |
| VIN 1 | 8687 | 27 | 8697 | 38 | 28.8 | -19.7, 58.2 |
| VaIN 1 | 8687 | 55 | 8697 | 72 | 23.5 | -10.2, 47.1 |
| VIN 2/3 or VaIN 2/3 | 8687 | 27 | 8697 | 52 | 48.0 | 15.7, 68.6 |
| VIN 2/3 | 8687 | 16 | 8697 | 32 | 49.9 | 6.0, 74.3 |
| VaIN 2/3 | 8687 | 12 | 8697 | 21 | 42.8 | -21.8, 74.3 |
| **Vulvar cancer** | 8687 | 1* | 8697 | 0 | NA | NA |

*The case of vulvar cancer was described in the MAA. A 22-year-old woman reported a small lesion on her perineum 18 months after completion of a 3-dose regimen of Silgard. The perineal swabs for HPV testing were positive for HPV 16 and HPV 59. The biopsy revealed a well differentiated squamous carcinoma. PCR of the biopsy was negative including 10 non-vaccine HPV types. The lesion was not visible during follow-up and no treatment was provided.

#### 1.2.1.4 Discussion on clinical efficacy

In this type II variation application for Silgard the MAH seeks approval for an extension of the indication to include protection against vulvar and vaginal cancer, low-grade vulvar dysplasia (VIN 1), high-grade and low-grade vaginal (VaIN 1/2/3) dysplasia and low-grade cervical dysplasia (CIN 1) based on one more year of follow-up of vaccine efficacy in the phase III program (FUTURE I and II) as well as post-marketing experience. The follow-up period after the first vaccine dose is at present approximately 3 years. The expansion of the database with longer term data on vaccine efficacy, made possible a definitive analysis of the impact of the vaccine on the overall HPV disease burden.

In the primary assessment of this variation the CHMP identified major objections and a number of other concerns. The MAH´s claims for vaginal and vulvar cancers and for low-grade cervical, vaginal and vulvar dysplasia (CIN 1, VIN 1, VaIN 1) in the indication were not considered approvable.

The updated results in the HPV-naïve populations (PPE and MITT-2) confirmed and strengthened the efficacy findings in the MAA. Vaccine efficacy against the primary endpoint, HPV 16/18-related CIN 2/3 or AIS, remained high and there was no evidence of waning immunity. The pooled efficacy analysis in the PPE-population was based on a total of 86 cases of HPV 16/18-related CIN 2/3 (compared to 53 cases in the MAA), whereof one case was detected in the vaccine group and 85 cases in the placebo group (VE: 99% (95% CI: 93.3, 100.0). The one case of CIN 2/3 in the vaccine group was likely causally related to a non-vaccine HPV type (HPV 52). With respect to the most relevant surrogate markers for cervical cancer, HPV 16/18-related CIN 3 and adenocarcinoma in situ (AIS), efficacy estimates were significant for both endpoints (VE: 98% and 100%, respectively) in the HPV naïve populations. In the MITT-3 population, that included subjects, who were already infected with a vaccine/non-vaccine HPV type at baseline, vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 44% (compared with 39% in the MAA). With respect to HPV 6/11/16/18-related CIN 1, efficacy remained high in all study populations with VE of 95.5% in the HPV naïve population and VE of 64.5% in the MITT-3 population. There was no evidence of therapeutic vaccine efficacy.

Efficacy against HPV 6/11/16/18-related genital warts (condyloma acuminata) remained high, with efficacy estimates of 99%, 95% and 77% in the PPE, MITT-2 and MITT-3 populations, respectively.

In the integrated summary analysis, significant vaccine efficacy against both HPV 16/18-related VIN 2/3 and VaIN 2/3 was demonstrated in all study populations, supporting the claim of the MAH to include also VaIN 2/3 in the indication. VE for VaIN 2/3 was 100% in the PPE population and 81.8% in the MITT-3 population. Hence, the supplementary data allowed for a conclusion that Silgard is efficacious against HPV 16/18-related VaIN 2/3, which support the inclusion of this condition in the indication.

In the MAH´s response to the first RSI, the claims for the prevention of vulvar and vaginal cancer was withdrawn. It was agreed that at the present stage neither international guidelines nor consensus statements of the scientific community are available to support high-grade vulvar/vaginal lesions as valid surrogate markers for cancer. The MAH also withdrew his claims for low-grade vulvar (VIN 1) and vaginal (VaIN 1) intraepithelial lesions in the indication.

The MAH´s claim for CIN 1 was retained and supported by a recent published European guideline for quality assurance in cervical screening. In the MAH´s view the need for clinical follow up, further diagnostic procedures and potentially therapy, as recommended in the guideline, is best addressed by having CIN 1 in the SPC section 4.1. In the EU guideline CIN 1 is recognised as a lesion that requires follow-up with repeat cytology, HPV testing, colposcopy and excision in selected cases. The CHMP agrees that the accuracy in the diagnosis of CIN 1 in clinical practice can be variable. The management of low-grade cervical lesions has to be balanced against the high chance of spontaneous regression (60-70%) and negative histology with the possible risk of not treating underreported and/or missed high-grade disease. Although CIN 1 is not a surrogate marker for cancer, the need to follow-up

these lesions translates to a substantial public health burden, since CIN 1 is the most common HPV-related cervical lesion. The vaccine HPV types are estimated to cause 30-50% of CIN 1 lesions, which in Europe corresponds to approximately 286 000 CIN 1 lesions annually. In the combined study protocols (007, 013, 015) vaccine efficacy against CIN 1 related to vaccine HPV types was 95.5% in the PPE population; 94.6% in the MITT-2 population and 64.5% in the MITT-3 population. Vaccine efficacy against CIN 1 due to any HPV type was 27.9% (95% CI: 12.0, 41.0) in the RMITT-2 population, 22.3% (95% CI: 11.2, 32.0) in the MITT-2 population and 19.0% (95% CI: 10.0, 27.0) in the MITT-3 population of the combined studies 013 and 015. The reduction in the overall burden of CIN 1 disease of 30% in the HPV naïve population would result in significant public health benefit.

The analysis of the public health impact revealed a significant reduction in the overall burden of CIN 2/3 or AIS in the HPV-naïve population, whereas the reduction in the general population (MITT-3) was limited. The vaccine efficacy against CIN 2/3 or AIS due to any HPV type in the RMITT-2 population was 46.1% (95% CI 23.6, 62.3). The observed efficacy in the MITT-3 population was only 13.5% (18% (95% CI: 6 to 28) (if studies 005 and 007 were included in the analysis). When analysed by disease severity, no significant efficacy against CIN 3 was documented (lower 95% CI <0%) in the MITT-3 population. With regard to the impact on invasive cervical procedures, it was shown that definitive therapy was reduced by 40% and colposcopy by 20% in the vaccinated RMITT-2 population and 20% and 11%, respectively, in the MITT-3 population. More long-term data are needed to evaluate the real public health impact of Silgard. However, these results are clinically relevant from a public health perspective and justify a statement in the section 5.1 of the SPC.

As regards the indication, SPC section 4.1, the MAH was requested to simplify the wording and use the more general term ´premalignant genital lesions´ instead of the list of study endpoints. Moreover, the SPC changes proposed by the MAH in section 5.1 required major revision.

In the response to the second RSI, the MAH accepted the requested simplified wording of the indication provided that the localisation of the genital lesions was defined and that the conditions covered in the indication were further specified in section 5.1. The proposed additions are considered reasonable except for the inclusion of CIN 1 in the introductory sentence in section 5.1, since low-grade cervical intraepithelial lesion is not considered a premalignant genital lesion. The estimated vaccine efficacy against CIN 1 is described elsewhere in section 5.1.

### 1.2.2 Clinical safety

**Patient exposure**
Overall, 21,480 subjects were vaccinated in protocols 007, 013, 015, 016 and 018. A total of 11,912 subjects received at least one dose of qHPV. This includes a total of 120 subjects in protocol 007 extension who received a 3-dose regimen of placebo in the main study and subsequently received qHPV in the extension phase of the study. A total of 9688 subjects received at least one dose of placebo.
Fourteen (14) subjects who were randomised to receive qHPV and 2 subjects randomised to receive placebo received protocol non-compliant vaccination regimens and were excluded from the safety summary.

**Common Adverse Experiences**
Injection-Site Adverse Experiences
As noted in the MAA and Safety Update Report (SUR) for the Detailed Safety Population, the proportion of subjects reporting an injection-site adverse experience within 5 days after any vaccination was higher in subjects who received qHPV compared with subjects who received aluminum-containing placebo or non-aluminum-containing placebo. The most common injection-site adverse experiences reported were pain, swelling, and erythema.

**Systemic Clinical Adverse Experiences**
As noted in the MAA and SUR for the Detailed Safety Population, the most common reported systemic clinical adverse experiences determined by the investigator to be vaccine related were headache, pyrexia, and nausea. The proportions of subjects who reported a systemic clinical adverse experience, and the proportions of subjects who reported a vaccine-related systemic clinical adverse experience, were comparable between the two vaccination groups.

**Death**
Overall, a total of 18 subjects died at any time during the studies. Of 11,464 subjects who received at least one dose of qHPV, 11 subjects (0.1%) died. Of 9686 subjects who received placebo, 7 subjects (0.1%) died. None of the deaths was considered placebo or procedure related. Compared with the SUR data one additional subject committed suicide 1177 days after completion of the primary vaccination series.
No causal relationship between the fatal outcomes and administration of qHPV vaccine was identified.

**Safety in special populations**
Pregnancy Outcomes in the Integrated Databases of Phase III Clinical Studies of qHPV
Overall, 2832 subjects experienced 3225 pregnancies (1396 recipients of qHPV (13.4%) and 1436 recipients of placebo (15.7%). The lower rate in the qHPV group is likely due to the higher proportions of 9- to 15-year-old subjects in this group as compared with the placebo group.
Among the 3225 pregnancies, outcomes were known for 2652 fetuses/infants (1315 qHPV recipients and 1337 placebo recipients). Since the cut-off date for the original SUR (Safety Update Report) 709 pregnancies have been reported. The majority of pregnancies with unknown outcomes were pregnancies that were ongoing at the time of cut-off date.

Live births: Cumulatively the proportions of pregnancies that resulted in a live birth were comparable between the vaccination groups.

Methods of delivery: Cumulatively the proportions of deliveries that were vaginal or by Caesarean section were comparable between the vaccinations groups.

Live- born Infants: The great majority of live-born infants in both vaccination groups were categorised as normal.

Congenital anomalies:
The proportion of live births that resulted in congenital anomalies was comparable between the vaccination groups. Congenital anomalies that occurred in the Phase III studies are cumulatively listed. NEW congenital anomalies were reported in 10 study subjects who received qHPV. These anomalies included cardiac septal defect, congenital pulmonary valve atresia, heart disease congenital, persistent fetal circulation, accessory auricle, choanal atresia, palpebral ptosis, thalassemia alpha, polydactyly and renal aplasia. Congenital anomalies were reported in 6 children born to subjects who received placebo. These anomalies included atrial septal defect, tricuspid valve incompetence, ventricular septal defect and persistent fetal circulation, tetralogy of Fallot, anotia, cleft lip and palate and chondrodystrophy.
None of the New congenital anomalies reported were determined by the investigator to be related to study vaccine or placebo.
The CHMP agrees that there is no identified causal relationship between any of the congenital anomalies and administration of qHPV.

➢ ***Postmarketing data***

qHPV was first licensed on 01-June-2006 in Mexico. Two 6-month Periodic Safety Update Reports (PSURs) for qHPV for the periods of 01-June-2006 thru 30-Nov-2006 and for 01-Dec-2006 thru 31-May-2007 are complete.

Of the total number of 4586 AE reports received during this time period, 317 (7%) reports were considered serious. The majority (3947 or 86%) of reports originated in the United States.

The EU SPC has been updated to include Syncope, Dizziness, Nausea, Vomiting, Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm and urticaria through the Type II variation II/05 which received an EU Commission Decision on 26 July 2007. In the scope of the current variation, the MAH proposes to update section 4.8 of the EU SPC and section 4.0 of the PL, with the following adverse events: Lymphadenopathy, Headache and Guillain-Barré Syndrome (GBS). The decision to include the adverse events Lymphadenopathy, Headache and Guillain-Barré Syndrome (GBS) was made subsequent to the review of the safety profile of the product.

**Lymphadenopathy**
A review of the NWARS database for the period 11 September 2006 to 11 April 2007 identified 18 reports of lymphadenopathy temporally associated with the administration of qHPV. Three of these reports included positive rechallenges. There were 7 reports with specified unilateral lymphadenopathy. Four of the 7 reports included the time to onset of lymphadenopathy post vaccination 3-11 days. The remaining 8 reports involved 4 which indicated only that the patients experienced “swollen glands” and 2 reports which indicated experience of swollen lymphnodes in more than one area. Time to onset was 1-5 days. The remaining reports were confounded by other factors.

**Headache**
A review of the NWARS database for the period 11September 2006 to 11 April 2007 identified 62 reports of headache temporally associated with the administration of qHPV. Five of these events were assessed as serious and 57 as non-serious. Headache was most often reported with nausea (20) dizziness(20), pyrexia (12), vomiting (6) and myalgia/arthralgia (6).

**Guillain-Barré Syndrome (GBS)**
A review of the NWARS database for the period 11 September 2006 to 11-Apr-2007 identified 14 reports of Guillain Barré syndrome temporally associated with the administration of qHPV. Five of the 14 reports included minimal detailed information. However, 2 of the reports included the time to onset of GBS post-vaccination Day 8 and Day 9. One case developed GBS on Day 15 after the second dose of qHPV. Assessment of seven of the remaining 9 reports was confounded by other plausible factors. Five of 7 reports involved patients who received concomitant quadrivalent meningococcal conjugate vaccine on the same date. Additionally one of these 7 patients has a working diagnosis of GBS, not yet confirmed. Another patient, who received concomitant meningococcal vaccine and had a LP confirmed GBS also had MRI results showing an old chronic, subarachnoid cyst. Follow-up information on a third patient that received concomitant meningococcal vaccine with EMG strongly positive for GBS revealed that the patients onset of symptoms preceded the vaccination. The 2 remaining reports including confounding factors involved one case with multiple medical conditions and one case with a family history of MS who experienced an URI before onset of GBS. The remaining two reports of GBS included abnormal EMG. The time to onset of GBS post vaccination was provided in 12 of the 14 reports and ranged from 6 to 15 days with a median of 9 days. Half of the cases had confounders. Five of the cases without confounders included little information to make an assessment. Two cases provided sufficient information to assess them as likely cases of GBS. The onset was 9-14 days from vaccination. The cause of GBS remains unknown but may involve a non-specific stimulus.
As the experiences were reported voluntarily from a population of uncertain size it is not possible to estimate the frequency or to establish a causal relationship to vaccine exposure.

**Non-specific arthritis/ arthropathy**
The MAH revised in section 4.8 the number of cases of non-specific arthritis/ arthropathy: 26 cases (19 in the Silgard group and 7 in the placebo group) reported as any new medical conditions during the follow up of up to four years.
The reports of the 19 cases of athralgia/arthropathy in temporal relationship to administration of Silgard occurred after 2 months (n=3), 6 months (n=4), 7 months (n=1), 12 months (n=1), 24 months (n=6), 30 months (n=2) and 36 months (n=2). The 7 placebo related reports occurred at month 12 (n=1), month 18 (n=2), month 24 (n=2) and month 36 (n=2). Adjudication of relatedness and/or causality was not accounted for although considering that some of these reactions might be of autoimmune origin a possible relationship can not be excluded. These reactions should be continuously monitored and commented on in the future PSURs.

**Neurological reactions**
Furthermore, a recent follow-up measure concerned reports on transverse myelitis, leukoencephalitis, optic neuritis, diplopia, vision blurred, papilloedema and demyelinating disorders in relation to vaccination with qHPV. The MAH provided updates and discussion of the cases of these events. Additional information was received regarding 16 cases of grand mal convulsion and 64 cases of convulsion. These reactions were evaluated within the PSUR 3 and no changes to the SPC are required at the moment.

**Adenopathies**
Additional analysis on a safety review of cases of adenopathies reported as temporally associated with the administration of Silgard was requested by the CHMP and the results should be presented in the next PSUR.

**Discussion**
Overall the post marketing experiences with qHPV has confirmed a favourable safety profile with a low frequency of reported serious adverse experiences. The data reviewed do not include any new or unexpected reports of adverse events.

The MAH proposes to change the term for the adverse reaction of “bleeding at the injection site” into the MedDRA preferred term "injection site bruising" for accuracy. At the time of the study coding,

bruising at the injection site coded up to "Hemorrhage" in the MedDRA system which then was changed to the word "bleeding" for the product information. In fact the subjects experienced bruising at the injection site. The MedDRA code has now been changed and injection site bruising is a preferred term. The CHMP agrees with this change.

The reports above discussed on GBS and Headache support the inclusion of these adverse reactions in the SPC section of Post Marketing experience.

The requested supplementary information has been provided.

Additional safety information on reports on lymphadenopathy was received during the assessment period. The PSUR 3 (covering period 1/06/2007-30/11/2007) reports on 18 cases of lymphadenopathy temporally associated with vaccination identified for the period of market introduction to 11-Apr-2007. Three of these reports include positive re-challenge. Because at least 2 of 3 cases of positive re-challenge were positive it is considered biologically plausible that vaccination could be causally associated with lymphadenopathy. This supports the inclusion of lymphadenopathy in section 4.8 of the SPC.

The 19 reported cases of arthritis/arthropathy occurred between 2 and 36 months after vaccination although adjudication of relatedness and/or causality was not accounted for. In consideration of that some of these reactions may be of autoimmune origin a possible relationship cannot be excluded. These cases are also discussed in PSUR 3. The inclusion in the SPC is considered adequate.

Regarding the adverse reactions of autoimmune diseases, i.e. rheumatoid arthritis, multiple sclerosis (MS), Chron´s disease and autoimmune thyroiditis it is considered that the occurrence of these adverse events will presently not deserve inclusion in the SPC. The majority of autoimmune diseases occurred 12 to 48 months post vaccination. Only one case of autoimmune thyroiditis occurred in temporal relatedness to vaccination at Month 2. Causality has not been clearly defined in any of these reports. The MAH has committed to continue close monitoring of all autoimmune diseases and to present such reports in the future PSURs in cumulative way.

A cumulative analysis of neurologic adverse events was evaluated in PSUR 3. The MAH should continue to monitor these adverse reactions.

The safety of the product and the specific adverse events:
- Autoimmune disorders
- Rheumatological conditions
- Non-specific inflammatory reactions
- Immunological events
- Skin and subcutaneous disorders

will continue to be thoroughly monitored through PSURs.

### 1.3 Pharmacovigilance system

#### 1.3.1 Risk Management Plan

The MAH has supplied a revised RMP updated with safety data.

The MAH as committed to provide a revised RMP by the next PSUR submission due on 30 July 2008.

### 1.4 Overall discussion and Benefit/Risk Assessment

The major objections were resolved as the claims for vulvar and vaginal cancers as well as for VIN 1 and VaIN 1 were withdrawn by the MAH. The supplementary data allowed for a conclusion that Silgard is efficacious against HPV 16/18-related VaIN 2/3, which support the inclusion of this condition in the indication. The recent EU guideline of the EU Commission/IARC on the management of CIN 1 supported that this low-grade cervical lesion is a clinically relevant endpoint requiring clinical follow-up, diagnostic procedures, and in selected cases, therapeutic intervention. Since the MAH was requested to simplify the wording of the indication (according to the SPC guideline and to be better understood by prescribers) to include premalignant genital lesions, the CHMP considered that there was no need to specifically mention CIN 1 in section 4.1. Because of the simplified wording for the therapeutic indication the MAH proposed the addition of an introductory sentence in section 5.1 specifying the type of lesions included in premalignant genital lesions. The CHMP, however, did not consider it applicable to CIN 1. Low-grade cervical intraepithelial lesions are not considered premalignant and CIN 1 should not be included in the paragraph referred on section 5.1. Vaccine efficacy against CIN 1 is already mentioned elsewhere in section 5.1.

All other concerns were resolved. Overall the post marketing experiences with qHPV has confirmed a favourable safety profile with a low frequency of reported serious adverse experiences. The data reviewed do not include any new or unexpected reports of adverse events.
The MAH has committed to submit an updated RMP at the time point of the next PSUR addressing some specified safety and post-marketing surveillance issues.

In conclusion, the Benefit/Risk ratio for Silgard in the indication for prevention of high-grade vaginal dysplastic lesions (VaIN 2/3) is considered positive. Therefore, the therapeutic indication for Silgard 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 was endorsed by the CHMP.

## 1.5 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 approved indication to include protection against vulvar and vaginal cancer, VIN 1, VaIN 1/2/3 and CIN 1.

There is sufficient evidence to allow an indication to include protection against VaIN 2/3. The claims for vulvar and VIN 1 and VaIN 1 were not accepted by the CHMP and were withdrawn by the MAH.

The CHMP considered that the wording proposed by the MAH including the different endpoint was too complex and could be simplified to be better understood by the prescribers.

The MAH´s claim for prevention of "high-grade cervical intraepithelial neoplasia (CIN 2/3), high-grade vulvar intraepithelial neoplasia (VIN 2/3) and high-grade vaginal intraepithelial neoplasia (VaIN 2/3)" is covered by the broader term of "premalignant genital lesions" and a description on section 5.1.

The MAH acknowledges the CHMP position and submitted a revised wording which was agreed with, as follows:

*"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)."*

**Section 4.2 "Posology and method of administration"**

The sentence on intravascular, subcutaneous and intradermal administration was reformulated for clarity.

A sentence was introduced to recommend that subjects who receive a first dose of Silgard complete the 3-dose vaccination course with Silgard .

**Section 4.4 "Special warnings and precautions for use"**

A paragraph was added to inform health care professionals that there no safety, immunogenicity or efficacy data is available to support interchangeability of Silgard with other HPV vaccines.

**Section 4.6 "Pregnancy and lactation"**

The MAH proposed to update the numbers on pregnant women and cases of congenital anomalies observed. The CHMP agreed with this proposal.

**Section 4.8 "Undesirable effects"**

For clarity bleeding was replaced by bruising.

The numbers of subjects experiencing arthritis/arthropathy were updated.

The post marketing experience section was revised to include lymphadenopathy, GBS and headache.

**Section 5.1 "Pharmacodynamic properties"**

The second paragraph on mechanism of action was updated based on data supported by literature concerning the percentages of the different diseases/endpoints resulting from HPV infections.

A paragraph was introduced to clarify the term "premalignant genital lesions" in section 4.1. that corresponds to high-grade cervical intraepithelial neoplasia (CIN 2/3), high-grade vulvar intraepithelial neoplasia (VIN 2/3) and high-grade vaginal intraepithelial neoplasia (VaIN 2/3).

The MAH proposed to update the section on clinical studies based on the results of the analysis submitted. The CHMP proposed the revision of the text submitted.
Efficacy results are presented for the combined analysis of study protocols. The efficacy for HPV 16/18 related CIN 2/3 or AIS is based on data from protocols 005 (16-related endpoints only), 007, 013, and 015. The efficacy for all other endpoints is based on protocols 007, 013, and 015. Results of individual studies support the results from the combined analysis.
Efficacy results are presented for 2- and 3-years results for the main endpoints and for the different relevant populations: subjects naïve to the relevant vaccine HPV type and subjects with and without prior infection or disease due to HPV 6, 11, 16, or 18.

Data on Table 3 concerning Immunogenicity bridging between 9- to 15-year-old male and female subjects and 16- to 26-year-old adult women (per-protocol population) based on titres of antibodies directed against known neutralizing epitopes as measured by cLIA was updated as submitted by the MAH.

**Annex IIB**
Annex II was updated concerning the RMP.

**PL**
The PL was updated in accordance with the changes proposed to the SPC.

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

## II. CONCLUSION

On 24 April 2008 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 subject to additional follow up measures undertaken.

## III. GLOSSARY

1. AIS – Cervical Adenocarcinoma In situ
2. CHMP – Committee for Medical Products for Human Use
3. CIN – Cervical Intraepithelial Neoplasia
4. cLIA – Competitive Luminex Assay
5. EGL – External Genital Lesion
6. EMEA – European Medicines Agency
7. FUM – Follow up measure
8. FUTURE – Females United To Unilaterally Reduce Endo/Ectocervical Disease
9. HPV – Human Papilloma Virus
10. LEEP – Loop Electrosurgical Excision Procedure
11. MAA – Marketing Authorisation Application
12. MAH – Marketing Authorisation Holder
13. PCR – Polymerase Chain Reaction
14. PYR – Person-Years at Risk
15. RRP – Recurrent Respiratory Papillomatosis
16. SPC – Summary of Product Characteristics
17. STD – Sexually Transmitted Disease
18. SUR – Safety Update Report
19. VaIN – Vaginal Intraepithelial Neoplasia
20. VE – Vaccine Efficacy
21. VIN – Vulvar Intraepithelial Neoplasia
22. VLP – Virus-like Particles
23. WHO – World Health Organisation