21 February 2013
EMA/277891/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cervarix

Common name: HUMAN PAPILLOMAVIRUS VACCINE [TYPES 16, 18] (RECOMBINANT, ADJUVANTED, ADSORBED)

Procedure No. EMEA/H/C/000721/II/0036

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals S.A. submitted to the European Medicines Agency on 16 March 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Cervarix	human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed the update of sections 4.1 and 5.1 of the Summary of Product Characteristics (SmPC) based on efficacy and immunological data obtained in study HPV-010 (Month 7 and Month 36). The MAH proposed to infer efficacy to Cervarix for premalignant vulvar and vaginal lesions in women and young girls aged 9 and above. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Pieter Neels

1.2. Steps taken for the assessment

Submission date:	16 March 2012
Start of procedure:	25 March 2012
Rapporteur's preliminary assessment report circulated on:	18 June 2012
Rapporteur's updated assessment report circulated on:	17 July 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 July 2012
MAH's responses submitted to the CHMP on:	14 September 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	5 October 2012
SAG vaccines	8 October 2012
Rapporteur's final assessment report on the MAH's responses circulated on:	09 November 2012

2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	15 November 2012
MAH's responses submitted to the CHMP on:	21 December 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	01 February 2013
Rapporteur's updated assessment report on the MAH's responses circulated on:	15 February 2013
CHMP Opinion:	21 February 2013

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/11/2009 on the granting of a product-specific waiver. At the time of the EMA Decision, Cervarix was already authorised for use in girls from 10 years of age onwards.

2. Scientific discussion

2.1. Introduction

Cervarix is a prophylactic vaccine which contains 20µg per 0.5 mL dose of HPV-16 L1 protein and 20µg per 0.5ml dose of HPV-18 L1 protein assembled as virus-like particles (VLPs) as active ingredients. The L1 proteins are formulated with AS04 adjuvant system, which is composed of 50µg of 3-O-desacyl-4'-mono-phosphoryl-lipid A (MPL) and 500µg of aluminium hydroxide salt. The vaccine is preservative-free.
Cervarix was first registered in 2007 and the vaccine is currently licensed for use in more than 110 countries worldwide. In Europe, Cervarix is indicated for use from the age of 9 for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types.
The use of Cervarix should be in accordance with official recommendations. The vaccination course consists of three doses administered according to a 0, 1, 6 month schedule via intramuscular injection.

The purpose of this variation is to provide the results from the analysis of study HPV-010 (Month 7 and Month 36). Study HPV-010 demonstrated the non-inferiority and superiority of the immune response (superiority of Cervarix to qHPV vaccine in terms of immune response measured by PBNA at Month 36) elicited by Cervarix over qHPV vaccine in women aged 18-45 years. The study results did not contain efficacy data related to the proposed variation. Based on the approved indication for qHPV vaccines and the immunogenicity data of study HPV-010, the MAH proposed to infer efficacy to Cervarix for premalignant vulvar and vaginal lesions in women and young girls aged 9 and above. The efficacy of Cervarix against vulvar and vaginal lesions was assessed as exploratory endpoints in the efficacy study HPV-008. The results of this analysis were submitted as supportive evidence.

In addition, a review of the scientific evidence supporting the extension of the indication to encompass protection against premalignant vulvar and vaginal lesions was provided.

2.2. Background

Lower genital tract neoplasia comprises cervical, vaginal and vulvar intraepithelial neoplasia (VIN), which in a small proportion of cases, progresses to invasive cancer. Virtually 100% of cervical, about 43% of vulvar, and approximately 70% of vaginal tumors are attributable to human papillomavirus infection annually (see Table 1) generating 530,000 cervical and 21,000 vulvar and vaginal cancers worldwide (Lowy 2012, Forman 2012). In the absence of a screening strategy, there has been an increase in the incidence of VIN and vulvar cancer in younger women (van de Nieuwenhof 2009). Treatment standards for HPV-associated anogenital lesions have primarily been by surgical excision. Screening identifies high-grade cervical intraepithelial neoplasia (CIN2/3) mainly in women of reproductive age with current treatment strategies very effective in eliminating the abnormal HPV-infected precancerous cells while minimizing harm to the cervical integrity (Stern, 2012).

Table 1. Estimated number of new cancer casesa occurring in 2008 attributable to HPV (adapted from Forman 2012 with data sourcing from de Martel 2012)

	Number of new cases in 2008	Number attributable to HPV	Population attributable fraction (HPV)	Number attributable to HPV by age group		
				<50 years	50 to 69 years	>70 years
Vulva	27000	12000	43.0	1700	3900	6000
Vagina	13000	9000	70.0	2000	4000	3100

[a] Numbers rounded to two significant digits

The standard of care for treating VIN has been, and remains, surgical excision for unifocal disease and lesions suspicious for possible invasion. More problematic is multifocal disease, which can affect a large proportion of the vulva (Herod 1996). Excision of such a large area of vulvar skin can result in loss of vulvar contours and sexual function, which can have a profound effect on a woman's self-esteem and quality of life (Shylasree 2008). Treatment failure in VIN is not only common, but risks development of invasive disease, which only adds to the challenge. These difficulties mean that surgical excision is not an optimal means of treating multifocal disease. Laser ablation has the advantage of precise application and avoidance of skin loss, but it is associated with a high rate of treatment failure. Vulvar cancer relies on surgery for localized disease and a combination of surgery and chemoradiation for nodal metastases. Only in very advanced disease, where surgery would necessitate defunctioning bowel or urinary tract, is chemoradiation preferred as sole therapy. The major development in vulvar cancer surgery in recent years has been sentinel node biopsy, which offers the means to avoid full groin dissection in sentinel node-negative women, thus reducing the risk of lower limb lymphoedema, which can be very disabling (RCOG 2011, Stern 2012).

Interestingly, vulvar or vaginal high grade lesions can result from intraepithelial spreading of single transformed cell clones initiated in the cervical region (Daling 2002, Vinokurova 2005, Hampl 2007). These findings reinforce the expectation that a vaccine highly efficacious against cervical disease will be efficacious against HPV-related vulvar and vaginal disease (Hampl 2006).

The overall impact of Cervarix on cervical lesions has been established in a large efficacy study in naïve young women aged 15 to 25 years. The vaccine was virtually 100% effective (95% CI: 81.8-100) against high grade cervical lesions (CIN3+) with HPV 16 or 18 (ATP cohort for efficacy using HPV type assignment analysis (TAA)) and protected against 93.2% (95% CI: 78.9; 98.7) of CIN 3 lesions, irrespective of the HPV type1 (Paavonen 2009). If the casual types and mechanisms of infection by HPV are similar for cervical and vulvar/vaginal diseases it can be reasonably expected that the vaccine will also protect against HPV-related vulvar and vaginal disease.

2.2.1. Natural history of papillomaviruses infection: Uptake and internalisation – Animal challenge models

HPV is a small virus of 55 nm diameter and comprises a double-stranded circular DNA of nearly 8000 base pairs. The HPV genome encodes eight proteins: early proteins E5, E6 and E7 are involved in cell proliferation and survival, and E6 and E7 play a key role in HPV-associated carcinogenesis; three other early proteins (E1, E2 and E4) are involved in control of viral gene transcription and viral DNA replication; two late proteins L1 and L2 are involved in assembly of new virus particles. The virus particle is composed of 72 capsomeres each composed of major L1 and minor L2 capsid proteins. The virus has evolved a replication cycle which is intimately linked to the life history of the differentiating epithelial cell where the small number of HPV genes coordinate in function with the host cell's own mechanisms to support viral replication and the production of large numbers of new infectious virions.

The dependence on epithelial differentiation for virion production has limited the study of the early steps in infection by native oncogenic HPV. However, using HPV L1 pseudo-virion particles, self-assembling proteins that resemble the HPV L1 capsid, in both in vitro and in vivo animal models has established some of the key factors involved. Heparan sulphate proteoglycans (HSPG) are the primary attachment factors for most HPV types (Shafti-Keramat 2003). These are ubiquitously expressed on mammalian cells and are integral components of the basement membrane (BM) and extracellular matrix that surrounds most tissues. It is thought that minor damage to the target exposure of the BM allowing for a primary step of viral capsid binding with a subsequent adsorption to the basal surface of epithelial cells during their regrowth and repair, which enables virion uptake. On virion binding, there is a capsid conformational change which exposes an L2 furin consensus site providing for N-terminal cleavage and further capsid structural alteration facilitating binding to an unknown cell receptor; subsequent internalisation can occur relatively rapidly (Richards 2006) (see Figure 1). This is consistent with the requirement of the minor capsid protein L2 for production of fully infectious HPV virions. An elegant murine cervicovaginal challenge model showed that HPV 16 L1/L2 pseudo-virion particles that resemble papillomavirus (Buck 2007) can cause widespread infection of epithelia within 48-72 hours (Roberts 2007). This time is insufficient for inducing a primary immune response leading to production of neutralizing antibodies or even for reactivating a memory immune response if levels of antibodies in situ are not high enough to thwart the infection. Once the viral genome is inside the cell, neutralizing antibodies against capsid proteins will be useless.

Recent studies describe the use of the cervicovaginal challenge murine model of HPV infection to dissect distinct steps in the process and the nature of the vaccine-induced antibodies that can interfere (Kines 2009, Day 2010). Importantly, the data emphasise how cell culture methods are unable to mimic the in vivo conditions and thus give potentially misleading results. This work provides formal proof that antibodies mediate the protective capacity of HPV VLP vaccines and a means for further refinement of the specificities and mechanisms involved. The in vivo model delineates the initial steps of HPV infection as taking place at the basement membrane (BM) followed by transition of the L1/L2 capsids to a furin (-like) protease cleaved version with exposure of L2 epitopes necessary for stable association with the epithelial target cell (Figure 1). L1 VLP vaccine induced protection was shown to include at least two distinct mechanisms mediated by polyclonal antibodies which are concentration dependent. High antibody levels can block binding to HSPG on the BM but lower amounts can block the secondary L1 receptor on epithelial cells. In the latter case, the number of different epitopes recognized has not been determined. As previously described (Gambhira 2007), anti-L2 antibody can also prevent binding and infection on the epithelial targets and importantly are not HPV type specific.

Figure 1. *In vivo* events leading to PV uptake by keratinocytes (Reproduced from Schiller 2010)

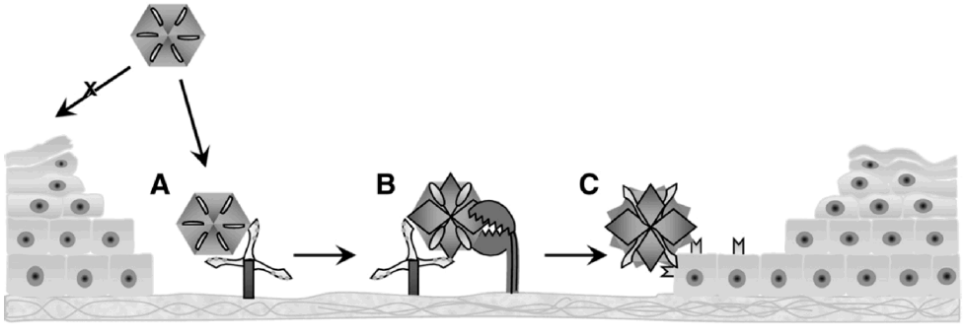


Fig. 1. The virion first binds to HSPGs on the BM exposed after disruption (A). This induces a conformational change exposing a site on L2 susceptible to proprotein convertase (furin or PC 5/6) cleavage (B). After L2 cleavage, an L2 neutralizing epitope is exposed and a previously unexposed region of L1 binds to an unidentified secondary receptor on the invading edge of the epithelial cells (C). BM = basement membrane; HSPG = heparan sulfate proteoglycan.

After the virus has entered cells in the basal layer of the epithelium, the genome is uncoated and transferred to the cell's nucleus where it exists as a non-integrated circular episome of less than 100 copies per cell; it is possible that the target cells include the reserve, or stem cell, population. The molecular and cell biology underwriting the natural history of the virus infection are intimately entwined (Roberts 2009). As these infected basal cells undergo cell division, the viral genome replicates and becomes equally segregated between the two daughter cells enabling maintenance of the HPV genome in this cell layer. New virus production is inhibited in the initial basal target cells and the productive infection process only begins with their migration upwards as suprabasal cells to generate the tissue architecture and maintain its constant renewal. In uninfected epithelium the upward migration of basal cells triggers their exit from the cell cycle and they enter the pathway of terminal differentiation. HPV relies upon the host cell for provision of key replication enzymes and other factors necessary to replicate its own genome and its HPV E6 and E7 proteins stimulate continued proliferation of the infected suprabasal cells (and therefore production of the cell's replication machinery) to potentiate survival long enough for the virus to replicate its own genome. Once the virus has amplified its genome, sometimes to levels exceeding many thousands of copies per cell, the HPV life cycle then switches to production of the coat proteins L1 and L2. This stage is controlled by the early E2 protein that down-regulates E6 and E7 protein expression by blocking the binding of transcription factors to the early virus promoter allowing the cell to continue the process of terminal differentiation. New virions are thus assembled in the uppermost cells of the lesion which undergo apoptosis and are sloughed off as the tissue is renewed from below (Conway 2009). If all the progeny of an initially infected stem cell differentiate with no reinfection, then the HPV infection will be selflimiting. On the other hand, if an infected stem cell remains out of cycle but with viral episomes, this provides the basis of a latent infection which could be revealed at some later time when there is a call for epithelial differentiation. An anogenital cancer is a late and rare complication of a persistent oncogenic type HPV infection and is the end result of a chain of events that can take many years to unfold - infection with HPV is a necessary initial event, but not a sufficient cause of cervical cancer.

2.2.2. Immune Evasion of HPV

The relatively poor humoral immunity detected in many individuals naturally exposed to oncogenic HPV infection is a consequence of a multifaceted adaption of HPV to avoid or hide from effective immune control. In some cases this allows for persistent infection and subsequent transforming events driven by genomic instability derivative from viral integration and can ultimately lead to the emergence of metastatic tumour cells that are also able to avoid critical cellular immunity. Thus, in some cases of HPV infection the sentinel or antigen presenting cells may fail to notice the infection. Without activation of the innate immunity no appropriate controlling proinflammatory response or adaptive immune

recruitment occurs. Importantly if the antigen presenting cells (APCs) identify HPV infection but are not properly activated they can send negative signals to the adaptive immune mechanisms inducing immune tolerance, thereby anergizing effectors which could otherwise combat the infection (Stanley 2007). The virus stealth strategy and only low expression of viral early gene targets within the basal and immediate suprabasal layers of the stratified squamous epithelium can fail to activate the local APCs. While the virions are highly immunogenic structures they are made only in the apical cell layers of the epithelium already committed to terminal differentiation and thus unavailable to engage with the local immune surveillance mechanisms. Langerhans' cells may in fact be resistant to direct activation by viral particle structures in contrast to dendritic cells (Fausch 2002), and in cervical intraepithelial neoplasia (CIN) there is a reduction in numbers and a change in their phenotype (Giannini 2002, Tay 1987, Guess 2005, Connor 1999, Hubert 2005). The virus has involved additional strategies to limit immune activation including E6 and E7 modulation of the infected cells sensitivity to anti-viral responses of the tissue such as production of interferons (Nees 2000, Chang 2000, Barnard 1999, Li 1999), other inflammatory mediators (Cho 2001), TLR9 activation (Hasan 2007) and E5 mediated down-regulation of HLA expression (Zhang 2003), all of which facilitate persistent HPV infection. With the latter, the viral and host genomes can become integrated leading to failure to respond to apoptotic signals and failure of programmed cell death as well as cellular immortalization. The increased expression of viral E6 and E7 oncoproteins interferes with the tumor suppressor genes which guard the host genome by delaying DNA replication if genes are damaged and normally allows sufficient time for their repair (Duensing 2004). When such errors occur, mutant cells will be generated and the properties enabling unlimited growth, avoidance of immune surveillance and spread will be selected with time and recognized as an invasive cancer. With persistent HPV infection, CIN or invasive cancer, the constitutive expression of the E6 and E7 oncogenes can provide for chronic antigenic stimulation of the specific T cells. However, the absence of the necessary co-stimulation provided but by optimal APC activation this can induce an anergic response (Kalinski 1999). Further, T regulatory cells (Treg), which are usually induced as a part of the homeostatic control of immune responses acting to reduce the levels of virus specific cellular immunity when the danger has passed (Wang 2004) can also be induced by these conditions, and contribute to tolerance of viral antigens and the promotion of neoplasia (Belkaid 2009). There are several studies showing increased numbers of Treg in HPV-associated diseases as well as tumors of different types including those of the cervix (van der Burg 2007, Fattorossi 2004, Molling 2007). These effectors can suppress the activity of cytotoxic cells either directly or by the production of cytokines like IL10 and tumour growth factor (TGF)-beta. In studies of recurrent respiratory papillomatosis (RRP), a disease caused by HPV-6 and -11 (two common but low oncogenic risk HPV types that also infect the cervix), there is a dramatic polarization of cell mediated immune responses that are biased towards Th2-like T-cells, cytokine and chemokine repertoires (Bonagura 1999, Bonagura 2004, DeVoti 2008, DeVoti 2004, Rosenthal 2005, Rosenthal 2006, Rosenthal 2008), and increased number of CD4+, Foxp3, regulatory Tcells (Treg) (Hatam 2008) in diseased, but not in normal laryngeal tissues.

2.2.3. Host tropism

To date, more than 180 papillomaviruses genotypes have been identified, based on their L1 sequence. HPVs display a preference regarding the site of infection, cutaneous or mucosal. Furthermore, highly homologous HPV types such as HPV6 or HPV11 (85% L1 identity) can have different site predilection. In an attempt to identify whether the tissue specificity is determined at the level of infectious entry (basement membrane binding to episomal integration), Handisurya et al used murine models for skin infection and mucosal cervicovaginal challenge using various L1L2 pseudovirions (human cutaneous types HPV5, 8, human mucosal low risk types HPV6,44 and high risk types HPV16,18,26,45,51,58, bovine BPV1 and murine MusPV1). In both cases the disruption of the epithelium was required. Using

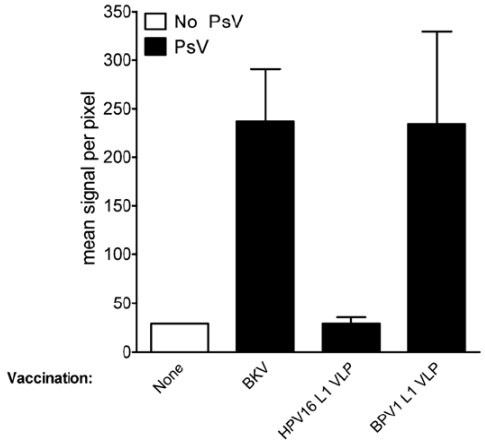
the skin murine model, no difference in patterns of pseudovirion entry was noted among individual pseudovirion types tested (HPV5, HPV16, MusPV1 and BPV1). The authors also tested the ability of diverse pseudovirions to infect murine tissues of cutaneous and mucosa-genital origin, following local abrasion or scarification. Although differences in terms of kinetics of infection were observed, it appeared that the infectivity of both tissues by pseudovirions was similar. The conclusion is that differences in the mechanism of viral entry do not account for tissue type or species-specific tropism of infection and that these must be determined by post-entry events (Handisurya, 2012).

2.3. Immunogenicity aspects

Since it is not possible to easily recapitulate the virus natural history of infection for the purposes of a high through put assay of antibody neutralising activity, all assays (ELISA, competitive Luminex (cLIA), PBNA or cervicovaginal murine challenge) are surrogates for activity in preventing natural infection in vaccinees. Each individual assay is able to detect overlapping activities but also distinct activities (e.g. ELISA and PBNA in Dessy 2008). Each individual assay may or may not encompass the complete range of antibody specificity, affinity or titre relevant in prevention of PV infection in the anogenital tract. The VLP induced antibodies are generally type specific and this may include recognition of different epitopes, with a range of affinity and where higher concentration may provide for cross reactivity against related types. Vaccination by L1-based HPV vaccine such as Cervarix induces high titres of neutralizing antibodies in serum of vaccinees, as measured using vaccine independent PBNA. Antibodies may either transudate (e.g., into cervico-vaginal secretions) or exudate at the site of infection. The current paradigm for prevention of HPV infection is that at high concentrations, vaccine-elicited L1 neutralizing antibodies located at the infection site coat the HPV capsids and neutralize the virus preventing entry into its target cells. The cervicovaginal challenge model does show VLP type specificity and cross protection similar to that documented in clinical efficacy studies (Day 2010, Paavonen 2009). While providing insights into processes likely more relevant to real infection in the genital tract than in vitro studies, the model is still a surrogate. It uses HPV L1/L2 pseudovirions for passive challenge and the multiplicity conditions of infection are obviously not physiological. It also does not exclude other methods of infection not dependent on exposure of the basement membrane and epithelial regrowth.

The role of antibodies in preventing HPV infection has been shown using different surrogate models. In the mouse model using HPV16 pseudovirions for cervicovaginal infection, it was shown using confocal microscopy that an intact genital epithelium was resistant to infection by HPV16 L1L2 pseudovirus. In contrast, gentle mechanical abrasion of the genital epithelium with a cytobrush that exposes the basement membrane permitted detectable levels of pseudovirus infection. A similar effect was observed following vaginal treatment with nonoxynol-9 (N-9), a non-ionic surfactant widely use as spermicide and known to disrupt the normal architecture of human and animal genital epithelium. Systemic immunisation by HPV16 L1 VLPs protected the mice against subsequent challenges with HPV16 L1L2 pseudovirus.

Figure 2.



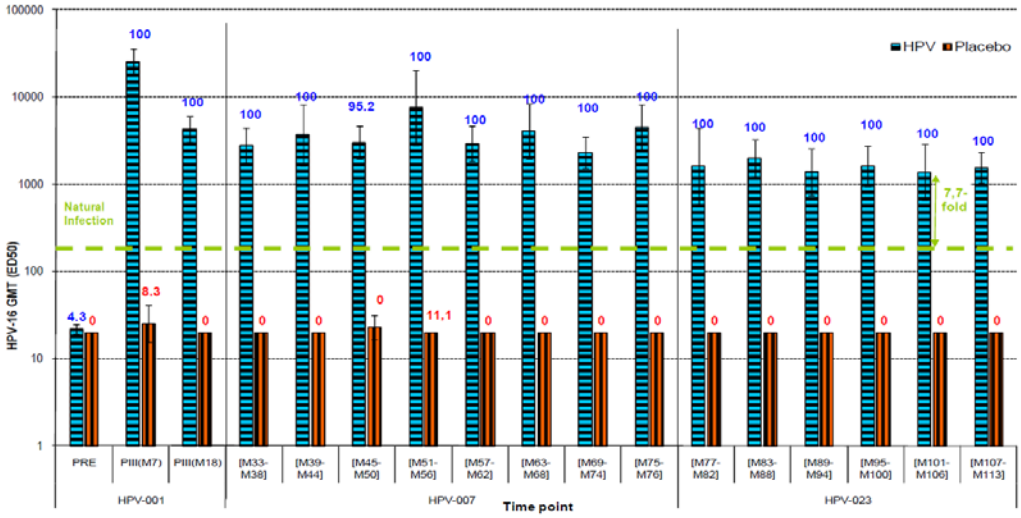
Virus-like particle (VLP) immunization protects against type-specific pseudovirus challenge. BKV: BK poliomavirus (sham vaccine); BPV1: bovine papillomavirus type 1 (Roberts, 2007)

The specificity of L1 VLP-induced protection from cervicovaginal challenge was examined in mice by Day et al in 2010 using HPV16 L1 VLPs (a similar experiment was described by Longet in 21011 using the quadrivalent HPV vaccine). In this study, partial protection was observed against HPV31 and no protection was shown against HPV58 or HPV45. Further experiments of serum passive transfer from a rabbit immunized with HPV16 L1 VLPs into naïve mice resulted in strong protection against HPV16 pseudovirion challenge and no protection from challenge with HPV45. This observation correlates with the cross-protective clinical efficacy against HPV31 seen in clinical trials with Cervarix (Paavonen 2009, Wheeler 2012) and is consistent with the observation of cross-reactive antibodies in humans (Kemp 2011). Last, cross-protective efficacy of Cervarix was assessed in a rabbit cutaneous quasivirion (HPV L1L2 pseudovirions including CRPV genome, nearly identical to native virions) challenge model, using CRPV (cottontail rabbit papillomavirus) as a control. In this model, Cervarix induced high level of specific and cross-protection against HPV16, 18, 31 and 45, but only partial protection against HPV58 (Giannini 2010).

2.3.1. Immune response elicited by Cervarix

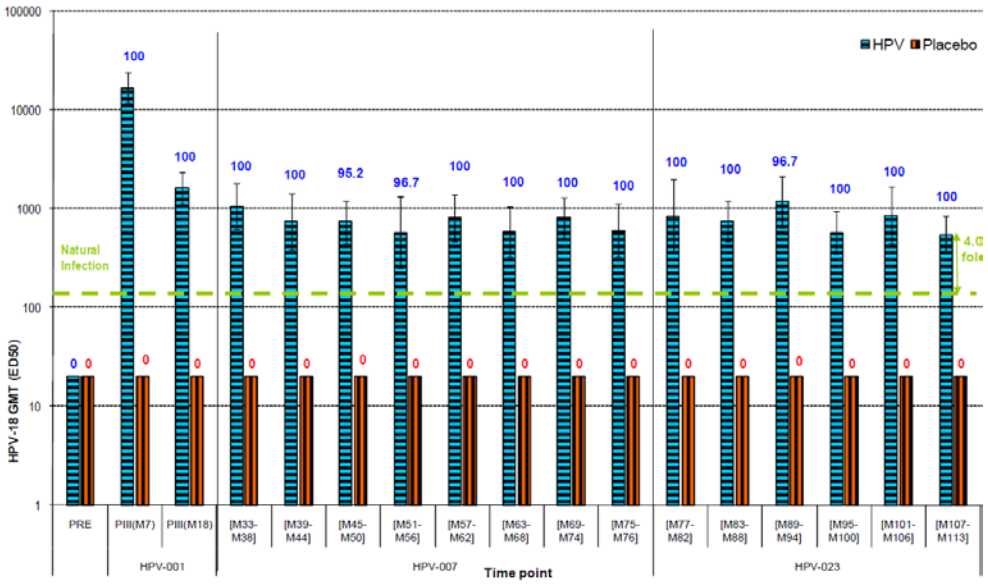
Long-term immunogenicity of Cervarix has been studied up to 9.4 years (mean of 8.9 years) after initial vaccination of young women 15-25 years in study HPV-001 and their long-term follow-up in studies HPV-007/023. Persistence of the immune response against both HPV-16 and HPV-18 antigens was observed with 100% of vaccinees remaining seropositive as measured by ELISA up to a mean of 8.9 years after initial vaccination. The GMTs showed a plateau at approximately one log below the peak response level one month after the full vaccination course, without substantial evidence of further decline during the long-term follow-up. In addition, all subjects included in the subset for PBNA testing (55 subjects in the vaccine and 23 subjects in the placebo groups in total) of who had received the HPV vaccine remained seropositive for neutralizing antibodies against both antigens (PBNA). In the Placebo group, none of the subjects had detectable levels of neutralizing antibodies against HPV-16 and HPV-18. The kinetics of the HPV-16 and HPV-18 neutralizing antibodies were similar to the one observed by ELISA (Figure 3 and Figure 4). Of note, at completion of study HPV-023 (with a mean of 8.9 years after initial vaccination),there were no cases of infection or histopathological lesions associated with HPV- 16 or HPV-18 in the vaccine group. In the placebo group, there were 4 cases of 6-month persistent infection and 1 case of 12-month persistent infection (HPV-023; Roteli-Martins, 2012 for follow-up up to 8.4 years after initial vaccination).

Figure 3. Kinetics of HPV-16 neutralizing antibody titers (PBNA) during studies HPV-001, HPV-007 and HPV-023 (ATP cohort for immunogenicity; subset)



HPV = subjects who received HPV 16/18 L1 VLP AS04 vaccine in the HPV-001 study Placebo = subjects who received placebo in the HPV-001 study
Note: antibody levels associated with naturally-acquired HPV-16/18 infection are shown by a horizontal line; GMT values for natural infection were obtained from baseline serum samples of subjects in the phase IIIb study HPV-010 who were seropositive and HPV DNA negative for the respective HPV type.
Note: The fold increase was computed by comparing the minimal GMT levels observed with the level of natural infection

Figure 4. Kinetics of HPV-18 neutralizing antibody titers (PBNA) during studies HPV-001, HPV-007 and HPV-023 (ATP cohort for immunogenicity; subset)



HPV = subjects who received HPV 16/18 L1 VLP AS04 vaccine in the HPV-001 study Placebo = subjects who received placebo n the HPV-001 study
Note: antibody levels associated with naturally-acquired HPV-16/18 infection are shown by a horizontal line; GMT values for natural infection were obtained from baseline serum samples of subjects in the phase IIIb study HPV-010 who were seropositive and HPV DNA negative for the respective HPV type.
Note: The fold increase was computed by comparing the minimal GMT levels observed with the level of natural infection

A key component of Cervarix is the AS04 adjuvant system, composed of 50 µg of MPL (3-O-desacyl-4'-monophosphoryl lipid A) and 500 µg of aluminium hydroxide salt. The effect of AS04 in terms of immunogenicity was assessed in early phase II studies (HPV-004 and HPV-005). Enhanced neutralizing antibody response was observed following vaccination and up to 3.5 years post vaccination with the adjuvanted formulation as compared with the formulation containing aluminium salt only, using either

V5/J4 inhibition ELISA or PBNA. The studies also showed that the AS04 formulation elicited an increased frequency of L1 VLPs specific memory B cells when compared to an aluminium salt-only formulation (2.2 – 5.2 fold increased ratio). Cervarix benefits from the AS04 adjuvant, leading to an improved immune response in terms of magnitude and duration and a higher priming quality compared to a vaccine containing aluminium salt only (Giannini 2006 and reviewed in Garçon 2011).

2.4. Clinical Efficacy aspects

2.4.1. Background

The report from the WHO/ICO HPV information center (February 19, 2010) described an increasing evidence linking HPV DNA with cancers in the genital region. Although their incidence is lower as compared to cervical cancer, their common cause of HPV infection make them potentially preventable and subject to similar preventive strategies (Vaccine 2006, Vol 24, Supp 3; Vaccine 2008, Vol 26 Supp 10; IARC monographs 2007, Vol 90).

Vulvar and vaginal cancers are rare diseases, representing an estimated 26,800 and 13,200 new cases worldwide in 2002, respectively, or about 6% of all gynaecological cancers (www.who.int/hpvcentre). The majority of vulvar and vaginal cancers (90%) are squamous cell carcinoma (SCC), and tends to be reported more frequently in developed countries, indicating a limited impact of preventive cervical screening programs on these types of malignancies. Furthermore, there are no dedicated screening programs for vaginal and vulvar malignancies.

HPVs are responsible for virtually 100% of cervical cancers, with types 16 and 18 causing about 70% of all cases. Oncogenic HPV DNA is also highly prevalent in many vulvar cancers and most vaginal cancers (70-80%). Low grade VIN1 cases were more likely to be associated with low-risk HPV type (i.e. HPV-6 or 11) and nearly all high-grade vulvar lesions (VIN3) were associated with HPV-16. It is however not clear if low grade lesions associated with low risk types have the potential to progress to high grade lesions. HPV-16 was observed in the large majority of VaIN1 cases and half of VaIN3 cases. Overall, the two low risk types HPV-6 and HPV-11 are usually not associated with high grade lesions (Srodon, 2006).

Vaccination with HPV vaccines stimulates the subject's immune system which elicits antibodies (both neutralizing and non-neutralizing) against the HPV L1 VLPs contained in the vaccines. Following a subsequent infection by HPV, the current paradigm is that L1 neutralizing antibodies elicited by vaccination which are located at the surface of the cervix will coat the HPV capsids and prevent their interaction with the basal membrane of the epithelium. At lower concentrations, L1 neutralizing antibodies may not prevent binding to the basement membrane, but may rather prevent the molecular conformational changes required for the virus to bind and then infect the epithelium cells (Schiller, 2010, Day, 2010). No serological correlate of protection has been established for HPV vaccines, however high levels of neutralizing antibodies against HPV-16/18 are indicative of an effective protection against HPV infection. Since women may be at risk for acquisition of HPV infection for as long as they are sexually active, vaccination needs to induce high levels of antibodies to provide long-term protective efficacy. Cervarix has demonstrated its ability to generate high levels of antibodies that transudate to the cervix and confer efficacy against HPV-related high grade cervical lesions in clinical studies. It is also supposed that the induced immune memory plays a role in the longer-term protection, when lower or non-detectable levels of antibodies are present at the infection site (Joura, 2008, Moscicki, 2010).

In the goal of comparing the immune response elicited by the two HPV vaccines, study HPV-010 is being conducted in women aged 18 to 45 years and provided up to three years of comparison data

(the study is planned for five years). To allow for the comparison between the two vaccines, and in line with the WHO guidelines (WHO, 2006), a vaccine-independent assay (pseudovirion based neutralization assay - PBNA) was used to measure the levels of neutralizing antibodies elicited against HPV-16 and HPV-18 following vaccination. Although it is acknowledged that superiority in terms of antibody levels may not directly transpose into clinical superiority which would be difficult to assess in the context of clinical trials, a similar clinical efficacy can be reasonably expected from a vaccine eliciting higher levels of neutralizing antibodies as compared to another vaccine for which efficacy has been demonstrated. This immunological bridging approach is also supported by the natural history of HPV infection, time to disease progression, and by the difficulty to conduct new large scale efficacy studies in women with Cervarix whereas a vaccine is already licensed for these indications and widely available. This approach is in line with the CHMP guideline on clinical evaluation of new vaccines as currently it may not be feasible to perform a lengthy placebo-controlled efficacy study in women (EMEA, 2005).

2.4.2. Clinical studies

Study HPV-008

The efficacy of Cervarix against vulvar and vaginal lesions was assessed as exploratory endpoints in the efficacy study HPV-008. These endpoints were not included in the initial HPV-008 study protocol, but they were added in a protocol amendment while the study was ongoing. In this study, not all subjects were systematically screened for VIN/VaIN: specific vulvo-vaginal examinations were only performed in women with abnormal cervical cytology referred for colposcopy. The number of VIN/VaIN lesions observed may therefore be an underestimate.

At the time of the final study analysis, statistically significant vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 was observed in both cohorts: 80.0% (96.1% CI: 0.3;98.1) in the ATP cohort and 83.2% (96.1% CI: 20.2;98.4) in the Total Vaccinated Cohort (TVC)-1 cohort. At the end of study analysis (Month 48), vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 was 75.1% (95% CI: 22.9; 94.0) in According To Protocol (ATP) cohort and 77.7% (95% CI: 32.4; 94.5) in TVC-1 (Table 2 and Table 3; Garland, 2011).

Cases of high grade VIN or VaIN were limited in study HPV-008. At the end of study analysis, there were only 9 cases of VIN2+ or VaIN2+ observed in the ATP cohort, of which 2 were in the vaccine group (and both caused by HPV-16) and 7 in the control group (4 were attributed to HPV-16 and 3 to HPV-18). Vaccine efficacy against VIN2+ for the combined HPV-16/18 endpoint was therefore 71.6% in the ATP cohort and 75.0% in TVC-1 (2 cases in the vaccine group and 8 in the control group) with a lower limit of the confidence interval below 0 in both cases (Table 2 and Table 3).

Table 2. Incidence rates and vaccine efficacy against VIN1+ or VaIN1+ and VIN2+ or VaIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (ATP cohort for efficacy

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
VIN1+ or VaIN1+											
HPV-16/18	HPV	7338	4	24138.29	0.02	0.00	0.04	75.1	22.9	94.0	0.0070
	HAV	7305	16	24017.23	0.07	0.04	0.11	-	-	-	-
HPV-16	HPV	6296	4	20739.18	0.02	0.01	0.05	64.4	-20.2	91.7	0.0737
	HAV	6160	11	20308.87	0.05	0.03	0.10	-	-	-	-
HPV-18	HPV	6789	0	22340.05	0.00	0.00	0.02	100	-8.2	100	0.0307
	HAV	6739	5	22154.90	0.02	0.01	0.05	-	-	-	-
VIN2+ or VaIN2+											
HPV-16/18	HPV	7338	2	24138.29	0.01	0.00	0.03	71.6	-49.4	97.1	0.1085
	HAV	7305	7	24025.42	0.03	0.01	0.06	-	-	-	-
HPV-16	HPV	6296	2	20739.18	0.01	0.00	0.03	51.0	-241.7	95.6	0.4481
	HAV	6160	4	20314.71	0.02	0.01	0.05	-	-	-	-
HPV-18	HPV	6789	0	22340.05	0.00	0.00	0.02	100	-140.0	100	0.1236
	HAV	6739	3	22157.26	0.01	0.00	0.04	-	-	-	-

HPV = Cervarix (three lots) HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects are in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Table 3. Incidence rates and vaccine efficacy against VIN1+ or VaIN1+ and VIN2+ or VaIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (TVC-1)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
VIN1+ or VaIN1+											
HPV-16/18	HPV	8068	4	30354.82	0.01	0.00	0.03	77.7	32.4	94.5	0.0043
	HAV	8103	18	30410.40	0.06	0.04	0.09	-	-	-	-
HPV-16	HPV	6946	4	26188.18	0.02	0.00	0.04	66.7	-9.7	92.2	0.0489
	HAV	6944	12	26130.78	0.05	0.02	0.08	-	-	-	-
HPV-18	HPV	7480	0	28167.83	0.00	0.00	0.01	100	15.1	100	0.0312
	HAV	7502	6	28164.72	0.02	0.01	0.05	-	-	-	-
VIN2+ or VaIN2+											
HPV-16/18	HPV	8068	2	30354.82	0.01	0.00	0.02	75.0	-25.6	97.4	0.1093
	HAV	8103	8	30421.12	0.03	0.01	0.05	-	-	-	-
HPV-16	HPV	6946	2	26188.18	0.01	0.00	0.03	60.1	-143.9	96.2	0.2889
	HAV	6944	5	26136.62	0.02	0.01	0.04	-	-	-	-
HPV-18	HPV	7480	0	28167.83	0.00	0.00	0.01	100	-142.0	100	0.2500
	HAV	7502	3	28169.60	0.01	0.00	0.03	-	-	-	-

HPV = Cervarix (three lots) HAV = Hepatitis A vaccine (three lots)
N=number of subjects included in each group
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects are in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=95% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Study HPV-010

HPV-10 was a phase IIIb, observer-blind, multicenter, randomized (1:1) trial with two parallel groups in healthy females 18-45 years of age:

- One group received the GSK HPV vaccine (N=553)
- One group received the Gardasil vaccine (N=553)

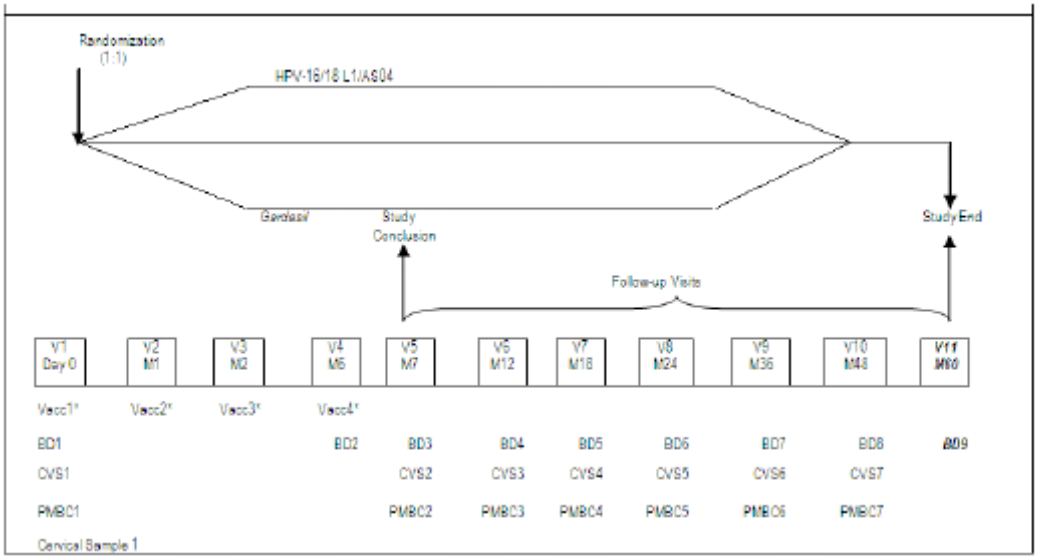
Enrollment into each treatment group was age-stratified with a slightly greater number of subjects in the 18-26 year-old cohort (417 subjects) than in the 27-35 year-old cohort (356 subjects) or the 36-45 year-old cohort (333 subjects). Three doses of vaccine were administered according to the recommended schedule for GSK HPV vaccine (0, 1, 6-months) and Gardasil (0, 2, 6-months). To maintain blinding, all subjects received injections at Months 0, 1, 2 and 6. Placebo [Al(OH)3] was administered at either Month 2 (GSK HPV recipients) or Month 1 (Gardasil recipients). The subjects, investigator, study personnel and MAH staff will remain blinded until completion of study follow-up. The method of data collection occurred through Remote Data Entry (RDE). Five visits were scheduled per subject on Day 0, at Months 1, 2, 6 and 7 in the active phase. Additionally, there were to be 6 follow-up study visits scheduled at Months 12, 18, 24, 36, 48 and 60. A cervical sample was collected from all subjects for HPV deoxyribonucleic acid (DNA) testing on Day 0. Blood samples of 20 mL were to be collected from all subjects on Day 0, at Months 6, 7, 12, 18, 24, 36, 48 and 60 for evaluation of antibody response. An additional 50 mL blood sample on Day 0, at Months 7, 12, 18, 24, 36 and 48 was to be collected for evaluation of CMI response in a subset of subjects from pre-selected sites. CVS were to be collected for HPV-16/18 antibody testing on Day 0, at Months 7, 12, 18, 24, 36 and 48 in a subset of subjects from preselected sites.

The safety of both vaccines was monitored during the follow-up phase as follows:

All serious adverse events (SAEs), new onset chronic diseases (NOCDs), and other medically significant conditions (MSCs) occurring throughout the study period were to be reported in all subjects regardless of causal relationship to vaccination and intensity.

All pregnancies and their outcomes were to be reported.

Figure 5. Study design



V = Visit; M = Month; Vacc = Vaccination; BD = Blood Draw; CVS = Cervicovaginal Secretion Sample; collected in a subset of subjects; PBMC = peripheral blood mononuclear cells; collected in a subset of subjects Doses have been administered according to the schedule for GSK HPV vaccine (0, 1, 6-months) and Gardasil (0, 2, 6-months). To maintain blinding, all subjects have received injections at Month 0, 1, 2 and 6. Placebo [Al(OH)3] has been administered at either Month 2 (GSK HPV recipients) or Month 1 (Gardasil recipients).

Study centers:
This study was a multicenter study conducted in 40 centers located in the USA.

2.4.3. Methods – analysis of data submitted

2.4.3.1. Primary endpoint

To compare the immune responses to HPV-16 and -18 induced by the GSK HPV vaccine and Gardasil, in terms of HPV-16 and -18 geometric mean titers (GMTs) measured by pseudovirion-based neutralization assay (PBNA), at Month 7 in healthy adult females 18-26 years of age.

2.4.3.2. Secondary endpoints :

Serology: Pseudovirion-Based Neutralization Assay (PBNA)

- To compare the immune responses in sera to HPV-16 and -18 induced by the GSK HPV vaccine and Gardasil in terms of HPV-16 and -18 GMTs at Month 7 in healthy adult females 27-35 years of age.
- To compare the immune responses in sera to HPV-16 and -18 induced by the GSK HPV vaccine and Gardasil in terms of HPV-16 and -18 GMTs at Month 7 in healthy adult females 36-45 years of age.
- To evaluate the immune responses in sera to HPV-16 and -18 induced by the GSK HPV vaccine and Gardasil in terms of HPV-16 and -18 GMTs and seroconversion rates in all subjects at Months 6, 12, 18, 24, 36, 48 and 60 and seroconversion rates at Month 7.
- To evaluate the immune responses in sera to other oncogenic HPV types (including HPV-31 and -45) induced by the GSK HPV vaccine and Gardasil in terms of GMTs and seroconversion rates at Month 7.

Serology: Enzyme-linked Immunosorbent Assay (ELISA)

To evaluate the immune responses in sera to HPV-16 and -18 induced by the GSK HPV vaccine and Gardasil in terms of HPV-16 and -18 GMTs and seroconversion rates in all subjects at Months 6, 7, 12, 18, 24, 36, 48 and 60.

To evaluate the immune responses in sera to other oncogenic HPV types (including HPV-31 and -45) induced by the GSK HPV vaccine and Gardasil in terms of GMTs and seroconversion rates in all subjects at Months 6, 7, 12, 18, 24, 36 and 48.

Cell-Mediated Immunity (CMI; target: 30% subset of subjects per age cohort per group)

To assess the T CMI responses specific to HPV types 16, 18 and other oncogenic HPV types (including 31 and 45) induced by the GSK HPV vaccine and Gardasil at Months 7, 12, 18, 24, 36 and 48.

To assess the memory B CMI responses specific to HPV types 16, 18 and other oncogenic HPV types (including 31 and 45) induced by the GSK HPV vaccine and Gardasil at Months 7, 12, 18, 24, 36 and 48.

Cervicovaginal Secretions (CVS; target: 30% subset of subjects per age cohort per group): immune response by PBNA and/or ELISA

To evaluate the immune responses in CVS to HPV-16 and HPV-18 induced by the GSK HPV vaccine and Gardasil in terms of HPV-16 and -18 GMTs and proportions of subjects with detectable antibody levels at Months 7, 12, 18, 24, 36 and 48.

2.4.3.3. Statistical methods

Analyses were performed as planned in the protocol and in the report analysis plan (RAP). Changes implemented in the analyses include the following:

Fewer CVS samples than planned were evaluable. Several changes in the planned analyses were implemented as result of the lower number of evaluable samples.

Some analyses were simplified to avoid multiple analyses on sub-cohorts. All sub-analyses will be performed at Month 60 (final analysis).

Demographics:

Demographic characteristics (age, ethnicity and race) of each study cohort were tabulated. The mean age (plus range and standard deviation [SD]) of each study cohort, as a whole, and per group, was calculated.

Immunogenicity:

The primary analysis is based on the Month 36 ATP cohort for analysis of immunogenicity (M36 ATP cohort for immunogenicity).

For each serology assay (PBNA and/or ELISA), for each treatment group (GSK HPV and Gardasil), for each age group (18-26, 27-35 and 36-45 years of age), at each time point that a blood sample result was available:

Seropositivity rates for HPV-16, HPV-18, HPV-31 and HPV-45 antibodies (with exact 95% confidence interval [CI]) were calculated, GMT with 95% CI and range of antibody titers were tabulated for antibodies against HPV-16, HPV-18, HPV-31 and HPV-45.

The distribution of antibody titers for HPV-16 and HPV-18 was displayed using reverse cumulative distribution curves (RCCs) in subjects seronegative for the corresponding antigen at Day 0. In addition, exploratory inferential analyses were performed to compare the two vaccine groups.

The analysis of the T-cell and B-cell response was performed by presenting the percentage of responders and descriptive statistical parameters. Exploratory inferential analyses were performed to compare the two vaccine groups.

The analysis of antibody titers measured by ELISA in CVS was also performed. The correlation between the serum and CVS antibody titers was calculated using the Pearson correlation coefficient.

2.4.4. Results

Number of subjects included in the study

A total of 1106 subjects were enrolled and vaccinated in the study. The Month 36 Total Vaccinated cohort (M36 TVC) included 557 subjects (279 in the GSK HPV vaccine group and 278 in the Gardasil group). Table 4 presents the number of subjects enrolled and eligible for the safety and immunogenicity analyses and the reasons for elimination from these analyses.

Table 4. Number of subjects enrolled into the study as well as the number excluded from ATP Ext M36 analyses with reasons for exclusion

	Total			GSK HPV		*Gardasil*	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	1106			553		553	
Total Vaccinated cohort (TVC)	**1106**		**100**	**553**		**553**	
Subjects who did not come at M36 (code 6000)	549	549		274	274	275	275
M36 TVC	**557**		**50.4**	**279**		**278**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	36	50		18	23	18	27
Randomisation failure (code 1050)	0	2		0	1	0	1
Randomisation code broken at the investigator site (code 1060)	19	36		8	12	11	24
Study vaccine dose not administered according to protocol (code 1070)	9	177		3	89	6	88
Protocol violation (inclusion/exclusion criteria) (code 2010)	8	10		5	6	3	4
Administration of any medication forbidden by the protocol (code 2040)	4	6		4	4	0	2
Underlying medical condition forbidden by the protocol (code 2050)	0	1		0	0	0	1
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	14	67		8	33	6	34
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	9	9		2	2	7	7
M36 ATP cohort for immunogenicity	**458**		**41.4**	**231**		**227**	

Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a previous elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the TVC

Immunogenicity data sets analysed

The primary analysis of immunogenicity (serological analysis of HPV-16, -18, -31 and - 45 by PBNA and/or ELISA and CMI analysis of HPV-16, -18, -31 and -45) was performed on the M36 ATP cohort for immunogenicity in subjects HPV DNA negative and seronegative for the corresponding type at baseline. Additional analysis for immunogenicity (M36 ATP cohort) were done irrespective of subject's initial HPV DNA and serostatus.
A secondary analysis based on the M36 TVC was performed to complement the ATP analysis. The M36 TVC was also the primary population for the immunogenicity exploratory superiority assessment.
In addition, the CVS analysis of HPV-16 and -18 by ELISA was performed in the M36 TVC as primary analysis and in the M36 ATP cohort for immunogenicity as secondary analysis.

2.4.4.1. HPV-16 (PBNA) Immune response in seronegative (by PBNA) and DNA negative (by PCR) subjects at baseline (M36 ATP cohort for immunogenicity)

An overview of the seropositivity rates and GMTs for HPV-16 neutralizing antibodies at Month 36 (i.e. two and a half years after receiving the last vaccine dose) for subjects who were seronegative and DNA negative at baseline is shown in Table 5. A graphical presentation of the GMTs at each time point and for each age group separately is shown in Figure 6. For all age groups combined, HPV-16 neutralizing antibodies GMTs measured by PBNA in women who had cleared natural infection (i.e., seropositive and DNA negative at Month 0 for the HPV antigen under analysis) were 180.1 ED50 [Einstein, 2009].

Table 5. Seropositivity rates and GMTs for HPV-16 PBNA antibodies in subjects seronegative (by PBNA) and DNA negative (by PCR) at baseline (M36 ATP cohort for immunogenicity)

				≥ 40 ED_{50}				GMT (ED_{50})				
						95% CI			95% CI			
Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
GSK HPV	18-26y	PRE	104	0	0.0	0.0	3.5	20.0	20.0	20.0	<40.0	<40.0
		PIII(M6)	104	104	100	96.5	100	1627.9	1304.0	2032.3	167.0	54235.0
		PIV(M7)	104	104	100	96.5	100	36791.8	29265.6	46253.6	959.0	438557.0
		PIV(M12)	101	101	100	96.4	100	14524.7	11069.7	19058.0	654.0	655360.0
		PIV(M18)	100	100	100	96.4	100	6000.3	4681.2	7691.0	570.0	114744.0
		PIV(M24)	97	97	100	96.3	100	5184.2	4015.0	6693.8	244.0	159517.0
		PIV(M36)	60	60	100	94.0	100	3844.7	2803.6	5272.3	426.0	165701.0
	27-35y	PRE	90	0	0.0	0.0	4.0	20.0	20.0	20.0	<40.0	<40.0
		PIII(M6)	90	90	100	96.0	100	1263.1	892.7	1787.2	46.0	504881.0
		PIV(M7)	90	90	100	96.0	100	23907.9	18912.7	30222.4	1937.0	609105.0
		PIV(M12)	91	91	100	96.0	100	7419.2	5592.1	9843.3	59.0	542704.0
		PIV(M18)	87	87	100	95.8	100	2907.9	2229.2	3793.1	289.0	62036.0
		PIV(M24)	84	84	100	95.7	100	2269.2	1765.8	2916.2	204.0	40416.0
		PIV(M36)	63	63	100	94.3	100	1897.6	1418.9	2537.8	172.0	40529.0
	36-45y	PRE	96	0	0.0	0.0	3.8	20.0	20.0	20.0	<40.0	<40.0
		PIII(M6)	96	95	99.0	94.3	100	1729.8	1214.8	2463.1	<40.0	234090.0
		PIV(M7)	96	96	100	96.2	100	17301.5	13605.3	22001.9	698.0	231986.0
		PIV(M12)	89	89	100	95.9	100	7110.4	5386.3	9386.4	219.0	182814.0
		PIV(M18)	90	90	100	96.0	100	2344.0	1807.7	3039.4	67.0	55415.0
		PIV(M24)	87	87	100	95.8	100	2058.5	1592.2	2661.3	76.0	64020.0
		PIV(M36)	61	61	100	94.1	100	1794.2	1278.1	2518.8	62.0	40070.0
Gardasil	18-26y	PRE	103	0	0.0	0.0	3.5	20.0	20.0	20.0	<40.0	<40.0
		PIII(M6)	102	101	99.0	94.7	100	1592.4	1204.3	2105.7	<40.0	70044.0
		PIV(M7)	103	103	100	96.5	100	10053.1	8135.8	12422.1	154.0	186351.0
		PIV(M12)	99	99	100	96.3	100	3265.2	2544.7	4189.7	53.0	49986.0
		PIV(M18)	91	91	100	96.0	100	1182.7	882.7	1584.8	46.0	42470.0
		PIV(M24)	89	87	97.8	92.1	99.7	893.5	672.2	1187.9	<40.0	21434.0
		PIV(M36)	62	61	98.4	91.3	100	653.2	460.4	926.7	<40.0	28726.0
	27-35y	PRE	85	0	0.0	0.0	4.2	20.0	20.0	20.0	<40.0	<40.0
		PIII(M6)	84	83	98.8	93.5	100	1014.1	737.6	1394.1	<40.0	49834.0
		PIV(M7)	85	85	100	95.8	100	4958.4	3895.6	6311.2	194.0	60591.0
		PIV(M12)	85	84	98.8	93.6	100	1755.9	1290.3	2389.7	<40.0	49429.0
		PIV(M18)	83	82	98.8	93.5	100	689.8	505.8	940.8	<40.0	23074.0
		PIV(M24)	79	77	97.5	91.2	99.7	618.8	447.4	856.0	<40.0	31987.0
		PIV(M36)	49	49	100	92.7	100	501.7	346.7	726.0	55.0	24480.0
	36-45y	PRE	83	0	0.0	0.0	4.3	20.0	20.0	20.0	<40.0	<40.0
		PIII(M6)	81	81	100	95.5	100	1916.5	1361.3	2698.2	47.0	507307.0
		PIV(M7)	83	83	100	95.7	100	7634.4	5915.7	9852.5	1228.0	146028.0
		PIV(M12)	83	83	100	95.7	100	2678.2	1986.8	3610.2	182.0	251921.0
		PIV(M18)	82	82	100	95.6	100	994.8	732.9	1350.4	54.0	47314.0
		PIV(M24)	80	80	100	95.5	100	874.7	636.9	1201.3	49.0	40478.0
		PIV(M36)	57	57	100	93.7	100	823.7	567.2	1196.1	85.0	42383.0

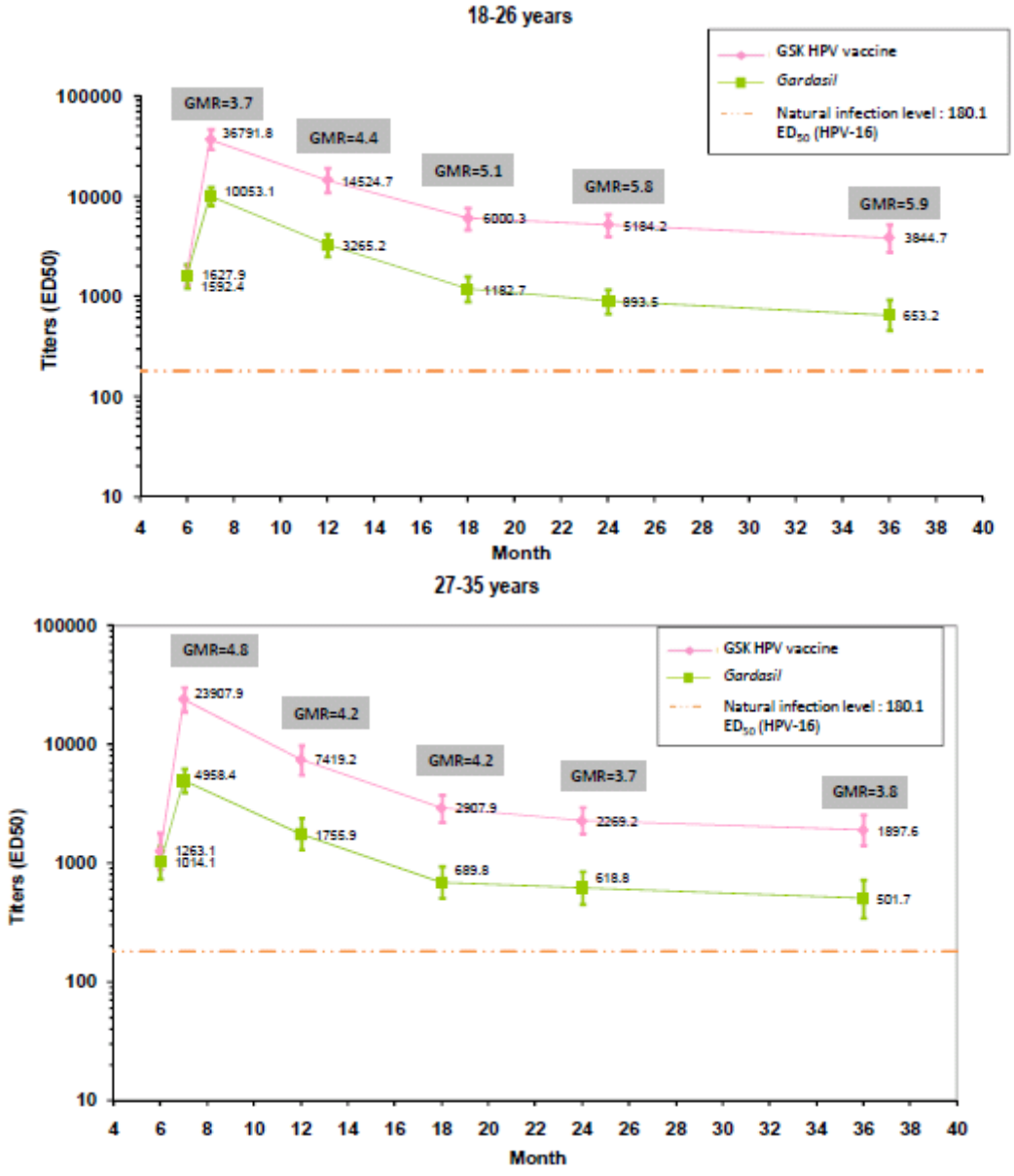
ED50 = Estimated Dose = serum dilution giving a 50% reduction of the signal compared to a control without serum
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (ATP cohort for immunogenicity)
PIII(M6) = Post GSK HPV Dose 2, Month 6 / Gardasil Dose 2, Month 6 (ATP cohort for immunogenicity)
PIV(M7) = Post GSK HPV Dose 3, Month 7 / Gardasil Dose 3, Month 7 (ATP cohort for immunogenicity)
PIV(M12) = Post GSK HPV Dose 3, Month 12 / Gardasil Dose 3, Month 12 (M12 ATP cohort for immunogenicity)
PIV(M18) = Post GSK HPV Dose 3, Month 18 / Gardasil Dose 3, Month 18 (M18 ATP cohort for immunogenicity)
PIV(M24) = Post GSK HPV Dose 3, Month 24 / Gardasil Dose 3, Month 24 (M24 ATP cohort for immunogenicity)
PIV(M36) = Post GSK HPV Dose 3, Month 36 / Gardasil Dose 3, Month 36 (M36 ATP cohort for immunogenicity)

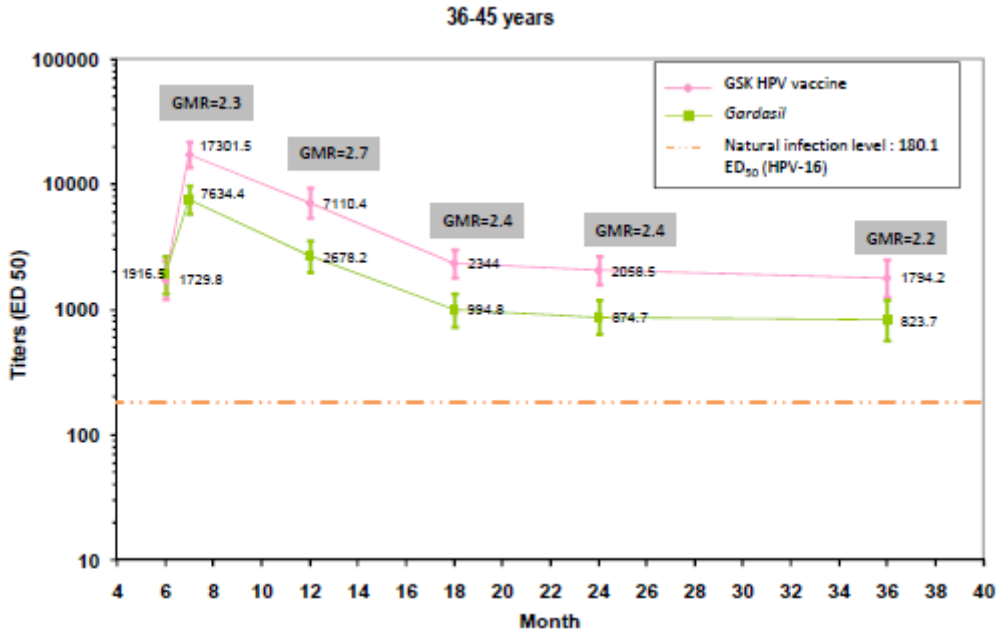
For seronegative and DNA negative subjects at baseline, HPV-16 antibody levels were higher in the GSK HPV vaccine group when compared with the Gardasil group for all age strata (see Table 3).

- In the 18-26 age group, HPV-16 GMTs in the GSK HPV vaccine group (3844.7 ED50) were 5.9-fold higher at Month 36 than in the Gardasil group (653.2 ED50).
- In the 27-35 age group, HPV-16 GMTs in the GSK HPV vaccine group (1897.6 ED50) were 3.8-fold higher at Month 36 than in the Gardasil group (501.7 ED50).
- In the 36-45 age group, HPV-16 GMTs in the GSK HPV vaccine group (1794.2 ED50) were 2.2-fold higher at Month 36 than in the Gardasil group (823.7 ED50).

All initially seronegative and DNA negative subjects in the GSK HPV vaccine group were still seropositive for HPV-16 antibodies at Month 36. In the Gardasil group, 98.4% to 100% of subjects were still seropositive for HPV-16 antibodies at Month 36.

Figure 6. GMTs with 95% CI for HPV-16 PBNA antibodies in subjects seronegative (by PBNA) and DNA negative (by PCR) at baseline (M36 ATP cohort for immunogenicity)





GMR: Geometric mean ratio; GSK-HPV vaccine: Cervarix

The GMT ratio (GSK HPV vaccine/Gardasil) was used to assess the between-group comparisons for non-inferiority. As the lower limits of the 95% CIs were greater than 0.5, non-inferiority of the GSK HPV vaccine over Gardasil at Month 36 was demonstrated for all age groups studied (see Table 6).

Table 6. Non-inferiority assessment in terms of GMT ratios between GSK HPV vaccine and Gardasil for HPV-16 PBNA antibodies in subjects seronegative (by PBNA) and DNA negative (by PCR) at baseline (M36 ATP cohort for immunogenicity)

					GMT ratio		
	GSK HPV		*Gardasil*			95% CI	
Age	N	GMT (ED_{50})	N	GMT (ED_{50})	Value	LL	UL
18-26y	60	3844.7	62	653.2	5.89	3.69	9.39
27-35y	63	1897.6	49	501.7	3.78	2.39	5.98
36-45y	61	1794.2	57	823.7	2.18	1.32	3.58

ED50 = Estimated Dose = serum dilution giving a 50% reduction of the signal compared to a control without serum
GMT = geometric mean antibody titer
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance)
LL = lower limit, UL = upper limit

In addition, as the lower limits of the CIs were greater than 1 for the non-inferiority measurement in all age groups, superiority was also tested. The primary analysis for superiority was performed on the TVC (regardless of serostatus and DNA status at baseline) as shown in Table 7. Superiority of the GSK HPV vaccine over Gardasil was demonstrated in all age groups (ANOVA $p < 0.05$).

Table 7. Superiority assessment in terms of antibody titers between GSK HPV vaccine and Gardasil for HPV-16 PBNA antibodies at Month 36 (TVC)

	GSK HPV		*Gardasil*			
Age	N	GMT (ED_{50})	N	GMT(ED_{50})	p-value ANOVA	p-value Kruskal-Wallis
18-26y	91	3806.34	93	782.29	<0.0001	<0.0001
27-35y	97	2373.73	84	945.09	<0.0001	<0.0001
36-45y	91	2610.51	101	1151.72	0.0004	0.00014

ED50 = Estimated Dose = serum dilution giving a 50% reduction of the signal compared to a control without serum
GMT = geometric mean antibody titer
N = Number of subjects with post-vaccination results available

2.4.4.2. HPV-18 (PBNA) Immune response in seronegative (by PBNA) and DNA negative (by PCR) subjectsat baseline (M36 ATP cohort for immunogenicity)

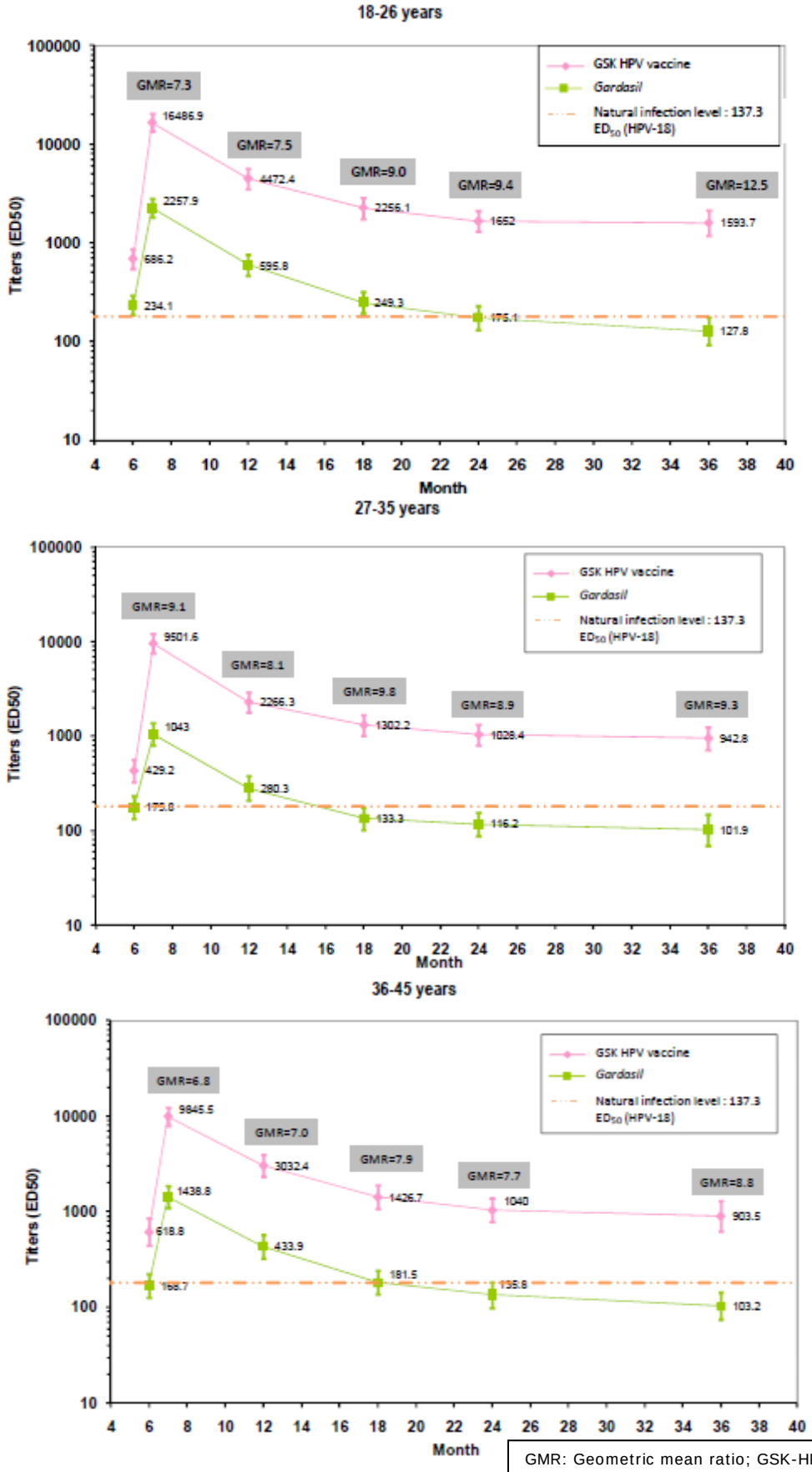
A graphical presentation of the GMTs at each time point and for each age group separately is shown in Figure 4. For all age groups combined, HPV-18 neutralizing antibodies GMTs measured by PBNA in women who had cleared natural infection (i.e., seropositive and DNA negative at Month 0 for the HPV antigen under analysis)] were 137.3 ED50 [Einstein, 2009]. This natural infection level is included in these graphs.

For seronegative and DNA negative subjects at baseline, HPV-18 antibody levels were higher in the GSK HPV vaccine group when compared to the Gardasil group for all age strata (see Table 8).

- In the 18-26 age group, HPV-18 GMTs in the GSK HPV vaccine group (1593.7 ED50) were 12.5-fold higher at Month 36 than in the Gardasil group (127.8 ED50).
- In the 27-35 age group, HPV-18 GMTs in the GSK HPV vaccine group (942.8 ED50) were 9.3-fold higher at Month 36 than in the Gardasil group (101.9 ED50).
- In the 36-45 age group, HPV-18 GMTs in the GSK HPV vaccine group (903.5 ED50) were 8.8-fold higher at Month 36 than in the Gardasil group (103.2 ED50).

In the GSK HPV group, 97.2% to 100 % of initially seronegative and DNA negative subjects were still seropositive for HPV-18 antibodies at Month 36 (two subjects in the 36-45 age group did not seroconvert at Month 36). In the Gardasil group, 70.5% to 78.9% of subjects were still seropositive for HPV-18 antibodies at Month 36.

Figure 7. GMTs with 95% CI for HPV-18 PBNA antibodies in subjects seronegative (by PBNA) and DNA negative (by PCR) at baseline (M36 ATP cohort for immunogenicity)



GMR: Geometric mean ratio; GSK-HPV vaccine: Cervarix

The GMT ratio (GSK HPV vaccine/Gardasil) was used to assess the between-group comparisons for non-inferiority. As the lower limits of the 95% CIs were greater than 0.5, non-inferiority of the GSK HPV vaccine over Gardasil was demonstrated for all age groups studied (see Table 7).

Table 8. Non-inferiority assessment in terms of GMT ratios between GSK HPV vaccine and Gardasil for HPV-18 PBNA antibodies in subjects seronegative (by PBNA) and DNA negative (by PCR) at baseline (M36 ATP cohort for immunogenicity)

					GMT ratio		
	GSK HPV		*Gardasil*			95% CI	
Age	N	GMT (ED_{50})	N	GMT (ED_{50})	Value	LL	UL
18-26y	64	1593.7	76	127.8	12.47	7.99	19.45
27-35y	75	942.8	61	101.9	9.25	5.85	14.64
36-45y	71	903.5	61	103.2	8.76	5.34	14.35

ED50 = Estimated Dose = serum dilution giving a 50% reduction of the signal compared to a control without serum
GMT = geometric mean antibody titer
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance)
LL = lower limit, UL = upper limit

As the lower limits of the CIs were greater than 1 for the non-inferiority measurement in all age groups, superiority was also tested. The primary analysis for superiority was performed on the TVC (regardless of serostatus and DNA status at baseline) as shown in Table 9. Superiority of the GSK HPV vaccine over Gardasil was demonstrated for all age groups (ANOVA $p < 0.05$).

Table 9. Superiority assessment in terms of antibody titers between Cervarix vaccine and Gardasil for HPV-16 PBNA antibodies at Month 36 (TVC)

	Cervarix		*Gardasil*			
Age	N	GMT (ED_{50})	N	GMT(ED_{50})	p-value ANOVA	p-value Kruskal-Wallis
18-26y	91	3806.34	93	782.29	<0.0001	<0.0001
27-35y	97	2373.73	84	945.09	<0.0001	<0.0001
36-45y	91	2610.51	101	1151.72	0.0004	0.00014

ED50 = Estimated Dose = serum dilution giving a 50% reduction of the signal compared to a control without serum GMT= geometric mean antibody titer
N = Number of subjects with post-vaccination results available

Anti-HPV-31 and anti-HPV-45 serological immune response (ELISA) in subjects seronegative and DNA negative (by PCR) at baseline (M36 ATP cohort for immunogenicity)

The percentage of subjects seropositive (by ELISA) for antibodies against HPV-31 at Month 36 ranged from 53.6% to 81.5% in the GSK HPV vaccine group and from 53.7% to 65.5% in the Gardasil group. The percentage of subjects seropositive for antibodies against HPV-45 at Month 36 ranged from 55.4% to 84.7% in the GSK HPV vaccine group and from 59.2% to 71.9% in the Gardasil group.

At Month 36, HPV-31 and HPV-45 antibody levels (by ELISA) were comparable between the vaccine groups in all age groups.

Anti-HPV-16 and anti-HPV-18 immune response in cervicovaginal secretions (M36 TVC)

HPV-16 and HPV-18 antibody positivity rates in CVS as measured by ELISA were 71.7% and 68.3% in the GSK HPV vaccine group, and 67.7% and 37.1% in the Gardasil group, respectively. GMTs for antibodies in CVS against HPV-16 and HPV-18 were comparable in each vaccine group.

2.4.4.3. Cell-mediated immune response (M36 ATP cohort for immunogenicity)

CD4 T-cell response in subjects seronegative (by PBNA), DNA negative (by PCR) and T-cell negative (specific CD4 T-cell < 500 cells/million cells) at baseline

The proportion of responders for HPV-16 and HPV-18 specific CD4 T-cells (>500 cells/million cells) expressing at least two immune markers (CD40L, IFNγ, IL-2 or TNFα) at Month 36 was higher in the GSK HPV vaccine group compared to the Gardasil group, but only reached statistical significance for HPV-16 (HPV-16: 80.0% vs 40.0%, Fisher p = 0.0322; HPV-18: 54.6% vs 29.4%, Fisher p = 0.1930).

The proportion of responders for oncogenic non-vaccine types HPV-31 specific CD4 T-cells expressing at least two immune markers at Month 36 was significantly higher in the GSK HPV vaccine group compared with the Gardasil group for HPV-31 (89.5% vs 45.5%, Fisher p = 0.0038) but did not reach statistical significance for HPV-45 (54.6% vs 33.3%, Fisher p = 0.2231).

Memory B-cell response in subjects seronegative (by PBNA), DNA negative (by PCR) and with no detectable B-cells at baseline

The proportion of subjects with detectable specific memory B-cells (responders) for HPV-16 and HPV-18 at Month 36 was not significantly different between the vaccine groups (HPV-16: 55.0% vs 68.8%,Fisher p = 0.5007; HPV-18: 54.6% vs 38.1%, Fisher p = 0.3640). Similarly, the Gmean ratios in responders were not significantly different between the vaccine groups (ANOVA p = 0.1106 and p = 0.2387).

The proportion of subjects with detectable memory B-cells for HPV-31 and HPV-45 at Month 36 was not significantly different between the vaccine groups (HPV-31: 30.0% vs 40.7%, Fisher p = 0.5460; HPV-45: 30.4% vs 46.4%, Fisher p = 0.2672). The magnitude of the memory B-cell response in these subjects was comparable between the vaccine groups.

Justification of immunogenicity as a correlate for protection/surrogate endpoint in the intended indications

A correlate of protection has not been established for HPV yet, probably due to the high vaccine efficacy and the limited number of cases occurring in clinical trials. Cervarix efficacy studies HPV-008 and HPV-001/007/023 have demonstrated high vaccine efficacy against histological and virological endpoints, while investigating antibody levels elicited by the vaccine in all or a subset of subjects. In study HPV-008, GMTs for anti-HPV-16 and anti-HPV-18 antibodies peaked at Month 7 and gradually declined until approximately Month 24 and then reached a plateau level. GMTs were well above levels elicited after naturally acquired infection at each time point post-vaccination (40.8-fold higher for HPV-16 and 21.6-fold higher for HPV-18 at Month 48). In study HPV- 001/007, a sustained immune response against both HPV-16 and HPV-18 was observed for up to 76 months of follow-up with approximately 99% or more of the vaccinees remaining seropositive as measured by ELISA and GMTs showing a plateau more than one log above levels associated with naturally acquired HPV-16 or HPV-18 infection (GlaxoSmithKline Vaccine HPV-007 Study Group 2009). Study HPV-023 confirmed the sustained immunogenicity up to 9.4 years (mean of 8.9 years) after initial vaccination. A similar pattern of functional antibody responses was observed by HPV-16 and HPV-18 PBNA in both studies.

In study HPV-008, geometric mean titres in women who had cleared HPV-16 and HPV- 018 following natural infection were determined (29.8 EU/mL [95%CI: 28.5; 31.0] and 22.6 [95% CI: 21.6; 23.6], respectively, using ELISA). Analysis of the placebo arm of the NCI study HPV-009 (and HPV-008) provided additional insights on antibody levels required to reduce the risk of subsequent infection.

Additional supportive evidence was generated evaluating the vaccine efficacy against VIN2+ and VaIN2+ at end of study analysis in HPV-008 as an exploratory endpoint. In total, there were 9 cases of

VIN2+ and/or VaIN2+ accrued in the ATP cohort for efficacy, of which 2 were in the vaccine group (both attributed to HPV-16) and 7 in the control group (4 were attributed to HPV-16 and 3 to HPV-18). Vaccine efficacy estimates were high (71.6% in the ATP cohort and 75.0% in TVC-1). Although statistical significance was not reached, likely due to the limited number of cases, analysis of VIN2+ and/or VaIN2+ data indicate that these observations are consistent with the vaccine efficacy against VIN1+ and/or VaIN1+.

HPV-16 and HPV-18 are implicated in the development of VIN and VaIN, of which VIN3 and VaIN3 are the immediate precursors of vulvar and vaginal invasive cancer. A proportion of extra-cervical lesions appear to be clonally related to cervical lesions that have occurred up to several years before. These findings suggest that a vaccine that is highly efficacious against cervical disease will probably also be efficacious against HPV-related vulvar and vaginal disease.

VIN1+ and VaIN1+ are not considered to be relevant surrogate endpoints for vulvar and vaginal invasive cancer. Supportive evidence was generated evaluating the vaccine efficacy against VIN2+ and VaIN2+ at the end of study analysis in HPV-008, where statistical significance was not reached, however, likely due to the limited number of cases. These results should therefore be interpreted with caution as bias in any direction cannot be excluded due to the low number of cases included in the study.

From data generated in efficacy studies, the link between high antibody levels elicited by the vaccine and protection against HPV is clearly established. The data gathered in study HPV-010 allow putting in perspective the immune response elicited by each of the two licensed vaccines.

2.4.5. Discussion

The proposed update on the SmPC, to include efficacy of Cervarix for premalignant vulvar and vaginal lesions, was based on the approved indication of qHPV vaccines, immunogenicity data from study HPV-010 (Month 7 and Month 36) and supportive efficacy data for Cervarix from study HPV-008.
Study HPV-010 demonstrated the non-inferiority and superiority of the immune response (superiority of Cervarix to Gardasil in terms of immune response measured by PBNA at Month 36) elicited by Cervarix over Gardasil in women aged 18-45 years. Based on the immunological data, the MAH proposed to infer efficacy to Cervarix for premalignant vulvar and vaginal lesions in women and young girls aged 9 and above. The efficacy of Cervarix against vulvar and vaginal lesions was assessed as exploratory endpoints in the efficacy study HPV-008. However, the number of cases of high grade VIN or VaIN was very limited. At the end of the study only 9 cases of VIN2+ or VaIN2+ were observed in the ATP cohort for efficacy, of which 2 were in the vaccine group (both caused by HPV-16) and 7 in the control group (4 were attributed to HPV-16 and 3 to HPV-18). Vaccine efficacy against VIN2+ for the combined HPV-16/18 endpoint was therefore 71.6% with a lower limit of the 95% confidence interval below 0. In view of the better immune responses observed with Cervarix in comparison with Gardasil and the fact that the occurrence of vaginal and vulvar lesions is not independent from previous cervical HPV infection or lesions as shown in the literature it can be concluded that Cervarix protects against vulvovaginal HPV infection, premalignant lesions and ultimately, cancer.
During the assessment, the CHMP identified concerns related to the justification to use immunogenicity as a correlate for protection/surrogate endpoint in the intended indications.
The CHMP noted from the MAH response that immunogenicity and efficacy data have established Cervarix as a vaccine in the prevention of premalignant cervical lesions causally related to certain oncogenic HPV types which are also implicated in the development of vaginal and vulvar invasive cancer. The immune response following vaccination, which included the production of neutralizing antibodies and L1 VLP specific memory B cells, superseded the levels detected following natural infection by HPV-16 and HPV-18. According to the CHMP guideline on the clinical evaluation of new

vaccines, in situations in which it is not feasible to perform an efficacy study and there is no established immunological correlate of protection, it may sometimes be justifiable to gauge the likely efficacy of a vaccine by comparison of immunological responses with those observed in past studies of similar vaccines with proven protective efficacy. Efficacy studies to demonstrate the efficacy of Cervarix against high grade VIN/VaIN are currently not feasible considering that functional vaccines have been commercialised and HPV vaccination is now widely implemented, which makes placebo-controlled trials non-justifiable.

In addition, the CHMP consulted the SAG vaccines on the acceptability to use immunogenicity data to derive vaccine efficacy of Cervarix for the intended indications. The SAG was of the view that despite no measures of immunogenicity are established as correlates of protection against HPV related premalignant lesions or cancer, considering the available scientific evidence about Cervarix, including its efficacy against premalignant cervical lesions, the available (but limited) descriptive data on VIN and VaIN protection, animal model data, and the evidence that protection has an antibody-mediated mechanism of action, the SAG agreed unanimously that there was a very high likelihood of actual vaccine efficacy against premalignant vulvar and vaginal lesions and that such efficacy could be inferred from the aforementioned package of data as a whole. The SAG were of the view that these considerations would allow support of the new proposed indication of prevention of premalignant genital lesions (cervical, vulvar and vaginal).

In summary, taken into account the available scientific evidence about Cervarix, including its efficacy against premalignant cervical lesions, the available (but limited) descriptive data on VIN and VaIN protection, animal model data, and the evidence that protection has an antibody-mediated mechanism of actionthe natural history of HPV infection, the CHMP considered that the aforementioned package of data as a whole is supportive to include the prevention of premalignant vulvar and vaginal to the indication.

2.5. Clinical Safety aspects

The analysis of safety was performed on the TVC (primary analysis) and the ATP safety cohort (secondary analysis). Compliance with completion of the 3-dose vaccination schedule was high in both schedule groups, i.e., 84.6% of subjects received all three doses of vaccine in the GSK HPV group and 84.4% of subjects in the Gardasil group. Similarly, the majority of subjects also received the placebo dose (89.9% in the GSK HPV group and 94.0% in the Gardasil group). As such, the majority of subjects were compliant with the full vaccination course.

Safety secondary endpoints of the study were:

- The percentage of subjects completing the three-dose vaccination schedule for the study vaccines (GSK HPV vaccine and Gardasil).
- The occurrence and intensity of solicited local symptoms (injection site pain, redness and swelling) during the 7-day period (Days 0-6) following each and any vaccination in both vaccine groups.
- The occurrence, intensity and relationship to vaccination of solicited general symptoms during the 7-day period (Days 0-6) following each and any vaccination in both vaccine groups.
- The occurrence, intensity and relationship to vaccination of unsolicited adverse events (AEs) during the 30-day period (Days 0-29) following each and any vaccination in both vaccine groups.
- The occurrence, intensity and relationship to vaccination of serious adverse events (SAEs) in both vaccine groups throughout the study.

- The occurrence, intensity and relationship to vaccination of new onset chronic disease (NOCD; e.g. autoimmune disorders, asthma, type I diabetes, allergies, etc.) and other medically significant conditions (AEs prompting emergency room or physician visits that are not related to common diseases or SAEs that are not related to common diseases) in both groups throughout the study regardless of causal relationship to vaccination and intensity.

2.5.1. Methods – analysis of data submitted

Statistical Methods:

The analyses of safety were performed on the TVC for data reported from Month 0 to Month 36.
Additional analyses were performed on the M36 TVC for data reported from Month 24 to Month 36.
The proportion of subjects with at least one report of a medically significant condition classified by Medical dictionary for Regulatory Activities (MedDRA), whenever available, was calculated with exact 95% CI.
The proportion of subjects with at least one report of NOCD classified by MedDRA, whenever available, was calculated with exact 95% CI. A separate table was produced for NOCD based on the MAH assessment and Investigator assessment respectively.
The proportion of subjects with at least one report of new onset autoimmune disease (NOAD) classified by MedDRA, whenever available, was calculated with exact 95% CI.

2.5.2. Results

The analyses of safety were performed on the TVC for data reported from Month 0 to Month 36.
Additional analyses were performed on the M36 TVC for data reported from Month 24 to Month 36.

Medically significant conditions

Up to Month 36, the percentage of subjects experiencing medically significant conditions was 43.2% in the GSK HPV vaccine group and 37.1% in the Gardasil group. The most common events in the GSK HPV vaccine group included bronchitis (2.7% in GSK HPV vs 1.8% in Gardasil), anxiety (2.4% vs 2.5%) and depression (2.0% vs 2.4%). The percentage of medically significant conditions reported from Month 24 to Month 36 was 13.3% in the GSK HPV vaccine group and 12.6% in the Gardasil group.

New onset chronic diseases

The number of subjects with a NOCD (as assessed by the MAH) up to Month 36 was low and similar in the two vaccine groups (27 [4.9%] subjects in the GSK HPV vaccine group and 29 [5.2%] subjects in the Gardasil group). The percentage of NOCDs reported from Month 24 to Month 36 was 1.4% in each vaccine group.

The most common NOCD was hypothyroidism, reported in five subjects in the GSK HPV vaccine group and in seven subjects in the Gardasil group. All other NOCDs were reported in at most three subjects in any vaccine group. The number of subjects experiencing a NOCD (as assessed by investigator) up to Month 36 was comparable in both vaccine groups (7.8%, 43 subjects in the GSK HPV vaccine group and 7.6%, 42 subjects in the Gardasil group).

New onset autoimmune diseases

Based on a pre-defined list of potential autoimmune events, the AEs were identified as NOCDs and classified as NOADs.

Up to Month 36, 16 subjects experienced an event classified as a NOAD (six [1.1%] subjects in the GSK HPV vaccine group and ten [1.8%] subjects in the Gardasil group). No NOAD events occurred in the follow-up period from Month 24 to Month 36.

The most common NOAD was hypothyroidism, reported in five subjects in each vaccine group. All other NOADs were reported in at most one subject in any vaccine group.

Serious adverse events

One subject died from a metastatic renal cell carcinoma in the follow-up period up to Month 24; this event was not considered to be related to vaccination by the investigator. A total of 58 subjects reported SAEs from Month 0 to Month 36.

Pregnancies

Women enrolled in the study were to be at least 3 months post-pregnancy. Additionally, women were to avoid pregnancy during approximately the first eight months of the study.

During the active phase of the study, 19 pregnancies were reported (10 in GSK HPV; 9 in Gardasil).A total of 106 pregnancies were reported up to Month 36 (57 in the GSK HPV vaccine group and 49 in the Gardasil group). From Month 24 up to Month 36, 26 pregnancies were reported (16 in the GSK HPV vaccine group and 10 in the Gardasil group).

2.5.3. Discussion

Cervarix (GSK HPV group) was more reactogenic than the Gardasil vaccine due to the higher incidence of solicited local and general symptoms in the 7-day postvaccination period. The difference in solicited symptoms was mainly observed in local rather than general symptoms, with pain as the most frequent local symptom. The higher reported frequency of solicited symptoms in the GSK HPV group did not affect compliance with vaccination, which was equivalent between groups.

No clinically meaningful differences were identified between vaccine groups in terms of reported, unsolicited AEs, medically significant AEs, NOCDs, NOADs, SAEs and pregnancy outcomes.

Up to Month 36, the percentage of subjects experiencing medically significant conditions was 43.2% in the GSK HPV vaccine group and 37.1% in the Gardasil group. The percentage of subjects in each vaccine group reporting NOCDs and NOADs up to Month 36 was comparable. A total of 30 subjects in the GSK HPV vaccine group and 28 subjects in the Gardasil group reported SAEs from Month 0 to Month 36. Pregnancies and pregnancy outcomes were comparable in both vaccine groups.

The safety profile observed in this study for the GSK HPV vaccine is consistent with the safety profile observed in other studies in the HPV development.

2.6. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

4.1 Therapeutic indications

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant genital (cervical, vulvar and vaginal) lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

5.1 Pharmacodynamic properties

Mechanism of action

Cervarix is an adjuvanted non-infectious recombinant vaccine . . . .

HPV-16 and HPV-18 are estimated to be responsible for approximately 70% of cervical cancers and 70% of HPV-related high grade vulvar and vaginal intraepithelial neoplasia. Other oncogenic HPV types can also cause cervical cancer (approximately 30%). HPV 45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%).

The term "premalignant ~~cervical~~ genital lesions" in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3), high-grade vulvar intraepithelial neoplasia (VIN2/3) and high-grade vaginal intraepithelial neoplasia (VaIN2/3).

Prophylactic efficacy against HPV-16/18 in women naïve to HPV-16 and/or HPV-18

At end of study analysis, there were 2 cases of VIN2+ or VaIN2+ associated with HPV-16 or HPV-18 in the vaccine group and 7 cases in the control group in the ATP cohort. The study was not powered to demonstrate a difference between the vaccine and the control group for these endpoints.

Package Leaflet

1. What Cervarix is and what it is used for

Cervarix is a vaccine intended to protect females from the age of 9 years against the diseases caused by infection with Human Papillomaviruses (HPV).

These diseases include:

- *cervical cancer (cancer of the cervix i.e. lower part of the uterus or womb),*
- *precancerous ~~cervical~~ lesions of the female genitals (changes in cells of the cervix, vulva and vagina that have a risk of turning into cancer).*

The Human Papillomavirus (HPV) types contained in the vaccine (HPV types 16 and 18) are responsible for approximately 70% of cervical cancer cases and 70% of HPV-related pre-cancerous lesions of the vulva and vagina. Other HPV types can also cause cervical cancer. Cervarix does not protect against all HPV types.

In addition, changes in the Annex II regarding Pharmacovigilance system, PSUR and RMP in line with the latest QRD template were introduced.

3. Overall conclusion and impact on the benefit/risk balance

The CHMP evaluated all the available scientific evidence on Cervarix and considered the natural history of HPV infection, the time to disease progression, challenge animal models, and the efficacy trend observed in study HPV 008 acceptable and supportive to add prevention of premalignant vulvar and vaginal lesions related to certain oncogenic Human Papillomavirus (HPV) types to the indication.

The current variation does not influence the known risks associated with the use of Cervarix. The benefit risk profile of the product remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		Type
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.1 and 5.1 of the SmPC with prophylactic efficacy data against premalignant vulvar and vaginal lesions. The Package Leaflet is updated in accordance. Changes in the Annex II regarding Pharmacovigilance system, PSUR and RMP were introduced. The MAH took the opportunity to update the "Information intended for healthcare professionals" with thermostability wording for the 2-dose vial. Furthermore, the MAH took the opportunity to update the local representatives of Cyprus in the Package leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.