CERVARIX

Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Briefing Document

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GENERAL ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices (US)
ADC	Adenocarcinoma
ADR	Adverse drug reaction
AE	Adverse event
AGC	Atypical glandular cells
AIS	Adenocarcinoma *in-situ*
$Al(OH)_3$	Aluminum hydroxide
APC	Antigen presenting cells
ASC	Atypical squamous cells
ASC-H	Atypical squamous cells / high-grade ASC-US; does not exclude HSIL
ASC-US	Atypical squamous cells of undetermined significance
≥ASC-US	ASC-US, LSIL, HSIL, AGC, ASC-H
AS04	Adjuvant containing aluminum salts and MPL
ATP	According to protocol
BEVS	Baculovirus expression vector system
BLA	Biologicals License Application
CBER	Center for Biological Evaluation and Research, USA
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use, European Union
CI	Confidence Interval
CIN	Cervical intraepithelial neoplasia
CIN1+	CIN1, CIN2, CIN3, AIS and ICC
CIN2+	CIN2, CIN3, AIS and ICC
CIN3+	CIN3, AIS and ICC
CMI	Cell mediated immunity
CR	Complete response
CVS	Cervico-vaginal sample
DC	Dendritic cells
DSMB	Data Safety Monitoring Board
ED_{50}	Effective dose producing 50% response
ELISA	Enzyme-linked immunosorbent assay
EL.U.	ELISA units
EL.U./mL	ELISA units per milliliter
FDA	Food and Drug Administration, USA
gD2	Glycoprotein D from HSV-2
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HCII	Hybrid capture 2
HPV	Human papillomavirus
HPV-16/18 vaccine	Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant
HR	High risk
HR-HPV	High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
HRW-HPV	All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HRW-HPV excluding HPV-16/18 co-infection	All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 and excluding lesions with HPV-16/18 co-infections
HSIL	High-grade squamous intraepithelial lesion
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease

ICC	Invasive Cervical Cancer
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL	Interleukin
IMRE	Immune-mediated rheumatologic events
IND	Investigational new drug
LEEP	Loop Electrosurgical Excision Procedure
LMP	Last Menstrual Period
LPS	Lipopolysaccharide
LSIL	Low-grade squamous intraepithelial lesion
MedDRA	Medical Dictionary for Regulatory Activities
MSC	Medically significant conditions
μg	Microgram
mL or ml	Milliliter
MHRA	Medicines and Healthcare products Regulatory Agency, United Kingdom
mg	Milligram
MPL	3-*O*-desacyl-*4'*-monophosphoryl lipid A
N	In data tables, number of subjects included in each group
n	In safety tables, number of subject with at least once the symptom. For pregnancies, number of pregnancies in a given category
NCI	National Cancer Institute, USA
NHIS	National Health Interview Survey
NOAD	New Onset of Autoimmune Disorder
NOCD	New Onset of Chronic Disease
PBNA	Pseudovirion based neutralization assay
PCR	Polymerase chain reaction
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SLE	Systemic lupus erythematosus
SOC	System Organ Class
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α
TVC	Total Vaccinated Cohort
TVC-1	Total Vaccinated Cohort 1
TVC-naïve	Total Vaccinated Cohort of naïve women
UK	United Kingdom
US or USA	United States or United States of America
VE	Vaccine efficacy
VaIN	Vaginal intraepithelial neoplasia
ViN	Vulvar intraepithelial neoplasia
VLP	Virus-like particle
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

TRADEMARKS

The following trademarks are used in the present document.

Note: In the body of the document, the names of the vaccines and/or medications will be written without the ™ or ® symbol.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Boostrix®	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
Boostrix Polio™	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis and polio vaccine
Cervarix®	Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant
Engerix B®	Hepatitis B (Recombinant)
Fendrix™	Hepatitis B vaccine (Recombinant, AS04 adjuvanted, adsorbed)
Havrix®	Hepatitis A (Inactivated, adsorbed)
Twinrix®	Hepatitis A (Inactivated) and Hepatitis B (Recombinant)

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Aimmugen™	Hepatitis A vaccine
Gardasil®	Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
Menactra®	Meningococcal (Groups A,C,Y and W-135) Polysaccharide Diptheria Toxoid Conjugate
Thinprep®	Liquid based pap test

1. INTRODUCTION AND EXECUTIVE SUMMARY

Cervarix (Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant) is a non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic human papillomavirus (HPV) types 16 and 18 adjuvanted with the AS04 adjuvant system, containing 3-*O*-desacyl-*4'* monophosphoryl lipid A (MPL) and aluminum.

Cervarix is intended for the vaccination of girls and women 10-25 years of age for the prevention of the following diseases caused by HPV types 16 and 18 included in the vaccine:

- Cervical cancer
- Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*
- Cervical intraepithelial neoplasia (CIN) grade 1

As outlined in the briefing material, data also support evidence of prophylactic efficacy of *Cervarix* against oncogenic HPV types beyond those included in the vaccine

The biologics license application (BLA) for *Cervarix* was submitted to the Food and Drug Administration (FDA) on March 29, 2007. The Investigational New Drug (IND) application was first submitted by MedImmune in 1998, following which GlaxoSmithKline (GSK) worked in partnership with MedImmune until 2002 with transfer of the IND to GSK in 2000. Since then and throughout the course of development, GSK has had frequent interactions with the FDA. In 2001, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) met to consider the endpoints for phase III development of a cervical cancer vaccine and recommended CIN2/3 or worse as the basis for licensure. Following this recommendation and in consultation with the FDA, the prevention of cervical intraepithelial neoplasia "CIN2+" [i.e. CIN2, CIN3, adenocarcinoma *in situ* (AIS) and invasive cervical cancer (ICC)] associated with HPV-16/18 was selected as the primary endpoint for evaluation of vaccine efficacy in the Phase III pivotal efficacy Study HPV-008. The *Cervarix* BLA, which was based on an interim analysis of this pivotal efficacy study, was submitted to FDA in March 2007. A Complete Response (CR) letter was received from the FDA in December 2007. GSK was able to respond to all the issues in the letter within a few months but elected to delay the declaration of the complete response and resumption of the review clock given that the availability of final data from HPV-008 was imminent and would lead to a more complete characterization of the clinical performance of *Cervarix*. As a result, the submission of the HPV-008 final report in March 2009 restarted the review clock. In addition, the resumption of BLA review at this time afforded an opportunity to include the final analysis of the Phase IIb efficacy Study (HPV-007), with up to 6.4 years of follow-up, and updated safety information.

Cervarix was first approved in Australia in May 2007 for use in girls and women 10-45 years of age. In September 2007, *Cervarix* was approved by the European Union for use in girls and women based on demonstration of efficacy in women 15-25 years of age and demonstration of immunogenicity in girls and women 10-25 years of age. *Cervarix* is

currently licensed in more than 95 countries worldwide including the 27 member countries of the European Union, Mexico, Brazil, Australia, India, South Africa, Singapore and the Philippines and is pre-qualified by the World Health Organization (WHO).

This briefing document provides information on epidemiology of human papillomaviruses, rationale for GSK's development program, and an overview of the clinical data supporting the immunogenicity, safety and efficacy of *Cervarix* for the prevention of cervical cancer in healthy girls and women 10 to 25 years of age.

HPV disease burden and epidemiology

There are a variety of cancers that have been shown to be associated with oncogenic HPV, including cervical, vulvar, vaginal, anal, penile and oro-pharyngeal (tonsil, pharynx and larynx) cancers. However, cervical cancer is the most common of these cancers, and is, after breast cancer, the most commonly occurring cancer in women worldwide [Ferlay, 2004].

Infection with an oncogenic HPV type is a necessary prerequisite for the development of cervical cancer and HPV DNA can be found in virtually all cervical carcinomas [Bosch, 1995; Walboomers, 1999]. Although, in the United States (US), the implementation of cervical screening programs has dramatically reduced the lifetime risk of cervical cancer, the absolute burden of the disease remains considerable such that vaccination, combined with effective screening programs, offers the best opportunity to prevent cervical cancer.

Fourteen HPV types are considered oncogenic. In North America, the five most common types (HPV-16, HPV-18, HPV-31, HPV-33 and HPV-45) account for nearly 88% of all cervical cancer cases [Smith, 2007] of which the two vaccine types (HPV-16 and HPV-18) are responsible for 76% of cervical cancer cases. HPV-18 and HPV-45 have a relatively greater contribution to adenocarcinoma (ADC) compared with squamous cell carcinoma and, combined with HPV-16, account for approximately 90% of ADC cases worldwide [Bosch, 2008].

Vaccine Composition and Manufacture

Cervarix contains 20µg of HPV-16 L1 protein and 20µg of HPV-18 L1 protein assembled as VLPs as the vaccine antigens. The L1 proteins are formulated with the AS04 adjuvant system, which is composed of 50µg of MPL and 500µg of aluminum hydroxide salt. The vaccine is preservative-free.

The vaccine antigens are produced using the recombinant Baculovirus expression vector system (BEVS), in a robust, well-controlled and characterized, animal-free manufacturing process. The expression system produces high yields of well-characterized non-infectious VLPs which are morphologically and antigenically almost identical to native HPV virions.

The AS04 adjuvant system consists of aluminum hydroxide, one of the most widely used adjuvants in vaccines globally with over 80 years of experience, and MPL, derived from lipopolysaccharide (LPS) of the gram-negative bacterium *Salmonella minnesota*. Such

gram-negative bacteria are ubiquitous in the environment and human exposure is common. Natural LPS is known to be an effective adjuvant and MPL, a purified form of LPS with highly reduced toxicity, retains this adjuvant effect [Johnson, 1987; Myers, 1990].

Vaccine Design

Cervarix was designed with the goal of bringing the most effective cervical cancer vaccine possible to young girls and women worldwide by taking into consideration the current understanding of the particularities of oncogenic HPV natural infection, including the ability of the virus to evade the immune system, the repeated exposure throughout life and lack of reliable protection against re-infection by natural immunity. Also, the prevalence of the most important oncogenic HPV types, the inherent risk of interference with multi-valent vaccines, the need for induction of high neutralizing antibodies at the cervix (the site of infection) and the need for long-term protection were taken into account in the development of *Cervarix*.

Also, research has shown that vaccine-induced neutralizing antibodies against L1 VLPs are a key mediator in vaccine-induced protection and indicate that long-term protection in humans will require vaccines that induce strong humoral immunity with activity at the site of infection.

Cervarix was therefore designed to induce high and sustained antibody responses that can transfer to the site of infection to provide long-term protection against infection and disease caused by HPV-16 and HPV-18, the two most frequent oncogenic HPV types in cervical cancer. By optimizing the HPV-16 and HPV-18 immune responses through the use of AS04, GSK's design strategy was to increase the likelihood of providing cross-reactive immune responses between the vaccine types and closely related HPV types, thus broadening the protection against cervical cancer.

Choice of the initial candidate vaccine formulation was supported by non-clinical dose-ranging data that supported a weight ratio of 1:1:25:2.5 of each L1 VLP antigen, $Al(OH)_3$ and MPL, respectively – a ratio also proven suitable for other AS04-adjuvanted vaccines, including a hepatitis B vaccine licensed as *Fendrix* in Europe. Preclinical immunogenicity and toxicology studies, and early clinical studies further confirmed the superior immune response of AS04-adjuvanted vaccine over aluminum adjuvant, the lack of interference between HPV-16 and HPV-18 antigens and the suitable balance between vaccine tolerability and the desired immune response to warrant further development.

In addition, preclinical studies have been conducted to elucidate the mode of action of AS04. These studies indicate that AS04 acts at the earliest step in the immune response by stimulating local recruitment and activation of antigen presenting cells (APCs). MPL acts on APCs via specific TLR4 receptor agonism and has no direct effect on T and B effector cells. Immune stimulation by MPL requires temporal and local presentation of the adjuvant with the antigen to induce a local and transient innate response resulting in high and sustained immunity. These characterization studies provide no evidence for a plausible mechanism to induce autoimmune disease in humans.

Overall, these data have supported the development and evaluation of the clinical impact of *Cervarix* in efficacy trials. Clinical trials showed that HPV-16/18 AS04-adjuvanted vaccine was not only associated with high efficacy against CIN2+ associated with HPV-16/18 but also non-vaccine oncogenic HPV types confirming the potential of *Cervarix* for protection against cervical cancer beyond HPV-16/18.

Cervarix clinical program

Cervarix has undergone an extensive clinical development program in a diverse population and broad age range. Studies include women naïve (without current infection and without prior exposure) or non-naïve (with current infection and/or with prior exposure) to HPV at the time of vaccination. The clinical development program includes approximately 30,000 healthy women, with over 16,000 women having received at least one dose of *Cervarix*. The development program involved over 30 countries from different geographical regions, including 4,322 subjects from the US. Data has been submitted from six controlled Phase II/III studies and four uncontrolled or consistency Phase II/III studies. The safety profile of *Cervarix* and the adjuvant system was further confirmed by data from completed and ongoing studies of *Cervarix* (in total over 57,000 women with over 33,000 of them receiving at least one dose of *Cervarix*) and other AS04-containing vaccines, including a meta-analysis (with more than 68,000 subjects and over 36,000 subjects receiving *Cervarix* and other AS04-containing vaccines). Collectively these data demonstrate clinical vaccine efficacy, immunogenicity, manufacturing and lot consistency and vaccine safety.

Efficacy and immunogenicity of *Cervarix*

Vaccine efficacy was assessed in 19,778 females 15 to 25 years of age with follow-up through a maximum of 6.4 years post vaccination. In an efficacy study enrolling women without regard to HPV DNA status (current infection) or serostatus (prior exposure), i.e., representing a general population of women, prophylactic efficacy against HPV-16/18 CIN2+ was demonstrated with up to 98% protection in women seronegative and HPV DNA negative for HPV-16/18 at baseline. Up to 100% prophylactic efficacy was also demonstrated against HPV-16/18 CIN2+ in women in whom there was no evidence of prior or current infection. There was no evidence of any therapeutic benefit (or any detriment) in those currently infected with HPV-16/18. Of note, there was evidence of benefit in those whose serostatus indicated a prior infection that had cleared (women seropositive and HPV DNA negative for HPV-16/18 at baseline). In these women, there was a consistent pattern of efficacy observed across virological and histopathological endpoints reaching statistically significance for protection against persistent infection and CIN1+. The number of CIN2+ endpoints was, however, too limited in this study cohort to reach statistical significance.

The overall impact of vaccination against CIN2+ and CIN3+ lesions irrespective of HPV type indicated efficacy beyond HPV-16/18. In women presenting with no evidence of oncogenic HPV infection, the vaccine prevented 70% of all CIN2+ lesions and 87% of all CIN3+ lesions. These levels of protection are greater than expected given the contribution of HPV-16 and HPV-18 to cervical pre-cancers. A high level of efficacy was observed against lesions associated with non-vaccine oncogenic types with protection

ranging from 37% to 54% in a sensitivity analysis accounting for the extent of co-infections with HPV-16/18. Analysis of histopathological and virological endpoints indicates that this excess overall protection appears to be predominantly mediated by protection specifically against types HPV-31, HPV-33 and HPV-45. *Cervarix* was also efficacious in the overall reduction of local cervical therapy (LEEP, Cone, Knife and Laser).

Immune responses, including neutralizing antibodies, were sustained at high levels for both HPV-16 and HPV-18 and a successful immunological bridge to pre-teenage girls 10-14 years was established.

Health outcomes following vaccination with *Cervarix*

Although the population impact of vaccination with *Cervarix* on cervical cancer can only be determined in the long term, a Markov model was used to estimate the lifetime impact of HPV vaccination in reducing cervical disease. The model assumed vaccine coverage of 75% in an US population of girls and women 10-25 years of age. With an efficacy of 95% against HPV-16/18 related CIN2+ lesions, *Cervarix* is estimated to prevent over 100,000 cervical cancer cases and 25,000 related deaths over the lifetime of vaccinated girls and women. Considering the cross-protective efficacy observed for *Cervarix* against non-vaccine types (i.e., 37% to 54%), protection against cervical cancer in this US population is increased by 9 to 14%. Thus, compared with a vaccine that offers oncogenic protection against HPV-16/18 only, *Cervarix* is estimated to prevent an additional 9,000 to 14,000 cancer cases and save an additional 2,000 to 3,000 lives due to cross-protection. This translates into preventing an additional 110-160 cervical cancer cases and saving 25-40 lives per year. Overall, when considering the average annual impact, *Cervarix* is estimated to prevent 1200-1300 cervical cancer cases and 300-320 lives every year.

Safety of *Cervarix* and Risk Management Plan

The safety database for *Cervarix* includes up to 57,323 females aged 10 years and above with a total follow-up of 129,454 person-years and a maximum individual follow-up of 88.8 months (7.4 years). In this population, 33,623 females received at least one dose of *Cervarix* alone or co-administered with another vaccine, with a follow-up of 70,086 person-years. This substantial database allows for a comprehensive assessment of the safety of *Cervarix*.

Solicited local symptoms (injection site pain, swelling and redness) and myalgia were reported more frequently in the HPV group as compared to control groups, in 10-25 year old girls and young women. However, events were generally mild to moderate in intensity. Compliance with dosing was equally high in HPV and control groups, indicating that *Cervarix* was well-tolerated.

Cervarix was generally well-tolerated across age groups studied (from 10 years to 25 years of age) and there was a similar safety profile in women with HPV exposure prior to vaccination and women with no evidence of prior exposure. Similar rates of unsolicited adverse events, serious adverse events (SAEs), medically significant conditions and adverse events (AEs) classified as new onset of autoimmune disorders (NOADs) were observed in vaccine and control groups alike.

With the majority of subjects in the clinical safety database consisting of women 15 to 25 years of age (i.e. women of child-bearing age who are also at an age in which a higher incidence of autoimmune disorders is expected) the follow-up of pregnancies and their outcomes and the reporting of autoimmune disorders were two aspects of safety reporting that that were thoroughly evaluated.

Similar overall rates of pregnancy outcomes were observed in vaccine and control groups. In an exploratory subanalysis of pregnancy outcomes around the time of vaccination, a numerical (non-significant) imbalance in the rates of spontaneous pregnancy loss was observed. However, the observed rate in the vaccine group was within the range of background rates. Pregnancies and pregnancy outcomes will be further monitored in the risk management program.

A large meta-analysis of potential autoimmune events in more than 68,000 subjects from controlled clinical studies of AS04-adjuvanted vaccines, demonstrated comparable event rates in vaccinees and controls with no significant increase in relative risk. Further analyses of neuroinflammatory and musculoskeletal events of potentially autoimmune etiology indicated that the reporting of events was low and comparable between vaccine and control groups. Events were also reviewed by external expert panels of neurologists and rheumatologists. From these data and the review by external experts, it can be concluded that there was no increased risk of neuroinflammatory or musculoskeletal autoimmune disorders following vaccination with AS04-containing vaccines.

Cervarix is currently licensed in over 95 countries worldwide. Approximately 7 million doses of *Cervarix* have been distributed (May, 2009) and the number of individuals exposed is estimated to be over 2 million. Following review of safety data arising from all sources with post-licensure data in particular, no safety concerns have been detected in post-marketing surveillance.

GSK is currently conducting an extensive risk management program to further monitor the safety of *Cervarix*, including further clinical trials, enhanced pharmacovigilance monitoring, and various Phase IV studies. The clinical studies will include: trials among HIV positive women, co-administration trials, and extension studies to measure the long-term immunogenicity, efficacy and safety of *Cervarix*.

We plan to further evaluate long-term safety of *Cervarix* - specifically the potential occurrence of autoimmune disorders and pregnancy outcomes - in two large Phase IV studies. The first study is a community-randomized study currently ongoing in Finland with a targeted enrollment of up to 70,000 adolescents of 12-15 year of age (with up to 30,000 adolescents receiving *Cervarix*). It will evaluate vaccine safety and effectiveness and the potential for HPV type replacement within the population. A second study is planned in the US. This large observational safety study will assess the occurrence of autoimmune disorders and abnormal pregnancy outcomes in 50,000 women vaccinated with *Cervarix*.

Conclusions

Based on the assessment and analysis of the clinical data, the overall risk/benefit for *Cervarix* is favorable. An excellent safety profile has been demonstrated across all age

cohorts and there is a high level of efficacy against cervical cancer and precancerous lesions with evidence of efficacy against vaccine and some non-vaccine types. There is a high and sustained immune response throughout a 6.4 year follow up. Pending longer term outcomes, disease modeling affords an estimate of public health benefit that indicates that *Cervarix* with protective efficacy against HPV types beyond those in the vaccine will prevent more cancers and save more lives than a vaccine that only prevents for HPV-16 and HPV-18.

As a result, *Cervarix* is expected to provide a significant public health benefit to girls and women 10 to 25 years of age.

2. BACKGROUND

2.1. HPV Disease Burden

Invasive cervical cancer is, after breast cancer, the most commonly occurring cancer in women worldwide, with an estimated 493 000 new cases and 273 000 deaths in the year 2002 [Ferlay, 2004; Sankaranarayanan, 2006]. Estimates indicate that in 2009, approximately 11,270 women will be diagnosed and 4,070 will die of cervical cancer in the US [Jemal, 2009]. Cervical cancer is often a fatal condition, with a five-year survival rate in the US of approximately 70% [Ries, 2004], and an estimated 2.7 million years of life lost in 2000 [Yang, 2004]. In the years following the implementation of cervical screening programs, the lifetime risk of cervical cancer in the US was reduced from 3-4% [Kim, 2002; Myers, 2000] to 0.85% [National Cancer Institute, 2001]. HPV associated non-cervical cancers include vulvar, vaginal, anal, penile and oro-pharyngeal cancers and account for a substantial number of cases annually in the US [Gillison, 2008], see Table 2. The diagnosis for cervical cancers usually occurs by 48 years of age [Horner, 2008].

In the US, cervical cancer is among the 15 most frequent cancers among women with an incidence rate of 8.7 per 100,000 women in 2002 [US Cancer Statistics Working Group, 2005]. This rate differs noticeably among ethnic groups, with Hispanic Americans (13.1 per 100,000) and African Americans (12.4 per 100,000) having the highest rates. Mortality rates among these groups mirror the incidence rates, with the highest rates observed among Hispanic Americans and African Americans [Saraiya, 2007].

Although many risk factors for the development of squamous cell carcinoma and ADC of the cervix are similar, incidence rates for both have diverged since the 1980s, possibly because cytological screening practices are insufficient to detect a significant proportion of ADC precursor lesions [Smith, 2000], which occur in younger women and have lower survival rates [Herzog, 2007]. In the US, the proportion of ADC has doubled from 1973 to 1996, accounting for approximately 20% of all cervical cancers [Watson, 2008; Smith, 2000] with approximately 2200 cases occurring annually.

The burden of precancerous cervical lesions is much broader than the absolute number of cervical cancer cases. Precancerous lesions detected through screening programs result in physical, psychosocial and emotional distress for women, in addition to substantial financial costs to health services. Sixty-five million Pap tests were performed in the US in 2005 [Eltoum, 2007]; each year, approximately 2 million Pap tests are diagnosed as

abnormal, prompting further evaluations [Insinga, 2004a]. The direct medical costs associated with cervical cancer for 2008 were $300-400 million [Insinga, 2008]. The estimated productivity loss in 2000 associated with cervical cancer mortality was $1.3 billion [Insinga, 2006].

Cervical screening is a multi-step process starting with the collection of a Pap or cervical smear which is evaluated for cytology. The Bethesda classification system is now widely used for reporting the results of cervical cytology [Burd, 2003] (Table 1). According to the current Bethesda system, most abnormalities can be divided into two types: squamous cell and glandular cell abnormalities. Squamous cell abnormalities include atypical squamous cells (ASC), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma (SCC). Glandular cell abnormalities include atypical glandular cells (AGC) and endocervical adenocarcinoma *in situ* (AIS). Subjects with abnormal cellular changes might be subsequently investigated through colposcopy. This may result in a cervical biopsy assessed for histology. The histopathological abnormality corresponding to the cytological definition of squamous intraepithelial lesion (SIL) is called cervical intraepithelial neoplasia (CIN), adenocarcinoma *in-situ* (AIS) and glandular atypia for glandular lesions.

Table 1 Bethesda and CIN Classification Systems

Bethesda System 1999	CIN System	Interpretation
Negative for intraepithelial lesions or malignancy	Normal	No abnormal cells
ASC ASC-US (atypical squamous cells of undetermined significance) ASC-H (atypical squamous cells, cannot exclude HSIL)		Squamous cells with abnormalities greater than those attributed to reactive changes but that do not meet the criteria for a squamous intraepithelial lesion
LSIL (low-grade squamous cell intra-epithelial lesions)	CIN1	Mildly abnormal cells; changes are almost always due to HPV
HSIL (high-grade squamous intraepithelial lesions) with features suspicious for invasion (if invasion is suspected)	CIN2/3	Moderately to severely abnormal squamous cells
Carcinoma	Invasive squamous cell carcinoma Invasive glandular cell carcinoma (adenocarcinoma)	The possibility of cancer is high enough to warrant immediate evaluation but does not mean that the patient definitely has cancer

Data source: Burd, 2003

In June 2006, the FDA approved an aluminum-adjuvanted quadrivalent HPV vaccine, *Gardasil*, containing VLPs for HPV-6 and HPV-11 in addition to VLPs for HPV-16 and HPV-18. HPV-6 and HPV-11 are non-oncogenic HPV types responsible for genital warts and a proportion of low-grade cervical cytology abnormalities, which are unlikely to

progress to cervical cancer. The vaccine has been licensed for girls and women 9 to 26 years of age for the prevention of cervical, vulvar, and vaginal cancer caused by HPV-16 and HPV-18, genital warts (condyloma acuminata) caused by HPV-6 and HPV-11 and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18: CIN2+, CIN1, VIN2+ and VaIN2+. The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for girls 11-12 years of age while stating that the vaccine can be administered as young as 9 years of age. Catch-up vaccination is recommended for women aged 13-26 years who have not been previously vaccinated. The ACIP states that vaccination is not a substitute for routine cervical cancer screening, and vaccinated women should continue screening as recommended [Centers for Disease Control and Prevention, 2007; Centers for Disease Control and Prevention, 2009; Centers for Disease Control and Prevention, 2008].

2.2. Distribution of oncogenic HPV in precursor lesions and cervical cancer

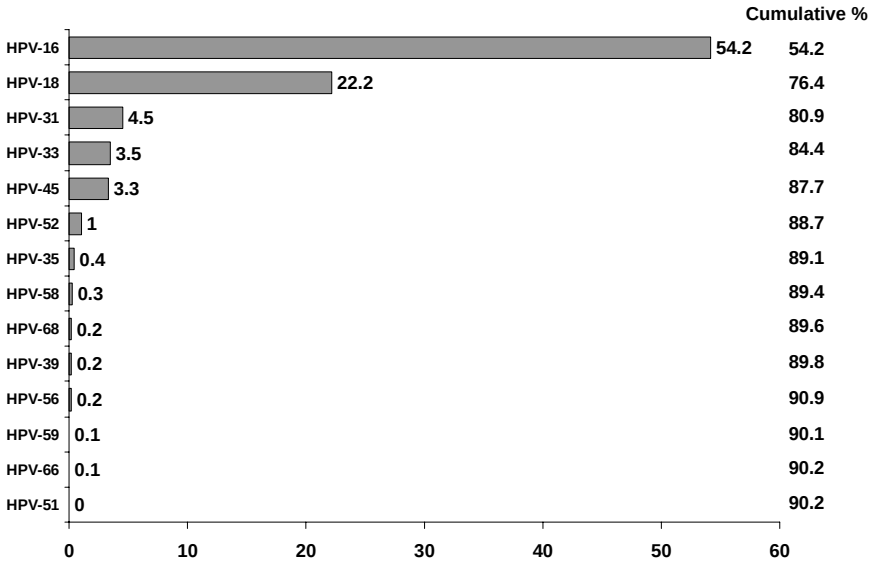
Persistent infection with an oncogenic HPV type is a necessary prerequisite for the development of cervical cancer and HPV DNA can be found in virtually 100% of all cervical carcinomas [Bosch, 1995; Walboomers, 1999].

Of the approximately 40 HPV types that infect the anogenital region, 14 types are considered oncogenic (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) [Walboomers, 1999] because of their association with cervical cancer and pre-invasive lesions and have been widely used as probes in diagnostic assays.

Worldwide estimates of the type-specific prevalence of HPV in women with cervical cancer show that HPV-16 and -18 account for 70% of cases [Smith, 2007]. The next 5 most common types globally in descending order are: HPV-33, -45, -31,-58 and -52. These types are also common in North America (Figure 1): HPV-16 and -18 are responsible for 76% of cases and additional non-vaccine types (HPV-31 and HPV-33 [16-related] and HPV-45 [18-related]) account for approximately 12% of cervical cancer cases, i.e. together HPV-16, HPV-18, HPV-31, HPV-33 and HPV-45 account for 88% of all cervical cancer cases [Smith, 2007]. In a recent study which utilized highly sensitive HPV detection assays as well as methods to control for multiple infections, 81% of ICC cases were related to HPV-16, 18, 31 and 45 [Wheeler, 2009].

Approximately 20% of all cervical cancers in the US are ADC [Watson, 2008]. Studies have shown that HPV-18 is more common in ADC (36%) than in SCC (13%) [Bosch, 2008]. Worldwide, HPV-16, HPV-18 and HPV-45 account for approximately 90% of ADC cases [Bosch, 2008].

Figure 1 North American Cervical Cancer Cases (%) Attributed to Oncogenic HPV Types [Smith, 2007]

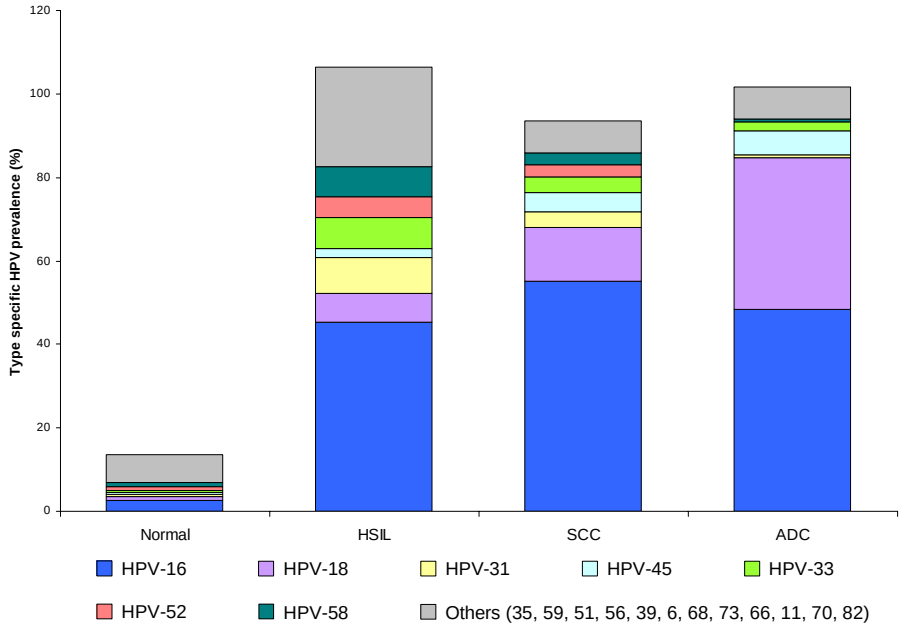


Total of all oncogenic HPV types does not equal 100% because of varying specificity of assays used for the detection of oncogenic HPV

In North America, the estimated proportion of HPV-16/18 in cervical abnormalities is: 19% in ASC-US, 28% in LSIL, 55% in HSIL and 76% in cancer [Clifford, 2006].

As shown in Figure 2, the contribution of HPV-16, HPV-18 and HPV-45 significantly increases in ICC (both SCC and ADC) as compared to HSIL. This highlights the importance of these 3 oncogenic types in the risk of progression to cancer in contrast to other oncogenic types (HPV- 31, HPV-33, HPV-52, and HPV-58) [Bosch, 2008; Clifford, 2006].

Figure 2 Type specific worldwide HPV prevalence in women with normal cytology, HSIL, SCC and ADC [Bosch, 2008]



Prevalence percentages can be > 100% because samples with multiple HPV types are counted more than once (for each type identified in the sample).

Other HPV-related cancers include vulvar, vaginal, anal, penile and oro-pharyngeal cancer [Parkin, 2006]. In the US, the HPV-16/18 attributable fraction of HPV-related cancers ranges from 31% to 76%, see Table 2 [Gillison, 2008].

Table 2 HPV-16/18 associated invasive cancers in the US, 1998-2003 [Gillison, 2008]

Cancer Type	HPV-16/18 associated (%)	Annual number of cases
Cervical	76	8243
Oropharyngeal	60	4416
Anal	87	2211
Vulvar	44	988
Vaginal	56	347
Penile	31	257

2.3. HPV frequency and natural history

Anogenital HPV infections are the most common sexually transmitted infection; an estimated 9.2 million persons are newly infected every year in the US [Weinstock, 2004]. Population-based studies in the US report an oncogenic HPV type prevalence rate in women aged 14 -59 years of 15-20% and 2-8% for HPV-16 and HPV-18 respectively [Manhart, 2006; Dunne, 2007].

Longitudinal studies suggest that acquisition of oncogenic HPV occurs rapidly following sexual debut. Approximately 50% of women who are initially HPV negative will acquire an infection within 3-4 years after onset of sexual activity [Winer, 2003; Moscicki, 2001]. Acquisition of HPV is highest among women younger than 25 but continues throughout life in sexually active women and remains substantial in older age groups [Munoz, 2004; Bory, 2002; Dalstein, 2003; Franco, 1999; Munoz, 2004; Grainge, 2005].

Although HPV infections are very common, most are transient in nature and 70-90% will clear [Brown, 2005; Richardson, 2003; Moscicki, 1998]. Those infections that persist are at the highest risk of developing into precancerous lesions and cancer [Ho 1995; Hildesheim, 1994; Schiffman, 2005; Schlecht, 2003]. HPV-16 tends to persist longer than any other type and has the highest probability of developing into cancer given persistence [Schiffman, 2005, Khan, 2005, Wheeler, 2006]. Consultations with the Committee for Medicinal Products for Human Use (CHMP), and guidelines published by the WHO [Pagliusi, 2004; WHO, 2006], have affirmed the predictive value of virological endpoints including persistent infection.

Both sequential and simultaneous infections with multiple oncogenic HPV types are common in sexually active young women and in those with cytological abnormalities [Ho, 1998; Herrero, 2000; Rousseau, 2003; Chaturved, 2005; Dunne, 2007; Sargent, 2008; Paavonen; 2007; Brown; 2009]. HPV-16 is the most prevalent type isolated in co-infections [Rousseau, 2003]. Cervical infections with multiple HPV types may increase the risk of dysplasia and cancer [Rousseau, 2003; Trottier, 2006; van der Graaf, 2002; Trottier, 2008].

HPV infection can lead to histological changes (CIN1 through CIN3). CIN1 reflects mild neoplasia and CIN2 and CIN3 represent more severe degrees of cervical neoplasia. CIN1 clears spontaneously in most cases and seldom develops to cancer (1%) [Moscicki, 2004]. CIN2 and CIN3 lesions have lower rates of regression (30-40%) and higher rates of progression to cancer [Ostor, 1993].

CIN3 generally occurs in women 25-30 years of age, and the time between HPV infection and CIN3 is approximately 7-15 years [Moscicki, 2006]. Nevertheless, cohort studies suggest that CIN2/3 can develop rapidly (in a period of months) [Winer, 2005]. Women with ICC are usually 10 years older than women with CIN3, suggesting a long period of time between CIN3 and development of ICC [Moscicki, 2006].

3. VACCINE DESIGN

3.1. Challenges associated with cervical cancer vaccine development

HPV infections have been shown to remain localized to the site of the initial infection with no viremia unlike most other viruses, such as hepatitis B virus (HBV). Lacking a blood-stream phase, HPV is minimally exposed to the systemic immune system and antibody levels induced by natural infection are very low and likely not to be protective during primary infection. The infectious cycle of genital HPV is adapted to the

differentiation cycle of the cells it infects, the basal keratinocytes. The time from infection to viral release coincides with the time for basal keratinocytes to undergo complete differentiation and natural death. This natural cell death does not present a danger signal to the immune system and therefore is not accompanied by inflammation. The adaptation of HPV to the differentiation program of keratinocytes is therefore an important mechanism to evade the host's immunity. Also, HPV proteins that would be recognized as foreign by the immune system are expressed only at low levels and are not secreted and not visible to the immune system. As a result of these and other host evasion mechanisms, the local innate immune responses which control or eradicate the virus are attenuated.

These immune escape mechanisms have enabled HPV to become one of the most common sexually transmitted infections worldwide. Most infections are transient and 70-90% of will clear [Brown, 2005; Richardson, 2003; Moscicki, 1998]. Approximately 50% of women who are initially HPV negative will acquire an infection within 3-4 years after onset of sexual activity [Winer, 2003; Moscicki, 2001]. Acquisition of HPV is highest among women younger than 25 years but continues throughout life in sexually active women and remains substantial in older age groups [Munoz, 2004b; Bory, 2002; Dalstein, 2003; Franco, 1999; Munoz, 2004; Grainge, 2005].

The precise sequence of immune events following HPV infection in the cervical tract is not fully understood, although it is clear that first innate and cell-mediated immunity and then humoral immunity play a role in the immune response at the site of the HPV infection [Stanley, 2006]. Low levels of neutralizing antibodies may appear in the serum of infected individuals, and specific IgG and secretory IgA might be found locally in the cervical mucosa, but at very low levels [Bontkes, 1999; Rocha-Zavaletta, 2003]. The antibodies generated by natural infection do not appear to be sufficient for long-term protection against re-infections [Viscidi, 2004].

Based on animal models, the key mechanism of protection induced by an L1 VLP-based vaccine is via serum neutralizing antibodies. Data from several animal challenge models, including passive transfer studies, have shown that serum neutralizing antibodies generated in response to L1 VLP vaccination are sufficient to afford protection against subsequent 'challenge' with papillomavirus [Breitburd, 1995; Christensen, 1996; Jansen, 1995; Kirnbauer, 1996; Suzich, 1995]. Importantly, systemic vaccination with canine oral papillomavirus L1 VLPs has been shown to protect against papillomavirus challenge infection by the mucosal route [Suzich, 1995], suggesting the feasibility for a parenteral vaccine to protect against a virus that enters only via the mucosal route and remains localized there.

HPV transmission and infection occur at the cervical epithelium, where HPV can be neutralized by local IgG, the main immunoglobulin present in the cervix [Franklin, 1999]. In vaccinated women, IgG are present in the cervical mucosa at the time of exposure. They are not produced locally but transudate or exudate from the serum to the cervical mucus [Parr, 1997; Nardelli-Haefliger, 2003; Schiller, 2004, Kemp, 2008]. The antibodies must reach the cervical mucosa, but they also need to be present at sufficient levels and in a timely manner to neutralize the virus. Although the minimum protective level of antibodies is unknown, antibody titers similar to or less than those induced by

natural infection – which have been shown not to be reliably protective – may not be sufficient.

After vaccination, exposure of individuals to the same HPV types is not likely to significantly boost the antibody level as infection at the cervix (with no viremia) and the infection process itself will make the virus invisible to the pool of memory cells. Therefore, to offer continued protection against oncogenic HPV types, vaccination should induce not only a strong but also a sustained antibody response systematically and by transudation and/or exudation of antibodies at the site of primary infection. Vaccine-induced cell mediated immunity can also play a role by supporting antibody production through T helper cells, long-lived plasma cells and memory B cells.

3.2. *Cervarix* Design Strategy

In the development of *Cervarix*, GSK considered the following factors:

- There are ~14 oncogenic HPV types, of which HPV-16 and HPV-18 are responsible for more than 70% of cervical cancers worldwide and more than 76% of cervical cancers in the US (Section 2.2). Vaccine development should balance type coverage with the formulation risks inherent to multi-valent vaccines. GSK chose to focus on HPV-16 and HPV-18 and not to include additional HPV types in its HPV vaccine, based initially on the theoretical risk of immunological interference and the lack of immunological interference for HPV-16 and HPV-18 antigens in the bivalent formulation. Preclinical and clinical data have shown that immune responses, especially to HPV-18, can be impaired when more L1 VLP types are added to the vaccine. Impairing the immune response to HPV-18 could potentially impact protection against HPV-18 as well as types phylogenetically related to HPV-18, such as HPV-45.
- HPV is adapted to avoid detection by the host's immune system. Even after natural clearance, re-infection can occur. Natural infection does not always adequately stimulate the immune system to clear and/or prevent re-infections. The immune response induced by vaccination must improve upon nature.
- HPV replicates outside of the blood stream therefore, experience with vaccines against viruses that induce viremia, such as HBV is unlikely to apply to HPV. However, induction of serum neutralizing antibodies that can reach the mucosal level through transudation and/or exudation from the blood is most likely to provide protection against infection.
- Following sexual debut, young girls and women remain at risk for oncogenic HPV infection. Long-term protection is therefore critical.
- In many countries, the HPV vaccine must complement established screening programs. Vaccination should ideally address the limitations of screening, including prevention of ADC. Therefore, high and sustained immune response leading to protective efficacy against HPV-18 and ideally HPV-45 should be induced by vaccination.

Cervarix was designed to induce high and sustained antibody responses of high quality that can transfer to the site of infection to provide long-term protection against infection and disease caused by HPV-16 and HPV-18, the two most frequent oncogenic HPV types in cervical cancer. By optimizing the HPV-16 and HPV-18 immune responses through the use of AS04, GSK's design strategy was to increase the likelihood of providing cross-reactive immune responses between the vaccine types and closely related HPV types, such as HPV-31 and HPV-33 (HPV-16 related types) and HPV-45 (HPV-18 related types) thus broadening the protection against cervical cancer.

3.3. Vaccine composition rationale

Data presented in this section support the selection of HPV-16/-18 L1 VLP AS04 formulation for the development of GSK's cervical cancer vaccine.

3.3.1. Immunogens

The non-infectious HPV-16 and HPV-18 L1 VLP antigens are composed of recombinant HPV L1 major capsid proteins and were shown to be morphologically and antigenically almost identical to native HPV virions using various physicochemical and immunological techniques.

The VLPs were shown to have a consistent composition profile with high purity as well as a consistent structural profile with virus-like particles resembling the native virions. Antigenic investigations showed that monoclonal antibodies against essential neutralizing epitopes bound with high affinity to the VLPs and further showed that the VLPs display a 3-dimensional conformation aligned with that of the native virions. Of note, the structural integrity of the VLP was shown to be maintained when adsorbed onto aluminum.

3.3.2. Adjuvant selection

3.3.2.1. Rationale for the use of AS04

The AS04 adjuvant system, which contains $Al(OH)_3$ and MPL, has been evaluated in two other GSK vaccines: as a potential adjuvant to promote a higher and more sustained humoral response (herpes simplex virus [HSV] vaccine currently in Phase III development) as well as to promote higher immune response in immunocompromised individuals (*Fendrix*, hepatitis B vaccine adjuvanted with AS04 and licensed in Europe since 2005 for patients with renal insufficiency, including prehemodialysis and hemodialysis patients).

AS04-adjuvanted vaccine for prevention of HSV infection at the level of the genital tract, through parenteral immunization

HSVs are common human pathogens with two subtypes, HSV-1 and HSV-2, infecting oral and genital areas. In preclinical guinea pig model, a vaccine candidate based on the glycoprotein D from HSV-2 (gD2) adjuvanted with AS04 demonstrated better protection against HSV primary genital infection and recurrent HSV disease than a gD2 vaccine

adjuvanted with aluminum salt alone. These data suggested that the addition of MPL to an aluminum-based vaccine could induce, through parenteral immunization, a protective immune response at the level of the genital tract. As parenteral immunization does not induce specific mucosal immune responses, it is hypothesized that the transudation of antibodies from the blood to the genital mucosal would be responsible for protection [Bourne, 2003]. The efficacy of the vaccine was evaluated in phase III, double blind, randomized and controlled studies in subjects whose regular partners had a history of genital herpes. The vaccine was shown to induce high titers of anti-HSV antibodies, as well as HSV-specific cellular immune responses, in both genders. Significant protection (73%) against the disease was observed in women that were seronegative for HSV-1 and HSV-2 before vaccination but not in men or in HSV-1 positive women [Stanberry, 2002]. The protection lasted for at least 2 years, the length of follow up in the study.

Fendrix, hepatitis B vaccine adjuvanted with AS04, enhances the immune response in immunocompromised individuals

Effective hepatitis B vaccines adjuvanted with aluminum hydroxide have been licensed for approximately two decades. However, in order to better protect certain groups that appear to be low responders, primarily immunocompromised populations such as hemodyalized patients, there was a need for a vaccine capable of inducing a higher level of antibody response with a more rapid onset. Preclinical studies showed that a hepatitis B virus (HBV) antigen adjuvanted with AS04 (*Fendrix*) was capable of inducing a higher immune response in elderly mice as compared to that observed in young mice with the aluminum adjuvanted vaccine (*Engerix-B*). Patients with end-stage renal diseases are at high risk for HBV infections. Clinical trials demonstrated that *Fendrix* led to a higher specific immune response in healthy subjects and in hemodyalized patients, with enhanced cell-mediated responses and increased seroprotection rate [Thoelen, 2001; Kundi, 2007]. Furthermore, the clinical data suggest that protective antibody levels persist longer with the AS04-adjuvanted vaccine, allowing for fewer booster injections in the target population [Kundi, 2007].

These preclinical and clinical data showed that HSV and HBV AS04-adjuvanted vaccines could induce protective immune responses greater than those observed after vaccination with alum-adjuvanted vaccines and thus supported the evaluation of an HPV AS04-adjuvanted vaccine, as maintaining high antibody levels at the site of infection, the cervix, were seen as key for long-term protection against HPV infection and disease (Section 3.2).

3.3.2.2. AS04 Mode of Action

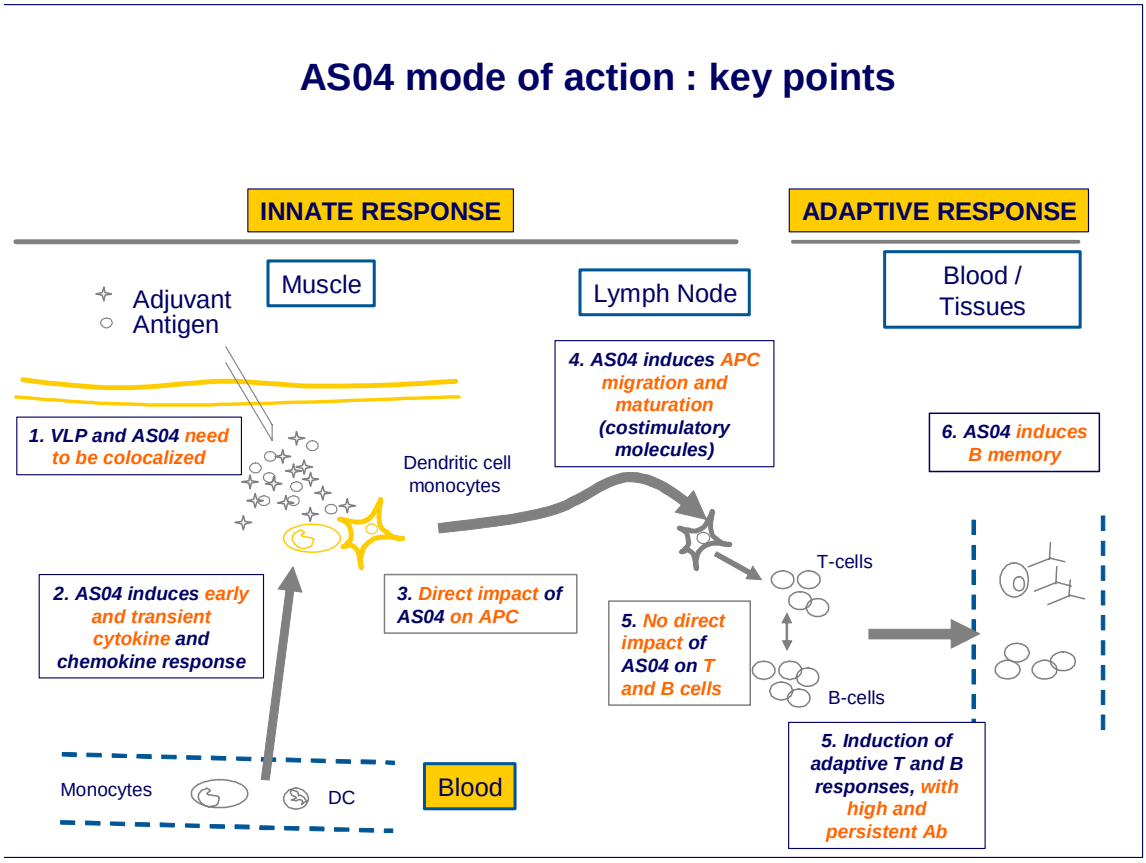
One of the major ways adjuvants can enhance antigen-specific T and B cell responses following vaccination is by stimulating the innate immune system and then the adaptive immune system through the following sequential steps:

- Induction of pro-inflammatory cytokine and chemokine secretion allows the recruitment and activation of APCs such as dendritic cells (DCs) and monocytes (innate immune response),

- Once the APCs are activated and loaded with the antigen at the site of injection, APCs then migrate to the local draining lymph node to specifically stimulate antigen-specific T and B cells (innate immune response),
- Antigen-specific T cells further support the differentiation of B cells not only into long-lived plasma cells, but also into antigen-specific memory B cells (adaptive immune response).

This classical way for adjuvants to induce antigen-specific immune responses appears to apply equally to aluminum and AS04 adjuvanted vaccines. Based on literature and on data generated by GSK Biologicals, a model for the mode of action of AS04 is shown in Figure 3. As the first line of defense, innate immunity is non-specific and without memory, while adaptive immune responses consist of antigen-specific antibodies and memory responses. Briefly, AS04 induces a local response (innate immune response) via specific molecular pathways that activates and recruits APCs at the injection site. Co-localization of AS04 with HPV-16/18 VLPs optimizes the uptake by APCs, and their activation and migration to the draining lymph node. There, antigen presentation results in the stimulation of antigen-specific lymphocytes and the production of antigen specific antibodies (adaptive immune response).

Figure 3 AS04 mode of action and impact on immune response

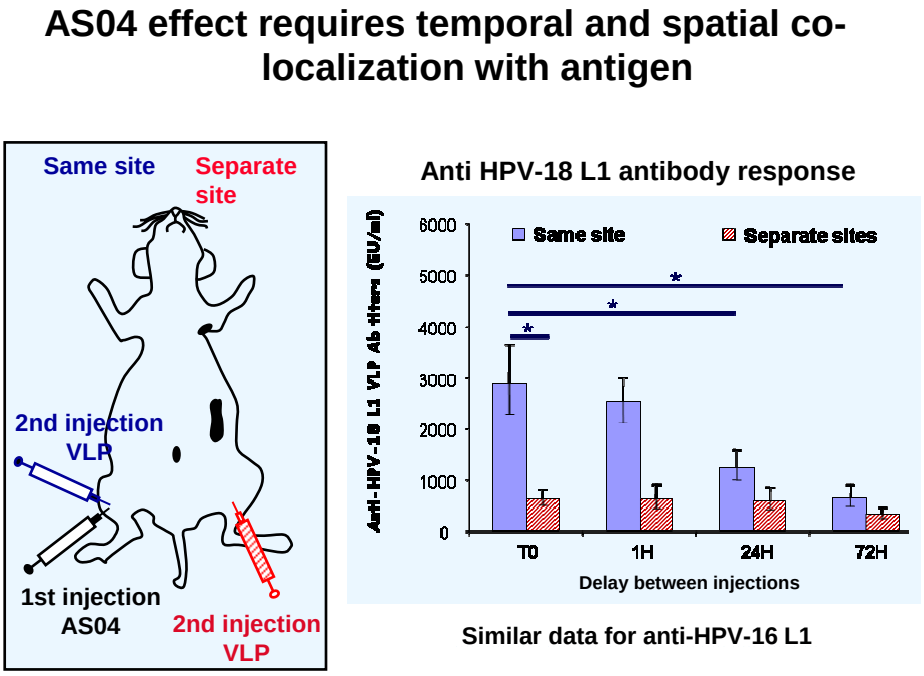


AS04 adjuvant effect requires temporal and spatial co-localization with antigen

In order to efficiently enhance antigen-specific immune responses, it is thought that the adjuvant and the antigen must be co-localized, i.e., present in the same location for a limited period of time. The potential requirement for co-localization of adjuvant and antigen was evaluated by injecting mice with AS04 and HPV-16 or HPV-18 L1 VLPs adsorbed on alum at the same site or at separate sites, with or without delay between immunizations.

As shown in Figure 4, HPV-16/18 VLP adsorbed on aluminum or AS04 were injected in mice at the same site (muscle of the left leg) or separate sites (left and right legs) simultaneously or with a delay of 1, 24 or 72 hours. Anti- HPV-16/18 L1 VLP antibody levels were measured in serum 14 days after the first and the second immunization as a marker of adjuvant activity.

Figure 4 Temporal and spatial localization of AS04 activity and with respect to antigen



These data show that the impact of AS04 on anti- HPV-16/18 L1 VLP antibody responses occurs within 24 hours of injection when injected at the same site since the optimal antibody response is observed when the antigen and the adjuvant are injected at the same time or within the hour. The effect of the AS04 adjuvant is observed only when both AS04 and antigen are co-localized. Indeed, injection of AS04 in a different site has no impact on the HPV-16/18 L1 VLP-induced response.

These data also suggest that, although MPL can be detected at the injection site from 3 to 7 days following *Cervarix* immunization, it does not have adjuvant activity for this entire period of time, but is restricted to less than 24 hours.

Impact of Aluminum and MPL on Immune Cells

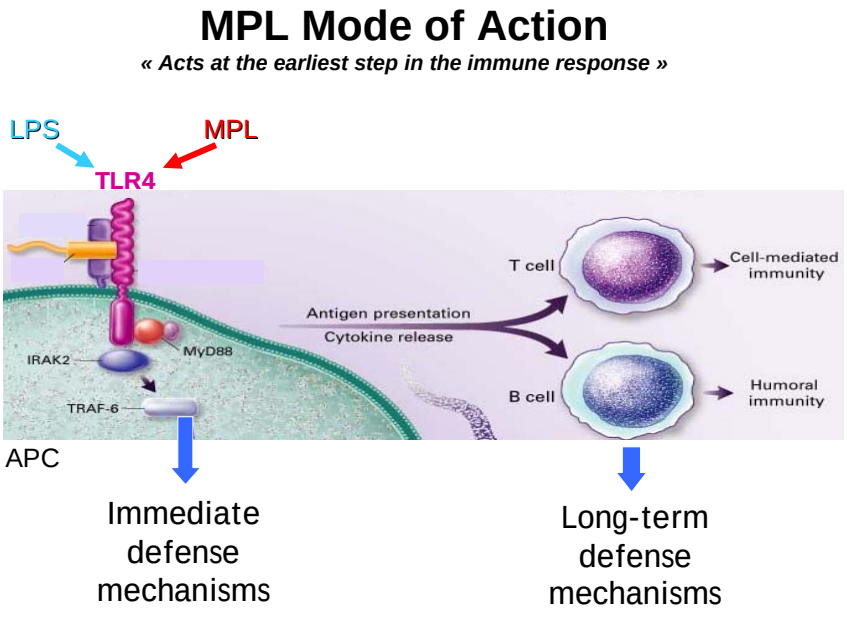
Mode of Action of Aluminum Salts

Although in use for decades, the molecular mechanisms involved in aluminum-induced activation of innate immunity were poorly understood until recently. In addition to its ability to induce IL-1β, aluminum is known to enhance the availability of the antigen by on one hand creating an antigen depot effect which maintains antigen presentation and therefore the persistence of antibody response and on the other hand by converting soluble antigens into particulate antigens. It has also recently been shown that monocytes recruited locally play a crucial role in the adjuvant properties of aluminum salts [Kool, 2008].

MPL acts through TLR4

Despite its detoxification, MPL has been shown to retain the capacity of the original LPS molecule to act as an immunostimulant in *in vitro* experiments. MPL acts at the earliest step in the immune response through toll-like receptor (TLR) 4, a receptor specific to bacterial LPS. TLR4 belongs to a family of receptors which recognize pathogen associated molecular patterns and has been shown to represent a critical molecular link between innate and adaptive immunity.

Figure 5 MPL mode of action



Modlin RL, et al. N Engl J Med 1999, 340: 1834-5

MPL is a weaker agonist than LPS

The MPL signaling pathway was investigated through a set of experiments carried out *in vitro* on human cells using LPS as a comparator. These experiments have shown that MPL acts through a signaling pathway, identical to the parent LPS molecule, leading to the production of cytokines and chemokines at a level 2 to 3 logs lower than LPS. A reduced response to MPL, as compared to LPS, was observed for all cytokines and chemokines tested, e.g. interferon (IFN)β was shown to be induced by LPS but was barely detectable in MPL-stimulated samples. Importantly, IFNα, a cytokine known to be involved in some autoimmune processes, is not induced by either MPL or LPS. MPL was thus shown to retain its potential of inducing cytokines and chemokines important for immune signaling however at lower levels while not inducing cytokines known to be involved in autoimmune processes.

MPL in AS04 activates APCs but has no direct impact on B and T cells in humans

TLR4 is not expressed on human B cells [Bourke, 2003], therefore there is no direct activation of such cells by MPL and AS04. Human T lymphocytes, however, are reported to express TLR4 [Zanin-Zhorov, 2007].

Therefore, experiments at GSK Biologicals were conducted to further evaluate the impact of MPL on T cells. Experiments showed that although MPL can up-regulate activation markers, this does not result in cytokines secretion. If CD4 T cells encounter MPL in the absence of antigen, no T-cell receptor stimulation was observed, and non-specific stimulation of those CD4 T cells does not occur. This ensures the specificity of the response, as only CD4 T cells recognizing their antigen on proximal APCs will receive a co-signal by MPL.

Summary

Over the past two decades, AS04/MPL has been evaluated as a vaccine adjuvant in animal models involving an array of experiments. Preclinical evaluations into the mode of action of AS04 have shown that while AS04 acts primarily at the starting point of the immune response, particularly on antigen presenting cell recruitment and activation without directly stimulating later immune effector cells, such as T and B cells, the resulting antigen-specific systemic immunity is high and sustained over time.

Similar to the parent LPS molecule, MPL acts through TLR4, but with a reduced response as compared to LPS. Data indicate that AS04 must be co-localized with the antigen within a limited period of time in order to efficiently enhance the immune response to that antigen. The time window in which AS04 impacts the antigen-specific immune response is restricted to 24 hours. Data also suggest that the early activation mediated by MPL plays a critical role in enhancing the immune response to antigen.

The theoretical risk of induction and/or exacerbation of autoimmune disease relies on the hypothesis that an adjuvant would be able to break tolerance mechanisms and immune regulation circuits, leading to priming or re-stimulation of pre-existing autoimmune T and B cells.

The results of investigations to elucidate the mode of action of AS04 provide no evidence for a plausible mechanism for AS04 to induce autoimmune disease in humans. AS04 induces a controlled activation of APCs, including the production of cytokines that is limited in time, as well as no non-specific activation of T and B cells. Additionally, MPL does not lead to the production of IFNα, a cytokine that has been associated with the precipitation of some autoimmune diseases.

3.3.3. Optimization of vaccine formulation

Non-clinical and clinical evaluations of immunogenicity including dose-finding led to the selection of a formulation of 20 µg of each L1 VLP antigen, 50 µg MPL and 500 µg $Al(OH)_3$ per human dose.

Non-clinical pharmacodynamic studies evaluated the weight ratio of each component of *Cervarix*. Three dose-range immunogenicity studies in BALB/c mice investigated the respective impact of $Al(OH)_3$, MPL and HPV-16/18 L1 VLP antigen doses on HPV-16 L1 VLP - and HPV-18 L1 VLP-specific humoral and cellular responses. These studies supported the development of an HPV-16/18 vaccine based on a 1:1:25:2.5 weight ratio of each L1 VLP antigen, $Al(OH)_3$ and MPL, respectively.

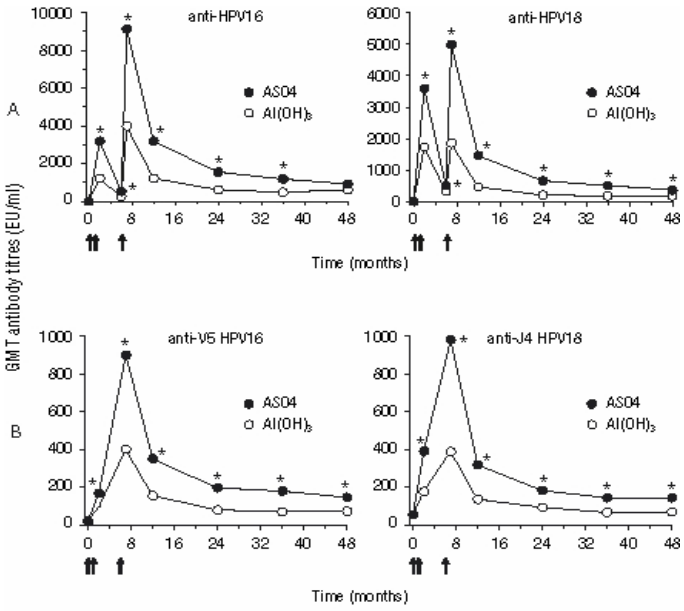
The same weight ratio for each antigen, aluminum salt and MPL was shown to be associated with clinical proof of concept including efficacy and/or immunogenicity and safety for two other AS04-adjuvanted vaccines: HSV vaccine (currently in Phase III development) and *Fendrix* (hepatitis B vaccine licensed in Europe since 2005).

In an initial HPV clinical trial (Study HPV-002), formulations containing this weight ratio (20 µg of each L1 VLP antigen, 50 µg MPL and 500 µg $Al(OH)_3$ per human dose) of monovalent HPV-16 or HPV-18 vaccines and of the bivalent HPV-16/-18 vaccine were confirmed to be immunogenic in humans. There was no evidence of immunological interference between the HPV-16 L1 and HPV-18 L1 vaccine components in the combined formulation.

An additional trial (Study HPV-004) testing a range of antigen doses (6, 20 or 60 µg of each L1-VLP) confirmed that the *Cervarix* formulation with 20 µg HPV-16 L1 VLP and 20 µg HPV-18 L1 VLP afforded the optimal balance between vaccine tolerability and the immune response elicited. The vaccination schedule of 0, 1, 6 months was chosen on the basis of effective priming and boosting of immune responses.

The final selection of AS04 for *Cervarix* was based on the demonstration of higher response for both antigens with the AS04 formulation compared to the $Al(OH)_3$ or unadjuvanted formulations. In a pooled analysis of Phase IIa studies HPV-004 and HPV-005, the antibody responses in subjects receiving the AS04 formulation compared with the $Al(OH)_3$ formulation were statistically significantly higher (as measured by binding enzyme-linked immunosorbent assay (ELISA) and inhibition assays with neutralizing epitopes V5 and J4 assessing functional antibodies for HPV-16 and HPV-18) over the 4-year observation period (Figure 6) [Giannini, 2006].

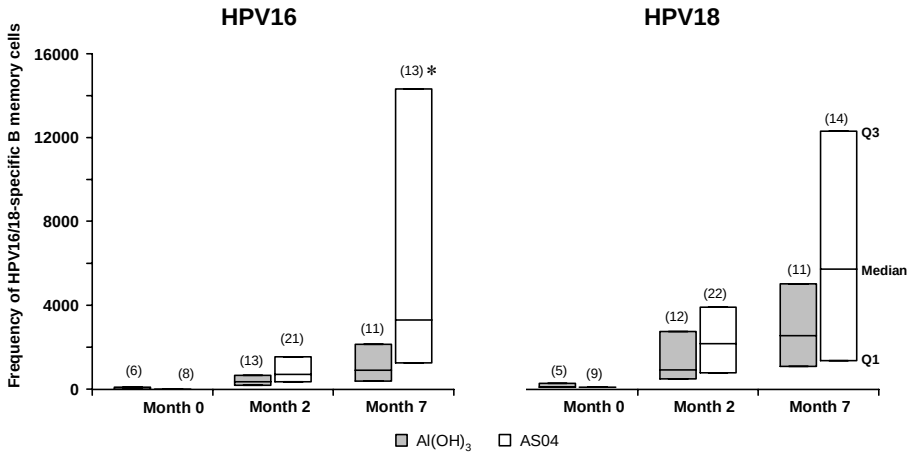
Figure 6 Studies HPV-004 and HPV-005 (pooled, Total Cohort): Persistence of anti-HPV-16 and anti-HPV-18 antibodies [Figure A: Binding ELISA; Figure B: Inhibition ELISA]



Significant differences ($p<0.05$) between the antibody titers of the AS04 and the aluminum group are indicated in the figure by asterisks. Arrows indicate vaccination timepoints (Month 0,1,6 schedule).

The induction of persistent serum antibodies following vaccination not only reflects the generation of long-lived plasma cells, but also the generation of antigen-specific memory B-cells. Substantially higher frequencies of memory B-cells were observed 1 month following completion of the vaccination series (at Month 7) with the AS04-adjuvanted formulation as compared to the $Al(OH)_3$-adjuvanted formulation (Figure 7) [Giannini, 2006].

Figure 7 Studies HPV-004 and HPV-005 (pooled): Frequency of HPV-16 and HPV-18 specific memory B-cells, Total Cohort



The number of subjects is given in parenthesis. *Significant difference between groups (p<0.05)

3.4. Vaccine composition and manufacture

Cervarix is a non-infectious, recombinant, AS04-adjuvanted vaccine that contains recombinant L1 proteins, the major antigenic capsid proteins of HPV types 16 and 18.

Cervarix contains 20µg of HPV-16 L1 protein and 20µg of HPV-18 L1 protein assembled as VLPs as the active ingredients. The L1 proteins are formulated with the AS04 adjuvant system, which is composed of 50µg of MPL and 500µg of aluminum hydroxide salt. The vaccine is preservative-free (Table 3).

Table 3 Composition of *Cervarix*

Ingredients	Quantity (per 0.5ml dose)	Function
Active ingredients		
HPV-16 L1 VLP	20 µg	Antigen
HPV-18 L1 VLP	20 µg	Antigen
Adjuvant system		
3-*O*-desacyl-*4'* monophosphoryl lipid A	50 µg	Immunostimulant
Aluminum (hydroxide salt)	500 µg	Immunostimulant
Excipients		
Sodium chloride (NaCl)	4.4 mg (150 mM)	Buffer
Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2H_2O$)	0.624 mg (8 mM)	Buffer
Water for injection	q.s. ad 0.5 ml	Solvent

The HPV L1 proteins are produced in separate bioreactors, using a recombinant BEVS, in a robust, well-controlled and characterized animal-free manufacturing process. BEVS was selected as it is known to be an effective production system for new pharmaceutical products, particularly those based on complex proteins such as VLPs. In addition, the expression system has been used in research settings for several decades and other vaccine candidates containing proteins produced using the BEVS technology have been reported to be well tolerated, safe and immunogenic [Treanor, 2006; Lakey, 1996]. BEVS allows for antigen production under animal free conditions with the high yields needed to support worldwide commercialization.

Following replication of the L1 encoding recombinant Baculovirus in *Trichoplusia ni* cells (an insect cell line), the L1 protein accumulates in the cytoplasm of the cells and is then released by cell disruption and purified through a multistage purification process including chromatographic and filtration methods. Assembly of the L1 proteins into VLPs occurs at the end of the purification process. Purified, non-infectious VLPs are then adsorbed onto $Al(OH)_3$ to prepare the HPV-16 and HPV-18 L1 VLP adsorbed monovalent bulks. *Cervarix* is prepared by combining the adsorbed monovalent bulks for each HPV type with AS04 and vaccine excipients to obtain the final HPV vaccine formulation. Quality control testing is performed throughout the manufacturing process, from starting materials to final product.

Relevant guidelines and regulations for establishing new cell lines and assuring their quality control and safety were utilized in the development of BEVS. Using guidance and regulation, and establishing early and regular consultation with scientific experts and regulatory authorities (including the FDA), the antigen production processes and antigen quality have been subject to extensive characterization, validation and quality control testing.

Selection of BEVS for the production of GSK's L1 VLPs was based on the production of high quality, pure, well characterized L1 VLPs which are morphologically and antigenically similar to native HPV virions thereby forming the basis for a specific and strong immune response. *Cervarix* is anticipated to be the first human vaccine licensed in the US using BEVS in the manufacturing process.

3.5. AS04 characterization and process

Over the past decade, GSK has developed new adjuvant systems intended to promote better and longer protection than alum-adjuvanted or non-adjuvanted vaccines through induction of high and persistent antibody titers and of cell-mediated immunity (CMI). One such proprietary adjuvant system, AS04, has been developed for prophylactic vaccines and is composed of aluminum salt and MPL as immunostimulants. The first AS04-containing vaccine, *Fendrix* (hepatitis B vaccine indicated for patients with renal insufficiency, including prehemodialysis and hemodialysis patients) was licensed in Europe in 2005

3.5.1. Aluminum salt

Aluminum salts have been used for over 80 years in the vaccine field and are currently the only adjuvants specifically added to vaccines licensed in the US.

The AS04 adjuvant system in *Cervarix* is composed of MPL adsorbed onto aluminum hydroxide, $Al(OH)_3$. The aluminum hydroxide salt is widely used as an adjuvant in a broad range of GSK licensed vaccines with a well defined safety profile. The aluminum hydroxide in *Cervarix* is quality controlled according to relevant guidelines and regulations for use in human vaccines.

3.5.2. 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)

Lipopolysaccharides are a group of structurally related complex molecules that are exclusively found in the outer leaflet of gram negative bacteria. Gram-negative bacteria are ubiquitous in the environment and human exposure to these bacteria, and therefore their LPS, is common during the course of life.

Many biological activities of LPS, such as toxicity, pyrogenicity and adjuvanticity, have been shown to be related to the lipid A moiety, the innermost region of LPS. The strong adjuvant effect associated with both LPS and lipid A has long been recognized but the toxicity of these molecules has precluded their use as such in vaccine formulations. MPL, the detoxified form of lipid A, is obtained by sequential acid and base hydrolyses of *Salmonella minnesota* R595 LPS. The resulting MPL molecule has been shown to retain the capacity of the natural LPS and lipid A compounds to act as an immunostimulant, but with a much reduced toxicity [Johnson, 1987; Myers, 1990].

Relevant guidelines and regulations were taken into account for the establishment of the characterization, validation and quality control testing of the manufacturing of MPL and MPL quality. The manufactured MPL molecules have been shown to be of consistent and high quality, compatible with use for human vaccine manufacture.

3.6. Summary

Cervarix was designed with the goal of bringing the most effective cervical cancer vaccine possible to young girls and women worldwide by taking into consideration the current understanding of the particularities of oncogenic HPV natural infection, including the ability of the virus to evade the immune system, the repeated exposure throughout life and lack of reliable protection against re-infection by natural immunity. Also, the prevalence of the most important oncogenic HPV types, the inherent risk of interference with multi-valent vaccines, the need for induction of high neutralizing antibodies at the cervix (the site of infection) and the need for long-term protection were taken into account in the development of *Cervarix*.

Cervarix is composed of high quality, pure HPV-16 and HPV-18 L1 VLPs (which resemble native virions but are not infectious and retain essential neutralizing epitopes) combined with the adjuvant system AS04.

Choice of the initial candidate vaccine formulation was directed by non-clinical dose-ranging data that supported a weight ratio of 1:1:25:2.5 of each L1 VLP antigen, $Al(OH)_3$ and MPL, respectively – a ratio also proven suitable for other AS04-adjuvanted vaccines, including an adjuvanted hepatitis B vaccine licensed in Europe. Preclinical immunogenicity and toxicology studies and early clinical studies further confirmed the superior immune response of AS04-adjuvanted vaccine over aluminum adjuvant, the lack of interference between HPV-16 and HPV-18 antigens and the suitable balance between vaccine tolerability and the desired immune response to warrant further development.

In addition, preclinical studies have been conducted to elucidate the mode of action of AS04. These studies indicate that AS04 acts at the earliest step in the immune response by stimulating local recruitment and activation of antigen presenting cells (APCs). MPL acts on APCs via specific TLR4 receptor agonism and has no direct effect on T and B effector cells. Immune stimulation by MPL requires temporal and local presentation of the adjuvant with the antigen to induce a local and transient innate response resulting in high and sustained immunity. These characterization studies provide no evidence for a plausible mechanism to induce autoimmune disease in humans.

These data led GSK to initiate evaluation of the clinical performance of *Cervarix* in Phase IIb and subsequently Phase III efficacy trials.

4. *CERVARIX* CLINICAL PROGRAM

The clinical development program included approximately 30,000 healthy girls and women from 10 years of age onwards, with over 16,000 women having received at least one dose of *Cervarix*, with long term follow-up to 6.4 years. This includes data from controlled Phase II/III studies and uncontrolled or consistency Phase II/III studies. Collectively these studies provide data on clinical vaccine efficacy, immunogenicity, manufacturing and lot consistency and vaccine safety (Table 4).

The development program was global and involved over 30 countries from different geographical regions, including 4,322 subjects from the US. Subjects who participated in clinical studies with *Cervarix* were representative of a broad range of ethnicities including: White/Caucasian (56.4%), Asian (25.8%), Hispanic (12.2%), Black (3.2%) and Other (including mixed racial and other minority groups, 2.3%).

The first Phase IIb efficacy study (HPV-001) was initiated after completion of the early development program, outlined in Section 3.3.3, which established the composition and preliminary safety and immunogenicity profile of the vaccine. Study HPV-001 evaluated the efficacy of the vaccine in a screened population of young women 15-25 years of age presumed to be naïve to oncogenic HPV infection prior to vaccination. Study participants were followed in a long-term extension study (HPV-007). Together, Studies HPV-001/007 provide data up to 6.4 years after first vaccination.

Following demonstration of efficacy in HPV-001, the Phase III clinical development was initiated, including the studies described below.

The pivotal Phase III efficacy Study HPV-008 evaluated efficacy in a 'general' population including women with current or prior infection with oncogenic HPV. The BLA for *Cervarix* was submitted upon availability of results of a predefined event-triggered interim analysis of HPV-008 (March 2007). Subsequently, the final event-triggered analysis was performed based on at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 detected in the According to Protocol (ATP) cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. The final analysis was provided to the Center for Biological Evaluation and Research (CBER) as part of GSK's responses to the CR Letter in March 2009.

The efficacy of the vaccine was evaluated in women 15-25 years of age; however, *Cervarix* is targeted for girls or women 10-25 years of age. Efficacy studies could not be conducted in girls 10-14 years of age as endpoint evaluation requires gynecological evaluation, which is not feasible in this age range. Therefore, immunobridging was performed in girls and women below 15 years of age. Study HPV-012 bridged the immune response from the efficacy trials in women 15-25 years of age to girls 10-14 years of age. Study HPV-013 provided additional safety and immunogenicity data in this younger age group. Study HPV-013 Extension provided data up to 18 months post-vaccination to support extension of the indication from 10 years through 25 years of age.

Study HPV-014 evaluated the immune responses in women ranging from 15-55 years of age. Study HPV-014 Extension provided data up to 18 months post vaccination in women in this age group and additionally examined the immune response in cervical secretions.

Two immunogenicity studies evaluated the lot-to-lot consistency of the manufacturing process: Study HPV-012 and Study HPV-16 (final consistency at final production scale).

Study HPV-015 is an ongoing efficacy study in women 26 years of age and older, for which an interim analysis for safety was included in the BLA to provide additional support to the proposed initial indication. A future supplemental BLA is planned to seek expansion of the indicated age to above 25 years.

Table 4 Clinical trials in the submission (Phase I to III)

Phase	Study No	Age	Countries	Description	N vaccinated (N*Cervarix*)
I	HPV-002	18-30	US	Assessment of formulation, mono/bivalent	49 (0)
I/IIa	HPV-003	18-30	US	Safety in DNA positive women	61 (31)
IIa	HPV-004	18-30	US	Adjuvant comparison study	60 (20)
IIa	HPV-005	18-30	US	Dose range study	209 (63)
IIb	HPV-001	15-25	Brazil, Canada, USA	Efficacy in an HPV naïve population	1113 (560)
IIb	HPV-007	15-25 in HPV-001 (primary study)	Brazil, Canada, USA	Follow-up efficacy in a HPV naïve population up to 6.4 years	776 (393)
III	HPV-008	15-25	Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK, US	Efficacy in a general population (naïve or non-naive to HPV)	18644 (9319)
III	HPV-012	10-25	Denmark, Estonia, Finland, Greece, Netherlands, Russia	Consistency Study Immunobridge 10-14 years	10-14 yrs: 158 (158) 15-25 yrs: 612 (612)
III	HPV-013 and Extension	10-14	Australia†, Columbia, Czech. Rep†, France†, Germany, Honduras, Korea, Norway†, Panama, Spain†, Sweden†, Taiwan	Safety and Immunogenicity in 10-14 years	2067(1035)
III	HPV-014 and Extension	15-55	Germany, Poland	Immunobridge to 26-55 years	15-25yrs: 229 (229) 26-45yrs: 226 (226) 46-55yrs: 211 (211)
III	HPV-016	18-25	Denmark, Lithuania, Poland	Final Consistency Study	798 (798)
IIIb	HPV-015	26+	Australia, Canada, Mexico, Netherlands, Peru, Philippines, Portugal, Russia, Singapore, Thailand, UK, US	Efficacy in women 26 years and older	5751 (2880)
Total					29953 (16142)

*Number of subjects who received the final formulation of *Cervarix;* †Country only participated in primary study and did not participate in the extension; ‡HPV-007 remains blinded as a follow-up study that includes subjects from Brazil is in progress (HPV-023); Underlined values are not included in the Total: Forty-nine subjects in HPV-002, 40 subjects in HPV-004 and 146 subjects in HPV-005 received a different vaccine formulation are not included in the Total. Subjects in HPV-007 were vaccinated in HPV-001 and are not recounted in the Total.

In addition to the reported studies mentioned above, additional safety data from completed and ongoing studies were also included in the BLA (see Section 7). This included data from one Phase III efficacy study, HPV-009, an ongoing collaborative study in 7,466 women 18-25 years of age conducted in Costa Rica under the direct supervision of the US National Cancer Institute (NCI), where 3782 women were

vaccinated with *Cervarix*. With the exception of this study, the Phase IIb and III development submitted in the BLA was solely performed under the sponsorship of GSK.

5. OVERVIEW OF EFFICACY AND IMMUNOGENICITY

The efficacy of *Cervarix* was assessed in two double-blind, randomized, controlled studies that included a total of 19,757 vaccinated adolescent and young adult women 15 to 25 years of age: Studies HPV-001/007 (Phase IIb; HPV-007 is the long term follow-up of HPV-001) and Study HPV-008 (Phase III).

5.1. Target population

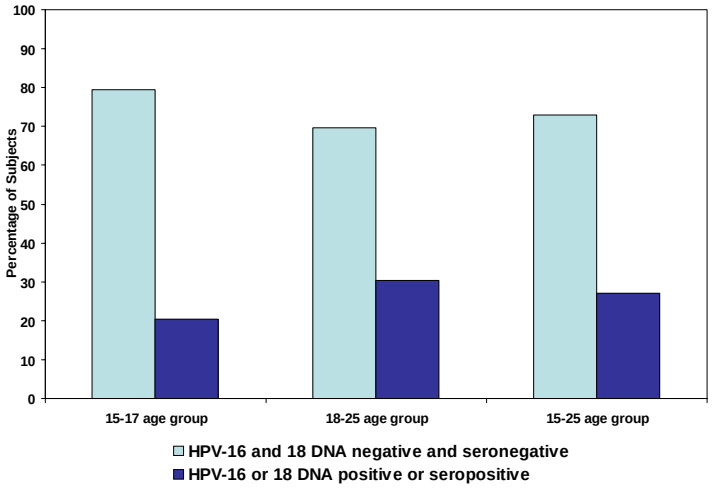
Cervical cancer accounts for the largest percent of cancers attributable to oncogenic HPV [Parkin, 2006] and therefore was selected as the main target for the GSK HPV vaccine. A female population was selected for clinical development with an age range of 10 years and older to provide benefits to susceptible women.

All vaccine efficacy studies for which data are currently available have been conducted in women 15-25 years of age. Efficacy studies are feasible in this age range with respect to endpoint ascertainment (pelvic examination and, if needed, colposcopy can be performed) and completion of studies in a reasonable timeframe. To further characterize *Cervarix,* immunobridging and safety studies were performed in girls and women below and above 15-25 years of age.

The prevalence of HPV is highest among young women. Biological changes in the cervix around the time of puberty render young girls particularly susceptible to HPV infection [Moscicki, 2005]. This period coincides with the initiation of sexual activity, which is considered an important factor in the acquisition of oncogenic HPV infection. To achieve the maximum benefit from a prophylactic vaccine, vaccination should occur before sexual debut. Adolescent girls (10-14 years of age) were therefore included in the development program.

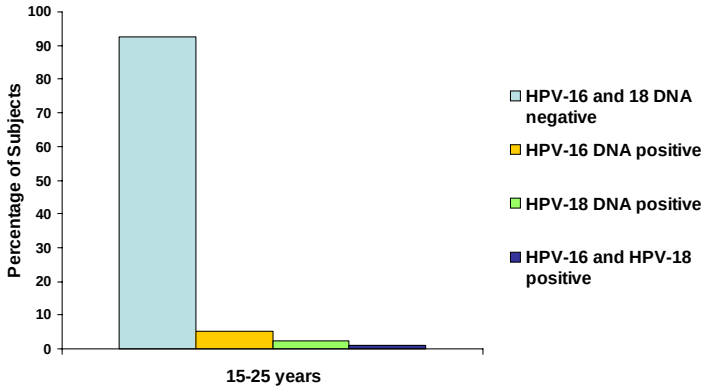
In the large phase III study HPV-008 in over 18,600 women, assessment of baseline data showed that the majority of women between the ages of 15 and 25 years had no evidence of previous exposure to HPV-16 or HPV-18, with 74% of women seronegative and DNA negative for both HPV-16/18 (HPV-16/18 naïve subjects) (Figure 8). Similarly, the majority of women at the higher end of the age range (18-25 years) had no evidence of previous exposure to HPV-16 and HPV-18.

Figure 8 Study HPV-008: pre-vaccination HPV-16 and HPV-18 serostatus and DNA status with respect to age (Total Vaccinated Cohort)



Few women were DNA positive for HPV-16 and HPV-18 (5.3% and 2.3% of women respectively) and less than 1% of women were DNA positive for both HPV-16 and HPV-18 (Figure 9). Women who are previously infected with one vaccine type are still at risk of infection with the other vaccine type. Furthermore, previous infection with one type may not confer protection against re-infection with the same type [Viscidi, 2004].

Figure 9 Study HPV-008: pre-vaccination HPV-16 and HPV-18 DNA status (Total Vaccinated Cohort)



According to these data, over 99% of women ages 15-25 could benefit from vaccination with *Cervarix*.

5.2. Methods to evaluate efficacy

5.2.1. Selection of endpoints for clinical trials

Licensure of a cervical cancer vaccine should be based, for ethical and practical reasons, on the demonstration of vaccine efficacy in the prevention of precursor surrogate markers. Since the threshold for treatment of a lesion in most countries is the detection of a CIN2 or worse lesion, CIN2+ is the most advanced endpoint that can be planned for evaluation in prospective clinical trials. Additionally, since the majority of these lesions progress, CIN2+ is an accepted surrogate endpoint for invasive cervical cancer. HPV-16 and 18 are responsible for approximately 52% of all high grade cervical lesions [Smith, 2007].

Following the opinion expressed by the VRBPAC [Vaccines and Related Biological Products Advisory Committee, 2001] and recommendation by the FDA, the primary endpoint selected for evaluation of vaccine efficacy in the pivotal efficacy study (HPV-008) was prevention of CIN2+ (CIN2, CIN3, AIS and ICC) associated with HPV-16/18.

Persistent infection with an oncogenic HPV type has been shown to increase the risk for progression and the development of cervical neoplasia [Ho, 1995; Hildesheim, 1994; Schiffman, 2005; Schlecht, 2003, Koshiol, 2008]. Epidemiological data and molecular mechanism data [Zur Hausen, 2000] support the use of both virological and clinical (cytology/histology) endpoints to define vaccine efficacy (VE) and highlight the requirement for persistent oncogenic HPV infection in cervical carcinogenesis. Consultations with the CHMP, and guidelines published by the WHO [Pagliusi, 2004; WHO, 2006], have affirmed the predictive value of virological endpoints. As a result, data from both virological and histopathological endpoints have been used to define the efficacy of *Cervarix*.

Additional endpoints, such as CIN1 and cytological abnormalities, contribute to the full assessment of vaccine impact on the morbidity and burden of disease.

5.2.2. Design of efficacy studies

Study HPV-001 was an IND, Phase IIb, double-blind, randomized, controlled study that assessed the efficacy of *Cervarix* in the prevention of HPV-16 and/or HPV-18 incident and persistent infections and their clinical outcomes (maximum follow-up time for efficacy: 27 months after the first vaccination). The study was conducted in 1113 healthy women 15-25 years of age in the US, Canada and Brazil. All subjects received either *Cervarix* or $Al(OH)_3$ control according to a 0, 1, 6 month schedule.

Study HPV-007 was an IND, Phase IIb, blinded, controlled, 3-year extension follow-up study of HPV-001 that assessed the long-term efficacy, immunogenicity and safety of *Cervarix* (administered in Study HPV-001). A total of 776 subjects who received 3 doses of either *Cervarix* or $Al(OH)_3$ in Study HPV-001 were enrolled in this extension study. The extension began approximately fourteen months after the completion of HPV-001 and provides up to 6.4 years of total follow-up time after first vaccination.

Study HPV-008 is an IND, Phase III, double-blind, randomized, controlled study to assess the efficacy of *Cervarix* in the prevention of CIN2+ lesions associated with HPV-16 or HPV-18 infection (referred to HPV-16/18). The Total Vaccinated Cohort included 18,644 healthy women 15-25 years of age in multiple regions of the world (North America, Latin America, Europe, Australia and Asia) who received either *Cervarix* or a Hepatitis A vaccine control according to a 0, 1, 6 month schedule. An interim analysis was performed when 23 events of CIN2+ associated with HPV-16 or HPV-18 infection were identified in the Total Vaccinated Cohort-1 (TVC-1) [Paavonen, 2007]. A final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 were detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. The study is ongoing in a blinded manner until all subjects have completed their Month 48 visit.

5.2.3. Study population

Vaccine efficacy against virological, cytological and histological endpoints was evaluated in Studies HPV-001/007 and HPV-008. Evaluation of efficacy for HPV vaccines requires follow-up in women exposed to HPV infection (i.e. sexually active) and collection of cervical specimens. Thus, Studies HPV-001/HPV-007 and HPV-008 have been conducted in young adult women 15-25 years of age, the age range with the highest incidence of HPV infections.

The design of GSK's HPV efficacy studies considered the different levels of prior HPV exposure in a general female population that might be targeted for vaccination including girls/women 10 to 25 years of age. In studies HPV-001/007, women were screened before vaccination and only women presumed naïve to HPV infection (i.e., without evidence of prior exposure to or current infection with oncogenic HPV) were enrolled. In HPV-008, both naïve as well as non naïve women were enrolled, as minimal study exclusion criteria directed to prior HPV exposure were imposed (Table 5) and women were not screened prior to enrollment.

The population of HPV 'naïve' women includes the population targeted by routine vaccination programs, i.e., young adolescents prior to sexual debut. The population of women non-naïve to HPV represents a general population, inclusive of women having been either previously exposed to oncogenic HPV infections or actively infected at the time of vaccination. The polymerase chain reaction (PCR) methodology utilized in the development program had high sensitivity and specificity, even in the presence of multiple infections, and was suitable to fully assess this diverse population (see Section 5.2.5).

Thus, together Studies HPV-001 and HPV-008 are representative of a broad spectrum of women with respect to HPV exposure at the time of vaccination and therefore provide information that can be used to infer vaccine efficacy in younger women (lower level of HPV exposure, e.g. 10-14 year olds) and older women 15-25 years of age (prior or current exposure/infection with HPV).

Table 5 Comparison of key eligibility criteria for efficacy studies

	HPV-001:	HPV-008:
Key Inclusion Criteria	No more than 6 lifetime sexual partners	
	Intact uterus	Intact cervix
	Cervical cytology (Pap smear) normal	No entry criteria for cytology classification, HPV-16/18 serostatus or high risk HPV DNA status
	Seronegative for HPV-16 and HPV-18 by ELISA	
	High risk HPV DNA negative by PCR	
Key Exclusion Criteria	Therapy for condylomata	History of colposcopy or planned colposcopy
	Cervical or extensive external genital herpes	
	History of abnormal cervical cytology (Pap smear)	
	Treatment for cervical disease	

5.2.4. Study cohorts

5.2.4.1. HPV-007

In Study HPV-007, the analysis of efficacy was performed on the ATP cohort for efficacy and was supplemented by an analysis on the Total Vaccinated Cohort. Analyses in the ATP cohort for efficacy included all vaccinated subjects (receiving 3 doses in HPV-001) compliant with procedures defined in the protocol and for whom data concerning efficacy endpoint measures were available. Analyses in the Total cohort included all vaccinated subjects for whom data concerning efficacy endpoint measures were available.

In Study HPV-007, vaccine efficacy against cytological and histological secondary endpoints is presented for the Total cohort, offering a more informative review of results for which the number of events is more limited in the ATP cohort for efficacy.

5.2.4.2. HPV-008

In Study HPV-008, the analyses of efficacy were performed on the ATP cohort for efficacy (primary analysis) and the TVC-1. Supplementary analyses were also performed in the Total Vaccinated Cohort (TVC) and Total Vaccinated Cohort of naïve women (TVC naïve). Definitions of the cohorts are provided in Table 6.

Table 6 HPV-008: Study Cohort Definitions

	Total Vaccinated Cohort (TVC)	Total Vaccinated Cohort-1 (TVC-1)	According to Protocol (ATP) cohort for efficacy†	Total Vaccinated Cohort Naïve (TVC naïve)
N	18644	18525	16162	11641
Doses Received	≥1 dose	≥1 dose	3 doses	≥1 dose
HPV DNA Status (Month 0)	Not considered	Negative for the type considered in the analysis	Negative for the type considered in the analysis	Negative for 14 high risk types
HPV DNA Status (Month 6)	Not considered	Not considered	Negative for the type considered in the analysis	Not considered
HPV-16/18 Serostatus (Month 0)	Not considered	Negative for the type considered in the analysis	Negative for the type considered in the analysis	Negative for HPV-16 and 18
Cytology (Month 0)	Not considered	Normal or low-grade cytology	Normal or low-grade cytology	Normal cytology
Case Count	Day after Dose 1	Day after Dose 1	Day after Dose 3	Day after Dose 1

† Compliant with procedures as defined in the protocol
Normal or low-grade cytology = negative or ASC-US or LSIL
Normal cytology = negative or ASC-US oncogenic HPV negative by Hybrid Capture 2 (HCII)

The analyses of various cohorts are valuable in their approximation of different populations that will benefit from vaccination.

The ATP cohort for efficacy examines the efficacy in the study population adherent to the protocol and provides an estimation of vaccine efficacy in a population using the vaccine as intended.

The TVC-1 excludes subjects who had prevalent high-grade lesions at baseline, and therefore provides an estimation of prophylactic vaccine efficacy in an unscreened population at enrollment.

The TVC is the broadest cohort, with minimal eligibility criteria (Table 5), including women both with and without oncogenic HPV infections and lesions at baseline. It approximates a population of sexually active young women and is therefore relevant to populations targeted for catch-up vaccination. As it is the most inclusive population, TVC was also used as the primary cohort for safety analyses.

The TVC naïve includes only women with no evidence of exposure to any of the 14 oncogenic HPV types at baseline and is closest to the population targeting by routine HPV vaccination (i.e., young girls before sexual debut).

5.2.5. PCR methodology

The efficacy evaluations were based on the detection of HPV DNA using state-of-the-art PCR assays performed on cervical or biopsy specimens. The HPV DNA assays (generic SPF_{10} PCR with LiPA, followed by HPV-16/18 type-specific PCR) applied in GSK Biologicals trials have been selected based on three pre-specified criteria:

- high sensitivity,
- high specificity, even in presence of multiple infections,
- typing of the most frequent genital HPV types.

The SPF10 HPV LiPA 25 version 1 and SPF10 HPV DEIA are manufactured by Labo Biomedical Products (Rijswijk,The Netherlands) based on licensed INNOGENETICS SPF10 technology [van Doorn, 2006]. Since the SPF_{10} PCR system uses consensus primers which are able to amplify many different HPV types, the testing algorithm used in the clinical program is able to detect 14 oncogenic HPV types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and 11 low risk HPV types. An HPV testing algorithm was developed to achieve a high sensitivity for detection of any HPV-16 or HPV-18 DNA, even at very low levels and in the presence of multiple infections in both cervical samples and biopsies, while permitting the detection of other HPV types.

5.2.6. Case definitions

The following case definitions were used for the efficacy data presented in this document:

- **Incident infection:** First detection of a specific HPV type (by PCR) in a subject previously negative for that HPV type.
- **Persistent infection** (6-month definition): Detection of the same HPV type (by PCR) in cervical samples at two consecutive timepoints with no negative samples in between. Sampling frequency was at 6 month intervals.
- **Persistent infection** (12-month definition): Detection of the same HPV type (by PCR) over approximately a 12-month interval, with no negative samples in between. Sampling frequency was at 6 month intervals.
- For **cytological endpoints**: Association with a specific HPV type was defined as the detection of this type by PCR in the cervical specimen.
- For **histopathological endpoints:** Association with a specific HPV type was defined as the detection of this type by PCR in the cervical tissue specimen, in which the lesion was diagnosed. This association with a specific HPV type was based solely on the detection of viral DNA by PCR in the biopsy sample without considering whether or not the specific HPV type detected was likely to be responsible for the development of the lesion in cases where multiple HPV types were detected in the lesion.

In Study HPV-008, for events considered to meet criteria for histopathological or virological endpoints, all available clinical and laboratory data were reviewed by an

endpoint committee, which was independent from GSK Biologicals, prior to analysis. This review was done in a blinded manner with respect to both the treatment received and the HPV PCR results for subjects who achieved histopathological endpoints.

At interim analysis, the observation that a high proportion of lesions contained DNA from multiple HPV types detected in temporal association with the lesion complicated the evaluation of vaccine efficacy against CIN2+ associated with HPV-16/18 [Paavonen, 2007]. Therefore, an algorithm was applied to attribute a likely causal association between a lesion and the HPV type (referred to as the 'HPV type assignment algorithm'). For this pre-defined exploratory analysis, the following rules were applied:

- If more than one HPV type was found in a lesion, the presence of HPV types in the two immediately preceding cytology samples was evaluated:
    - The HPV type present in both the lesion and in at least one of the two immediately preceding cytology samples was considered to be associated with that lesion.
    - If none of the HPV types present in the lesion were found in any of the two immediately preceding cytology samples, the HPV types present in the lesion were considered to be associated with that lesion (as per original analysis).
- If only a single HPV type was found in a lesion, then this type was considered to be associated with the lesion (as per original analysis).

Since persistent oncogenic HPV infection is required for development of invasive cervical lesions, HPV persistent infection was considered to represent a valuable endpoint for evaluation of efficacy [Pagliusi, 2004]. Unlike histopathological endpoints, virological endpoints (e.g. persistent infection) are not complicated by multiple infections [Jenkins, 2008; Koshiol, 2008]. Therefore, GSK has used both virological and histopathological endpoints for the clinical evaluation of prophylactic HPV efficacy.

5.2.7. Methodologies for cytological and biopsy assessment

Cervical specimens were assessed for cytology on a regular basis, and abnormal results were followed according to a referral algorithm for the study. Abnormal cervical cytology, such as ASC-US with HCII positive result, or LSIL triggered referral for a repeat cervical smear or colposcopy. Results of AGC, HSIL and ASC-H triggered referral for immediate colposcopy and appropriate medical follow-up. At the colposcopic examination, a biopsy sample of tissue from any cervical lesion observed was to be taken for histopathological diagnosis and HPV DNA analysis. Guidance for the management of women with cytological abnormalities was based upon standards of care within a range of national screening programs. Study subjects obtained self-collected cervico-vaginal samples in HPV-001, but not HPV-007 or HPV-008. Cytology and virological results are based on cervical samples taken at study visits, and not self-collected samples.

At the initiation of the study (2004), non-cervical lesions were not collected in a prospective manner. In a 2008 protocol amendment, sites were instructed to biopsy VIN/VaIN lesions suspected to be Grade 2 or higher. The collection of vaginal and vulvar samples was however limited to the subjects referred for colposcopy as a result of

abnormal cervical cytology. All confirmed VIN1+ and VaIN1+ lesions were tested by PCR.

Quest Diagnostics (Teterboro, NJ, USA) processed and diagnosed all *ThinPrep* Pap Test (Cytec, Boxborough, MA, USA) specimens and HPV PCR testing was performed by GSK Biologicals in Rixensart. Quest Diagnostics performed histopathological endpoint determination on tissue specimens (biopsies and excisions) and HPV PCR testing was performed by DDL. HPV testing by HCII was performed on residual *ThinPrep* material for subjects with a Pap test result of ASC-US, except in Study HPV-001.

Pathology Panel

In studies HPV-007 and HPV-008, all biopsy and excisional treatment specimens were evaluated by two panels of histopathologists. First, the specimens were examined by a panel of histopathologists who provided the histopathological diagnosis used for clinical management of the subject (routine panel).

Following the review by the routine panel, tissue samples and slides with a diagnosis of CIN1, VIN1, VaIN1 or higher, were sent to a second panel of histopathologists (the study panel) for the purpose of endpoint determination. This second histopathological review process was performed in a blinded manner, without knowledge of the diagnosis previously made by the routine panel. The study panel consisted of three expert gynecological pathologists under the supervision of a fourth pathologist. This fourth pathologist coordinated the independent and blinded review process, and ensured that agreement on the grade level and location of the lesion in the tissue was obtained between at least two members of the study panel. When multiple areas of abnormality were present in a single tissue specimen, the most severe area constituted the study endpoint. Lesional biopsies (CIN1, VIN1, VaIN1 or higher) were sent to DDL for HPV PCR.

In Study HPV-008, prior to the analysis, all endpoints were confirmed by an independent endpoint committee in a blinded manner, as described in Section 5.2.6.

In Study HPV-001, histopathology review processes were developed during the course of the study, and were used as a reference to establish the best practices for subsequent studies. At the end of Study HPV-001, a retrospective review of all sections was made by an expert gynecological pathologist at Quest allowing the final classification of cases using the CIN classification system.

5.2.8. Statistical methods

For studies in the clinical program, the methodology, design and statistical plan were appropriate to generate an unbiased and unconfounded evaluation of the results to support licensure.

A report analysis plan was defined for each study prior to initiation of the analysis.

To maintain the integrity of the blinded efficacy studies, the HPV-001 and HPV-007 and HPV-008 analyses were performed by a statistician external to GSK such that clinical

data from these studies remain blinded at the individual subject level for all study personnel and GSK staff involved in the HPV project.

Study subjects from Brazil in HPV-007 were entered in Study HPV-023, a long-term blinded follow-up study scheduled to complete in 2010. Study HPV-008 will remain blinded until all subjects have completed their Month 48 visit and associated study activities (scheduled to occur in 4th quarter 2009). To maintain the integrity of the ongoing and follow-up efficacy studies, study personnel and GSK staff involved with these studies remain appropriately blinded.

5.2.8.1. Studies HPV-001 and HPV-007

In Study HPV-001, the primary endpoint was VE against HPV-16 and/or HPV-18 incident infection. The sample size was calculated to have 80% power for the primary endpoint analysis (α=0.023, one-sided test), assuming an annual attack rate of HPV-16 and/or HPV-18 incident infection of 6% in the control group and an expected vaccine efficacy of 70%. The overall alpha of 0.05 was adjusted according to the O'Brien-Fleming adjustment for two interim analyses, such that an alpha value of 0.005 was used for each interim analysis, leading to an alpha for the final analysis of 0.046. The adjustment for alpha applied for the primary endpoint as well as for secondary endpoints.

In follow-up Study HPV-007, the primary endpoint was VE against HPV-16 and/or HPV-18 incident infection. The sample size was calculated to have at least 80% power to detect a VE level of 70%, assuming an annual attack rate of 3.5% in the control group. Two interim analyses were performed and for both interim analyses, an alpha value of 0.001 (2-sided test) was used, leading to an alpha for the final analysis of 0.049 (2-sided test) and an overall alpha of 0.05 (2-sided test). The adjustment for alpha applied for the primary endpoint as well as for secondary endpoints.

A descriptive combined analysis of Studies HPV-001 and HPV-007 was performed. The rationale for performing a combined analysis of Studies HPV-001 and HPV-007 was to provide an estimation of the efficacy of the vaccine over the full follow-up period. This approach is justified by the fact that both studies evaluate the same population (subjects were enrolled and vaccinated in Study HPV-001 and then followed in Study HPV-007), had comparable study designs and used similar study procedures.

A supplementary analysis was performed on the combined analysis of the HPV-001 and HPV-007 studies in order to account for repeated observations of the data by adjustment of type I error (alpha). The adjustment was done by giving a similar alpha to each evaluation using the Pocock method [Peto, 1976], which gives an approximately similar two-sided alpha of 1.33% for each repeated observation of the data, i.e. 98.67% CI.

5.2.8.2. Study HPV-008

In Study HPV-008, the event-triggered final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 were to be detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. For the final analysis, the assumption for HPV-16/18 was a CIN2+ attack rate

of 0.0055 and a vaccine efficacy against CIN2+ of 85% with a power of 94% to confirm a 96.1% CI lower limit above 30%.

An event-triggered interim analysis was performed in 2006 when 23 cases of CIN2+ associated with HPV-16 or HPV-18 were detected in TVC-1. The overall alpha of 0.05 was split into 0.021 for the interim analysis and 0.039 for the final analysis. No stopping rules were applied.

At final analysis, the study had less power to evaluate CIN2+ lesions associated with the non-vaccine oncogenic HPV types, as these lesions are not as common as lesions caused by HPV-16 and HPV-18. Additionally, non-vaccine oncogenic HPV types have a slower progression from persistent infection to lesions and ultimately cervical disease compared to HPV-16 and HPV-18, see Section 2.2.

5.2.8.3. Calculation of vaccine efficacy

The vaccine efficacy for all endpoints in Study HPV-007, the combined analysis of Studies HPV-001 and HPV-007 and Study HPV-008 was calculated using a conditional exact method. This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the follow-up time of the subjects within each group. VE is then defined as 1 minus the rate ratio. This approach was taken to account for a different duration of follow-up for each subject in the efficacy analyses.

For each efficacy endpoint, the point estimate for vaccine efficacy and confidence interval were calculated. In addition, for HPV-007 and HPV-008 analyses, p-values were calculated using a Fisher's exact test to compare the attack rates between both groups.

The total number of women included in the evaluation of each efficacy endpoint was determined by the number of women at risk for the endpoint, which depended on the nature of the endpoint (virological, cytological or histopathological) and the follow-up time of each woman. Additionally, for specific HPV type evaluations, the baseline and/or Month 6 status was considered depending on the cohort for analysis.

5.3. Efficacy of *Cervarix* against HPV-16/18

5.3.1. Efficacy in a presumed oncogenic HPV-naïve population, HPV-001/007

Study HPV-001 enrolled a screened population of women who were negative for oncogenic HPV DNA, seronegative for HPV-16 and HPV-18 antibodies and had normal cytology prior to vaccination.

The primary objective of Study HPV-001 was to evaluate vaccine efficacy against HPV-16/18 incident infections. Main secondary objectives of the study were to evaluate vaccine efficacy against persistent infections (based on a 6-month definition), cytological abnormalities and histopathological lesions associated with HPV-16/18 or associated

with other oncogenic HPV types. The duration of Study HPV-001 was a minimum of 18 months and up to 27 months in a subset of subjects.

Study HPV-007 was the extension of Study HPV-001 and evaluated the long-term efficacy, immunogenicity and safety in 776 subjects vaccinated in Study HPV-001 over an additional 3 years. At final analysis, the mean follow-up period from the start of Study HPV-001 until Year 3 in Study HPV-007 was approximately 5.9 years with a maximum duration of approximately 6.4 years. A descriptive combined analysis of Studies HPV-001 and HPV-007 was performed to provide an estimation of the efficacy of the vaccine over the full follow-up period.

As the study population was screened prior to vaccination, these data provide insights into the vaccine benefits against HPV infection and disease progression in a population presumed naïve to oncogenic HPV prior to vaccination, which is closely representative of the group of young adolescents targeted for HPV vaccination and primary prevention of cervical cancer.

5.3.1.1. Virological endpoints for HPV-16/18, HPV-001/007

Table 7 presents vaccine efficacy against virological endpoints reported in HPV-007 as well as HPV-001 and HPV-007 combined. The HPV-007 analysis provides vaccine efficacy up to 6.4 years, and the combined analysis provides an estimation of vaccine efficacy over the full follow-up period of Studies HPV-001 and HPV-007.

In women presumed to be HPV naive, a high level of efficacy was observed against incident, 6-month and 12-month persistent infection with HPV-16/18 in both the HPV-007 analysis and in the HPV-001/007 combined analysis. The long-term protective effect of *Cervarix* is particularly evident in this follow-up evaluation. Analysis of HPV-007 as an independent study is relevant as it demonstrates sustained protection of the vaccine against a background of continued accrual of events in the placebo group during the long-term follow-up.

Table 7 Studies HPV-007 and HPV-001/007: efficacy results against HPV-16/18 incident and persistent infection (6-month and 12-month definition) (ATP cohort for efficacy)

Endpoint	*Cervarix*	Control	Vaccine Efficacy		
	N (Cases)	N (Cases)	%	95% CI*	P-value
Incident infection					
HPV-007	303 (2)	267 (47)	96.7	87.4, 99.6	<0.001
Combined 001/007	401 (4)	372 (70)	95.3	87.4, 98.7	
Persistent infection (6-month definition)					
HPV-007	304 (0)	277 (24)	100	85.9, 100	<0.001
Combined 001/007	401 (0)	372 (34)	100	90.0, 100	-
Combined 001/007 (Adjusted)*	401 (0)	372 (34)	100	86.2, 100	-
Persistent infection (12-month definition)					
HPV-007	304 (0)	285 (15)	100	75.0, 100	<0.0001
Combined 001/007	401 (0)	372 (20)	100	81.8, 100	-
Combined 001/007 (Adjusted)*	401 (0)	372 (20)	100	74.4, 100	-

The statistical methods for the Combined HPV-001/007 analysis were identical to the methods used for the HPV-007 analysis, except that no p-value was calculated (descriptive analysis).*A supplementary analysis was performed in

order to account for repeated observations of the data by adjustment of type I error (alpha). A 98.67% CI was used for this analysis.

5.3.1.2. Cytological abnormalities and histopathological lesions for HPV-16/18, HPV-001/007

The observed vaccine efficacy against CIN1+ and CIN2+ associated with HPV-16/18 was 100% in HPV-007 and in the combined analysis (Table 8) showing maintenance of high vaccine efficacy up to 6.4 years post-vaccination. Of note, all subjects with CIN2 lesions associated with HPV-16 or HPV-18 at the time of biopsy showed previous infection with the same HPV type detected in preceding cervical samples.

Additionally, a high level of vaccine efficacy against any cytological abnormality (≥ ASC-US) associated with HPV-16/18 was achieved in women presumed to be HPV naïve (Table 8).

Table 8 Studies HPV-007 and HPV-001/007: incidence rates and vaccine efficacy against cytological abnormalities and CIN associated with HPV-16/18 (by PCR in the lesion) (Total cohort)

Endpoint	*Cervarix* N (Cases)	Control N (Cases)	Vaccine Efficacy		
			%	95% CI	P-value
≥ ASC-US					
HPV-007	357 (0)	335 (19)	100	80.5, 100	<0.0001
Combined 001/007	505 (1)	497 (34)	97.3	83.6, 99.9	-
CIN1+					
HPV-007	358 (0)	339 (9)	100	52.6, 100	0.0014
Combined 001/007	481 (0)	470 (15)	100	73.4, 100	-
Combined 001/007 (Adjusted)*	481 (0)	470 (15)	100	62.1, 100	-
CIN2+					
HPV-007	358 (0)	342 (6)	100	19.7, 100	0.0133
Combined 001/007	481 (0)	470 (9)	100	51.3, 100	-
Combined 001/007 (Adjusted)*	481 (0)	470 (9)	100	28.4, 100	-

The statistical methods for the Combined HPV-001/007 analysis were identical to the methods used for the HPV-007 analysis, except that no p-value was calculated (descriptive analysis).
*A supplementary analysis was performed in order to account for repeated observations of the data by adjustment of type I error (alpha). A 98.67% CI was used for this analysis.

The data confirm a high level of concordance between efficacy results for virological endpoints (6-month and 12-month persistent infection) and histopathological endpoints (CIN2+ and CIN1+).

5.3.1.3. Efficacy beyond HPV-16/18

In the population of women naive to oncogenic HPV types prior to vaccination, there was evidence of vaccine efficacy beyond HPV-16/18.

In order to evaluate the overall vaccine benefit, the vaccine efficacy irrespective of HPV DNA results in the lesions was performed on the Total Cohort (combined analysis of HPV-001/007). In this analysis, the overall vaccine efficacy was shown to be 71.9% (95% CI: [20.6; 91.9]) for CIN2+. Based on epidemiological considerations, the expected

proportion of CIN2+ lesions attributed to HPV-16/18 is approximately 52% [Smith, 2007]. Therefore, as the observed vaccine efficacy is above 52%, this suggests that the efficacy of *Cervarix* extends beyond protection against HPV-16/18.

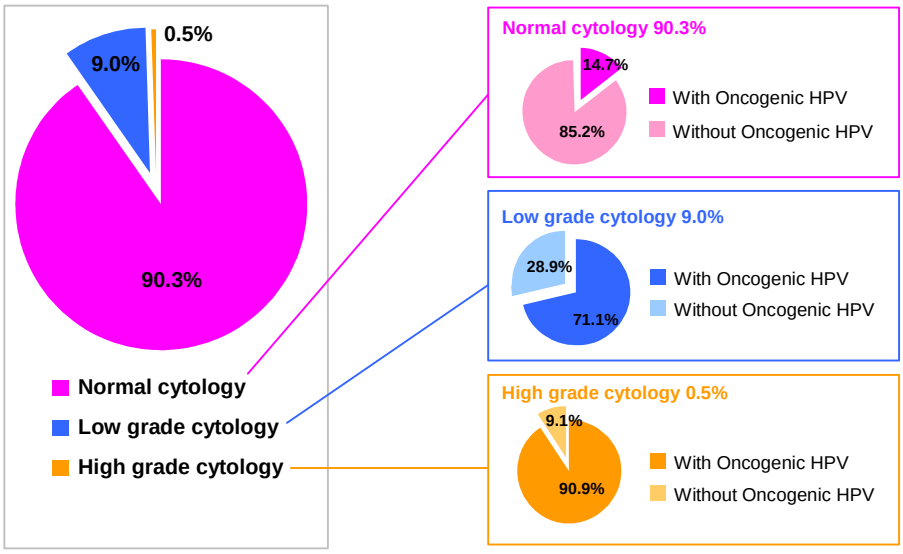
Additionally, the results of vaccine efficacy against individual non-vaccine oncogenic HPV types provided the first indication of the potential for cross protection. From among the 12 non-vaccine oncogenic types evaluated in the study, sustained efficacy against incident infections with HPV-31 (VE=59.8% [20.5; 80.7]) and HPV-45 (VE=77.7% [39.3; 93.4]) was observed up to 6.4 years post first vaccination in the HPV-001/007 combined analysis. As a result of this finding, pre-specified endpoints for cross-protection were implemented in the Phase III Study HPV-008.

5.3.2. Efficacy in a general population for HPV-16/18, HPV-008

Study HPV-008 was conducted in North America, Latin America, Europe, Asia and Australia. Women aged 15-25 years were vaccinated regardless of their HPV DNA and serological status and their cervical cytology status. Therefore, Study HPV-008 provides efficacy data in a 'general' population inclusive of women naïve (without current infection and without prior exposure) and non-naïve (with current infection and/or with prior exposure) to HPV. Before vaccination, 74% of subjects were naïve to HPV-16 and HPV-18 (HPV DNA negative and seronegative to both HPV-16 and HPV-18). Among subjects, 54.8% of subjects were Caucasian, 31.5% Asian/Chinese, 7.1% Hispanic, 3.7% Black and 2.9% were of other racial/ethnic groups. The mean age of women at study entry was 20 years, and the majority of women (96%) had at least one sexual partner in the year prior to study entry (Total Vaccinated Cohort).

There were minimal study exclusion criteria related to prior HPV exposure or infection present at study entry. Consequently, 14.7% of subjects with normal cytology and 71.1% of subjects with low grade cytology tested positive for oncogenic HPV at study entry (Figure 10). A significant proportion of women presenting with abnormal cytology results at study entry would be expected to have underlying cervical lesions prior to vaccination. Since the colposcopy referral algorithm did not require immediate referral to colposcopy, except for high grade cytology, (see Section 5.2.7), in many cases the first opportunity to detect prevalent lesions present at study entry was during the study follow-up period. Therefore, this study design provides a very conservative approach for evaluation of vaccine efficacy.

Figure 10 HPV-008: Cervical cytology and HPV DNA status at study entry (Total Vaccinated Cohort)



Efficacy data presented in this document from Study HPV-008 are based upon an event-triggered final analysis with a mean length of follow-up of 34.9 months (2.9 years) after the third vaccine dose in the ATP cohort for efficacy and 39.4 months (3.3 years) after the first vaccine dose in the TVC-1.

5.3.2.1. Efficacy in women HPV DNA negative and seronegative for the corresponding type at baseline

5.3.2.1.1. Histopathological lesions

CIN2+ cases

The primary objective of the study was to demonstrate the efficacy of the vaccine for prevention of histopathologically-confirmed CIN2+ cases associated with HPV-16/18 in women who were negative for HPV DNA for the corresponding type considered in the analysis.

The objective was met with a vaccine efficacy of 92.9% [79.9, 98.3], p<0.0001 in the ATP cohort for efficacy and 94.5% [86.2, 98.4], p<0.0001 in TVC-1 (Table 9). Statistically significant vaccine efficacy was also observed individually for CIN2+ associated with HPV-16 (VE=95.7% [82.9, 99.6], p<0.0001) and HPV-18 (VE=86.7% [39.7, 98.7], p<0.0001) in the ATP cohort for efficacy. Similar point estimates for the ATP cohort for efficacy and TVC-1, which included women incompletely vaccinated and women who had lesions that developed from infections acquired prior to completion of vaccination, support the robustness of the results in the ATP cohort for efficacy.

Table 9 Study HPV-008: incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline

HPV Type	ATP cohort for efficacy					TVC-1				
	Cervarix	Control	Vaccine Efficacy			*Cervarix*	Control	Vaccine Efficacy		
	N(Cases)	N(Cases)	%	96.1% CI	P-value	N(Cases)	N(Cases)	%	96.1% CI	P-value
HPV-16/18	7344 (4)	7312 (56)	92.9	79.9, 98.3	<0.0001	8040 (5)	8080 (91)	94.5	86.2, 98.4	<0.0001
HPV-16	6303 (2)	6165 (46)	95.7	82.9, 99.6	<0.0001	6921 (3)	6923 (73)	95.9	87.0, 99.3	<0.0001
HPV-18	6794 (2)	6746 (15)	86.7	39.7, 98.7	0.0013	7455 (2)	7480 (24)	91.6	64.6, 99.2	<0.0001

The protocol-specified case assignments considered the association with HPV-16/18 based solely on the detection of viral DNA by PCR in the biopsy sample and did not consider whether or not the HPV-16/18 DNA detected was likely to be responsible for the development of the lesion.

The PCR methodology used in Study HPV-008 is highly sensitive and allows for the detection of a broad range of oncogenic and non-oncogenic HPV types, including types not contained in the vaccine, thus providing a more complete understanding of the HPV natural history in this study population.

A high proportion of histopathological lesions had multiple HPV types detected in the lesion. Systematic evaluation of all data available from these cases showed that for some of them, HPV-16 or HPV-18 were detected in the histopathological lesion without detection of the same type in any preceding cytology sample, while other high-risk HPV types concomitantly detected in the lesion were also present at study start and in preceding cytology samples. The complexity of the efficacy analyses resulting from the detection of multiple HPV types in lesions required an additional exploratory analysis to adequately assign likely causality to cervical lesions and therefore the 'HPV type assignment algorithm' was utilized. In this pre-defined analysis, the association with HPV-16 and/or HPV-18 was based not only on the detection of HPV DNA in the lesion, but also considered the presence of HPV types in the two immediately preceding cytology samples if more than one HPV type was found in the lesion. See Section 5.2.6 for details on this analysis.

Of the 60 women with CIN2+ cases in the ATP cohort for efficacy that triggered the final analysis:

- 36 subjects (60%) had lesions that contained multiple HPV types detected in the biopsy sample or in excision samples. A total of 33 of those subjects (55%) had lesions that contained oncogenic HPV DNA other than HPV-16/18,
- 24 subjects were infected with at least one HPV type at the Month 0 and/or Month 6 visit (19 of these subjects had oncogenic HPV infection).

Out of the 60 events considered for the primary analysis, there were 6 events with multiple HPV types detected in the CIN2+ lesion (including HPV-16/18) with no prior detection of the vaccine type (HPV-16 or 18 infection) in cervical samples. These cases therefore did not qualify for inclusion in the exploratory analysis using the HPV type assignment algorithm. Further details regarding these cases can be found in Appendix 1.

The observed vaccine efficacy against CIN2+ associated with HPV-16/18 using the HPV type assignment algorithm was 98.1% [88.4, 100], p<0.0001 for the ATP cohort for efficacy and was 97.7% [91.0, 99.8], p<0.0001 for TVC-1 (Table 10).

Table 10 Study HPV-008: incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline (HPV type assignment algorithm)

HPV Type	ATP cohort for efficacy					TVC-1				
	Cervarix	Control	Vaccine Efficacy			*Cervarix*	Control	Vaccine Efficacy		
	N(Cases)	N(Cases)	%	96.1% CI	P-value	N(Cases)	N(Cases)	%	96.1% CI	P-value
HPV-16/18	7344 (1)	7312 (53)	98.1	88.4, 100	<0.0001	8040 (2)	8080 (87)	97.7	91.0, 99.8	<0.0001
HPV-16	6303 (0)	6165 (45)	100	91.0, 100	<0.0001	6921 (1)	6923 (71)	98.6	91.5, 100	<0.0001
HPV-18	6794 (1)	6746 (13)	92.3	45.7, 99.9	0.0009	7455 (1)	7480 (22)	95.4	70.1, 99.9	<0.0001

In the TVC-1 analysis using the HPV type assignment algorithm, there were 2 cases of CIN2+ associated with HPV-16/18 remaining in the *Cervarix* group:

The first case was a CIN2 lesion detected 40 months after the first vaccination, with HPV-18 and HPV-52 found in the lesion. There was evidence of prior infection with both types in the cytology sample taken at the time of lesion detection and treatment (Month 40) and also in a cytology sample taken 6 months earlier (Month 34). As there was previous infection with HPV-18, this case was not eliminated using the HPV type assignment algorithm. This subject also showed evidence of exposure to other types. As this subject presented with an infection with HPV-18 of less than 6 months in duration and a long lasting persistent infection of HPV-52 for over 3 years, prior to lesion detection, it is probable that HPV-52 contributed to the development of the lesion. This case was included in both the ATP and TVC-1 analyses.

The second case was a CIN2 lesion with HPV-16 detected 21 months after the first vaccination. In this case, the subject received all 3 doses of vaccine. HPV-16 was the only type found in the CIN2 lesion and there was evidence of HPV-16 infection in the 3 previous cytology samples (taken at Months 6, 12 and 18). The subject had a normal cytology and was seronegative and HPV DNA negative for both HPV-16 and HPV-18 at baseline. HPV-16 DNA was detected at Months 6, 12 and 18. In addition, HPV-43 DNA was detected at Month 6 and HPV-42 DNA was detected at Month 18. As there was HPV-16 DNA in preceding samples, and only HPV-16 was detected in the lesion, this case was not eliminated using the HPV type assignment algorithm. However, since HPV-16 DNA was detected at the Month 6 visit and at all subsequent visits prior to CIN2+ lesion detection, it should be noted that this subject acquired the HPV-16 infection responsible for development of the lesion prior to completion of the full three-dose series. This case was included in the TVC-1 analyses only.

CIN3+ cases

Of the 60 identified cases of CIN2+ associated with HPV-16/18, there were 12 cases of CIN3+ with HPV-16/18: 9 cases of CIN3, 2 cases of AIS and 1 case of both CIN3 and AIS in the ATP cohort for efficacy in subjects DNA negative and seronegative at baseline. Vaccine efficacy against CIN3+ associated with HPV-16/18 was statistically

significant at 80.0% [0.3, 98.1], p=0.0221 in the ATP cohort for efficacy, with 2 cases in the *Cervarix* group and 10 cases in the control group and 90.9% [60.8, 99.1], p<0.0001 in TVC-1, with 2 cases in the *Cervarix* group and 22 cases in the control group. Using the HPV type assignment algorithm, the observed vaccine efficacy was 100% [36.4, 100], p=0.0038 in the ATP cohort for efficacy, with 0 cases in the *Cervarix* group and 8 cases in the control group, and 100% [78.1, 100], p<0.0001 in TVC-1, with 0 cases in the *Cervarix* group and 20 cases in the control group.

CIN1+ cases

Similar analyses were performed for the CIN1+ endpoint. In the pre-specified analysis, the observed vaccine efficacy against CIN1+ associated with HPV-16/18 was statistically significant (VE=91.7% [82.4, 96.7], p<0.0001) in the ATP cohort for efficacy in subjects DNA negative and seronegative at baseline. The vaccine efficacy against CIN1+ associated with HPV-16 was 93.0% [82.2, 97.9], p<0.0001 and was 90.4% [67.7, 98.3], p<0.0001 for CIN1+ associated with HPV-18 in the ATP cohort for efficacy. The vaccine efficacy against CIN1+ associated with HPV-16/18 was statistically significant (VE=91.8% [84.5, 96.2], p<0.0001) in TVC-1.

Using the HPV type assignment algorithm, the observed vaccine efficacy was 97.8% [91.4, 99.8], p<0.0001 against CIN1+ associated with HPV-16/18, 98.5% [91.0, 100], p<0.0001 for lesions associated with HPV-16 and 96.6% [78.1, 99.9], p<0.0001 for lesions associated with HPV-18 in the ATP cohort for efficacy. The vaccine efficacy for CIN1+ against HPV-16/18 was 96.1% [90.3, 98.8], p<0.0001 in TVC-1.

Vulval or vaginal intraepithelial neoplasia (VIN or VaIN)1+

The observed vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16 and/or HPV-18 was statistically significant in the ATP cohort for efficacy and the TVC-1 (Table 11).

It should be noted that collection of these data was initiated later in the course of the study and was limited to collection of samples in subjects referred for colposcopy as a result of abnormal cervical cytology. Therefore, few cases were accrued at the time of final analysis.

Table 11 HPV-008: efficacy results against HPV-16/18 VIN1+/VaIN1+ in HPV DNA negative and seronegative subjects at baseline

ATP cohort for efficacy					TVC-1				
Cervarix	Control	Vaccine Efficacy			*Cervarix*	Control	Vaccine Efficacy		
N(Cases)	N(Cases)	%	96.1% CI	P-value	N(Cases)	N(Cases)	%	96.1% CI	P-value
7344 (2)	7312 (10)	80.0	0.3,98.1	0.0221	8040(2)	8080(12)	83.2	(20.2,98.4)	0.0129

5.3.2.1.2. Virological endpoints

Statistically significant vaccine efficacy was observed for persistent infection (6-month and 12-month definitions) associated with HPV-16/18 (Table 12).

Table 12 HPV-008: efficacy results against HPV-16/18 persistent infection (6 and 12-month definitions) in HPV DNA negative and seronegative subjects at baseline

Endpoint	ATP cohort for efficacy					TVC-1				
	Cervarix	Control	Vaccine Efficacy			*Cervarix*	Control	Vaccine Efficacy		
	N(Cases)	N(Cases)	%	96.1% CI	P-value	N(Cases)	N(Cases)	%	96.1% CI	P-value
6-month	7177 (32)	7122 (497)	93.8	91.0,95.9	<0.0001	7941 (71)	7964(671)	89.8	86.8,92.2	<0.0001
12-month	7035 (21)	6984 (233)	91.2	85.9,94.8	<0.0001	7812 (53)	7823(347)	85.0	79.7,89.2	<0.0001

The results for persistent infection (6-month and 12-month) are in line with the results observed for histopathological endpoints and confirm the predictive value of virological endpoints.

5.3.2.1.3. Cytological abnormalities

The observed vaccine efficacy against any cytological abnormality (≥ASC-US) associated with HPV-16/18 was statistically significant in the ATP cohort for efficacy (VE = 88.5% [84.4, 91.7], p<0.0001) and TVC-1 (VE = 86.1% [82.2, 89.3], p<0.0001.

5.3.2.2. Vaccine efficacy in women previously or currently exposed to HPV-16/18

Women enrolled in Study HPV-008 were not screened prior to enrollment and were therefore vaccinated irrespective of their cytological, serological or DNA status. Efficacy in subjects by baseline HPV DNA and serostatus was further investigated to determine the contribution of the different subpopulations in this analysis.

5.3.2.2.1. Efficacy in HPV-16/18 DNA negative women, regardless of serostatus at baseline

Vaccine efficacy in subjects regardless of their initial HPV-16/18 serostatus at study entry was comparable to vaccine efficacy in subjects who were seronegative for the HPV type considered in the analysis (Table 13). The majority of women in this analysis were seronegative at baseline (see Section 5.1); therefore, the efficacy in this population is primarily due to the subset of women seronegative at baseline. However, seronegative women may have been previously exposed to HPV but without seroconversion or may have seroconverted but not maintained detectable antibody levels.

Table 13 Study HPV-008: incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) regardless of initial serostatus in HPV DNA negative subjects at baseline

Endpoint	ATP cohort for efficacy					TVC-1				
	Cervarix	Control	Vaccine Efficacy			*Cervarix*	Control	Vaccine Efficacy		
	N(Cases)	N(Cases)	%	96.1% CI	P-value	N(Cases)	N(Cases)	%	96.1% CI	P-value
HPV-16/18	7814(6)	7767(65)	90.8	78.1, 96.9	<0.0001	8562(8)	8575(104)	92.3	83.8,96.9	<0.0001
HPV-16	7372(4)	7276(54)	92.7	79.3. 98.2	<0.0001	8140(6)	8203(86)	93.0	83.5,97.6	<0.0001
HPV-18	7645(2)	7583(16)	87.6	44.1, 98.8	0.0007	8407(2)	8426(25)	92.0	66.2,99.2	<0.0001
HPV-16/18 TAA	7814(1)	7767(61)	98.4	90.0, 100	<0.0001	8562(3)	8575(99)	97.0	90.5,99.4	<0.0001
HPV-16 TAA	7372(0)	7276(52)	100	92.2,100	<0.0001	8140(2)	8203(83)	97.6	90.5,99.8	<0.0001
HPV-18 TAA	7645(1)	7583(14)	92.9	50.3,99.9	0.0005	8407(1)	8426(23)	95.6	71.6,99.9	<0.0001

TAA=HPV type assignment algorithm

5.3.2.2.2. Efficacy in women HPV DNA negative and seropositive for corresponding type at baseline

The majority of the study population was seronegative for HPV-16/18 at baseline (see Section 5.1). For subjects who were DNA negative but seropositive for the corresponding type at baseline (subjects who had evidence of prior but not current infection), significant vaccine efficacy was demonstrated for virological endpoints (Table 14). There was a consistent pattern of efficacy observed across virological and histopathological endpoints reaching statistically significance for protection against persistent infection and CIN1+. The number of CIN2+ endpoints was, however, too limited in this study cohort to reach statistical significance. In the analyses that reached statistical significance, the level of efficacy was consistent with results in initially seronegative subjects, suggesting that the vaccine efficacy of *Cervarix* in initially seropositive women is similar to that in seronegative women.

Table 14 Study HPV-008: incidence rates and vaccine efficacy against histopathological and virological endpoints associated with HPV-16 and/or HPV-18 (by PCR) in seropositive and HPV DNA negative subjects at baseline

Endpoint	ATP cohort for efficacy					TVC-1				
	Cervarix	Control	Efficacy			*Cervarix*	Control	Vaccine Efficacy		
	N(Cases)	N(Cases)	%	96.1% CI	P-value	N(Cases)	N(Cases)	%	96.1% CI	P-value
Persistent infection (6-month)										
HPV-16/18	1462(9)	1496(47)	80.6	58.6,92.0	<0.0001	1667(21)	1729(73)	70.6	50.4,83.3	<0.0001
Persistent infection (12-month)										
HPV-16/18	1427(2)	1461(24)	91.5	64.0,99.2	<0.0001	1630(13)	1693(39)	65.6	32.2,83.8	0.0004
CIN1+										
HPV-16/18	1510 (4)	1547(12)	65.8	-18.8,92.6	0.0764	1699(6)	1763(19)	67.2	11.0,89.9	0.0147
HPV-16/18 TAA	1510 (0)	1547(10)	100	50.6,100	0.0019	1699(2)	1763(17)	87.8	45.8,98.8	0.0007
CIN2+										
HPV-16/18	1510(2)	1547(6)	65.8	-105.7,97.1	0.2887	1699(3)	1763(10)	68.8	-28.2,95.0	0.0924
HPV-16/18 TAA	1510(0)	1547(5)	100	-22.9,100	0.0624	1699(1)	1763(9)	88.5	10.8,99.8	0.0215

TAA=HPV type assignment algorithm

5.3.2.2.3. Efficacy in HPV-16/18 DNA positive women at baseline

Although *Cervarix* was not designed to be a therapeutic vaccine, efficacy against CIN in subjects HPV DNA positive at baseline for the type considered in the analysis was an exploratory objective. TVC-1 was used for this analysis; however, it should be noted that the randomization scheme used in the study did not take into account the HPV DNA or cytological status at baseline. These results are to be considered with caution, as the analysis was conducted in a subset of subjects (1,184 subjects HPV DNA positive at baseline) in the TVC-1 and included women with baseline cytological abnormalities. Nevertheless these evaluations provide relevant information on the efficacy profile of *Cervarix*.

As expected, the vaccine did not show a therapeutic effect in subjects HPV DNA positive at baseline for the type considered in the evaluation (Table 15).

Table 15 Study HPV-008: overview of vaccine efficacy against histological lesions associated with HPV-16/18 (by PCR) in HPV DNA positive subjects at baseline (TVC-1)

Endpoint	*Cervarix*		Control		Vaccine Efficacy		
	N	Cases	N	Cases	%	96.1% CI	P-value
HPV DNA positive subjects at baseline, irrespective of initial serostatus							
CIN2+	617	62	567	58	0.5	-47.7, 32.9	0.9235
CIN1+	617	72	567	76	13.0	-23.8, 38.9	0.3801
HPV DNA positive and seronegative subjects at baseline							
CIN2+	303	18	285	27	37.8	-20.9,68.8	0.1216
CIN1+	303	27	285	36	30.5	-20.9,60.5	0.1819
HPV DNA positive and seropositive subjects at baseline							
CIN2+	315	43	290	31	-32.5	-123.1,20.4	0.3205
CIN1+	315	44	290	40	-3.0	-66.0,35.9	1.0000

Further analyses were conducted on the broadest cohort, TVC. In this analysis, vaccine efficacy against HPV-16/18 CIN2+ was:

- 5.8% [-34.3, 33.9], p=0.7251 in DNA positive women (irrespective of initial serostatus),
- 35.2% [-22.2, 66.3], p=0.1374 in DNA positive and seronegative women, and
- -13.8% [-77.6, 26.7], p=0.5835 and in DNA positive and seropositive women.

In DNA positive and seropositive women, the number of CIN2+ cases was higher in the *Cervarix* group (15.9%; 53 of 333) as compared to control (14.3%; 44 of 307), but not significantly. This difference in the number of CIN2+ cases resulted in a vaccine efficacy of -13.8% [-77.6, 26.7], and could possibly be attributed to an imbalance in the baseline cytology diagnosis in this subgroup, with 155 women in the *Cervarix* group compared with 131 women in the control group who had baseline cytological abnormalities [Paavonen, 2009].

When looking at the overall number of subjects with abnormal cytology at entry progressing to CIN2+ (a total of 1484 subjects had abnormal cytology at baseline: 759 in the *Cervarix* group, 725 in the control group) there were 103 (13.6%) subjects in the

Cervarix group and 101 (13.9%) in the control group with progression to CIN2+. This suggests that overall, the progression of abnormal cytology to CIN2+ was similar in the two groups.

These data indicate that as expected, *Cervarix* did not protect against histopathological lesions caused by HPV-16/18 infections present at the time of vaccination. Conversely, there was no evidence that cervical disease caused by HPV-16/18 in these subjects was enhanced.

Vaccine efficacy in the clearance of HPV-16 or HPV-18 cervical infection

There was no significant difference between the vaccine and control group in the clearance rates of HPV-16/18 in HPV DNA positive subjects at baseline in Study HPV-008 (VE = -3.0% [-58.4, 32.9]), which indicates that *Cervarix* does not accelerate clearance or prolong HPV-16/18 infection already present at the time of vaccination. These data indicate the absence of a therapeutic effect of *Cervarix*, which has been developed as a prophylactic vaccine.

5.3.2.2.4. Vaccine efficacy associated with HPV-16 or HPV-18 in women infected prior to vaccination with the other vaccine HPV type

Vaccine efficacy against HPV-16/18 in subjects who are currently infected or have been previously infected with the other vaccine type at baseline (seropositive and/or DNA positive) was 80.3% [66.4, 89.2] $p<0.0001$ for 6-month persistent infection and 81.3% [8.9, 98.2], $p=0.0224$ for CIN2+ in TVC-1. Administration of *Cervarix* to a subject who has a genital infection with one HPV vaccine type does not affect the prophylactic efficacy of the vaccine against the other HPV vaccine type. As the proportion of women who are simultaneously infected with HPV-16 and HPV-18 was low in the study (<1% were infected with both HPV-16 and HPV-18 at baseline, see Figure 9), this finding indicates that the majority of the female population could benefit from protection against HPV-16/18 infection provided by the vaccine.

5.3.2.2.5. Efficacy regardless of initial HPV 16/18 DNA or serostatus at baseline

Vaccine efficacy against CIN2+ associated with HPV-16/18 regardless of HPV DNA status (current infection) and serostatus (prior infection) in TVC-1 was 55.6% [40.0, 67.5], $p<0.0001$, with 70 cases in the *Cervarix* group and 158 cases in the control group. It should be noted that many lesions were a result of infections that were present prior to vaccination.

5.4. Efficacy in a general population beyond HPV-16/18, HPV-008

5.4.1. Overall vaccine efficacy irrespective of the HPV type in the lesion

The impact of *Cervarix* against the overall burden of oncogenic HPV-related cervical disease results from a combination of prophylactic efficacy against HPV-16, HPV-18 and

non-vaccine oncogenic HPV types, and the contribution of these types to the endpoints evaluated.

Overall vaccine efficacy was assessed by looking at the total number of lesions in *Cervarix* and control groups, independently of the PCR results on these lesions. The overall efficacy was evaluated in several cohorts, but is presented below for two cohorts, the TVC and TVC naïve. These cohorts are presented as they represent the lower and upper range of the expected impact of the vaccine. Hence, the TVC includes all women who have received at least one dose of vaccine, regardless of their baseline HPV DNA, serostatus and cytology, thereby including women with prevalent infections/lesions. This cohort is representative of a population of women that would be targeted by catch-up vaccination programs. Conversely, the TVC-naive included women who received at least one dose of vaccine and who were HPV DNA negative for 14 oncogenic types, serologically negative for 16/18 and with normal cytology at baseline. The TVC naïve population is representative of the population that is targeted by routine vaccination (young adolescents before sexual debut).

In the broader TVC population, statistically significant overall vaccine efficacy was observed for CIN1+ and CIN2+ (Table 16). Vaccine efficacy was also observed for CIN1+ and CIN2+ in the TVC naïve sub-population, where higher point estimates of vaccine efficacy were observed. Using the endpoint closest to cervical carcinoma (CIN3+) which is less likely to regress compared with lower grade lesions [Ostor, 1993], vaccine efficacy was also demonstrated in both cohorts. Of note, the point estimates of efficacy increased with lesion severity, with the highest efficacy observed for CIN3+.

The overall efficacy of *Cervarix* was due to reductions in lesions caused by HPV-16 and HPV-18 in women HPV DNA negative and seronegative for the relevant HPV type, as well as reductions in disease caused by oncogenic HPV types beyond those included in the vaccine (i.e., cross-protective efficacy).

Cervarix prevented 70.2% [54.7, 80.9], $p<0.0001$ of all CIN2+ lesions and 87.0% [54.9, 97.7], $p<0.0001$ of all CIN3+ lesions in the TVC naïve population. It is expected that the proportion of lesions attributed to HPV-16/18 is approximately 52% for CIN2+ and 70% for CIN3+ [Smith, 2007]. The control group of HPV-008 provided an estimate of the proportion of CIN2+ lesions associated with HPV-16/18 in an unvaccinated population, which ranged from 31.6% (lesions with only HPV-16 and/or HPV-18 present) to 64.3% (lesions with HPV-16 and/or HPV-18 plus at least one additional HPV type). These efficacy point estimates for CIN2+ and CIN3+ therefore indicate that the efficacy of *Cervarix* extends beyond protection against HPV-16/18.

In HPV-001/007, a similar analysis showed an overall vaccine efficacy against CIN2+ of 71.9% (95% CI: [20.6; 91.9]), see Section 5.3.1.3. This corroborates the efficacy observed in HPV-008 with data up to 6.4 years. This point estimate is also in a range indicating vaccine efficacy beyond HPV-16/18.

These results are noteworthy as they provide an overall indication of efficacy, without regard to the HPV type or types in the lesion, and are therefore not confounded by multiple infections or limitations of HPV typing. As the vaccine is intended for use

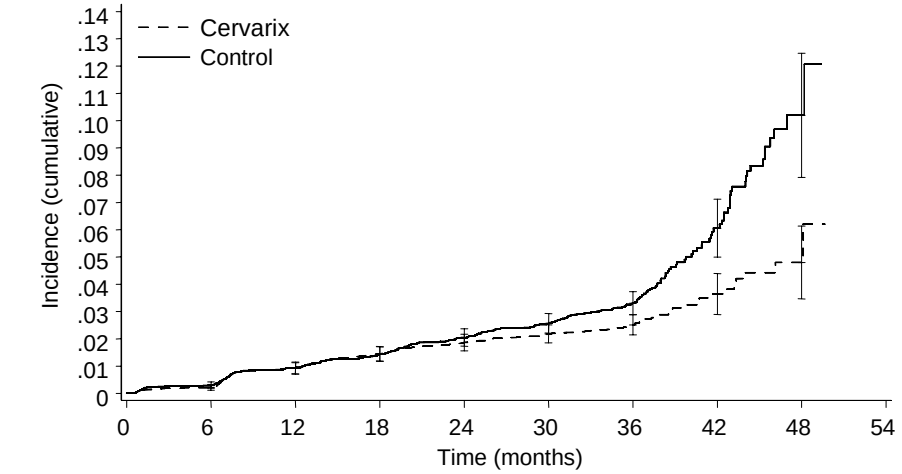
without screening, overall robust efficacy (irrespective of the HPV DNA type in the lesion) is an important clinical measure.

Table 16 HPV-008: Summary table of vaccine efficacy against CIN1+, CIN2+, and CIN3+ irrespective of HPV DNA in the lesion (TVC and TVC-naïve)

Endpoint	*Cervarix* N (Cases)	Control N (Cases)	Vaccine Efficacy		
			%	96.1% CI	P-value
TVC					
CIN1+	8667 (451)	8682 (577)	21.7	10.7, 31.4	<0.0001
CIN2+	8667 (224)	8682 (322)	30.4	16.4,42.1	<0.0001
CIN3+	8667 (77)	8682 (116)	33.4	9.1, 51.5	0.0058
TVC-naïve					
CIN1+	5449 (106)	5436 (211)	50.1	35.9, 61.4	<0.0001
CIN2+	5449 (33)	5436 (110)	70.2	54.7, 80.9	<0.0001
CIN3+	5449 (3)	5436 (23)	87.0	54.9, 97.7	<0.0001

Figure 11 presents the cumulative incidence of CIN2+, irrespective of HPV DNA results in the lesion in the broad Total Vaccinated Cohort to provide an overview of efficacy over time. The cumulative incidence curves for the *Cervarix* group and the control group follow a similar course for the first 18 months of follow-up time, likely indicating the detection of prevalent CIN2+ lesions or lesions resulting from oncogenic HPV infections already present at baseline (see Figure 10). The curves begin to separate after the Month 18 timepoint once an increasing number of lesions resulting from new infections (i.e., acquired after study entry) are detected. At the time of the final event-driven analysis the majority of subjects had completed the Month 30 visit. Data were available for approximately half of the subjects that had completed the Month 36 visit (3400 subjects in the *Cervarix* group and 3391 subjects in the control group) at the final analysis, and at this time point and thereafter the divergence in the curves illustrated the overall efficacy of the vaccine. As there were few subjects who attended the Month 42 visit or completed the study (Month 48 visit) at this time, the confidence intervals at these time points are larger, but are not overlapping between the groups.

Figure 11 Cumulative incidence curve for CIN2+ irrespective of HPV DNA results in all subjects, irrespective of their baseline HPV DNA and serostatus (Total Vaccinated Cohort)



Number at risk										
Cervarix	8667	8628	8414	8190	7796	7319	3400	622	72	0
Control	8682	8634	8412	8170	7795	7321	3391	700	62	0
Number of cases (cumulative)										
Cervarix	0	19	79	124	158	181	202	218	223	224
Control	0	26	81	122	173	212	261	301	321	322

Time in months represents the actual time from first vaccination to when the case was identified.

Cervarix was also shown to induce a significant reduction of cervical excision procedures [LEEP, Cone, Knife and Laser] in both the TVC and TVC-naïve populations.

Table 17 HPV-008: Vaccine efficacy in the reduction of cervical excision procedures (TVC and TVC-naïve)

Cohort	*Cervarix* N (Cases)	Control N (Cases)	Vaccine Efficacy		
			%	96.1% CI	P-value
TVC	8667 (180)	8682 (240)	24.7	7.4, 38.9	0.0035
TVC-naive	5449 (26)	5436 (83)	68.8	50.0, 81.2	<0.0001

5.4.2. Vaccine efficacy against non-vaccine oncogenic HPV types

5.4.2.1. Virological and histopathological combined endpoints associated with non-vaccine oncogenic HPV types

Pre-specified analyses of vaccine efficacy were conducted against composite endpoints of 14 combined oncogenic HPV types including HPV-16/18 (HR-HPV) and 12 combined oncogenic HPV types excluding HPV-16/18 (HRW-HPV).

Consistently high levels of statistically significant vaccine efficacy for histopathological and virological endpoints were observed in the HR-HPV analyses, with a VE against CIN2+ of 61.9% [46.7, 73.2], p<0.0001. High levels of statistically significant vaccine

efficacy for histopathological and virological endpoints were also observed for HRW-HPV, with a VE against CIN2+ of 54.0% [34.0, 68.4], p<0.0001.

As the analysis of vaccine efficacy for histopathological endpoints with HRW-HPV is complicated by co-infections of lesions with HPV-16/18, a post hoc analysis of efficacy was performed, in which lesions containing non-vaccine types were excluded if they were co-infected with HPV-16 and/or HPV-18. This analysis is conservative as it automatically allocates all cases containing non-vaccine type HPV DNA with HPV-16/18 co-infections as being caused by HPV-16/18. Of the 50 cases in the *Cervarix* group and 109 cases in the control group, 2 cases in the *Cervarix* group and 32 cases in the control group were co-infected with HPV-16/18, hence 48 cases in the *Cervarix* group and 77 cases in the control group were infected with at least one non-vaccine oncogenic HPV type with no co-infection with HPV-16/18. Vaccine efficacy against CIN2+ associated with HRW-HPV excluding HPV-16/18 co-infection was also statistically significant, 37.4% [7.4, 58.2], p=0.0092 (Figure 12).

Globally, 70% of cervical cancer is estimated to be caused by HPV-16/18 with the remaining 30% caused by other oncogenic HPV types [Bosch, 2008]. Therefore, with VE against CIN2+ associated with HRW-HPV ranging from 37-54%, the cross-protective efficacy of *Cervarix* would represent 11-16% protection against cervical cancer in addition to the protection afforded by efficacy against HPV-16/18.

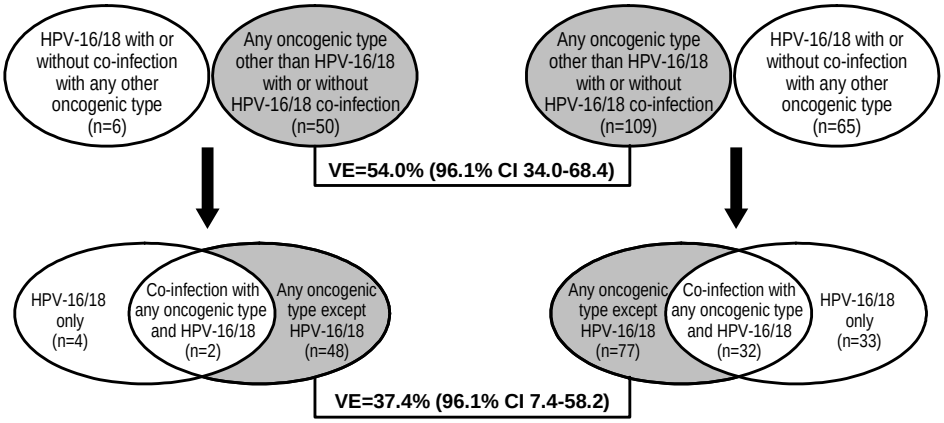
The 'HRW-HPV' and 'HRW-HPV excluding HPV-16/18 co-infection' analyses should be considered together to determine the potential extent (upper and lower limits of range) of cross-protection afforded by *Cervarix* and the overall impact on vaccine efficacy against CIN2+ lesions.

Table 18 HPV-008: Summary of vaccine efficacy against histopathological and virological endpoints associated with 14 oncogenic HPV types (by PCR) in HPV DNA negative subjects at baseline (ATP cohort for efficacy)

Endpoint	*Cervarix* N (Cases)	Control N (Cases)	Vaccine Efficacy %	96.1% CI	P-value
Associated with HR-HPV					
Persistent infection (6-month)	7665 (1271)	7640 (1647)	25.0	18.9, 30.6	<0.0001
CIN1+	7863 (151)	7853 (279)	45.9	33.1, 56.4	<0.0001
CIN2+	7863 (54)	7853 (142)	61.9	46.7, 73.2	<0.0001
Associated with HRW-HPV					
Persistent infection (6-month)	7665 (1247)	7640 (1406)	12.1	4.7, 19.0	0.0005
CIN1+	7863 (146)	7853 (233)	37.3	21.7, 49.9	<0.0001
CIN2+	7863 (50)	7853 (109)	54.0	34.0, 68.4	<0.0001
Associated with HRW-HPV excluding HPV-16/18 co-infections					
CIN2+	7863 (48)	7853 (77)	37.4	7.4,58.2	0.0092

HR-HPV= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
HRW-HPV = All high-risk (oncogenic) HPV types other than HPV-16 and HPV-18 (HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68)
HRW-HPV excluding HPV-16/18 co-infections = All high-risk (oncogenic) HPV types other than HPV-16 and HPV-18 and excluding lesions with HPV-16/18 co-infections

Figure 12 HPV-008: Vaccine efficacy against CIN2+ associated with 14 oncogenic HPV types (by PCR) in HPV DNA negative subjects at baseline, accounting for co-infections with HPV-16/18 (ATP cohort for efficacy)



5.4.2.2. Virological and histopathological endpoints associated with individual non-vaccine oncogenic HPV types

As the importance of individual oncogenic HPV types in cervical cancer varies, vaccine efficacy against individual types was also evaluated to have a more complete understanding of cross-protection. Cross-protection was evaluated by considering both histopathological and virological endpoints across different study cohorts. Analyses for histopathological endpoints considered detection of HPV DNA in lesions with or without HPV-16/18 co-infections. Unlike histopathological endpoints (e.g. CIN2+), virological endpoints (e.g. persistent infection) are not complicated by multiple infections and are therefore valuable to evaluate cross-protection [Jenkins, 2008; Koshiol, 2008]. Table 19 presents data for each of the 12 non-vaccine oncogenic types.

Table 19 HPV-008: Vaccine efficacy against CIN2+ and 6-month persistent infection associated with specific oncogenic HPV types (by PCR) in subjects HPV DNA negative at baseline (ATP cohort for efficacy)

HPV Type	6-month persistent infection				CIN2+			
	Cervarix/ Control Cases	Vaccine Efficacy			*Cervarix*/ Control Cases	Vaccine Efficacy		
		%	96.1% CI	P-value		%	96.1% CI	P-value
HPV-16 related types								
HPV-31	46/215	78.7	(70.2,85.2)	<0.0001	2/25	92.0	66.0, 99.2	<0.0001
HPV-33	67/123	45.7	(25.1,60.9)	<0.0001	12/25	51.9	-2.9,78.9	0.0332
HPV-35	56/46	-22.2	(-88.5, 20.4)	0.3714	1/6	83.3	-49.1, 99.7	0.0702
HPV-52	314/339	7.8	(-8.7, 21.8)	0.2796	12/14	14.3	-108.1, 65.4	0.7000
HPV-58	144/147	1.8	(-26.0, 23.4)	0.8592	6/17	64.5	1.5, 89.2	0.0225
HPV-18 related types								
HPV-39	147/149	1.0	(-26.7, 22.7)	0.9066	3/10	69.8	-24.2, 95.2	0.0921
HPV-45	23/94	75.7	(60.4, 85.7)	<0.0001	0/4	100	-67.8,100	0.0619
HPV-59	97/111	12.4	(-17.8, 34.9)	0.3291	1/4	74.9	-178.6, 99.6	0.3749
HPV-68	138/134	-3.1	(-33.4, 20.3)	0.8545	5/11	54.4	-49.8, 88.4	0.1428
Other types								
HPV-51	304/354	14.5	(-0.8,27.4)	0.0418	10/27	62.9	18.0,84.7	0.0050
HPV-56	182/174	-5.0	(-31.5, 16.1)	0.7075	4/10	59.9	-47.1, 91.5	0.1181
HPV-66	168/178	5.7	(-18.4, 24.9)	0.5501	4/10	60.0	-46.7, 91.6	0.1176

Note: Results shown in grey are statistically significant. CIN2+ analyses considered detection of HPV DNA in lesions with or without HPV-16/18 co-infections.

To further evaluate the protection against the individual oncogenic HPV types, the vaccine efficacy of the five non-vaccine HPV types most commonly associated with ICC (HPV-31, -33, -45, -52, and -58) [Smith, 2007] is presented in Table 20. Results are presented for several cohorts to provide perspective on the expected protection in different populations that will benefit from vaccination.

Table 20 HPV-008: Vaccine efficacy against histopathological and virological endpoints associated with HPV-31, 33, 45, 52 and 58 (by PCR) in subjects HPV DNA negative at baseline

HPV Type	Endpoint	ATP cohort for efficacy			TVC-1			TVC naïve			TVC		
		%	96.1% CI	P-value	%	96.1% CI	P-value	%	96.1% CI	P-value	%	96.1% CI	P-value
HPV-31	6M PI	78.7	70.2, 85.2	<0.0001	66.9	57.6,74.4	<0.0001	77.5	66.1,85.5	<0.0001	67.2	57.9, 74.6	<0.0001
	12M PI	79.4	66.1, 88.1	<0.0001	62.3	46.9, 73.6	<0.0001	72.9	51.7, 85.6	<0.0001	65.6	47.4,73.8	<0.0001
	CIN1+	87.7	70.2, 95.9	<0.0001	69.0	46.9, 82.8	<0.0001	90.0	66.5, 98.2	<0.0001	69.5	47.8, 83.0	<0.0001
	CIN2+	92.0	66.0, 99.2	<0.0001	67.4	32.0,85.7	0.0008	100	78.3,100	<0.0001	68.4	34.2, 86.1	0.0005
HPV-33	6M PI	45.7	25.1, 60.9	<0.0001	42.2	24.3,56.1	<0.0001	43.5	18.6,61.2	0.0008	39.9	21.6, 54.1	<0.0001
	12M PI	38.0	-1.4, 62.6	0.0344	36.8	6.3, 57.8	0.0146	27.3	-22.2, 57.3	0.1916	35.0	4.2, 56.3	0.0202
	CIN1+	38.1	-13.0, 66.9	0.0806	38.9	-2.3, 64.2	0.0469	62.0	7.2, 86.2	0.0159	37.2	-3.5, 62.6	0.0530
	CIN2+	51.9	-2.9, 78.9	0.0332	49.8	2.9,75.2	0.0291	72.3	19.1,92.5	0.0065	49.8	4.8, 74.6	0.0239
HPV-45	6M PI	75.7	60.4, 85.7	<0.0001	71.6	57.6,81.5	<0.0001	81.4	64.3,91.2	<0.0001	72.1	58.3, 81.8	<0.0001
	12M PI	63.0	18.4, 84.7	0.0049	55.8	20.4, 76.4	0.0022	79.1	34.2, 95.2	0.0015	55.8	20.4, 76.4	0.0022
	CIN1+	91.7	39.9, 99.9	0.0018	93.3	53.8, 99.9	0.0005	90.0	25.1, 99.8	0.0063	94.1	60.1, 99.9	0.0001
	CIN2+	100	-67.8, 100	0.0619	100	-20.2,100	0.0625	100	-19.5,100	0.0310	100	7.0, 100	0.0312
HPV-52	6M PI	7.8	-8.7, 21.8	0.2796	10.6	-3.1,22.5	0.0942	21.0	3.6,35.3	0.0127	11.0	-2.6, 22.8	0.0820
	12M PI	-4.7	-34.3, 18.3	0.7679	6.0	-15.7, 23.7	0.5183	6.3	-26.2, 30.4	0.6730	6.0	-15.6, 23.6	0.5193
	CIN1+	34.2	-10.3, 61.3	0.0789	35.4	-0.9, 59.1	0.0411	43.0	-4.4, 69.8	0.0433	33.1	-3.6, 57.3	0.0561
	CIN2+	14.3	-108.1,65.4	0.7000	-0.4	-117.1, 53.6	1.0000	36.5	-88.4,80.3	0.3583	-0.4	-111.9, 52.5	1.0000
HPV-58	6M PI	1.8	-26.0,23.4	0.8592	0.5	-24.1,20.3	0.9579	3.7	-31.7,29.6	0.8250	0	-24.7, 19.8	1.0000
	12M PI	-14.9	-70.7,22.5	0.5213	-17.0	-64.6, 16.6	0.3413	-24.5	-110.0, 25.6	0.4082	-18.2	-65.7, 15.6	0.3070
	CIN1+	67.5	32.2, 85.8	0.0005	48.4	8.3, 71.9	0.0150	71.5	23.9, 91.2	0.0036	49.7	10.8, 72.5	0.0110
	CIN2+	64.5	1.5, 89.2	0.0225	49.6	-17.1,79.9	0.0985	72.8	-8.9,95.6	0.0348	49.6	-17.1, 79.9	0.0985

6M PI = 6-month persistent infection; 12M PI = 12-month persistent infection; Note: Results shown in grey are statistically significant. CIN1+ and CIN2+ analyses considered detection of HPV DNA in lesions with or without HPV-16/18 co-infections.

Type-specific cross protection was observed for several non-vaccine HPV types (Table 20). A high level of protection was observed for HPV-31, HPV-45 and HPV-33.

For HPV-31, data were consistent for all endpoints evaluated, including CIN2+ and persistent infection in all cohorts. In the TVC, vaccine efficacy was also significant (68.4% [34.2, 86.1], p=0.0005) among women who were HPV-31 negative at baseline.

The evaluation of vaccine efficacy against HPV-45 is limited by the low prevalence of HPV-45 in CIN2+ lesions, whereas its prevalence is higher in cervical cancer [Bosch, 2008; Wheeler, 2009]. Vaccine efficacy against persistent infection with HPV-45 was highly significant as well as vaccine efficacy against CIN1+. As expected, the number of CIN2+ associated with HPV-45 was limited, with vaccine efficacy of 100% [-67.7, 100] p=0.0619 in ATP and 100% [-20.2, 100], p=0.0625 in TVC-1. In the broadest cohort (TVC), vaccine efficacy reached statistical significance with 100% [7.0, 100], p=0.0312 among women who were HPV-45 DNA negative at baseline.

There was also consistent evidence of protection against HPV-33 associated endpoints, although statistical significance was not reached in all analyses. In the TVC, vaccine efficacy against CIN2+ associated with HPV-33 was significant (49.8% [4.8, 74.6], p=0.0239) among women who were HPV-33 negative at baseline.

No consistent evidence of cross protection was observed for HPV-52 or HPV-58 or for any of the other oncogenic HPV types.

5.5. Methods used to evaluate the immune response

5.5.1. Evaluation of the humoral antibody response

The primary immunogenicity assessment in GSK's HPV program was based on the measurement of anti-HPV-16 and anti-HPV-18 IgG antibodies by ELISA, where HPV-16 and HPV-18 VLP antibodies (anti-VLP-16 and anti-VLP-18) were quantified by ELISA using either HPV-16 or HPV-18 VLPs as coated antigens. A seropositive subject is a subject whose titer is greater than or equal to the cut-off value (≥ 8 EL.U./mL for HPV-16 and ≥7 EL.U./mL for HPV-18). Seroconversion was defined as the appearance of antibodies (i.e., titer greater than or equal to the cut-off value) in the serum of a subject seronegative before vaccination.

The pseudovirion based neutralization assay (PBNA) was developed by the NCI [Pastrana, 2004] and measures biologically relevant antibodies. It is recommended for use by the WHO for assay harmonization, and implemented by GSK Biologicals. The assay cut-off value for PBNA is 40 ED_{50} for HPV-16 and HPV-18. Neutralizing assays have a limited throughput rendering their use in large scale clinical trials difficult. However, PBNA was used to validate the ELISA, with an excellent correlation demonstrated between the GSK binding ELISA and PBNA for the immune responses elicited by *Cervarix* [Dessy, 2008].

Of note, HPV-16 and HPV-18 assays have each been defined against two independent sets of internal references and thus comparison of results between HPV types is not valid.

Additional evaluations to characterize the immune response are detailed in Sections 5.5.2 and 5.5.3.

5.5.2. Assessment of the immune response in cervico-vaginal secretions

IgG is the predominant form of Ig found in vaginal secretions. It is thought that most cervical IgG is serum-derived [Franklin, 1999].

The immune response at the level of the cervix was assessed by measuring anti-HPV-16 and anti-HPV-18 IgG antibodies in cervico-vaginal secretions (CVS) following HPV-16/18 vaccination and comparing the antibody levels by ELISA with the corresponding serum antibody levels. For each subject, both serum and CVS vaccine-specific IgG titers were normalized against the total serum and CVS IgG titers of that same subject (HPV-16 and HPV-18 IgG divided by the total amount of IgG for each sample) in order to account for variations during the menstrual cycle.

5.5.3. Cell-mediated immunity assays

B-cell memory response was evaluated by B-cell Elispot technology. The B-cell Elispot technology allows the quantitation of B-cell memory specific to a given antigen. The B-cell Elispot assay used was adapted from the assay developed by the Lanzavecchia laboratory [Bernasconi, 2002].

T-cell immunity was assessed using (1) lymphoproliferation assay and/or (2) cytokine production (evaluation of cytokines Interleukin (IL)-5 and IFN-γ in culture supernatant by ELISA) and/or (3) evaluation of CD4 and CD8 T-cell responses detected by intracellular staining assay [for expression of CD40L, IFN-γ, IL-2 and tumor necrosis factor-α (TNF-α)].

5.5.4. Statistical methods for immunogenicity analyses

The primary analysis of vaccine immunogenicity was performed in each study on the ATP cohort for immunogenicity. One of the elimination criteria for the ATP immunogenicity cohort in the efficacy studies (Studies HPV-001, HPV-007 and HPV-008) was presence of a concomitant infection related to the vaccine which may influence immune response, i.e. intercurrent HPV infection.

In Study HPV-012 (immunological bridging study in 10-14 year old girls), two criteria for non-inferiority were assessed sequentially: HPV-16 and HPV-18 seroconversion rates and geometric mean titer (GMT) ratios. The criterion for clinical non-inferiority was based on a 10% margin of non-inferiority for seroconversion rates and less than a two-fold difference in GMTs between groups.

5.6. Immune response in women 15-25 years of age

5.6.1. Natural Infection

Antibody titers produced in response to natural infection for ELISA were assessed in the subset of women enrolled into Study HPV-008, who had successfully cleared an HPV infection prior to enrollment and had mounted an immune response to natural infection (i.e., HPV DNA negative and seropositive for HPV-16/-18 at baseline). The level of anti-HPV-16 antibody was 29.8 EL.U./mL [28.6; 31.0] and the level of anti-HPV-18 antibody was 22.6 EL.U./mL [21.6; 23.6].

Antibody titers produced in response to natural infection for PBNA were assessed in HPV-010 (an ongoing Phase IIIb study) in women who had successfully cleared an HPV infection prior to enrollment and had mounted an immune response to natural infection (i.e., HPV DNA negative and seropositive for HPV-16/-18 at baseline). The level of anti-HPV-16 antibody was 180.1 ED_{50} [153.3, 211.4] and the level of anti-HPV-18 was 137.3 ED_{50} [112.2, 168.0].

As antibody levels induced by clearance of a natural infection do not reliably protect against subsequent infections, antibody levels induced by vaccination should be higher in order to confer long-term protection [Einstein, 2009].

5.6.2. Peak immune response one month after 3rd vaccine dose

In Study HPV-008, GMTs for ELISA and PBNA at Month 7 (one month after the third dose) are shown in Table 21. Of subjects seronegative at baseline, 99.5% had seroconverted for anti-HPV-16 and anti-HPV-18 at Month 7 in the *Cervarix* group as measured by both assays.

Table 21 HPV-008: GMTs for anti-HPV-16 and anti-HPV-18 antibodies at Month 7 in subjects seronegative at baseline (binding ELISA and PBNA) (ATP cohort for immunogenicity)

	Cervarix			Control		
	N	% Seropositive	GMT (95% CI)	N	% Seropositive	GMT (95% CI)
	ELISA (EL.U./mL)					
HPV-16	861	99.5	9,206.4 (8,607.2, 9,847.2)	738	4.6	4.4 (4.2, 4.6)
HPV-18	924	99.5	4,744.6 (4,454.1, 5,053.9)	769	4.0	3.8 (3.6, 3.9)
	PBNA (ED_{50})					
HPV-16	46	100	27364.8 (19780.1,37857.9)	44	0	20.0 (20.0, 20.0)
HPV-18	46	100	9052 (6851.8, 11960.5)	44	0	20.0 (20.0, 20.0)

5.6.3. Kinetics of the immune response including persistence in women 15-25 years, HPV-001/007

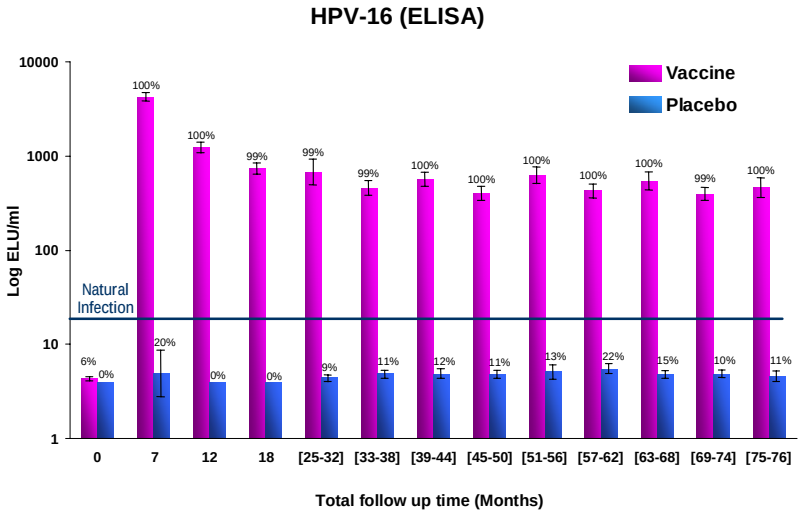
In the absence of a correlate of protection, immunogenicity data from HPV-001 and its long-term follow-up (HPV-007) are valuable as these antibody levels are known to be associated with clinical protection for up to 6.4 years (Figure 13). The plateau phase of

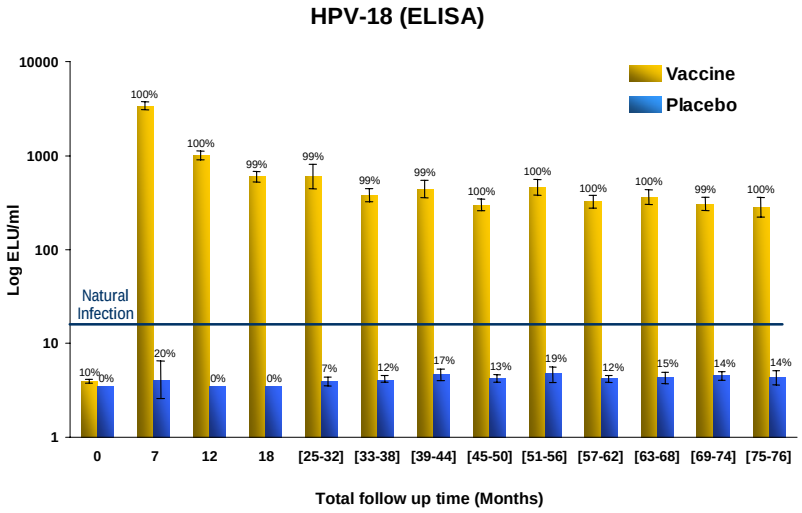
the immune response therefore provides a biological basis for protection. Figure 13 shows the kinetic profiles of HPV-16 and HPV-18 as measured by ELISA. Up to 76 months following first vaccination, 98% or more of the vaccinees remained seropositive for both HPV-16 and HPV-18. For both antigens, the GMTs showed a plateau between Months 18 and the last time intervals evaluated (Months 69-74 and 75-76) at approximately one log below the peak response without substantial evidence of further decline. GMTs were at least 11-fold higher than GMTs observed after natural infection. The kinetic profiles of the HPV-16 and HPV-18 responses were very similar.

Figure 14 shows the kinetic profiles of HPV-16 and HPV-18 as measured by PBNA in a subset of subjects. The GMTs for both HPV-16 and HPV-18 with PBNA showed a similar kinetic profile as with the ELISA, with at least 98% of subjects seropositive throughout the follow-up.

Statistical models predict that antibody levels will remain above levels induced by natural infection for at least 20 years [David, 2009].

Figure 13 Studies HPV-001/007: Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies (binding ELISA) (ATP cohort for immunogenicity)

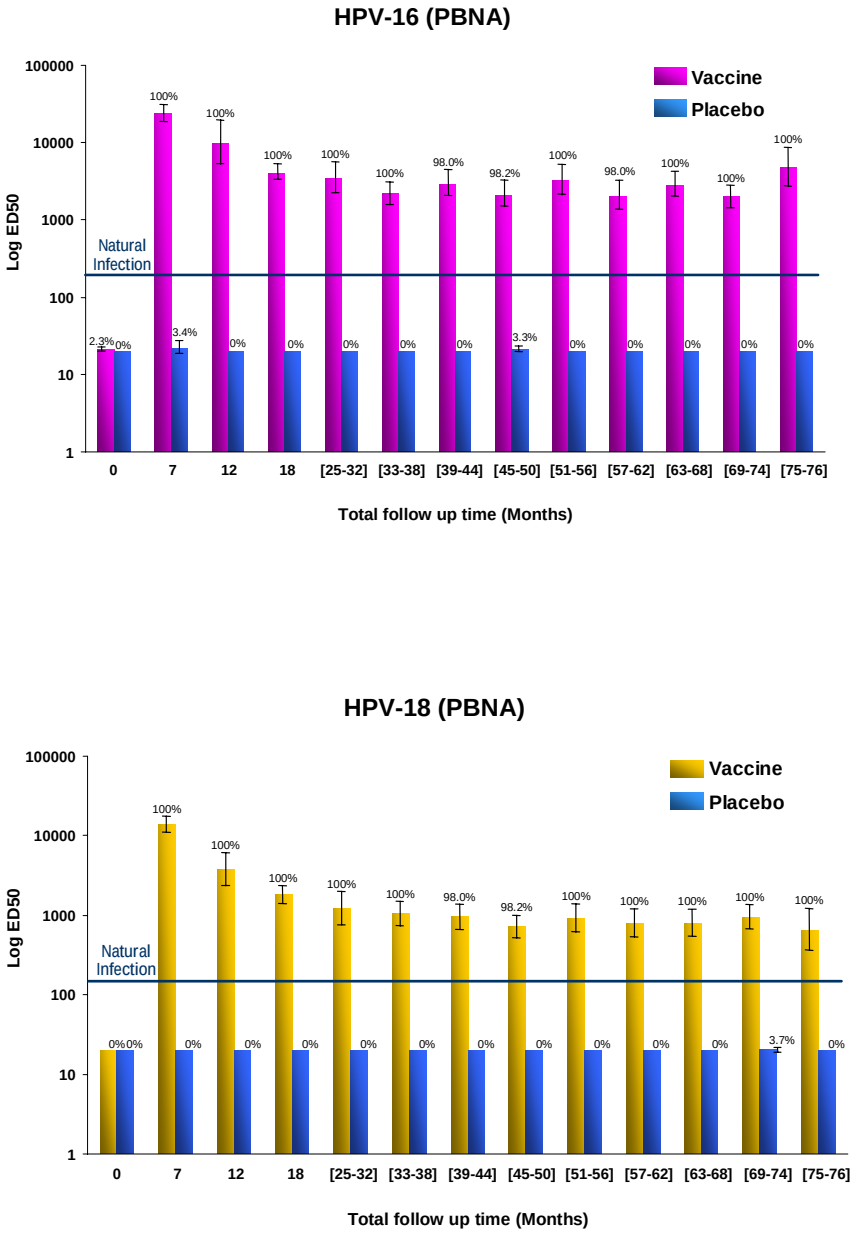




Percentages of subjects that were seropositive are shown above bars.

Percentages of subjects that were seropositive are shown above bars. 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 sera samples of subjects in Study HPV-008 who were seropositive and HPV DNA negative for the respective HPV type (29.8 EL.U./mL for HPV-16 and 22.6 EL.U./mL for HPV-18).

Figure 14 Studies HPV-001/007: Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies (PBNA) (ATP cohort for immunogenicity)



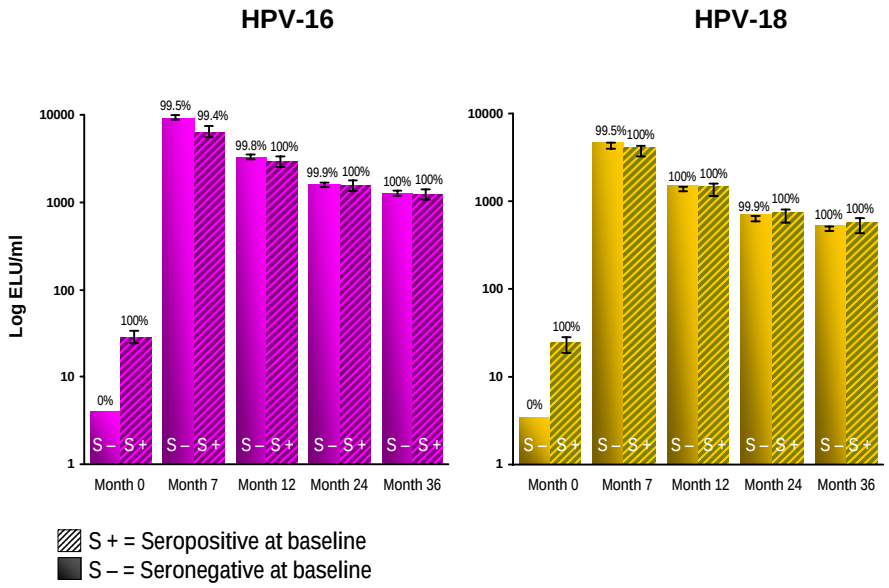
Percentages of subjects that were seropositive are shown above bars.

Percentages of subjects that were seropositive are shown above bars. 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 sera samples of subjects in Study HPV-010 (an ongoing Phase 3b study) who were seropositive and HPV DNA negative for the respective HPV type (180.1 ED_{50} for HPV-16 and 137.3 ED_{50} for HPV-18).

5.6.4. Immune response stratified by initial serostatus, HPV-008

In HPV-008, HPV-16 and HPV-18 immunogenicity was assessed in a subset of 1,933 subjects. At baseline, approximately 16% and 11% of subjects were seropositive to HPV-16 and HPV-18 respectively in this subset. Seropositivity rates and GMTs at Month 7, 12, 24 and 36 were similarly high for initially seronegative and seropositive subjects (Figure 15).

Figure 15 Study HPV-008: Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies by pre-vaccination status in subjects receiving *Cervarix* (binding ELISA) (ATP cohort for immunogenicity)



Percentages of subjects that were seropositive are shown above bars.

These results show that *Cervarix* is highly immunogenic regardless of baseline serostatus.

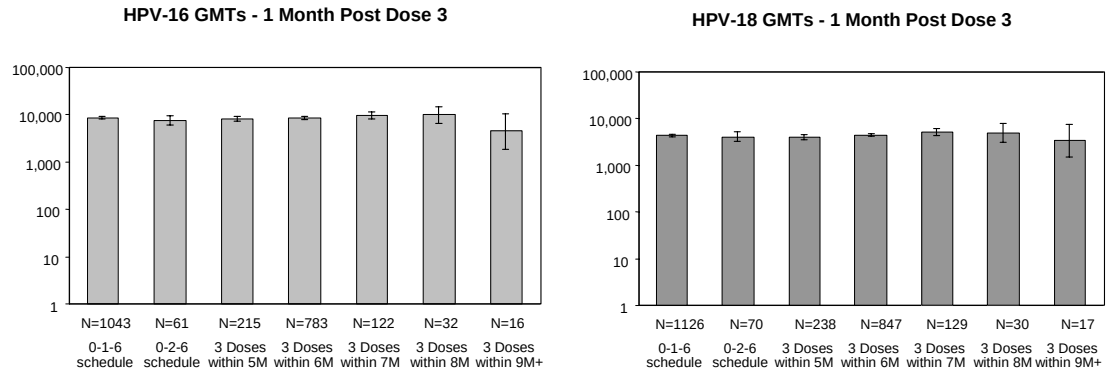
5.6.5. Analysis of a flexible dosing schedule

In Study HPV-008, GMTs in subjects receiving the second dose between 15 and 45 days after the first dose (corresponding to a 0, 1, 6 month schedule) were similar to GMTs in subjects receiving the second dose between 46 and 75 days after the first dose (corresponding to a 0, 2, 6 month schedule) for HPV-16 and HPV-18.

An additional analysis comparing the GMTs in subjects receiving all three doses within 5, 6, 7, 8 and 9 or more months (of note, only a small number of subjects were available for analysis of all three doses within 9 or more months) showed that the immune response against HPV-16 and HPV-18 elicited in subjects receiving *Cervarix* within all these timeframes was similar.

If flexibility in the schedule is required, these data support the administration of the second dose between 1 and 3 months after the first dose and administration of the third dose between 5 and 9 months after the first dose.

Figure 16 Study HPV-008: GMTs by schedule for anti-HPV-16 and anti-HPV-18 antibodies one month after Dose 3 in initially seronegative subjects receiving *Cervarix* (binding ELISA) (Total Vaccinated Cohort, subset of subjects receiving all 3 doses)

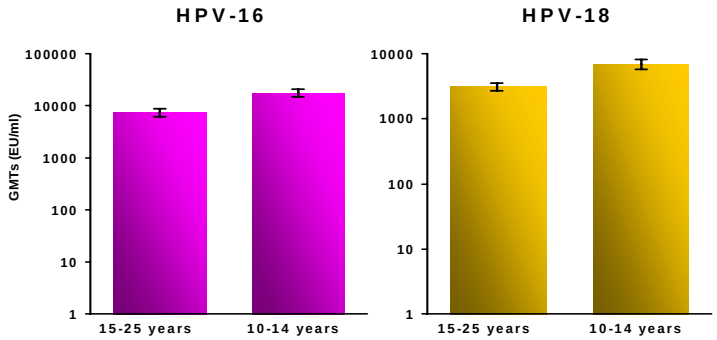


5.7. Immunological bridge to girls 10-14 years

The safety and immunogenicity of the vaccine in girls 10-14 years of age was evaluated in a total of 2,225 subjects in two Phase 3 studies (HPV-012 and HPV-013), with 1,193 subjects receiving *Cervarix*.

Study HPV-012 included both subjects 10-14 years of age and subjects 15-25 years of age and thus allowed a direct comparison of the immune responses to the vaccine between these two age groups. In the younger age group (10-14 years), *Cervarix* was highly immunogenic with 100% seroconversion rate to HPV-16 and HPV-18 and antibody titers at least 2-fold higher than in 15-25 year old subjects (Figure 17). Non-inferiority of the immune response was demonstrated in 10-14 year olds as compared with 15-25 year olds for both seroconversion rates (upper limit of the CI was less than the pre-defined limit of 10%; 2.62 for HPV-16 and 2.65 for HPV-18) and GMT ratio (the upper limit of the 2-sided 95% CI less than the predefined limit of 2; 0.53 for HPV-16 and 0.55 for HPV-18).

Figure 17 Study HPV-012: GMTs for anti-HPV-16 and anti-HPV-18 at Month 7 for 10-14 year olds and 15-25 year olds receiving *Cervarix* (binding ELISA) (ATP cohort for immunogenicity)



The robust immunogenicity in the 10-14 year age group was confirmed in a large subset (N=1341) of subjects in Asia, Latin America and Europe from Study HPV-013. The racial and ethnic distribution in this female population included White/Caucasian (34.3%), Asian (Chinese, 16.1%) and Hispanic (44.3%) girls. In this study, the kinetic profile of antibody responses was similar to HPV-001/007 with peak GMTs for HPV-16 and HPV-18 at Month 7 followed by sustained antibody levels up to Month 18 (Table 22).

Table 22 Study HPV-013 Ext: GMTs for anti-HPV-16 and anti-HPV-18 antibodies (binding ELISA) in subjects receiving *Cervarix* (ATP cohort for immunogenicity)

Antibody	Timing	N	GMT (EL.U./mL)		
			Value	95%	
				LL	UL
HPV-16	Month 7	619	19882.0	18626. 7	21221.9
	Month 18	556	3888.8	3605.0	4195.0
HPV-18	Month 7	628	8262.0	7725.0	8836.2
	Month 18	562	1539.4	1418.8	1670.3

GMTs at Month 18 in the 10 to 14 year olds were 4.8-fold and 3.2-fold higher for HPV-16 and HPV-18, respectively than the antibody levels observed during the plateau phase of Study HPV-007 (for which sustained efficacy has been demonstrated) and far higher than those observed after natural infection (107.5-fold and 59.3-fold higher for HPV-16 and HPV-18, respectively). These data suggest that *Cervarix* will be effective in girls 10 to 14 years of age and that protection will be sustained for at least several years.

5.8. Further characterization of the immune response

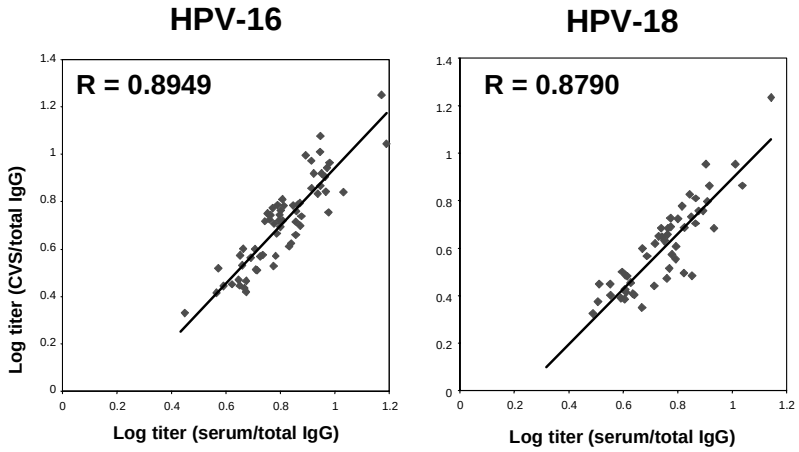
5.8.1. Antibodies in cervico-vaginal secretion samples

Pre-clinical studies and studies in humans strongly suggest that vaccine-induced serum neutralizing antibody responses are an important, if not an essential factor in providing

protection against oncogenic HPV cervical infections. It is widely accepted that IgG is the main immunoglobulin in the female genital tract, and that the transfer of serum antibodies into the cervical secretions is likely to be an important mechanism of protection against cervical HPV infection [Schwarz, 2009]. It is anticipated that the higher the systemic immune response elicited by a parenterally administered vaccine, the higher the level of transferred antibodies and, as consequence, the better the protection.

Induction of anti-HPV-16 IgG and anti-HPV-18 IgG in cervico-vaginal secretions after vaccination with *Cervarix* was assessed in a subset of vaccinees in 2 studies (HPV-005 and HPV-014) in women aged 15-55 years [Schwarz, 2009]. The presence and level of antibodies in the CVS were shown to be well correlated to serum antibodies (Figure 18). In a study of women 15 to 55 years of age (HPV-014), more than 73% for HPV-16 and 61% for HPV-18 had detectable antibodies in CVS at Month 18. As antibody detection is technically more difficult and less sensitive in CVS than serum, seropositivity rates are lower in CVS than serum.

Figure 18 Study HPV-014: Correlation between serum and cervical secretion antibody titers for HPV-16 and HPV-18 at Month 18 (standardized for total IgG) (Total Vaccinated Cohort - subset)



The presence and level of antibodies in CVS shown to highly correlate with serum antibodies, suggest that the specific HPV-16 and HPV-18 IgG antibodies detected in CVS after vaccination with *Cervarix* result from transfer to the site of infection.

5.8.2. Cell-mediated immune response

For all age groups targeted for vaccination, and especially pre-adolescents and adolescents, the generation of long-lasting immunity is an important consideration. The kinetics of the humoral immune response suggests the generation of long-lived plasma cells and the induction of memory B-cells that replenish the plasma pool [Lanzavecchia,

2005, Bernasconi, 2002]. HPV-specific B-cell memory and central memory T-cell mediated immunity have been assessed in the development program.

5.8.2.1. B-cell mediated immunity

The B-cell mediated immunity was evaluated by B-cell Elispot technology in 2 early development studies [HPV-004 (adjuvant comparison study) and HPV-005 (dose-ranging study) (see Figure 7)] as well as one study from an investigational tetravalent HPV program in which 69 subjects received *Cervarix* in the control arm. In this group, ≥ 90% of subjects receiving *Cervarix* had specific B-cell responses to HPV-16 and 18 one month post-vaccination, with a significant boost in the frequencies of specific memory B-cells after the third dose. The long-term presence of HPV-16 and HPV-18 specific memory B-cell responses were observed up to 2 years following first vaccination was demonstrated in Study HPV-004.

5.8.2.2. T-cell mediated immunity

During clinical development of the vaccine, T-cell-mediated immunity was evaluated in terms of lymphoproliferation responses and in terms of cytokine production. The pooled analysis of Studies HPV-004 and HPV-005 showed that significant specific CD4 T-cell responses were induced and persisted for up to 2 years following HPV vaccination, suggesting that central memory T-cells are induced following HPV vaccination. One study from an investigational tetravalent HPV program used *Cervarix* as the control arm. In this study, CD4 specific responses were induced to HPV-16 and HPV-18 in the *Cervarix* group.

5.9. Absence of immune correlates of protection

The adjuvant and VLPs selected for inclusion in the vaccine were designed to produce a high and sustained immune response to vaccine types. In the absence of an established correlate of protection, it was believed that this approach would be most likely to: 1) result in a high level of protection against HPV-16 and 18 outcomes of long duration; 2) provide some degree of cross protection against phylogenetically-related oncogenic HPV types.

The clinical program has demonstrated high level protection against HPV-16 and 18 outcomes as well as protection against endpoints associated with some important phylogenetically related non-vaccine oncogenic types, with a consistent pattern of efficacy observed against virological and histopathological endpoints for HPV-16, 18, 31, 33 and 45 (see Section 5.4.2). Types 31, 33, and 45 have a close phylogenetic relationship to vaccine types, with HPV-31 and HPV-33 related to HPV-16 and HPV-45 related to HPV-18.

The cross protective efficacy for these types is likely due to their phylogenetic similarity to vaccine types. The proprietary adjuvant system AS04 and the structural properties of the vaccine's VLPs are also likely to be factors contributing to the cross-protective effect of *Cervarix*. Cross-protection could theoretically be mediated by induction of cross-

reactive antibody responses and/or by cross-reactive T- or B-cell responses to specific epitopes on the VLPs.

GSK Biologicals is currently in the process of investigating the humoral and cell mediated immune responses to vaccine and non-vaccine types in several studies. However, since cross protective epitopes have not yet been mapped, relevance of available immunological data on non-vaccine responses has not been determined. Nevertheless, the use of HPV-16 and 18 immunological data as a bridging tool is considered valid for extrapolation of efficacy to other target populations (e.g., 10-14 year old girls) and has been accepted for other vaccines (e.g., *Gardasil*).

5.10. Efficacy and immunogenicity conclusions

Prophylactic efficacy against HPV Types 16 and 18 (Studies HPV-001/007 and HPV-008)

- In the 'general' population of Study HPV-008, a high level of protection was demonstrated against CIN2+ lesions associated with HPV-16/18 with vaccine efficacy of 92.9% for the primary endpoint (98.1% with the type assignment algorithm). Additionally, protection was shown for CIN3+ (the immediate precursor to cervical cancer) with vaccine efficacy of 80.0% (100% with type assignment algorithm) and CIN1+ with vaccine efficacy of 91.7% (97.8% with type assignment algorithm) in the ATP cohort for efficacy.
- *Cervarix* also demonstrated a high level of protection against cytological abnormalities, specifically ≥ASC-US, and virological endpoints (HPV-008).
- In the HPV 'naïve' population of Study HPV-001/007, *Cervarix* demonstrated a high level of efficacy (up to 100%) for CIN2+, CIN1+, virological endpoints and cytological abnormalities for up to 6.4 years from first vaccination, without evidence of waning protection over time.

Efficacy against HPV Types 16 and 18, regardless of current infection or prior exposure to HPV-16 or HPV-18 (Study HPV-008)

- *Cervarix* was efficacious in the prevention of CIN2+ in a population of women regardless of HPV DNA status (current infection) and serostatus (prior exposure).
- In subjects who were HPV DNA negative, high vaccine efficacy was shown regardless of baseline serostatus. In DNA negative and seropositive subjects, there was a consistent pattern of efficacy observed for CIN2+ and persistent infection endpoints, although the number of CIN2+ endpoints was very limited in some of these analyses. In the analyses that reached statistical significance, the level of efficacy was consistent with results in initially seronegative subjects.
- In subjects who were DNA positive, there was no evidence of efficacy against histopathological endpoints. Data indicate the absence of a therapeutic effect of *Cervarix*, which has been developed as a prophylactic vaccine. There was no evidence that cervical disease was enhanced.

- The prophylactic efficacy of the vaccine has been shown in women infected with one HPV vaccine type against the other HPV vaccine type. Since the proportion of women who are simultaneously infected with HPV-16 and HPV-18 is low (<1%) [Paavonen, 2009], the vast majority of women could obtain some benefit from *Cervarix.*

Overall vaccine efficacy irrespective of the HPV type in the lesion (Studies HPV-008 and HPV-001/007)

- In HPV-008, the overall vaccine efficacy was demonstrated against CIN1+, CIN2+ and CIN3+ irrespective of the HPV type found in the lesion in a broad population of women including those with current HPV infection and/or prior exposure (TVC) as well as women naïve to oncogenic HPV (TVC-naïve).
- *Cervarix* showed a similar and high level of efficacy for CIN2+irrespective of the HPV DNA in the lesion in HPV-001/007 (71.9%) and HPV-008 (70.2%, TVC-naive), with point estimates indicating efficacy beyond HPV-16/18 when compared to the expected proportion of lesions attributed to HPV-16/18 (52%) [Smith, 2007].
- Overall vaccine efficacy against CIN3+ in HPV-008 (87%, TVC-naive) exceeded the expected prevalence of cervical cancer attributable to HPV-16/18 (70%) [Smith, 2007].
- In HPV-008, vaccine efficacy was observed in the overall reduction of local cervical therapy (LEEP, Cone, Knife and Laser) in both the TVC (24.7%) and TVC-naïve populations (68.8%).

Efficacy against infection by non-vaccine oncogenic HPV Type (Studies HPV-008 and HPV-001/007)

- In HPV-008, vaccine protection was observed beyond vaccine types HPV-16 and HPV-18: evaluation of combined endpoints of oncogenic HPV types excluding HPV-16/18 demonstrated efficacy against CIN2+ associated with non-vaccine oncogenic HPV types, ranging from 37% to 54% depending on the extent of co-infections with HPV-16/18.
- Initial evidence of protection against HPV-31 and HPV-45 was observed in HPV-001/007 with significant efficacy against incident infections sustained up to 6.4 years.
- In HPV-008, consistent evidence of protection against histopathological and virological endpoints was observed for oncogenic HPV types other than HPV-16 and HPV-18, including the three most frequent types after HPV-16/18 globally: the phylogenetically related types HPV-31 and HPV-33 (related to HPV-16) and HPV-45 (related to HPV-18). These findings suggest that the efficacy against both vaccine and non-vaccine HPV types contribute to the observed high overall vaccine efficacy results for CIN2+ and CIN3+ irrespective of the HPV type in the lesion.

Immunogenicity

- *Cervarix* is highly immunogenic in girls and women between the ages of 15-25 years, in women who were HPV 16/18 naïve at the time of vaccination and in women who had evidence of prior HPV-16/18 infection.

- *Cervarix* was shown to induce a strong and durable immune response to both HPV-16 and HPV-18 in serum up to 6.4 years
- Vaccine induced antibodies were shown to transfer to the site of infection (as measured in the cervical-vaginal secretions) following administration of *Cervarix*.
- In the younger age group (10 to 14 years of age), the immune response was shown to be non-inferior to the age group with demonstrated efficacy (15-25 years), inferring that *Cervarix* will be efficacious in this population.

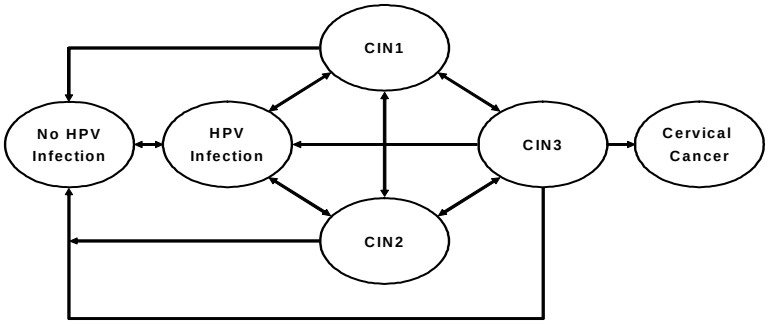
6. HEALTH OUTCOMES

Given the natural history of HPV disease, reduction in cervical cancer due to vaccination will take years and even decades. GSK has developed a model using a standardized approach (details of methodology are currently undergoing independent review by the Centers for Disease Control and Prevention [CDC]) in order to estimate how *Cervarix* may impact future cervical cancer incidence and related deaths in US girls and women.

A Markov model was developed to simulate the natural history of cervical disease and was used to estimate the lifetime impact of HPV vaccination in reducing cervical disease [Kohli, 2007; Debicki, 2008]. The model is composed of a set of mutually exclusive, collectively exhaustive health states (Figure 19) and the natural history of cervical disease is modeled as a series of transitions between these states. Transitions were allowed to occur at 6-month increments, referred to as Markov cycles. Probabilities governing these transitions were conditional on the age of the female and the type of HPV infection.

Health-states were classified according to the natural history of cervical disease, detected CIN, and cancer: normal (no HPV infection); HPV infection with no lesion; CIN1; CIN2; CIN3; invasive cervical cancer (stage 1, stage 2, stage 3, or stage 4); and death from cervical cancer as well as other causes. The four stages of cancer are subdivided according to the status of diagnosis (detected or undetected). Transitions between the Markov states are allowed to occur for seven types of HPV infections: types 16, 18, 31, 45, 52, other high-risk, and other low-risk. It was assumed that in the absence of treatment, females with no HPV infection could develop an infection and those with CIN1 could progress, regress, or stay the same. CIN2, CIN3, and cancer could only develop in the presence of persistent HPV infection, defined as at least two positive HPV tests for the same viral genotype over a minimum interval of six months. In each cycle, females with cancer could progress to the next stage of cancer but no regression to the previous health state was allowed. Movement from undetected cancer to detected cancer was defined by the stage-dependent probability of developing symptoms. Transitions to death were determined by cancer-stage-specific survival rates and competing all-cause mortality risks. The model uses a societal perspective and considers a lifetime horizon, following female cohorts for up to 89 years.

Figure 19 Simplified structure of the HPV natural history model



Input parameters for Markov models are informed by existing data obtained from the published literature, clinical trials, and public domain databases. Systematic calibration was used to empirically derive input parameters that allow the model to accurately reflect the outcomes of interest including prevalence of pre-cancerous cervical lesions, cervical cancer incidence and cervical cancer-related mortality [Benard, 2004; Ries, 2007]. The model did not account for the heterogeneity that characterizes the cervical cancer disease process. Additional model parameters, such as those related to cervical screening, were derived from published literature [Benard, 2004; Ries, 2007], all other model parameters were derived from published literature [Kulasingam, 2002; Hopman, 1998; Mitchell, 1998; Lousuebsakul, 200; Benard, 2005; Chesson, 2004; Koshiol , 2004; Scheinfeld , 2006; Jay, 2000; Brown, 1999, Sherlaw-Johnson, 2004]. Cervical screening rates were estimated based on current screening practices [Insinga, 2004b; Sirovich, 2004], calibrated to US data, and were assumed to remain constant following the introduction of vaccination. Note that the model assumed previously infected females were susceptible to re-infection. Further, these analyses did not account for herd immunity and thus results reflect only direct protection to vaccinated females; a conservative approach. In addition, the natural history of multiple HPV infections was not explicitly modeled; therefore, the possibility that suppression of types HPV-16 and 18 could allow for the prevalence of other oncogenic HPV types in invasive cervical cancer to increase was not explored.

Analyses were performed for a cohort of females 10-25 years of age, the proposed age indication for initial licensure of *Cervarix*, with 75% vaccination coverage and compared with no vaccination. Two different vaccine efficacy scenarios were considered, including (1) 95% against types 16/18 and 37.4% against 12 other high-risk oncogenic HPV types (*Cervarix* lower limit) (see Section 5.4.2.1), and (2) 95% against types 16/18 and 54% against 12 other high-risk HPV types (*Cervarix* upper limit) (see Section 5.4.2.1). These two scenarios include an adjustment for multiple co-infections and therefore represent the upper and lower limits of protection against non-vaccine oncogenic HPV types. The 12 other high-risk types were 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Also evaluated was the impact of a vaccine that offers 95% oncogenic protection against HPV 16/18 alone (i.e., no efficacy against non-vaccine types). Clinical outcomes included cervical cancer cases and cervical cancer-related deaths.

For an individual 12-year-old female, the model predicts a lifetime risk reduction in cervical cancer cases and deaths of 81-85% and 82-85% using the two different vaccine efficacy scenarios, compared with no vaccination.

As noted previously, a lifetime perspective was considered from the time from HPV infection to cancer and subsequent treatment and follow-up. With continued screening and no vaccination, the model predicts these 16 cohorts of girls and women will experience approximately 214,000 cases of cervical cancer and 56,000 related deaths in the course of their lifetime. By vaccinating 75% of the cohort, the model further estimates *Cervarix* may prevent 111,000 – 115,000 (52-54%) of those cervical cancers and 27,000 – 28,000 (48-50%) of the related deaths. In comparison, a vaccine that offers oncogenic protection against HPV 16/18 alone is estimated to prevent 101,000 (47%) of cervical cancers and 25,000 (44%) of related deaths compared with no vaccination. Thus, *Cervarix* is estimated to increase protection against cervical cancer cases and cervical cancer deaths by 9-14% relative to a vaccine that offers oncogenic protection against HPV 16/18 alone. This translates into an additional 9,000 – 14,000 cancer cases prevented and 2,000 – 3,000 lives saved over the lifetime of girls and women 10-25 years of age due to cross protection. It is estimated that 110-160 cervical cancer cases and 25-40 lives every year would be prevented due to the cross protective efficacy of *Cervarix*. Overall, when considering the average annual impact, *Cervarix* is estimated to prevent 1,200-1,300 cervical cancer cases and 300-320 lives every year.

High levels of clinical benefits can also be expected for *Cervarix* at lower coverage levels if disease transmission dynamics are included in the Markov model. These clinical benefits would be due to additional indirect protection offered to non-vaccinated females as a result of herd immunity. It is important to note that these findings must be considered within the limitations of the study design.

7. OVERVIEW OF SAFETY

This section summarizes the results of safety analyses that demonstrate that *Cervarix* is generally well tolerated with a satisfactory safety profile and support the licensure of *Cervarix* for vaccination of girls and women of 10-25 years of age. An overview of the safety submissions to the BLA and analyses presented in this section by endpoint and data lock-point is provided in Figure 20 and Table 23. With many studies still ongoing in GSK's HPV program and in an effort to provide safety data that is as complete and as updated as possible, the information provided in this briefing document is derived from several analyses that were based on different analyses and may have different data lock-points. In general, the information provided for each part of the safety evaluation comes from the most complete and most recent analysis performed for that specific part of the safety profile of *Cervarix*.

A pooled safety analysis was submitted to CBER in the initial BLA (March 2007). This analysis includes all reported studies with *Cervarix* in approximately 30,000 female subjects, of which over 16,000 subjects received at least one dose of *Cervarix*, and who were enrolled in 11 Phase II/III clinical studies and two extension studies (HPV-001 and its long-term follow-up study HPV-007 [Month 24 interim analysis], HPV-003, HPV-004, HPV-005, HPV-008 [interim analysis], HPV-012, HPV-013 and its extension study

HPV-013 Ext, HPV-014 and its extension study HPV-014 Ext, HPV-015 [Month 7 safety interim analysis] and HPV-016) (see Table 4 for further details of these studies). Data on solicited and unsolicited adverse events are based on this analysis (referred to as the Pooled Safety Analysis). This initial analysis was updated with the results of the final analysis of Study HPV-007 (data up to 6.4 years) and Study HPV-008 (event-triggered final analysis at approximately 3.3 years of follow-up). Data on NOADs are based on the update of the pooled safety analysis (referred to as the Updated Pooled Safety Analysis).

A further update of this pooled safety analysis was performed for a cumulative analysis of selected categories of events (i.e. medically significant conditions, AEs leading to discontinuation and pregnancies/pregnancy outcomes) with data lock-point of August 31, 2008 (referred to as the Extended Pooled Safety Analysis). This update included data from the 11 Phase II/III clinical studies (with final analyses of Studies HPV-007 and HPV-008) plus the ongoing extension studies (HPV-012 Ext, HPV-013 Ext, HPV-014 Ext and HPV-023 [follow-up study of HPV-001/007]) and data from HPV-009 (ongoing Phase III study sponsored by NCI).

Finally, an analysis was performed based on all completed and ongoing studies in which *Cervarix* has been administered (33 studies including the above-listed studies and their extensions) with a data lock-point of August 31, 2008 (referred to as All Studies Safety Analysis). As these analyses included ongoing studies for which interim or final analyses have not yet been performed, this extended pooled safety analysis was not performed on completely validated and reconciled databases. Nevertheless, this analysis provides safety data over a follow-up period of up to 7.4 years in over 57,000 women with over 33,000 receiving at least one dose of *Cervarix*. Data on deaths and other SAEs are based on this analysis.

In addition to the safety data reported in clinical trials, data from post-marketing surveillance is also presented from the first commercial launch of *Cervarix* up to the data lock-point of the latest Periodic Safety Update (May 17, 2009) and following the distribution of approximately 7 million doses of *Cervarix*.

Figure 20 Overview of safety submissions to *Cervarix* BLA

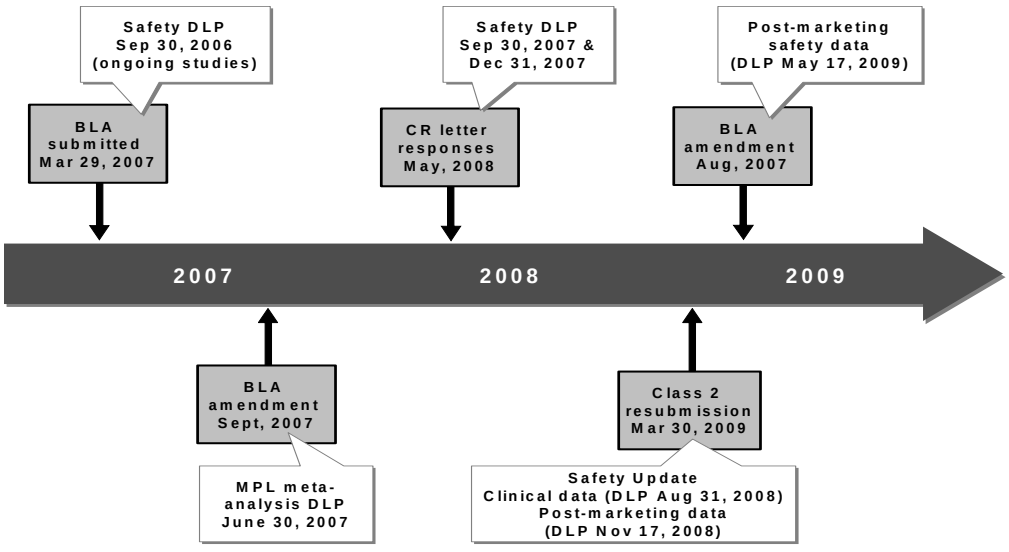


Table 23 Overview of safety analyses for *Cervarix* by endpoint and data lock-point

Safety endpoint	Analysis (Studies in analysis)	Data lock-point	Age range (years)	No. of female subjects in analysis	
				HPV group	Pooled control group
Solicited symptoms*	Pooled Safety Analysis (11 studies reported in BLA, see Table 4)	Depending on study	10-25	6,432	4,655
Unsolicited symptoms*	Pooled Safety Analysis (11 studies reported in BLA, see Table 4)	Depending on study	10-25	6,654	4,799
New onset of autoimmune disorders (NOADs)	Updated Pooled Safety Analysis (11 studies reported in BLA, see Table 4)	Depending on study	10-25	12,533	10,730
Deaths	All Studies Safety Analysis (33 clinical studies in which *Cervarix* has been administered)	August 31, 2008	10-72	31,472*	23,700
Other serious adverse events	All Studies Safety Analysis (33 clinical studies in which *Cervarix* has been administered)	August 31, 2008	10-72	31,472*	23,700
Study discontinuations due to adverse events	Extended Pooled Safety Analysis (11 studies reported in BLA, see Table 4, plus ongoing extension studies and HPV-009)	August 31, 2008	10-72	19,871	17,548
Pregnancies and pregnancy outcomes	Extended Pooled Safety Analysis (11 studies reported in BLA, see Table 4, plus ongoing extension studies and HPV-009)	August 31, 2008	10-72	19,871	17,548
Medically significant conditions (MSC)**	Extended Pooled Safety Analysis (11 studies reported in BLA, see Table 4, and ongoing extension studies)	August 31, 2008	10-72	15,469	13,228

*Solicited symptoms were reported in a diary card subset of 6,371 subjects of Study HPV-008 and in all other subjects of 10-25 years of age in the Pooled Safety Analysis.
**2,151 subjects received HPV-16/18 vaccine co-administered with another study vaccine but are not included in analyses presented as follow-up in these subjects was less than in the HPV and Pooled Control groups.
***MSCs not reported as a separate category in all studies in Extended Pooled Safety Analysis (see Section 7.1.2)

7.1. Methodology for safety evaluations

Prior to starting clinical development, the safety of *Cervarix*, AS04 and MPL were thoroughly evaluated in non-clinical studies. In total, 20 non-clinical studies were performed with *Cervarix* or other HPV-16/18 vaccine formulations (7 studies of which 4 studies contained AS04 as a control), and MPL (13 studies). Overall, there was no evidence of any toxicologically relevant systemic, reproductive, developmental, neurological, immunological or autoimmune effect. Toxicity studies showed that *Cervarix* and MPL were well tolerated with no consistent signs of systemic toxicity. The only conclusive effects seen were local and transient, as expected from formulations that induce recruitment of inflammatory cells. As the intended population for vaccine administration includes young women of child-bearing potential, reproductive and

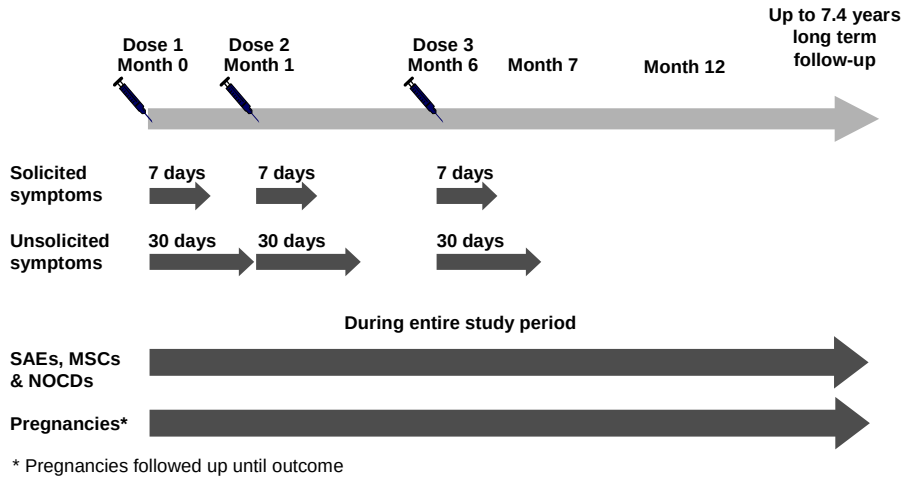
developmental toxicity studies were performed and showed no adverse effects induced by *Cervarix* or MPL on fertility or pre-or post-natal development.

Although non-clinical studies did not identify any areas of concern requiring specific follow-up in clinical development, two areas of special interest resulted from the focus on adolescent females and young women in the clinical trial program. The target population for *Cervarix* includes young women of child bearing potential. Therefore, all pregnancies were to be reported throughout follow-up in clinical studies and were followed until outcome. In addition, autoimmune disorders occur more frequently in young women than other demographic groups. The assessment of autoimmune disorders was based on a thorough and rigorous reporting and analysis of specific adverse events extended throughout the follow-up of clinical studies, i.e. up to 7.4 years of follow-up (129,454 person-years of follow-up for safety endpoints [70,086 person-years for the HPV group and 59,053 person-years for the pooled controls]). In addition, external expertise was sought for the evaluation of these two areas of special interest (see Section 7.1.4 for further details).

7.1.1. Data collection

Safety assessment in GSK's HPV vaccine program was comprehensive with thorough collection of relevant safety data over extensive reporting periods after vaccine administration (Figure 21).

Figure 21 Overview of data collection for safety reporting



SAE: serious adverse event, MSCs: medically significant conditions, NOCDs: new onset of chronic diseases

Diary cards were provided to the subjects or the subjects' parents/guardians to record solicited local and general signs and symptoms for 7 days after each vaccination as well as unsolicited events for 30 days after each vaccination. This active surveillance method

allowed for an objective assessment of the frequency, intensity and duration of signs and symptoms that occurred after vaccine administration. Solicited and unsolicited symptom reporting was performed in all studies in all subjects except in Study HPV-008, in which a subset of 6,371 subjects (at least 1,000 subjects from the four geographic regions included in the study) received diary cards to report solicited and unsolicited symptoms. In Study HPV-015, an interim safety analysis was performed when a subset of 1,987 subjects had completed their Month 7 visit, with solicited symptom reporting in this subset of subjects.

Except for solicited local symptoms, which were regarded as related to vaccination *a priori*, the investigator determined the relationship to vaccination of solicited general symptoms and all other adverse events.

Subjects were asked at each study visit about the occurrence of any symptoms and medications taken. In all studies, the subjects or parents/legally acceptable representative were instructed to immediately inform the investigator of the occurrence of any SAE at any time throughout the study period. SAEs were to be reported within 24 hours by investigators to the sponsor, regardless of causality.

For the analysis of NOADs, the safety database was searched for new medical conditions indicative of potential autoimmune diseases. An event was considered to be a potential "new onset" if it was not recorded in the previous medical history of the subject and an autoimmune disorder if the GSK physician reviewing the event confirmed that it matched a term on a predefined list of autoimmune disorders (see Appendix 2).

All subjects of child-bearing potential were instructed to either be abstinent or use an effective method of birth control during the vaccination period up to at least 2 months after the last vaccination. Pregnant or breast-feeding women were excluded from enrolment. Pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued in case of a positive pregnancy test. In all clinical trials, pregnancies were to be reported throughout the entire study period and followed until outcome.

In GSK Biologicals' sponsored studies (i.e. all studies except Study HPV-009 which is sponsored by the NCI), all subject information (e.g., medical history, demography, vaccination, diary card information, adverse event, medication, etc.) was collected using GSK's validated computer application (Remote Data Entry) at the study site.

7.1.2. Endpoints for assessment of safety and reactogenicity

The following endpoints were evaluated in individual clinical studies:

- **Solicited local and general signs and symptoms** were reported in all studies (safety diary card subset in Study HPV-008).
- **Unsolicited adverse events within 30 days post-vaccination** were reported in all studies (safety diary card subset in Study HPV-008).

- **Medically significant conditions** were defined as conditions prompting emergency room or physician visits that were not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that were not related to common diseases. Common diseases included: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury. Medically significant conditions were reported in Studies HPV-008, HPV-012, HPV-013, HPV-013 Ext, HPV-014, HPV-014 Ext, HPV-015 and HPV-016. Medically significant conditions were not collected as a separate category in Studies HPV-001/007, HPV-003, HPV-004 and HPV-005.
- **New Onset of Chronic Disease and New Onset of Autoimmune Disorders** were identified in the study clinical database according to a list of chronic diseases and potential autoimmune events, respectively. Lists were approved by the Independent Data Safety Monitoring Committee (IDMC) overseeing large phase III studies in the HPV project. NOCDs were reported in Studies HPV-007, HPV-008, HPV-012, HPV-013, HPV-013 Ext, HPV-014, HPV-014 Ext, HPV-015 and HPV-016. NOCDs and NOADs were not collected as a separate category in Studies HPV-001, HPV-003, HPV-004 and HPV-005.
- **Serious Adverse Events (SAEs)** were reported in all studies, throughout the entire study period (except for HPV-004 and HPV-005 in which reporting was through Month 12), regardless of causality.
- **Pregnancies and pregnancy outcomes** were reported in all studies, throughout the entire study period (except for HPV-004 and HPV-005 in which reporting was through Month 12) and followed until outcome.
- **Biochemical and hematological evaluations** were conducted in Studies HPV-001, HPV-003, HPV-004, HPV-005 and HPV-013.
- **Vital signs assessments** were performed 30 minutes after each vaccination, in Studies HPV-003, HPV-004 and HPV-005. In all studies, subjects were observed closely after each vaccination for at least 30 minutes to detect and treat any potential acute reaction.

7.1.3. Statistical methodology for pooled safety analyses

Demographic, reactogenicity and safety data from the 11 Phase II/III clinical studies having undergone a final or interim analysis and submitted to the BLA were pooled to provide an extensive safety database of validated and reconciled data. Analysis of this database was performed in the Total Vaccinated Cohort, which included all subjects with at least one vaccine administration documented, analyzed according to the vaccine actually received.

Pooling safety data within the HPV clinical program was considered valid since the studies included in the pooled analysis had similar study designs (i.e., same vaccination schedule, similar reporting periods and similar methods of determination and capture of adverse events).

Two reporting periods were considered for safety analysis: the entire study period (overall) and the vaccination period (Month 0 to Month 7). All analyses were performed

overall and stratified by age (10-14 years, 10-25 years, 15-25 years and older than 25 years). All age groups were controlled by placebo (alum) or a vaccine appropriate for the age group and with the same vaccination schedule as *Cervarix* (Table 24). For Phase III development in 10-14 year old girls and adolescents, *Havrix* (licensed hepatitis A vaccine with 250 µg of $Al(OH)_3$**)** was used. In 15-25 year olds in phase III development, an investigational formula based on the licensed *Havrix* vaccine (HAV720) was given to allow for the use of a control with the same vaccination schedule and alum content as *Cervarix*.

Table 24 Selection of control in HPV clinical development

Control	Trial Age	$Al(OH)_3$ content
Licensed hepatitis A vaccine (HAV360)	10-14 years	250 µg
Hepatitis A vaccine (HAV720)	15-25 years	500 µg
Placebo (Alum)	15-25 years and > 25 years	500 µg

In the analysis of deaths and other SAEs in all completed and ongoing studies in which *Cervarix* has been administered (All Studies Safety Analysis), results for control vaccines (Hepatitis A vaccine containing 360 EL.U. hepatitis A antigen per dose, Hepatitis A vaccine containing 720 EL.U. hepatitis A antigen per dose, *Aimmugen* (500 µg of inactivated hepatitis A viral antigen)*, Gardasil, Menactra, Boostrix, Boostrix Polio, Engerix B* or *Twinrix Paediatric)* and placebo (alum) were pooled together.

7.1.4. Supervision and review of safety data by independent data monitoring committees and external experts

The large Phase III efficacy trial HPV-008 (in 15 to 25 year old women), the safety trial HPV-013 (in 10 to 14 year old adolescents) and the Phase III efficacy trial HPV-015 (in women older than 25 years) are under the supervision of a single IDMC. Similarly, the ongoing efficacy trial HPV-009 is under the supervision of a separate data safety monitoring board (DSMB). These committees include as members, clinical experts in gynecological pathology and HPV, adolescent health, public health, consumer advocacy, immunization research, pediatric endocrinology and obstetrics and gynecology as well as biostatisticians. There is one common member in both committees. The overall responsibility of these committees is to protect the ethical and safety interests of the subjects recruited into the studies and to monitor the safety data.

In addition to the oversight by independent data monitoring committees, relevant expertise has been sought externally:

- An Autoimmunity Advisory Board consisting of independent experts in pharmaco-epidemiology, neuro-immunology, autoimmune diseases, vaccine safety and endocrine autoimmune diseases. This Board assists GSK in interpreting any data or scientific information related to autoimmune disorders and in some cases assists to review and validate the methodology for data collection and to review reports of potential autoimmune disorders in HPV trials.

- Assessment of neuroinflammatory events of potentially autoimmune etiology was performed by a panel of three external and independent experts in the field of neurology (see Section 7.3.8.2).
- Assessment of musculoskeletal events of potentially autoimmune etiology was performed by a panel of four external and independent experts in the field of rheumatology (see Section 7.3.8.2).
- Pregnancy and pregnancy outcomes experts to provide additional analyses of data:
- Congenital anomalies reported in offspring of study subjects enrolled in the HPV clinical program were reviewed by an independent expert panel of teratologists/geneticists.
- In response to a request by the DSMB with oversight for Study HPV-009, the NCI performed an independent analysis of spontaneous loss data inclusive of data from Studies HPV-008 and HPV-009, in consultation with two experts in the epidemiology of reproductive health [Wacholder, 2009].

7.2. Clinical safety database

The clinical development program for *Cervarix* is outlined in Section 4, which provides an overview of the 11 Phase II/III studies (six controlled studies) included in the Pooled Safety Analysis. Collectively the evaluation of vaccine safety in this analysis encompasses a large database of 29,953 subjects, in which 16,142 subjects received at least one dose of *Cervarix*. The database includes subjects 10 to 72 years of age (mean age of 23.1 years) with: 23,713 girls and women of 10-25 years of age (of which 12,785 received at least one dose of *Cervarix*), and 6,240 women more than 25 years of age (of which 3,357 received at least one dose of *Cervarix*) (see Table 25). All age groups are well represented in the Pooled Safety Analysis.

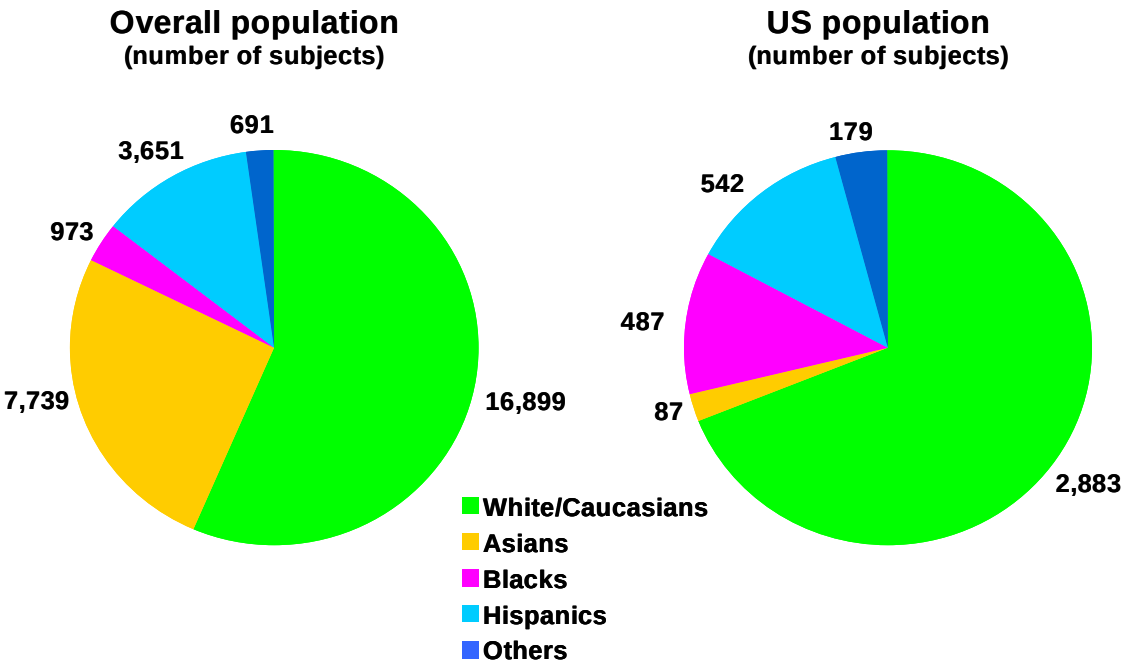
Table 25 Pooled safety analysis: number of subjects per treatment and age stratum

Age (years)	Group				Total
	HPV	HAV720	HAV360	Placebo	
10-14	1,194	-	1,032	-	2,226
15-25	11,591	9,315	-	581	21,487
Subtotal 10-25	12,785	9,315	1,032	581	23,713
> 25	3,357	10*	-	2,873	6,240
Total All subjects	16,142	9,325	1,032	3,454	29,953

HPV group: ≥ 10 years, HAV720 group: 15-25 years, HAV360 group: 10-14 years, Placebo group: ≥ 15 years
*10 subjects randomized to receive control vaccine in Study HPV-008 over the age of 25 years were enrolled into the study even though the protocol specified an enrolment age of 15 to 25 years.

Enrolment in the HPV clinical development program was global with the Pooled Safety Analysis including subjects from over 30 countries in North America, Latin America, Europe, Asia and Australia and thus encompassing women with varied ethnic and racial backgrounds (Figure 22). Of the 29,953 subjects included in the pooled safety analysis, there were 4,322 subjects from US, of which 2,198 received *Cervarix*.

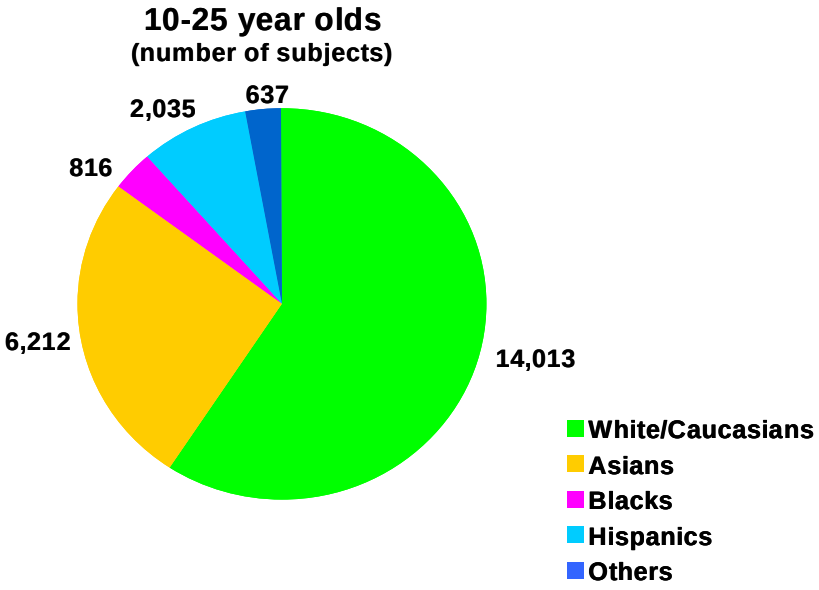
Figure 22 Ethnic and racial profile of subjects in the safety database of reported studies (all ages)



Others = Mixed Ethnicities, Aboriginal, American Indian, Native American, Native Canadian, Cape Colored, First Nations, Gypsy

In the 23,713 girls and women of 10-25 years of age in the Pooled Safety Analysis, the ethnic profile was similar to the overall population (Figure 23).

Figure 23 Ethnic and racial profile of subjects in the safety database of reported studies (10-25 years of age)



Others = Mixed Ethnicities, Aboriginal, American Indian, Native American, Native Canadian, Cape Colored, First Nations, Gypsy

In Phase III studies, there was no HPV serological, HPV DNA or cervical cytological screening for study enrolment purposes, which allowed for the inclusion of women with previous or current HPV disease, infection or exposure in the safety database.

The mean follow-up time for the reporting of safety endpoints in the pooled analysis (including the final analyses of Studies HPV-007 and HPV-008) was 30.3 months (2.5 years) representing 75,631 person-years for all subjects (38,875 person-years for HPV group and 36,599 person-years for the pooled controls) with a maximum follow-up of 76.8 months (6.4 years).

In addition to the Pooled Safety Analysis described above, a further safety analysis was performed including data from all studies in which *Cervarix* has been administered up to the data-lock point of August 31, 2008 (i.e. All Studies Analysis). In addition to the 11 Phase II/III clinical studies and their extension studies included in the initial pooled analysis, this updated analysis included 6 Phase I/II studies, 14 Phase III/IIIb studies (including co-administration and local registration studies), the NCI-sponsored Phase III efficacy study of subjects aged 18-25 years (Study HPV-009) and a Phase III/IV study in Finland. This updated analysis provided a total of 129,454 person-years of follow-up for safety endpoints (70,086 person-years for the HPV group and 59,053 person-years for the pooled controls) in 57,323 female subjects (33,623 received at least one dose of *Cervarix* alone or co-administered with another vaccine) and a maximum length of follow-up of 7.4 years. Long-term follow-up data are currently available for subjects 10-14 years old (up to 36 months following vaccination), 15-25 years old (up to 7.4 years following vaccination) and 26-55 years old (up to 36 months following vaccination).

In All Studies Analysis, results for subjects receiving controls were pooled to allow for comparison with the HPV group.

7.3. Analyses of clinical safety database

7.3.1. Solicited symptoms

The proposed age indication for *Cervarix* is 10-25 years of age, therefore, solicited symptoms are presented for this age range.

The reactogenicity of *Cervarix* has been evaluated in a total of 11,087 female subjects of 10-25 years of age who received a total of 31,922 doses. In this age range, 6,432 subjects received 18,548 doses of *Cervarix* and a total of 549, 1,027 and 3,079 subjects received 1,567, 3,059 and 8,748 doses of placebo, HAV360 and HAV720, respectively.

The incidence of solicited local symptoms (any intensity and grade 3) is presented for all doses (overall/dose) in Table 26. Vaccination with *Cervarix* was shown to be generally well tolerated. Although solicited local symptoms were reported more frequently in the HPV group as compared to control groups, events were generally mild to moderate in intensity.

Table 26 Pooled safety analysis: percentage of doses (overall/dose) followed by solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort, 10-25 year olds)

Symptom	Type	HPV group	HAV720 group	HAV360 group	Placebo group
No. of doses		18548	8747	3059	1567
Pain	Any	80.7	58.9	41.3	72.9
	Grade 3	7.0	1.8	0.8	7.8
Redness	Any	30.9	16.0	13.7	12.8
	> 50mm	0.6	0.0	0.1	0.1
Swelling	Any	26.7	10.1	8.6	10.8
	> 50mm	1.2	0.2	0.2	0.0

HPV group: 10-25 years, HAV720 group: 15-25 years, HAV360 group: 10-14 years, Placebo group: 15-25 years
Grade 3 pain = pain defined as spontaneously painful (Study HPV-001) or pain that prevented normal daily activities (Studies HPV-008, HPV-012, HPV-013, HPV-014, HPV-016).
Grade 3 redness/swelling = redness/swelling >50 mm

The most frequently reported solicited local symptom in all groups was pain. Pain was reported less frequently after Dose 2 and 3 of *Cervarix* in contrast to redness and swelling, where there was a small increase in incidence (Table 27). However, grade 3 redness and swelling (>50mm) occurred at low frequencies in all treatment groups.

Table 27 Pooled safety analysis: percentage of subjects reporting solicited local symptoms by dose during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort, 10-25 year olds)

Symptom	HPV group			HAV720 group			HAV360 group			Placebo group		
Post-Dose	1	2	3	1	2	3	1	2	3	1	2	3
N	6415	6197	5936	3070	2919	2758	1027	1021	1011	546	521	500
Pain	86.9	76.2	78.7	65.6	54.4	56.1	48.5	38.5	36.9	79.1	66.8	72.4
Redness	27.8	29.6	35.6	16.6	15.2	16.1	15.6	13.3	12.1	11.5	11.5	15.6
Swelling	22.7	25.2	32.7	10.5	9.4	10.5	9.4	8.6	7.6	10.3	10.4	12.0

HPV group: 10-25 years, HAV720 group: 15-25 years, HAV360 group: 10-14 years, Placebo group: 15-25 years

Overall, solicited general symptoms were reported less frequently than local symptoms. Fatigue, headache and myalgia were the most frequent general symptoms with a higher incidence of myalgia in the HPV group (Table 28). Arthralgia was reported more frequently in the HPV group than in the HAV720 group. The frequencies of fever, rash and urticaria were consistently low in the HPV group and similar to those in control groups. Grade 3 solicited general symptoms (symptoms that prevent normal or daily activities; fever [oral/axillary temperature] > 102.2°F; urticaria on at least four body areas) were uncommon, reported following 1.8% or less of doses. There was no increase in solicited general events with successive doses. The mean duration of solicited local and general symptoms, including grade 3 symptoms, was evaluated in the large phase III Study HPV-008, which showed generally similar duration between HPV and control groups.

The compliance with the full vaccination course was equally high in both HPV and control groups (Section 7.3.3.1, Figure 24), indicating that *Cervarix* was well tolerated.

Table 28 Pooled safety analysis: percentage of doses (overall/dose) followed by solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort, 10-25 year olds)

Symptom	Type	HPV group	HAV720 group	HAV360 group	Placebo group
General					
No. of doses		18544	8748	3058	1565
Fatigue	Any	35.5	35.3	24.6	31.7
	Grade 3	1.7	1.3	1.1	2.0
Fever	≥ 99.5°F	5.3	4.6	6.8	5.5
	> 102.2°F	0.2	0.1	0.6	0.4
GI	Any	13.9	14.0	11.3	15.9
	Grade 3	0.8	0.7	0.8	0.5
Headache	Any	31.3	30.8	25.4	36.5
	Grade 3	1.8	1.4	1.6	2.1
Rash	Any	4.2	3.6	2.6	4.2
	Grade 3	0.1	0.1	0.1	0.0
Other General*					
No. of doses		16964	8748	3058	-
Arthralgia	Any	10.4	8.6	9.3	-
	Grade 3	0.4	0.3	0.2	-
Myalgia	Any	31.0	26.5	17.1	-
	Grade 3	1.6	0.6	0.5	-
Urticaria	Any	3.3	3.7	2.1	-
	Grade 3	0.2	0.4	0.2	-

HPV group: 10-25 years, HAV720 group: 15-25 years, HAV360 group: 10-14 years, Placebo group: 15-25 years
GI = Gastrointestinal, including nausea, vomiting, diarrhea, and/or abdominal pain.
* Arthralgia, myalgia and urticaria not solicited in Phase II study (HPV-001) using Placebo as a control
Grade 3 symptoms = symptoms that prevent normal activity Grade 3 fever = oral/axillary temperature > 102.2°F

7.3.2. Safety and reactogenicity in 10-14 year old adolescent girls and 15-25 year old young women

The pooled data was also stratified according to age (10-14 years and 15-25 years). As described in Section 7.1.3, appropriate controls were selected in the HPV program depending on the age of study subjects. Thus, for the pooled safety analysis, age groups included a control vaccine/placebo but the latter varied with age.

Table 29 and Table 30 summarizes, for subjects receiving *Cervarix,* the incidence of any local and general symptom reported during the 7-day post-vaccination period following all doses in two age groups (10-14 years and 15-25 years).

Subjects 10-14 years of age reported fewer solicited local symptoms than subjects 15-25 years of age but comparable rates of solicited general symptoms.

The majority of the solicited local and general symptoms reported were mild to moderate in each age group: grade 3 local symptoms were reported after up to 4.8% and 7.2% of doses in the 10-14 years and 15-25 years age groups respectively (Table 29); grade 3 general symptoms were reported after up to 2.5% and 1.5% of doses in the 10-14 years and 15-25 years age groups, respectively (Table 30).

Based upon analysis of the individual age groups (10-14 years and 15-25 years), the pattern of solicited symptoms was similar across both ages groups.

Table 29 Pooled safety analysis: percentage of doses (overall/dose) followed by any or grade 3 local symptoms during the 7-day (Days 0-6) post-vaccination period in the HPV group stratified by age (Total Vaccinated Cohort, 10-14 year olds and 15-25 year olds)

Symptom	Type	10-14 year olds	15-25 year olds
No. of doses		3528	15020
Pain	All	71.9	82.8
	Grade 3	4.8	7.5
Redness (mm)	All	28.8	31.4
	>50	0.4	0.6
Swelling (mm)	All	24.8	27.2
	>50	1.2	1.2

Grade 3 pain = pain defined as spontaneously painful (Study HPV-001) or pain that prevented normal daily activities (Studies HPV-008, HPV-012, HPV-013, HPV-014, HPV-016).

Table 30 Pooled safety analysis: percentage of doses (overall/dose) followed by any or grade 3 general symptoms during the 7-day (Days 0-6) post-vaccination period in the HPV group stratified by age (Total Vaccinated Cohort, 10-14 year olds and 15-25 year olds)

Symptom	Type	10-14 year olds	15-25 year olds
No. of doses		3529	15015
Fatigue	Any	29.2	37.0
	Grade 3	1.6	1.7
Fever	≥ 99.5°F	7.3	4.8
	> 102.2°F	0.7	0.1
GI	Any	12.4	14.3
	Grade 3	1.1	0.7
Headache	Any	28.8	31.9
	Grade 3	2.5	1.6
Rash	Any	4.6	4.1
	Grade 3	0.3	0.1
No. of doses		3529	13435
Arthralgia	Any	11.7	10.1
	Grade 3	0.7	0.3
Myalgia	Any	29.2	31.5
	Grade 3	2.0	1.5
Urticaria	Any	2.5	3.6
	Grade 3	0.3	0.2

GI = Gastrointestinal, including nausea, vomiting, diarrhea, and/or abdominal pain.
* Arthralgia, myalgia and urticaria not solicited in Phase II study (HPV-001) using Placebo as a control
Grade 3 symptoms = symptoms that prevent normal activity Grade 3 fever = oral/axillary temperature > 102.2°F

7.3.3. Safety and reactogenicity in HPV non-naïve women at baseline

Women enrolled in Phase III trials were enrolled regardless of their HPV DNA or serostatus prior to study entry. Consequently Study HPV-008 included women who were HPV DNA positive and/or HPV seropositive prior to vaccination, allowing for safety assessment in:

- subjects with no evidence of previous or current HPV-16/18 infection (HPV-16 and HPV-18 seronegative and DNA negative cohort),
- subjects previously exposed to HPV-16/18 (HPV-16 or HPV-18 seropositive and/or DNA positive cohort),
- subjects currently infected with HPV-16/18 (HPV-16 or HPV-18 DNA positive cohort).

The incidence of solicited local and general symptoms observed for subjects who were seropositive and/or DNA positive for either HPV-16 or HPV-18 at baseline, seronegative and DNA negative for HPV-16 and HPV-18 at baseline, or DNA positive for either HPV-16 or HPV-18 at baseline was comparable to the incidence observed for the Total Vaccinated cohort (Table 31 and Table 32 respectively).

Table 31 Study HPV-008: percentage of doses (overall/dose) followed by local symptoms during the 7-day period in 15-25 years subjects, stratified by baseline sero/DNA status (Total Vaccinated Cohort, diary card subset)

Symptom	Type	Total Vaccinated cohort	Vaccinated seropositive and/or DNA positive cohort	Vaccinated seronegative and DNA negative cohort	Vaccinated DNA positive cohort
No. of doses		8692	2323	6272	653
Pain	All	80.2	78.7	80.8	83.5
	Grade 3	7.3	8.1	6.9	8.9
Redness (mm)	All	28.1	25.6	29.2	25.9
	>50	0.4	0.5	0.4	0.8
Swelling (mm)	All	25.4	23.5	26.2	23.4
	>50	1.0	0.9	1.1	1.4

Grade 3 pain =or pain that prevented normal daily activities.

Table 32 Study HPV-008: percentage of doses (overall/dose) followed by general symptoms during the 7-day period in 15-25 years subjects, stratified by baseline sero/DNA status (Total Vaccinated Cohort, diary card subset)

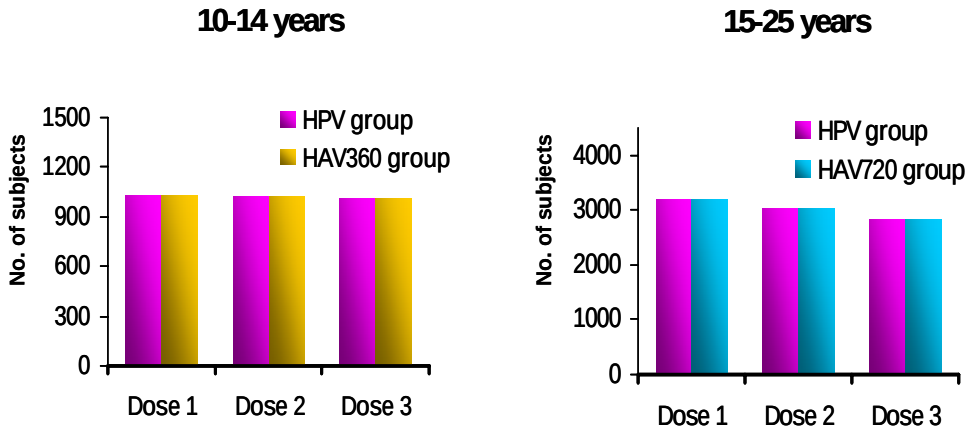
Symptom	Type	Total Vaccinated cohort	Vaccinated seropositive and/or DNA positive cohort	Vaccinated seronegative and DNA negative cohort	Vaccinated DNA positive cohort
No. of doses		8687	2322	6268	651
Arthralgia	Any	10.7	9.7	11.1	13.4
	Grade 3	0.4	0.5	0.3	1.1
Fatigue	Any	38.8	35.5	40.2	38.6
	Grade 3	1.6	2.2	1.4	1.8
Fever	≥ 99.5°F	5.3	6.4	4.9	6.3
	> 102.2°F	0.2	0.4	0.1	0.2
GI	Any	14.3	15.1	14.1	17.1
	Grade 3	0.7	0.8	0.7	0.8
Headache	Any	32.9	31.6	33.4	35.2
	Grade 3	1.7	1.7	1.6	0.9
Myalgia	Any	34.3	31.1	35.6	33.9
	Grade 3	1.8	2.2	1.6	2.5
Rash	Any	4.4	5.3	4.1	6.6
	Grade 3	0.1	0.1	0.1	0.0
Urticaria	Any	4.6	5.0	4.4	5.7
	Grade 3	0.3	0.4	0.3	0.6

GI = Gastrointestinal, including nausea, vomiting, diarrhea, and/or abdominal pain.
Grade 3 symptoms = symptoms that prevent normal activity Grade 3 fever = oral/axillary temperature > 102.2°F

7.3.3.1. Compliance with vaccination

Figure 24 provides information concerning the compliance with dosing in subjects with diary cards in large controlled studies representative of two age groups (10-14 years in Study HPV-013 and 15-25 years in Study HPV-008). The number of subjects who received three doses of the vaccine was equally high in both HPV and control groups, indicating that *Cervarix* was well-tolerated.

Figure 24 **Studies HPV-008 and HPV-013: Number of subjects who received study vaccine doses by age group and treatment group in subjects evaluated for reactogenicity (Total Vaccinated Cohort)**



7.3.4. Unsolicited adverse events up to 30 days post-vaccination

The overall incidence of unsolicited AEs in 10-25 year old subjects during the 30-day post-vaccination period was similar in the HPV and control groups (Table 33). The percentage of subjects reporting individual unsolicited symptoms at an incidence of 1% or greater in any group is presented in Table 33. The incidence of individual unsolicited adverse events was for the most part balanced between treatment groups.

Grade 3 reports were uncommon, with similar levels between the HPV group and control groups (6.2%, 6.9%, 5.1% and 6.0% of subjects reporting at least one grade 3 unsolicited symptom in the HPV, HAV720, HAV360 and Placebo groups respectively).

Table 33 Pooled safety analysis: percentage of subjects reporting unsolicited AEs (incidence ≥ 1% for *Cervarix* and ≥ control) within the 30-day post-vaccination period (Total Vaccinated Cohort, 10-25 year olds)

Event	HPV N = 6654		HAV720 N = 3186		HAV360 N = 1032		Placebo N = 581	
	n	%	n	n	%	%	n	%
At least one symptom	2690	40.4	1388	43.6	427	41.4	296	50.9
Headache	350	5.3	241	7.6	34	3.3	54	9.3
Nasopharyngitis	237	3.6	109	3.4	61	5.9	19	3.3
Influenza	210	3.2	177	5.6	13	1.3	11	1.9
Pharyngolaryngeal pain	193	2.9	86	2.7	23	2.2	13	2.2
Dizziness	146	2.2	83	2.6	15	1.5	18	3.1
Gynecological chlamydia infection	131	2.0	140	4.4	0	0	0	0.0
Upper respiratory tract infection	130	2.0	43	1.3	69	6.7	9	1.5
Dysmenorrhoea	130	2.0	74	2.3	20	1.9	23	4.0
Pharyngitis	98	1.5	56	1.8	23	2.2	3	0.5
Vaginal infection	93	1.4	70	2.2	1	0.1	5	0.9
Injection site bruising	91	1.4	57	1.8	7	0.7	9	1.5
Injection site pruritus	89	1.3	17	0.5	6	0.6	1	0.2
Back pain	75	1.1	40	1.3	7	0.7	18	3.1
Urinary tract infection	68	1.0	46	1.4	3	0.3	7	1.2

HPV group: 10-25 years, HAV720 group: 15-25 years, HAV360 group: 10-14 years, Placebo group: 15-25 years

7.3.5. Deaths

In the analysis of all clinical studies in which *Cervarix* has been administered (up to the data lock-point of August 31, 2008), 37 subjects were reported with a fatal outcome: 20 subjects of 31,472 subjects (0.64 per 1000 subjects) in the HPV group and 17 subjects of 23,700 subjects (0.72 per 1000 subjects) in the control group. The median interval between the date of last vaccination and the date of death was 1.5 years (range 30 days to 3.3 years). Of note, the mean duration of follow-up was 2.2 years in HPV group and 2.5 years in the control group.

A summary of the number of deaths by group classified by its underlying cause is presented in Table 34. All the fatalities in vaccinated subjects occurred more than 1 month after the last study vaccine administration, with a median interval between the date of last vaccination and the date of death of 1.5 years (range 30 days to 3.3 years). Road traffic accidents (10 cases) and suicides (7 cases) were the most common underlying causes of death.

In the group that received *Cervarix*, the following case fatalities were reported:

- road traffic accidents (5 cases): with intervals ranging from 386 to 124 days from last vaccination to death,
- homicide (2 cases): with intervals of 217 days and 826 days from last vaccination to death,
- suicide (2 cases, one case reported as gun shot wound possibly related to suicide) with 148 and 686 days from last vaccination to death,

- neoplasms: gestational trophoblastic neoplasia (onset 151 days after last dose), ovarian cancer (onset 1,127 days after last dose) and cervical cancer (46 year old in Study HPV-015 with normal cytology at enrollment but HPV-18 DNA positive, developed metastatic cervical cancer 205 days after last dose; study population of HPV-015 mainly consists of healthy women but includes also a subset of women with previous history of HPV infection),
- autoimmune diseases (3 cases): systemic lupus erythematosus (SLE) with Candida sepsis (SLE pre-existing with renal complications 6 months after first dose leading to sepsis and eventually death 21 months after the first and only dose), inflammatory bowel disease (IBD) with pyoderma gangrenosum (IBD diagnosed 2 months after third dose with multiple complications and eventually a pyoderma gangrenosum with a fatal outcome 22 months after last dose) and Crohn's disease with toxic megacolon and septic shock (Crohn's disease diagnosed 16 months after second dose, complicated with toxic megacolon and septic shock with fatal outcome 17 months after the second and last dose),
- infectious diseases (3 cases): septicemia (onset 758 days after last dose), bacterial septicemia (onset 770 days after last dose) and acquired immune deficiency syndrome(onset 254 days after last dose),
- cardiovascular disorders (2 cases): vascular thromboembolism (onset 1167 days after last dose) and acute myocardial infarction (onset 485 days after last dose).
- In the pooled controls group, the following case fatalities were reported:
- road traffic accidents (5 cases): with intervals ranging from 30 days to 862 days from last vaccination to death
- homicide: death 961 days after last dose
- suicide (5 cases): with 49 days to 817 days from last vaccination to death,
- neoplasms (2 cases): osteosarcoma (onset 165 days after last dose) and colon adenocarcinoma (onset 112 days after last dose)
- autoimmune diseases: insulin-dependent diabetes mellitus with diabetic ketoacidosis (onset 154 days after last dose)
- infectious disease: septicemia (onset 650 days after last dose)
- unknown cause of death (2 cases): sudden death 67 days after last dose in a subject with medical history of valvulopathy and hepatopathy prior to vaccination and one case for which study staff read in a newspaper that the subject was found dead; as an autopsy report cannot be released until all forensic analyses are completed, insufficient documentation for a complete assessment of the diagnosis and the cause of death is available.

No safety signal has been identified based on medical review of these 37 individual case fatalities.

Table 34 All Studies Safety Analysis: Number of subjects with underlying causes of death by group (all ages, data lock-point August 31, 2008)

Causes of death	HPV vaccine N = 31472*		Pooled controls N = 23700	
	n	Per 1000	n	Per 1000
Road traffic accident	5	0.16	5	0.21
Homicide	2	0.06	1	0.04
Suicide	2	0.06	5	0.21
Neoplasm	3	0.10	2	0.08
Autoimmune disease	3	0.10	1	0.04
Infectious disease	3	0.10	1	0.04
Cardiovascular disorders	2	0.06	0	0.00
Unknown	0	0.00	2	0.08
TOTAL	20	0.64	17	0.72

* 2,151 subjects received *Cervarix* co-administered with another study vaccine but are not included in table: no deaths were reported among these subjects.
HPV vaccine= HPV-16/18 vaccine, HPV-16/18/31/45 vaccine, HPV-16/18/33/58 vaccine
Pooled controls = $Al(OH)_3$, Hepatitis A vaccine containing 360 EL.U. hepatitis A antigen per dose, Hepatitis A vaccine containing 720 EL.U. hepatitis A antigen per dose, *Aimmugen* (500 µg of inactivated hepatitis A viral antigen), *Gardasil, Menactra, Boostrix, Boostrix Polio, Engerix B* or *Twinrix Paediatric.*

7.3.6. Other serious adverse events

In the analysis of all clinical studies in which *Cervarix* has been administered (up to the data lock-point of August 31, 2008), overall, there was no increase in the reporting of SAEs in subjects that received *Cervarix* compared to subjects that received control (54.65 per 1000 subjects and 67.89 per 1000 subjects, respectively) (Table 35). The reporting of SAEs during the entire follow-up period according to Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class was balanced between the HPV and control groups except for Pregnancy, puerperium and perinatal conditions, for which less events were reported in the HPV group than in the pooled controls group (22.08 per 1000 subjects in the HPV group versus 29.66 per 1000 subjects in the control group). More details on pregnancies and pregnancy outcomes are provided in Section 7.3.9.

When limiting the analysis to the vaccination period (i.e., from first vaccination to 1 month post-last vaccination; Month 0 to Month 7 post-vaccination), there was also no difference in the reporting rates for SAEs between the HPV and control groups: 11.95 per 1000 subjects in the HPV group and 12.95 per 1000 subjects in the control group.

The most commonly individual SAEs reported during the vaccination period were:

- Spontaneous pregnancy loss (including incomplete and complete spontaneous loss and missed abortion) with 59 subjects (1.87 per 1000 subjects) in HPV group and 51 subjects (2.15 per 1000 subjects) in the control group,
- Appendicitis with 25 subjects (0.79 per 1000 subjects) in the HPV group and 27 subjects (1.14 per 1000 subjects) in the control group,
- Dengue fever with 10 subjects (0.32 per 1000 subjects) in the HPV group and 10 (0.42 per 1000 subjects) in the control group,

When looking at differences in reporting rates between the HPV and control group, for the vaccination period, among the 316 different types of SAEs reported, two of the three SAEs types with the largest absolute difference in reporting rates are among the previously mentioned most frequently reported SAEs (i.e., spontaneous pregnancy loss and appendicitis).The third SAE type in terms of absolute difference was infectious mononucleosis, which was reported in 3 subjects (0.10 per 1000 subjects) in the HPV group and 9 subjects (0.38 per 1000 subjects) in the control group. Of note, all these SAEs were reported at higher rates in the control group.

Finally, when looking at relative reporting rates for events of which at least 3 reports occurred in each group, the largest differences were noted for infectious mononucleosis, missed abortion and depression which all occurred more frequently in the control group, with a relatively higher reporting rate of 3.8, 2.0 and 1.7, respectively.

Table 35 All Studies Safety Analysis: Number of subjects reporting SAEs classified by MedDRA Primary System Organ Class, during the entire follow-up period (Total Vaccinated Cohort, all ages, data lock-point August 31, 2008)

MedDRA Primary System Organ Class	HPV N = 31472*		Control N = 23700	
	n	Per 1000	n	Per 1000
At least one symptom	1720	54.65	1609	67.89
Blood and lymphatic system disorders	19	0.60	21	0.89
Cardiac disorders	22	0.70	16	0.68
Congenital, familial and genetic disorders	3	0.10	6	0.25
Ear and labyrinth disorders	6	0.19	8	0.34
Endocrine disorders	10	0.32	4	0.17
Eye disorders	6	0.19	4	0.17
Gastrointestinal disorders	101	3.21	80	3.38
General disorders and administration site conditions	14	0.44	9	0.38
Hepatobiliary disorders	60	1.91	50	2.11
Immune system disorders	8	0.25	14	0.59
Infections and infestations	425	13.50	368	15.53
Injury, poisoning and procedural complications	147	4.67	137	5.78
Investigations	0	0.00	3	0.13
Metabolism and nutrition disorders	19	0.60	18	0.76
Musculoskeletal and connective tissue disorders	35	1.11	22	0.93
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	51	1.62	46	1.94
Nervous system disorders	65	2.07	45	1.90
Pregnancy, puerperium and perinatal conditions	695	22.08	703	29.66
Psychiatric disorders	91	2.89	75	3.16
Renal and urinary disorders	12	0.38	9	0.38
Reproductive system and breast disorders	84	2.67	82	3.46
Respiratory, thoracic and mediastinal disorders	34	1.08	23	0.97
Skin and subcutaneous tissue disorders	7	0.22	6	0.25
Social circumstances	2	0.06	1	0.04
Surgical and medical procedures	42	1.33	52	2.19
Vascular disorders	16	0.51	18	0.76

* 2,151 subjects received *Cervarix* co-administered with another study vaccine but are not included in table: 22 subjects (10.23 per 1000 subjects) reported at least one SAE.
HPV vaccine= HPV-16/18 vaccine, HPV-16/18/31/45 vaccine, HPV-16/18/33/58.
Pooled controls = $Al(OH)_3$, Hepatitis A vaccine containing 360 EL.U. hepatitis A antigen per dose, Hepatitis A vaccine containing 720 EL.U. hepatitis A antigen per dose, *Aimmugen* (500 µg of inactivated hepatitis A viral antigen), *Gardasil, Menactra, Boostrix, Boostrix Polio, Engerix B* or *Twinrix Paediatric.*
Person years of follow-up: HPV = 68,714; Pooled controls = 59,053.

7.3.7. Other adverse events

7.3.7.1. Adverse events leading to study discontinuation

From a total of 37,419 subjects included in the extended pooled safety analysis (data lock-point of August 31, 2008), only 92 (0.3%) subjects withdrew due to an AE or SAE (52 subjects of the 19,871 subjects that received *Cervarix* and 40 subjects of the 17,548 that received control vaccine or placebo) (Table 36).

Table 36 Extended Pooled Safety Analysis: percentage of subjects withdrawn due to AEs or SAEs (Total Vaccinated Cohort, all ages, data lock-point August 31, 2008)

	HPV N = 19871		Pooled controls N = 17548	
	n	%	n	%
Withdrawals due to AE/SAE	52	0.3	40	0.2
Withdrawals due to AE	34	0.2	15	0.1
Withdrawals due to SAE	18	0.1	25	0.1

Pooled Control = ALU, HAV360 and HAV720 groups

Of the 43 subjects who withdrew due to SAEs, study discontinuation resulted from a fatal event in 28 subjects (11 subjects in HPV group and 17 subjects in pooled controls; one subject in HAV720 group withdrew because of the death of her child due to congenital heart disease). See Section 7.3.5 for further details of all fatal events reported all clinical studies in which *Cervarix* has been administered. The other 15 subjects withdrew due to non-fatal SAEs, none of which were considered as causally related to vaccination by the study investigator:

- 7 subjects received *Cervarix*: the withdrawals were due to multiple sclerosis, a prolapsed vertebral disc, moderate dermatological infection, invasive ductal carcinoma stage I (left breast), cervical adenocarcinoma and spontaneous pregnancy loss (2 subjects);
- 8 subjects received control or placebo: anorexia nervosa, cervical carcinoma stage 0, malignant neoplasm, uterine procidentia, multiple trauma following an automobile crash, renal abscess, enteritis and abdominal pain.

In total 49 non-serious adverse events led to subject withdrawal, of which 16 events were solicited symptoms (12 subjects received *Cervarix* and 4 subjects received control vaccine or placebo) and 32 events were unsolicited symptoms (21 subjects received *Cervarix* and 11 subjects received control vaccine or placebo); one subject that received *Cervarix* withdrew due to both solicited (rash) and unsolicited (acne and pruritus) symptoms. Among the solicited symptoms in the HPV group, there were: 3 subjects with fatigue, 3 subjects with injection-site pain, 1 subject with malaise, fatigue and headache, 1 subject with fatigue and malaise, and 1 subject each with headache, arthralgia, urticaria and rash. Unsolicited events leading to withdrawal of subjects that received *Cervarix* included: acne, abortion threatened, asthma, breast neoplasm, bronchopneumonia, cystitis, depression, emotional disorder, erysipelas, headache, herpes zoster, influenza, lymphadenopathy, nausea, ovarian cyst, pruritus, rash, reactive arthritis, syncope, thyroid neoplasm, vaginal discharge. In the control group, the solicited symptoms leading to withdrawal were headache in 1 subject, injection site pain in 1 subject, arthralgia in 1 subject, and fatigue and malaise in 1 subject. Unsolicited symptoms leading to withdrawal of subjects in the control group included: dizziness, dyspepsia, facial pain, gastroenteritis, hypoesthesia, joint swelling, mental disorder, migraine, muscle spasms, uterine hemorrhage, and vaginal hemorrhage.

7.3.7.2. Medically significant conditions

The extended pooled safety analysis of medically significant conditions included data from Studies HPV-008, HPV-012, HPV-012 Ext, HPV-013, HPV-013 Ext, HPV-014, HPV-014 Ext, HPV-015 and HPV-016 using the data lock-point of August 31, 2008, with the maximum length of follow-up of 51.7 months (83,700 person-years).

For the entire follow-up period, similar rates of medically significant conditions were observed between the HPV group and the pooled controls (29.0% and 31.4%, respectively).

Also, the incidence rates of events classified by MedDRA system organ class (SOC) and Preferred Term were similar between the two groups during the entire follow-up period. The most commonly reported medically significant conditions were gynecological Chlamydia infections, reported in 5.9% of subjects in the HPV group and 7.2% of subjects in the pooled controls. Of note, regular screening for *Chlamydia trachomatis* and *Neisseria gonorrhea* was performed during the course of Study HPV-008. Medically significant conditions not related to gynecological chlamydia infections and genitourinary tract gonococcal infections were reported much less frequently with the next most common event being depression (in 1.2% of subjects in each group) and bronchitis (in 0.7% of subjects in the HPV group and 0.6% of subjects in the pooled controls).

7.3.7.3. New Onset of Autoimmune Disorders

Overall, the percentage of subjects 10-25 years of age reporting the occurrence of new onset of potential autoimmune disorders was low and there were no apparent differences in the reporting rates between the HPV group (93 subjects reporting at least one event, 0.74%) and pooled controls (86 subjects reporting at least one event, 0.80%) for the entire follow-up period (Table 37).

In the largest randomized controlled trial (Study HPV-008), the incidence of NOADs was 0.8% in both the groups receiving *Cervarix* and control, with 78 events among 9,319 subjects receiving *Cervarix* and 77 events among 9,325 subjects receiving control.

No cluster (i.e. unanticipated grouping or pattern) of events was detected (Table 37). The most frequently reported events were related to thyroid disease as would be expected based on the background incidence rates of disease in a young female population. There was no observed difference in the reported rates of thyroid disease between treatment groups.

Data from clinical studies with *Cervarix* demonstrate that no increased risk of NOAD following vaccination with *Cervarix* has been identified. Although this analysis was based on 23,263 subjects, the low frequency of autoimmune disorders in the general population constitutes a limitation of their assessment in a clinical program. Therefore, additional assessments were performed on a larger database (see Section 7.3.8).

Table 37 Updated Pooled Safety Analysis: Percentage of subjects reporting NOADs (Total Vaccinated Cohort, 10-25 year olds)

MedDRA Preferred Term	HPV N = 12533		Pooled Controls N = 10730	
	n	%	n	%
At least one symptom	93	0.74	86	0.80
Hypothyroidism	22	0.18	24	0.22
Psoriasis	7	0.06	7	0.07
Goitre	6	0.05	8	0.07
Autoimmune thyroiditis	5	0.04	4	0.04
Hyperthyroidism	5	0.04	5	0.05
Arthritis reactive	5	0.04	0	0.00
Arthritis	4	0.03	4	0.04
Rheumatoid arthritis	4	0.03	3	0.03
Multiple sclerosis	4	0.03	1	0.01
Basedow's disease	3	0.02	2	0.02
Colitis ulcerative	3	0.02	1	0.01
Diabetes mellitus	3	0.02	5	0.05
Erythema nodosum	3	0.02	0	0.00
Thyroiditis	2	0.02	0	0.00
Coeliac disease	2	0.02	5	0.05
Crohn's disease	2	0.02	2	0.02
Proctitis ulcerative	2	0.02	0	0.00
Type 1 diabetes mellitus	2	0.02	0	0.00
Systemic lupus erythematosus	2	0.02	2	0.02
Optic neuritis	2	0.02	1	0.01
Vitiligo	2	0.02	2	0.02
Idiopathic thrombocytopenic purpura	1	0.01	0	0.00
Inflammatory bowel disease	1	0.01	1	0.01
Myelitis transverse	1	0.01	0	0.00
Optic neuritis retrobulbar	1	0.01	0	0.00
Leukocytoclastic vasculitis	1	0.01	0	0.00
Thrombocytopenia	0	0.00	1	0.01
Psoriatic arthropathy	0	0.00	1	0.01
Cutaneous lupus erythematosus	0	0.00	1	0.01
Dermatomyositis	0	0.00	1	0.01
Guttate psoriasis	0	0.00	1	0.01
Nail psoriasis	0	0.00	1	0.01
Raynaud's phenomenon	0	0.00	1	0.01
Vasculitis	0	0.00	3	0.03

HPV group: 10-25 years, Pooled controls group: 10-25 years
Pooled controls = ALU+HAV360+HAV720

7.3.8. Disorders of potential autoimmune etiology

7.3.8.1. Meta-analysis in clinical studies with MPL-containing vaccines

Data from clinical studies with *Cervarix* did not indicate any increased incidence of autoimmune diseases after vaccination with *Cervarix* compared to administration of control vaccine. However, such diseases occur at a very low frequency, thus a clinical database including 23,263 subjects might not be sufficient to rule out such an effect.

In response to a request from CBER, GSK Biologicals performed a meta-analysis of disorders of potentially autoimmune etiology [Verstraeten, 2008]. Included were all controlled studies conducted with HPV vaccines and other AS04-adjuvanted vaccines (an adjuvanted prophylactic HBV vaccine licensed in Europe, *Fendrix,* and investigational prophylactic HSV vaccine). *Fendrix* was licensed in Europe in 2005 for patients with renal insufficiency (including pre-hemodialysis and hemodialysis patients), from the age of 15 years onwards.

In total, 68,512 subjects from randomized, controlled trials of HPV, HSV and HBV vaccines were included in these meta-analyses, of which 36,744 subjects received over 93,997 doses of AS04-containing vaccines up to the data lock-point of June 30, 2007 (except for Study HPV-009 [March 31, 2007] and Study HPV-008 [July 31, 2007]), see Figure 20.

A pre-specified list of terms grouped according to categories of the disease (CBER category of diseases and verbatim terms) was used to identify events of interest among all reported SAEs and unsolicited adverse events, including the following:

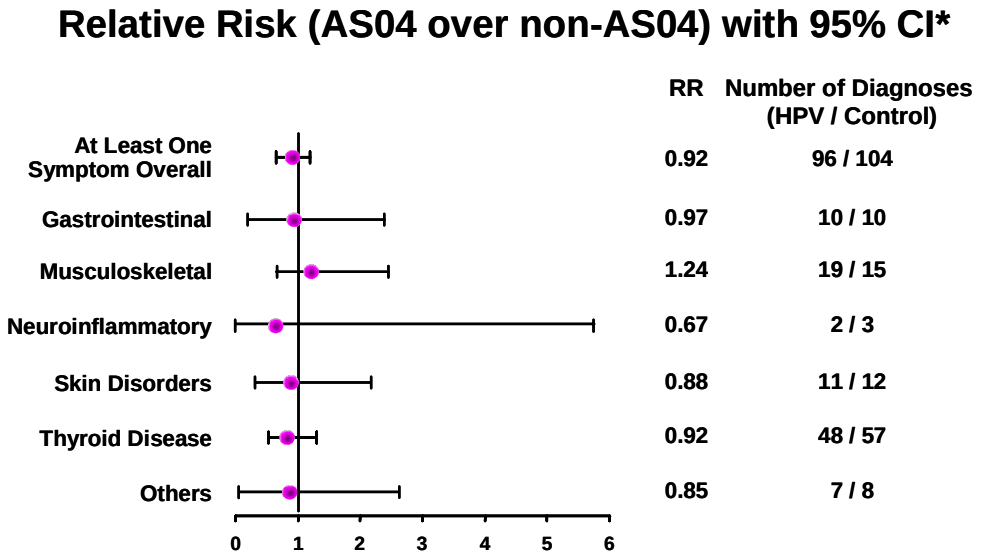
- Category of neuroinflammatory events: optic neuritis, multiple sclerosis, demyelinating disease, myasthenia gravis, transverse myelitis, myelitis, encephalitis and Guillain-Barré syndrome;
- Category of musculoskeletal disorders: systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, juvenile rheumatoid arthritis, arthritis, reactive arthritis and scleroderma;
- Category of gastrointestinal disorders: inflammatory bowel disease, Crohn's disease, ulcerative colitis, ulcerative proctitis and coeliac disease;
- Category of thyroid diseases: Graves' disease, thyroiditis, hyperthyroidism, hypothyroidism and goiter;
- Category of skin disorders: cutaneous lupus, dermatomyositis, vitiligo, erythema nodosum, psoriasis, psoriatic arthropathy, Stevens-Johnson syndrome and Raynaud's phenomenon;
- Category of other disorders: autoimmune haemolytic anaemia, antiphospholipid syndrome, insulin-dependent diabetes mellitus, idiopathic thrombocytopenic purpura, autoimmune hepatitis, nephritis, autoimmune glomerulonephritis, uveitis, sarcoidosis, Addison's disease and vasculitis.

Event rates were estimated by treatment group (vaccines containing AS04 [AS04 group] and vaccines not containing AS04 or placebo [non-AS04 group]) and were compared between treatment groups. The common relative risk across studies and its 95% CI was estimated on the exact conditional likelihood approach adjusted for the study effect.

Meta-analyses were performed on two levels, the first level including all studies in the HPV program, including investigational HPV vaccines as well as *Cervarix*, (HPV vaccine analysis) and the second level including all studies performed with AS04-containing vaccines, i.e. HSV adjuvanted vaccines containing AS04 and *Fendrix*, in addition to investigational HPV vaccines and *Cervarix*, (pooled HPV, HSV, HBV vaccine analysis).

In both analyses, the overall occurrence rate of potential autoimmune disorders was comparable between the AS04 group and the control (non-AS04) group (relative risk [AS04 group/non-AS04 group] of 0.92 [95% CI 0.70; 1.22] and 0.98 [95% CI 0.80; 1.21] for the HPV vaccine and pooled HPV, HSV, HBV vaccine analyses respectively) (Figure 25 and Figure 26 respectively). As expected, the most frequently occurring disorders were diseases of the thyroid, followed by musculoskeletal disorders. No imbalances were seen when comparing the event rates by individual disorder or groups of disorders.

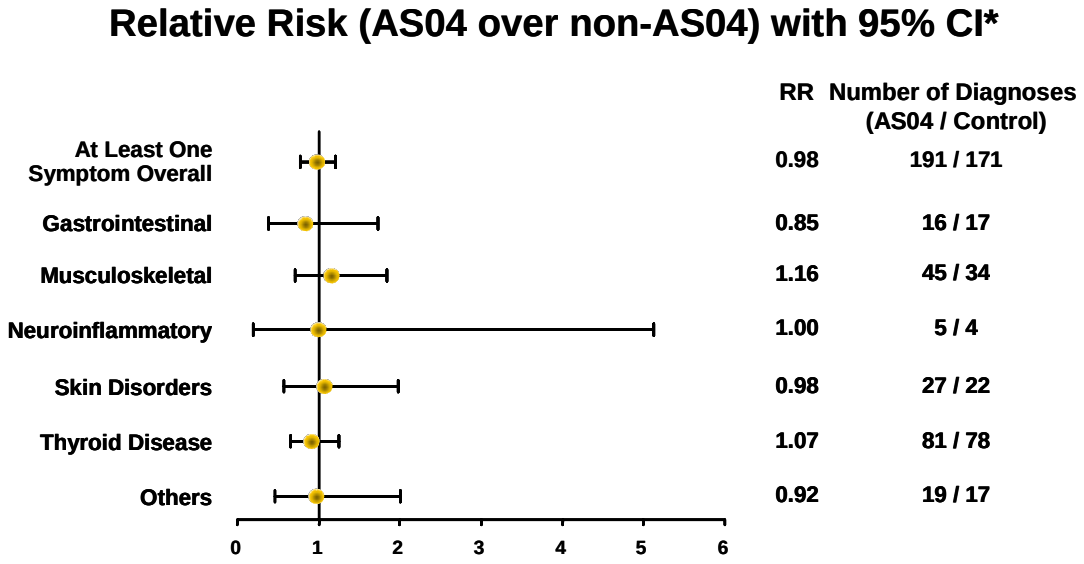
Figure 25 Estimated Relative Risks for reporting of adverse events, classified by CBER categories of diseases, during the entire study period (HPV vaccine analysis)



*** 95% CI = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)**

Data lock-point: June 30, 2007

Figure 26 Estimated Relative Risks for reporting of adverse events, classified by CBER categories of diseases, during the entire study period (pooled HPV, HSV, HBV vaccine analysis)



*** 95% CI = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)**

Data lock-point: June 30, 2007

In conclusion, these analyses did not suggest any causal association between AS04-containing vaccines and the development of disorders of potentially autoimmune etiology.

Despite the large size of the safety database for AS04-containing vaccines, an increased risk for the more rare events can only be excluded with a limited degree of certainty, as reflected in the width of some of the confidence intervals of the relative risk estimates. Consequently, surveillance of potential autoimmune disorders will continue in the ongoing clinical development program and in the planned post-marketing activities (see Section 8 for further details).

7.3.8.2. Update of the meta-analysis with respect to neuroinflammatory and musculoskeletal events

7.3.8.2.1. Neuroinflammatory and musculoskeletal events (data lock-point of August 31, 2008)

At the request of CBER, further analyses for neuroinflammatory and musculoskeletal terms were performed and submitted to the BLA. These analyses include an update of the events reported up to the data lock-point of August 31, 2008 and a review of the events by an external expert panel. The results of expert review and assessment of neuroinflammatory and musculoskeletal events reported up to the data lock-point of December 31, 2007 are presented in Section 7.3.8.2.2. The external expert panel review and assessment of events reported up to the later data lock-point is ongoing and are therefore not currently available.

Besides extending the data lock-point, the updated analyses also include the following changes:

- Inclusion of additional terms on request of FDA. In addition to the terms listed in Section 7.3.8.1, arthropathy, spondyloarthropathy and fibromyalgia were also included in the updated analysis of musculoskeletal events.

- Differentiation of reporting period. For the analysis of events reported up to the data lock-point of August 31, 2008, two reporting periods were considered with respect to the start date of the reported events: throughout the entire follow-up period and for a follow-up period from dose 1 up to 6 months after the last dose the subject received. The follow-up period from dose 1 up to 6 months after the last vaccination corresponds to a "theoretical risk" period covering the 6-month period of active vaccination during which three doses of *Cervarix* were administered and the 6-month period following last vaccination, during which the active immune response to vaccination is expected to be high. This period was proposed by an autoimmune expert panel as the period where the likelihood of observing an increased risk of new events was highest if there would be a causal link between the events and the vaccines.

As expected, the number of neuroinflammatory events reported was very low, both in the 6-month period following vaccination and in the entire follow-up period. Whereas there were slightly more cases in the AS04 group for the entire follow-up period, there were fewer cases in the AS04 group in the month 0 to month 12 risk period (Table 38).

As was seen in the original meta-analysis, musculoskeletal events were much more frequent but generally occurred at comparable rates in the AS04 and control groups. A slightly increased rate observed in the HPV vaccines only analysis for the month 0 to month 12 risk is no longer seen in the extended analysis including all AS04-containing vaccines (Table 39).

For both groups of events and for all individual events, all 95% CIs included 1, indicating that there was no statistically significant difference in relative risk in the AS04 groups compared with the control groups for this analysis of unadjudicated events.

In summary, the results of this updated MPL meta-analysis do not suggest a causal association between MPL-containing vaccines and the development of neuroinflammatory or musculoskeletal disorders.

Table 38 Percentage of subjects reporting neuroinflammatory events with estimated relative risks (Total Vaccinated Cohort, controlled studies, data lock-point August 31, 2008*)

Level of analysis	Reporting period	AS04					Non-AS04					Relative Risk		
		N	n	%	95% CI		N	n	%	95% CI		RR	95% CI**	
					LL	UL				LL	UL		LL	UL
HPV vaccines	Month 0 to Month 12	27515	0	0.00	0.00	0.01	27742	2	0.01	0.00	0.03	0.00	0.00	5.33
	Entire follow-up period	27515	7	0.03	0.01	0.05	27742	3	0.01	0.00	0.03	2.33	0.53	13.97
HPV, HSV, HBV vaccines	Month 0 to Month 12	44787	1	0.00	0.00	0.01	40335	2	0.00	0.00	0.02	0.39	0.01	7.82
	Entire follow-up period	44787	10	0.02	0.01	0.04	40335	5	0.01	0.00	0.03	1.74	0.54	6.54

* For Study HPV-009, the data lock-point was July 1, 2008
RR = relative risk (groups AS04 over non-AS04)
** 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

Table 39 Percentage of subjects reporting musculoskeletal events with estimated relative risks (Total Vaccinated Cohort, controlled studies, data lock-point August 31, 2008*)

Level of analysis	Reporting period	AS04					Non-AS04					Relative Risk		
		N	n	%	95% CI		N	n	%	95% CI		RR	95% CI**	
					LL	UL				LL	UL		LL	UL
HPV vaccines	Month 0 to Month 12	27515	19	0.07	0.04	0.11	27742	12	0.04	0.02	0.08	1.58	0.73	3.57
	Entire follow-up period	27515	39	0.14	0.10	0.19	27742	29	0.10	0.07	0.15	1.31	0.79	2.20
HPV, HSV, HBV vaccines	Month 0 to Month 12	44787	49	0.11	0.08	0.14	40335	42	0.10	0.08	0.14	0.99	0.63	1.54
	Entire follow-up period	44787	76	0.17	0.13	0.21	40335	59	0.15	0.11	0.19	1.14	0.80	1.63

* For Study HPV-009, the data lock-point was July 1, 2008
RR = relative risk (groups AS04 over non-AS04)
** 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

7.3.8.2.2. Neuroinflammatory and musculoskeletal events with assessment and review by expert panels of neurologists and rheumatologists (data lock-point of December 31, 2007)

In addition to updating the initial analysis of musculoskeletal and neuroinflammatory events, GSK also consulted two panels of external experts in the fields of neurology and rheumatology to confirm the diagnosis for neuroinflammatory and musculoskeletal events reported in the meta-analysis of clinical studies with MPL-containing vaccines. The expert panels performed a blinded review of the clinical information as well as source documents provided by study sites on all neuroinflammatory and musculoskeletal events, respectively, reported to GSK up to a data lock-point of December 31, 2007 (data lock-point for Study HPV-009 was December 14, 2007). Based on this blinded review, the experts reached a consensus diagnosis for each event, identifying those for which the data supported an immune-mediated etiology, and also considering the degree of diagnostic certainty. The experts also determined the onset date of the disorders and

considered the period of 12 months following first vaccination to be the period of highest theoretical risk. This information allowed GSK to perform a time to onset analysis of events with a confirmed immune mediated etiology.

For neuroinflammatory events, the expert panel reviewed in total 17 cases of potential neuroinflammatory disorders. A confirmed diagnosis was reached for 12 events reported (9 cases of clinically isolated syndrome, 1 case of multiple sclerosis and 2 cases of Guillain Barré Syndrome) of which 8 occurred in controlled trials.

Table 40 summarizes the relative risks for "at least one confirmed neuroinflammatory event" according to onset date. Overall, there were very few neuroinflammatory events with a confirmed diagnosis with small numerical differences between the AS04 and non-AS04 groups and no relative risk above 1.

Table 40 Percentage of subjects reporting neuroinflammatory events with a confirmed diagnosis by external experts with estimated relative risks (Total Vaccinated Cohort, controlled studies, data lock-point December 31, 2007*)

Reporting period	Term	AS04					Non-AS04					Relative Risk		
		N	n	%	95% CI		N	n	%	95% CI		RR	95% CI**	
					LL	UL				LL	UL		LL	UL
HPV vaccines														
Month 0 to Month 12	At least one symptom	25580	0	0.00	0.00	0.01	25438	2	0.01	0.00	0.03	0.00	0.00	5.33
	Multiple sclerosis	25580	0	0.00	0.00	0.01	25438	1	0.00	0.00	0.02	0.00	0.00	39.00
	Optic neuritis	25580	0	0.00	0.00	0.01	25438	1	0.00	0.00	0.02	0.00	0.00	39.03
Entire follow-up period	At least one symptom	25580	3	0.01	0.00	0.03	25438	3	0.01	0.00	0.03	1.00	0.13	7.47
	Multiple sclerosis	25580	1	0.00	0.00	0.02	25438	1	0.00	0.00	0.02	1.00	0.01	78.52
	Myelitis transverse	25580	1	0.00	0.00	0.02	25438	0	0.00	0.00	0.01	INF	0.03	INF
	Optic neuritis	25580	2	0.01	0.00	0.03	25438	2	0.01	0.00	0.03	1.00	0.07	13.80
HPV, HSV, HBV vaccines														
Month 0 to Month 12	At least one symptom	42600	1	0.00	0.00	0.01	37769	3	0.01	0.00	0.02	0.23	0.00	2.96
	Guillain-barre syndrome	42600	1	0.00	0.00	0.01	37769	1	0.00	0.00	0.01	0.50	0.01	39.38
	Multiple sclerosis	42600	0	0.00	0.00	0.01	37769	1	0.00	0.00	0.01	0.00	0.00	39.00
	Optic neuritis	42600	0	0.00	0.00	0.01	37769	1	0.00	0.00	0.01	0.00	0.00	39.03
Entire follow-up period	At least one symptom	42600	0	0.00	0.00	0.01	37769	4	0.01	0.00	0.03	0.84	0.15	4.61
	Guillain-barre syndrome	42600	1	0.00	0.00	0.01	37769	1	0.00	0.00	0.01	0.50	0.01	39.38
	Multiple sclerosis	42600	1	0.00	0.00	0.01	37769	1	0.00	0.00	0.01	1.00	0.01	78.52
	Myelitis transverse	42600	1	0.00	0.00	0.01	37769	0	0.00	0.00	0.01	INF	0.03	INF
	Optic neuritis	42600	2	0.00	0.00	0.02	37769	2	0.01	0.00	0.02	1.00	0.07	13.80

* For Study HPV-009, the data lock-point was December 14, 2007
RR = relative risk (groups AS04 over non-AS04)
** 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

For musculoskeletal disorders, the expert panel of rheumatologists reviewed in a blinded fashion in total of 146 musculoskeletal events, reported in 142 subjects. As part of their review, the experts adjudicated whether an event was an immune-mediated inflammatory

rheumatologic event or not and considered the diagnostic level of certainty for each event (confirmed, uncertain or no immune-mediated rheumatologic event). A consensus and final diagnosis was reached on the classification of all reported events. Nearly half of all events were considered not to be immune-mediated rheumatologic events (IMREs) (67 events) and were mainly degenerative or traumatic disorders. For a further 49 events, 30 were uncertain to be immune-mediated rheumatologic events (of which 24 were reported in controlled studies) and 19 events had a diagnosis assigned by the experts that was not included in the CBER list of terms for musculoskeletal events. Thus, there remained 30 events as confirmed IMREs under the CBER list of terms for musculoskeletal events (Table 41) with two events reported in one subject (rheumatoid arthritis twice).

From the confirmed 30 IMREs, 21 events were classified as occurring with new onset post-vaccination (Anytime-at-risk), of which eight events were classified as occurring within the period between the first vaccination and 6 months after last vaccination (Time-at-risk), and nine events were classified as pre-existing conditions (Table 41). The analysis of time-to onset excluded the nine pre-existing events and focused on 19 events of new onset (excluding one subject reporting rheumatoid arthritis twice in an uncontrolled study).

Table 41 Summary of all confirmed IMREs included in the CBER list of terms for musculoskeletal events, adjudicated by the expert panel of rheumatologists (AS04 and nonAS04 groups combined)

Confirmed diagnosis	Pre-existing confirmed IMRE	Confirmed IMRE with new onset		All Confirmed IMRE
		Time-at-risk	Anytime-at-risk	
Arthritis	3	3	6	9
Juvenile arthritis	2	0	0	2
Reactive arthritis	0	2	2	2
Rheumatoid arthritis	2	2	9*	11*
Systemic lupus erythematosus	2	1	4	6
Total	9	8	21	30

Time-at-risk: event with onset between the first vaccination and 6 months after last vaccination.
Anytime-at-risk: event with onset following first vaccination.
*Two events (rheumatoid arthritis) were reported by the same subject and counted as one event for analysis.

Table 42 summarizes the distribution of the cases and the associated relative risks for "at least one confirmed IMRE" according to onset date. None of the relative risk estimations indicate any statistically significant increased risk for musculoskeletal disorders following receipt of AS04 containing vaccines. Although there are a limited number of events in some of the subanalyses, in the broadest analysis (all HPV, HSV and HBV vaccines including the entire follow-up period), the relative risk is 1.07 and a numerical imbalance in the number of confirmed cases is not observed.

Table 42 Percentage of subjects reporting musculoskeletal events with a confirmed diagnosis by external experts with estimated relative risks (Total Vaccinated Cohort, controlled studies, data lock-point December 31, 2007*)

Reporting period	Term	AS04					Non-AS04					Relative Risk		
		N	n	%	95% CI		N	n	%	95% CI		RR	95% CI**	
					LL	UL				LL	UL		LL	UL
HPV vaccines														
Month 0 to Month 12	At least one symptom	25580	3	0.01	0.00	0.03	25438	1	0.00	0.00	0.02	3.00	0.24	157.41
	Arthritis reactive	25580	2	0.01	0.00	0.03	25438	0	0.00	0.00	0.01	INF	0.19	INF
	Rheumatoid arthritis	25580	1	0.00	0.00	0.02	25438	1	0.00	0.00	0.02	1.00	0.01	78.52
Entire follow-up period	At least one symptom	25580	7	0.03	0.01	0.06	25438	7	0.03	0.01	0.06	1.00	0.30	3.34
	Arthritis	25580	0	0.00	0.00	0.01	25438	3	0.01	0.00	0.03	0.00	0.00	2.42
	Arthritis reactive	25580	2	0.01	0.00	0.03	25438	0	0.00	0.00	0.01	INF	0.19	INF
	Rheumatoid arthritis	25580	4	0.02	0.00	0.04	25438	3	0.01	0.00	0.03	1.33	0.23	9.09
	Systemic lupus erythematosus	25580	1	0.00	0.00	0.02	25438	1	0.00	0.00	0.02	1.00	0.01	78.54
HPV, HSV, HBV vaccines														
Month 0 to Month 12	At least one symptom	42600	5	0.01	0.00	0.03	37769	3	0.01	0.00	0.02	1.58	0.30	10.30
	Arthritis	42600	1	0.00	0.00	0.01	37769	2	0.01	0.00	0.02	0.44	0.01	9.06
	Arthritis reactive	42600	2	0.00	0.00	0.02	37769	0	0.00	0.00	0.01	INF	0.19	INF
	Rheumatoid arthritis	42600	1	0.00	0.00	0.01	37769	1	0.00	0.00	0.01	1.00	0.01	78.52
	Systemic lupus erythematosus	42600	1	0.00	0.00	0.01	37769	0	0.00	0.00	0.01	INF	0.02	INF
Entire follow-up period	At least one symptom	42600	10	0.02	0.01	0.04	37769	9	0.02	0.01	0.05	1.07	0.39	2.99
	Arthritis	42600	1	0.00	0.00	0.01	37769	5	0.01	0.00	0.03	0.18	0.00	1.69
	Arthritis reactive	42600	2	0.00	0.00	0.02	37769	0	0.00	0.00	0.01	INF	0.19	INF
	Rheumatoid arthritis	42600	4	0.01	0.00	0.02	37769	3	0.01	0.00	0.02	1.33	0.23	9.09
	Systemic lupus erythematosus	42600	3	0.01	0.00	0.02	37769	1	0.00	0.00	0.01	2.70	0.22	142.12

RR = relative risk (groups AS04 over non-AS04)

* For Study HPV-009, the data lock-point was December 14, 2007

** 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

For individual terms, there were few confirmed events for each term with mostly balanced reporting between AS04 and non-AS04 groups and relative risks below or close to 1 (Table 42). The numerical imbalances noted for reactive arthritis and SLE, with relative risks above 1, result from two cases of reactive arthritis reported in two subjects vaccinated with *Cervarix* and two cases of SLE reported in two subjects following vaccination with the investigational HSV vaccine:

- The first reactive arthritis case occurred 6 months after third HPV dose in a 17 year old girl who also experienced a Chlamydia infection. The second reactive arthritis case occurred in a 44 year old woman 4 days after the first dose of *Cervarix* with a concurrent acute gastro-enteritis episode. No symptoms occurred after administration of the second dose of *Cervarix*.
- The first SLE case occurred 3 months after the second dose of HSV in a 24 year old woman with a medical history of frequent upper respiratory tract infection, depression, infectious mononucleosis, bronchitis/asthma and seizures. The second SLE case occurred approximately 11 months after the third dose of HSV in a 25 year old woman with history of neck swelling, possible vasculitis and swelling of the legs.

For events with an uncertain diagnosis (i.e., events that the experts considered the available information was insufficient to confirm or reject the possible immune-mediated nature of the event), a sensitivity analysis was performed by GSK (Table 43). The relative risks for the HPV vaccines analysis and the pooled HPV, HSV, HBV vaccines analysis were 1.88 [95% CI 0.21; 23.88] and 1.15 [95% CI 0.46; 2.96] respectively, indicating that there was no significant imbalance in the distribution of uncertain events between the AS04 and non-AS04 groups. It should be note that this analysis includes pre-existing conditions as well as those of new onset. A separate analysis of confirmed IMREs with new onset after vaccination is summarized in Table 42.

Table 43 Relative risks of immune-mediated rheumatologic events with a uncertain diagnosis adjudicated by the expert panel for subjects reporting at least one event (Total Vaccinated Cohort, controlled studies, data lock-point December 31, 2007*)

Level of analysis	AS04					Non-AS04					Relative Risk		
	N	n	%	95% CI		N	n	%	95% CI		RR	95% CI**	
				LL	UL				LL	UL		LL	UL
HPV vaccines	25580	3	0.01	0.00	0.03	25438	2	0.01	0.00	0.03	1.88	0.21	23.88
HPV, HSV, HBV vaccines	42600	14	0.03	0.01	0.05	37769	10	0.03	0.01	0.05	1.15	0.46	2.96

* For Study HPV-009, the data lock-point was December 14, 2007
RR = relative risk (groups AS04 over non-AS04)
** 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

In conclusion, the expert panel review of neuroinflammatory and musculoskeletal events indicated that, although several of the few neuroinflammatory disorders reported could be considered as true immune-mediated events, only a small fraction of the musculoskeletal events reported should be considered as true immune-mediated events. While there are some numerical imbalances among the distribution of the musculoskeletal events between the AS04 and control groups, these are not consistent in the various analyses and occur in both directions and are related to cases that are unlikely to be vaccine related. The large variations in the relative risk estimates with points estimates both below and above 1 further suggest that the imbalances are most likely to be due to the small numbers and not suggestive of a true causally-related association to vaccination with HPV or AS04.

7.3.9. Pregnancies and pregnancy outcomes

With the majority of subjects included in the clinical safety database consisting of women of child-bearing potential, the follow-up of pregnancies and their outcomes was an aspect of safety reporting that was thoroughly evaluated.

Adequate and well-controlled studies of *Cervarix* specifically targeting pregnant women have not been conducted. Pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued in the event of a positive pregnancy test. In all clinical trials, subjects were instructed to take precautions to avoid pregnancy until 2 months after the last vaccination. For all studies, throughout the study period, subjects were instructed to report any pregnancy, which was then followed until outcome.

An evaluation of pregnancy outcomes was performed by GSK based on data from studies in the pooled analysis, including their extension studies and Study HPV-009, with a later data lock-point of August 31, 2008 (7,276 pregnancies reported in 37,419 female subjects in total). The majority of pregnancies (6,838 pregnancies) were reported in young women between 15 to 25 years of age, i.e., the age group considered for the two large phase III studies HPV-008 and HPV-009 (including more than 26,000 subjects). No imbalances in the rates of any specific pregnancy outcome were observed between the HPV vaccine and control groups based on this analysis of all pregnancies (Table 44).

Table 44 Extended Pooled Safety Analysis: Pregnancy outcomes over the total number of pregnancies reported overall (Total Vaccinated Cohort, data lock-point of August 31, 2008, all ages)

Pregnancy outcomes	HPV (19871 subjects)		ALU (3454 subjects)		HAV360 (1032 subjects)		HAV720 (13062 subjects)		Pooled Control (17548 subjects)	
	N = 3696		N = 380		N = 10		N = 3190		N = 3580	
	n	%	n	%	n	%	n	%	n	%
Normal Infant	2300	62.2	221	58.2	7	70.0	2012	63.1	2240	62.6
Pregnancy ongoing	490	13.3	37	9.7	0	0.0	422	13.2	459	12.8
Spontaneous loss	408	11.0	65	17.1	0	0.0	323	10.1	388	10.8
Elective termination	216	5.8	22	5.8	1	10.0	194	6.1	217	6.1
Infant peri-natal conditions	105	2.8	8	2.1	0	0.0	106	3.3	114	3.2
Premature birth	73	2.0	9	2.4	2	20.0	51	1.6	62	1.7
Congenital anomaly	30	0.8	6	1.6	0	0.0	22	0.7	28	0.8
Lost to follow-up	24	0.7	1	0.3	0	0.0	24	0.8	25	0.7
Ectopic pregnancies	22	0.6	6	1.6	0	0.0	15	0.5	21	0.6
Still birth	20	0.5	2	0.5	0	0.0	17	0.5	19	0.5
Therapeutic abortion	4	0.1	3	0.8	0	0.0	1	0.0	4	0.1
Not applicable	4	0.1	0	0.0	0	0.0	3	0.1	3	0.1

Pooled Control = ALU, HAV360 and HAV720 groups
N = number of pregnancies
n = number of pregnancies in a given category
Notes:
Twin pregnancies counted as one pregnancy
Spontaneous loss includes missed abortion
Infant peri-natal conditions: not including congenital anomalies
Not applicable: e.g. mole, trophoblastic tumor

Of note, the pooled safety analysis differentiates outcomes "Infant peri-natal conditions not including congenital anomalies" and "congenital anomaly", according to the CDC Metropolitan Atlanta Congenital Defects Program criteria (Centers for Disease Control and Prevention, 1989). The category of infant peri-natal conditions includes medically significant outcomes (such as neonatal icterus or hypoxia) and other congenital disorders of non-structural-morphological, chromosomal or genetic etiology (e.g. hydrocele, infectious conditions or minor congenital conditions such as single benign hemangioma). Among the 219 reported pregnancy cases which resulted in an infant peri-natal condition (excluding congenital anomalies) (105 in the HPV group and 114 in the control group), no unexpected pattern of events or distinctive malformations were identified. An evaluation of congenital anomalies showed no imbalance in the number of reports. A total of 60 cases of congenital anomalies were reported in 59 subjects (1 twin pregnancy): 30 subjects that received *Cervarix* (30/3696 pregnancies) and 28 subjects that received control (28/3580 pregnancies) and one subject did not receive study vaccination. There

was no specific pattern or cluster of the type of defects reported. The independent expert panel of teratologists/geneticists concluded that the currently available data do not indicate an increased risk of congenital anomalies in subjects vaccinated with *Cervarix*.

An additional exploratory analysis was performed in a non-randomized subset of subjects with pregnancies around vaccination (defined as last menstrual period [LMP] from 30 days before until 45 days post-vaccination) (Table 45). A total of 761 subjects with LMP around vaccination reported pregnancies. The proportion of subjects who experienced specific pregnancy outcomes remained similar between treatment groups with the exception of spontaneous loss, for which a numerical imbalance was observed with a higher rate in the HPV group (54/396 pregnancies, 13.6%) when compared to the pooled controls (35/365 pregnancies, 9.6%). Note that the pregnancy data is mainly driven by the large phase III studies HPV-008 and HPV-009, with a combined sum of 6,395 pregnancies reported out of the total of 7,276 pregnancies in the updated pooled analysis.

Table 45 Extended Pooled Safety Analysis: Pregnancy outcomes over the total number of pregnancies reported around vaccination (Total Vaccinated Cohort, data lock-point of August 31, 2008, all ages)

Pregnancy outcomes	HPV (19871 subjects)		ALU (3454 subjects)		HAV360 (1032 subjects)		HAV720 (13062 subjects)		Pooled Control (17548 subjects)	
	N = 396		N = 43		N = 1		N = 321		N = 365	
	n	%	N	%	N	%	N	%	n	%
Normal Infant	258	65.2	22	51.2	0	0.00	231	72.0	253	69.3
Spontaneous loss	54	13.6	7	16.3	0	0.0	28	8.7	35	9.6
Elective termination	39	9.9	8	18.6	0	0.0	27	8.4	35	9.6
Infant peri-natal conditions	20	5.1	1	2.3	0	0.0	16	5.0	17	4.7
Premature birth	10	2.5	2	4.7	1	100.0	6	1.9	9	2.5
Congenital anomaly	7	1.8	1	2.3	0	0.0	4	1.3	5	1.4
Lost to follow-up	4	1.0	0	0.0	0	0.0	5	1.6	5	1.4
Ectopic pregnancies	2	0.5	0	0.0	0	0.0	1	0.3	1	0.3
Therapeutic abortion	1	0.3	0	0.0	0	0.0	1	0.3	1	0.3
Still birth	1	0.3	1	2.3	0	0.0	2	0.6	3	0.8
Pregnancy ongoing	0	0.0	1	2.3	0	0.0	0	0.0	1	0.3
Not applicable	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Pooled Control = ALU, HAV360 and HAV720 groups
N = number of pregnancies around vaccination (pregnancy in a subject for which LMP occurred between 30 days before and 45 after vaccination)
n = number of pregnancies in a given category
Notes:
Twin pregnancies counted as one pregnancy
Spontaneous loss includes missed abortion
Infant peri-natal conditions: not including congenital anomalies
Not applicable: e.g. mole, trophoblastic tumor

In light of the numerical imbalance observed in the number of spontaneous pregnancy losses in the analysis of pregnancies around vaccination, further evaluation and review of pregnancy outcomes was undertaken. Information is provided below:

- Preclinical studies with *Cervarix* do not indicate a potential risk with vaccination, with respect to pregnancy or pregnancy outcomes. Reproduction studies have been performed in rats at doses up to approximately 56 times the human dose (4 µg each of HPV-16 L1 and HPV-18 L1 protein), and revealed no evidence of impaired fertility

or harm to the fetus due to *Cervarix*. The dose selected was previously shown to induce significant antibody responses in the rat (inclusive of gestation and post-natal periods). Vaccination of female rats with *Cervarix* 30 days before pairing did not affect estrous cycles, mating behavior, or fertility.

- Additional analyses were conducted to determine the distribution of spontaneous loss by gestational age and by timing of exposure relative to vaccination:

  Further comparison of the data from the two large phase III studies HPV-008 and HPV-009 that contributed to the majority of pregnancy outcomes failed to establish any consistent pattern to relate the imbalance in spontaneous loss around vaccination to dosing or gestational age of the fetus at the time of abortion. The difference in the rates between the two groups did not differ with increasing doses and the average gestational age at which the abortion occurred was also not different between the HPV and control groups.

  In an independent evaluation of spontaneous loss rates based on a pooled dataset of studies HPV-008 and HPV-009 [Wacholder, 2009], conducted by the NCI, it was concluded that the analysis did not establish a relationship between HPV vaccination and the risk of spontaneous loss but was insufficient to rule out a small effect in pregnancies conceived in the 3 months immediately after vaccination.

- Since the original observations were made with data from the Phase III trials HPV-008 and HPV-009, a separate analysis was performed on studies in the analysis excluding HPV-008 and HPV-009 in which 79 pregnancies were reported around vaccination (35 pregnancies in the HPV group and 44 pregnancies in the pooled control group). In the analysis limited to these trials, no imbalance occurred with spontaneous loss rates (14.3% and 15.9% in the HPV and control groups, respectively).

- Consideration of the biological plausibility that vaccination with *Cervarix* may cause an increase in the rate of spontaneous loss concluded that there are no known theoretical mechanisms by which the vaccine might induce spontaneous loss. A theoretical link to the anti-phospholipid syndrome is not supported by the observations (no repeated losses) nor by the fact that the target antigens for the anti-phospolipid syndrome (β-2 glycoprotein) and cardiolipin show no similarity to any of the vaccine components.

- A comparison with the background rates of spontaneous losses in the US determined that the rates of spontaneous loss observed following vaccination with *Cervarix* were closer to the lower limit of the reported background rates of spontaneous loss in the US (9.1% to 21.2%) [Zinaman, 1996; Goldhaber, 1991; Goldhaber, 2000; Swan, 1998; Li, 2002; Massad, 2004; Jones, 2007; Wilcox, 1981; Savitz, 2008; Wilcox, 1988; Harlap, 1980; Ellish, 1996; Eskenazi, 1995; Hakim, 1995; Sweeney, 1988]. Since pregnancies were actively screened for in the trials, proper comparison is most likely to be to the higher reported background rates.

In conclusion, the results of pregnancy outcomes have been rigorously assessed both internally and externally. Although there is an observed numerical imbalance in spontaneous loss rates in subjects receiving *Cervarix* whose onset of pregnancy is within

2 months following vaccination compared with controls, the numbers are small and not consistent between studies. There is no relationship to dosing or to the actual gestational age at the time of the loss. There is no evidence in preclinical reproductive studies supporting the imbalance and the rates of spontaneous loss observed in the clinical trials are in the range of published incidence rates in the US for studies in which ascertainment of pregnancy/pregnancy loss and population were similar to *Cervarix* clinical studies.

Nevertheless, as with any vaccine that has not formally been studied with respect to pregnancy outcomes, GSK acknowledges the need for close monitoring of pregnancy-related events in ongoing clinical trials and will further monitor pregnancy outcomes in Pregnancy Registries and post-licensure studies (see Section 8).

7.4. Post-Marketing Data

Cervarix was first approved in Australia on May 18, 2007 and is currently registered in over 95 countries worldwide. Since its first launch in Australia on 18 May 2007 up to the data lock point of the last Periodic Safety Update (May 18, 2009), 6,815,163 vaccine doses have been distributed worldwide. As *Cervarix* is a three-dose vaccine, the number of individuals exposed is estimated to be between a minimum of 2,271,721 and a maximum of 6,815,163 subjects. Assuming that vaccine regimens are well followed and that vaccine doses distributed have been administered, the number is more likely to be closer to 2 million. A significant number of doses of *Cervarix* have been distributed across the United Kingdom (UK) as part of the HPV routine immunization program that was initiated in September 2008. The program involves universal annual immunization of 12-13 year-old girls. In some regions, a catch-up immunization program has also been initiated for older age groups in women from 13 to 18 years that will be conducted over 3 years. According to the UK health authorities (Medicines and Healthcare products Regulatory Agency [MHRA]), at least 1 million doses have actually been administered (based on UK-wide vaccine uptake data up to April 2009). Enhanced safety monitoring is in place in close coordination between the MHRA and GSK. The MHRA analyzes adverse drug reaction (ADR) reports (Yellow Cards) received for *Cervarix* on a daily basis and publishes a weekly assessment of these data on their website at www.mhra.gov.uk/HPVvaccine. No safety concerns have been identified from these reviews so far.

From launch up to the data lock point of May 18, 2009, GSK has received a total of 1,680 reports of spontaneous adverse events of which the majority originated from the UK (629 reports, 37%), Italy (235 reports, 14%) and Germany (144 reports, 9%). The majority of these 1,680 case reports received were non-serious (i.e. 1225 reports [73%] were classified as non-serious and 455 reports [27%] as serious).

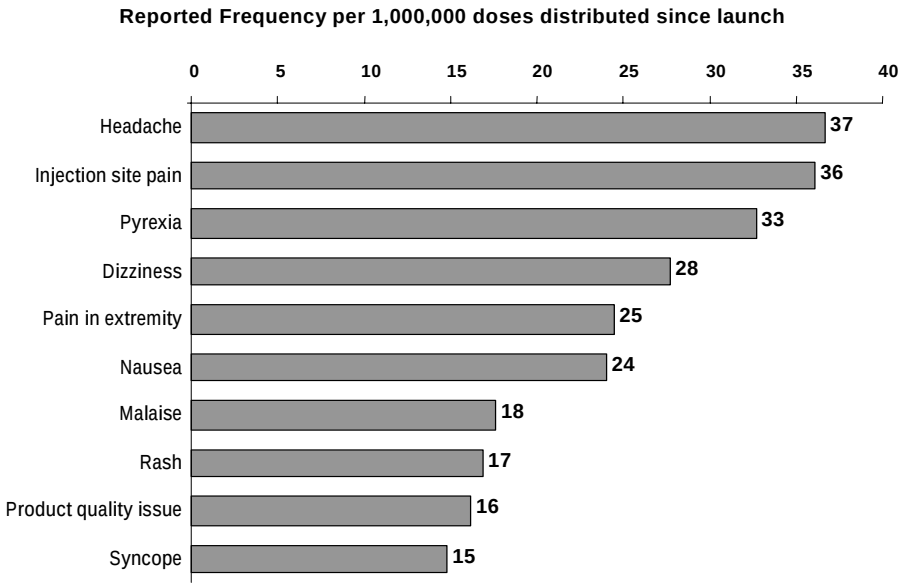
One report with a fatal outcome has been received from an individual who received *Cervarix*. This case was reported by the MHRA in the UK and described the occurrence of streptococcal septicemia in a 12-year-old female who was vaccinated with *Cervarix.* At an unspecified time after the second dose of *Cervarix*, the subject experienced streptococcal septicemia. The subject died 3 weeks following 2nd vaccination. An autopsy, death certificate and medical records were not available; however the cause of

death was reported as Streptococcal A Septicemia. There was no evidence to suggest that the death was related to the vaccine.

The most frequently reported events are events under the SOC of general disorders and administration site conditions, followed by nervous system disorders, and skin and subcutaneous tissue disorders. The vast majority of events under general disorders and administration site conditions SOC are related to injection site pain, pyrexia, and malaise. For nervous system disorders SOC, the events include headache, dizziness and syncope. Skin and subcutaneous tissue disorders include rash, urticaria and pruritus.

Figure 27, presents the ten most frequently reported events cumulatively from launch up to May 18, 2009. From a total of 4,813 events reported, the majority were non-serious: 4475 (93%) were classified as non-serious and 338 events (7%) as serious. Headache is the most frequently reported event after *Cervarix* vaccination followed by injection site pain and pyrexia. Most of these events are recognized as adverse reactions in the Reference Safety Information (i.e. in currently approved labels) for *Cervarix*. With the exception of syncope, all events included in Figure 27 are non-serious.

Figure 27 Ten most frequently reported events; post-marketing experience with *Cervarix* (DLP: 18 May 2009)



Among the reported serious adverse events, syncope is the most frequent event after vaccination with *Cervarix* with a frequency of 15 reports per 1 million doses distributed, followed by loss of consciousness (4 reports per 1 million doses distributed). These serious events are related to vasovagal reactions to injection which have been observed at comparable rates with other vaccines administered to adolescents. During the syncopal episodes, movements such as twitching and jerking or tonic-clonic movements resembling convulsions occurred in about 4% of reports. These episodes were sometimes categorized as seizures or convulsions.

Up to the data lock point of May 18, 2009, GSK has received a total of 76 spontaneous reports of pregnancy. The majority of these pregnancies (i.e. 47) were ongoing at time of reporting and the known pregnancy outcomes appear to be very limited in numbers. The pregnancy outcomes thus far include: 7 live healthy infants, 10 spontaneous losses, 1 ectopic pregnancy and 6 elective terminations (due to socioeconomic reasons). GSK has not identified any safety concern from the available pregnancy outcomes in reports that were received from spontaneous reporting.

For the isolated cases of other serious conditions reported, the available data does not suggest that the vaccine caused the condition and these events may have been coincidental in nature. Some cases of autoimmune diseases have been reported in temporal association with *Cervarix* vaccination. However, there is no clustering of autoimmune disorders and the reporting rates are broadly in line with those reported in the literature. Of interest, two serious spontaneous reports of Guillain-Barré Syndrome were identified from the UK up to the data lock point of May 18, 2009. A review performed by the MHRA concluded that there is no evidence that the vaccine has increased the frequency of Guillain-Barré Syndrome above that expected to occur naturally in the population.

In summary, following the regular review of safety data arising from all sources with post-licensure data in particular, the known benefits and risks balance of *Cervarix* remain favorable. GSK will continue to monitor ADRs to detect any emerging safety signal(s).

7.5. Safety Conclusions

The safety database for *Cervarix* includes up to 57,323 females aged 10 years and above with a total follow-up of 129,454 person-years and a maximum individual follow-up of 7.4 years. In this population, 33,623 females received at least one dose of *Cervarix* alone or co-administered with another vaccine with a follow-up of 70,086 person-years. This substantial database allows for a comprehensive assessment of the safety of *Cervarix*:

- Solicited local symptoms (injection site pain, swelling and redness) and myalgia were reported more frequently in the HPV group as compared to control groups, in 10-25 year old girls and young women. However, events were generally mild to moderate in intensity. Compliance with dosing was equally high in HPV and the control groups, indicating that *Cervarix* was well tolerated.
- *Cervarix* was generally well tolerated across age groups studied (from 10 years to 25 years of age).
- A comparable safety profile was observed in women with HPV exposure prior to vaccination and women with no previous exposure.
- Comparable rates of unsolicited adverse events, SAEs, medically significant conditions and AEs classified as NOADs were observed in vaccine and control groups.
- Similar overall rates of pregnancy outcomes were observed in vaccine and control groups. A numerical (non-significant) imbalance in the rate of spontaneous pregnancy loss was observed in a subanalysis of pregnancy outcomes around vaccination,

although the observed rate was within the range of background rates. Nevertheless, pregnancies and pregnancy outcomes will be further monitored in the risk management program.

- Meta-analysis of potential autoimmune events demonstrated comparable rates in vaccinees and controls with no significant increase in relative risk.
- Following the distribution of approximately 7 million vaccine doses worldwide, no safety concerns have been detected in post-marketing surveillance.

Based on the assessment and analysis of these data, the reactogenicity and safety profile of *Cervarix* is satisfactory and indicates that *Cervarix* can be used in the target population of 10-25 year old girls and women.

8. PHARMACOVIGILANCE PLAN

Pre-licensure clinical trial data evaluated in over 57,000 female subjects support the safety profile of *Cervarix*. Although the clinical safety database is substantial in size, some infrequent events might not be detected pre-licensure. GSK will continue to monitor the safety of *Cervarix* after licensure through routine pharmacovigilance and an extensive post-licensure clinical program.

The extensive Phase III clinical development program includes studies for which follow-up is planned post-licensure. These studies will provide additional data to further characterize the impact of *Cervarix*, including:

- assessment of the prevalence of non-vaccine oncogenic HPV types following vaccination with *Cervarix* (type replacement),
- efficacy against clinical endpoints for HPV-16/18 related non-cervical cancers,
- long-term data on vaccine efficacy and safety.

Data on co-administration of other vaccines that are likely to be given concomitantly with *Cervarix* is being generated. Clinical data have demonstrated acceptable safety and immunogenicity when *Cervarix* is co-administered with:

- dTpa-IPV vaccine (*Boostrix-Polio*) conducted in the European Union.

Further data on co-administration with other vaccines will be available post-licensure. Clinical studies in North America and the European Union will generate data on co-administration of *Cervarix* with:

- meningococcal serogroups A, C, Y and W-135 polysaccharide diphtheria toxoid (MCV4) conjugate vaccine (*Menactra*) and Tdap vaccine adsorbed (*Boostrix*) conducted in the US.
- combined hepatitis A and B vaccine (*Twinrix*)
- hepatitis B vaccine (*Engerix B*).

GSK intends to evaluate safety and immunogenicity in HIV-infected subjects in a post-licensure study.

As part of the Phase IV activities for *Cervarix*, two major studies are designed to address areas of special interest including but not limited to: vaccine effectiveness, HPV type replacement, role of males in HPV transmission and vaccine safety (including autoimmune disorders and pregnancy outcomes).

Vaccine effectiveness, HPV type replacement and role of males in HPV transmission

GSK has designed a phase III/IV study (HPV-040) as a Community Randomized Controlled Trial in Finland to evaluate the overall impact (direct and indirect effectiveness) of immunization with *Cervarix* in a community setting in adolescents 12-15 years of age with targeted enrolment of up to 70,000 subjects (with up to 30,000 adolescents receiving *Cervarix*). Effectiveness will be evaluated in girls who live in communities that have received *Cervarix* vaccination in comparison to girls who live in communities that have not received *Cervarix* vaccination. Studies conducted to date have only assessed the direct benefits in vaccinated women and their designs have not allowed assessment of important indirect effects on the entire female population, including unvaccinated women. These indirect effects may include the potential changes in HPV-16 and HPV-18 prevalence in unvaccinated women and the potential impact of vaccination on oncogenic HPV types other than those contained in the vaccine.

This study is also evaluating the effectiveness of HPV vaccination in communities where vaccination has been introduced in girls only, compared with communities where vaccination has been introduced in both girls and boys. Therefore, this study will also study the role of vaccinated males in inducing herd immunity as part of the evaluation of vaccine effectiveness in females as well as an assessment of the benefit of population-based immunization strategies that include vaccination of males. In addition, safety reporting in this study will provide more data in males and contribute to the already substantial safety database in women.

Autoimmune disorders

GSK is developing a phase IV study to further evaluate the safety profile of *Cervarix* in relation to autoimmune diseases. This US-based phase IV observational safety study is planned to enroll 100,000 women 10-25 years of age with 50,000 women vaccinated with *Cervarix*. The primary objective of this study will be to evaluate the incidence of a predefined list of autoimmune disorders (including those considered relevant by experts in autoimmunity and by regulatory authorities) within 12 months following administration of at least the first of three doses of *Cervarix*, compared to a concurrent unexposed cohort. Secondary objectives will include grouping of autoimmune disorders into three related families based on biological plausibility and on underlying immunological mechanisms of disease: (1) systemic diseases, (2) organ-specific T-cell mediated diseases, and (3) organ-specific antibody-mediated diseases.

In addition, the phase III/IV study (HPV-040: Community Randomized Controlled Trial in Finland) will include the reporting of autoimmune disorders in a population of adolescents 12-15 years of age at first vaccination. Safety surveillance based on registries will be performed throughout the entire study duration (i.e., from first vaccination until follow-up visit at 18.5 years of age). All SAEs considered by the investigator as possibly related to the vaccination will also be reported to GSK.

Pregnancy outcomes

Targeted studies assessing the use of *Cervarix* in pregnant women were not conducted in clinical trials. The safety of *Cervarix* in women inadvertently exposed to the vaccine during pregnancy was evaluated in clinical development and will continue to be evaluated by reporting outcomes in:

- Pregnancy registry (US-based registry to be initiated immediately after vaccine licensure in the US; EU [United Kingdom]-based registry)
- Phase III/IV community randomized study (HPV-040) will use the Medical Birth Registry in Finland for the follow-up of pregnancies and pregnancy outcomes,
- US-based Phase IV observational study in 100,000 women of 10-25 years of age, with 50,000 women vaccinated with *Cervarix*, will include the evaluation of pregnancies and pregnancy outcomes including spontaneous loss.

9. BENEFITS AND RISKS

9.1. Benefit

Cervical cancer is the most common HPV-related malignancy. The five most common oncogenic types (HPV-16, HPV-18, HPV-31, HPV-33 and HPV-45) account for the vast majority (approximately 88%) of all cervical cancers in North America. Although implementation of cervical screening programs has drastically reduced the lifetime risk of cervical cancer in the US, the absolute burden of disease due to cancerous and precancerous lesions still remains considerable. It is estimated that 11,270 women will be diagnosed with cervical cancer and 4,070 will die from the disease in 2009. Cervical screening practices can frequently miss the precursor lesions of adenocarcinoma, the most aggressive form of cervical cancer, resulting in an increase in its incidence to approximately 20% of all cervical cancers in the US. A complementary impact of prophylactic HPV vaccination, as a primary intervention, and effective screening programs on cervical cancer prevention can be expected.

Ideally, HPV vaccine should be administered before sexual debut (e.g. vaccination at 11-12 years of age), and duration of protection should extend for many years, providing protection throughout a woman's sexually active lifetime. Following sexual debut, women continue to be exposed to incident HPV infections dependent on their sexual activity. Clinical data indicate that only a minority of women (0.5%) would be expected to be infected with both HPV-16/18 at the time of vaccination. Therefore, the majority of women 10 to 25 years of age can benefit from an effective HPV vaccine.

To offer continued protection against oncogenic HPV types, HPV vaccination should induce not only a strong but also a sustained antibody response at the systemic level and consequently, by transfer, at the cervical mucosa, the site of primary infection. Vaccine-induced CMI can also play a role by supporting antibody production by maintaining memory B cells and inducing T-cell responses.

Cervarix was designed to induce high and sustained antibody responses of high quality that can transfer to the site of infection to provide long-term protection against infection

and disease caused by HPV-16 and HPV-18, the two most frequent oncogenic HPV types in cervical cancer. By optimizing the HPV-16 and HPV-18 immune responses through the use of AS04, GSK's design strategy was to increase the likelihood of providing cross-reactive immune responses between the vaccine types and closely related HPV types, such as HPV-31 and HPV-33 (HPV-16 related types) and HPV-45 (HPV-18 related types) thus broadening the protection against cervical cancer.

Early Phase IIa development demonstrated a significantly higher immune response induced by the HPV-16/18 vaccine adjuvanted with AS04 (*Cervarix*) as compared to an aluminum adjuvanted formulation with respect to serum antibodies (including neutralizing antibodies) and memory B-cell response. In further studies, vaccine-induced antibodies were shown to transfer to the site of infection (as measured in cervical-vaginal secretions) and the persistence of serum antibody levels several years after vaccination was demonstrated at significantly higher levels than the antibody response induced by natural infection. Based on these data, statistical models predict that antibody levels will last for at least 20 years.

Immuno-bridging from 10 to 14 year old girls to the age range in which efficacy has been demonstrated (15-25 year olds) supports the indicated age range of 10 to 25 years. The observed vaccine efficacy and modeling of long-term immunogenicity indicate the potential of *Cervarix* to offer the long-term protection against HPV-16/18 infection.

Cervarix was highly efficacious in the prevention of CIN2+ associated with HPV-16 or HPV-18 in a 'general' population inclusive of women 15-25 years old, naïve or non-naïve to HPV (regardless of their serostatus or HPV DNA status at baseline). In subjects with evidence of a cleared HPV infection at study entry (i.e. seropositive for HPV-16 or HPV-18 and HPV DNA negative), there was evidence across several endpoints that *Cervarix* prevented infection with HPV-16/18 and associated lesion development. In the subset of women with a current infection for the type considered in the analysis (i.e. HPV DNA positive regardless of serostatus at baseline), there was no evidence of efficacy, which was expected as *Cervarix* was developed as a prophylactic vaccine, not a therapeutic vaccine. Accordingly, in women infected with HPV-16 or HPV-18 at baseline, efficacy was not demonstrated for the corresponding type, but *Cervarix* was efficacious for the other vaccine type. Therefore, sexually active women with infection with one of the vaccine types can still benefit from vaccination with *Cervarix.*

The overall benefit of vaccination with *Cervarix* was demonstrated by the statistically significant efficacy of *Cervarix* against all CIN2+ lesions and against all CIN3+ lesions (the immediate precursor to cervical carcinoma) in the study populations that approximate the target for catch-up vaccination programs and for routine vaccination programs, i.e. the 'general' population inclusive of women naïve or non-naïve to HPV and in the population presumed naïve without current HPV infection or prior exposure to HPV-16 or HPV-18. In these two populations, vaccination with *Cervarix* also demonstrated a reduction in the number of cervical excision procedures.

HPV vaccination is primarily aimed at prevention of HPV-16 and HPV-18, the two most common cervical cancer-causing types. However, analyses from two clinical efficacy studies of the overall impact of *Cervarix* in the prevention of CIN2+ lesions (irrespective

of HPV DNA in the lesion) in a population presumed HPV naïve showed a similarly high level of efficacy (70% to 72% protection against CIN2+ lesions irrespective of the HPV type in the lesion) indicative of vaccine efficacy beyond HPV-16/18. Overall, non-vaccine HPV types account for 30% of cervical cancers globally. In the US, 24% of cervical cancers are not due to HPV-16/18 of which the types phylogenetically related to these two vaccine types, i.e., HPV-31 and HPV-33 (related to HPV-16) and HPV-45 (related to HPV-18) are responsible for 12% of cervical cancers.

According to a pre-specified analysis plan, GSK evaluated the potential for cross-protective effect by considering several endpoints across different study cohorts, including persistent infection. Unlike histopathological endpoints (e.g. CIN2+), persistent infection is not complicated by multiple infections and is therefore valuable to evaluate cross-protection [Jenkins, 2008; Koshiol, 2008]. The evaluation of combined endpoints of oncogenic HPV types excluding HPV-16/18 confirmed the observation of efficacy beyond HPV-16/18, with statistically significant efficacy against CIN2+ associated with non-vaccine oncogenic HPV types, ranging from 37% to 54% depending on the extent of co-infections with HPV-16/18. This level of cross-protective efficacy would result globally in an additional 11%-16% benefit in protection against cervical cancer over and above protection afforded by efficacy against HPV-16/18 alone.

Although lower incidences of non-vaccine HPV types and their slower progression to cervical cancer reduce the power to demonstrate clinical efficacy against individual non-vaccine types, there is evidence that *Cervarix* induces cross-protection to the three most frequent types after HPV-16/18 globally, i.e. the phylogenetically related types HPV-31, HPV-33 and HPV-45 with concordant and mostly significant estimates of vaccine efficacy for persistent infection and histopathological endpoints.

Although the population impact of vaccination with *Cervarix* on cervical cancer can only be determined in the long term, mathematical modeling was used to provide a current estimate of the impact of vaccination with *Cervarix* among US girls and women. The model used the proposed indicated age range for *Cervarix*, girls and women 10-25 years of age and assumed vaccine coverage of 75%. With an efficacy of 95% against HPV-16/18 related CIN2+ lesions, *Cervarix* is estimated to prevent over 100,000 cervical cancer cases and 25,000 related deaths over the lifetime of vaccinated girls and women. Considering the cross-protective efficacy observed for *Cervarix* against non-vaccine types (i.e., 37% to 54%), protection is increased by 9% to 14%. Thus, compared with a vaccine that offers oncogenic protection against HPV-16/18 only, *Cervarix* is estimated to prevent an additional 9,000 to 14,000 cancer cases and save an additional 2,000 to 3,000 lives due to cross-protection. This translates into preventing an additional 110-160 cervical cancer cases and saving 25-40 lives per year. Overall, when considering the average annual impact, *Cervarix* is estimated to prevent 1,200-1,300 cervical cancer cases and 300-320 lives every year.

9.2. Risks

Cervarix will be the first vaccine to be licensed with AS04 in the US. *Cervarix* is proposed for use in girls and women 10 to 25 years of age, i.e. an age range including women of child-bearing potential and in which a higher background incidence of

autoimmune disorders is expected. The nature and extent of the safety assessment in development of *Cervarix* reflects these considerations. The safety and mechanism of action of AS04 have been evaluated fully. The MPL component of AS04 is a detoxified form of LPS for which the activity is restricted to TLR4 receptor interactions. MPL acts at the earliest step of the immune response inducing a local and transient innate antigen specific response, without directly stimulating later immune effector T and B cells. This mode of action provides no evidence to support a plausible mechanism for the induction of autoimmune diseases. Non-clinical studies of *Cervarix* and MPL, including a reproductive-developmental toxicity study, demonstrated an adequate safety profile with no signs of systemic toxicity apart from local and transient effects, as expected from formulations that induce recruitment of inflammatory cells.

Clinical development of *Cervarix* included a comprehensive and rigorous assessment of safety in a database of over 57,000 female subjects (with over 33,000 female subjects receiving *Cervarix*) with up to 7.4 years of follow-up, with prospective reporting of events of special interest (e.g. new onset autoimmune disorders) and a meta-analysis on safety data across all studies in which vaccines containing AS04 have been used and including over 68,000 subjects (of which over 37,000 subjects received AS04-containing vaccines), recently updated with data for neuroinflammatory and musculoskeletal events of potential autoimmune etiology in over 84,000 subjects. Oversight by independent safety review committees and guidance of external experts in neurology, rheumatology and congenital anomalies were included in safety evaluations. As of May 2009, post-licensure experience included distribution of approximately 7 million doses of *Cervarix* with 2 million individuals estimated to have received at least one dose of vaccine.

Safety analyses showed that, although injection site reactions and myalgia were reported more frequently following vaccination with *Cervarix* as compared to controls, compliance with the full vaccination schedule was equally high in all groups, indicating the tolerability of *Cervarix*. Similar overall rates of pregnancy outcomes were observed in vaccine and control groups. A numerical (non-significant) imbalance in the rate of spontaneous pregnancy loss was observed in a subanalysis of pregnancy outcomes around vaccination, although the observed rate was within the range of background rates. Pregnancies and pregnancy outcomes will be further monitored in the risk management program. Based on the assessment and analysis of all the safety data generated, GSK considers that the reactogenicity and safety profile of *Cervarix,* including AS04, is clinically acceptable.

Nevertheless, GSK recognizes that even such a large clinical development database is limited for the detection of certain rare events such as some autoimmune disorders and that the large-scale implementation of a new vaccine in a population of adolescent girls and young women will inevitably be associated with the reporting of cases of autoimmune disorders occurring in temporal association with vaccination. In addition, the baseline incidences of many of these disorders have not been studied in these populations. Therefore, the occurrence of autoimmune disorders will be further evaluated in the ongoing clinical development program and in post-licensure activities, including a US-based observational Phase IV study specifically designed to address this outcome.

It is proposed that vaccination of pregnant women with *Cervarix* should be avoided until after pregnancy. As with any new vaccine that has not been studied formally with respect to pregnancy outcomes, GSK acknowledges the need for continued close monitoring of pregnancy-related events in ongoing trials, controlled Phase IV trials and post-licensure pharmacovigilance. GSK thus plans to evaluate pregnancy outcomes in a US observational study in 50,000 women vaccinated with *Cervarix* and to maintain pregnancy registries in the UK and US to prospectively collect pregnancy outcome data in pregnant women who receive *Cervarix.*

Theoretical concerns about HPV type replacement following the widespread introduction of HPV vaccines will be addressed post-licensure. Clinical studies with follow-up of up to 6.4 years do not suggest the occurrence of type replacement after vaccination. Nevertheless, effectiveness of *Cervarix* to decrease HPV-16 and HPV-18 related diseases and the possibility of replacement by non-vaccine types will be addressed.

9.3. Overall conclusion

Data generated during the clinical development of *Cervarix* and post-marketing surveillance provide evidence of high and sustained vaccine efficacy and immunogenicity with an excellent safety profile, demonstrating a clearly positive benefit/risk profile for *Cervarix*. These data provide strong evidence to support the licensure of *Cervarix* in girls and women 10-25 years of age for the prevention of the following diseases caused by HPV types 16 and 18 included in the vaccine:

- Cervical cancer
- Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*
- Cervical intraepithelial neoplasia (CIN) grade 1

The data also provide evidence of the prophylactic efficacy of *Cervarix* against oncogenic HPV types beyond those included in the vaccine.

Surveillance programs are ongoing or being developed in order to continue monitoring the long-term safety, efficacy and immunogenicity of the vaccine.

Pending longer term disease outcomes, modeling affords an estimate of public health benefit that indicates that *Cervarix* with protective efficacy against HPV types beyond those in the vaccine will prevent more cancers and save more lives than a vaccine that only prevents HPV-16 and HPV-18 cancer outcomes.

The availability of a second licensed HPV vaccine, which prevents cervical cancer and precancerous lesions due to HPV-16 and HPV-18 and has been shown to be efficacious against oncogenic HPV types other than HPV-16 and HPV-18, will enable wider vaccine distribution and coverage of HPV immunization programs, will reinforce supply in the US and will represent a significant public health benefit to girls and women 10 to 25 years of age.

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Appendix 1: Study HPV-008: overview of the 7 cases of CIN2+ with HPV-16/18 DNA detected in lesions but not in any of the preceding cervical specimens in HPV DNA negative and seronegative subjects at baseline (ATP cohort for efficacy/TVC-1)

Case # Group Cohort	Cervical Samples (HPV DNA)								Clinical Diagnosis (Visit leading to biopsy)
	M0	M6	M12	M18	M24	M30	M36	M42	
1* *Cervarix* ATP TVC-1	HPV-58	HPV-58	HPV-58	Neg	Neg	Neg	Neg	NA	Punch: CIN3 HPV-16/58 (M12)
2 *Cervarix* ATP TVC-1	HPV-58	Neg	HPV-58	Neg	Neg	Neg	Neg	NA	Punch: CIN2 HPV-18/58 (M12)
109* *Cervarix* ATP TVC-1	HPV-18/31	HPV-31	Neg	HPV-58	HPV-58	HPV-58/68	HPV-56/58/68	NA	LEEP: CIN3 HPV-16/31 (M6)
22* control ATP TVC-1	HPV-16/51/52/54	HPV-16/51/52	HPV-16	HPV-06/18	HPV-16/18/44	HPV-18	Neg	NA	Punch: CIN3 HPV-16 (M12) Cone: CIN3 HPV-16 (M12) Cone: CIN3 HPV-16/18 (M12)
52 control ATP TVC-1	Neg	Neg	Neg	Neg	Neg	HPV-31/66	HPV-31	NA	Punch: CIN2 HPV-16/31 (M36)
77* control ATP TVC-1	HPV-66/68	HPV-33/51/66/68	HPV-51/66	HPV-51/66	HPV-33/51/66	HPV-33/66	Neg	Neg	Punch: CIN3 HPV-18/33/66 (M30)
85 control TVC-1	Neg	NA	NA	NA	HPV-16/51	HPV-31/51/66/68	HPV-68	NA	Punch: CIN1 HPV-31 Punch: CIN2 HPV-16/31/06 (M36)

Types shown in **bold** are those associated with the lesion and counted as primary endpoints according to the pre-specified protocol definition. Types underlined are those considered to be causally associated with the lesion, according to the HPV Type Assignment Algorithm. Case numbers (#) were assigned by GSK and are not chronological as only selected cases are shown in this table. Visits occurring before biopsy are shaded in grey.

* Indicates cases with CIN3 or AIS lesions in addition to CIN2 lesions.

Negative for HPV DNA by PCR = Neg

Not available = NA

Appendix 2: List of MedDRA Preferred Terms for identification of autoimmune disorders in analysis of NOADs

Event Category	Immune-Mediated Disorder	MedDRA Preferred Term	MedDRA Code
Neuroinflammatory disorders	Cranial nerve disorders	Optic neuritis	10030942
		Neuritis cranial	10029244
		Cranial nerve palsies multiple	10011314
	Multiple sclerosis	Multiple sclerosis	10028245
		Primary progressive multiple sclerosis	10063401
		Progressive multiple sclerosis	10053395
		Marburg's variant multiple sclerosis	10067067
		Secondary progressive multiple sclerosis	10063400
		Multiple sclerosis relapse	10048393
		Progressive relapsing multiple sclerosis	10067063
		Relapsing-remitting multiple sclerosis	10063399
	Demyelinating disease	Demyelination	10012305
		Leukoencephalomyelitis	10048999
		Acute disseminated encephalomyelitis	10000709
		Concentric sclerosis	10010252
		Neuromyelitis optica	10029322
		Chronic inflammatory demyelinating polyradiculoneuropathy	10057645
		Demyelinating polyneuropathy	10061811
	Transverse myelitis	Myelitis transverse	10028527
		Myelitis	10028524
	Guillain-Barré syndrome	Guillain-Barré syndrome	10018767
		Miller Fisher syndrome	10049567
	Myasthenia gravis	Myasthenia gravis	10028417
		Ocular myasthenia	10049168
	Encephalitis	Encephalitis	10014581
		Encephalomyelitis	10014619
		Encephalitis post immunisation	10014602
		Encephalitis toxic	10014607
	Neuritis	Neuritis	10029240
		Cervical neuritis	10008293
		Mononeuritis	10027910
		Mononeuropathy multiplex	10027918
		Brachial plexopathy	10065417
		Radiculopathy	10037779
		Radiculitis	10061928
		Radiculitis brachial	10037778
		Radiculitis cervical	10050092
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus	10042945
	Cutaneous lupus	Cutaneous lupus	10056509
	Sjogren's syndrome	Sjogren's syndrome	10040767
	Scleroderma	Scleroderma	10039710
		Systemic sclerosis	10042593
		CREST syndrome	10011380
		Morphoea	10027982
	Dermatomyositis	Dermatomyositis	10012503
	Polymyositis	Polymyositis	10036102
	Rheumatoid arthritis	Rheumatoid arthritis	10039073
		Juvenile arthritis	10059177

Event Category	Immune-Mediated Disorder	MedDRA Preferred Term	MedDRA Code
	Polymyalgia rheumatica	Polymyalgia rheumatica	10036099
	Reactive arthritis	Arthritis reactive	10003267
		Reiter's syndrome	10038294
	Psoriatic arthritis	Psoriatic arthropathy	10037162
	Ankylosing spondylitis	Ankylosing spondylitis	10002556
	Undifferentiated spondyloarthropathy	Spondyloarthropathy	10051265
	Mixed connective tissue disease	Mixed connective tissue disease	10027754
Gastrointestinal disorders	Crohn's disease	Crohn's disease	10011401
	Ulcerative colitis	Colitis ulcerative	10009900
	Ulcerative proctitis	Proctitis ulcerative	10036783
	Celiac disease	Coeliac disease	10009839
Metabolic disorders	Autoimmune thyroiditis	Autoimmune thyroiditis	10049046
	Hashimoto's thyroiditis		
	Grave's or Basedow's disease	Basedow's disease	10004161
	Insulin-dependent diabetes mellitus	Type 1 diabetes mellitus	10067584
	Addison's disease	Addison's disease	10001130
Skin disorders	Psoriasis	Psoriasis	10037153
	Vitiligo	Vitiligo	10047642
	Raynaud's phenomenon	Raynaud's phenomenon	10037912
	Erythema nodosum	Erythema nodosum	10015226
	Autoimmune bullous skin diseases	Pemphigus	10034280
		Pemphigoid	10034277
		Dermatitis herpetiformis	10012468
Other	Stevens-Johnson syndrome	Stevens-Johnson syndrome	10042033
		Erythema multiforme	10015218
		Toxic epidermal necrolysis	10044223
	Autoimmune hemolytic anemia	Anemia heamolytic autoimmune	10002046
	Thrombocytopenias	Thrombocytopenia	10043554
		Autoimmune thrombocytopenia	10050245
		Idiopathic thrombocytopenic purpura	10021245
		Thrombocytopenic purpura	10043561
		Thrombotic thrombocytopenic purpura	10043648
	Antiphospholipid syndrome	Antiphospholipid syndrome	10002817
	Vasculitis	Vasculitis	10047115
		Diffuse vasculitis	10012798
		Leukocytoclastic vasculitis	10024377
		Behcet's syndrome	10004213
		Temporal arteritis	10043207
		Takayasu's arteritis	10043097
		Microscopic polyangiitis	10063344
		Polysrteritis nodosa	10036024
		Wegener's granulomatosis	10047888
		Allergic granulomatous angiitis	10048594
		Henoch-Schonlein purpura	10019617
		Kawasaki's disease	10023320
	Pernicious anemia	Pernicious anaemia	10034695
	Autoimmune hepatitis	Autoimmune hepatitis	10003827
	Primary biliary cirrhosis	Biliary cirrhosis primary	10004661

Event Category	Immune-Mediated Disorder	MedDRA Preferred Term	MedDRA Code
	Primary slerosisng cholangitis	Cholangitis sclerosing	10008609
	Autoimmune glomerulonephritis	Glomerulonephritis	10018364
	Autoimmune uveitis	Uveitis	10046851
	Autoimmune myocarditis	Autoimmune myocarditis	10064539
	Sarcoidosis	Sarcoidosis	10039486