1. Introduction

Human Papillomaviruses and Disease Background

It is widely accepted that infection with human papillomavirus (HPV) is the central causal factor for the development of cervical cancer. Recent studies have shown that HPV can be identified in 98.7% of all cervical carcinomas. Furthermore HPV infections are among the most common sexually transmitted infections in most populations and estimates of exposure range from 25% in many European countries to 70% in the US or 95% in high risk populations in Africa.

HPV are non-enveloped, double-stranded DNA viruses that infect the epithelial cells of the skin or mucosa. Based on their genomic differences within the oncogenes E6 and E7 and the capsid protein L1 over 100 genotypes are described to date. Thereof approximately 40 different genotypes lead to infections of the anogenital tract and about 16 are highly oncogenic with HPV types 16 and 18, being the most frequent found in cervical cancer. HPV-16 is detected in about 54% of cervical cancer cases, and the second type is HPV-18, detected in about 17% of cases.

The time from occurrence of HPV infection to cancer development usually exceeds 20 years. However, persistent HPV infection is a necessary but not a sufficient factor for the development of cervical carcinoma. Other factors such as smoking, long-term use of oral contraceptives or high parity are suggested to play a role in the process that lead to cancer.

The majority of genital HPV infections (>90%) however are transient sub-clinical infections that will be cleared or suppressed below the limits of detection by host cell defences within one to two years. In addition, any cervical lesion may spontaneously regress to normal without treatment with a probability of about 57% for CIN1, 43% for CIN2 and 32% for CIN3. The determinants leading to regression are not well understood.

It is confirmed that persistent cervical infection by high risk HPV types is a precursor event to cervical cancer.

The primary screening tool for cytological abnormalities is still the PAP smear test. Due to limitations of the original PAP test new methods have been developed. Currently liquid based PAP tests are routinely used. Nowadays the Bethesda classification system is used. This classification system specifies squamous cell abnormalities into four categories: atypical squamous cells (ASC), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma (SCC).

Although the immune response to HPV cervical infections is not fully understood, there is evidence that the host humoral and cell mediated immune responses are responsible for regression of HPV infection. With respect to the humoral immune responses anti-HPV antibodies are only detected in 50 to 70% of infected women. Whereas the antibodies occur usually after several months post infection, they are long-lasting with steady levels. Because of the high level of antigenic specificity of HPV capsid antigens, there is no cross protection among subtypes but a type specific immunity develops.

The interaction of cytokines, chemokines liberated during humoral and cell mediated immune reactions is assumed to be responsible for the regression associated with HPV. The severe outcome of HPV infection in immunosuppressed individuals as transplant recipients and HIV-positive women suggests that cell-mediated immunity is also important. Furthermore a polarisation of the immune response for a Th2 directed response was observed in woman with HPV infections that evolve into high grade lesions.
2. Quality aspects

Introduction

Cervarix, HPV-16/18 L1 AS04 vaccine contains recombinant C-terminally truncated major capsid L1 proteins of HPV types 16 and 18 as active ingredients. The L1 proteins of HPV-16 and HPV-18 are separately produced using a recombinant Baculovirus expression system and the insect cell line Hi-5 Rix4446 derived from *Trichoplusia ni*. After expression of the L1 proteins and further purification, the L1 proteins assembled separately as virus-like particles (VLP). The VLPs of each HPV type are formulated with the AS04 adjuvant system composed of aluminium hydroxide and 3-*O*-desacyl-4-*O*-monophosphoryl lipid A (MPL). The MPL immunostimulant is a detoxified derivative of the lipopolysaccharide of the gram negative bacterium *Salmonella minnesota* R595 strain.

One dose of Cervarix, contains 20µg of HPV-16 L1 and 20µg of HPV-18 L1 proteins adjuvanted with AS04 and is presented as a sterile turbid liquid suspension for injection, filled as a 0.5ml monodose in either syringes or vials stored at 2-8°C. A shelf life of 3 years is proposed. The vaccination schedule includes 3 doses administered at 0, 1, and 6 months intramuscularly.

Active Substance

The drug substance consists of two monovalent antigen bulks each containing C-terminally truncated versions of the major capsid L1 proteins of either type 16 or 18 HPV. These proteins are produced in separate production runs using the Baculoviruses expression vector system (BEVS) using GSK’s insect cell line cloned from the Hi-5 *Trichoplusia ni* insect cell line and HPV-16 L1 or HPV-18 L1 encoding recombinant Baculoviruses. Following expression the L1 proteins are purified by a series of chromatographic and filtration procedures and are finally assembled into (VLP) closely resembling the configuration of native HPV virus particles.

- Manufacture

Cell and Seed Banking

The manufacturing of the HPV-16 L1 VLP and HPV-18 L1 VLP makes use of an established two-tiered cell bank system of the Hi-5 Rix4446 cell line (Master and Working Cell Banks (MCB and WCB)) and an established two-tiered baculovirus Seed Lot system set up for the HPV-16 L1 and HPV-18 L1 gene-encoding recombinant baculoviruses (HPV-16 or HPV-18 Master and Working Seeds (MS and WS)).

Satisfactory quality control testing are in place and satisfactory stability data and storage conditions have been described for these cell banks and seed lots. The MCB and WCB, as well as the End of Production Cells (EPC) were tested for identity, purity and safety (adventitious agents). The MS and WS, and their related control cells, were tested for identity, safety (adventitious agents) and Baculovirus content.

This application concerns the first vaccine for human use that has been produced with a Baculovirus Expression Vector System. Hence, an extensive characterization was performed to confirm the safety and applicability of the integral elements of this novel system. The biological properties and characteristics of the Hi-5 Rix4446 cell line were extensively investigated. In particular, the Hi-5 Rix4446 insect cell line has been examined for the presence of adventitious agents not only by applying the classical testing protocol but also by a variety of assays specifically designed for the detection of insect-specific viral contaminants. In addition, the tumorigenic potential of the cell line was investigated. The baculovirus seeds were also checked for classical and insect-specific contaminating viruses. Also, the construction and genetic stability of the recombinant baculovirus has been described in sufficient detail.
Manufacture and purification:

A two-step process has been established for the large scale expression of L1 proteins in the Hi-5 Rix4446 insect cells.

First, recombinant baculovirus inocula of each serotype are prepared by amplification of the respective working seeds in the Hi-5 insect cell cultures. Next, these inocula are used for the infection of Hi-5 production cell cultures. L1 protein is released from the cells by osmotic shock and subsequently purified by a series of chromatographic columns, a nanometric filtration, an ultrafiltration and a final sterile filtration to generate the L1 VLP purified bulks.

The capacity of the individual steps of the purification cascade to efficiently eliminate viral contaminants has been demonstrated in viral clearance studies.

The purified HPV-16 L1 VLP and HPV-18 L1 VLP protein bulks are stored in stainless steel vessels dedicated to the adsorption to aluminium for up to 3 days at 2°C-8°C or at room temperature.

Process control and validation:

The company has established a system of process control during the manufacturing of the active substance using in-process tests with assigned specifications and monitoring tests used to monitor the process consistency and performance.

Validation of the HPV-16 L1 VLP and HPV-18 L1 VLP antigen production process was performed by the demonstration of process consistency through compliance with the pre-established QC standards and by the identification and validation of the manufacturing process critical parameters.

Consistency was demonstrated for the three unit-steps of the drug substance production process: the recombinant HPV-16/18 baculovirus inoculum production process, the L1 single harvest production and L1 extraction and the L1 antigen purification process.

Critical process parameters have been satisfactorily identified and batch data provided.

Manufacturing process development:

The comparability of HPV-16/18 L1 VLP antigen purified bulks prepared during the phase IIb and phase III development, including the final process purified bulks, was assessed by subjecting each type of materials to a series of physico-chemical analyses and by evaluation of the immunogenic properties. The results demonstrated satisfactory comparability.

Elucidation of structure and other characteristics:

An extensive number of batches of HPV-16 and HPV-18 drug substance produced by the final process has to date been subjected to structural and functional characterization. The physico-chemical properties of the L1-VLP assemblies were assessed in a multidisciplinary approach by identifying the electrophoretic profiles and molecular weight of L1 proteins (SDS-PAGE, Western blotting, and capillary electrophoresis, mass spectrometry), the primary (amino acid analysis, peptide mapping, N- and C-terminal analysis), the secondary (Infra-Red and circular dichroism spectroscopy) and the VLP structure and size (size exclusion chromatography, electron microscopy, and disc centrifugation size analysis). In addition, drug substances were also characterized focussing on their immunological properties (antigenic activity, binding to polyclonal sera and immune response elicited in mice). The clear identity (match with the theoretical sequence) and consistent quality of drug substance material from different batches was confirmed in these studies.
**Impurities:**

The applicant has considered host cell proteins (HCP), DNA, and infectious recombinant baculoviruses as potential impurities to be expected in drug substance purified bulks. Impurities are removed by the process very efficiently. Residual amounts of HCP were quantified by western blot and ELISA procedures. Also, data have been gathered to adequately demonstrate that other impurities such as lipids or carbohydrates are present only in negligible trace amounts.

- **Specification:**

The release specifications for the drug substance include identity, purity by Coomassie-stained SDS-PAGE, endotoxin content, total protein content, and antigenic activity.

Analytical methods have been adequately described and validated.

Batch analysis data were presented for four (HPV-16 L1 VLP) and five (HPV-18 L1 VLP) batches produced according to the final manufacturing process scale. Additional information was provided for batches from earlier process developmental stages. The data were satisfactory.

The Reference Standards established for the testing of the antigenic activity of drug substance bulks are the routine purified bulk batches for HPV-16 and for HPV-18. These batches complied with the specifications for identity, purity, sterility, endotoxin content, and protein content as set for drug product release control.

**Adjuvants:**

Satisfactory specifications and controls have been applied as appropriate to the adjuvants: O-desacyl-4'-monophosphoryl lipid A (MPL) and aluminium hydroxide, hydrated (Al(OH)₃). Non-Pharmacopoeial methods have been satisfactorily validated.

A detailed description of the analytical methods and their validation has been provided for the MPL powder and it is considered that the methods used are adequate to control the MPL powder on a routine basis. Manufacturing of MPL has already been extensively assessed during the evaluation of Fendrix (EMEA/H/C/550, Hepatitis B (rDNA) Vaccine absorbed and adjuvanted): [http://www.emea.europa.eu/humandocs/Humans/EPAR/fendrix/fendrix.htm](http://www.emea.europa.eu/humandocs/Humans/EPAR/fendrix/fendrix.htm).

See also Section 3.3 of this Assessment report for non-clinical evaluation of MPL itself as well as Cervarix.

- **Stability**

The stability data obtained on purified bulks showed that the HPV-16 L1 VLP and HPV-18 L1 VLP antigen purified bulks are not affected by storage at +25 ± 2.5°C for 3 days or at +2 to +8°C for 3 days. No loss of antigen integrity (both at the protein or the VLP structure levels) and L1 VLP antigenic activity were observed. Similarly, storage of the purified bulks has had no impact on the quality of the derived adsorbed monovalent bulks, as evidenced by the similar immunogenicity profiles in mice and similar quality properties for all adsorbed monovalent bulks irrespective whether they were made with stored or freshly produced purified bulk material.

Based on these data, the Company proposes a shelf life of 3 days at room temperature or at +2.0 to +8.0°C for the storage of HPV-16 L1 VLP and HPV-18 L1 VLP antigen purified bulks.

**Medicinal Product**

The HPV vaccine is prepared from HPV-16 L1 VLP and HPV-18 L1 VLP formulated with the AS04 adjuvant system composed of aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A (MPL). The vaccine is presented as a sterile turbid liquid suspension for injection, filled as a monodose in either syringes or vials stored at 2-8°C.
Pharmaceutical Development

Formulation development

The composition of Cervarix was determined based on the data obtained from non-clinical challenge animal models and from clinical epidemiological and natural history studies. These studies showed that in order to be efficacious against HPV infection and related clinical lesions an HPV vaccine would need to induce strong antibody responses against the L1 capsid protein (assembled as VLPs), B-cell memory and T-cell responses.

The Cervarix vaccine formulation was therefore selected to be a combination of L1 proteins assembled as VLPs, to induce the inactivation of protective anti-HPV L1 antibodies, and the proprietary adjuvant AS04 developed by GSK Biologicals, to induce the production of persistently high levels of antibodies as well as the induction of a specific cell-mediated immunity.

Data from pre-clinical immunogenicity studies supported the formulation of the vaccine containing an antigen to aluminium to MPL weight ratio of 1:25:2.5, respectively. The clinical study HPV-005 evaluated three HPV-16/18 L1 AS04 candidate vaccine formulation with 6 µg, 20 µg or 60 µg of each antigen in comparison to the Al(OH)$_3$ adjuvanted vaccine. There was a trend for higher antibody titres with increasing antigen dose levels that suggested that the 12 µg L1 dose was less immunogenic than the other antigen doses. Based on clinical data it was concluded that the HPV-16/18 L1 AS04 vaccine formulated with 20µg HPV-16 L1 and 20µg HPV-18 L1 afforded an acceptable balance between vaccine tolerability and the immune response elicited.

The applicant quotes additional studies performed in the context of the approval of the Fendrix® anti hepatitis B vaccine (containing 20 µg of antigen in combination with 50 µg of MPL adsorbed to AlPO$_4$) in order to support the formulation development strategy chosen for Cervarix.

Manufacturing process development

To allow for the withdrawal of the nominal content (0.5 ml), each syringe or vial is filled with an overfill. No overage of the active ingredient is applied for the formulation of the HPV vaccine.

The Company made several optimisations during the development of the HPV-16/18 vaccine manufacturing process. The comparability of the drug product prepared during the phase IIb and phase III development, including the final process drug product, has been carried out by comparing properties of vaccine lots from different stages of the process development. Physicochemical characterization confirmed that the lots of the different process development stages were comparable. Preclinical comparison of the immunogenicity induced by the different process development stages vaccine lots showed that all lots were able to elicit humoral and cellular immune responses which were consistent and comparable.

Immunogenicity of different vaccine lots prepared during Phase IIb and Phase III development was further investigated in humans in clinical study HPV-012. The results showed that the Phase IIb and Phase III HPV vaccine formulations had comparable immunological properties (induction of antibodies, rate of seroconversion).

Adventitious Agents

In general, robust measures and precautions have been taken to ensure the safety of the HPV vaccine against non viral as well as viral adventitious agents.

With respect to non-viral adventitious agents:

- Appropriate precautions have been taken during the preparation of the HPV vaccine to ensure the final product is free of bacteria, mycoplasma and fungi
- A cellular feature identified in the Hi-5 Rix4446 cells was not considered to be associated with replicative or infectious properties
• No materials of animal origin are used in the current routine production process of the HPV vaccine except casamino-acids that are used in the preparation of the MPL immunostimulant and for which the source is compliant with the current CPMP Note for Guidance (EMEA/CPMP/410/01).

With respect to viral adventitious agents:

The investigations performed demonstrated satisfactory viral clearance capacity of the HPV-16 L1 VLP and HPV-18 L1 VLP antigen production processes and the absence of infectivity during QC testing or specific infectivity experiments both in the starting materials as well as during routine production; thereby supporting the viral safety of the HPV vaccine.

• Manufacture of the Product

Drug product manufacture is a step-wise process in which the HPV-16 L1 VLP and HPV-18 L1 VLP as well as the liquid MPL are first individually adsorbed to Al(OH)₃ to generate adsorbed bulks. The final bulk vaccine is produced by mixing defined amounts of adsorbed bulks and adding buffer solutions and Al(OH)₃ to reach the intended final formulation. The MPL immunostimulant utilized here has previously been employed by GSK as a component of the Fendrix hepatitis B vaccine and the pertaining documentation has been reviewed and approved in the context of the licensing of the latter.

The final vaccine is filled as a monodose in either sterile syringes (type 1 glass) or sterilised type I glass vials. Both container types are closed with grey butyl rubber stoppers. The same container/closure material is used for other commercial vaccines manufactured by GSK Bio.

The qualitative and quantitative composition of Cervarix is shown below.

One dose of Cervarix (0.5 ml) contains:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Papillomavirus type 16 L1 protein</td>
<td>20 micrograms</td>
</tr>
<tr>
<td>Human Papillomavirus type 18 L1 protein</td>
<td>20 micrograms</td>
</tr>
<tr>
<td>3'-O-desacyl-4' monophosphoryl lipid A (MPL)</td>
<td>50 micrograms</td>
</tr>
<tr>
<td>adsorbed on aluminium hydroxide, hydrated (Al(OH)₃)</td>
<td>0.5 milligrams Al³⁺ in total</td>
</tr>
</tbody>
</table>

²Human Papillomavirus = HPV
³adjuvanted by AS04 containing:
⁴L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from Trichoplusia ni.

And the following excipients: Sodium chloride (NaCl), Sodium dihydrogen phosphate dihydrate (NaH₂PO₄.2 H₂O) and Water for injection.

A satisfactory description of the manufacturing process has been provided, including flow chart describing unit operations and controls.

Process Control and validation

The following intermediates are generated during the manufacture of the final drug product:

- HPV-16 and HPV-18 adsorbed monovalent bulks (AMBs)
- MPL liquid bulk (MLB)
- MPL adsorbed bulk (MAB)

GSK has established a system of process control during the manufacturing of the drug product using in-process tests with assigned specifications and monitoring tests used to monitor the process consistency and performance.
All critical tests ensuring the product quality are performed during the Quality Control testing of the HPV-16 L1 and HPV-18 L1 AMBs and MPL liquid bulk.

No process controls are applied for AMBs and MABs production. The process control of MLB production is tested by measuring the MPL particle size during the microfluidization procedure and before the final sterile filtration. In addition, the bioburden before sterile filtration is monitored.

The QC testing programme established for AMBs addresses identity of the L1 protein, sterility, protein content and completeness of adsorption. Specifications and results of analysis are provided for four HPV-16 L1 VLP and five HPV-18 L1 VLP AMB batches.

Satisfactory validation of the methods used for control testing has been provided.

Validation of the HPV vaccine production process was performed by the demonstration of process consistency through compliance with the pre-established QC standards and by the identification and validation of the manufacturing process critical parameters.

These QC data met the specifications considered to be indicators of the consistency and robustness of the mentioned process steps.

For the MPL liquid bulk production process additional data have been collected for consistency batches by investigating the effect of different process parameters of the microfluidization step.

Critical process parameters have been satisfactorily identified and batch data provided.

The validation of final HPV vaccine production step was further confirmed by means of *in vivo* consistency studies addressing immunogenicity issues for the final product. For this, the ability of three final process HPV vaccine lots to induce the production of HPV-L1 specific antibodies and a cellular immune response (IFN-γ and IL-5) was studied in BALB/c mice. These experiments confirmed that all three batches were capable of inducing a consistent immune response.

In conclusion, validation of the manufacturing was satisfactory.

**Control of excipients**

Satisfactory specifications and controls (Pharmacopoeials and in-house) have been applied as appropriate to the excipients. Non-Pharmacopoeial methods have been satisfactorily validated.

- **Product Specification**

The final bulk vaccine is tested for sterility. Final containers are subjected to tests for identity, sterility, general safety, *in vitro* relative potency, pH, volume, protein content, aluminium content, MPL content and completeness of adsorption for MPL, HPV-16 L1 VLP and HPV-18 L1 VLP proteins. Satisfactory data from the analysis of consistency batches and from stability studies have been provided.

Analytical methods used for release testing have been satisfactorily validated.

Satisfactory batch analysis data have been provided for 3 lots of each final bulk and final containers.

**Reference Standards or Materials**

Two types of reference standard preparations are currently used for HPV vaccine testing:

- Purified bulk reference standard: Two routine HPV-16 L1 VLP and HPV-18 L1 VLP purified bulk preparations are used for testing completeness of adsorption to aluminium (unbound HPV-16 L1
VLP and HPV-18 L1 VLP, respectively). Batch analysis data for these two batches has been provided.

- Final container reference standard: A routine final container preparation of HPV vaccine is employed for potency testing.

Reference standards used for MPL testing:

- Three reference standard established for the testing of the MPL content of HPV final container vaccines is a routine MPL liquid bulk batch. This batch complied with the specifications set at the time of release.

- Stability of the Product

**Final bulk:**
Three final bulk lots have been followed in long-term stability studies. Results available at this time for the final process consistency lots stored in polyethylene containers at +2 to +8°C provide evidence for a stability period for at least 18 months.

**Finished product**
Stability data presented have been generated on the three consistency lots produced according to the final manufacturing process and on vaccine lots representative of the proposed consistency formulation and presentation but derived from earlier production process stages administered in Phases IIb/III of the clinical development.

A number of stability studies are ongoing and will be completed as post-approval commitments. During the procedure, stability data was updated and from the data provided, no signs of instability were evident.

The proposed shelf life for the vaccine finished product is 36 months at +2-8°C and is considered to be satisfactory.

**Overall Conclusions on chemical, pharmaceutical and biological aspects**

Cervarix is composed of recombinant C-terminally truncated HPV-16 L1 and HPV-18 L1 proteins, assembled into virus-like particles (VLPs) adjuvanted with AS04 adjuvant system, composed of an aluminium salt, Al(OH)₃ and 3-O-desacyl-4'-monophosphoryl lipid A, (MPL). One dose of Cervarix contains 20µg of HPV-16 L1 VLP and 20µg of HPV-18 L1 VLP proteins adjuvanted with AS04 consisting of 500µg of aluminium and 50µg of MPL. Cervarix is a preservative-free vaccine presented as a 0.5 ml monodose in either glass syringes or glass vials and is presented as a turbid liquid suspension for injection.

The assessment focused on the novel Baculovirus expression vector system, which is used in a Marketing Authorisation Application for a medicinal product for human use for the first time. There were no major objections raised during the assessment.

The Applicant has provided sufficient detail for the manufacturing processes, including the monitoring, in process control and acceptance criteria. Extended characterisation studies were presented for the Trichoplusia ni Hi-5 Rix4446 insect cell bank system and the baculovirus seed system.

Satisfactory characterization of the HPV-16 L1 VLP and HPV-18 L1 VLP antigen Drug Substances, including impurities, and quality control of HPV-16 L1 VLP and HPV-18 L1 VLP adsorbed monovalents bulks and of HPV vaccines have been described.
The analytical control procedures are summarized and the validation parameters, acceptance criteria and validation results are reported for the drug substances, the intermediates and the bivalent vaccine as drug product.

Satisfactory stability data and data to demonstrate the removal of adventitious agents has been provided.

Following the assessment there were no outstanding quality concerns which would preclude the authorisation of Cervarix. A number of quality Follow Up Measures were raised to be addressed post-authorisation.

3. Non-clinical aspects

Introduction

Non-clinical pharmacological, pharmacokinetics and toxicology studies were undertaken on HPV-16/18 L1 VLP AS04 in parallel with studies on AS04 and MPL, based on
- the CPMP Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95),
- the Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004),
- the Note for Guidance on Reproductive Toxicology: Detection of Toxicity to Reproduction for Medicinal Products (CPMP/ICH/386/95).

Based on these same guidelines secondary pharmacodynamic, pharmacodynamic drug interaction, pharmacokinetics, genotoxicity and carcinogenicity studies were not performed on the HPV-16/18 L1 VLP AS04 vaccine and secondary pharmacodynamic, pharmacodynamic drug interaction and carcinogenicity studies were not performed on MPL.

GLP

Primary pharmacology studies were not performed under GLP conditions.
Safety pharmacology and toxicology studies were carried out under GLP conditions.

Pharmacology

- Primary pharmacodynamics

Given the species specificity of HPV precluding the evaluation of any human HPV-16/18 vaccine in protection animal models, primary pharmacodynamic studies aimed at the preclinical evaluation of the immunogenicity of the HPV-16/18 L1 VLP AS04 vaccine were carried out in mice and Rhesus monkeys.

- A first group of experiments in BALB/c mice compared the immunogenicity of different HPV-16/18 L1 VLP AS04 formulations containing various doses of aluminium salt (Al(OH)₃), MPL or HPV-16/18 L1 VLP antigen.

- A second group of experiments in BALB/c mice targeted the characterisation of both humoral and cellular immune responses induced by HPV-16/18 L1 VLP AS04 by comparing the immune responses to the immunogenicity of plain HPV-16/18 L1 VLP and HPV-16/18 L1 VLP Al(OH)₃.

These pre-clinical experiments demonstrated that the HPV-16/18 L1 VLP AS04 vaccine provides a superior immunogenicity profile for a protective HPV vaccine compared to the HPV-16/18 L1 VLP Al(OH)₃ and the plain HPV-16/18 L1 VLP formulations. The HPV-16/18 L1 VLP AS04 vaccine was indeed able to induce higher and more persistent anti-HPV-16/18 L1 VLP antibody levels, higher levels of IgG2a antibodies and superior levels of IFN-γ and TNF-α, cytokines with known antiviral properties. In addition, HPV-16/18 L1 VLP AS04 also induced elevated frequencies of memory B-cells which should have a positive impact on antibody persistence. The comparison of the immunogenicity of HPV-16/18 L1 VLP Al(OH)₃ and HPV-16/18 L1 VLP AS04 formulations in rhesus monkeys, more closely related to humans, confirmed the superior
immunogenicity profile associated to the use of the HPV-16/18 L1 VLP AS04 vaccine including the induction of higher levels of neutralizing antibodies.

Another series of experiments was performed to evaluate the immunostimulatory properties of the AS04 adjuvant containing 3-O-desacyl-4’-monophosphoryl lipid A (MPL), a derivative from Salmonella minnesota Lipopolysaccharides (LPS), and aluminium salt (Al(OH)3).

- Two experiments, performed on human peripheral blood mononuclear cells (PBMCs) and on a human monocyteic cell line (U937), demonstrated that AS04, like MPL, is a potent inducer of pro-inflammatory cytokine (IL-6 and TNF-α) secretion by monocytes in vitro.
- A third experiment performed in mice demonstrated that AS04 is functionally equivalent to MPL regarding the in vivo induction of antigen-presenting cell maturation as evaluated by the upregulation of CD40 expression.

Secondary pharmacodynamics

No secondary pharmacodynamic studies were performed according to the Note for Guidance on Preclinical Pharmacological and Toxicological testing of vaccines (CPMP/465/95) and Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004).

Safety pharmacology programme

The possible side effects of the HPV-16/18 L1 VLP AS04 vaccine on cardiovascular and respiratory parameters in the anaesthetized SPF female Wistar rats were investigated. Intramuscular administration of 0.1ml/animal of the HPV-16/18 L1 VLP AS04 vaccine did not produce any treatment-related effects on blood pressure, heart rate, ECG (lead II) or respiration depth and rate.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed according to the Note for Guidance on Preclinical Pharmacological and Toxicological testing of vaccines (CPMP/465/95) and Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004).

Pharmacology / MPL

The activity of 3-O-desacyl-4’-monophosphoryl Lipid A (MPL), a derivative from Salmonella minnesota LPS, regarding the induction of co-stimulatory molecules (APC maturation) and the induction of pro-inflammatory cytokines and chemokines has been investigated. A first set of primary pharmacodynamic studies performed in mice or on murine cells demonstrated that MPL plays a key role in inducing antigen-presenting cell (APC) maturation by the up-regulation of CD80, CD86 and CD40 co-stimulatory molecules both in vitro and in vivo, and by inducing the secretion of pro-inflammatory cytokines (IL-6, TNF-α) by APC in vitro. The experiments emphasize that MPL plays a significant role in the activation of innate immunity, which is critical for the induction of antigen-specific adaptive immune response. The role played by MPL on the induction of co-stimulatory molecules, pro-inflammatory cytokines and chemokines on human cells was further confirmed by in vitro studies on peripheral blood mononuclear cells (PBMCs) or on whole blood. MPL stimulation of human whole blood was shown to induce a panel of cytokines (IL-12, IFN-γ, IFN-α, IL-10), pro-inflammatory cytokines (IL-6, TNF-α, IL-8, IL-1β) as well as chemokines (PCP-1, MIP-1α, MIP-1β). Finally, in vitro studies on human PBMCs were shown to be supportive of the hypothesis that MPL acts through interactions with the human TLR4 receptor, but not with the human TLR2 receptor, to activate peripheral blood monocytes.

A cardiovascular and respiratory safety pharmacology study was performed in Beagle dogs and did not show any statistically significant nor physiologically relevant effects on the blood pressure, heart rate, respiration depth or rate or any abnormalities in the electrocardiogram waveform.

The Pharmacology studies showed that MPL plays a significant role in the activation of innate immunity and does not induce undesirable pharmacological effects on cardio-respiratory functions in animal models.
Pharmacokinetics

Studies to demonstrate absorption, distribution, metabolism, and excretion of the active ingredients in Cervarix have not been performed for any of the component viruses. This is in line with Note for guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95).

Pharmacokinetics / MPL

The pharmacokinetics, absorption, distribution and elimination of $^{14}$C-MPL have been investigated following a single intramuscular or a single intravenous administration to the male Han Wistar rat at nominal dose levels of 100 $\mu$g/kg bodyweight. For both routes of administration, the dose was formulated as an aqueous solution, and was administered as a bolus injection over ca. 30 seconds. The highest observed concentrations of radioactivity in blood were 14.9 (occurring at 4 hours post-dose) and 248 (occurring at 5 minutes post-dose) ng equivalents of MPL/g of sample, following intramuscular and intravenous administration, respectively. The concentration remained relatively constant thereafter following intramuscular administration, and at 168 hours post-dose was 11.4 ng equivalents of MPL/g. The elimination half-life following intravenous administration was 76.5 hours. Relatively low quantifiable levels of radioactivity were detected in all tissues investigated at 56 days post-dose in both studies, with the highest concentrations observed in the fat and spleen.

The routes and rates of elimination were similar following both intramuscular and intravenous administration. The major route of elimination of MPL-related material was via the faeces accounting for a mean of approximately 24% of the dose for both routes, with urinary elimination accounting for a mean of approximately 4% of the dose. Radioactivity in the expired air traps accounted for a mean of approximately 2% of the dose for each set of air traps. The mean total of radioactivity in the tissues and residual carcass was approximately 6% of the dose, with the injection site accounted for approximately 0.2% of the dose. The mean total recovery of radioactivity (including cage washes and cage debris) was approximately 38%. The low total recovery is considered to be due to the elimination of volatile organic molecules that had not been trapped efficiently by the chosen trapping solution used in these studies.

Based on the MPL-related material recovered in the faeces, urine, expired air traps, tissues (excluding the injection site) and residual carcass following intramuscular administration, approximately 35% of the dose appeared to be absorbed. However, the total absorption is likely to be much higher than this value since only 0.2% of the dose was recovered from the injection site.

In conclusion the pharmacokinetic studies conducted in rats have shown that MPL-related material is widely distributed throughout the body, notably to the fat and spleen, and is then likely eliminated mainly via the expired air, with only low levels of radioactivity remaining in the carcass.

Toxicology

- Single dose toxicity

Single-dose toxicity of the HPV-16/18 L1 VLP AS04 vaccine was assessed as part of the repeat-dose toxicity study in rabbits. The treatment was well tolerated and no treatment-related systemic effect was noticed on haematology, body-weight, clinical signs, mortality and clinical chemistry over a 14-day observation period.

- Repeat dose toxicity (with toxicokinetics)

Repeated-dose toxicity studies have been performed with Cervarix and AS04 (intramuscular administration in rabbits).

The HPV-16/18 L1 VLP AS04 vaccine and the AS04 adjuvant were well tolerated. The organ-weight data, macroscopic pathology evaluation, and evaluation of systemic effects showed no consistent treatment-related findings. Signs of inflammation at the injection sites of the test vaccine were observed. Histological examination of the administration sites a few days after vaccination with HPV-16/18 L1 VLP AS04 revealed evidence of sub-acute inflammation with slight to moderate focal degeneration, necrosis, or regeneration of myofibres. Animals which solely received aluminium hydroxide or AS04 also showed evidence of inflammation at the injection site although the
inflammation was of shorter duration and less extensive. Examination after a treatment free period (4 or 13 weeks) revealed evidence of histological changes (i.e. myofibres regeneration) that were indicative of an ongoing process of recovery.

The injection site reaction was accompanied with a temporary increase in the number of neutrophils and in fibrinogen, which may be a consequence of the recruitment of inflammatory cells following injections of the formulations.

- **Genotoxicity**

According to the Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95) and the Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004) genotoxicity studies are not required for this vaccine.

- **Carcinogenicity**

According to the Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95) and the Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004) carcinogenicity studies are not required for this vaccine.

- **Reproduction Toxicity**

The reproductive and developmental toxicity of Cervarix and the AS04 adjuvant alone was assessed in a study in female rats of the CD strain. The influence of Cervarix on fertility, embryo-fetal, peri-natal and post-natal survival and development was examined.

The study did not show any effect of vaccination with Cervarix or administration of AS04 on any phases of reproduction and foetal development in rats.

An immune response to the vaccine was observed, and antibodies were transferred to the offspring during gestation and also during lactation.

- **Local tolerance**

Local tolerance was assessed as part of the toxicity studies by intramuscular administration of the vaccine in rabbits.

The in vitro mutagenicity (Ames) and clastogenicity (CHO cells) tests, and in vivo micronucleus assay demonstrated no genotoxic potential of the MPL adjuvant.

**Toxicology / MPL**

Pre-clinical toxicity studies have been carried out to detect potential toxic signs associated with MPL administration and are shortly summarized below:

**Acute toxicity** of MPL was tested in Sprague-Dawley rats by intraperitoneal injections of single dosages of 10, 40, 400, and 4000 μg of MPL per body weight kg. Dosage-related effects were restricted to a slight increase in the incidence and relative severity of interstitial infiltration of mononuclear inflammatory cells in the omentum most probably due to the route of injection (intraperitoneal). This slightly irritating effect of MPL was neither apparent at dosages below 400 μg/kg nor was it correlated with any other anatomical or clinical changes.

**Repeat-dose toxicity** of MPL administered intravenously was examined in two rat studies with dosage levels of 100, 1000, or 2500 μg/kg/day for 8 days, and of 40, 200, or 1000 μg/kg/day for 7 days, respectively, and in dogs with dosage levels of 6, 120, or 1200 μg/kg/day during 14 days. In the first study, a dosage of 5000 μg/kg/day was initially tested and decreased to 2500 μg/kg/day due to excessive mortality. In contrast, no mortality occurred in the second study. In rats, reversible decreased body weight gain and food consumption were observed at all dosages. The incidence of clinical signs was increased at MPL dosage of 2500 μg/kg/day while no remarkable clinical signs were
observed at lowest dosages. A decrease in platelets was observed in males at MPL dosage ≥ 1000 μg/kg/day level, but not in females. A dose-dependent decrease was noted in erythrocytes, haemoglobin and hematocrit. A dose–related increase in segmented neutrophils was also noted. Organ weight increase was noticed in all groups, with a wider organ distribution at higher MPL dosages. The histopathological examination performed in the first study revealed changes generally characterized by infiltration of mononuclear inflammatory cells in several organs. These effects were minor at the 40 μg/kg/day dose, which was therefore considered well-tolerated. In dogs, repeated intravenous administrations of MPL only produced mild toxicity at dosage levels of 120 and 1200 μg/kg/day. A dosage level of 6 μg/kg/day was considered a no-observed-effect-level for this study.

No toxicokinetic studies were performed during the repeated-dose toxicity study program, according to the Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95 guidance), and the Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004).

Genotoxicity studies performed in vitro did no reveal any MPL-related mutagenic activity or genotoxic effect. In vivo studies did not show any evidence of increased frequency of micronucleated immature erythrocytes or bone marrow cell toxicity linked to MPL.

Reproductive and developmental studies carried out in rats and rabbits by subcutaneous administration of MPL at dosage levels of up to 100 μg/kg/day showed no indication of maternal or embryo toxicity or teratogenicity, and no adverse effects of the maternal treatment on the F1 generation, their maturation and reproductive performance.

In conclusion, MPL showed effects expected from a strong stimulation of the immune system. Under the reported studies, MPL appears to have a high safety margin and is suitable as human vaccine immunostimulant at the proposed dosage of 50 μg/vaccine dose, which corresponds to a 1.7–0.7 μg/kg dose for a 30–70 kg-weighing person.

Ecotoxicity / environmental risk assessment

According the Guideline on the Environmental Risk Assessment (ERA) of medicinal products for human use (EMEA/CHMP/SWP/4447/00), an ERA is not required for vaccines.

Overall, it can be concluded that none of the ingredients of the HPV-16/18 L1 VLP AS04 vaccine will enter the environment in quantities that merit ecological concern following its prescribed use in humans. Therefore, no specific precautionary and safety measures need to be taken regarding the environmental release from use in patients, and disposal of unused products or waste materials derived from the vaccine

Discussion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

4. Clinical aspects

Introduction

The clinical development programme to support licensure of the Cervarix consisted of 9 clinical studies. Approximately 24348 subjects were included.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.
The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**Pharmacokinetics**

No clinical pharmacology studies describing the pharmacokinetic properties of Cervarix were conducted in support of this application. This is in accordance with the Guideline on clinical evaluation of new vaccines (EMEA/VWP/164653/05), which states, that pharmacokinetic studies are generally not required for injectable vaccines because they do not provide information useful for establishing adequate dosing recommendations. Pharmacodynamic evaluations related to the humoral and cellular immune responses to HPV were assessed in Phase I through Phase III studies.

**Pharmacodynamics / Immunogenicity**

The pharmacodynamics of the vaccine relate to its interaction with the immune system. Therefore, this section will discuss the data on the systemic immune response to vaccination.

The antibody response and cell mediated immune response to the candidate HPV-16/18 L1 VLP AS04 vaccine was investigated in exploratory phase I/IIa studies HPV-003, HPV-004 and HPV-005 (see Table below) and pivotal studies HPV-012, HPV-013 and HPV-014 (see Table below). In addition, immunogenicity was also evaluated in the efficacy studies HPV-001, HPV-007 and HPV-008 (see section Clinical Efficacy).
<table>
<thead>
<tr>
<th>Study No/ Phase / Countries</th>
<th>Study Design / Posology</th>
<th>Study population Gender / Total No /Age range</th>
<th>Key study endpoints (Initial Phase)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-003 Phase I/II USA 1999-2001</td>
<td>Double-blind, randomised, controlled Arm 1: HPV-16/18 20µg/20µg, AS04 Arm 2: Al(OH)₃ 3 doses at 0, 1, 6 months</td>
<td>Healthy HPV DNA positive females N=61 18-30 years</td>
<td><strong>Primary endpoint:</strong> Occurrence of SAEs throughout the entire study period (up to Month 7). <strong>Secondary endpoints (selected):</strong> Anti-HPV-16/18 antibody titres assessed at Months 0, 2, 7 and 12. Anti-HPV-16/18 antibody titres in HPV DNA positive women at study entry assessed at Months 2, 7 and 12.</td>
<td>3 years</td>
</tr>
<tr>
<td>HPV-004 Phase IIa USA 2000-2001</td>
<td>Double-blind, randomised Arm 1: HPV-16/18 20µg/20µg, AS04 Arm 2: HPV-16/18 20µg/20µg, Al(OH)₃ Arm 3: HPV-16/18 20µg/20µg 3 doses at 0, 1, 6 months Arm 4: HPV-16/18 20µg/20µg, Al(OH)₃ 3 doses at 0, 1, 6 months</td>
<td>Healthy females N=60 18-30 years</td>
<td><strong>Primary endpoints:</strong> Safety assessment Anti-HPV-16/18 antibody titres assessed 30 days after third injection <strong>Secondary endpoints:</strong> Anti-HPV-16/18 antibody titres at days 0, 7, 30, 60, 180, 210, 360 Neutralising anti-HPV-16/18 antibody titres at days 0, 60, 210, 360 Lymphoproliferation, IL-5 and IFN-γ assays at days 0, 60, 210, 360</td>
<td>4 years Initial phase 12 months Extension to 4 years to evaluate long-term persistence of antibodies</td>
</tr>
<tr>
<td>HPV-005 Phase IIa USA 1999-2001</td>
<td>Double-blind, randomised Dose escalating Arm 1: HPV-16/18 6µg/6µg, AS04 Arm 2: HPV-16/18 20µg/20µg, AS04 Arm 3: HPV-16/18 60µg/60µg, AS04 Arm 4: HPV-16/18 20µg/20µg, Al(OH)₃ 3 doses at 0, 1, 6 months</td>
<td>Healthy females N=210 18-30 years</td>
<td><strong>Primary endpoints:</strong> Safety assessment Evaluation of antibody response <strong>Secondary endpoints:</strong> Anti-HPV-16/18 antibody titres, neutralising HPV-16/18 antibody titres and CMI (lymphoproliferation, IL-5 and IFN-γ) through 30 days after 3rd injection Anti-HPV-16/18 antibody titres, neutralising HPV-16/18 antibody titres and CMI through 360 days after 1st injection Antibody titres (ELISA, NT) in cervical and vaginal secretions at 30 and 180 days after 3rd injection</td>
<td>4 years Initial phase 12 months Extension to 4 years to evaluate long-term persistence of antibodies</td>
</tr>
</tbody>
</table>
Antibody titres and seroconversion rates following vaccination were investigated in main studies HPV-012, HPV-013 and HPV-14. In order to assess the long-term persistence of the antibody responses studies HPV-004, HPV-005, HPV-012, HPV-013 and HPV-014 were extended. NB study HPV-001/007 evaluated long-term antibody response for 5.5 years - should also be mentioned. The vaccination schedule was identical to those preferred for recombinant Hepatitis B vaccines, which is the 0, 1, 6 months interval schedule.

<table>
<thead>
<tr>
<th>Study No / Phase / Countries</th>
<th>Study Design / Posology</th>
<th>Study Population / Total No / Age range</th>
<th>Key Study endpoints (Initial Phase)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-012 Phase III DK, FI, NL, Estonia, Greece, Russia 17 centres 2004-2005</td>
<td>Blinded, randomised, multicentric study with five parallel arms:  - HPV-16/18 AS04, Lot 1  - HPV-16/18 AS04, Lot 2  - HPV-16/18 AS04, Lot 3  - HPV-16/18 AS04, previous formulation  - HPV-16/18 AS04, Lot 1 3 doses, i.m., 0, 1, 6 months</td>
<td>HPV-16 / HPV-18 seronegative high risk HPV DNA negative healthy women N= 770 Age range: Arm 1-4: 15-25 years Arm 5: 10-14 years</td>
<td><strong>Primary endpoints</strong>  To demonstrate lot-to-lot consistency of HPV-16/18 vaccine (3 lots, 15-25 year olds) Clinical bridge to previous formulation <strong>Secondary endpoints (selected)</strong> Immunogenicity: immune non-inferiority in the 10-14 year old age group compared with 15-25 year old age group by ELISA (pooled lots, 15-25 years and single lot, 10-14 years) Safety assessment</td>
<td>1 year</td>
</tr>
<tr>
<td>HPV-013 Phase III CZ, FR, DE, NO, ES, SE, Australia, Columbia Honduras Korea Panama Taiwan 57 centres 2004-2005</td>
<td>Double-blind, randomised, controlled, multicentric study with two parallel groups:  - HPV-16/18 L1 VLP AS04  - Havrix 3 doses, i.m., 0, 1, 6 months</td>
<td>HPV-16 / HPV-18 seronegative high risk HPV DNA negative healthy women N= 2067 Age range: 10-14 years</td>
<td><strong>Primary endpoint</strong> Occurrence of SAEs throughout the entire study period (up to Month 7) by ELISA. <strong>Secondary endpoints (selected)</strong> Anti-HPV-16 and anti-HPV-18 antibody titres at month 0, 2 and 7 Anti-MPL antibody titres at month 0, 2 and 7 Safety assessment</td>
<td>1 year 3-year extension to evaluate long-term persistence of antibodies</td>
</tr>
<tr>
<td>HPV-014 Phase III DE, PL 6 centres</td>
<td>Open, multi-centre, age-stratified study with 3 arms 3 doses, i.m., 0, 1, 6 months  - HPV-16/18 L1 VLP AS04  - HPV-16/18 L1 VLP AS04</td>
<td>Females N= 626 15-55 yrs 15-25 yrs 26-45 yrs</td>
<td><strong>Primary endpoint</strong> Anti-HPV-16 and anti-HPV-18 seroconversion rates at Month 7 by ELISA in age groups 15-25 years and 26-45 years <strong>Secondary endpoints (selected)</strong> Anti-HPV-16 and anti-HPV-18 seroconversion rates at Month 7 (46–55 years). Anti-HPV-16 and anti-HPV-18 antibody titres (GMTs) at each time point in all</td>
<td>1 year</td>
</tr>
<tr>
<td>2004-2005</td>
<td>HPV-16/18 L1 VLP AS04</td>
<td>46-55 yrs</td>
<td>Anti-HPV-16 and anti-HPV-18 seroconversion rates at Month 2 and 7 in all subjects. Safety assessment</td>
<td></td>
</tr>
</tbody>
</table>
For all studies anti-HPV-16/18 antibody titres were summarized by geometric mean titres (GMTs) with their 95% confidence intervals prior to vaccination and at relevant time points following vaccination. Furthermore reverse cumulative distribution curves for these antibody titres were displayed. In addition seropositivity rates and their exact 95% confidence intervals were calculated.

**Dose response study**

In the dose escalating and selection study HPV-005 (for study outline see table in Pharmacodynamic section) the appropriate amount of the L1 derived VLPs for HPV-16 and HPV-18 were evaluated with respect to the safety profile and the immunogenicity (antibody responses). HPV-16/18 vaccine lots of different antigen content ranging from 6µg, 20µg and 60µg of each of the two HPV-16 and HPV-18 L1 VLP per dose were investigated. A total of 210 healthy women 18 to 30 years of age were enrolled in this study.

**Study HPV-005: anti-HPV-16 and anti-HPV-18 antibody titres at Month 7 (expressed in Log₁₀ ELISA titres) for volunteers who received all scheduled injections of study vaccine with AS04**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>N</th>
<th>GMT</th>
<th>Log₁₀ mean</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>AS04 12µg</td>
<td>51</td>
<td>3655.7</td>
<td>3.6</td>
<td>3.4</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>AS04 40µg</td>
<td>47</td>
<td>5248.2</td>
<td>3.7</td>
<td>3.6</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>AS04 120µg</td>
<td>42</td>
<td>5944.5</td>
<td>3.8</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>HPV-18</td>
<td>AS04 12µg</td>
<td>51</td>
<td>3402.6</td>
<td>3.5</td>
<td>3.4</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>AS04 40µg</td>
<td>47</td>
<td>3443.4</td>
<td>3.5</td>
<td>3.4</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>AS04 120µg</td>
<td>42</td>
<td>4228.5</td>
<td>3.6</td>
<td>3.5</td>
<td>3.7</td>
</tr>
</tbody>
</table>

AS04 12µg = HPV-16/18 vaccine L1 VLP AS04 (6µg/6µg)
AS04 40µg = HPV-16/18 vaccine L1 VLP AS04 (20µg/20µg)
AS04 120µg = HPV-16/18 vaccine L1 VLP AS04 (60µg/60µg)

*In computation of means, titres <LOQ were set to 1.
N = number of subjects with available results
LL/UL = Lower/Upper limits of the 95% confidence interval on the Log₁₀ mean titre

While differences in immunogenicity are marginal or not significant – depending on the type of recombinant L1 - choice of the 40 µg dose (20 µg HPV 16 L1 and 20 µg HPV 18 L1) appears to be appropriate and represents a conservative dose selection.

A candidate vaccine with an antigen content of 20µg HPV-16 L1 and 20µg HPV-18 L1 per dose was chosen for the further clinical development program.

**AS04 Adjuvanting System**

Consistently high immunogenicity of Cervarix is largely mediated by the use of AS04 as an adjuvanting system. The following table shows superiority of AS04 compared to conventional aluminium hydroxide or plain VLPs:
Study HPV-004: anti-HPV-16 and anti-HPV-18 ELISA titres at Month 7 and Month 12 for volunteers who received all scheduled injections (0, 1, 6 months schedule)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Group</th>
<th>Timepoint</th>
<th>N</th>
<th>GMT</th>
<th>Log_{10} mean</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-16</td>
<td>AS04 40µg</td>
<td>Month 7</td>
<td>19</td>
<td>11199</td>
<td>4.0</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>18</td>
<td>4550.5</td>
<td>3.7</td>
<td>3.4</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>ALU 40µg</td>
<td>Month 7</td>
<td>17</td>
<td>4076</td>
<td>3.6</td>
<td>3.4</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>15</td>
<td>2076.9</td>
<td>3.3</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>No adjuvant</td>
<td>Month 7</td>
<td>20</td>
<td>2488</td>
<td>3.4</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>18</td>
<td>935.3</td>
<td>3.0</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-18</td>
<td>AS04 40µg</td>
<td>Month 7</td>
<td>19</td>
<td>4794</td>
<td>3.7</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>18</td>
<td>1536.1</td>
<td>3.2</td>
<td>2.9</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>ALU 40µg</td>
<td>Month 7</td>
<td>17</td>
<td>1960</td>
<td>3.3</td>
<td>3.1</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>15</td>
<td>637.1</td>
<td>2.8</td>
<td>2.6</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>No adjuvant</td>
<td>Month 7</td>
<td>20</td>
<td>1305</td>
<td>3.1</td>
<td>2.0</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>18</td>
<td>229.7</td>
<td>2.4</td>
<td>2.1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

AS04 40µg = HPV-16/18 L1 VLP AS04 vaccine (20µg/20µg)
ALU 40µg = HPV-16/18 L1 VLP Al(OH)3 vaccine (20µg/20µg)

*In computation of means, titres <LOQ were set to 1
N = number of subjects with available results
GMT = geometric mean titre
LL/UL = Lower/Upper limits of the 95% confidence interval on the Log_{10} mean titre

Results shown above (with regard to GMTs) are, in principle, representative and consistent for all clinical trials conducted throughout the pharmaceutical development program and support the use of AS04 as the preferred adjuvantage system for recombinant HPV 16/18 L1 particles.

Humoral immune response:

The immunogenicity induced by three doses of Cervarix has been evaluated in 5,303 female subjects from 10 to 55 years of age.

A number of different approaches were pursued, finally evolving into three different assay systems that were applied in all pivotal clinical studies for qualitative and quantitative analysis of the immune response induced. These assays include:

- An ELISA binding assay for antibody quantification (determination of GMTs)
- An inhibition assay to measure the amount of serum antibodies against neutralizing epitopes present on the surface of HPV 16 and 18
- A neutralization assay involving HPV pseudoparticles developed by the US National Cancer Institute

These assays were carefully cross validated against each other showing reasonable concordance of assay results. Thus, antibodies measured by ELISA in individual clinical trials are to a great extent functional. Consequently, the humoral part of the immunological mode of action of Cervarix may be explained by neutralization of wild-type HPV 16 and 18, respectively.

Measuring GMTs themselves does not provide sufficient information on the quality of the immune response. The following graphs provide some insight into the correlation between vaccine-induced serum antibody titres and their capacity to inhibit binding of neutralizing monoclonal antibodies (V5 and J4) to their corresponding epitopes on the viral surface. Moreover, the graphs illustrate again the superiority of the AS04 adjuvantage system over Al(OH)3 with regard to GMTs, titres of functional antibodies and persistence of functional, i.e. virus neutralizing antibodies.
Significant differences (p<0.05) between the antibody titers of the AS04 and the aluminium group are indicated in the figure by asterisks (n=9-19 subjects for the aluminium salt group, n=21-37 subjects for the AS04 group). Arrows indicate vaccination timepoints. The two lower figures demonstrate the correlation between vaccine-induced serum antibody titres and their capacity to inhibit binding of neutralizing monoclonal antibodies (V5 and J4) to their corresponding epitopes on the viral surface.

Persistence of a quantitatively and qualitatively acceptable immune response is an important element to assure long-term protection from disease as well as to define the correct time point for booster vaccination.

Local immunity:

A key element to understand the immunological mode of action of Cervarix is to investigate the local activity of antibodies, such as IgGs transudated from the serum to the cervical mucosa. The first issue, i.e. the local immune response, was addressed in the very early phase of the clinical development program and was aimed at measuring IgG activity in cervical samples and correlating these activities to serum antibody activities. These early results of Study HPV-005 are presented in the table below.
**Study HPV-005 : Summary of specific HPV-16 and HPV-18 activity* in serum and cervico-vaginal secretions at Month 7 and Month 12 after vaccination with the HPV-16/18 vaccine**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Study Group</th>
<th>Time point</th>
<th>N</th>
<th>CVS</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N+</td>
<td>%+</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV-16/18 L1 VLP AS04 12μg</td>
<td>PIII(M7)</td>
<td>7</td>
<td>4</td>
<td>57.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIII(M12)</td>
<td>5</td>
<td>3</td>
<td>60.0</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV-16/18 L1 VLP AS04 40μg</td>
<td>PIII(M7)</td>
<td>1</td>
<td>9</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIII(M12)</td>
<td>6</td>
<td>4</td>
<td>66.7</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV-16/18 L1 VLP AS04 120μg</td>
<td>PIII(M7)</td>
<td>8</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIII(M12)</td>
<td>5</td>
<td>3</td>
<td>60.0</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV-16/18 L1 VLP Al(OH)₃ 40μg</td>
<td>PIII(M7)</td>
<td>4</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIII(M12)</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>HPV-18</td>
<td>HPV-16/18 L1 VLP AS04 12μg</td>
<td>PIII(M7)</td>
<td>7</td>
<td>5</td>
<td>71.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIII(M12)</td>
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<td>2</td>
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<tr>
<td>HPV-18</td>
<td>HPV-16/18 L1 VLP AS04 40μg</td>
<td>PIII(M7)</td>
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<td>PIII(M12)</td>
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</tr>
<tr>
<td>HPV-18</td>
<td>HPV-16/18 L1 VLP AS04 120μg</td>
<td>PIII(M7)</td>
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<td>8</td>
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<tr>
<td></td>
<td></td>
<td>PIII(M12)</td>
<td>5</td>
<td>4</td>
<td>80.0</td>
</tr>
<tr>
<td>HPV-18</td>
<td>HPV-16/18 L1 VLP Al(OH)₃ 40μg</td>
<td>PIII(M7)</td>
<td>4</td>
<td>4</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>PIII(M12)</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

* Specific activity = reactivity per IgG
CVS = cervico-vaginal secretions
n+ = number of subjects positive
%+ = percentage of subjects positive
PIII(M7) = Post Dose III, Month 7
PIII(M12) = Post Dose III, Month 12

Careful interpretation of data allows the conclusion that there is a dose-effect-relationship, however, the clinical significance of local antibody activity and titres remains unclear. Nevertheless some evidence has been provided that i.m. injection of recombinant HPV 16 and 18 L1 particles do trigger an immune response at the target organ/tissue.

A subset of approximately 90 subjects in study HPV-014 provided blood samples and had cervico-vaginal secretion (CVS) samples collected one year after the third dose of the vaccine (Month 18). Cervico-vaginal HPV-16 VLP antibodies were detected in 85.7%, 80.8% and 77.3% of subjects in the [15-25], [26-45] and [46-55] age groups, respectively. Similarly, cervico-vaginal HPV-18 VLP antibodies were detected in CVS in 71.4%, 61.5% and 68.2% of subjects in the [15-25], [26-45] and [46-55] age group, respectively.

**Cell mediated immunity:**

Vaccine efficacy and, in particular, long-term efficacy requires evaluation of the involvement of the cellular part of the immune system. A battery of methods has been developed and applied in a variety of studies to investigate activation of T-cell response and formation of memory B cells following
vaccination with Cervarix. A summary of these methodologies and clinical studies where these have been applied is outlined below.

Overview of analyses conducted to assess cell-mediated immunity to HPV-16/18 vaccine

<table>
<thead>
<tr>
<th>Study No</th>
<th>T Cell Response</th>
<th>B Cell Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lymphoproliferation</td>
<td>Cytokine production†</td>
</tr>
<tr>
<td>HPV-002 (MI-CP-044)</td>
<td>Day 0 and 56</td>
<td>Day 0 and 56</td>
</tr>
<tr>
<td></td>
<td>Day 112 and 140*</td>
<td>Day 112 and 140*</td>
</tr>
<tr>
<td></td>
<td>Months 18, 24, 30, 36, 42, 48 and 54 (planned)</td>
<td>Months 18, 24, 30, 36, 42, 48 and 54 (planned)</td>
</tr>
<tr>
<td>HPV-004 (MI-CP-055)</td>
<td>Days 0, 60, 210 and 360</td>
<td>Days 0, 60, 210 and 360</td>
</tr>
<tr>
<td></td>
<td>Months 18 and 24</td>
<td>Months 18 and 24</td>
</tr>
<tr>
<td>HPV-005 (MI-CP-057)</td>
<td>Day 0, 60, 210 and 360</td>
<td>Day 0, 60, 210 and 360</td>
</tr>
<tr>
<td>HPV-TETRA-051</td>
<td>ND</td>
<td>Day 0, Month 2</td>
</tr>
<tr>
<td></td>
<td>Month 7</td>
<td>Month 7</td>
</tr>
</tbody>
</table>

ND = not done subjects in the HPV-16 group who received a third dose of vaccine
† = IFN-γ and IL-5
‡ = CD40L, IL-2 and TNF-α

In essence, vaccination with Cervarix apparently addresses a number of immunological compartments which is evidenced by specific expression of cytokine profiles. Expression levels and proliferative responses were strongly depended on antigen doses administered and reacted anamnestically on a multiple dose vaccination schedule indicating development of an immunological memory. Also for the cell mediated immune response AS04 turned out to be superior with regard to its capacity to stimulate various elements of the cellular immune system compared to Al(OH)₃.

In conclusion, there is sufficient evidence that Cervarix induces a strong cell mediated immune response. For the time being none of the cell-mediated immunity (CMI) parameters measured can, however, be correlated with clinical efficacy.
Antibody response against MPL (AS04):

**Study HPV-013: Seropositivity rates and GMTs for anti-MPL antibodies by pre-vaccination status (ATP cohort for immunogenicity)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-vacc status</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>GMT</th>
<th>LL</th>
<th>UL</th>
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<tbody>
<tr>
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<td>0.0</td>
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<td>29.5</td>
<td>29.5</td>
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<tr>
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<td>5</td>
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<tr>
<td></td>
<td></td>
<td>PIII(M7)</td>
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<td>6</td>
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<td>54.1</td>
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<td>100</td>
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<td>100</td>
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<tr>
<td>S+</td>
<td>PRE</td>
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<td>132</td>
<td>100</td>
<td>97.2</td>
<td>100</td>
<td>156.3</td>
<td>141.8</td>
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<tr>
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<td>132</td>
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<tr>
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<td>130</td>
<td>100</td>
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<td>100</td>
<td>741.5</td>
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<tr>
<td>Total</td>
<td>PRE</td>
<td>138</td>
<td>132</td>
<td>95.7</td>
<td>90.8</td>
<td>98.4</td>
<td>145.4</td>
<td>130.3</td>
<td>162.2</td>
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<tr>
<td></td>
<td>PII(M2)</td>
<td>138</td>
<td>137</td>
<td>99.3</td>
<td>96.0</td>
<td>100</td>
<td>402.8</td>
<td>354.0</td>
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<td>25.5</td>
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<td>149.5</td>
<td>137.5</td>
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<tr>
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<td>120</td>
<td>94.5</td>
<td>89.0</td>
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<td>138.9</td>
<td>124.4</td>
<td>155.1</td>
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<tr>
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<td>PIII(M7)</td>
<td>127</td>
<td>118</td>
<td>92.9</td>
<td>87.0</td>
<td>96.7</td>
<td>140.6</td>
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<td>84.7</td>
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<td>128.7</td>
<td>115.4</td>
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<tr>
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<td>PII(M2)</td>
<td>140</td>
<td>122</td>
<td>87.1</td>
<td>80.4</td>
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<td>121.9</td>
<td>109.7</td>
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<tr>
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<td>PIII(M7)</td>
<td>140</td>
<td>119</td>
<td>85.0</td>
<td>78.0</td>
<td>90.5</td>
<td>122.7</td>
<td>107.2</td>
<td>140.3</td>
<td></td>
</tr>
</tbody>
</table>

HPV  = HPV-16/18 L1 VLP AS04 (Hi-5 Rix4446) (10-14 years)
HAV  = Havrix group
S- = seronegative subjects (antibody titre < 59 EU/ML) prior to vaccination
S+ = seropositive subjects (antibody titre >= 59 EU/ML) prior to vaccination
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range
LL/UL = Lower/Upper limit of the 95% Confidence Interval
PRE = Pre-vaccination; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)

Only an MPL-containing vaccine such as Cervarix has a booster effect on a confirmed pre-existing anti-MPL immune response. A HAV (Hepatitis A) vaccine that does not contain MPL components has no such effect. However, even for Cervarix the booster effect on a pre-existing MPL “immunity” is weak to moderate and, most likely, will have no clinical effect. Such type of anti-MPL immune response is expected upon contact with any type of MPL-like substance which in most instances will be bacterial antigens containing MPL components in their outer cell wall structure.

Whether or not residual MPL “immunity” might impair immunogenicity of Cervarix has been addressed by grouping a subset of the study population from study HPV-013 into four different anti-MPL titer categories.
Study HPV-013: Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies according to anti-MPL level before vaccination in initially seronegative subjects (ATP cohort for immunogenicity):

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>nS+</th>
<th>%S+</th>
<th>LL</th>
<th>UL</th>
<th>GMT</th>
<th>LL</th>
<th>UL</th>
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<td>4.0</td>
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<tr>
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<td>32</td>
<td>100</td>
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<td>16765.5</td>
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<td>10.9</td>
<td>4.0</td>
<td>4.0</td>
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<td>10.3</td>
<td>4.0</td>
<td>4.0</td>
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</tr>
<tr>
<td></td>
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<td>100</td>
<td>9079.2</td>
<td>6632.0</td>
<td>12429.4</td>
</tr>
</tbody>
</table>

- Level 1 = HPV group with Anti-MPL<103 at PRE
- Level 2 = HPV group with 103<=Anti-MPL<136 at PRE
- Level 3 = HPV group with 136<=Anti-MPL<214 at PRE
- Level 4 = HPV group with 214<=Anti-MPL at PRE
- GMT = geometric mean antibody titre calculated on all subjects
- N = number of subjects with available results
- n S+/% S+ = number/percentage of subjects seropositive (antibody titre ≥ 8 EL.U/mL for HPV-16 or antibody titre ≥ 7 EL.U/ML for HPV-18)
- LL/UL = Lower/Upper limit of the 95% Confidence Interval
- PRE = Prevaccination
- PII(M2) = Post Dose II (Month 2)
- PIII(M7) = Post Dose III (Month 7)

While no specific difference can be observed post dose II (PII(M2)) a titre-dependent stimulating effect of a pre-existing anti MPL “immunity” can be interpreted post-dose III (PIII(M7)). This effect is slightly more pronounced for HPV 16 L1 compared to HPV 18 L1. Overall, anti HPV L1 titres are higher in this specific subset of a study population. Apparently, pre-existing anti MPL “immunity” is an advantage rather than a risk with regard to the potential to trigger an optimal immune response following vaccination with Cervarix.

Other immunogenicity studies:

Persistence of Immunity

Phase IIb efficacy/long-term efficacy studies HPV 001 and HPV 007 provide the currently best available overview on the long-term persistence of immunity. The outline of these studies is described under supportive studies further below.
Studies HPV-001 and HPV-007: Persistence of Anti-HPV-16 and Anti-HPV-18 Antibodies (Binding ELISA) after Vaccination (0, 1, 6 Month Schedule, Serology Post-Dose III)

These data are a good indicator for long term persistence of vaccine induced immune response until at least month 64 post dose 1. Evaluation of the long-term persistence of the initial immune response is ongoing in a number of studies (see table below).

Timepoints for immunogenicity evaluations

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 6</th>
<th>Month 7</th>
<th>Month 12</th>
<th>Month 18</th>
<th>Month 24</th>
<th>Month 36</th>
<th>Month 48</th>
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<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>HPV-007</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
</tr>
<tr>
<td>HPV-012</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
</tr>
<tr>
<td>HPV-013</td>
<td>●</td>
<td>●</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
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<td>(●)</td>
</tr>
<tr>
<td>HPV-014</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
<td>(●)</td>
</tr>
</tbody>
</table>

(●) = planned timepoint

The presented data does not allow conclusions about the need and timing of booster doses.
Rationale for bridging to 10-14 years old individuals

Study HPV-012

Information about the study outline can be found in the table provided in the beginning of the Pharmacodynamic/Immunogenicity section of this report.

A total of 770 subjects were vaccinated in this study. Of these, 458 subjects 15-25 years of age (mean: 20.2+/-3.0 years) received one of three lots of HPV-16/18 vaccine, 154 subjects 15-25 years of age (mean: 20.3+/-3.0 years) received a previous formulation and 158 subjects 10-14 years of age (mean: 12.4+/-1.4 years) also received one of the three vaccine lots.

At Month 7, all initially seronegative subjects, regardless of their age and regardless of the vaccine they received, had seroconverted to both HPV-16 and HPV-18.

Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 at Month 7 in initially seronegative subjects (binding ELISA) (ATP cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group</th>
<th>N</th>
<th>n S+</th>
<th>% S+</th>
<th>LL</th>
<th>UL</th>
<th>GMT</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>Lot 1</td>
<td>118</td>
<td>118</td>
<td>100</td>
<td>96.9</td>
<td>100</td>
<td>7438.9</td>
<td>6324.6</td>
<td>8749.6</td>
</tr>
<tr>
<td></td>
<td>Lot 2</td>
<td>122</td>
<td>122</td>
<td>100</td>
<td>97.0</td>
<td>100</td>
<td>7150.3</td>
<td>6038.1</td>
<td>8467.3</td>
</tr>
<tr>
<td></td>
<td>Lot 3</td>
<td>119</td>
<td>119</td>
<td>100</td>
<td>96.9</td>
<td>100</td>
<td>7297.2</td>
<td>6136.8</td>
<td>8677.0</td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>359</td>
<td>359</td>
<td>100</td>
<td>99.0</td>
<td>100</td>
<td>7232.9</td>
<td>6623.7</td>
<td>8029.7</td>
</tr>
<tr>
<td></td>
<td>Previous</td>
<td>111</td>
<td>111</td>
<td>100</td>
<td>96.7</td>
<td>100</td>
<td>9595.5</td>
<td>8027.4</td>
<td>11469.9</td>
</tr>
<tr>
<td></td>
<td>10-14 years</td>
<td>143</td>
<td>143</td>
<td>100</td>
<td>97.5</td>
<td>100</td>
<td>17272.5</td>
<td>15117.9</td>
<td>19734.1</td>
</tr>
<tr>
<td>HPV-18</td>
<td>Lot 1</td>
<td>116</td>
<td>116</td>
<td>100</td>
<td>96.9</td>
<td>100</td>
<td>3070.1</td>
<td>2600.0</td>
<td>3625.4</td>
</tr>
<tr>
<td></td>
<td>Lot 2</td>
<td>126</td>
<td>126</td>
<td>100</td>
<td>97.1</td>
<td>100</td>
<td>3173.4</td>
<td>2714.3</td>
<td>3710.2</td>
</tr>
<tr>
<td></td>
<td>Lot 3</td>
<td>122</td>
<td>122</td>
<td>100</td>
<td>97.0</td>
<td>100</td>
<td>3743.3</td>
<td>3173.3</td>
<td>4415.7</td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>364</td>
<td>364</td>
<td>100</td>
<td>99.0</td>
<td>100</td>
<td>3318.8</td>
<td>3023.1</td>
<td>3643.5</td>
</tr>
<tr>
<td></td>
<td>Previous</td>
<td>117</td>
<td>117</td>
<td>100</td>
<td>96.9</td>
<td>100</td>
<td>4164.7</td>
<td>3552.0</td>
<td>4882.9</td>
</tr>
<tr>
<td></td>
<td>10-14 years</td>
<td>141</td>
<td>141</td>
<td>100</td>
<td>97.4</td>
<td>100</td>
<td>6863.8</td>
<td>5976.3</td>
<td>7883.0</td>
</tr>
</tbody>
</table>

Lot 1 = 15-25 years
Lot 2 = 15-25 years
Lot 3 = 15-25 years
Pooled = Combined lots 1, 2 and 3 (15-25 years)
Previous = Previous formulation (15-25 years)
[10-14] = Lot 1 (10-14 years)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with results available
n S+/% S+ = number/percentage of subjects seropositive (antibody titre ≥ 8 EL.U/mL for HPV-16 or antibody titre ≥ 7 EL.U/ML for HPV-18)
LL/UL = Lower/Upper Limit of the 95% Confidence Interval

Both co-primary objectives (i.e., to demonstrate consistency of three lots in subjects 15-25 years and the clinical bridge) in subjects 15-25 years were met.

The secondary objective of demonstrating non-inferiority of the 10-14 year age group compared to the 15-25 year age group when receiving the same production lot was also met, since at Month 7, the upper limit of the 95% CI on the difference between the percentage of subjects who seroconverted in the older age group versus the younger age group was <10% and that the upper limit of the 95% CI on the GMT ratio between the older age group and younger age group was <2. Overall, adolescents achieved significantly higher GMTs for both antigens (>2-fold) as compared to subjects 15-25 years of age.
Study HPV-013
Information about the study outline can be found in the table provided at the beginning of the Pharmacodynamic/Immunogenicity section of this report.

Secondary objectives included evaluation of antibody responses against HPV-16, HPV-18 and MPL (by ELISA) at Month 0, 2 and 7.

A total of 2067 subjects were vaccinated in this study: 1035 subjects in the HPV group (mean age: 12.1 +/- 1.4 years) and 1032 subjects in the control group (mean age: 12.1 +/- 1.4 years). Of these, 675 subjects were included in the immunogenicity subset.

After the third dose, all initially seronegative subjects had seroconverted for both antigens and had achieved GMTs of 19882.0 EU/mL for anti-HPV-16 antibodies and 8262.0 EU/mL for anti-HPV-18 antibodies.

Seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies in initially seronegative subjects (binding ELISA) (ATP cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Timing</th>
<th>N</th>
<th>n S+</th>
<th>% S+</th>
<th>LL</th>
<th>UL</th>
<th>GMT</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>PRE</td>
<td>630</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.6</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>PII(M2)</td>
<td>625</td>
<td>622</td>
<td>99.5</td>
<td>98.6</td>
<td>99.9</td>
<td>4696.9</td>
<td>4388.6</td>
<td>5026.8</td>
</tr>
<tr>
<td></td>
<td>PIII(M7)</td>
<td>619</td>
<td>519</td>
<td>100</td>
<td>99.4</td>
<td>100</td>
<td>19882.0</td>
<td>18626.7</td>
<td>21221.9</td>
</tr>
<tr>
<td>HPV-18</td>
<td>PRE</td>
<td>639</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.6</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>PII(M2)</td>
<td>633</td>
<td>531</td>
<td>95.7</td>
<td>98.9</td>
<td>100</td>
<td>3741.7</td>
<td>3498.3</td>
<td>4000.9</td>
</tr>
<tr>
<td></td>
<td>PIII(M7)</td>
<td>628</td>
<td>528</td>
<td>100</td>
<td>99.4</td>
<td>100</td>
<td>8262.0</td>
<td>7726.0</td>
<td>8836.2</td>
</tr>
</tbody>
</table>

GMT = geometric mean antibody titre calculated on all subjects (expressed in EU/ML)
N = number of subjects with pre-vaccination results available
n S+/% S+ = number/percentage of subjects seropositive by binding ELISA (antibody titre ≥ 8 EL.U/mL for HPV-16 or antibody titre ≥ 7 EL.U/ML for HPV-18)
LL/UL = Lower/Upper limit of the 95% Confidence Interval
PRE = Pre-vaccination
PII(M2) = Post Dose II (Month 2)
PIII(M7) = Post Dose III (Month 7)

Initially seropositive subjects also elicited immune responses to the vaccine and achieved GMTs levels for both antigens that were comparable to initially seronegative subjects.

In the above described two clinical trials (HPV-012 and HPV-013) performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.

Study HPV-014
In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7). The GMTs were, however, lower in women above 25 years. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude above those encountered after natural infection. Information about the study outline can be found in the table presented in the Pharmacodynamics / Immunogenicity section of this report.

Older age, smoking, and, even more pronounced a combination of both may significantly reduce the immunogenicity.

Factors such as hormone contraception, hormone replacement therapy, pre- or post menopausal status, do not significantly reduce immunogenicity of Cervarix.
Study HPV-014 further demonstrated, that seropositivity with regard to HPV 16 and 18 at the time of vaccination has some marginal influence on the kinetics of the immune response as well as on final GMTs and is more pronounced in older individuals compared to those who are younger.

Whether or not vaccination of a seropositive female population has any effect on clinical efficacy of Cervarix cannot be assessed for the time being.

**Immunogenicity in Other Populations:**

The effect of other medicinal products including vaccines on the immunogenicity of Cervarix has not been investigated.

Cervarix has not been investigated in male subjects.

Cervarix has not been investigated in pregnant and lactating women.

**Clinical efficacy**

The efficacy of Cervarix was assessed in 2 controlled, double-blind, randomised Phase II and III clinical studies that included a total of 19,778 women aged 15 to 25 years.

In the phase II HPV-001/007 study (described in this report under supportive studies) only HPV naïve women (negative for oncogenic HPV DNA [HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68], seronegative for HPV-16 and HPV-18 and normal cytology at study entry) were enrolled. In the pivotal phase III trial HPV-008 women were included without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status.
<table>
<thead>
<tr>
<th>Study No / Phase / Countries</th>
<th>Study Design / Posology</th>
<th>Study Population / Total No / Age range</th>
<th>Key Study endpoints (Initial Phase)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV-001</strong> Phase IIb, Brazil, Canada, USA 32 centres 2001-2003</td>
<td>Multicentre, randomized, double-blind, placebo controlled study with two groups - HPV-16/18 AS04 (Hi-5/Sf-9) - Al(OH)₃ 3 doses, i.m., 0, 1, 6 months</td>
<td>HPV-16 / HPV-18 seronegative high risk HPV DNA negative healthy women N= 1113 Age range: 15-25 years</td>
<td><strong>Primary endpoints:</strong> Incident cervical infection with HPV-16 and HPV-18 analysed using all HPV-16 and/or HPV-18 DNA results determined for all specimens (i.e. self-obtained cervicovaginal specimens and physician-obtained cervical specimens combined). In addition, a separate analysis of only physician-obtained cervical specimens was conducted. Defined as at least one positive HPV-16 or HPV-18 DNA PCR assay&lt;br&gt;&lt;br&gt;<strong>Secondary endpoints (selected)</strong>&lt;br&gt;- Persistent infection with HPV-16 and/or HPV-18 defined at least two positive HPV DNA PCR assays for the same viral genotype over a minimum interval of 6 months. Cytologically-confirmed or histopathologically-confirmed LSIL, HSIL, squamous cell cancer, or adenocarcinoma concurrently associated with HPV-16 and/or HPV-18 cervical infection</td>
<td>27 months</td>
</tr>
<tr>
<td><strong>HPV-007</strong> follow-up to study to HPV-001</td>
<td>Randomized, double-blind, placebo controlled study 3-year long-term extension of Study HPV-001 with interim analysis at Month 12 and 24*  * Study vaccines were administered in study HPV-001</td>
<td>HPV-16 / HPV-18 seronegative high risk HPV DNA negative healthy women N= 776 Age range: 15-25 years</td>
<td><strong>Primary endpoint</strong> Long-term efficacy against incident cervical infection with HPV-16 and/or HPV-18.&lt;br&gt;&lt;br&gt;<strong>Secondary endpoints (Selected)</strong>&lt;br&gt;- Long-term Efficacy against persistent cervical infection (6-month definition) with HPV-16 and/or HPV-18.&lt;br&gt;- Histopathologically-confirmed CIN 1+ or CIN 2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR).&lt;br&gt;- Long-term immunogenicity&lt;br&gt;- Long-term safety</td>
<td>3 years interim analysis after 24 months completed</td>
</tr>
<tr>
<td><strong>HPV-008</strong> 14 countries</td>
<td>Randomized, double-blind, placebo controlled study</td>
<td>HPV-16 / HPV-18 seronegative high risk HPV DNA negative healthy women N=18665 Age range: 15-25 years</td>
<td><strong>Primary endpoint</strong> Control in the prevention of histopathologically confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of cervical tissue by PCR.&lt;br&gt;&lt;br&gt;<strong>Secondary endpoints (selected)</strong>&lt;br&gt;- To evaluate the safety of the candidate vaccine in adolescent and young adult women</td>
<td>Final analysis when 36 cases CIN 2+ are found. Long-term follow-up to 48 months</td>
</tr>
<tr>
<td>- Persistent cervical infection (6 and 12-month definitions) with HPV-16 and/or HPV-18. Histopathologically-confirmed CIN 1+ or CIN 2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR).</td>
<td>Interim analysis when 23 CIN 2 cases are found</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Main studies

The Applicant performed two sets of trials, the 001 – 007 set (of which the data were initially submitted) listed in this report under supportive studies and the 008 trial, of which the data of an interim analysis was submitted with the response to the CHMP LoQ at day 120 of the review. Both trials 007 and 008 are still ongoing and continue to generate data on both efficacy and safety. Data is available from studies HPV-001/007 (5.5 years) and HPV-008 (15 months).

Study HPV-008

HPV-008 is a controlled, double blinded Phase III randomized clinical trial performed in Asia Pacific, Europe, Latin America and North America. HPV-008 has been conducted under the supervision of an Independent Data Monitoring Committee (IDMC) with duration of 48 months of follow-up.

The presented event-driven interim analysis was to be performed when at least 23 cases of CIN2+ with HPV-16 or HPV-18 DNA detected in the lesion.

METHODS

Study Participants and Sample sizes

A total of 18729 subjects were enrolled in the study. The study is conducted in 133 centres in 14 countries spread across four study regions: Asia Pacific, Europe, Latin America and North America. The target was to enrol approximately 18 000 unscreened women aged 15 to 25 years.

The inclusion and exclusion criteria were selected to allow enrolment of a broad population of women, including both those previously uninfected with HPV (HPV naïve) and those previously or currently infected with HPV (HPV non-naïve). No HPV serological testing, HPV DNA screening or cervical cytological screening was performed prior to enrolment.

Inclusion Criteria

- A woman between, and including, 15 and 25 years of age at the time of the first vaccination.
- Subject must be free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Subject must have a negative urine pregnancy test.
- Subject must be of non-childbearing potential (e.g. surgically sterilized) or, if of childbearing potential, she must be abstinent or must be using adequate contraceptive precautions for 30 days prior to the first vaccination and must agree to continue such precautions for two months after completion of the vaccination series.
- Has had no more than 6 lifetime sexual partners prior to enrollment. This criterion may not be applicable in subjects less than 18 years of age, according to local regulatory/ethical requirements.
- Subject must have intact cervix (e.g. no history of cauterization or surgical treatment involving damage to the transformation zone of the cervix).

Main Exclusion Criteria

- Pregnant or breastfeeding. Women must be at least 3 months post-pregnancy and not breastfeeding to enter the study.
- A woman planning to become pregnant or planning to discontinue contraceptive precautions during approximately the first nine months of the study (Months 0-8).
- Previous administration of monophosphoryl lipid A (MPL) or AS04 adjuvant.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the
study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-
  modifying drugs within six months prior to the first vaccine dose. Inhaled and topical steroids
  were allowed.
- Planned administration of a vaccine not foreseen by the study protocol within 30 days before and
  30 days after (i.e. days 0-29) each dose of vaccine.
- History of having had colposcopy or has planned a colposcopy to evaluate an abnormal cervical
  cytology (Pap smear) test.
- Received immunoglobulins and/or blood product within 90 days preceding enrollment.
  Enrollment will be deferred until the subject is outside of specified window.

Study cohorts/data sets analyzed

At the interim analysis analysis of efficacy is performed on the Total Vaccinated cohort for efficacy
1 (primary analysis) and on the Total Vaccinated cohort for efficacy 2.
Analysis of safety is performed on the Total Vaccinated cohort (primary analysis) and on the ATP
cohort for safety.
Analysis of immunogenicity is performed on the ATP cohort for immunogenicity (primary analysis)
and on the Total Vaccinated cohort.

Total Vaccinated cohort for efficacy 1 (TVC-1)
The Total Vaccinated cohort for efficacy 1 (TVC-1) includes all vaccinated subjects (at least one
dose) for whom data concerning efficacy endpoint measures are available and who were HPV DNA
negative and seronegative to the relevant HPV type (HPV-16 or HPV-18) at study entry. Women
with high-grade or missing cytology (0.5%) were excluded from the efficacy analysis.
For this cohort, the follow-up time for a subject started at the day after Dose 1.

Total Vaccinated cohort for efficacy 2 (TVC-2)
A pre-specified analysis, Total Vaccinated cohort for efficacy 2 (TVC-2) was identical to the TVC-1
analysis except that it excluded women with abnormal cytology at study entry.
In addition, subjects must be negative for HPV DNA (by PCR) at Month 0 for the corresponding
HPV type considered in the analysis (i.e. HPV type associated with the efficacy endpoint). For this
cohort, the follow-up time for a subject started at the day after Dose 1. For all stratified efficacy
endpoints, the principal analysis is performed on subjects who were seronegative (by ELISA) prior
to vaccination for the corresponding HPV type considered in the analysis.
This analysis complements the analysis on TVC-1 and is performed at the interim analysis on
primary and secondary endpoints that are associated with HPV-16 and/or HPV-18 only.

According-to-protocol (ATP) cohort for analysis of efficacy
The ATP cohort for analysis of efficacy includes all evaluable subjects (i.e. those meeting all
eligibility criteria, complying with the procedures defined in the protocol, with no elimination
violations) for whom data concerning efficacy endpoint measures are available and have a normal or
low-grade cytology (i.e. negative or ASCUS or LSIL) at Month 0. In addition, subjects must be
negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type considered in
the analysis (i.e. HPV type associated with the efficacy endpoint). For this cohort, the follow-up time
for a subject started at the day after Dose 3. For all stratified efficacy endpoints, the principal
analysis is performed on subjects who were seronegative (by ELISA) prior to vaccination for the
 corresponding HPV type considered in the analysis. At the final analysis, the ATP cohort for
efficacy will be the primary cohort for all endpoints, except for endpoints evaluated in HPV DNA
positive woman at Month 0.

According-to-protocol (ATP) cohort for analysis of immunogenicity
The ATP cohort for analysis of immunogenicity includes all evaluable subjects (i.e. those meeting all
eligibility criteria, complying with the procedures defined in the protocol, with no elimination
criteria during the study) for whom data concerning immunogenicity endpoint measures are
available. This includes subjects for whom assay results are available for antibodies against at least
one study vaccine antigen component after vaccination. Subjects who acquire either HPV-16 or
HPV-18 infection during the trial are excluded from the ATP cohort for immunogenicity.
Treatments

The candidate HPV vaccine and hepatitis A control vaccine were administered (0.5 ml dose) intramuscularly into the deltoid of the non-dominant arm according to a 0, 1, 6-month schedule. For the immunogenicity subset blood samples were drawn from all subjects at Months 0, 7 and 24 for HPV-16/18 serology testing by ELISA. Exit colposcopy was performed within 30 days after cytology results of the Month 48 visit depending on the cytological results.

Objectives

The primary objective of study HPV-008 was to demonstrate, that Cervarix protects individuals from histopathologically confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 and/or 18 serostatus (by ELISA). CIN2+ is defined as CIN2, CIN3, adenocarcinoma in-situ (AIS) and invasive cervical cancer.

Secondary objectives included the prevention of CIN 1, protection against persistent infection with HPV-16 and/or HPV-18 and the immunological response to vaccination.

Outcomes/endpoints

The primary endpoint for the interim analysis was protection against CIN2+ lesions associated with HPV-16 and/or HPV-18 among subjects who are negative for HPV DNA (by PCR) at baseline for the corresponding HPV type.

Secondary Endpoints included
- Protection against persistent infection (6-month and 12-month definition) with HPV-16 or HPV-18 among subjects who are negative for HPV DNA at baseline for the corresponding HPV type.
- Protection against persistent infection (6-month definition) with the following oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
- Protection against CIN2+ and CIN1+ associated with HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
- Immune response in a subset of subjects from selected study sites and immune correlates of protection against persistent infection (presented under PD/Immunogenicity).

Statistical methods

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 have been calculated using the conditional exact method.

RESULTS

Participant flow/ Numbers analysed
18644 subjects were vaccinated and included in the study, of whom 9319 subjects received the HPV vaccine (vaccine group) and 9325 subjects received the hepatitis A vaccine (control group).

Of the 18644 vaccinated subjects in the study, 954 subjects withdrew from the study at the time of the interim analysis: 496 subjects in the vaccine group and 458 subjects in the control group (see table). The majority of these subjects (46.8%) were lost to follow-up (446 subjects), withdrew their consent not due to an adverse event (279 subjects), or migrated or moved from the study area (113 subjects). Eight subjects withdrew due to a SAE (3 subjects in the vaccine group and 5 subjects in the control group). Nine subjects withdrew due to a non-serious AE (6 subjects in the vaccine group and 3 subjects in the control group).

**Recruitment**

The study initiation date was 06 May 2004. An event-triggered interim analysis was planned when at least 23 cases of CIN2+ with HPV-16 or HPV-18 DNA were detected in TVC-1. At the time of the interim analysis, the majority of subjects (N=13046) had completed their Month 18 visit. The interim analysis has been performed on 03 November 2006.
Conduct of the study

Because potential study conduct and data integrity issues were identified at one study site, all 21 subjects from this site were excluded from the analyses. Additionally, 64 subjects were randomized but not vaccinated. There were four amendments to the study protocol dated 12 March 2004.

Baseline data

The demographic profiles of both groups of subjects were comparable with respect to mean age, regional distribution, racial distribution, mean height and weight. The mean age was 20 years and the population was predominantly of Caucasian or East & South East Asian origin (54.8% and 23.3%, respectively).

Overall, 29.8% of the subjects were identified as smokers, 92.2% of the subjects had less than three sexual partners during the past year, and 94.5% of the subjects were negative for Chlamydia.

Regarding the HPV-16 status, 80.9% of the subjects were DNA negative and seronegative, 13.9% of the subjects were DNA negative and seropositive, 2.5% of the subjects were DNA positive and seronegative, and 2.8% of the subjects were DNA positive and seropositive. Regarding the HPV-18 status, 87.2% of the subjects were DNA negative and seronegative, 10.5% of the subjects were DNA negative and seropositive, 1.3% of the subjects were DNA positive and seronegative, and 1% of the subjects were DNA positive and seropositive.

Outcomes and estimation

In study 008 the primary analyses of efficacy included only women who were HPV DNA negative and seronegative to the relevant HPV type (HPV 16 or HPV 18) prior to study entry and had received at least one dose of Cervarix or the control. Women with high-grade or missing cytology (0.6%) were excluded from the efficacy analysis.

Overall, 74.0% of women enrolled were naïve to both HPV16 and HPV18 at study entry. A total of 22% of women enrolled into study 008 had abnormal low grade cytology and/or evidence of infection with an oncogenic HPV type at baseline.

Histopathology

Protection against CIN2+ associated with HPV-16/18 (primary endpoint)

In the protocol-specified primary endpoint interim analysis, the observed vaccine efficacy (VE) against CIN2+ associated with HPV-16 and/or HPV-18 was statistically significant (VE = 90.4% [53.4%, 99.3%], p<0.0001), i.e. 2 cases in the vaccine group vs. 21 cases in the control group. The observed vaccine efficacy against CIN2+ associated with HPV-16 alone was 93.3% [47%, 99.9%], i.e. 1 case in the vaccine group vs. 15 cases in the control group. The observed vaccine efficacy against CIN2+ associated with HPV-18 alone was not statistically significant 83.3% [-78.8%, 99.9%] due to a limited number of events at the time of the analysis, i.e. 1 case in the vaccine group vs. 6 cases in the control group.

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 (primary endpoint)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T(year)</th>
<th>n/T (Per 100)</th>
<th>VE %</th>
<th>LL</th>
<th>UL</th>
<th>LL</th>
<th>UL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16/18*</td>
<td>HPV</td>
<td>7788</td>
<td>2</td>
<td>9613.75</td>
<td>0.02</td>
<td>0.00</td>
<td>0.09</td>
<td>90.4</td>
<td>53.4</td>
<td>99.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>7838</td>
<td>21</td>
<td>9682.00</td>
<td>0.22</td>
<td>0.12</td>
<td>0.35</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV</td>
<td>6701</td>
<td>1</td>
<td>8279.75</td>
<td>0.01</td>
<td>0.00</td>
<td>0.08</td>
<td>93.3</td>
<td>47.0</td>
<td>99.9</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>6717</td>
<td>15</td>
<td>8284.32</td>
<td>0.18</td>
<td>0.09</td>
<td>0.32</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
The regional distribution of the 23 cases of CIN2+ associated with HPV-16 and/or HPV-18 was as follows: 7 cases in Asia Pacific (N=5368), 10 cases in Europe (N=5934), 1 case in Latin America (N=2164) and 5 cases in North America (N=2160).

For this analysis, the association with HPV-16 and/or HPV-18 was based only on the detection of viral DNA by PCR in the biopsy sample and did not consider whether or not the HPV-16 and/or HPV-18 detected was likely to be responsible for the development of the lesion. Other oncogenic HPV types were frequently detected in lesions and in some cases subjects had longstanding infections with the other type(s) detected.

Therefore an additional post-hoc analysis was conducted to evaluate vaccine efficacy against lesions likely to be causally associated with HPV-16 and/or HPV-18. This post-hoc analysis (clinical case assignment) assigned causal association of an HPV type with the lesion based on the presence of the HPV type in cytology samples prior to detection of the lesion. Based on this case assignment, the analysis excluded 3 CIN2+ cases (2 in the vaccine group and 1 in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial.

The following table therefore presents results of the clinical case assignment analysis. The observed vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 was 100% [74.2%, 100%], i.e. 0 cases in the vaccine group vs. 20 cases in the control group. The observed efficacy against CIN2+ associated with HPV-16 alone was 100% [64.5%, 100%], i.e. 0 cases in the vaccine group vs. 15 cases in the control group. The observed efficacy against CIN2+ associated with HPV-18 alone was 100% [-49.5%, 100%], i.e. 0 cases in the vaccine group vs. 5 cases in the control group. Since the majority of CIN2+ cases in the control group resulted from infections, which were first detected prior to completion of the full three-dose schedule, the absence of cases in the vaccine group reflects the onset of a vaccine effect prior to completion of the full vaccination course.

### Table: Person-year rate and Vaccine Efficacy (VE)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T(year)</th>
<th>n/T (Per 100)</th>
<th>LL</th>
<th>UL</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-18</td>
<td>HPV</td>
<td>7221</td>
<td>1</td>
<td>8903.55</td>
<td>0.01</td>
<td>0.00</td>
<td>0.07</td>
<td>83.3</td>
<td>-78.8</td>
<td>99.9</td>
<td>0.1249</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>7258</td>
<td>6</td>
<td>8947.82</td>
<td>0.07</td>
<td>0.02</td>
<td>0.16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Protocol-specified endpoint

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots) = Vaccine group
HAV = Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects are in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative and seronegative for the corresponding HPV type at Month 0
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=97.9% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test
Post-hoc analysis: 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 using conditional exact method (TVC-1/Clinical Case Assignment)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T(year)</th>
<th>n/T (Per 100)</th>
<th>LL</th>
<th>UL</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16/18</td>
<td>HPV</td>
<td>7788</td>
<td>0</td>
<td>9614.95</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
<td>100.0</td>
<td>74.2</td>
<td>100.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>7838</td>
<td>20</td>
<td>9682.45</td>
<td>0.21</td>
<td>0.12</td>
<td>0.34</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV</td>
<td>6701</td>
<td>0</td>
<td>8280.64</td>
<td>0.00</td>
<td>0.00</td>
<td>0.06</td>
<td>100.0</td>
<td>64.5</td>
<td>100.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>6717</td>
<td>15</td>
<td>8284.32</td>
<td>0.18</td>
<td>0.09</td>
<td>0.32</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV-18</td>
<td>HPV</td>
<td>7221</td>
<td>0</td>
<td>8903.86</td>
<td>0.00</td>
<td>0.00</td>
<td>0.05</td>
<td>100.0</td>
<td>-49.5</td>
<td>100.0</td>
<td>0.0625</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>7258</td>
<td>5</td>
<td>8948.26</td>
<td>0.06</td>
<td>0.01</td>
<td>0.15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots) = Vaccine group
HAV = Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects are in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative and seronegative for the corresponding HPV type at Month 0
Additional analysis: The lesion is assigned to an HPV type found in the lesion if
a) the same HPV type is found in at least one of the two immediately preceding cytology samples, or
b) none of the HPV types found in the lesion are found in any of the two preceding cytology samples
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=97.9% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Protection against cervical intraepithelial neoplasia (CIN) 1+ associated with HPV-16/18 (secondary endpoint)

The following table shows the incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 in HPV DNA negative and seronegative subjects at baseline. It should be noted that for this analysis, the association with HPV-16 and/or HPV-18 was based on the detection of viral DNA by PCR in the biopsy sample and did not consider the presence of other oncogenic type(s) in the biopsy sample or the detection of HPV type(s) in the cervical samples prior to collection of the biopsy.

Incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 in HPV DNA negative and seronegative subjects at baseline

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T(year)</th>
<th>n/T (Per 100)</th>
<th>LL</th>
<th>UL</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16/18*</td>
<td>HPV</td>
<td>7788</td>
<td>3</td>
<td>9613.42</td>
<td>0.03</td>
<td>0.00</td>
<td>0.10</td>
<td>89.2</td>
<td>59.4</td>
<td>98.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>7838</td>
<td>28</td>
<td>9681.19</td>
<td>0.29</td>
<td>0.18</td>
<td>0.44</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV</td>
<td>6701</td>
<td>2</td>
<td>8279.42</td>
<td>0.02</td>
<td>0.00</td>
<td>0.10</td>
<td>88.9</td>
<td>44.6</td>
<td>99.2</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>6717</td>
<td>18</td>
<td>8283.71</td>
<td>0.22</td>
<td>0.12</td>
<td>0.37</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV-18</td>
<td>HPV</td>
<td>7221</td>
<td>1</td>
<td>8903.55</td>
<td>0.01</td>
<td>0.00</td>
<td>0.07</td>
<td>90.9</td>
<td>22.1</td>
<td>99.9</td>
<td>0.0063</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>7258</td>
<td>11</td>
<td>8947.48</td>
<td>0.12</td>
<td>0.05</td>
<td>0.24</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Protocol-specified endpoint
HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots) = Vaccine group
HAV = Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects are in the analysis of at least one single type)

n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative and seronegative for the corresponding HPV type at Month 0
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=97.9% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Efficacy of Cervarix against CIN 1 associated with HPV16 and/or HPV 18 related CIN1 was 89.2% (97.9% CI: 59.4; 98.5). Statistically significance was reached for both HPV 16 and HPV 18 when analysed separately.

Virology

Protection against persistent infection (12-month definition) associated with HPV-16/18 (secondary endpoint) in HPV DNA negative and seronegative subjects at baseline.

The following table shows the incidence rates and vaccine efficacy against persistent infection (12-month definition) with HPV-16 and/or HPV-18 in HPV DNA negative and seronegative subjects at baseline.

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T(year)</th>
<th>Person-year rate</th>
<th>VE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/T (Per 100)</td>
<td>LL</td>
<td>UL</td>
</tr>
<tr>
<td>HPV-16/18</td>
<td>HPV</td>
<td>3386</td>
<td>11</td>
<td>5062.64</td>
<td>0.22</td>
<td>0.09</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>3437</td>
<td>46</td>
<td>5104.85</td>
<td>0.90</td>
<td>0.62</td>
<td>1.26</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV</td>
<td>2945</td>
<td>7</td>
<td>4407.73</td>
<td>0.16</td>
<td>0.05</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>2972</td>
<td>35</td>
<td>4422.78</td>
<td>0.79</td>
<td>0.52</td>
<td>1.16</td>
</tr>
<tr>
<td>HPV-18</td>
<td>HPV</td>
<td>3143</td>
<td>4</td>
<td>4711.21</td>
<td>0.08</td>
<td>0.02</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>3190</td>
<td>12</td>
<td>4774.48</td>
<td>0.25</td>
<td>0.11</td>
<td>0.48</td>
</tr>
</tbody>
</table>

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots) = Vaccine group
HAV = Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
Subjects have at least 10 months of follow-up after Month 6
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects are in the analysis of at least one single type)

n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative and seronegative for the corresponding HPV type at Month 0
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=97.9% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

For HPV-16 protection against persistent infection (12-month definition) in HPV DNA negative and seronegative subjects at baseline reached statistical significance, whereas for HPV-18, the difference between the vaccine and control groups was not statistically significant

However, in a pre-specified analysis (TVC-2) who’s cohort excluded women with abnormal cytology at study entry, the 12 month persistent infection endpoint for HPV 18 reached statistical significance with vaccine efficacy of 89.9% (97.9% CI: 11.3; 99.9). One case was observed in the vaccine group versus 10 cases in the control group.

Protection against persistent infection (6-month definition) associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline.
The following table shows the incidence rates and vaccine efficacy against persistent infection (6-month definition) with HPV-16 and/or HPV-18 in HPV DNA negative and seronegative subjects at baseline.

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T(year)</th>
<th>n/T (Per 100)</th>
<th>LL</th>
<th>UL</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16/18</td>
<td>HPV</td>
<td>6344</td>
<td>38</td>
<td>8149.58</td>
<td>0.47</td>
<td>0.31</td>
<td>0.67</td>
<td>80.4</td>
<td>70.4</td>
<td>87.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>6402</td>
<td>193</td>
<td>8129.85</td>
<td>2.37</td>
<td>2.00</td>
<td>2.80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV-16</td>
<td>HPV</td>
<td>5493</td>
<td>23</td>
<td>7076.92</td>
<td>0.33</td>
<td>0.19</td>
<td>0.52</td>
<td>84.1</td>
<td>73.5</td>
<td>91.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>5520</td>
<td>144</td>
<td>7035.66</td>
<td>2.05</td>
<td>1.67</td>
<td>2.48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPV-18</td>
<td>HPV</td>
<td>5896</td>
<td>15</td>
<td>7590.88</td>
<td>0.20</td>
<td>0.10</td>
<td>0.35</td>
<td>74.0</td>
<td>49.1</td>
<td>87.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HAV</td>
<td>5939</td>
<td>58</td>
<td>7635.60</td>
<td>0.76</td>
<td>0.55</td>
<td>1.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HPV = HPV-16/18 L1 VLP/AS04 vaccine (three lots) = Vaccine group
HAV = Hepatitis A vaccine (three lots) = Control group
N=number of subjects included in each group
Subjects have at least 5 months of follow-up after Month 6
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (subjects are in the analysis of at least one single type)
n=number of subjects reporting at least one event in each group
Subjects with an event are DNA negative and seronegative for the corresponding HPV type at Month 0
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=97.9% Lower and Upper confidence limits
P-value=Two-sided Fisher Exact test

Study HPV-008 was designed to evaluate vaccine efficacy against 6 Month HPV-16/18 persistent infection as a secondary endpoint. Despite the presented results in the table above 6-month protection against persistence HPV 16 / 18 infection is not accepted as a pre-defined endpoint and is therefore not considered in the assessment of efficacy.

Protection against persistent infection (6-month definition) associated with HPV-16/18 regardless of their initial serostatus at baseline.

The vaccine efficacy against persistent infection (6-month definition) with HPV-16 alone in HPV DNA negative subjects at baseline, regardless of their initial serostatus, was 81.1%; 95% CI; 0.5%, 88.4%. The efficacy against persistent infection with HPV-18 alone was 72.6% (95% CI; 49.3%, 86.3%).

Furthermore statistically significant protection against persistent infection (6-month) associated with oncogenic HPV types in HPV DNA negative subjects at baseline was observed for HPV-31, HPV-45 and HPV-52 (VE = 36.1% (95% CI, 0.5%, 59.5%), 59.9% (95% CI, 2.6%, 85.2%) and 31.6% (95% CI, 3.5%, 51.9%), respectively). However, VE against 12-month persistent infection and CIN2+ did not reach statistical significance. There is currently no firm evidence for cross-protection against non-vaccine HPV types.
Ancillary analyses

- Clinical studies in special populations

Currently no data in the male population has been provided.

Supportive studies

**HPV-001 and HPV-007**

Study HPV-001 was a double-blind, randomised, controlled study conducted in 32 centres in the US, Canada and Brazil. The primary objective of Study HPV-001 was to evaluate vaccine efficacy against HPV-16 and/or HPV-18 incident infections which has not been an accepted endpoint for the demonstration of efficacy in the claimed indication. Main secondary objectives of the study were to evaluate vaccine efficacy against persistent infections, cytological abnormalities and histopathological lesions associated with HPV-16 and/or HPV-18 or associated with other high-risk HPV types. The study also evaluated the safety and immunogenicity of the vaccine. Study HPV-001 is completed.

Study HPV-007 is the extension of study HPV-001 and evaluates the long-term efficacy of the HPV-16/18 vaccine in a subset of subjects (70 %) vaccinated in Study HPV-001 for an additional 36 months. The maximum follow-up period in Study HPV-001 was 27 months. For all subjects, there was an interval between completion of Study HPV-001 and their first visit in Study HPV-007 (mean: 14 months). In total, from the time of first vaccination in Study HPV-001 until their Month 24 visit in Study HPV-007, subjects have been evaluated for up to 64 months (i.e., 58 months after the third dose), with a mean follow-up period of 60 months (i.e., 54 months after the third dose). Study HPV-007 is ongoing and interim data (a 24 months interim analysis, mean follow-up of 60 months after dose 1 administered in Study HPV-001) are presented. The design of Study HPV-007 closely follows that of Study HPV-001 to ensure consistency in collection of information on efficacy of the vaccine.

**Results**

**Prophylactic efficacy against HPV-16/18 in a population naïve to oncogenic HPV types**

Women were vaccinated in study 001 and evaluated for efficacy up to month 27 and then a subset (N=776) was followed in study 007 up to 5.5 years after the first dose. The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as additional efficacy endpoint. There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group in study 001. In study 007 the efficacy of Cervarix against 12-month persistent HPV-16/18 infection was 100% (95% CI: 66.5; 100). There were ten cases of persistent HPV-16 infection, and four cases of persistent HPV-18 infection, all in the control group.

- Discussion on clinical efficacy

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years.

The phase III trial (HPV-008) enrolled women regardless of baseline cytology and HPV serological and DNA status. The primary efficacy endpoint was CIN2+ associated with HPV-16 and/or HPV-18. Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 was used in the clinical trials as a surrogate marker for cervical cancer. The secondary endpoints included 12-month persistent infection. The primary analyses of efficacy (TVC-1) included only women who were HPV DNA negative and seronegative to the relevant HPV type (HPV-16 or HPV-18) at study entry and had received at least one dose of Cervarix or the control (74.0% of women enrolled). An interim analysis with mean
follow-up 15 months was provided, however, the vaccine efficacy (ATP cohort post-dose 3) has not been evaluated in the primary efficacy population.

For HPV-16 all endpoints reached statistical significance. For HPV-18, the difference between the vaccine and control groups was not statistically significant for CIN2+ and 12 month persistent infection, due to a limited number of events at the time of the analysis. However, in a pre-specified analysis (TVC-2) that excluded women with abnormal cytology at study entry, the 12 month persistent infection endpoint for HPV-18 reached statistical significance with vaccine efficacy of 89.9% (97.9% CI: 11.3; 99.9).

An additional post-hoc analysis was conducted to determine vaccine efficacy against lesions likely to be causally associated with HPV-16 and/or HPV-18. This post-hoc analysis (clinical case assignment) assigned causal association of an HPV type with the lesion based on the presence of the HPV type in cytology samples prior to detection of the lesion. Based on this case assignment, the analysis excluded 3 CIN2+ cases (2 in the vaccine group and 1 in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial. Based on this analysis there were no cases in the vaccine group and 20 cases in the control group (Efficacy 100%; 97.9% CI: 74.2, 100).

The phase II trial (HPV-001/007) enrolled only women who were tested negative for 14 oncogenic HPV DNA types, seronegative for HPV-16 and HPV-18 and had normal cytology. The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Women were vaccinated and evaluated for efficacy up to month 27 and then followed in study 007 up to 5.5 years. There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group. The efficacy of Cervarix against 12-month persistent HPV-16/18 infection was 100% (95% CI: 66.5; 100).

There was no evidence of protection from disease caused by the HPV types for which subjects were HPV DNA positive at study entry. However, individuals already infected with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining HPV type.

The immunogenicity induced by three doses of Cervarix has been evaluated in 5,303 female subjects from 10 to 55 years of age. No minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines.

In clinical trials, 99.9% of initially seronegative subjects had seroconverted to both HPV types 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres were well above titres observed in women previously infected but who cleared HPV infection. Initially seropositive and seronegative subjects reached similar titres after vaccination.

The phase II study (HPV-001/007) evaluated the immune response against HPV-16 and HPV-18 up to 64 months post dose 1. Vaccine-induced IgG Geometric Mean Titres for both HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau from month 18 up to the end of the follow-up (month 64). At the end of the follow-up period, GMTs for both HPV-16 and HPV-18 were still at least 11-fold higher than titres observed in women previously infected but who cleared HPV infection and >98% of the women were still seropositive for both antigens.

In subjects above 25 years of age in study 014 all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7). The GMTs were, however, lower in women above 25 years. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) with GMTs that were still at least 9 fold higher than in subjects from a control group who had cleared an HPV infection (seropositive and PCR negative).

In two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.
Clinical safety

- Patient exposure

The safety information presented here is derived from the studies that were included in the pooled analysis of safety (HPV-003, 004, 005, 001, 007, 008, 012, 013, 014, 015 and 016 studies) as summarised in the following. The current pre-licensure safety database included females only. Of the 29,953 healthy girls and women included in the overall clinical development program of the HPV-16/18 vaccine candidate, 16,142 subjects have received at least one dose of HPV 16-18 vaccine and 13,811 subjects have received one of the control vaccines (Havrix 720, Havrix 360 or Al(OH)3).

### Pooled safety analysis: number and percentage of subjects who received study vaccine doses by group (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Total number of doses received</th>
<th>HPV  N = 16142</th>
<th>ALU N = 3454</th>
<th>HAV360 N = 1032</th>
<th>HAV720 N = 925</th>
<th>Total N = 2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>436</td>
<td>2.7</td>
<td>61</td>
<td>2.3</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>1566</td>
<td>9.7</td>
<td>905</td>
<td>26.5</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>14,403</td>
<td>87.6</td>
<td>2,990</td>
<td>89.2</td>
<td>1,013</td>
</tr>
<tr>
<td>Avg</td>
<td>16,142</td>
<td>100</td>
<td>3,454</td>
<td>100</td>
<td>1,032</td>
</tr>
</tbody>
</table>

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 006, 008, 012, 013, 014, 015 and 016)
ALU = Al(OH)3 control group (Studies HPV-001, 003 and 015)
HAV360 = Hepatitis A control group containing 560 EU hepatitis A antigen per dose (Study HPV-013)
HAV720 = Hepatitis A control group containing 720 EU hepatitis A antigen per dose (Study HPV-003)
N = number of subjects in each group included in the considered cohort
n% = number percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose
Data source = Pooled safety analysis

Subjects included in various clinical trials covered a broad age range, starting from 10 years of age onwards. The studies were conducted in Europe, Asia Pacific, North and Latin America and consequently included a range of ethnicities, including subjects of Caucasian, Hispanic, Black and Asian origin.

All women and girls enrolled in the trials were to be free of obvious health problems based on medical history and clinical examination and had to have a negative urine pregnancy test prior to administration of each vaccine dose.

### Pooled safety analysis: summary of demographic characteristics (Overall, Total Vaccinated Cohort)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parameter or Category</th>
<th>Value or n</th>
<th>% Value or n</th>
<th>% Value or n</th>
<th>% Value or n</th>
<th>% Value or n</th>
<th>% Value or n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>N</td>
<td>16142</td>
<td>3454</td>
<td>1032</td>
<td>3925</td>
<td>925</td>
<td>2035</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>23.3</td>
<td>34.1</td>
<td>12.1</td>
<td>20.0</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.8</td>
<td>9.1</td>
<td>1.4</td>
<td>3.1</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>21.0</td>
<td>34.0</td>
<td>12.0</td>
<td>20.0</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>10.0</td>
<td>15.0</td>
<td>10.0</td>
<td>15.0</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>17.0</td>
<td>28.0</td>
<td>14.0</td>
<td>33.0</td>
<td>72.0</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>1488</td>
<td>35.0</td>
<td>311</td>
<td>8.4</td>
<td>10.0</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>White/Caucasian</td>
<td>9594</td>
<td>94.9</td>
<td>1829</td>
<td>51.7</td>
<td>54.9</td>
<td>16899</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>3882</td>
<td>24.0</td>
<td>754</td>
<td>21.9</td>
<td>14.2</td>
<td>3797</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>1822</td>
<td>11.3</td>
<td>350</td>
<td>10.0</td>
<td>30.3</td>
<td>666</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>356</td>
<td>2.2</td>
<td>106</td>
<td>3.1</td>
<td>2.0</td>
<td>227</td>
</tr>
</tbody>
</table>

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 006, 008, 012, 013, 014, 015 and 016)
ALU = Al(OH)3 control group (Studies HPV-001, 003 and 015)
HAV360 = Hepatitis A control group containing 560 EU hepatitis A antigen per dose (Study HPV-013)
HAV720 = Hepatitis A control group containing 720 EU hepatitis A antigen per dose (Study HPV-003)
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
n% = n/Number of subjects with available results x 100
Data source = Pooled safety analysis
The current safety database allows for the detection of rare adverse events and vaccine-related rare events compared with the reporting of events in the control groups. Studies that were pooled had similar study designs with respect to vaccination schedule and methods of determination and capture of adverse events. Long-term follow-up data is available from studies HPV-001/007 (5.5 years), HPV-008 (approximately Month 24 for some subjects), HPV-013 (Month 18) and HPV-014 (Month 18).

- **Adverse events**

The following endpoints were evaluated in clinical studies:

Solicited symptoms: Occurrence of solicited local (injection site pain, redness and swelling) or general symptom (fatigue, fever, gastrointestinal symptoms, including nausea, vomiting, diarrhoea and/or abdominal pain), headache, rash, pruritus, myalgia, arthralgia and urticaria, (within 7 days (Day 0-6) after each vaccination)

- Unsolicited symptoms: Occurrence of unsolicited symptoms within 30 days (Day 0-29) following each vaccination.
- Serious Adverse Events (SAEs): Occurrence of SAEs following vaccination.
- New Onset of Chronic Disease (NOCD)/ New Onset of Autoimmune Disease (NOAD)

- **Medically Significant Conditions**: Occurrence of medically significant conditions (MSCs) throughout the study period, regardless of causal relationship to vaccination and intensity.

- **Pregnancies**: Occurrence of pregnancies and pregnancy outcomes.

The following Adverse Reactions are reflected in the SPC (section 4.8)

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency. Frequencies are reported as very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100).

The most common adverse reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting.

**Nervous system disorders**:
- Very common: headache
- Uncommon: dizziness

**Gastrointestinal disorders**:
- Common: gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain

**Skin and subcutaneous tissue disorders**:
- Common: itching/pruritus, rash, urticaria

**Musculoskeletal and connective tissue disorders**:
- Very common: myalgia
- Common: arthralgia

**Infections and infestations**:
- Uncommon: upper respiratory tract infection

**General disorders and administration site conditions**:
- Very common: injection site reactions including pain, redness, swelling; fatigue
- Common: fever (≥38°C)
- Uncommon: other injection site reactions such as induration, local paraesthesia
A similar safety profile has been observed in subjects with prior or current HPV infection as compared to subjects negative for oncogenic HPV DNA or seronegative for HPV-16 and HPV-18 antibodies.

Assessment of the Safety data set:

The overall incidences for each of the three local symptoms were higher in the HPV group compared to the control groups. The most frequently reported solicited local symptoms reported was pain (reported following 78.0% of HPV, 52.5% of ALU, 41.3% of HAV360 and 58.9% of HAV720 doses). Most of the pain was mild to moderate in intensity, and grade 3 pain was reported following 6.3% of HPV doses. There was a slight increase in the incidence of redness and swelling with subsequent doses. Grade 3 redness and swelling occurred at low frequencies.

Reporting rates of fever and particularly urticaria within 30 minutes after vaccination were consistently low whereas reporting rates of rash or itching were common but similar between the HPV-16/18 vaccine group and the control groups.

Fatigue, headache and myalgia were the most frequently reported solicited general symptoms. There were no differences in the percentages of doses followed by any or grade 3 fatigue, gastrointestinal symptoms and headache between the HPV vaccine group and the HAV720 vaccine group. The incidence of grade 3 symptoms did not increase with subsequent doses.

There was a slightly higher incidence of arthralgia in the HPV group when compared to the control HAV720 vaccine (reported after 10.2% (95% CI [9.8; 10.6]) of HPV doses versus 8.6% (95% CI [8.0; 9.2]) of HAV doses). There were no differences in the percentages of doses followed by grade 3 arthralgia between the HPV vaccine group and the HAV720 vaccine group. The incidences of grade 3 symptoms did not increase with subsequent doses.

There was a slightly higher incidence of myalgia in the HPV group when compared to the HAV720 control vaccine (reported after 28.1% (95% CI [27.5; 28.7]) of HPV doses versus 26.5% (95% CI [25.6; 27.5]) of HAV doses). Grade 3 myalgia also occurred more frequently in the HPV group and was reported after 1.4% (95% CI [1.3; 1.6]) of HPV vaccine doses as compared to 0.2% (95% CI [0.1; 0.5]) of ALU, 0.5% (95% CI [0.3; 0.8]) of HAV360 and 0.6% (95% CI [0.4; 0.8]) of HAV720 doses (see following Table). There was no significant increase of grade 3 myalgia with subsequent doses (1.3%, 1.1% and 1.7% following dose 1, dose 2 and dose 3 of HPV vaccine, respectively).

Pooled safety analysis: incidence of solicited local and general symptoms reported during the 7-day (Days 0-6) postvaccination period following all doses

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>All</td>
<td>1185</td>
<td>76.0</td>
<td>77.4</td>
<td>78.5</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1434</td>
<td>5.3</td>
<td>6.0</td>
<td>6.6</td>
<td>4435</td>
</tr>
<tr>
<td>Redness (mm)</td>
<td>All</td>
<td>2675</td>
<td>29.6</td>
<td>29.0</td>
<td>30.2</td>
</tr>
<tr>
<td></td>
<td>≥ 50</td>
<td>126.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Swelling (mm)</td>
<td>All</td>
<td>262</td>
<td>1.1</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>≥ 50</td>
<td>126.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>All</td>
<td>7945</td>
<td>33.1</td>
<td>32.5</td>
<td>33.7</td>
</tr>
<tr>
<td>Grade 3</td>
<td>340</td>
<td>1.5</td>
<td>1.3</td>
<td>1.7</td>
<td>4401</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>All</td>
<td>2843</td>
<td>0.9</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>176</td>
<td>0.7</td>
<td>0.6</td>
<td>0.8</td>
<td>4401</td>
</tr>
<tr>
<td>Headache</td>
<td>All</td>
<td>2802</td>
<td>23.5</td>
<td>20.5</td>
<td>20.9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>361</td>
<td>7.3</td>
<td>6.5</td>
<td>8.1</td>
<td>4401</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>All</td>
<td>2122</td>
<td>204.6</td>
<td>16.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Grade 3</td>
<td>82.8</td>
<td>0.4</td>
<td>0.3</td>
<td>0.6</td>
<td>2916</td>
</tr>
<tr>
<td>Myalgia</td>
<td>All</td>
<td>2122</td>
<td>5571</td>
<td>23.1</td>
<td>27.5</td>
</tr>
<tr>
<td>Grade 3</td>
<td>300</td>
<td>1.4</td>
<td>1.3</td>
<td>1.6</td>
<td>2916</td>
</tr>
</tbody>
</table>
HAV720 = Hepatitis A control group containing 720 EU hepatitis A antigen per dose (Study HPV-008 subset; adolescent girls and women 15-25 years of age)

N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Grade 3 Pain: Spontaneously painful (HPV-001) or Pain that prevents normal activity (HPV-008, HPV-012, HPV-013, HPV-014, HPV-015 and HPV-016)

Data Source = Pooled safety analysis

For an additional evaluation of the incidence of myalgia and arthralgia, the safety data collected from the large controlled efficacy trial HPV-008 (conducted in subjects aged 15 to 25 years) were also reviewed. Although there was a slightly higher percentage of HPV doses followed by arthralgia, myalgia and grade 3 myalgia when compared to the HAV720 control, these symptoms were of short duration, not associated with other symptoms that may evoke a general disease associated with arthralgia/myalgia, and did not result in a high level of absenteeism from work or school.

- Serious adverse events

All reports of serious adverse events and case fatalities in studies HPV-003, HPV-004, HPV-005, HPV-001, HPV-007, HPV-008, HPV-012, HPV-013, HPV-014, HPV-015 and HPV-016 were included in the analysis. From a total of 29,953 subjects vaccinated in these studies, 882 subjects reported at least one SAE during the entire follow up period (see table below). There was no difference on the overall reporting rates of SAEs during the different follow-up periods.

Global Summary of Serious Adverse Events reported

<table>
<thead>
<tr>
<th>Group</th>
<th>HPV (N=16142)</th>
<th>ALU (N=344)</th>
<th>HAV360 (N=1032)</th>
<th>HAV720 (N=9325)</th>
<th>Total (N=29953)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with at least one serious adverse event reported</td>
<td>459</td>
<td>75</td>
<td>25</td>
<td>323</td>
<td>682</td>
</tr>
<tr>
<td>Number of doses followed by at least one serious adverse event</td>
<td>472</td>
<td>78</td>
<td>25</td>
<td>335</td>
<td>910</td>
</tr>
<tr>
<td>Number of serious adverse event reported</td>
<td>542</td>
<td>56</td>
<td>28</td>
<td>372</td>
<td>1028</td>
</tr>
</tbody>
</table>

HPV = HPV-16/18 vaccine group (Studies HPV-001/007, 003, 004, 005, 008, 012, 013, 014, 015 and 016)
ALU = Al(OH)3 control group (Studies HPV-001/007, 003 and 015)
HAV360 = The control group who received Hepatitis A vaccine containing 360 ELU hepatitis A viruses and 250 μg Al(OH)3 (Study HPV-013)
HAV720 = The control group who received Hepatitis A vaccine containing 720 ELU hepatitis A viruses and 500 μg Al(OH)3 (Study HPV-008)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom

Data source = Pooled safety analysis

A total of 27 subjects reported SAEs assessed by the investigator as possibly related to vaccination. From these, 11 subjects received HPV-16/18 vaccine, 13 subjects received the control vaccine (either Aluminium or HAV) and 3 subjects received a blinded vaccine. Overall, the most frequently reported SAEs were pregnancy-related events: spontaneous abortions (2 HPV; 2 HAV; 3 ALU) and 2 foetal malformations (2 HAV). Five reported events were considered as potentially immune mediated (optic neuritis, thrombocytopenia, erythema nodosum, inflammatory bowel disease and arthritis reactive).

- Laboratory findings

Blood samples were collected to evaluate changes in biochemical and haematological parameters. For all studies where these parameters were evaluated, the haematology and biochemistry profiles were similar for all groups and there were no values out of range that were considered to be clinically significant.
Safety in special populations

Regardless of serological HPV status, HPV DNA status or previous/current HPV disease status the incidence of solicited symptoms was closely aligned to that observed in HPV DNA negative and HPV seronegative subjects and to the one observed in the overall population (Pooled Total Vaccinated Cohort).

The pooled safety analysis for studies HPV-012, 013 and 014 was stratified according to age. A slight decrease in the reactogenicity profile of the HPV-16/18 vaccine with increasing age was observed.

Pregnancy

A total of 1,737 pregnancies have been reported over the entire follow-up period for completed or ongoing clinical studies (see following Table for details). A total of 503 pregnancies (29%) are still ongoing. The majority of pregnancies were reported in subjects between 15 to 25 years of age, i.e., the age group where the largest clinical study, HPV-008, is currently ongoing in more than 18,000 subjects. Of these 1,737 pregnancies, 769 (44.3%) resulted in the delivery of a normal infant, 210 (12.1%) pregnancies were terminated by an elective abortion and 155 (8.9%) resulted in a spontaneous abortion. Of note, the rates of spontaneous abortion (8.9%) from this analysis are below reported background rates of spontaneous abortion in the general population. Literature reviews show a range from 12-15% for clinically recognised pregnancies and from 17-22% for early pregnancy losses which may be defined as pregnancy losses within 14 days after conception, around the next menstruation, and which could be confused with menstrual bleeding. In addition, a total of six stillbirths occurred, five of which were in women whose treatment status remains blinded (i.e., these subjects received either the HPV-16/18 vaccine or the HAV720 control vaccine).

When comparing the pregnancy outcomes per treatment group, there were no major differences in the rates of any specific pregnancy outcome between the HPV-16/18 vaccine group and the control groups. The rate of abnormal infants in the HPV-16/18 group was lower than the control group HAV720.

Concerning abnormal infants information available so far show that from the 18 reported pregnancy cases (6 in the HPV group, 4 in the ALU group and 8 in the HAV720 group), no cluster of events was identified. Nine pregnancies resulted in 11 neonatal deaths. Five of these deaths were related to prematurity. The remaining 6 neonatal deaths were related to respiratory distress syndromes (2 cases), aspiration pneumonia, intracranial haemorrhage, polycystic kidney disease with anhydramnios or gastrochisis.
### Pooled safety analysis: number of subjects with pregnancies** and pregnancy outcomes overall (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HPV N = 870</th>
<th>ALU N = 172</th>
<th>HAV360 N = 9</th>
<th>HAV720 N = 686</th>
<th>Total N = 1737</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Value or n</td>
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<td>Value or n</td>
<td>%</td>
<td>Value or n</td>
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<td>241</td>
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<td>Premature birth</td>
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<td>3</td>
<td>1.7</td>
<td>1</td>
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<tr>
<td>Abnormal infant</td>
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<td>0.7</td>
<td>4</td>
<td>2.3</td>
<td>0</td>
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<tr>
<td>Elective termination</td>
<td>103</td>
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<td>13</td>
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<tr>
<td>Therapeutic abortion</td>
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<td>0</td>
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<tr>
<td>Ectopic pregnancies</td>
<td>6</td>
<td>0.7</td>
<td>1</td>
<td>0.6</td>
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<tr>
<td>Spontaneous abortion</td>
<td>81</td>
<td>9.3</td>
<td>22</td>
<td>12.8</td>
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<tr>
<td>Stillbirth</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Lost to follow-up</td>
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<tr>
<td>Not applicable</td>
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</table>

HPV = HPV-16/18 vaccine group (Studies HPV-001/007, 003, 004, 005, 008, 012, 013, 014, 015 and 016; adolescent girls and women 10 years of age onwards)

ALU = Al(OH)₃ control group (Studies HPV-001, 003 and 015; adolescent girls and women 15 years of age onwards)

HAV360 = Hepatitis A control group containing 360 EU hepatitis A antigen per dose (Study HPV-013; girls 10-14 years of age)

HAV720 = Hepatitis A control group containing 720 EU hepatitis A antigen per dose (Study HPV-008; adolescent girls and women 15-25 years of age)

N = number of pregnancies
n = number of pregnancies in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
Spontaneous abortion includes missed abortion
Not applicable: e.g. mola, trophoblastic tumor
* = cases which remain blinded as studies HPV-001/007, HPV-008 and HPV-015 are ongoing
** = twin pregnancies counted as one pregnancy
Data source = Pooled safety analysis

A secondary analysis of pregnancies and pregnancy outcomes was conducted that focused on pregnancies in women for which their last menstrual period (LMP) occurred from -30 days to +45 days around vaccination. These pregnancies occurred despite the fact that subjects were strongly advised (through the informed consent process) to take precautions to avoid pregnancy until 2 months after the last vaccination, and that pregnancy testing was conducted prior to vaccination.

A total of 415 subjects reported pregnancies around vaccination (defined as LMP initiated from -30 days to +45 days around vaccination). 57.3% of subjects gave birth to normal infants, 16.1% of pregnancies resulted in elective abortion and 8.9% resulted in spontaneous abortion, whereas 9.4% of pregnancies are still ongoing. Except for a slight increase in the proportion of elective abortions, these rates are comparable to the outcome rates for all pregnancies. A total of 7 women delivered an abnormal infant. Outcomes in one of the control groups (HAV720), was observed when compared to the HPV group (5 in HAV720 group and 2 in HPV group). No reports of abnormal infants were received in the ALU and HAV360 control groups.

When comparing the outcomes between treatment groups, an imbalance with higher rates of spontaneous abortion was observed in the HPV group compared to the HAV720 group (11.0% versus 5.7%). This imbalance was not observed between the HPV group and the ALU group (11.0% versus 13.8%).
Pooled safety analysis: number of subjects with pregnancies around vaccinations and their outcomes (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HPV N = 210</th>
<th>ALU N = 29</th>
<th>HAV360 N = 1</th>
<th>HAV720 N = 175</th>
<th>Total N = 415</th>
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</thead>
<tbody>
<tr>
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<td>%</td>
<td>Value or n</td>
<td>%</td>
<td>Value or n</td>
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<tr>
<td>Pregnancy ongoing</td>
<td>21</td>
<td>10.0</td>
<td>9</td>
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<tr>
<td>Normal Infant</td>
<td>115</td>
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<tr>
<td>Premature birth</td>
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<td>Abnormal infant</td>
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<tr>
<td>Elective termination</td>
<td>37</td>
<td>17.6</td>
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<tr>
<td>Therapeutic abortion</td>
<td>*</td>
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<tr>
<td>Ectopic pregnancies</td>
<td>2</td>
<td>1.0</td>
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<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>23</td>
<td>11.0</td>
<td>4</td>
<td>13.8</td>
<td>0</td>
</tr>
<tr>
<td>Still birth</td>
<td>*</td>
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<td>0</td>
<td>0.0</td>
<td>0</td>
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<tr>
<td>Lost to follow-up</td>
<td>2</td>
<td>1.0</td>
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<tr>
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</tbody>
</table>

HPV = HPV-16/18 vaccine group (Studies HPV-001, 008, 012, 013, 014, 015 and 016; adolescent girls and women 10 years of age onwards)

ALU = Al(OH)3 control group (Studies HPV-001 and 015; adolescent girls and women 15 years of age onwards)

HAV360 = Hepatitis A control group containing 360 EU hepatitis A antigen per dose (Study HPV-013; girls 10-14 years of age)

HAV720 = Hepatitis A control group containing 720 EU hepatitis A antigen per dose (Study HPV-008; adolescent girls and women 15-25 years of age)

N = number of pregnancies

n = number of pregnancies in a given category

Value = value of the considered parameter

% = n / Number of subjects with available results x 100

Pregnancies around vaccinations: Pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination (Subjects with missing date for last menstrual period are not included)

Spontaneous abortion includes missed abortion

Not applicable: e.g. mola, throphoblastic tumor

* = cases which remain blinded since HPV-001/007, HPV-008 and HPV-015 are ongoing

Data source = Pooled safety analysis

To further evaluate this observed imbalance, the ongoing study HPV-009 was also analysed in this respect. While cases of any abnormal pregnancy outcome experienced by a subject whose last menstrual period (LMP) occurred within 60 days of vaccination was unblinded the overall number of pregnancies per group are not available from study 009 since these pregnancies are still blinded and, contrary to study HPV-008, an interim analysis is not foreseen. Only the absolute numbers and not the rates of pregnancy outcomes can therefore be compared between the treatment groups. Therefore it is currently unknown whether the number of pregnancies would be comparable in the two treatment groups.

The observed imbalance in study HPV-008 appears to be mostly concentrated in the group of women who had their LMP within 30 days before vaccination. In study HPV-009 a similar, albeit smaller, imbalance is seen. The reported frequencies of spontaneous abortions following HPV-16/18 vaccine administration among women whose pregnancy occurred around vaccination can be considered close to the lower limit (12-22%) of the range of background incidence rates of spontaneous abortion reported in the medical literature.

Several studies, including the large study HPV-008, are still ongoing and further follow-up will be collected on all pregnancies occurring among women in these studies. Close monitoring of pregnancy-related events is covered post-licensure (see RMP).

The effect on breast-fed infants of the administration of Cervarix to their mothers has not been evaluated in clinical studies.

Cervarix should only be used during breast-feeding when the possible advantages outweigh the possible risks.
• Safety related to drug-drug interactions and other interactions

In Studies HPV-001, 012, 013 and 014 the use of medication, including anti-pyretic medication, was recorded. Overall, no major differences concerning use of anti-pyretics was observed.

• Discontinuation due to adverse events/deaths

The number of subjects vaccinated, completed and withdrawn with the reasons for withdrawal are summarised in the table below. A total of 55 subjects were withdrawn from the study due to serious or non-serious adverse events (including 33 subjects in the HPV-16/18 vaccine group) as described below:

Five case fatalities were reported in the overall HPV clinical development. None of these were assessed by the investigator as possibly related to vaccination. Two case fatalities were associated with motor vehicle accidents. One case fatality was associated with homicide. The remaining 2 cases refer to death due to osteosarcoma complications and ketoacidosis due to diabetes.

In addition to the 5 case fatalities described above, 13 foetal deaths were also reported to the Company as pregnancy outcomes. These cases were kept blinded as they were reported from studies that are currently ongoing. Although these case fatalities remain blinded, no safety signal has been identified based on the description of these events.

Number of subjects vaccinated and withdrawn due to serious or non-serious adverse events

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<thead>
<tr>
<th></th>
<th>HPV</th>
<th>ALU</th>
<th>HPV</th>
<th>HPV</th>
<th>HPV</th>
<th>HPV</th>
<th>HPV</th>
<th>HPV</th>
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</table>

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 008, 012, 013, 014, 015 and 016)
ALU = Al(OH)3 control group (Studies HPV-001, 003 and 015)
HAV360 = The control group who received Hepatitis A vaccine containing 360 ELU hepatitis A viruses and 250 μg Al(OH)3 (Study HPV-013)
HAV720 = The control group who received Hepatitis A vaccine containing 720 ELU hepatitis A viruses and 500 μg Al(OH)3 (Study HPV-008)
Study HPV-007 is not included since subjects from this study were enrolled and vaccinated in Study HPV-001 and no vaccination was administered in Study HPV-007
Studies 008 and 015 are still ongoing and represent the information that was available at the time of the respective interim analyses in the different studies

New Onset of Chronic Disease (NOCD)

New on-chest chronic diseases (NOCD) were reported throughout the study periods regardless of causal relationship to vaccination and intensity. All adverse events reported during the trial were compared with a pre-defined list of symptoms/conditions that may evoke chronic diseases. The number of subjects experiencing an NOCD was similar between HPV vaccine and the control groups in any given reporting period (see following table).

The most commonly reported NOCD were asthma, urticaria and hypersensitivity, which were each reported at similar frequencies in the HPV vaccine and control groups.
New Onset of Autoimmune Disease (NOAD)

Overall, the reporting rates of NOAD were low and no cluster of events has been detected in any treatment group. The most frequently reported events were related to thyroid disease as would be expected based on the background incidence rates of thyroid disease in young female population. No clear difference in the reported rates of thyroid disease between treatment groups in any of the follow-up periods has been observed to date. No cluster in terms of either time to onset of AEs and number of doses has been observed. The other events were kept blinded as most of these events have been reported only once. The low frequency of autoimmune diseases constitutes a limitation of their assessment in the clinical program. Therefore, they will be further evaluated in ongoing and the planned post-licensure activities.

Seven cases of neurological disorders (five cases in the HPV group and two in the control group) have been identified. These cases appear to be isolated events. Final diagnoses are unclear for 3 cases. The time to onset varies between 9 days to 7 months. Thus, no cluster in terms of either time to onset of AEs and number of doses has been observed. The other events were kept blinded as most of these events have been reported only once. The low frequency of autoimmune diseases constitutes a limitation of their assessment in the clinical program. Therefore, they will be further evaluated in ongoing and the planned post-licensure activities.

• Discussion on clinical safety

The most frequently reported solicited symptoms after administration of the HPV-16/18 L1 VLP AS04 vaccine were injection site reactions including pain, redness and swelling, all reported more frequently in the HPV group as compared to the control groups. Solicited general symptoms were reported less frequently than local symptoms after vaccination. Among these, myalgia and arthralgia were reported more frequently in the HPV-16/18 vaccine group as compared to control groups. The majority of the reports were of low grade intensity and the symptoms were transient, not associated with any general disease and resolved without sequelae.

There was no clinically meaningful increase of symptoms with increasing number of doses. The majority of the solicited local and general symptoms reported were mild to moderate in intensity, and usually resolved within 3 or 4 days after vaccination.

Compliance with the full vaccination course was equally high in both HPV-16/18 vaccine and control groups, suggesting that the higher rates of local and general symptoms following HPV-16/18
vaccine did not negatively impact tolerability or acceptance of the vaccination treatment. There were no unusually high rates of occurrence of unsolicited adverse events, and there was no evidence that any unsolicited adverse event occurred more frequently in the HPV-16/18 vaccine group than in control groups. Separate analysis of NOAD revealed no clear trend or cluster, although as the incidence rates of autoimmune diseases are low, further post-marketing evaluation is necessary to fully assess the issue. Discontinuation rates due to adverse events were low and similar between groups.

The impact on pregnancy and pregnancy outcome could not be fully analysed at the time of assessment, since most of the pregnancies were ongoing and/or remained blinded concerning allocation to vaccine. Use of contraceptives was required per protocol for the period during the vaccination period and therefore, there is currently no robust data available on the use of Cervarix in pregnant women. A slight imbalance of spontaneous abortions in study HPV-008 was mostly observed in the group of women who had their LMP within 30 days before vaccination.

The reported frequencies of spontaneous abortions following HPV-16/18 vaccine administration among women whose pregnancy occurred around vaccination can be considered close to the lower limit (12-22%) of the range of background incidence rates of spontaneous abortion reported in the medical literature. However, vaccination should be postponed until after completion of pregnancy. Close monitoring of pregnancy-related events is covered postlicensure (see RMP).

The reporting rates of New Onset of Autoimmune Disease (NOAD) were low. No cluster in terms of either time to onset of AEs and number of doses has been observed. A review of the cases and analyses from the overall database do not indicate an increased risk for demyelinating disease or nerve disorders. Autoimmune diseases including demyelinating neurological diseases as well as neurological inflammatory disorders are addressed in the RMP.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities</th>
<th>Proposed risk minimisation activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto-immune diseases (AIDs)</td>
<td>Ongoing Study HPV 008</td>
<td>Not applicable at this stage.</td>
</tr>
<tr>
<td></td>
<td>Post-licensure prospective cohort study (AIDs study, Scotland)</td>
<td>Not applicable at this stage.</td>
</tr>
</tbody>
</table>
Use in HIV positive women

<table>
<thead>
<tr>
<th>Use in co-administration with other vaccines</th>
<th>HPV-018 (US)</th>
<th>HPV-029 (Europe)</th>
<th>HPV-042 (Europe)</th>
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</thead>
<tbody>
<tr>
<td>Use in co-administration with other vaccines</td>
<td>Ongoing Study HPV 008</td>
<td>Ongoing Study HPV 009</td>
<td>Ongoing Study HPV-007</td>
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<tr>
<td>Pregnancy outcomes after vaccination</td>
<td>Ongoing Study HPV-015</td>
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<td>Pregnancy outcomes after vaccination</td>
<td>US-based Pregnancy Register</td>
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<tr>
<td>Pregnancy outcomes after vaccination</td>
<td>HPV-040 CRT (Finland)</td>
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<td>Pregnancy outcomes after vaccination</td>
<td>Post-licensure prospective cohort study (Scotland)</td>
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Other Plans and Considerations

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<th>Long-term efficacy</th>
<th>HPV-008 LTFU (Finland cohort) via Finnish Cancer Registry</th>
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<tr>
<td>Males</td>
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The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Overall conclusions, risk/benefit assessment and recommendation

Quality

During the evaluation of Cervarix, no major objections were identified. A number of minor concerns were raised in regard to the novel insect cell production system and these have been adequately addressed, however several commitments have been made by the applicant, and several follow-up measures defined to provide further information post-approval. In conclusion, all quality issues can be considered resolved.

Non-clinical pharmacology and toxicology
No animal model exists for human papilloma virus infection. Consequently Cervarix has not been
tested for protection. Pharmacology studies in animals show that MPL induces innate immunity and
showed no induction of undesirable pharmacological effects on cardio-respiratory functions.
Primary pharmacodynamic studies in mice and monkeys show that the activation of the innate
immunity by AS04 is paralleled by the induction of a strong and persistent specific immune response
by the Cervarix vaccine. Safety pharmacology studies on cardio-respiratory functions showed no
undesirable pharmacological effects with Cervarix.

Studies on secondary pharmacology or pharmacodynamic drug interactions have not been
performed, which is acceptable for this vaccine.

Two studies targeting the determination of the pharmacokinetics of MPL-related material following
intravenous and intramuscular administration in rats were carried out. The MPL-related material is
widely distributed throughout the body, notably in the fat and spleen, and is then likely eliminated
via the expired air with only low levels remaining in the carcass.

Signs of inflammation at the injection sites of the test vaccine were observed. These injection site
reactions were local and followed by a recovery process. This local effect is most likely the sign of
the strong adjuvant effect induced by AS04. Furthermore, up to three times the full human dosage
was used in the rabbit studies, probably amplifying this local reaction. The injection site reaction was
accompanied with a temporary increase in the number of neutrophils and in fibrinogen, which may
be a consequence of the recruitment of inflammatory cells following injections of the formulations.

In vitro mutagenicity and clastogenicity tests, and in vivo micronucleus assay demonstrated no
genotoxic potential of the MPL adjuvant. The mutagenic and carcinogenic potential of the Cervarix
vaccine was not further evaluated, which is accepted since the vaccine is based on L1 protein and
HPV oncoproteins are absent.

The reproductive toxicity study in CD rats did not show any effects of vaccination or AS04
administration on fertility, embryofoetal development and pre- and post-natal development.
Antibodies from vaccinated dams cross the placenta and are secreted in the milk.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety
pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and
postnatal toxicity (up to the end of the lactation period).

**Efficacy**

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III
clinical trials that included a total of 19,778 women aged 15 to 25 years.

Endpoints included CIN2+ associated with HPV-16 and/or HPV-18 and 12-month persistent
infection.
For HPV-16 all endpoints reached statistical significance.
For HPV-18, the difference between the vaccine and control groups was not statistically significant
for CIN2+ and 12-month persistent infection due to a limited number of events at the time of the
analysis. However, in a pre-specified analysis that excluded women with abnormal cytology at study
entry, the 12-month persistent infection endpoint for HPV-18 reached statistical significance with
vaccine efficacy of 89.9% (97.9% CI: 11.3; 99.9).

An additional post-hoc analysis based on the presence of the HPV type in cytology samples prior to
detection of the lesion excluded 3 CIN2+ cases which were not considered to be causally associated
with HPV-16 or HPV-18 infections acquired during the trial. Based on this analysis there were no
cases in the vaccine group and 20 cases in the control group (Efficacy 100%; 97.9% CI: 74.2, 100).

There was no evidence of protection from disease caused by the HPV types for which subjects were
HPV DNA positive at study entry. However, individuals already infected with one of the vaccine-
related HPV types prior to vaccination were protected from clinical disease caused by the remaining HPV type.

In clinical trials assessing immunogenicity, 99.9% of initially seronegative subjects had seroconverted to both HPV types 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres were well above titres observed in women previously infected but who cleared HPV infection. Initially seropositive and seronegative subjects reached similar titres after vaccination.

Study HPV-014 demonstrated, that seropositivity with regard to HPV 16 and 18 at the time of vaccination has some marginal positive influence on the kinetics of the immune response as well as on final GMTs and is more pronounced in older individuals compared to those who are younger: Whether or not vaccination of a seropositive female population has any effect on clinical efficacy of Cervarix cannot be assessed for the time being.

In two further clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.

Safety

The most frequently reported solicited symptoms after administration of the HPV-16/18 L1 VLP AS04 vaccine were injection site reactions including pain, redness and swelling, headache, myalgia and arthralgia. Solicited general symptoms were reported less frequently than local symptoms after vaccination. The majority were of low grade intensity and the symptoms were transient and resolved without sequelae.

There was no clinically meaningful increase of symptoms with increasing number of doses. No unusually high rates of occurrence of unsolicited adverse events, and no evidence that any unsolicited adverse event occurred more frequently in the HPV-16/18 vaccine group than in control groups were observed. Discontinuation rates due to adverse events were low and similar between groups.

The impact on pregnancy and pregnancy outcome could not be fully analysed at the time of assessment, since most of the pregnancies were ongoing and/or remained blinded concerning allocation to vaccine. A slight imbalance of spontaneous abortions in study HPV-008 was mostly observed in the group of women who had their LMP within 30 days before vaccination.

The reported frequencies of spontaneous abortions following HPV-16/18 vaccine administration among women whose pregnancy occurred around vaccination can be considered close to the lower limit (12-22%) of the range of background incidence rates of spontaneous abortion reported in the medical literature. However, vaccination should be postponed until after completion of pregnancy. Close monitoring of pregnancy-related events is covered post authorisation (see RMP).

The effect on breast-fed infants of the administration of Cervarix to their mothers has not been evaluated in clinical studies. Cervarix should only be used during breast-feeding when the possible advantages outweigh the possible risks.

Administration of Cervarix should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunisation.

The reporting rates of New Onset of Autoimmune Disease (NOAD) were low. Seven cases of neurological disorders were of particular interest (five cases in the HPV group and two in the control group). The cases appear to be isolated events and no cluster in terms of either time to onset of AEs and number of doses has been observed. The cases do not indicate an increased risk for
demyelinating disease or nerve disorders. Autoimmune diseases including demyelinating neurological diseases as well as neurological inflammatory disorders are addressed in the RMP. Cervarix should not be used in case of hypersensitivity to the active substances or to any of the excipients.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A user consultation has been performed and was considered to be satisfactory.

**Risk-benefit assessment**

The benefits of Cervarix are currently based on 2 controlled, double-blind, randomised Phase II and III clinical studies. Both trials are still ongoing and continue to generate data on both efficacy and safety. Data is available from studies HPV-001/007 (5.5 years) and HPV-008 (mean follow-up 15 months). The phase III interim analysis was event driven.

The primary efficacy composite endpoint, protection against CIN2+ associated with the HPV-16/18, was met.

Other composite HPV-16/18 endpoints (6-months and 12-months persistence, CIN1+ and ASCUS+) were also statistically significant but not considered for the demonstration of efficacy against cervical cancer.

For HPV-16 all endpoints reached statistical significance. For HPV 18 the difference between the vaccine and control groups was not statistically significant for CIN 2+ and 12-month persistent infection. However, in a pre-specified analysis that excluded women with abnormal cytology at study entry, the 12-month persistent infection endpoint for HPV-18 also reached statistical significance.

The safety profile of Cervarix was comparable to the control groups. No clear evidence for a serious safety risk has been identified.

Taking all of the data into consideration the benefits of Cervarix outweighs the risks and the risk/benefit ratio is positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- no additional risk minimisation activities were required beyond those included in the product information.
Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Cervarix in

The prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18.

The indication is based on demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years.

See section 5.1 for information on the evidence that supports the efficacy of Cervarix in prevention of CIN grades 2 and 3 associated with HPV-16 and/or HPV-18.

was favourable and therefore recommended the granting of the marketing authorisation.